I kombinuar me një statinë në dozën maksimale të toleruar[1]

DY ARSYE PSE E DUA LEQVIO®

(inclisiran)



Dy doza në vit.[1]

Reduktim efektiv dhe i qëndrueshëm i LDL-C.[1]

NË TRAJTIMIN E
Sëmundjeve Kardiovaskulare Aterosklerotike dhe Hiperkolesterolеminë Familjare Heterozigote

1. Leqvio. Summary of product characteristics. Novartis Pharma AG; 2020.

NOVARTIS

Novartis Pharma Services Inc., Zyra e Përfaqësisë
Tiranë Rruga "Hoxha Tasim", Nr. 23,
Tiranë, Shqipëri
Tel: +355 4 2232444
LEQ - AD1 - 10/02/2025 - FA-11356185

LEQVIO®
inclisiran

Albanian Journal of Internal Medicine Vol.1 Issue 2 2024

Albanian Journal of Internal Medicine

ALBANIAN JOURNAL OF INTERNAL MEDICINE

Vol.1 Issue 2
©2024
ISSN 3007-6692

ALBANIAN SOCIETY OF INTERNAL MEDICINE

AstraZeneca

forxiga®
(dapagliflozin)

1 BAR
3 INDIKACIONE[1]

DIABET MELLITUS TIPI 2

INSUFICIENCË KARDIAKE

SËMUNDJE RENALE KRONIKE



ALTERNATIVË E VETME E RIMBURSUAR 100%
NË LISTËN E BARNAVE TË RIMBURSUESHME

Referenca:
1. FORXIGA 10 mg Përmbledhja e Karakteristikave të Produktit 20.12.2024

VETËM PËR PROFESIONISTË TË KUJDESIT SHËNDETËSOR

Kontakt lokal për raportimin e efekteve të padëshiruara të barnave: medinfo.albania@swixxbiopharma.com
Kontakt lokal për pyetje specifike në lidhje me produktet mjekësore të AstraZeneca: medinfo.albania@swixxbiopharma.com
Amicus Pharma shpk a Swixx Biopharma | Rruga "Deshmoret e 4 Shkurtit", Apartamenti N19, Numri I pasurise 3/280-N19. Tirane

PM-AL-2025-2-402; 02/2025

AstraZeneca

Amicus
a Swixx BioPharma company

ALBANIAN JOURNAL
OF INTERNAL MEDICINE

ALBANIAN SOCIETY OF INTERNAL MEDICINE

BRAINSTORM EDUCATION • HEALTH • SCIENCE

Vol.1 Issue 2
©2024
ISSN 3007-6692

Vol.1 Issue 2
©2024
ISSN 3007-6692

Albanian Journal of Internal Medicine

EDITOR IN CHIEF

Prof. Dr. Margarita Gjata Resuli

EDITORES EMERITI

Adriana Babameto
Alban Dibra
Agron Ylli
Arben Ivanaj
Arjana Stakosha
Etleva Qirko Loloçi
Ermira Vasili
Silvana Bala
Teuta Çiço Backa

EDITORIAL BOARD

Alma Idrizi
Adela Perolla
Dorina Ylli
Edite Sadiku
Elizana Petrela
Eneida Hoxha
Ergita Nelaj
Gentjan Asllanaj
Ledio Çollaku
Monika Fida

Vol.1 Issue 2
©2024
ISSN 3007-6692

Albanian Journal of Internal Medicine

INTERNATIONAL SCIENTIFIC BOARD

Corin Badiu	Romania
Dirk Pickuth	Germany
Emi Dika	Italy
George Mastorakos	Greece
Rümeyza Kazancioglu	Turkey
Vesna Tomic	Serbia

EDITORIAL OFFICE

Feisi Gjolena
Fribianka Hoxha
Ilir Gjermeni
Irida Kecaj
Kriselda Krashi
Lubana Bodurri
Pandush Pojani
Somida Kuka
Valbona Duraj

Contact number : +355 694040521

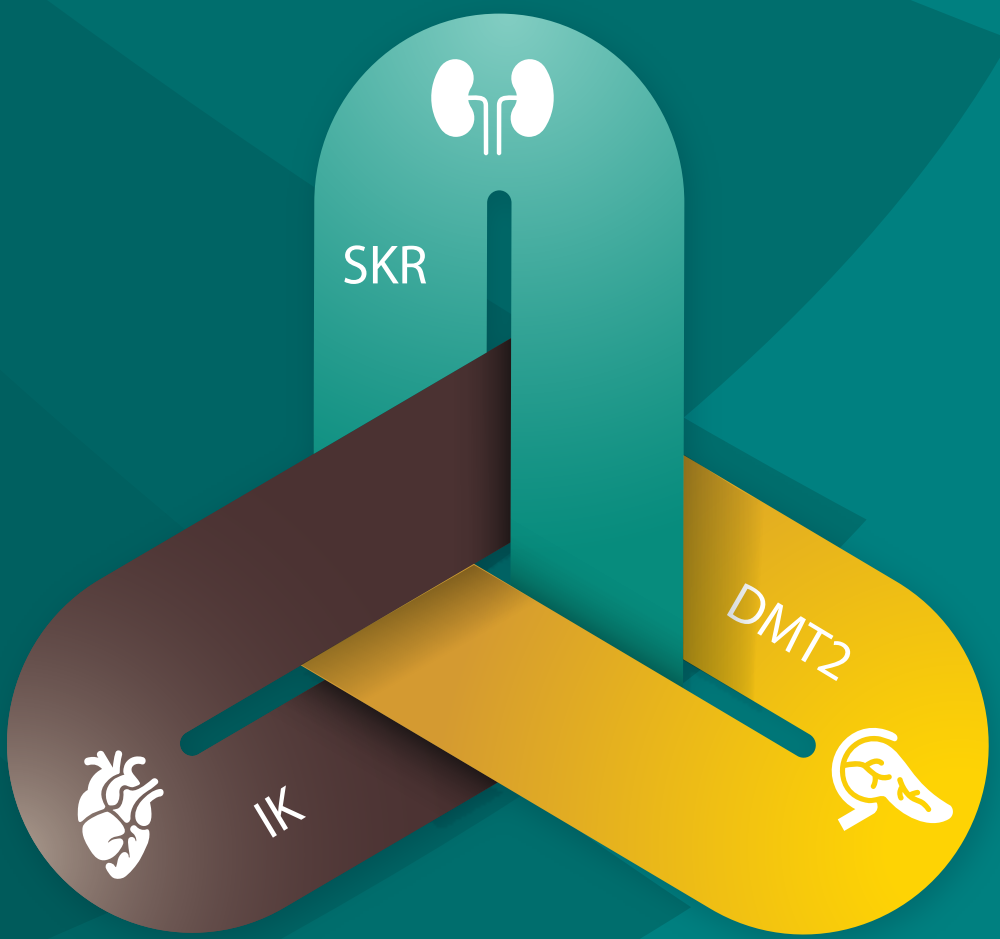
Editorial e-mail :alb.journalofinternalmedicine@gmail.com

Web: www.ajim.health

Jardiance®
(emagliflozin)

JARDIANCE OFRON MBROJTJE TË TREFISHTË[1]

DUKE ULUR RISKUN PËR NJË GAMË TË GJERË PACIENTËSH ME DMT2, SKR OSE IK.



Përfitime klinike në:

✓ **Menaxhimin e Diabetit** - Ul në mënyrë efektive nivelet e HbA1c.
✓ **Mbrojtjen Kardiovaskulare** - Redukton vdekshmërinë kardiovaskulare dhe hospitalizimet prej insuficiencës kardiake (studimet EMPA-REG, EMPEROR).
✓ **Mbrojtjen Renale** - Ngadalëson përparimin e SRK dhe ul rrezikun e dializës (studimi EMPA-KIDNEY).
✓ **Reduktimin e Peshës dhe Tensionit të Gjakut** - Mbështet shëndetin metabolik në përgjithësi.

E Mbështetur nga Shkenca, e Besuar nga Ekspertët!
Empagliflozina rekomandohet nga udhëzimet kryesore mjekësore për pacientët me diabet tip 2, insuficiencë kardiake dhe SRK.

EM-RCV-100532

Boehringer Ingelheim

Për më shumë informacion, skanoni QR kodin për të parë të dhënat klinike.

Roteas®

edoxaban

I ZHVILLUAR DUKE PASUR TË MOSHUARIT NË MENDJE[1,2,3]

Roteas® u zhvillua për një grup të gjerë të pacientëve të moshuar me FAJV.[1,2] Duke ofruar një kombinim unik të përfitimeve klinike[1-3] dhe praktike[4,5,] Roteas® mund të ndihmojë në reduktimin e kompleksitetit të menaxhimit të parandalimit të goditjes në tru në pacientët tuaj të moshuar me FAJV.



AL_ROT_07-2023_V01_BANNER 1 Nëntor 2023

Ky material i referohet bamave me përshkrim dhe i drejtohet vetëm profesionistëve të shëndetësisë.

EMRI I PRODUKTIT MJEKËSOR: Roteas 15 mg tableta të veshura me film, Roteas 30 mg tableta të veshura me film, Roteas 60 mg tableta të veshura me film. PËRBËRJA CILËSORE DHE SASIORE: Roteas 15 mg tableta të veshura me film. Çdo tabletë e veshur me film përmban 15 mg edoksaban (në trajtën e edoksaban tosilat). Roteas 30 mg tableta të veshura me film. Çdo tabletë e veshur me film përmban 30 mg edoksaban (në trajtën e edoksaban tosilat). Roteas 60 mg tableta të veshura me film. Çdo tabletë e veshur me film përmban 60 mg edoksaban (në trajtën e edoksaban tosilat). FORMA FARMACEUTIKE: Tableta të veshura me film. INDIKIMET TERAPEUTIKE: Roteas indikohet për parandalimin e insultit cerebral (goditjes në tru) dhe embolisë sistemike në pacientët e mitur me fibrilacion atrial jovalvular (NVAF) me një ose më shumë faktorë rreziku, të tillë si insuficienca kardiake kongjestive hipertensioni, moshа ≥75 vjeç, diabeti mellit, insulti cerebral ose ataku iskemik tranzitor (TIA) i mëparshëm. Roteas indikohet për trajtimin e trombozës së venave të thella (DVT) dhe embolisë pulmonare (PE), dhe për parandalimin e DVT dhe PE rekurente tek të rritur. DOZIM DHE MËNYRA E PËRDORIMIT: Dozimi: Parandalimi i insultit cerebral dhe embolisë sistemike. Doza e këshilluar është 60 mg edoksaban një herë në ditë. Terapia me edoksaban në pacientët me NVAF duhet të vazhdojë për një kohë të gjatë. Trajtimi i DVT, trajtimi i PE dhe parandalimi i DVT dhe PE (VTE) rekurrente. Doza e këshilluar është 60 mg edoksaban një herë në ditë pas përdorimit fillestar të një antikoagulanti parenteral për të paktën 5 ditë. Edoksaban dhe antikoagulanti parenteral fillestar nuk duhet të administrohen njëkohësisht. Kohëzgjatja e terapisë për trajtimin e DVT dhe PE (tromboembolisë venoze (VTE)) dhe parandalimin e VTE rekurrente duhet të individualizohet pas një vlerësimi të kujdesshëm të përfitimit të trajtimit përkundrejt rrezikut për gjakderdhje (shih paragrafin 4.4). Kohëzgjatja e shkurtër e terapisë (të paktën 3 muaj) duhet të bazohet në faktorë të mirëkuti të përkohshëm (p.sh. ndërhyrje kirurgjikale, trauma, imobilizim në kohët e fundit), ndërsa kohëzgjatjet më të gjata duhet të bazohen në faktorë të rrezikut të përhershëm ose në DVT apo PE idiopatike. Për NVAF dhe VTE, doza e këshilluar është 30 mg edoksaban një herë në ditë tek pacientët me një ose më shumë nga faktorët klinikë të mëposhtëm: • Dëmtim renal i formës së mesme ose të rëndë (klirensi i kreatininës (CrCl) 15 - 50 mL/min). • Peshë trupore e ulët ≤ 60 kg. • Përdorimi i njëkohshëm i frenuesve të mëposhtëm të P-glikoproteinës (P-gp): diklosporinë, dronedaron, eritromicinë ose ketokonazol. KUNDËRINDIKIMET: Mbindjeshtmëria ndaj lëndës vepruese ose ndaj ndonjë prej lëndëve të ljera përbërëse (eksципientëve) të produktit. Hemorragji aktive klinikisht e rëndësishme. Sëmundja hepatike të shoqëruara me koagulopati dhe rrezik për gjakderdhje klinikisht të rëndësishme. Gjendje ose lezione, në nastet kur konsiderohen se janë një rrezik i rëndësishëm për gjakderdhje madhore. Këto mund të përfshijnë ulceracionet gastrointestinale aktuale ose të ndodhura kohët e fundit, neoplazitë malinje me rrezik të lartë për gjakderdhje, dëmtimet e trurit ose të palcës kurrizore të ndodhura kohët e fundit, ndërhyrjet kirurgjikale në tru, palcës kurrizore ose sy të knyera kohët e fundit, hemorragjinë intrakraniale të pësuar kohët e fundit, varicet ezofagiale të njohura ose të dyshuara, keqformimet arteriovenoze, aneurizmat vaskulare ose anomalitë vaskulare madhore intraspinale ose intracerebrale. Hipertensioni i rëndë i pakontrolluar. Trajtim shoqërues me ndonjë antikoagulant tjetër, p.sh. heparinë e pafraksionuar (UFH), heparina me peshë të ulët molekulare (enoksaparinë, dalteparinë, etj.), derivate të heparinës (fondaparinux, etj.), antikoagulantë orale (warfarinë, dabigatran eteksilat, rivaroksaban, apiksaban etj), përveç methanave specifike të ndryshimit të terapisë me antikoagulantë oralë ose kur UFH jepet në doza të nevojshme për të mbajtur një kateter venoz qendror ose arterial të hapur. 2 DATA E RISHIKIMIT TË TEKSTIT 12/2021 Për më shumë informacion lexoni SmPC e plotë.

RX status: merret vetëm me përshkrimin e mjekut

BERLIN-CHEMIE AG Zyra e përfaqësisë Tiranë, Rr. e Kavajës P1/11/1, Tiranë, +35542259908, albania@berlin-chemie.com

BERLIN-CHEMIE MENARINI

1. Giuliano RP et al. N Engl J Med 2013; 369(22):2093–2104; and supplementary appendix. 2. Kato ET et al. J Am Heart Assoc 2016; 5(5). pii: e003432. 3. Ruff CT et al. Lancet 2015; 385(9984):2288–95. 4. Roteas®. Summary of Product Characteristics. 12/2021. 5. Steffel J et al. Eur Heart J 2018; 39:1330–1393.

Table of Contents

HEPATITIS C AND LYMPHOMA: A LESS NOTICED BUT IMPORTANT LINK 2
Adela Perolla **2**
PULMONARY HYPERTENSION AND LUNG CANCER IN COMBINED PULMONARY FIBROSIS AND EMPHYSEMA SYNDROME 4
Jolanda Nikolla, Hasan Hafizi 4
THE ROLE OF AUTONOMIC DYSFUNCTION IN OUTCOME OF STROKE PATIENTS 14
Entela Basha, Eris Ranxha, Olsi Taka, Vera Ostreni 14
REFRACTORY PATHOLOGIES IN SCHOOL AGE 20
Orgeta Dervishi, Migena Gega, Admir Nake, Zamir Damani, Klerida Shehu 20
MECHANICAL JAUNDICE AND CLINICAL-LABORATORY CORRELATIONS 30
Klerida Shehu, Migena Gega, Orgeta Dervishi, Adriana Babameto, Benard Shehu, Erald Vasili[3] 30
SGLT2 INHIBITOR - A NEW HYPOGLYCEMIC AGENTS WITH POTENTIAL EFFECT IN CARDIOVASCULAR RISK *"An apple a day keeps heart failure, kidney disease, and myocardial infarction away"* 39
Ergita Nelaj, Irida Kecaj, Kei Xhixhabesi, Zheni Gjergj, Arjana Stojku 39
SEVERE BRONCHIAL ASTHMA, A DISEASE OR A SYNDROME? 46
Mehmet Hoxha, Ester Ndreu, Etleva Qirko Loloçi 46
EXOSOMES — A NEW WINDOW OF HEALTH FROM DISEASE, TREATMENT, DIAGNOSIS, AESTHETICS, AND LIFESPAN 55
Migena Gega, Admir Nake, Klerida Shehu, Jonida Stefa, Orgeta Dervishi 55
COLORECTAL CANCER OR INFLAMMATORY BOWEL DISEASE? 65
IrgenTafaj, Frosilda Kola 65
PULMONARY HYPERTENSION IN A GERIATRIC PATIENT WITH ANEMIA FROM HEREDITARY HEMORRHAGIC TELANGIECTASIA: CASE REPORT 71
Irida Kecaj, Rizvan Myrtaj, Ergita Nelaj, Ilir Gjermeni, Ina Refatllari, Kei Xhixhabesi, Margarita Gjata 71
A NONTRAUMATIC, RIGHT-SIDED DIAPHRAGMATIC HERNIA, IN AN ADULT, DIAGNOSED DURING AN ASTHMA ATTACK. 79
Eris Mesonjesi, Klea Xhelilaj, Denisa Spahiu, Albana Gjeli, Viola Nushi, Etleva Qirko Loloci 79
DISSEMINATED TUBERCULOSIS (POTT'S DISEASE AND BILATERAL TUBERCULOUS PLEURAL EFFUSION) ASSOCIATED WITH PULMONARY THROMBOEMBOLISM 86
Eugerta Dilka, Klara Ziu, Amarilda Dyrmishi, Silva Tafaj, Amela Hasa 86
RAPID DISEASE PROGRESSION IN A RHEUMATOID ARTHRITIS AND SYSTEMIC SCLEROSIS OVERLAP SYNDROME: A CASE REPORT 94
Valbona Duraj, Joana Hankollari, Ornela Gelaj, Jonida Xhixho, Ligea Gjoni 94

HEPATITIS C AND LYMPHOMA: A LESS NOTICED BUT IMPORTANT LINK

Dear Editor,

there is more and more proof that hepatitis C virus (HCV) infection is linked to lymphoproliferative disorders, especially non-Hodgkin's lymphoma (NHL) (1). While some studies have shown this link, it is not well understood in the therapy setting as a whole. This shows the need for more education and all-encompassing management plans.

About 71 million people around the world are infected with HCV, an illness known for its effects on the liver. But its effects outside of the liver, like mixed cryoglobulinemia and weakening of the immune system, may make lymphoid cancers more likely to form (2).

Researchers have found that people who have HCV have a much higher chance of getting B-cell lymphomas like marginal zone lymphoma, diffuse large B-cell lymphoma, and lymphoplasmacytic lymphoma compared to people who don't have HCV. The immune system stays active because of an HCV virus, which causes this to happen. This makes B cells multiply, which could lead to clonal spread and the growth of cancerous cells (3).

Finding HCV RNA in lymphoid organs also shows that the virus plays a direct role in cancer development. These results show that HCV is important as both a direct and an indirect cause of cancer (4,5). Antiviral treatment, especially using direct-acting antivirals (DAAs), has been shown to stop the spread of viruses and bring about remission in lymphomas that are linked to HCV (6). This makes it even more important for cancer patients to get an early diagnosis and complete treatment for HCV.

I believe that all people with lymphomas, especially those with B-cell subtypes, should be routinely screened for HCV to improve their health results. Antiviral medicine should be a part of the treatment plan for people with HCV-positive lymphoma. Longitudinal studies are being done to better understand the connections between HCV genotypes, treatment reactions, and lymphoma outcomes.

Recognising HCV as both an infection of the liver and a systemic disruptor that can cause cancer may improve care for patients and lower the public health cost of HCV and lymphoma.

I'm glad I had the chance to look into this important topic, and I hope it will lead to more talk and research in this area.

Sincerely,

ADELA PEROLLA

Hematologist
Service of Hematology

References

1. Couronné L, Bachy E, Roulland S, et al. From hepatitis C virus infection to B-cell lymphoma. *Ann Oncol*. 2018;29(1):92-100. doi:10.1093/annonc/mdx635

2. Suhail M, Sohrab SS, Kamal MA, Azhar EI. Role of hepatitis c virus in hepatocellular carcinoma and neurological disorders: an overview. *Front Oncol*. 2022;12:913231. Published 2022 Jul 29. doi:10.3389/fonc.2022.913231

3. Dai B, Chen AY, Corkum CP, et al. Hepatitis C virus upregulates B-cell receptor signaling: a novel mechanism for HCV-associated B-cell lymphoproliferative disorders. *Oncogene*. 2016;35(23):2979-2990. doi:10.1038/onc.2015.364

4. Vescovo T, Refolo G, Vitagliano G, Fimia GM, Piacentini M. Molecular mechanisms of hepatitis C virus-induced hepatocellular carcinoma. *Clin Microbiol Infect*. 2016;22(10):853-861. doi:10.1016/j.cmi.2016.07.019

5. Heredia-Torres TG, Rincón-Sánchez AR, Lozano-Sepúlveda SA, et al. Unraveling the Molecular Mechanisms Involved in HCV-Induced Carcinogenesis. *Viruses*. 2022;14(12):2762. Published 2022 Dec 11. doi:10.3390/v14122762

6. Salama II, Raslan HM, Abdel-Latif GA, et al. Impact of direct-acting antiviral regimens on hepatic and extrahepatic manifestations of hepatitis C virus infection. *World J Hepatol*. 2022;14(6):1053-1073. doi:10.4254/wjh.v14.i6.1053

PULMONARY HYPERTENSION AND LUNG CANCER IN COMBINED PULMONARY FIBROSIS AND EMPHYSEMA SYNDROME

Jolanda Nikolla[1], Hasan Hafizi[2]
[1]Pulmonologist, American Hospital Tirana, Albania
[2]Pulmonologist, Head of Pulmonology Department, UH "Shefqet Ndroqi", Tirana ,Albania

Corresponding E-mail: nikollajola@gmail.com

Abstract

Introduction: Combined pulmonary fibrosis with emphysema syndrome and idiopathic pulmonary fibrosis represent different conditions defined by unique clinical, functional, radiological and pathological characteristics. Both diseases frequently exhibit comorbidities and complications.

Objectives: Our aim was to examine which comorbidities are more prevalent and what is their impact on the outcome of this syndrome and idiopathic pulmonary fibrosis. Their demographic and clinical information was also analyzed.

Materials and Methods: This is a retrospective study. We examined the medical record data of individuals diagnosed with interstitial lung disease at the University Hospital of Lung Diseases "Shefqet Ndroqi", Tirana, during the timeframe from January 2012 to April 2019. The patients (51 in total) were categorized into two groups: those diagnosed with pulmonary fibrosis syndrome in combination with emphysema (25) 49% and the second group (26) 51% comprising those with a diagnosis of idiopathic pulmonary fibrosis. To assess the influence of comorbidities on this syndrome, we employed linear regression with multiple factors utilizing the EViews 7 software. Student's t test was applied to determine the significance of comorbidities and complications across both groups. Demographic and clinical information was reported in mean values using standard deviations .

Results: All patients presented with comorbidities and complications. In cases of pulmonary syndrome combined with emphysema, there was a predominance of male current or former smokers. The annual smoking measurement unit was greater in the group of patients with syndromes. The duration from symptom onset to diagnosis was also extended in this group compared to patients with idiopathic pulmonary fibrosis. Comorbidities exerted a more significant influence on the syndrome ($p = 0.01$) than in the group with idiopathic pulmonary fibrosis, where no statistically significant correlation with comorbidities was identified, possibly due to the small sample size of patients in the study.

Conclusions: Comorbidities are prevalent in both groups of individuals with pulmonary fibrosis combined with emphysema and in those with idiopathic pulmonary fibrosis.Certain conditions, particularly lung cancer, significantly affect the survival rate, while others, like respiratory failure, may have a crucial impact on the disease's mortality. Nonetheless, additional studies are required to better understand the effects of comorbidities on this syndrome in larger groups of patients and for a longer time.

Keywords: Combined Pulmonary Fibrosis and Emphysema, Idiopathic Pulmonary Fibrosis

HIPERTENSIONI PULMONAR DHE KANCERI I MUSHKËRIVE NË SINDROMËN E KOMBINUAR TË FIBROZËS PULMONARE DHE EMFIZEMËS

Abstrakt

Hyrje: Sindroma e fibrozes pulmonare te kombinuar me emfizeme dhe fibroza pulmonare idiopatike janë entitete të veçanta të karakterizuara nga karakteristika të dallueshme klinike, funksionale, radiologjike dhe patologjike. Komorbiditetet dhe komplikimet zakonisht shihen në të dyja sëmundjet.

Objektivi: Qëllimi ynë ishte të hetonim se cilat sëmundje shoqëruese janë më të zakonshme dhe cili është ndikimi i tyre në rezultatin e kesaj sindrome dhe fibrozes pulmonare idiopatike. U studiuan gjithashtu të dhënat demografike dhe klinike te tyre

Materiali dhe metoda: Ky është një studim retrospektiv. Ne kemi shqyrtuar të dhënat e karteles mjekësore të pacientëve të diagnostikuar me sëmundje intersticiale të mushkërive në Spitalin Universitar të Sëmundjeve të Mushkërive "Shefqet Ndroqi", Tiranë, në periudhën janar 2012 deri në prill 2019. Subjektet (51 në total) u ndanë më tej në dy grupet: pacientët e diagnostikuar me sindromen e fibrozes pulmonare te kombinuar me emfizeme (25) 49% dhe grupi tjeter (26) 51% ata me diagnoze fibroze pulmonare idiopatike. Për testimin e ndikimit të komorbiditeteve në kete sindromë, ne kemi përdorur regresionin linear me faktorë të shumtë duke përdorur programin EViews 7.Testi i Studentit u përdor për të vlerësuar rëndësinë e sëmundjeve shoqëruese dhe komplikacioneve në te dy grupet.Të dhënat demografike dhe klinike u shprehen në vlera mesatare duke përdorur devijimet standarde ± deviacioni standart.

Rezultatet: Të gjithë pacientët kishin komorbiditete dhe komplikacione. Në sindromën pulmonare te kombinuar me emfizemë mbizotëronin meshkujt duhanpirës aktual ose ish-duhanpirës. Njesia matese e duhanpirjes per vit ishtë më e lartë në grupin e pacienteve me sindrome. Koha nga shfaqja e simptomave deri në vendosjen e diagnozës gjithashtu ishtë më e gjatë në kete grup sesa në pacientët me fibroze pulmonare idiopatike. Komorbiditetet kishin më shumë ndikim në sindromë ($p = 0.01$) krahasuar me grupin me fibroze pulmonare idiopatike, ne te cilin nuk u gjet lidhje statistikisht e rendesishme me semundjet shoqeruese, ndoshta sepse numri i pacientëve te mostres studiuese ishte i vogël.

Konkluzionet: Semundjet shoqeruese janë të shpeshta në si ne pacientët me fibroze pulmonare te kombinuar me emfizemë ashtu edhe ne ata me fibrozë pulmonare idiopatike. Disa prej tyre, veçanërisht kanceri i mushkërive, ndikojnë fuqishëm në shkallën e mbijetesës dhe disa të tjera, si insuficienca respiratore, mund të luajnë një rol të rëndësishëm në mortalitetin e sëmundjes. Megjithatë, nevojiten kërkime të mëtejshme për të sqaruar ndikimin e sëmundjeve shoqëruese në kete sindrome ne grupe me te medha pacientesh dhe per nje kohe me te gjate.

Fjalë kyçe: fibroza pulmonare e kombinuar me emfizemë, fibrozë pulmonare idiopatike

Introduction

A recently described syndrome called Combined Pulmonary Fibrosis and Emphysema (CPFE) was introduced by Cottin et al in 2005 (1). It is a unique condition characterized by the simultaneous presence of upper lobe emphysema and lower lobe fibrosis. Most CPFE patients are male, heavy smokers, or former smokers. Despite their worsening clinical state, they tend to have nearly normal or slightly reduced pulmonary function along with significant diffusion capacity impairment. The prognosis and mortality associated with this condition are not yet clearly understood. Currently, there is no targeted treatment for individuals with CPFE syndrome (1).

Idiopathic Pulmonary Fibrosis (IPF) represents the most common type of interstitial lung disease (ILD). The typical signs and symptoms of IPF include a dry cough and dyspnea during exertion. The lung tissue affected by IPF is stiffer, leading to a loss of elasticity. The etiology and physiopathology related to IPF are not well understood. Patients with IPF experience a high mortality rate (2,3,5).

Both CPFE and IPF can be linked to various comorbidities and complications (4-6). In our investigation, we aimed to examine the presence of comorbidities and complications in a cohort of 51 patients; to identify the most prevalent and their significance in the outcomes of CPFE and IPF. We also gathered data regarding the baseline demographics, such as age, gender, smoking habits (pack years), pulmonary function tests, and diagnostic methods. All findings were reviewed during discussions in a multidisciplinary board comprised of clinical, radiological, and pathological specialists within our hospital.

Materials and Methods

The research protocol was approved by Ethics Committees of the University of Medicine and the University Hospital "Shefqet Ndroqi", Tirana, Albania; the institutions in which the work was undertaken.

Patient selection: 51 patients in total with Interstitial Lung Diseases (ILD) were included in the study.

Inclusion criteria: IPF patients were diagnosed with the HRCT scan imaging patterns according to the new ATS/ERS criteria (2,3). CPFE patients were identified based on the following features prescribed by Cotin et al on CT findings (1).

- The presence of bilateral emphysema and/or multiple bullae (>1 cm) with upper zone predominance
- The presence of bilateral significant pulmonary fibrosis, with peripheral and basal predominance

Exclusion criteria: Patients were not included in this study if they exhibited any of the following:

- Who had drug-associated ILD
- Who had occupationally related ILD, such as asbestosis and silicosis

In total 26 (51%) were diagnosed with IPF, and 25 (49%) with CPFE. There were 10 (38. 4%) male and 15 (57.6%) female in IPF, and in the CPFE group 16 (64%) males and 14 (36%) females. Mean age for CPFE group was 68 ± 7 years, and for IPF patients 68 ± 8 years. All patients were current smokers or ex-smokers. Smoking status for every patients was estimated using the Unit Pack Year (UPY).

Statistical analysis

All data recorded in the study were analyzed using EViews 7 program, a software that processes econometric various statistical differences for testing any hypothesis. Average values and standard deviations ± SD for the demographic data were collected. For determining the relationship between comorbidities in CPFE and IPF we have used the analysis of the logistic regression. To test the impact of variables in CPFE syndrome we have used linear regression with multiple factors. As influential variables are taken comorbidities and complications.For testing the importance of them in CPFE and IPF is used "The Student test" (t). R-square is used to determine the importance of the model. As statistically significant we have accepted $p < 0.05$ values.

Results

In our group we had in total 51 subjects with ILD. 26 (51%) with IPF and 25 (49%) with CPFE.The subdivision of male/female ratio in CPFE was 16 (64%) males and 9 (36 %) females, in IPF group 10 (38. 5%) males and 16 (61.5%) females.As noted in CPFE predominates males, meanwhile in IPF are females,considering that all patients were smokers or heavy ex smokers. Almost always different studies have shown that more men have been diagnosed with IPF than women, but IPF in women appears to be on the rise (15). Mean age for CPFE was 68 ± 7 and for IPF patients 68 ± 8. Table 1 shows some demographic and clinical data as: age, gender, the time of symptoms since diagnosis and smoking history using UPY. It is clearly visible that the age of the patients for both groups are nearly the same.

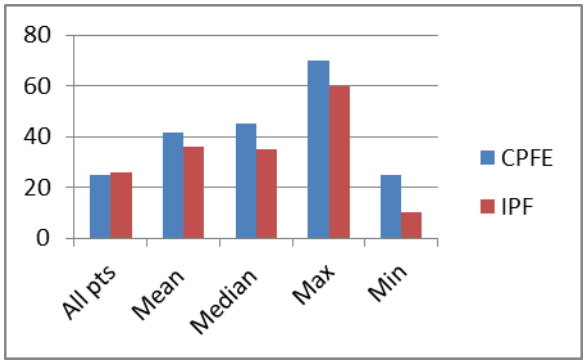
Table 1. Demographic and clinical data

	CPFE (N=25)	**IPF** (N=26)
Gender, male/female %	16 (64%)/9 (36%)	10 (38.5%)/16 (61.5%)
Age, years, mean ± SD	68 ± 7	68 ± 8
UPY, mean ± SD	45 ± 7	36.15 ± 10
Symptoms, months,mean ± SD	27.07 ± 5	27.8±8

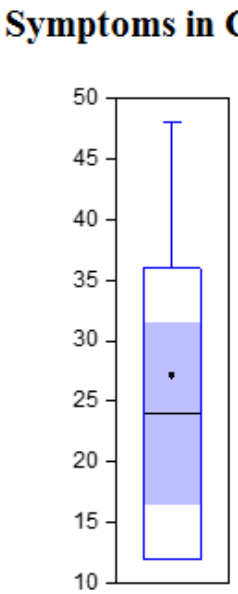
Patients with CPFE had higher values of UPY compared to the other group. This supports the fact that patients with this syndrome are heavier smokers and their clinical characteristics and outcomes are poorer than those with IPF only (14).

We compared UPY values in months for both diseases and the difference between them is evident (Graph 1). Smoking is the main risk factor in patients with IPF and in some others with CPFE syndrome (9,14). The time of symptoms had differences too among both groups. We think that this might be due to underdiagnosing of CPFE as a result of its lack of significant changes in pulmonary volumes in spirometry.

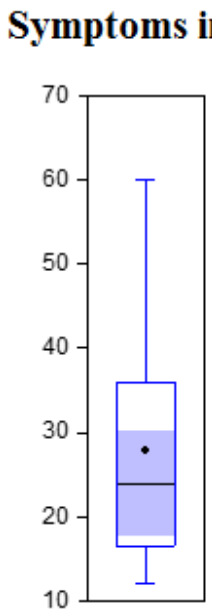
Graph 1. Unit Pack Year (UPY), CPFE vs IPF



Patients with CPFE syndrome tend to have longer time with symptoms compared to those with IPF. Probably this is due to the fact that these patients until recent years, have been misdiagnosed as IPF .(graph 2 and 3).



Graph 2



Graph 3

The comorbidities and complications that we found more commonly in the medical records in both diseases are as listed: Pulmonary Hypertension (PH), Respiratory Failure (RF), Lung Cancer (L.Ca), Pulmonary Embolism (PE), Arterial Hypertension (HTN), Cardiac diseases (CD), Anemia,Gastritis,Rheumatic Diseases (Rh. D), Diabetes Mellitus (DM).

Table 2 analyses and interprets comorbidities and complications in patients with IPF. If t values > 2, a variable is statistically important. P value expresses the error margin. If $p < 0.05$ with 5% of error margin, this means that t value is correct (17). If $p>0.05$,the results may be changed. As it is noticed in the following table, nearly all comorbidities and complications have $p>0.05$, $t < 2$in all of them and $r = - 0.01$.

These statistical findings of our study explain that none of the comorbidities is so important to affect the outcome of the diseases in our group,but the small number of subjects participating in the survey should be noted.

Table 2. Comorbidities and complications in IPF

	Coefficient	Std. Error	t-Statistic	Prob.
Anemia	0. 235333	0. 336809	0. 698713	0. 4887
L. Ca	-0. 108913	0. 288217	-0. 377884	0. 7075
DM	0. 052993	0. 296853	0. 178516	0. 8592
Gastritis	0. 048979	0. 200653	0. 244100	0. 8084
HTN	0. 566592	0. 143710	3. 942614	0. 0003
PH	0. 068783	0. 223648	0. 307551	0. 7600
CD	-0. 225784	0. 321192	-0. 702958	0. 4861
RF	-0. 060192	0. 182060	-0. 330618	0. 7426
Rh. Diseases	-0. 413312	0. 306065	-1. 350405	0. 1843
PE	-0. 104099	0. 386508	-0. 269331	0. 7890
R-squared	-0. 019869			

Table 3 shows comorbidities and complications in CPFE syndrome. Some of them have p value > 0.05 such as RF ($p=0.01$, $t=2.6$), Rh. d ($p=0.008$, $t=2.7$). These two factors, rheumatic diseases and respiratory failure are statistically important in CPFE syndrome.The variables (comorbidities) studied in regression, according to the r-square values in table 3, explain that 11% of the factors affect the results in CPFE syndrome.

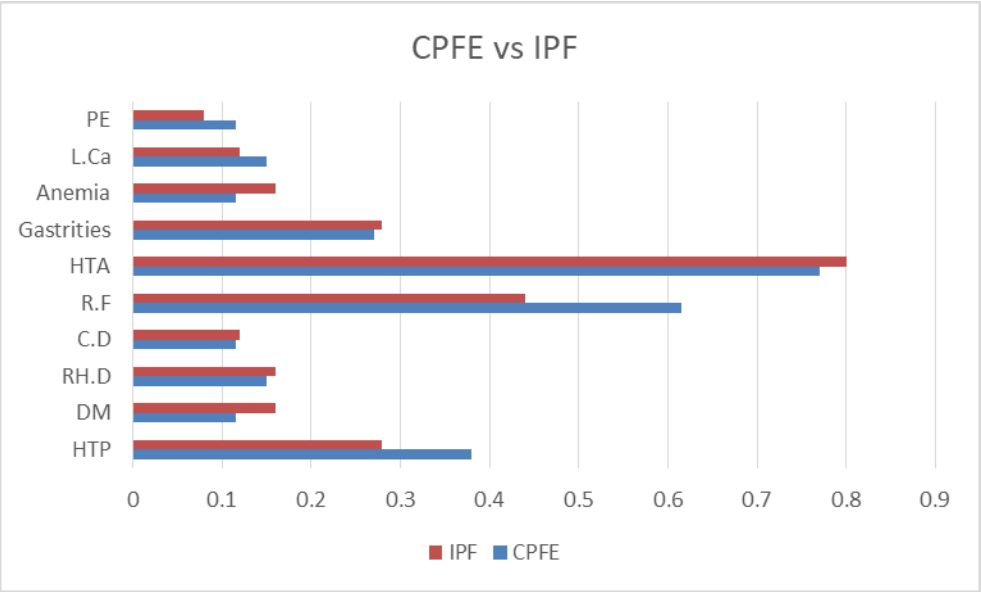
There are several papers that have investigated the prevalence of CPFE in patients with lung cancer more than fibrosis and they have concluded that CPFE patients had a poor prognosis (8,11,12).

CPFE syndrome may be present too in some of the connective tissue diseases, especially rheumatoid arthritis and systemic sclerosis and here it is defined as 'idiopathic' (tobacco-related) CPFE (16). Another factor that plays an important role in the exacerbation of CPFE is respiratory failure (7). If we analyze the results for lung cancer, interestingly p and t values tend to go respectively p = 0.1 and t = 1.5.

Table 3. Comorbidities and complications in CPFE syndrome

	Coefficient	Std. Error	t-Statistic	Prob.
Anemia	-0. 200062	0. 313296	-0. 638572	0. 5267
L. Ca	0. 419345	0. 268096	1. 564158	0. 1255
DM	-0. 236357	0. 276129	-0. 855966	0. 3970
Gastritis	0. 254718	0. 186645	1. 364720	0. 1798
HTN	0. 095510	0. 133677	0. 714483	0. 4790
PH	0. 101406	0. 208035	0. 487447	0. 6285
C. D	0. 056605	0. 298769	0. 189460	0. 8507
RF	0. 451897	0. 169351	2. 668408	0. 0109
Rh. D	0. 792904	0. 284698	2. 785069	0. 0081
PE	-0. 266165	0. 359525	-0. 740324	0. 4633
R-squared	0. 117557			

Graph 4. The frequency of comorbidities and complications



Graph 4 explains the frequency of comorbidities and complications in CPFE vs IPF. Gastritis and anemia are highly prevalent in patients with Idiopathic Pulmonary Fibrosis (13). It is clearly seen that respiratory failure, pulmonary hypertension and lung cancer are encountered more often in CPFE syndrome. CPFE patients appears to have a higher incidence of lung cancer (6.1–46.8%) compared to IPF (7–20%) . Lung cancer in CPFE was typically diagnosed in elderly, heavy smokers who are predominately male with a median survival

time of 19.5 months . The most common histopathologic subtypes of lung cancer in CPFE are squamous cell carcinoma and adenocarcinoma ((16,17).

Table 4. The correlation of some variables in CPFE

	Anemia	L.Ca	CPFE/IPF	DM	Gastrities	HTA	C. D	RESP	RHEUMO	TEP
Anemia	1. 000000	0. 006494	-0. 064814	0. 337662	0. 265378	0. 070627	0. 561769	0. 376051	-0. 116360	0. 443346
L. Ca	0. 006494	1. 000000	0. 049169	0. 503247	0. 010014	0. 070627	-0. 145644	-0. 080582	-0. 116360	0. 251730
CPFE/IPF	-0. 064814	0. 049169	1. 000000	-0. 064814	-0. 012064	-0. 132762	-0. 007161	0. 175655	0. 286065	0. 059485
DM	0. 337662	0. 503247	-0. 064814	1. 000000	0. 137696	0. 209165	0. 208063	0. 147734	-0. 116360	0. 251730
Gastrities	0. 265378	0. 010014	-0. 012064	0. 137696	1. 000000	0. 108921	0. 048131	-0. 124274	-0. 016022	0. 388218
HTN	0. 070627	0. 070627	-0. 132762	0. 209165	0. 108921	1. 000000	0. 191485	-0. 016855	-0. 024338	0. 012574
C. D	0. 561769	-0. 145644	-0. 007161	0. 208063	0. 048131	0. 191485	1. 000000	0. 344265	-0. 106525	0. 084270
R. F	0. 376051	-0. 080582	0. 175655	0. 147734	-0. 124274	-0. 016855	0. 344265	1. 000000	-0. 163308	0. 178730
Rh. D	-0. 116360	-0. 116360	0. 286065	-0. 116360	-0. 016022	-0. 024338	-0. 106525	-0. 163308	1. 000000	0. 149080
PE	0. 443346	0. 251730	0. 059485	0. 251730	0. 388218	0. 012574	0. 084270	0. 178730	0. 149080	1. 000000

The correlation of some comorbidities and complications with CPFE syndrome are evaluated in table 4.As it is noticed, rheumatic diseases, lung cancer and respiratory failure have a higher correlation coefficient than the others.

Discussion

CPFE is a clinical condition impacting heavy smokers and is defined by a mix of upper lobe emphysema and lower lobe fibrosis. CPFE symptoms involve hypoxemia during exercise and later while at rest, normal lung volumes, and a considerable decline in diffusing capacity, often linked with pulmonary hypertension. It is a diverse condition affecting a wide range of individuals (1). As noted in the literature, we observed that patients with CPFE were either current heavy smokers or ex-smokers and were mainly male. Smoking is identified as the primary causative factor and in all reported cohorts, there is a consistent history of smoking as a persistent factor (9,10,14).

This condition exhibits a broad range of imaging and histopathological features. From a clinical viewpoint, CPFE merges the impacts of emphysema and fibrosis, leading to patients experiencing heightened symptoms that are often associated with serious comorbidities like lung cancer and pulmonary hypertension, which contribute to a poor prognosis and higher mortality. Comorbidities and complications are frequently encountered. They primarily add to the morbidity and mortality associated with these two distinct conditions. At times, it can be challenging to discern which conditions are comorbidities and which are complications in IPF and CPFE syndrome. In our research, we did not identify any significant link between comorbidities and IPF. In CPFE, it is rheumatic diseases and respiratory failure that show a stronger correlation. Our study had certain limitations: the number of recorded patients was somewhat low and this is a retrospective data collection from just one institution (17).

Conclusion

The number of published papers about CPFE is in rising.The interest for this new phenotype is increasing and this is due to its particular clinical, functional, and radiological profile. Little is known about what role the comorbidities and complications play in CPFE outcome and survival. However, further studies are needed to elucidate certain ambiguities in CPFE syndrome because despite numerous case series and studies, many important questions remain unanswered.

Conflicts of Interest: No conflict of interest

References

1. Cottin V, Nunes H, Brillet PY, et al. Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. Eur Respir J. 2005; 26(4):586-593. doi:10.1183/09031936.05.00021005
2. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183(6):788-824. doi:10.1164/rccm.2009-040GL
3. American Thoracic Society; European Respiratory Society. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001 [published correction appears in Am J Respir Crit Care Med2002 Aug 1;166(3):426]. Am J Respir Crit Care Med. 2002;165(2):277-304. doi:10.1164/ajrccm.165.2.ats01
4. Hyldgaard C, Hilberg O, Bendstrup E. How does comorbidity influence survival in idiopathic pulmonary fibrosis?. Respir Med. 2014;108(4):647-653. doi:10.1016/j.rmed.2014.01.008
5. Fell CD. Idiopathic pulmonary fibrosis: phenotypes and comorbidities. Clin Chest Med. 2012;33(1):51-57. doi:10.1016/j.ccm.2011.12.005
6. Cottin V. Clinical case: Combined pulmonary fibrosis and emphysema with pulmonary hypertension--clinical management. BMC Res Notes. 2013;6 Suppl 1(Suppl 1):S2. doi:10.1186/1756-0500-6-S1-S2.
7. Ryerson CJ, Hartman T, Elicker BM, Ley B, Lee JS, Abbritti M,Jones KD, King Jr TE, Ryu J, Collard HR. Clinical features andoutcomes in combined pulmonary fibrosis and emphysema in idiopathicpulmonary fibrosis. Chest.2013;144:234–40.
8. Kishaba T, Shimaoka Y, Fukuyama H, Yoshida K, Tanaka M,Yamashiro S, Tamaki H. A cohort study of mortality predictorsand characteristics of patients with combined pulmonary fibrosisand emphysema.BMJ Open.2012;2:e000988.
9. King TE Jr. Smoking and subclinical interstitial lung disease. N Engl J Med. 2011;364(10):968-970. doi:10.1056/NEJMe1013966
10. Schiess R, Senn O, Fischler M, Huber LC, Vatandaslar S, SpeichR, Ulrich S. Tobacco smoke: a risk factor for pulmonary arterialhypertension? A case-control study.Chest.2010;138:1086–92.

11. Usui K, Tanai C, Tanaka Y, Noda H, Ishihara T. The prevalence of pulmonary fibrosis combined with emphysema in patients with lung cancer. Respirology.2011;16:326–31.
12. Kwak N, Park CM, Lee J, Park YS, Lee SM, Yim JJ, Yoo CG,Kim YW, Han SK, Lee CH. Lung cancer risk among patients with combined pulmonary fibrosis and emphysema. Respir Med. 2014;108:524–30.
13. Lee JS, Ryu JH, Elicker BM, Lydell CP, Jones KD, Wolters PJ, et al. Gastroesophageal reflux therapy is associated with longer survival in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011; 184(12):1390–1394
14. K. Portillo Carroz and J. Rold´an S´anchez, "Combination of pulmonary fibrosis and emphysema: is tobacco once again the protagonist?" *Medicina Clinica*, vol. 136, no. 1, pp. 18–20,2010.
15. Kaunisto J, Salomaa ER, Hodgson U, Kaarteenaho R, Myllärniemi M. Idiopathic pulmonary fibrosis--a systematic review on methodology for the collection of epidemiological data. BMC Pulm Med. 2013;13:53. Published 2013 Aug 20. doi:10.1186/1471-2466-13-53
16. Vincent Cottin and Jean-Franc¸ois Cordier. Combined pulmonary fibrosis and emphysema in connective tissue disease.Review.CurrOpin Pulm Med 2012, 18:418–427
17. Oh, J.Y.; Lee, Y.S.; Min, K.H.; Hur, G.Y.; Lee, S.Y.; Kang, K.H.; Shim, J.J. Impact and prognosis of lung cancer in patients with combined pulmonary fibrosis and emphysema. Sarcoidosis Vasc. Diffus. Lung Dis. 2020, 37, e2020020.

THE ROLE OF AUTONOMIC DYSFUNCTION IN OUTCOME OF STROKE PATIENTS

Entela Basha, Eris Ranxha, Olsi Taka, Vera Ostreni

Neurovascular Service, UHC "Mother Theresa", Tirana, Albania
Correspondence E-mail: bashaentela@gmail.com

Abstract

Introduction. Stroke is a major cause of morbidity and mortality in world and in Albania. Several studies have demonstrated that cardiac dysfunction may occur after vascular brain injury without any evidence of primary heart disease. During acute stroke, autonomic dysfunction elevated arterial blood pressure, atrial fibrillation, and ischemic cardiac damage, has been reported, which may worsen the prognosis. Autonomic disorders following a stroke can occur due to damage to brain regions that regulate the autonomic nervous system (ANS). The ANS controls involuntary functions such as heart rate, blood pressure, digestion, and thermoregulation.

Methods. We conducted a prospective study in Neurovascular Service. During 2023 in our service are been treated 1234 patients from 18 -102 years old. Patents with autonomic dysfunctions after stroke were included in our study were 126, 76 females and 50 males and who fulfilled all the criteria's study.

Discussion. The clinical relevance of autonomic nervous system imbalance after ischemic stroke is further confirmed in this study. We found that lability of arterial hypotension, arterial hypertension and heart rate variability may also predict an unfavorable outcome and dependency in post-stroke patients.

Conclusion. Effective management and early rehabilitation can improve outcomes, but persistent autonomic dysfunction may complicate recovery and increase mortality risk.

Keywords. stroke, autonomic dysfunctions, arterial hypotension, arterial hypertension, heart rate variability

ROLI I ÇRREGULLIMEVE AUTONOME NË ECURINË E PACIENTËVE ME AKSIDENTE CEREBRALE VASKULARE

Abstrakt

Hyrje. Aksidentet vaskulare cerebrale janë shkaku kryesor i sëmundshmërisë dhe vdekshmërisë në botë dhe në Shqipëri. Disa studime kanë treguar se disfunksioni kardiak mund të ndodhë pas nje dëmtimi vaskular cerebral pa asnjë të dhënë për patologji primare kardiake. Gjatë aksidenteve vaskulo-cerebrale (AVC) ishemike akute, është raportuar disfunksion autonom, hipertension dhe hipotension arterial, fibrilacion atrial dhe dëmtime ishemike kardiake, të cilat mund të përkeqësojnë prognozën. Çrregullimet autonome pas një AVC mund të ndodhin për shkak të dëmtimeve strukturore të trurit që rregullojnë sistemin

nervor autonom (ANS). ANS kontrollon funksionet e pavullnetshme si rrahjet e zemrës, presioni i gjakut, tretja dhe termorregullimi.

Metoda. Në Shërbimin Neurovaskular është realizuar në vitin 2023 një studim prospektiv mbi rolin e crregullimeve autonome në ecurinë e AVC ishemike. Gjatë një viti janë hospitalizuar 1234 pacientë nga mosha 18 -102 vjeç. Numri i pacientëve të përfshire në studim duke selektuar një kategori të vecantë pacientësh që nuk kanë faktorë konfondues që mund të ndikojnë në ndryshimin e rezultateve të studimit tonë ishin 126, 76 femra dhe 50 meshkuj.

Diskutimi. Rëndësia klinike e disfunksionit të sistemit nervor autonom pas AVC konfirmohet në këtë studim. Ne zbuluam se luhatjet e hipotensionit arterial, hipertensionit arterial dhe crregullimet e ritmit kardiak mund të parashikojnë gjithashtu një ecuri të pafavorshme në pacientët pas AVC.

Konkluzion. Menaxhimi efektiv dhe rehabilitimi i hershëm mund të përmirësojnë rezultatet, por mosfunksionimi i vazhdueshëm autonom mund të komplikojë rikuperimin dhe të rrisë rrezikun e vdekshmërisë.

Fjale kyce: AVC, crregullime autonome, hipotensioni arterial, hipertensioni arterial, crregullime te ritmit kardiak.

Introduction

Stroke is a major cause of morbidity and mortality in world and in Albania. Several studies have demonstrated that cardiac dysfunction may occur after vascular brain injury without any evidence of primary heart disease (1,2). During acute stroke, autonomic dysfunction, elevated arterial blood pressure, arrhythmia, and ischemic cardiac damage, has been reported, which may worsen the prognosis (3,4,5). Autonomic disorders following a stroke can occur due to damage to brain regions that regulate the autonomic nervous system (ANS). The ANS controls involuntary functions such as heart rate, blood pressure, digestion, and thermoregulation. Disruptions in these functions can significantly impact recovery and quality of life post-stroke. Management focuses on stabilization and improving functional outcomes while addressing the risk of complications like sudden cardiac events. Increased or decreased blood pressure occur during acute phase of stroke. Post-stroke hypertension is common, and blood pressure lability may complicate recovery. Atrial fibrillation or other arrhythmias may arise due to stroke-related damage to autonomic centers.

Methods

We conducted a prospective study in Neurovascular Service due to 2023 in our service are been treated 1234 patients from 18 -102 years old. Patents including in our study with autonomic dysfunctions after stroke were 126, 76 females and 50 males.

1. The first-ever acute ischemic stroke,
2. Absence of diabetes mellitus or any other concomitant nervous system, cardiac that will affect the autonomic nervous system,
3. Absence of any clinically relevant arrhythmia on admission, including atrial fibrillation,
4. Absence of any pharmacological treatment, including beta-blockers, possibly affecting the autonomic nervous system,
5. Absence of any major concurrent illness, including renal failure and malignancies,
6. Absence of fever, hypoxia, severe hypertension, alterations in consciousness, or any relevant hemodynamic during the recovery.

All the patients were submitted to clinical, neurological, and functional examinations on 7th day and on 30 days after stroke. Stroke severity was assessed by the National Institutes of Health Stroke Scale (NIHSS), autonomy in activities of daily living (ADL) by the Barthel Index (BI), and global disability by the modified Rankin Scale (mRS) on day 7 and 30 after stroke. HVR measured with electrocardiogram monitoring on the 1-st, 7-th and 90-th day and electrocardiogram monitor

In order to limit confounding interactions, we decided to consider a homogeneous cohort of patients with acute first-ever ischemic stroke and without major cardiovascular and metabolic comorbidities. Patients with any form of structural heart disease, heart failure, atrial fibrillation and diabetes mellitus were preliminarily excluded, avoiding any possible effect on clinical outcome of stroke.

Results and discussion

A preserved autonomic balance represents one of the most relevant factors influencing post-stroke outcome. Activity of Living (ADL) and Barthel Index (BI) score was divided into 2 ranges (BI>=40 and <40). During the acute period (from onset to approximately 7 days), all patients with a BI>=40 and absence of autonomic disorders could improve their ADL in 30 days. Patients with a BI<40 and the presence of autonomic disorders exhibited two ADL recovery outcomes (improved and no change) at 30 days. (Tab.1) We also found that the skill level of basic activities related to standing was significant indicator of BI improvement. BI scores determined at approximately 1 week were reliable predictors of ADL disabilities at 1 month.

Table 1. NIHSS (National Institute of Health Stroke Scale), ADL (Activity of Daily Living), mRS (modified Rankin Score), BI (Barthel Index), HO (hypotension orthostatic), HA (Hypertension Arterial), HVR (Heart Rate Variability), LVO large vessel occlusion.

	Total **N= 126**	**Favorable outcome**	**Unfavorable outcome**	**p value**
Female	76 (60.3%)	50 (65.7 %)	26 (34.3%)	0.001
Ages	68±12.3	64±11.3	73±10.5	0.03
Male	50 (39.7%)	39 (78%)	11(22%)	0.03
Ages	66±11.3	64±12.4	68±12.6	0.01
Day 7				
NIHSS	7.6±10.3	6.8±6.5	8.4±5.6	0.04
ADL	3.5±2.1	4.2±1.1	2.8±1.9	0.02
mRS	2.4±1.9	2.1±1.1	2.9±1.9	0.02
BI	38±35.1	56±24.6	35±26.8	0.01
HO	33 (26.1%)	8 (0.6%)	25 (19,8%)	0.01
HA	54(42.8%)	21(16.6%)	33 (26.1%)	0.03
HVR	41 (32.5%)	8 (0.6%)	33 (26.1 %)	0.13
Day 30				
NIHSS	6.6±8.3	5.5±4.5	8.5±4.9	0.02
ADL	3.1±1.6	3.2±1.6	2.8±1.9	0.01
mRS	2.4±1.9	1.9±1.2	2.9±1.9	0.02
BI	38±35.1	46±21.6	35±18.8	0.03
HO	16 (12.6%)	6 (0.47%)	10 (0.79%)	0.01
HA	21 (16.6%)	8 (0,6%)	13 (10.3 %)	0.014
HVR	13 (10.3)	5 (0.39%)	8 (0.63%)	0.021
Stroke subtype				
Cardioembolic	31 (24.6%)	20 (15.8%)	11 (0.8%)	0.02
LVO	59 (46,8%)	41 (32.5%)	18 (14.2 %)	0,01
Un. Etiology	36 (28.5%)	21(16.6%)	15 (11.9%)	0.012

A major correlation between autonomic nervous system dysfunctions and cardiovascular morbidity in patients with heart disease has been consistently established in different clinical study, as confirmed by a recent review of the extensive available literature (8). Recent studies have shown that also in post-stroke patients there is an association between direct and derived measures of increased sympathetic activation and/or reduced vagal activity and a greater propensity for an adverse clinical outcome (9).

We found that age and severity of presenting neurological deficit, as assessed by currently clinical scales, have a major impact on rehabilitation outcome (7). We also observed that functional outcome was clearly affected by the presence of autonomic nervous system dysfunction, as expressed by a decreased or increased HRV (heart rate variability). In particular, patients with decreased HRV were more likely to experience an unfavorable outcome, even in the absence of any major comorbidity. The clinical relevance of autonomic nervous system imbalance after ischemic stroke is further confirmed in this study. In fact, we found that lability of arterial hypotension, arterial hypertension and heart rate variability may also predict an unfavorable outcome and dependency in post-stroke patients.

According to the findings, differences in the initial functional outcomes and recovery after follow-up were shown among the two groups. Differences were observed in all three functional outcomes, including ADL, mRS, BI. This result suggests that the severity of autonomic dysfunction influences the functional prognosis in patients with acute stroke. Additionally, when comparing the differences between the two groups, LVO group and cardio embolic group showed statistically differences. This indicates that functional recovery was more unfavorable in the LVO group. However, there was significant difference between the moderate and severe groups based on NIHSS, suggesting that autonomic dysfunction, HO, HA, HVR were more prominent in patients with high NIHSS, severe stroke. Autonomic dysfunction can lead to impaired functional outcomes for several reasons. First, symptoms due to autonomic dysfunction, including dizziness and orthostatic hypotension, can reduce the frequency and intensity of rehabilitation. Second, the dysregulation of the sympathetic and parasympathetic nervous systems can lead to insufficient blood supply to the injured brain tissue. Third, the autonomic nervous system is important for regulating stress and maintaining homeostasis in response to the brain's perception of stressors such as acute and chronic stroke (10). Fourth, autonomic dysfunction after acute stroke can lead to down regulation of cardiac function. According to a study by Scheitz et al., this phenomenon is called stroke–heart syndrome and is characterized by changes in cardiomyocyte metabolism, the deregulation of the leukocyte population, and vascular changes, which can lead to stroke-induced cardiac stress and a 2- to 3-fold increased risk of short-term mortality.

Conclusion

The extent and type of autonomic dysfunction often depend on the location, severity and mechanism of the stroke. Patients with LVO has no favorable outcome compare with cardio embolic stroke. Effective management and early rehabilitation can improve outcomes, but persistent autonomic dysfunction may complicate recovery and increase mortality risk.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"All procedures performed in this study were in accordance with the ethical standards of the institutional and/ or national research committee(s) and with the Helsinki Declaration (as revised in 2013), as well as the national law. Informed consent was obtained from the patients included in the study"

"No funding for this study"

References

1. Koennecke HC, Belz W, Berfelde D, Endres M, Fitzek S, et.al. Berlin Stroke Register Investigators. Factors influencing in-hospital mortality and morbidity in patients treated on a stroke unit. Neurology. 2016;77:965–72.
2. Smith EE, Shobha N, Dai D, et al. A risk score for in-hospital death in patients admitted with ischemic or hemorrhagic stroke. J Am Heart Assoc. 2019;
3. Orlandi G, Fanucchi S, Strata G, Pataleo L, Landucci Pellegrini L, et.al. Transient autonomic nervous system dysfunction during hyperacute stroke. Acta Neurol Scand. 2017;102:317–21.

4. Xiong L, Leung H, Chen XY, Han JH, Leung T, Soo Y, et.al. Preliminary findings of the effects of autonomic dysfunction on functional outcome after acute ischemic stroke. Clin Neurol Neurosurg. 2012;114:316–20.
5. Bassi A, Colivicchi F, Santini M, Caltagirone C. Cardiac autonomic dysfunction and functional outcome after ischaemic stroke. Eur J Neurol. 2017;14:917–22.
6. Colivicchi F, Bassi A, Santini M, Caltagirone C. Prognostic implications of right-sided insular damage, cardiac autonomic derangement, and arrhythmias after acute ischemic stroke. *Stroke* 2015; **36**: 1710–1715.
7. Appelros P, Nydevik I, Viitanen M. Poor outcome after first-ever stroke. Predictors for death, dependency, and recurrent stroke within the first year. *Stroke* 2023; **34**: 122–126.
8. Seely AJ, Macklem PT. Complex systems and the technology of variability analysis. *Critical Care* 2014; **8**: R367–R384.
9. Sander D, Winbeck K, Klingelhofer J, *et al.* Prognostic relevance of pathological sympathetic activation after acute thromboembolic stroke. *Neurology* 2021; **57**: 833–838.
10. Ulrich-Lai Y.M., Herman J.P. Neural regulation of endocrine and autonomic stress responses. Nat. Rev. Neurosci. 2009;10:397–409.

REFRACTORY PATHOLOGIES IN SCHOOL AGE

Orgeta Dervishi, Migena Gega, Admir Nake, Zamir Damani, Klerida Shehu

Faculty of Medical and Technical Sciences, University of Medicine, Tirana, Albania
Correspondence E-mail: orgetadervishi@live.com

Abstract

Introduction. Nowadays, the progressive increase of eye pathologies comes alongside genetic and individual factors, mostly from the so-called “internet game disorders,” as well as global warming and staying indoors for a long time. Early detection in the paediatric age is the right choice to minimise this pathology and the negative individual consequences, up to blindness and its economic ones. Our study aimed to evaluated the situation, emphasizing the importance of their early detection (from a paediatric age) in maximizing the success of treatment and performance for these children in the future.

Materials and Methods. As part of the project "Healthy Eyes for Successful Education," the eyes of 2583 kids in kindergartens, primary schools, and secondary schools near Tirana and Fushë-Krujë were checked. We also read new studies, primarily from PubMed, Elsevier, Lancet, MDPI, Nature, and Sage Journal, to gain a deeper understanding of refractive eye diseases.

Results. Refractive eye pathologies were about 10% (9.6%) of the studied population, with a doubling (about 2.2 times) from the age group 3-6 years to the age group 7-14 years, which indicates the necessity of medical monitoring and early intervention (first ophthalmological visit), with a prevalence of hyperopia (65%) versus myopia (35%), and a prevalence of accommodative hyperopia (80%) about four times versus congenital hyperopia (20%) (4:1 ratio).

Conclusions. Refractive eye pathologies should be caught as early as possible in order to minimise the consequences of education and life performance because if not treated in time, even in a very low percentage, they can lead to lifelong blindness.

Keyword. Refractive eye pathologies, artificial intelligence, early diagnosis

PATOLOGJITË REFRAKTARE NË MOSHËN SHKOLLORE

Abstrakt

Hyrje: Rritja progresive e patologjive të syrit vjen krahas faktorëve gjenetikë dhe individualë në kohët e sotme dhe nga të quajturat “internet game disorders,” si dhe ngrohja globale, qëndrimi për një kohë të gjatë mbyllur në shtëpi. Kapja e hershme dhe hulumtimi i duhur në moshën pediatrike është zgjedhja e duhur për të minimizuar këto patologji dhe pasojat negative individuale deri tek verbëria, si dhe ato sociale dhe ekonomike të tyre.

Qëllimi: Fotografimi i situatës, theksimi i rëndësisë së kapjes së hershme të tyre (që në moshën pediatrike), në maksimizimin e suksesit të trajtimit dhe performancës së këtyre fëmijëve në të ardhmen.

Materiali dhe Metoda: U realizuan vizitat e syve në 2583 fëmijë në kopshtet, shkollat fillore dhe nëntëvjecare në rrethinat e Tiranës dhe Fushë-Krujës , në kuadër të projektit "Sy të shëndetshëm, për arsimim të suksesshëm", si dhe u hulumtuan studimet më të fundit të literaturës, më së shumti në PubMed, Elsevier, Lancet, MDPI, Nature, dhe Sage Journal, për një parashtrim sa më të qartë të patologjive refraktare të syrit.

Rezultatet: Patologjitë refraktare të syrit ishin rreth 10% (9.6%) e popullatës së hulumtuar, me dyfishim (rrreth 2.2 herë) nga grupmosha 3-6 vjeç, në moshën 7-14 vjeç, që tregon domosdoshmërinë e monitorimit mjekësor dhe ndërhyrjes së hershme. (vizita okulistike e parë), me mbizotërim të hipermetropisë (65%), kundrejt miopisë (35%), dhe mbizotërim të hipermetropisë akomodative (80%) rreth katër herë kundrejt asaj kongenitale (20%) (raporti 4:1).

Përfundime: Problemat e refraktaritetit të syve duhet të kapen sa më herët, në mënyrë që të minimizohen pasojat e performancës arsimore dhe jetësore, sepse nëse nuk trajtohen në kohë, edhe përqindje shumë të ulët, mund të japin verbëri gjatë gjithë jetës.

Fjalë Kyç: Patologji refraktare të syrit, inteligjencia artificiale, diagnoza e hershme,

Introduction

The problems of visual impairment are becoming increasingly concerning worldwide, with an estimated 43.3 million people being blind and 295 million with visual impairment, expected to rise to 61 million blind and 474 million with visual impairment by 2050 (2). According to WHO, approximately 2.2 million people suffer from visual impairment (2). Refractive diseases are the second leading cause of visual impairment globally, according to WHO (2). The Global Action Plan for the years 2015-2019 states that in children aged 5-15 years, these pathologies are the leading cause of visual impairment (3). The attention paid to refractive eye diseases and the huge rise in studies around the world from 2000 to 2022 show that these diseases are becoming a bigger problem (1, 2). Industrialised countries like China, the United States, and Japan conduct the majority of studies (1). According to a study published in Lancet, medical interventions have contributed to avoiding a higher number of individuals becoming blind, but not those with moderate or severe visual impairment (4). However, a study from 2023 reports that cataracts, albinism, nystagmus, and retinal diseases are the main causes of decreased vision in children. Nevertheless, there are several risk factors and causes contributing to decreased vision in children (5). The causes of eye pathologies are also of genetic and environmental nature, among other individual factors (6-10). Some genes that may be involved in eye problems are OPA1, which is linked to ethambutol-induced neuropathy; BM4, which is linked to nearsightedness and farsightedness; FBN1, which is linked to congenital ectopia lentis; GJA8; LSS, which is linked to hereditary congenital cataracts; and more (6). Climate change and global warming have various negative impacts on health, including eye diseases. For example, high temperatures, especially in the summer,

can lead to retinal inflammation. Additionally, solar radiation can cause subcapsular or early cataracts and retinal pathologies, while environmental high temperatures and air pollution are responsible for glaucoma (7). The consequences are in social, psychological, and economic aspects (7-10). Aside from glaucoma and other biological, ophthalmological, and genetic factors, stress is also thought to cause and worsen vision loss (8-10).

In another study, although conducted with a relatively small number of cases (114 children), it is emphasised that 86% of them were bullied due to eye problems, with 64% experiencing verbal bullying, 21% experiencing physical bullying, and 50% being bullied in physical education class by the physical education teacher and 93% by their peers (9). As a result, these children may experience stress, anxiety, depression, and further consequences on academic achievements, personal development, social interaction, and self-esteem (10). Visual problems are significant causes of poor performance in children's schools, and their correction has improved their performance (10,11). In a meta-analysis study from 1990–2013, referring to 15 countries, conducted by the European Eye Association, it was observed that myopia accounted for 30.6%, with a higher prevalence in young people (25–29 years) at 47.2%, hyperopia at 25.2%, and astigmatism at 23.9% among the 61,946 individuals examined (12). Genetic, environmental, social, and individual factors are key factors in refractive eye pathologies (10-14, 19-21). Referring to refractive eye pathologies, especially severe myopia, is a major risk factor for future eye conditions (13). The study and use of computers or cell phones at work and school, or uninterrupted electronic games for more than 1 hour, affect the worsening of myopia. However, short breaks reduce this impact (14, 15). Recent technological developments and dependence on the internet, minimising outdoor activities and staying at home, are important social and individual risk factors for developing "internet game disorders" and are seen as risk factors for the development of refractive eye pathologies (14,15). Moderate light exposure slows the progression of refractive eye diseases. Doing activities outside, limiting electronic activities or games, and getting enough screen time have all been shown to slow or reverse refractive eye diseases (14-16). Homes with smaller spaces due to urbanisation are more likely to develop myopia than private homes with larger indoor spaces (16). Due to time and healthy exposure to natural light, myopia decreases in the summer and worsens in the winter (16). On the other hand, children with myopia may have a disruption in their sleep-wake rhythm and a delay in waking up compared to emmetropia (16). Recent studies do not show a correlation between the use of vitamin D, A, or specific diets and the reduction of myopia (16). However, studies show a positive correlation between high insulin levels and myopia (16). Hazardous industrial and environmental pollutants for human health such as carbon oxide, air pollutants like PM 2.5, PM10, O3, NO2, SO2, are significant factors in refractive eye diseases, through the mechanism of increased oxidative stress, promoting apoptosis, inflammation, necrosis, or ferroptosis (10,20,21). Furthermore, genetic-based studies have been conducted, identifying genes and epigenetic factors that influence the development of refractive eye pathologies (17, 18). Early detection and examination of risk factors using the latest technology and modern equipment, including artificial intelligence, along with raising public awareness of personalized medicine concepts, are important approaches to proper medical management of these pathologies (19-23). Given that the increase in refractive eye pathologies is a global concern, we conducted a project where we specifically investigated refractive eye pathologies in paediatric age in Tirana and the Kruja and Fushe Kruja region.

Aims and objectives

The aim was to assess the situation and evaluate the extent of the problem, as well as emphasise the importance of early detection (in paediatric age) to maximise treatment success and the performance of these children in the future. Our objectives were assessment and monitoring of eye diseases in schools with the aim of taking awareness and specific measures according to the disease.

Material and method

Kindergartens, primary schools, and eight-year schools in the districts of Tirana and Fushë-Kruja were reviewed as part of the project "Healthy Eyes for Successful Education," organised by the DAER association in collaboration with the municipalities of Tirana and Kruja and carried out in two phases: the first phase in 2017–2018 and the second phase in 2021.

In the first phase of the study, 2583 children aged 3 to 14 were investigated through an ophthalmic visit using a portable autorefractometer and a portable vision chart.

In the second phase, kids who might have refractive disorders like myopia, astigmatism, or hyperopia went to a clinic in Tirana to get a more thorough examination of the anterior segment using a Topcon KR-800 autorefractometer, a vision chart, and a Topcon SI-D4 slit lamp.

Results

Table 1. Gender variation is expressed in tables and graphs.

Female	1321(52%)
Male	1262(48%)

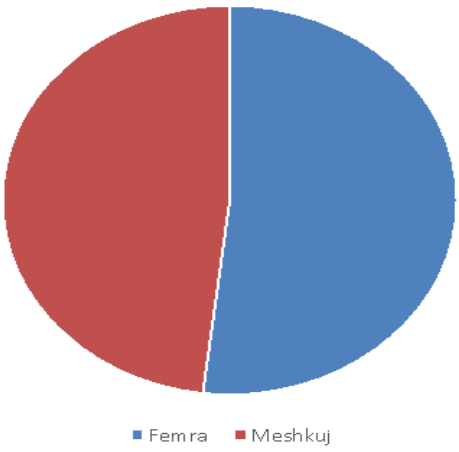


Table 2. Graphical and tabular expression of individuals with refractive pathologies

Individuals	Nr(%)
Total	2583
Individuals with refractive pathologies	250(9.6%)

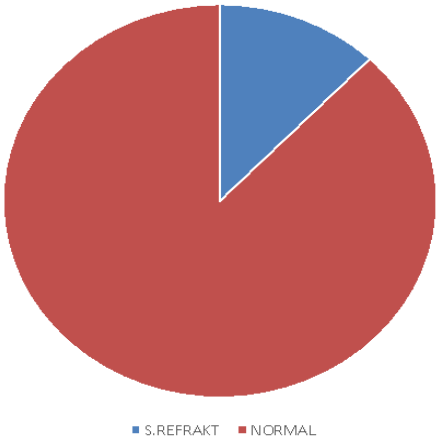


Table 3. Number of children with refractive pathologies according two age groups.

Age groups	Number of children with refractive diseases	Percentage
3-6 year old	78	31%
7-14 year old	172	69%



Table 4. Tabular and graphical representation of refractive pathologies of the eye according to the nature of myopia and hyperopia

	Number of children with refractive pathologies	Percentage
Hypermetropia	163	65%
Miopia	87	35%

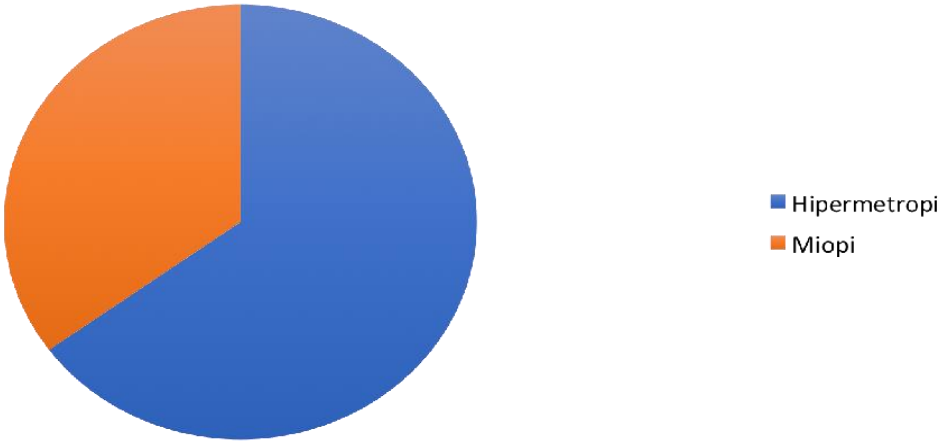
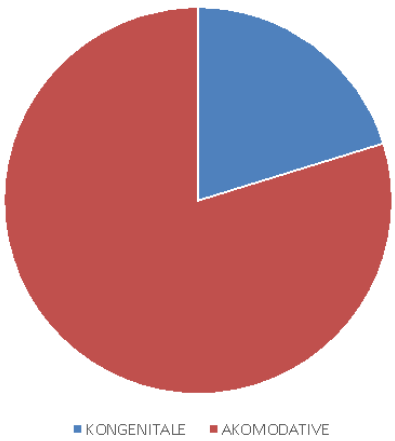


Table 5. Tabular and graphical presentation according to the nature of hypermetropia

Hypermetropia	Nr	(%)
Congenital	32	19.6%
Accommodative	131	80.4
Total	163	100%



Discussion

The findings of this study emphasize the critical importance of early identification and intervention in managing refractive eye pathologies among children, a population significantly impacted by these conditions. The prevalence of refractive issues in 9.6% of the examined population underscores the necessity of integrating ophthalmic evaluations into routine pediatric health care. The doubling of refractive pathologies from the 3–6 age group to the 7–14 age group (31% to 69%, respectively) signals an alarming trend, which aligns with global patterns indicating an increasing burden of visual impairment over time (2, 3).

Hypermetropia, constituting 65% of the detected cases compared to 35% for myopia, highlights the predominance of farsightedness among the surveyed cohort. Furthermore, the data revealing that accommodative hyperopia accounts for 80% of hyperopia cases emphasizes the potential for therapeutic interventions to mitigate its impact on children's vision and academic performance (16). These findings resonate with broader epidemiological studies, such as the meta-analysis from 1990–2013, which also highlighted the significant role of refractive errors in visual impairment (12).

This study brings to light the multifactorial nature of refractive eye diseases. Beyond genetic predispositions involving genes like OPA1 and FBN1, environmental and lifestyle factors play an equally crucial role (6, 7). Modern technological advancements, which increase screen exposure, reduce outdoor activities, and constrain living spaces due to urbanization, exacerbate the risk of myopia. Conversely, structured breaks during screen time and outdoor activities can mitigate these risks, as supported by recent studies (14, 15).

The social and psychological implications of visual impairment in children are profound. Reports of bullying affecting 86% of children with eye problems emphasize the urgent need for holistic interventions that address not only the medical but also the socio-emotional challenges faced by affected individuals (9). The associated stress, anxiety, and diminished self-esteem further underscore the ripple effects of untreated refractive errors on personal development and academic success (10).

Environmental pollutants such as carbon monoxide and particulate matter (PM2.5, PM10) have emerged as significant contributors to oxidative stress and inflammation, thus worsening refractive eye conditions. These findings highlight the intersection of public health and environmental factors, suggesting that strategies to reduce environmental pollution may concurrently benefit ocular health (10, 20, 21).

This study also points to promising advancements in the early detection of refractive errors. The integration of modern technology, including portable autorefractometers and slit lamps, facilitates precise diagnostics even in resource-limited settings. Such innovations, coupled with artificial intelligence and personalized medicine approaches, pave the way for more effective and tailored management of these pathologies (19, 22, 23).

The role of public health initiatives, such as the Healthy Eyes for Successful Education project, cannot be overstated. By targeting schools and collaborating with local municipalities, this initiative underscores the potential of community-based interventions in enhancing awareness and ensuring timely ophthalmic care. The observed gender parity in

refractive pathologies (52% female, 48% male) further supports the inclusivity of such programs.

Conclusion

This study reaffirms the critical need for early and sustained ophthalmologic care for children, particularly given the rising prevalence of refractive errors globally. By addressing modifiable risk factors, leveraging technological advancements, and fostering public health awareness, the burden of refractive eye diseases can be significantly reduced, thereby enhancing the quality of life and educational outcomes for affected children. Refractive eye problems should be detected as early as possible to minimise the consequences on educational and life performance, as if left untreated in time, although at a very low percentage, they can lead to blindness throughout life.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"All procedures performed in this study were in accordance with the ethical standards of the institutional and/ or national research committee(s) and with the Helsinki Declaration (as revised in 2013), as well as the national law. Informed consent was obtained from the patients included in the study"

"No funding for this study"

Acknowledgements: None

References

1. Yang J, Yu S, Zhang C, Dai R, Ch Y. Global trends and frontiers of research on pathologic myopia since the millennium: A bibliometric analysis. Front Public Health 2022;10:836394. doi:10.3389/fpubh.2022.836394.
2. Hashemi A, Khabazkhoob M, Hashemi H. High prevalence of refractive errors in an elderly population; a public health issue. BMC Ophthalmol 2023;23(1):116. doi:10.1186/s12886-023-02750-2.
3. Cao H, Cao X, Cao Z, Zhang L, Han Y, Guo C. The prevalence and causes of paediatric uncorrected refractive error: pooled data from population studies for Global Burden of Disease (GBD) sub-regions. Br J Ophthalmol 2023;107:1224-1232.
4. Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the Right to Sight: An analysis for the Global Burden of Disease Study. Lancet 2022;399(10329):1248-1263. doi:10.1016/S0140-6736(22)01429-3.
5. Garzón-Rodríguez MC, Reyes-Figueredo LS, Velandia-Rodríguez LA, Méndez-Ruiz OD, Gómez-Rodríguez MA, Esguerra-Ochoa LT, García-Lozada D. Causes of low vision in children: A systematic review. Ophthalmologia 2023;39(3):92-101. doi:10.1055/a-1754-2316.
6. Xu E, Liu X, Han E, Li Z. Editorial: Genetic features contributing to eye development and disease. Front Cell Dev Biol 2023;11:735980. doi:10.3389/fcell.2023.735980.

7. Echevarría-Lucas L, Senciales-González M, Medialdea-Hurtado M, Rodrigo-Comino J. Impact of climate change on eye diseases and associated economic costs. Int J Environ Res Public Health 2021;18(13):7197. doi:10.3390/ijerph18137197.
8. Sabel B, Yang J, Cárdenas-Morales L, Faiq M, Heim C. Mental stress as consequence and cause of vision loss: The dawn of psychosomatic ophthalmology for preventive and personalised medicine. EPMA J 2018;9:133-160. doi:10.1007/s13167-018-0141-1.
9. Ball L, Lieberman L, Tirone K. Bullying in physical education of children and youth with visual impairments: A systematic review. Br J Vis Impair 2021;39(2):151-167. doi:10.1177/02646196211009935.
10. Vacca M, Cerolini S, Zegretti A, Lombardo C. Bullying victimisation and adolescent depression, anxiety, and stress: The mediation of cognitive emotion regulation. Children 2023; 10(7):1846. doi:10.3390/children10071846.
11. Latif M, Hussain I, Afzal S, Naveed M, Shakil M, Akhtar A, Hussain SH, Gilani S. Impact of refractive errors on the academic performance of high school children of Lahore. Front Public Health 2022;10:718283. doi:10.3389/fpubh.2022.718283.
12. William K, Pozarickij A, Hysi P, Ohno-Matsui K, Williams C, Guggenheim J. Prevalence of refractive error in Europe: The European Eye Epidemiology (E3) Consortium. Eur J Epidemiol 2015;30(4):287-303. doi:10.1007/s10654-015-9992-6.
13. Yang Y, Huang C, Tseng Y, Zhong T, Li X. Refractive error and eye health: An umbrella review of meta-analyses. Front Med 2021;8:720513. doi:10.3389/fmed.2021.720513.
14. Li R, Zhang J, Zhang Y, Tang E, Ao D, He L, Yang K, Qi X. Lifestyle and risk of developing myopia in school children in Chongqing, China. Front Med 2024;11:42. doi:10.3389/fmed.2024.00042.
15. Floros G, Glynatsis M, Mylona I. No end in sight; assessing the impact of internet gaming disorder on digital eye strain symptoms and academic success. Eur J Investig Health Psychol Educ 2024;14(1):81-92. doi:10.3390/ejihpe14010081.
16. Bises S, Kareh A, Qureshi M, Lee D, Sun L, Lam J, Sa S, Najjar R. The influence of the environment and lifestyle on myopia. J Physiol Anthropol 2024;43(1):1-10. doi:10.1186/s40101-024-00275-3.
17. Alvarez-Peregrina C, Sánchez-Tena M, Martinez-Perez C, Santiago-Dorrego C, Yvert T, Andreu-Vazquez C, Villa-Collar C. The influence of genetics in myopia control: A pilot study. J Clin Med 2021;10(16):3604. doi:10.3390/jcm10163604.
18. Clark R, Pozarickij A, Hysi P, Ohno-Matsui K, Williams C, Guggenheim J. Education interacts with genetic variants near GJD2, RBFOX1, LAMA2, KCNQ5, and LRRC4C to confer susceptibility to myopia. PLoS Genet 2022; 18(6): e1010478. doi:10.1371/journal.pgen.1010478.
19. Lin C, Chiu C, Lee P, Chen K, He C, Hsu S, Cheng K. The adverse effects of air pollution on the eye: A review. Int J Environ Res Public Health 2022;19(13):8086. doi:10.3390/ijerph19138086.
20. Han J, Amri C, Lee H, Hur J. Pathological mechanisms of particulate matter-mediated ocular disorders: A review. Int J Mol Sci 2024;25(22):12107. doi:10.3390/ijms252212107.
21. Lopez-Munoz A, et al. Key factors in early diagnosis of myopia progression within ocular biometric parameters by Scheimpflug technology. Life 2023; 13(2):447. doi:10.3390/life13020447.

22. Iwanczuk, J. The Pentacam Family. In: Aramberri, J., Hoffer, K.J., Olsen, T., Savini, G., Shammas, H.J. (eds) Intraocular Lens Calculations. Essentials in Ophthalmology. Springer, 2024, Cham. https://doi.org/10.1007/978-3-031-50666-6_26.
23. Li Z, Yang L, Yu X, Qiang J, Xie H, Zhou H, Yu S, Shao Y, Chen E. Artificial intelligence in ophthalmology: The path to the real-world clinic. Cell Rep Med 2023;4(1):100157. doi:10.1016/j.xcrm.2023.100157.

MECHANICAL JAUNDICE AND CLINICAL-LABORATORY CORRELATIONS

Klerida Shehu[1], Migena Gega[1], Orgeta Dervishi[1], Adriana Babameto[2], Benard Shehu[2], Erald Vasili[3]

[1] *Faculty of Medical Technical Sciences, Tirana, Albania*
[2] *University Hospital Center "Mother Teresa", Tirana, Albania*
[3]*Tirana Polyclinic, Tirana, Albania*

Abstract

Introduction: Post-hepatic or mechanical jaundice is a pathology of the biliary tract usually caused by biliary calculi and tumors. The aim of the study is to evaluate the clinical-laboratory correlations in patients with mechanical jaundice.

Material and Methods: This is a prospective study conducted during the period 2012–2015 at the "Mother Teresa" University Hospital Center in Tirana, specifically in the Department of Gastroenterology. The study included patients admitted to the Gastroenterology ward with the clinical diagnosis of "Obstructive Jaundice."

Results: The study included 163 patients, with a mean age of 63.5 (±13.1) years, ranging from 20–85 years; 35.2% were male and 65.6% were female. According to the admission diagnosis, mechanical jaundice cases predominated (62.6%), followed by acute pancreatitis (12.8%). Malignant diagnoses were observed in 45.4% of patients. Men were 1.3 times more likely to develop malignancies. In the multivariate logistic regression model, it was found that direct bilirubin (mg/dl), CA 19-9 (U/mL), and GGT (U/L) are independent predictors of malignancy. Furthermore, the combination of predictors for malignancy—weight loss >10%, bilirubin >3 mg/dl, and CA 19-9 >35 U/ml—significantly increased the sensitivity, specificity, and positive predictive value (100%) compared to each factor individually.

Conclusion: The importance of early diagnosis and timely treatment of obstructive jaundice or cholestasis is crucial, as early etiological treatment of mechanical jaundice can prevent complications from disease progression. The investigation and management of obstructive jaundice require a multidisciplinary team composed of surgeons, radiologists, pathologists, gastroenterologists, and oncologists.

Keywords: Mechanical jaundice, jaundice, calculosis, tumor

IKTERI MEKANIK DHE KORRELACIONET KLINIKO LABORATORIKE

Abstrakt

Hyrje: Ikteri post hepatik ose mekanik eshte nje patologji e traktit biliar qe zakonisht shkaktohet nga kalkuloza biliare dhe tumore. Qellimi i studimit eshte vlerësimi i korrelacioneve kliniko-laboratorike tek pacientet me ikter mekanik.

Materiali dhe Metodat: Ky është një studim prospektiv i kryer në periudhën 2012-2015 në Qendrën Spitalore Universitare "Nënë Tereza" Tiranë si dhe në repartin e Gastroenterologjisë. Në studim janë përfshirë pacientët e shtruar në repartin e Gastroenterologjisë me diagnozë klinike "Verdhëz obstruktive".

Rezultate: Në studim morën pjesë 163 pacientë, mosha mesatare e të cilëve është 63.5 (±13.1) rangu 20-85 vjeç; (35.2%) meshkuj dhe (65.6%) femra. Sipas diagnozës së shtrimit, mbizotërojnë rastet me Ikter mekanik (62.6%) ndjekur nga pankreatiti akut (12.8%). Me diagnozë malinje rezultuan 45.4% e pacientëve. Meshkujt kanë 1.3 here më tepër gjasa të preken nga malinjiteti. Në modelin e regresionit logjistik multivariat u gjet që: B.direkte (mg/dl),CA19_9 (U/mL), GGT (U/L) janë faktorë të pavarur prediktorë të malinjitetit. Gjithashtu, u gjet që kombinimi i faktorëve parashikues të malinjitetit: rënia në peshë më > 10%, bilirubina >3 mg / dl dhe CA 19-9 > 35 U / ml rrit ne menyre te ndjeshme vlerat e sensitivitetit, specificitetit dhe vleres parashikuese positive (100%) krahasuar me secilin nga faktoret veçmas.

Përfundim: Rëndësia e diagnozës së hershme dhe trajtimi në kohë i verdhëzës ose kolestazës obstruktive është vendimtare, meqenëse trajtimi etiologjik ne kohe I ikterit mekanik do parandalonte komplikacionet nga ecuria e semundjes.Investigimi dhe menaxhimi i verdhëzës obstruktive kerkon nje ekip multidisiplinar të përbërë nga kirurgë, radiologë, patologë, gastroenterologë dhe onkologë.

Fjalët kyçe: ikter mekanik, verdhëz, kalkulozë, tumor

Introduction

Mechanical jaundice refers to a specific condition in medicine that deals with a particular type of jaundice, a state caused by the accumulation of bilirubin in the blood, and how this increase influences laboratory tests and the patient's clinical signs (1). Mechanical jaundice typically occurs due to an obstruction in the biliary pathways, which can be blocked by stones, tumors, or inflammation. This blockage prevents the normal flow of bile from the liver to the intestines, resulting in elevated bilirubin levels in the blood and the characteristic yellow discoloration of the skin and eyes (2). The clinical-laboratory correlations in cases of mechanical jaundice include findings from blood analyses, such as elevated direct bilirubin levels, and other specific changes like increases in liver enzyme levels, indicating damage or inflammation of the liver and biliary pathways. These laboratory findings, together with clinical symptoms and imaging techniques such as ultrasound or MRCP (magnetic resonance cholangiopancreatography), help in diagnosing and managing this condition (3). In diagnosing mechanical jaundice and detecting possible malignancy in the liver, biomarkers play a critical role. Their values help doctors differentiate between various causes of jaundice and identify the presence of cancer in the liver or bile ducts (4). The use of these biomarkers, in combination with imaging techniques, offers a comprehensive approach that assists in accurate diagnosis and appropriate medical intervention (5). This is essential for effective patient management and improving health outcomes. The aim of the study is to evaluate the clinical-laboratory correlations in patients with mechanical jaundice.

Material and Methods

This is a prospective study conducted during the period 2012–2015 at the "Mother Teresa" University Hospital Center in Tirana, specifically in the Gastroenterology Department.

Inclusion Criteria

Our study included patients admitted to the Gastroenterology ward with a clinical diagnosis of "Obstructive Jaundice."

ExclusionCriteria

Patients were excluded from the study based on the following criteria: primary or metastatic malignancy of the liver (hepatocellular carcinoma), chronic or parallel liver diseases, primary sclerosing cholangitis, choledochocele, congenital hepatobiliary anomalies, endoscopic sphincterotomy or stent placement, and sphincter of Oddi dysfunction.

Data Collection

Data for each patient were collected using a structured questionnaire. All patients underwent a detailed medical history, clinical examination, and laboratory investigations, including liver function tests. Laboratory parameters of blood and urine were studied as potential predictive factors for differentiating choledocholithiasis from biliopancreatic malignancy. All patients underwent liver function tests to assess bilirubin levels, alkaline phosphatase (ALP), ALT, and AST. Bilirubin levels were measured upon patient admission and again 48 hours after admission.

Statistical analysis

Data analysis was performed using the SPSS 20.0 statistical package. The Kolmogorov-Smirnov test was used to assess the distribution of continuous variables. Descriptive statistics of continuous variables were presented as means and standard deviations, while categorical variables were presented as absolute frequencies and percentages. The chi-square test and Fisher’s exact test were used to compare proportions between categorical variables. The Student's t-test was used for comparing means of continuous variables. A multivariate logistic regression model was employed to control for all possible confounders and to assess biomarkers as independent predictors of malignancy. Statistical significance was determined at $p \leq 0.05$. All statistical tests were two-tailed.

Results

The study included 163 patients with a mean age of 63.5 (±13.1) years, ranging from 20–85 years. Of these, 35.2% were male (n=56) and 65.6% were female (n=107), with a statistically significant difference between the groups ($p<0.05$). The mean age of male patients was 65.7 (±11.5) years (range 31–85), while the mean age of female patients was 59.6 (±15.1) years (range 20–82), showing no statistically significant difference ($t=1.9$, $p=0.06$).

Table 1. Characteristics of patients in the study (N=163)

Variables	N	%
Gender		
Female	107	65.6
Male	56	35.2
Age, Mean (SD)	63.5	(13.1)
Age group, years		
20–29	4	2.5
30–39	4	2.5
40–49	14	8.6
50–59	30	18.4
60–69	51	31.3
≥70	60	36.8
Employment Status		
Economic assistance	49	30.1
Pension	78	47.9
Employed	36	22.1

Admission Diagnosis

Of the total 163 cases, the most frequent diagnosis was mechanical jaundice (62.6%) followed by acute pancreatitis (12.3%). Other diagnoses included ampullary tumors (1.8%), pancreatic cancer (4.9%), and acute cholangitis (6.7%). Mechanical jaundice cases showed a statistically significant difference compared to other diagnoses (χ^2=121, p<0.01).

Table 2. Distribution of cases according to admission diagnosis

Admission Diagnosis	N	%
Ampullary tumor	3	1.8
Pancreatic cancer	8	4.9
Acute cholangitis	11	6.7
Head of pancreas mass	3	1.8
Jaundice	5	3.1
Mechanical jaundice	102	62.6
Ventricular neoplasm	8	4.9
Acute pancreatitis	20	12.3
Biliary acute pancreatitis	3	1.8
Total	**163**	**100.0**

Malignancy Distribution

In total, 45.4% of patients (n=74) were diagnosed with malignant conditions (95% CI: 37.95–53.06), while 54.6% (n=89) had benign diagnoses (95% CI: 46.93–62.05).

Table 3. Frequency of malignancy

Malignancy	N	%	95% CI
No	89	54.6	46.93 – 62.05
Yes	74	45.4	37.95 – 53.06
Total	**163**	**100.0**	

Comparison of Biomarkers

Statistically significant differences were observed between patients with benign and malignant pathologies in the values of certain biomarkers:

- Higher WBC, RBC, and PLT levels were seen in benign cases.
- Higher total bilirubin, direct bilirubin, CA 19-9, ALT, AST, ALP, and GGT levels were found in malignant cases.

Table 4. Comparison of hematobiochemical biomarkers by pathology

Biomarkers	Benign Pathology M (SD)	Malignant Pathology M (SD)	P
WBC (10^3µL)	7.6 (2.8)	6.8 (2.1)	0.04*
RBC (10^6µL)	4.3 (2.5)	3.8 (1.9)	0.04*
PLT (10^5µL)	316.0 (99.1)	181.1 (97.4)	0.02*
Hb (g/dl)	12.1 (1.8)	11.0 (1.8)	0.7
HCT (%)	38.0 (3.4)	32.7 (4.1)	0.4
Glucose (mg/dl)	102 (2.1.1)	108 (20.3)	0.8
BUN (mg/dl)	28 (4.2)	31 (4.8)	0.2
Creatinine (mg/dl)	0.8 (0.2)	0.9 (0.2)	0.9
Total bilirubin (mg/dl)	3.8 (3.2)	13.1 (5.3)	<0.01*
Direct bilirubin (mg/dl)	1.5 (2.1)	8.5 (4.3)	<0.01*
CA 19-9 (U/mL)	90 (41.1)	324 (63.8)	0.01*
ALT (U/L)	91 (28.9)	137 (66.3)	0.02*
AST (U/L)	88 (30.2)	129 (53.6)	0.03*
ALP (U/L)	168 (54.2)	301 (65.9)	0.02*
GGT (U/L)	196 (77.3)	424 (91.4)	<0.01*

*Statistically significant difference

Changes after 48 hours of treatment

For patients with benign conditions, ALT (U/L), AST (U/L), direct bilirubin (mg/dl), and WBC (10^3/µL) values significantly decreased 48 hours after treatment compared to admission values. In contrast, for patients with malignant conditions, these values showed no significant change, and direct bilirubin levels even increased.

Multivariate Logistic Regression

In the multivariate logistic regression model, the following were identified as independent predictors of malignancy:

- **Direct bilirubin** (mg/dl) (OR=3.5, 95% CI: 1.73–10.30, p<0.01),
- **CA 19-9** (U/mL) (OR=4.4, 95% CI: 2.86–11.57, p<0.01),

- **GGT** (U/L) (OR=3.8, 95% CI: 2.25–7.19, p<0.01).

The combination of malignancy predictors—weight loss >10%, bilirubin >3 mg/dl, and CA 19-9 >35 U/ml—significantly increased sensitivity, specificity, and positive predictive value to 100% compared to each factor alone.

Table 5. Risk factors for malignant pathology: Multivariate logistic regression

Variables	N (%)	OR	95% CI	P
Age, Mean (SD)	65.5 (±14.4)	1.4	0.24 – 8.42	0.7
Gender				
Male	21 (37.5)	Ref		
Female	30 (28.0)	1.5	0.53 – 3.17	0.5
Biomarkers*				
AFP (ng/ml)	64 (39.3)	1.7	0.64 – 9.12	0.2
Total bilirubin (mg/dl)	98 (60.2)	2.4	0.73 – 2.77	0.3
Direct bilirubin (mg/dl)	59 (36.2)	3.5	1.73 – 10.30	<0.01
CA 19-9 (U/mL)	64 (39.3)	4.4	2.86 – 11.57	<0.01
CEA (ng/ml)	91 (55.8)	2.2	0.32 – 8.41	0.09
GGT (U/L)	62 (38.0)	3.8	2.25 – 7.19	<0.01
ALP (U/L)	73 (44.8)	1.9	0.38 – 11.54	0.2
ALT (U/L)	91 (55.8)	2.1	0.78 – 5.13	0.1
AST (U/L)	96 (58.9)	1.8	0.57 – 10.11	0.2

*Values above cut off.

Discussion

Obstructive jaundice is a common surgical problem that occurs when there is an obstruction preventing the conjugated bilirubin from passing from the liver cells to the intestines (6). It remains one of the most challenging surgical conditions, significantly contributing to high morbidity and mortality (7–10). Given that patients with obstructive jaundice have high morbidity and mortality rates, early diagnosis of the cause of obstruction is critical, especially in malignant cases, as surgical resection is only possible in the early stages (11). Obstructive jaundice can be caused by a heterogeneous group of diseases, including both benign and malignant conditions (12). The common etiologies of obstructive jaundice differ from individual to individual (13). Obstructive jaundice is not a final diagnosis, and early investigation to clarify its exact cause is of great importance because systemic pathological changes can occur if the obstruction is not relieved. Several invasive and non-invasive diagnostic tests exist to determine the cause of obstructive jaundice, including laboratory and imaging tests (14). An interesting observation in this study was the importance of elevated CA 19-9 levels in patients with a mass in the head of the pancreas. CA 19-9 antigen is synthesized by both normal biliary epithelial cells and tumor cells and is excreted through bile (15). It has been suggested that elevated CA 19-9 levels in patients with both benign and malignant obstructive jaundice reflect the reflux of bile into the bloodstream due to biliary stasis and increased permeability between bile and blood (16). In the absence of obstructive jaundice, CA 19-9 present in the blood originates exclusively from tumor cells, excluding the possibility of false positivity caused by the biliary epithelium. Therefore, patients with a mass

in the head of the pancreas without jaundice but with elevated CA 19-9 levels are more likely to have malignancy compared to jaundiced patients. Other authors (17) have compared CA 19-9 levels in patients with benign and malignant pancreatic pathologies with and without jaundice and observed similar importance of elevated CA 19-9 levels in patients without jaundice. However, this observation requires further studies with larger cohorts. At a CA 19-9 value of 300 U/ml, both specificity and positive predictive value were high for predicting malignancy. Although isolated cases of elevated CA 19-9 have been reported in benign conditions (18), it is still considered an independent predictor of malignancy in pancreatic masses. This finding has also been confirmed by other researchers studying massive lesions in chronic pancreatitis (19). Nonetheless, dedicated studies on extremely high CA 19-9 levels would provide further clarity.

Combination of Predictors. It was observed that the combination of predictive factors for malignancy—weight loss >10%, bilirubin >3 mg/dl, and CA 19-9 >35 U/ml—significantly increased sensitivity, specificity, and positive predictive value compared to each factor alone.

In this study, the demographics were comparable between the benign and malignant groups. For most patients, weight documented at hospital admission was used, while for others, weight from six months prior to diagnosis was referenced. Weight loss, jaundice, and CA 19-9 levels were significantly higher in the malignant group and were further analyzed to determine the optimal cut-off values for predicting malignancy with maximum accuracy. A weight loss of more than 10% of body weight was used as the clinical cut-off for significant weight loss (20). In the multivariate analysis, the combination of weight loss >10%, bilirubin >3 mg/dl, and CA 19-9 >35 U/ml showed a specificity and positive predictive value of 100% for identifying malignancy in the pancreatic head mass. To our knowledge, Tessler et al. (21) were the first to correlate the combination of clinical and biochemical parameters to enhance the efficiency of differentiating malignant from benign lesions without requiring histological diagnosis and its associated complications. In their study of 150 patients, they found that weight loss and bilirubin levels were significantly higher in the malignant group. In the multivariate analysis, a combination of weight loss >10%, bilirubin >3 mg/dl, and CA 19-9 >37 U/ml achieved a specificity and positive predictive value of 100% for predicting malignancy. Our study findings align with other studies reported in the literature (22). Early diagnosis and timely treatment of obstructive jaundice or cholestasis are crucial because pathological changes can develop in the liver if mechanical jaundice is not treated according to its etiology. Investigating and managing obstructive jaundice requires a multidisciplinary team consisting of surgeons, radiologists, pathologists, gastroenterologists, and oncologists.

Conclusion: The importance of early diagnosis and timely treatment of obstructive jaundice or cholestasis is crucial, as early etiological treatment of mechanical jaundice can prevent complications from disease progression. The investigation and management of obstructive jaundice require a multidisciplinary team composed of surgeons, radiologists, pathologists, gastroenterologists, and oncologists.

Conflict of interests. None

References

1. Khan SA, Toledano MB, Taylor-Robinson SD. Epidemiology, risk factors, and pathogenesis of cholangiocarcinoma. HPB (Oxford) 2008;10:77-82.

2. Gatto M, Bragazzi MC, Semeraro R et al. Cholangiocarcinoma: update and future perspectives. Dig Liver Dis 2010;42:253-260.
3. Khan SA, Davidson BR, Goldin RD et al. British Society of Gastroenterology. Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update. Gut 2012;61:1657-1669.
4. Jimeno A, Hidalgo M. Molecular biomarkers: their increasing role in the diagnosis, characterization, and therapy guidance in pancreatic cancer. Mol Cancer Ther 2006;5:787-796.
5. Rückert F, Pilarsky C, Grützmann R. Serum tumor markers in pancreatic cancer-recent discoveries. Cancers (Basel) 2010;2:1107-1124.
6. Morris-Stiff G, Teli M, Jardine N, Puntis MC. CA19-9 antigen levels can distinguish between benign and malignant pancreaticobiliary disease. Hepatobiliary Pancreat Dis Int 2009;8:620-626.
7. Duraker N, Hot S, Polat Y, Höbek A, Gençler N, Urhan N. CEA, CA19-9, and CA125 in the differential diagnosis of benign and malignant pancreatic diseases with or without jaundice. J Surg Oncol 2007; 95:142-147.
8. Murray MD, Burton FR, Di Bisceglie AM. Markedly elevated serum CA19-9 levels in association with a benign biliary stricture due to primary sclerosing cholangitis. J Clin Gastroenterol 2007;41:115-117.
9. Razumilava N, Gores GJ. Classification, diagnosis, and management of cholangiocarcinoma. Clin Gastroenterol Hepatol, 2013, 11(1):13-21.
10. Singh P, Patel T, Singh P, Patel T. Advances in the diagnosis, evaluation, and management of cholangiocarcinoma. [Review] [41 refs]. Current Opinion in Gastroenterology 2006; 22(3):294-299.
11. Chen CY, Shiesh SC, Tsao HC, Lin XZ. The assessment of biliary CA125, CA19-9, and CEA in diagnosing cholangiocarcinoma—the influence of sampling time and hepatolithiasis. Hepatogastroenterology 2002;49:616-620.
12. Fritz S, Hackert T, Hinz U, Hartwig W, Büchler MW, Werner J. Role of serum carbohydrate antigen 19-9 and carcinoembryonic antigen in distinguishing between benign and invasive intraductal papillary mucinous neoplasm of the pancreas. Br J Surg 2011;98:104-110.
13. Wang YF, Feng FL, Zhao XH et al. Combined detection tumor markers for diagnosis and prognosis of gallbladder cancer. World J Gastroenterol 2014;20:4085-4092.
14. Wongkham S, Silsirivanit A. State of serum markers for detection of cholangiocarcinoma. Asian Pac J Cancer Prev 2012;13:17-27.
15. Lin MS, Jun-Xing Huang, and Hong Yu. Elevated serum level of carbohydrate antigen 19-9 in benign biliary stricture diseases can reduce its value as a tumor marker. Int J Clin Exp Med 2014; 7(3):744-750.
16. Marrelli D, Caruso S, Pedrazzani C, Neri A, Fernandes E, Marini M, Pinto E, Roviello F. CA19-9 serum levels in obstructive jaundice: clinical value in benign and malignant conditions. Am J Surg. 2009 Sep;198(3):333-9.
17. Anand S, Panda C, Senapati AT, Behera MR, Thatei C. A study on incidence, clinical profile, and management of obstructive jaundice. J Evid Based Med Healthc. 2016;3:3139-3145.
18. Chen CY, Shiesh SC, Tsao HC, Lin XZ: The assessment of biliary CA 125, CA 19-9 and CEA in diagnosing cholangiocarcinoma-the influence of sampling time and hepatolithiasis. Hepato-Gastroenterology 2002; 49:616-620.

19. Malaguarnera G, Giordano M, Paladina I et al. Markers of bile duct tumors. World J Gastrointest Oncol 2011;3:49-59.
20. Shehu K, Babameto A, Sonela Xinxo, Benard Shehu, Albana Duni, Steka Taci, Luljeta Cakerri. Relation between the Demographic and Clinical Characteristics and the Etiology of Obstructive Jaundice. Mediterranean Journal of Medical Sciences. 2015;2:1-8.
21. Tessler DA, Catanzaro A, Velanovich V, Havstad S, Goel S. Predictors of cancer in patients with suspected pancreatic malignancy without a tissue diagnosis. Am J Surg. 2006 Feb;191(2):191-7.
22. Lawal D, Oluwole S, Makanjuola D, Adekunle M. Diagnosis, management, and prognosis of obstructive jaundice in Ile-Ife, Nigeria. West African Journal of Medicine. 2008;17:255-260.

SGLT2 INHIBITOR - A NEW HYPOGLYCEMIC AGENTS WITH POTENTIAL EFFECT IN CARDIOVASCULAR RISK

"An apple a day keeps heart failure, kidney disease, and myocardial infarction away"

Ergita Nelaj[1], Irida Kecaj[1], Kei Xhixhabesi[2], Zheni Gjergj[3], Arjana Stojku[4]

[1]*Department of Internal Medicine, University Hospital Center "Mother Teresa", Tirana, Albania*
[2]*Faculty of Medicine, University of Medicine, Tirana, Albania*
[3]*Department of Internal Medicine, Hospital Center "Xhaferr Kongoli" Elbasan, Albania*
[4]*Nephrologist, Specialties Health Center No. 2, Tirana, Albania*

Correspondence E-mail: dr_ergi@yahoo.com

Abstract

Type 2 diabetes mellitus, along with complications that accompany it, have become a major threatening life disease in the 21st century. Although the association between glycated hemoglobin (HbA1c) and macrovascular complications has been known for many years, antidiabetic drugs have not been able to reduce these problems. The 2019 European Association of Cardiology/European Association for the Study of Diabetes guidelines on diabetes, prediabetes and heart disease recommend sodium-glucose cotransporter 2 inhibitors (SGLT2i) over metformin as first-line therapy in patients with atherosclerotic cardiovascular disease (ASCVD) or high or very high risk. Unlike many other antihyperglycemic therapies, increasing glucose excretions via SGLT2 inhibition provides hypoglycemic effects independent of insulin. The use of SGLT2 inhibitors may have beneficial effects on biomarkers such as blood glucose, blood pressure, body weight, intrarenal hemodynamics and proteinuria, and may also reduce cardiovascular complications, kidney disease and diabetes. The American Diabetes Association now recommends the use of SGLT2 inhibitors after initial treatment with dietary and lifestyle changes in addition to metformin in patients with T2DM and all cardiovascular diseases, including heart failure. SGLT2 inhibitors will become an important tool in the hands of physicians in daily practice targeting this vulnerable population.

Key words: SGLT2**,** cardiovascular, heart failure, inhibition, glycemic

FRENUESIT SGLT2 - NJË AGJENT I RI HIPOGLICEMIK ME EFEKT POTENCIAL NË RREZIKUN KARDIOVASKULAR

Abstrakt

Diabeti Melitus tip 2, së bashku me komplikacionet e tij, është një sëmundje jetëkërcënuese në shekullin e 21-të. Edhe pse lidhja midis hemoglobinës së glukozuar (HbA1c) dhe komplikacioneve makrovaskulare është e njohur për shumë vite, preparatet antidiabetike nuk kanë qenë në gjendje t'i reduktojnë këto komplikacione. Udhëzimet e Shoqatës Evropiane të

Kardiologjisë 2019/Shoqatës Evropiane për Studimin e Diabetit, për diabetin, prediabetin dhe sëmundjet e zemrës, rekomandojnë frenuesit e bashkëtransportuesit natrium -glukozë 2 (SGLT2) mbi metforminën, si terapi të linjës së parë në pacientët me sëmundje aterosklerotike kardiovaskulare (ASCVD), me rrezik të lartë ose shumë të lartë. Ndryshe nga shumë terapi të tjera antihiperglicemike, rritja e ekskretimit të glukozës nëpërmjet frenimit të SGLT2 siguron efekte hipoglicemike të pavarura nga insulina. Përdorimi i SGLT2i mund të ketë efekte të dobishme në biomarkerët si glukoza në gjak, presioni i gjakut, pesha trupore, hemodinamika intrarenale dhe proteinuria, si dhe mund të reduktojë komplikacionet kardiovaskulare, sëmundjet e veshkave dhe diabetin. Shoqata Amerikane e Diabetit tani rekomandon përdorimin e frenuesve SGLT2 pas trajtimit nëpërmjet ndryshimit të stilit të jetesës dhe rregjimit dietetik, përveç metforminës, në pacientët me DM tip 2 dhe të gjitha sëmundjet kardiovaskulare, përfshirë insuficiencën kardiake. Frenuesit SGLT2 do të jenë një mjet i rëndësishëm në duart e mjekëve, në praktikën e përditshme, duke patur synim këtë grup popullatë.

Fjalë kyç: SGLT2, kardiovaskular, insuficiencë kardiake, frenim, glicemik

Introduction

Type 2 diabetes mellitus (T2DM) is a complex chronic disease. Its prevalence has increased over the past several decades. T2DM is associated with an increased risk of several cardiovascular diseases (CVD), with heart failure (HF) being a more common early symptom than myocardial infarction (MI) (1). Patients with heart failure often have insulin resistance, which may eventually promote the development of diabetes or worsen it. Several large cohort studies have reported a prevalence of diabetes in patients with heart failure of 30–50%, further suggesting a link between the two diseases (1). In 2008, the US Food and Drug Administration issued pharmaceutical industries to assess the cardiovascular outcome of antidiabetic therapy, beyond glycemic control (2). Prior to the advent of gliflozin, no antidiabetic therapy had shown significant improvement in HF hospitalizations (3). Therefore, SGLT2 inhibitors, also known as gliflozin, represent an effective and innovative treatment option for patients with T2DM.

The origin of SGLT2i can be traced to phlorizin, an organic compound first discovered and extracted from the bark of the apple tree, by De Koninck and Stas in 1835 (4). SGLT1 is expressed mainly in the proximal renal tubules of the nephrons, small intestine, and myocardium, while SGLT2i is found only in the brush borders of epithelial cells in the S1 and S2 segments of the proximal renal tubules. Its expression and activity are increased by increased plasma glucose but do not inhibit renal gluconeogenesis, which may be increased in diabetes, and cause osmotic diuresis in individuals with or without diabetes (5). Administration of SGLT2i results in a daily loss of 60–100 g of glucose in the urine, thereby reducing energy expenditure and leading to significant changes in the body's metabolism (6). SGLT2i treatment has been associated with significant improvements in insulin resistance and insulin secretion. In addition, SGLT2 inhibitors directly stimulate the α cells of the pancreas to increase glucagon secretion. This reduces hepatic triglyceride synthesis, reduces liver fat and blood triglyceride concentration, and increases liver ketone body production (7). Therefore, SGLT2 inhibitor therapy improves many atherosclerotic risks in patients with type 2 diabetes. SGLT2 inhibitors also have hemodynamic effects: they increase urine output and sodium loss, thereby reducing body weight and systolic and diastolic blood pressure (8,9).

This medication goes beyond glycemic control and has been shown to be effective in the medium- to long-term treatment of T2DM complications. SGLT2 inhibitors have also shown significant reductions in cardiovascular events, heart failure hospitalizations, and cardiovascular and all-cause mortality (10–13). Over the past 5 years, evidence from randomized controlled trials (RCTs) has demonstrated unequivocal efficacy and safety for most cardiovascular (CV) and renal outcomes, independent of the effect on glycemic control. In patients with high risk of ASCVD or established ASCVD, GLP-1RA or SGLT2 inhibitors should be considered; in patients with CKD or heart disease failure with reduced ejection fraction, SGLT2 inhibitors should be the first choice. Given the beneficial cardiovascular and metabolic effects of SGLT2 inhibitors, they may be useful in preventing cardiovascular disease in patients with T2DM and a history of cardiovascular disease. SGLT2 inhibitors are also useful in the primary and secondary prevention of in-hospital heart failure in patients with T2DM and various risk factors.

Although SGLT2i were initially considered and developed as hypoglycemic agents, they unexpectedly noted a reduction in mortality and cardiovascular events and demonstrated cardiorenal protection even in the absence of hyperglycemic status. The results were seen regardless of the presence of diabetes, if the patients were male or female, young or old, or receiving neprilysin inhibitors. This combination of results is unique among current heart failure drugs (14).

Cardiac benefits

The four direct effects of SGLT2i on the myocardium are: improvement of the energy and metabolism of the myocardium; reduction of mass and hypertrophy of the left ventricle as well as apoptosis of cardiomyocytes; reduction of myocardial inflammation and the level of proinflammatory cytokines; improvement of myocardial and ECM remodeling (15).

The dual natriuretic and diuretic effects of SGLT2 affect the reduction of intra- and extracellular volume, and the reduction of intravascular volume and arterial pressure decreases the load before and after cardiac surgery, thus influencing the relief of cardiac load and improving left ventricular function (16). The cardio-renal effects of SGLT2 natriuresis inhibitors are mediated by inhibition of the myocardial sodium-proton exchanger, and have been shown to reduce cardiac hypertrophy and heart failure (17). Through glycosuria induced by SGTLT2, it affects a wide range of metabolic changes that can reduce both fibrosis and the creation of plaques, all of which are related to the heart. Based on previous studies, SGLT2 can reduce both myocardial fibrosis and cardiac remodeling by regulating macrophage morphology, as well as protect the heart from ischemia/reperfusion injury (18-20). One of the effects of SGLT2, which helps to reduce the unfavorable remodeling of heart failure, is realized between the reduction of the epicardial fat mass and the level of inflammatory cytokines such as tumor necrosis factor-a and plasminogen activator inhibitor-1 in diabetic patients with CVD (21). It has been speculated that SGLT2 increases the concentration of mitochondrial calcium through the direct inhibitory effect of the sodium-hydrogen (Na+/H+) exchange in the myocardium, influencing in this way the improvement of mitochondrial function and the reduction of oxidation (17). All of the above-mentioned mechanisms underlie the cardioprotective effects of SGLT2, including the reduction of cardiac interstitial fibrosis, coronary fibrosis, arterial thickness, cardiac interstitial macrophage infiltration, and cardiac superoxide levels. In various research studies, it has

been reported that empagliflozin increases the utilization of fatty acids, ketone bodies, and branched-chain amino acids, decreases ATP inhibition, increases myocardial ATP, and increases fuel consumption in diabetic cardiomyopathy rats, which affect in increasing their cardiac activity (22).

Renal benefits

The American Diabetes Association/European Association for the Study of Diabetes now recommends the use of SGLT2 inhibitors after initial therapy with dietary and lifestyle modifications in addition to metformin in patients with T2DM and all cardiovascular diseases, including heart failure (23,24). SGLT2 inhibitors will become an important tool in the hands of physicians in daily practice targeting this group population.

SGLT2 inhibitors not only reduce proteinuria, but also preserve eGFR and reduce the risk of end-stage renal disease (25,26). SGLT2i have been shown to reduce HbA1c levels without causing hypoglycemic events. In the long term, lowering blood sugar and improving insulin resistance may reduce microvascular complications. SGLT2i inhibits the toxic effects of high glucose on the proximal renal tubular cells by causing oxidative stress and advanced glycation endproducts, p21-mediated senescence, and the production of proinflammatory and profibrotic mediators (27). This protection by SGLT2i is related to the development of renal failure. On the other hand, there is a protective effect of associated with altered renal hemodynamics. SGLT2 inhibition increases distal sodium transport, which promotes glomerular feedback and results in an improvement in intraglomerular pressure (28) – slowing the progression of kidney disease. At the same time, the effect of urinary sodium is associated with a decrease in blood pressure, usually around 4 mmHg systolic and 2 mmHg diastolic (29), exerting an indirect kidney-protective effect. They also have to deal with weight loss due to the loss of sugar (calories) in the urine and the osmotic diuresis caused by sugar (30), and we know that obesity is one of the most important factors for incipient CKD (31).

In addition, SGLT-2i reduce blood uric acid in patients with type 2 diabetes, which is useful given the evidence that hyperuricemia is a risk factor for hypertension, kidney disease, and heart disease. The mechanism is that high glucose levels in the renal tubules facilitate the exchange of glucose and urate, leading to increased urinary excretion of urate (32). Thus, there are multiple direct and indirect mechanisms that may influence the reno-protective effects of SGLT2i (33).

In **conclusion**, we believe that this drug class is becoming important in the treatment of heart and kidney disease, given the bidirectional nature of cardio-renal interactions and the predisposition of T2DM patients to heart failure and kidney disease. Considering the origin of SGLT2i we can say “An apple a day keeps heart failure, kidney disease, and myocardial infarction away”.

Acknowledgements: None declared

Conflict of interest: The authors declare that they have no conflict of interest**.**

References

1. Shah, A.D.; Langenberg, C.; Rapsomaniki, E.; et.al. Type 2 diabetes and incidence of cardiovascular diseases: A cohort study in 1.9 million people. Lancet Diabetes Endocrinol. 2015, 3, 105–113. [CrossRef]
2. Hwang, T.; Franklin, J.; Kesselheim, A. Effect of US Food and Drug Administration's Cardiovascular Safety Guidance on Diabetes Drug Development. Clin. Pharmacol. Ther. 2017, 102, 290–296. [CrossRef]
3. Custodio, J.S.; Duraes, A.R.; Abreu, M.; Rocha, N.A.; Roever, L. SGLT2 inhibition and heart failure—current concepts. Heart Fail. Rev. 2018, 23, 409–418. [CrossRef]
4. Ehrenkranz, J.R.L.; Lewis, N.G.; Kahn, C.R.; Roth, J. Phlorizin: A Review. Diabetes Metab. Res. Rev. 2005, 21, 31–38. [CrossRef] [PubMed]
5. Daniel Hssia, Owen Grove, William T Cefalu. An update on SGLT2 inhibitors for the treatment of Diabetes Mellitus. 1st Ed, 2018
6. Kashiwagi A, Araki S, Maegawa H. Sodium-glucose cotransporter 2 inhibitors represent a paradigm shift in the prevention of heart failure in type 2 diabetes patients. J Diabetes Investig. 2021 Jan;12(1):6-20. doi: 10.1111/jdi.13329. Epub 2020 Aug 5. PMID: 32563214; PMCID: PMC7779279
7. Cefalu WT. Paradoxical insights into whole body metabolic adaptations following SGLT2 inhibition. J Clin Invest 2015;124: 485–487
8. Tikkanen I, Narko K, Zeller C, et al. Empagliflozin reduces blood pressure in patients with type 2 diabetes and hypertension. Diabetes Care 2015; 38: 420–428.
9. Kashiwagi A, Yoshida S, Kawamura K, et al. Effects of ipragliflozin, a selective sodium–glucose co-transporter 2 inhibitor, on blood pressure in Japanese patients with type 2 diabetes mellitus: a pooled analysis of six randomized, placebo-controlled clinical trials. Diabetol Int 2017; 8: 76–86
10. Zelniker, T.A.; Braunwald, E. Mechanisms of Cardiorenal Effects of Sodium-Glucose Cotransporter 2 Inhibitors. J. Am. Coll. Cardiol. 2020, 75, 422–434. [CrossRef]
11. Swoboda, P.P.; McDiarmid, A.K.; Erhayiem, B.; et al. Diabetes Mellitus, Microalbuminuria, and Subclinical Cardiac Disease: Identification and Monitoring of Individuals at Risk of Heart Failure. J. Am. Heart Assoc. 2017, 6. [CrossRef]
12. Lenti, M.V.; Pasina, L.; Cococcia, S.; Cortesi, L.; et al. Mortality rate and risk factors for gastrointestinal bleeding in elderly patients. Eur. J. Intern. Med. 2019, 61, 54–61. [CrossRef]
13. Palmiero G, Cesaro A, Vetrano E, et.al. Impact of SGLT2 Inhibitors on Heart Failure: From Pathophysiology to Clinical Effects. Int J Mol Sci. 2021 May 30;22(11):5863. doi: 10.3390/ijms22115863. PMID: 34070765; PMCID: PMC8199383.
14. Zannad, Faiez, et al. "SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials." The Lancet 396.10254 (2020): 819-829.
15. Sabouret P, Galati G, Angoulvant D, Germanova O, Castelletti S, et al (2020) The interplay between cardiology and diabetology: a renewed collaboration to optimize cardiovascular prevention and heart failure management. Eur Heart J Cardiovasc Pharmacother 13:pvaa051. https://doi.org/10.1093/ehjcvp/pvaa051
16. Kario K, Okada K, Kato M, et al. 24-hour blood pressure-lowering effect of an SGLT-2 inhibitor in patients with diabetes and uncontrolled nocturnal hypertension: results from the randomized, placebo-controlled SACRA Study. Circulation. 2018;139(18):2089–2097.

17. Packer, M.; Anker, S.D.; Butler, J.; Filippatos, G.; Zannad, F. Effects of sodiumglucose cotransporter 2 inhibitors for the treatment of patients with heart failure: Proposal of a novel mechanism of action. JAMA Cardiol. 2017, 2, 1025–1029. [CrossRef]
18. Vallon, V.; Thomson, S.C. Targeting renal glucose reabsorption to treat hyperglycaemia: The pleiotropic effects of SGLT2 inhibition. Diabetologia 2017, 60, 215–225. [CrossRef] [PubMed]
19. Lee, T.M.; Chang, N.C.; Lin, S.Z. Dapagliflozin, a selective SGLT2 Inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts. Free Radic. Biol. Med. 2017, 104, 298–310. [CrossRef] [PubMed]
20. Lim, V.G.; Bell, R.M.; Arjun, S.; Kolatsi-Joannou, M.; Long, D.A.; Yellon, D.M. SGLT2 inhibitor, canagliflozin, attenuates myocardial infarction in the diabetic and nondiabetic heart. J. Am. Coll. Cardiol. Basic. Trans. Science. 2019, 4, 15–26. [CrossRef]
21. Sato, T.; Aizawa, Y.; Yuasa, S.; Kishi, S.; et al. The effect of dapagliflozin treatment on epicardial adipose tissue volume. Cardiovasc. Diabetol. 2018, 17, 1–9. [CrossRef] [PubMed]
22. Verma, S.; Rawat, S.; Ho, K.L.; Wagg, C.S.; Zhang, L.; Teoh, H.; Lopaschuk, G.D. Empagliflozin increases cardiac energy production in diabetes: Novel translational insights into the heart failure benefits of SGLT2 inhibitors. J. Am. Coll. Cardiol. Basic Trans. Sci. 2018, 3, 575–587.
23. J.B. Buse, D.J. Wexler, A. Tsapas, et al. 2019 update to: Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) Diabetologia, 63 (2020), pp. 221-228
24. American Diabetes Association. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2021 Diabetes Care, 44 (2021), pp. S111-S124.
25. O. Mosenzon, S.D. Wiviott, A. Cahn, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial Lancet Diabetes Endocrinol, 7 (2019), pp. 606-617.
26. Nelaj, E., Kecaj, I., Feracaku, J., Xhixhabesi, K., & Tase, M. (2024). Benefits of SGLT2 inhibitors on renal and cardiovascular protection, in diabetic patients. South Eastern European Journal of Public Health, 200–206. https://doi.org/10.70135/seejph.vi.689
27. Podestà, M.A.; Sabiu, G.; Galassi, A.; Ciceri, P.; Cozzolino, M. GLT2 Inhibitors in Diabetic and Non-Diabetic Chronic Kidney Disease. Biomedicines 2023, 11, 279. https://doi.org/10.3390/ biomedicines11020279
28. Anders, H.-J.; Davis, J.M.; Thurau, K. Nephron Protection in Diabetic Kidney Disease. N. Engl. J. Med. 2016, 375, 2096–2098. [CrossRef] [PubMed]
29. Chao EC. SGLT-2 Inhibitors: A New Mechanism for Glycemic Control. Clin Diabetes. 2014 Jan;32(1):4-11. doi: 10.2337/diaclin.32.1.4. PMID: 26246672; PMCID: PMC4521423.
30. Ferrannini E, Baldi S, Frascerra S, Astiarraga B, Heise T, Bizzotto R, Mari A, Pieber TR, Muscelli E (2016) Shift to fatty substrate utilization in response to sodium-glucose cotransporter 2 inhibition in subjects without diabetes and patients with type 2 diabetes. Diabetes. 65(5):1190–1195

31. Kovesdy CP, Furth SL, Zoccali C (2017) Obesity and kidney disease: hidden consequences of the epidemic. Afr J Prim Health Care Fam Med 26:9(1)
32. Musso G, Gambino R, Cassader M, Pagano G: A novel approach to control hyperglycemia in type 2 diabetes: sodium glucose co-transport (SGLT) inhibitors: systematic review and meta-analysis of randomized trials. Ann Med 44:375–393, 2012
33. Storgaard, H.; Gluud, L.L.; Bennett, et.al. Benefits and Harms of Sodium-Glucose Co-Transporter 2 Inhibitors in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. PLoS ONE 2016, 11, e0166125.

SEVERE BRONCHIAL ASTHMA, A DISEASE OR A SYNDROME?

Mehmet Hoxha, Ester Ndreu, Etleva Qirko Loloçi

Service of Allergology and Clinical Immunology, University Hospital Center "Mother Teresa", Tirana, Albania

Corresponding E-mail: esterndreu3@gmail.com

Abstract

Background. The World Health Organization defines asthma as a disease characterized by repeated attacks of dyspnea and wheezing, which vary in frequency from person to person. According to another definition, asthma is considered a complex syndrome that cannot be classified as a single disease but as a series of overlapping individual diseases and phenotypes, the expression of which is the result of a unique interplay between genetic and environmental factors. This conglomerate of diseases is more pronounced precisely in the severe form of asthma, which by definition is the most serious and life-threatening form, the adequate control of which often cannot be achieved even with high doses of medication.

Clinical experience and now genetic data are increasingly leaning towards the concept of asthma as a heterogeneous clinical syndrome; clinical cases erupt, progress and respond to treatments in different ways. Currently, the diagnosis of asthma is based on incisive clinical methods that rely on pulmonary function tests, which prove the reversibility of bronchial obstruction. But this approach alone is not enough to address the diagnostic and therapeutic challenges resulting from the heterogeneity of asthma; among others, regarding the management of asthma, current guidelines pay special attention to the identification of comorbidities and the role they play.

Methods. In this article, we briefly discuss some of the health conditions that coexist with severe bronchial asthma, following a systematic literature review approach.

Conclusion. Bronchial asthma coexists with many other comorbidities, which are often overlooked. In order to have a more comprehensive management of this pathology, a diagnostic and therapeutic approach of the contributing factors and comorbidities, should be taken.

Key words. severe asthma, comorbidity, syndrome, disease

ASTMA E RËNDË BRONKIALE, SËMUNDJE APO SINDROM?

Abstrakt

Hyrje. Organizata Botërore e Shëndetësisë e përkufizon astmën si një sëmundje të karakterizuar nga atake të përsëritur të dispnesë dhe fishkëllimave, të cilat ndryshojnë në frekuencë nga një person në tjetrin. Sipas një tjetër përkufizimi, astma konsiderohet si një

sindromë komplekse që nuk mund te klasifikohet dot si një sëmundje e vetme por si një seri sëmundjesh dhe fenotipesh individuale të mbivendosura, shprehja e të cilave është rezultat i ndërthurjes unike midis faktorëve gjenetikë dhe mjedisorë. Ky konglomerat sëmundjesh shoqëruese është më i theksuar dhe i ndërlikuar pikërisht në formën e rëndë të astmës e cila për definicion është forma më serioze dhe jetëkërcënuese, kontrolli adekuat i së cilës shpesh nuk mund të arrihet madje edhe me doza të larta medikamentoze.

Eksperienca klinike dhe tashmë edhe të dhënat gjenetike po anojnë gjithnjë e më shumë nga koncepti i astmës si një sindromë klinike heterogjene; rastet klinike shpërthejnë, progresojnë dhe i përgjigjen trajtimeve në mënyra të ndryshme. Aktualisht diagnoza e astmës bazohet në metoda klinike incizive që mbështeten në teste të funksionit pulmonar, që vërtetojnë reversibilitetin e obstruksionit bronkial. Por nuk mjafton vetëm kjo qasje për të adresuar sfidat diagnostikuese dhe terapeutike që vijnë si pasojë e heterogjenecitetit të astmës; ndër të tjera, sa i përket menaxhimit të astmës, udhërrëfyesit aktuale i kushtojnë një vëmëndje të veçantë identifikimit të komorbiditeteve dhe rolit që ato luajnë.

Metodologji. Për punimin e këtij artikulli, është kryer një rishikim sistematik i literaturës mbi gjendjet shëndetësore që bashkëekzistojnë me astmën bronkiale.

Konkluzione. Astma bronkiale bashkëshoqërohet me shumë sëmundje të tjera, që shpeshherë nuk u kushtohet vëmendja e duhur. Çdo faktori kontribues apo komorbiditeti, i duhet kushtuar një qasje diagnostike dhe terapeutike, me qëllim që të arrihet një menaxhim sa më optimal i astmës bronkiale.

Fjalë kyc. astma e rëndë, komorbiditete, sindromë, sëmundje

Introduction

Asthma is considered severe when adequate symptomatic control is not achieved with high doses of inhaled corticosteroids and additional medications (LABA, montelukast and/or theophylline) or with oral corticosteroids for at least 6 months, or when this control is lost after medication reduction. This form is present in 9.5% of all asthmatic patients and accounts for about 60% of the total medical costs of asthma. (1). Its features include hyperactivity, constriction and thickening of the bronchial smooth muscle, inflammation and subepithelial fibrosis, mucus hypersecretion and its clearance deficit, as well as an increase in the level of eosinophils and neutrophils.

Severe bronchial asthma should be differentiated from uncontrolled asthma. Although both are part of what is recently known as "difficult asthma", the second (difficult-to-treat-asthma) is related to poor inhalation adherence/technique and exposure to triggering factors, while severe asthma is related to worsening of the patient's condition, regardless of proper adherence to medication or effective avoidance of triggering factors. Numerous studies prove the connection of asthma with health conditions or other diseases such as: obesity, GERD, CRSwNP, hyperventilation, epiglottic dysfunction, psychopathologies, smoking and nicotine addiction, COPD, respiratory infections, atopic dermatitis, sleep apnea, hormonal disorders,

etc (2). The following will discuss some of the clinical entities that more often coexist with severe bronchial asthma.

Severe asthma and obesity

Researchers link the prevalence of obesity in asthmatics with the obesogenic effect of systemic corticosteroids, but there is evidence that obesity itself increases the risk of asthma and its severity. Hadar et al. first mentioned the concept of "obese asthma" regarding patients with common features such as late onset of asthma, female predominance, severe symptoms, sputum with insignificant eosinophils, low atopy, severe bronchial hyperactivity and low response to ICS (3).

The first common mechanism of obesity and severe asthma is thought to be vitamin D deficiency which is 35% higher in obese asthmatic patients, mainly in women(4). The higher the vitamin deficiency, the more frequent exacerbations of severe asthma; a reduction of the latter has been observed with increased exposure to the sun, which is related to an increase in vitamin D production.

The second mechanism is systemic inflammation, resulting from infiltration of cytokines from the hypoxic death of adipocytes increased in obesity. Production of IL-1, TNF alpha and IL-6 damage the lungs after entering the bloodstream. The higher the level of IL-6 and CRP, the higher the probability that the patient is obese, hypertensive, diabetic and has more frequent asthma exacerbations. (5)

The third mechanism is damage to the microbiome, mainly pulmonary and gastrointestinal (from early exposure to antibiotics, formula versus breast milk, cesarean versus vaginal delivery, exposure to domestic or farm animals) which increases the risk of developing allergic asthma, as well as the frequency of its exacerbations (6).

Severe asthma and cardiovascular disease

In a meta-analysis of cohort studies on 3700 individuals aged 17-77 years, from 1979 to 2014, it was found that severe asthma increases the risk of death from cardiovascular diseases, arterial hypertension, ischemic stroke (in contrast to patients with mild/moderate asthma, in whom no significant association was observed), coronary artery disease in females over 18 years of age, and myocardial infarction in hypertensive asthmatic patients, particularly in those treated with inhaled LABAs or systemic corticosteroids. (7)

The first mechanism that connects asthma with cardiovascular diseases is the chronic inflammation of the airways, the chronicity of which leads to increased vulnerability of blood vessels, activation of coagulability, dysfunction of vascular endothelial cells. The second mechanism is related to chronic airway obstruction, the hypoxemia caused by which leads to increased secretion of inflammatory mediators and accumulation of lipids in macrophages. Both of these mechanisms, aided by risk factors such as smoking, hypertension, diabetes and dyslipidemia, affect the progression of atherosclerosis and increased incidence of other cardiovascular diseases.

The following scheme (Fig. 1) (8) schematically shows the physio-pathological mechanisms that link severe asthma with cardiovascular diseases. Among other things, the study examines

the connection of IgE with FcεR1 receptors in lymphocytes, smooth muscles, macrophages, endothelial cells and mast cells, their activation (which is interrupted by medications such as omalizumab and glucocorticoids) as a result of the connection with this immunoglobulin and its impact on the pathogenesis of asthma, atherosclerosis and aortic aneurysms (9).

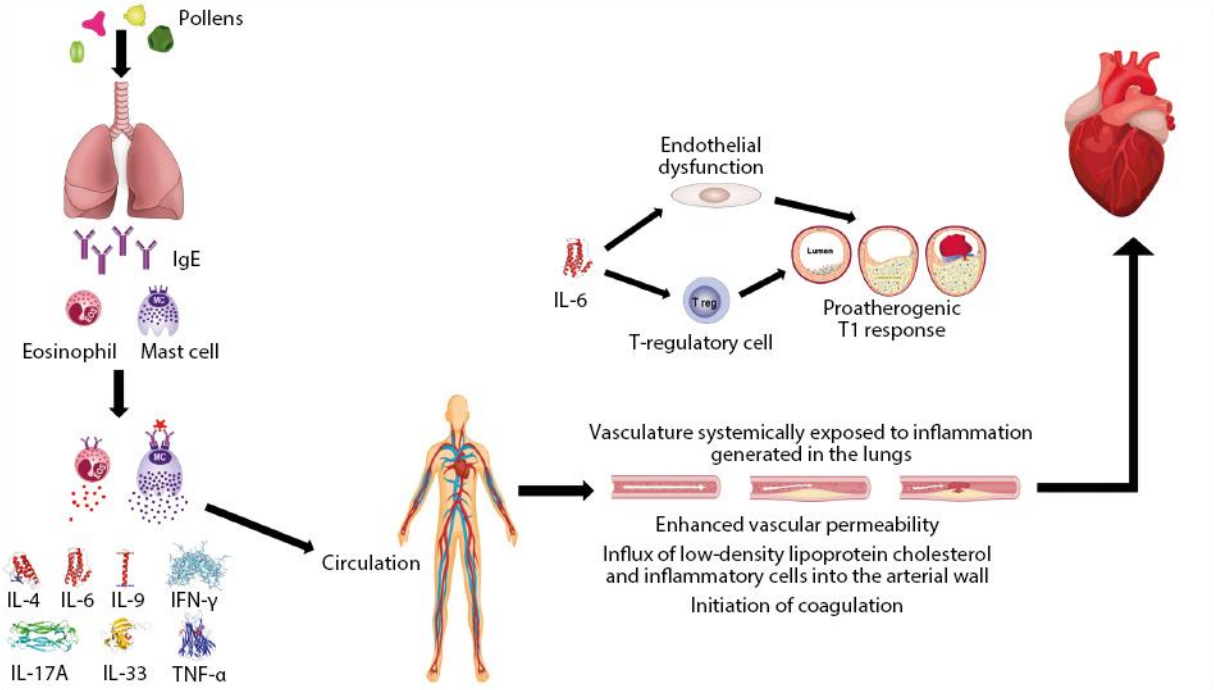


Figure 1. Pathophysiologic mechanisms connecting asthma with cardiovascular diseases (8).

Severe asthma and autoimmunity

Both asthma and autoimmunity result from a disorder of the immune system. Autoimmunity is an exaggerated TH1 response, while asthma is mainly a TH2 response. During the last decades, circulating autoantibodies against beta 2 adrenergic receptors, epithelial and nuclear antigens have been frequently reported, especially in patients with severe asthma, and are believed to be epiphenomena from chronic airway inflammation (10).

The hypothesis of autoimmunity (Fig. 2) is getting more and more attention, especially in intrinsic asthma (late onset in adult, non-atopic patients). It is based on three main mechanisms; the first consists of the classical TH2 cascade, with release of IL-5, Il-4 and IL-13., eosinophilic and lymphocyte recruitment and release of IgE-s, which together cause tissue damage (9). The second mechanism is chronic inflammation which increases the expression of IL15, IL16 BCA1 BAFF and CC17, which contribute to the formation of "B cell clusters" and autoantibodies. The third mechanism consists of increased levels of IgG, anti EPX and ANA, which cause cytolysis of eosinophils and increased exposure to autoantigens (11).

In patients with severe asthma, pulmonary infections cause the release of pro-inflammatory mediators such as IL-18 and neutrophilic degranulation (NETosis). Their consequences include tissue damage, accumulation of autoantigens, and production of autoantibodies (12).

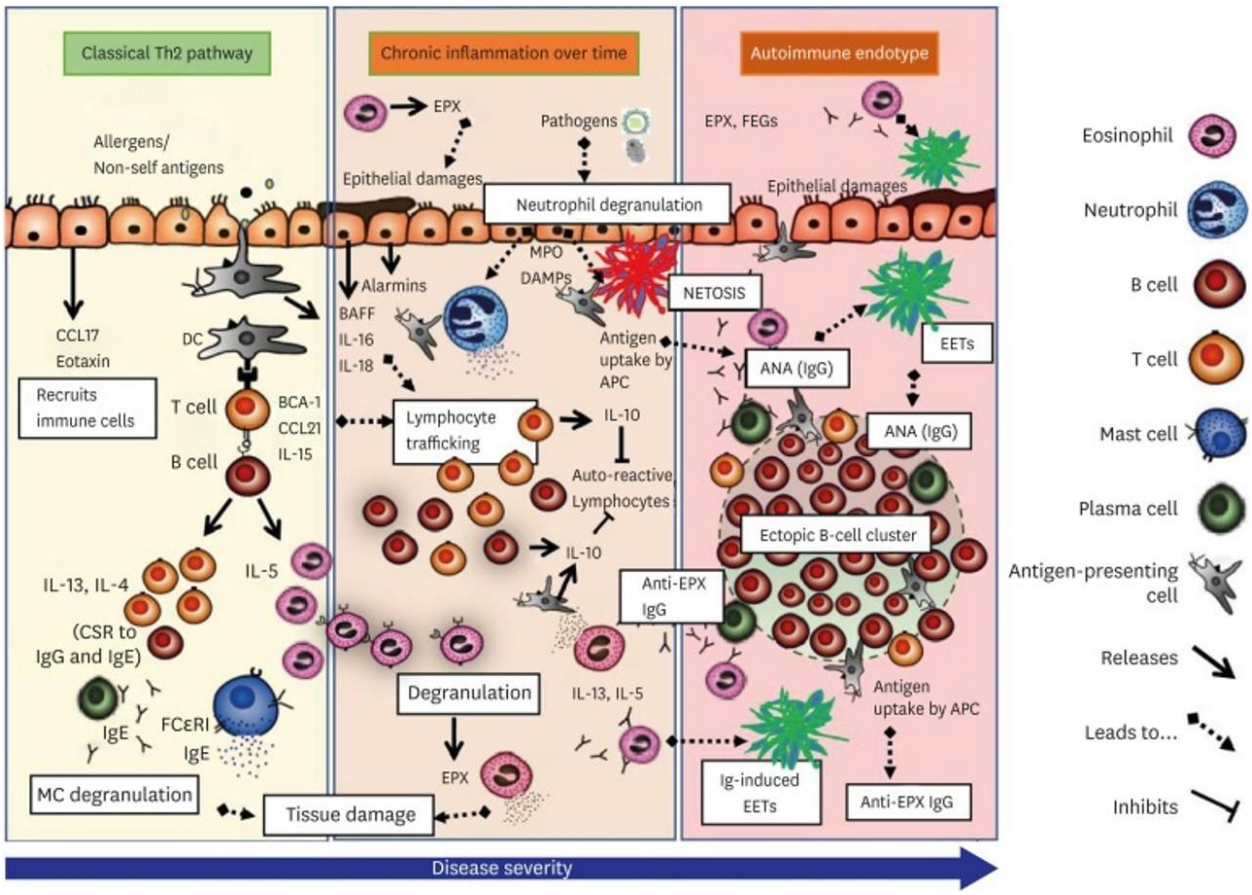


Figure 2. The hypothesis of autoimmunity in asthma (12).

Perimenstrual asthma

Perimenstrual asthma is defined as cyclic exacerbation of asthma symptoms during the luteal phase and/or during the first days of the menstrual cycle. The first case was reported in 1931, in a woman in whom, with the cessation of ovarian function, the symptoms subsided, and with its return, they reappeared. Coexistence of asthma with exacerbations during hormonal changes is reported in 19-40% of women with asthma. (13) These data, together with the evidence of gender differences in asthmatic patients, support the hypothesis that hormonal fluctuations (especially estrogenic ones) significantly affect asthma (14). Studies have concluded that the appearance of PMA correlates with increased emergency room presentations, which peak in the preovulatory and perimenstrual phase. Hospitalizations of asthmatic patients do not show gender differences in pre-pubertal ages and in those over 50 years old, while from the age of 13-50 years the ratio of hospitalizations is 3:1 in favor of women. (15)

It has also been noted that patients with severe asthma show clinical improvement when progesterone concentrations are increased. In these patients, unlike estrogens, free

testosterone correlated positively with pulmonary function. This can be explained by the fact that testosterone is derived from aldosterone, the precursor of which is progesterone (16).

Asthma with chronic rhinosinusitis and nasal polyposis

Patients with CRSwNP are characterized by eosinophilia and high local IgE, poor quality of life (especially when associated with asthma), frequent coexistence with severe bronchial asthma, accompanied by frequent exacerbations, chronic obstruction and 1more pronounced serum eosinophilia. Both of these pathologies, together with hypersensitivity to aspirin, constitute the Samter triad or AERD (aspirin-exacerbated respiratory disease). It is present in about 2.5% of the population, mostly in women, in 20% of patients with asthma and in 30% of those suffering from the severe form of asthma. (17)

GA²LEN (Global Allergy and Asthma European Network) data show that 67% of patients with CRSwNP have coexisting asthma, which in 62% of cases is of a severe form and, in many cases, may remain undiagnosed. In these patients, asthma has an adult-onset (early onset: 18-39 or late, after the age of 40) and is usually not associated with childhood asthma. (18)

The most frequent sequence (36%) of Samter's triad diagnosis starts with bronchial asthma, is followed by nasal polyposis and ends with aspirin hypersensitivity diagnosis, while the reverse sequence of the above is the rarest one (6%). (19)

Asthma and CRSwNP share a common pathophysiological pathway, which begins with the activation of TH2 cells by antigen-presenting cells. They then produce IL-4, IL-13, and IL-5, interleukins that are capable of recruiting mast cells, eosinophils, goblet cells, macrophages, and B cells. The result is a cascade of inflammatory responses shown in the picture below (Figure 3). (20)

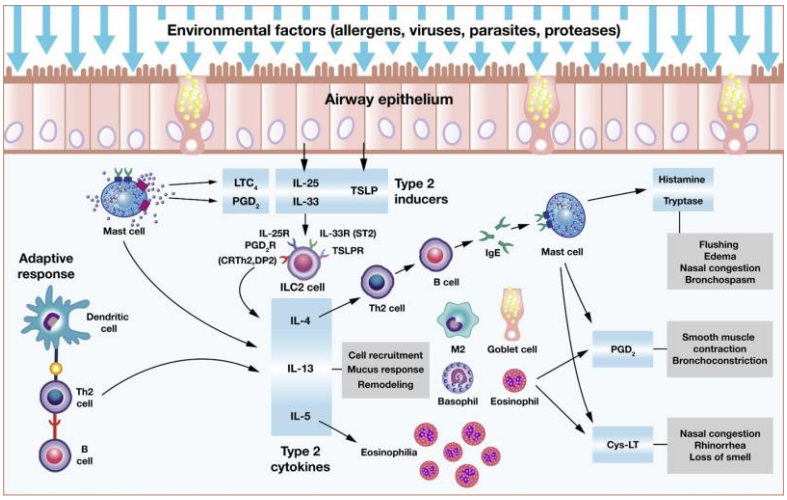


Figure 3. Pathogenesis of nasal polyps and bronchial asthma (20).

ACOS – Asthma and COPD Overlap Syndrome

ACOS is defined as an obstructive lung condition with clinical and inflammatory features of asthma and COPD. There are several hypotheses about the etiopathogenesis of this clinical entity. According to the Dutch theory, asthmatics exposed to inhalants that cause COPD can develop ACOS, and COPD patients can develop asthma-like symptoms when sensitized to allergens. According to the British hypothesis, asthma and COPD are separate diseases from ACOS; the development of ACOS is related to pulmonary injury of early origin (prenatal or pediatric) combined with genetic and epigenetic factors (21).

GOLD and GINA have published a joint document where they suggest a diagnostic approach to ACOS, but it does not present actual criteria. According to them, the characteristics that support the diagnosis of ACOS are older than 40 years but reporting symptoms in childhood or later, the presence of respiratory symptoms, including dyspnea on exertion, airflow limitation that is not fully reversible, diagnosis of asthma and/or inhalant exposure, comorbidities affecting clinical and functional deterioration, COPD-like findings on X-ray, sputum eosinophilia, with or without neutrophils. Meanwhile, according to the Spanish Thoracic Society, the diagnosis of ACOS is confirmed by confirming the following 2 major criteria, or by fulfilling 1 major criterion and 2 minor criteria (Table 1) (22).

Table 1. Minor and major diagnostic criteria for ACOS.

Major	Minor
1. Bronchodilator test significantly positive (increased FEV1% > 15% and >400 ml)	1. High total IgE
2. Eosinophilia in sputum	2. Personal history of atopy
3. Personal history of asthma	3. Positive bronchodilator test (increase in FEV1 by at least 12% or 200 ml)

Discussion

Asthmatic patients often have co-morbidities that may directly or indirectly affect the level of therapeutic asthma control. For example, they may be responsible for the development or further evolution of a different asthma phenotype (as in the case of obesity, smoking, aspirin hypersensitivity and allergic bronchopulmonary aspergillosis), may be part of the same pathophysiological process (such as allergic rhinitis), may act as confounding factors in the diagnosis or therapeutic approach (obesity and obstructive sleep apnea) and/or may be associated with a specific factor or condition that may modulate the clinical presentation of asthma or affect efficacy/compliance with treatment (GERD, respiratory infections, smoking and psychopathologies such as stress and depression).

In this literature review, we briefly discussed some of those health conditions that coexist with severe bronchial asthma, which cannot be ignored when discussing a more comprehensive management of this pathology. In recent years, Fitzpatrick's (2020) definition, which qualifies asthma as a spectrum of co-existing disorders, is becoming more acceptable; considering it as a single disease is a reductionist point of view, which constitutes the main barrier against advances towards personalized treatment. (23)

Conclusion. Bronchial asthma coexists with many other health conditions, such as obesity, cardiovascular diseases, chronic rhinosinusitis with nasal polyps, autoimmune diseases etc., which are often overlooked. In order to have a more comprehensive management of this pathology, a diagnostic and therapeutic approach of the contributing factors and comorbidities, should be taken.

References

1. Rönnebjerg, Lina et al. "Severe Asthma in a General Population Study: Prevalence and Clinical Characteristics." Journal of asthma and allergy vol. 14 1105-1115. 16 Sep. 2021.
2. Tashiro H, Shore SA. Obesity and severe asthma. Allergol Int. 2019
3. Szentpetery SE, Han YY, Brehm JM, Acosta-Perez E, Forno E, Boutaoui N, et al. Vitamin D insufficiency, plasma cytokines, and severe asthma exacerbations in school-aged children. The journal of allergy and clinical immunology In practice 2018
4. Lin YL, Chen SH, Wang JY. Critical role of IL-6 in dendritic cell-induced allergic inflammation of asthma. Journal of molecular medicine 2016;94(1):51–9.
5. Peters MC, McGrath KW, Hawkins GA, et al. Plasma interleukin-6 concentrations, metabolic dysfunction, and asthma severity: a cross-sectional analysis of two cohorts [published correction appears in Lancet Respir Med. 2018 Mar;6(3):e10. doi: 10.1016/S2213-2600(18)30073-0]. *Lancet Respir Med*. 2016;4(7):574-584. doi:10.1016/S2213-2600(16)30048-0
6. Bokulich NA, Chung J, Battaglia T, et al. Antibiotics, birth mode, and diet shape microbiome maturation during early life. *Sci Transl Med*. 2016;8(343):343ra82. doi:10.1126/scitranslmed.aad7121
7. Pollevick ME, Xu KY, Mhango G, et al. The Relationship Between Asthma and Cardiovascular Disease: An Examination of the Framingham Offspring Study. Chest. 2021;159(4):1338-1345. doi:10.1016/j.chest.2020.11.053
8. Cazzola M, Hanania NA, Rogliani P, Matera MG. Cardiovascular disease in asthma patients: From mechanisms to therapeutic implications. Kardiol Pol. 2023;81(3):232-241. doi:10.33963/KP.a2023.0038
9. Pollevick ME, Xu KY, Mhango G, et al. The Relationship Between Asthma and Cardiovascular Disease: An Examination of the Framingham Offspring Study. Chest. 2021;
10. Venegas Garrido, Carmen et al. "Airway autoimmunity, asthma exacerbations, and response to biologics." Clinical and experimental allergy: journal of the British Society for Allergy and Clinical Immunology vol. 52,12,2022
11. Fuentes N, Silveyra P. Endocrine regulation of lung disease and inflammation. Exp Biol Med (Maywood). 2018;243(17-18):1313-1322. doi:10.1177/1535370218816653
12. Akdis CA. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions?. Nat Rev Immunol. 2021;21(11):739-751. doi:10.1038/s41577-021-00538-7
13. Yung JA, Fuseini H, Newcomb DC. Hormones, sex, and asthma. Ann Allergy Asthma Immunol. 2018;120(5):488-494. doi:10.1016/j.anai.2018.01.016
14. Ambhore NS, Kalidhindi RSR, Loganathan J, Sathish V. Role of Differential Estrogen Receptor Activation in Airway Hyperreactivity and Remodeling in a Murine Model of Asthma. Am J Respir Cell Mol Biol. 2019;61(4):469-480. doi:10.1165/rcmb.2018-0321OC

15. Zein JG, Erzurum SC. Asthma is Different in Women. Curr Allergy Asthma Rep. 2015;15(6):28. doi:10.1007/s11882-015-0528-y Klein DK, Silberbrandt A, Frøssing L, et al. Impact of former smoking exposure on airway eosinophilic activation and autoimmunity in patients with severe asthma. Eur Respir J. 2022;60(4):2102446. Published 2022 Oct 6. doi:10.1183/13993003.02446-2021
16. Calcaterra V, Nappi RE, Farolfi A, Tiranini L, Rossi V, Regalbuto C, Zuccotti G. Perimenstrual Asthma in Adolescents: A Shared Condition in Pediatric and Gynecological Endocrinology. Children (Basel). 2022 Feb 10;9(2):233. doi: 10.3390/children9020233. PMID: 35204953; PMCID: PMC8870409.
17. Skiba MA, Bell RJ, Islam RM, Handelsman DJ, Desai R, Davis SR. Androgens During the Reproductive Years: What Is Normal for Women?. J Clin Endocrinol Metab. 2019;104(11):5382-5392. doi:10.1210/jc.2019-01357
18. Bachert C, Bhattacharyya N, Desrosiers M, Khan AH. Burden of Disease in Chronic Rhinosinusitis with Nasal Polyps. J Asthma Allergy. 2021;14:127-134. Published 2021 Feb 11. doi:10.2147/JAA.S290424
19. Kisiel MA, Berglund C, Janson C, et al. Quality of life and asthma control related to hormonal transitions in women's lives. J Asthma. 2022;59(9):1869-1877. doi:10.1080/02770903.2021.1963768
20. Hulse KE, Stevens WW, Tan BK, Schleimer RP. Pathogenesis of nasal polyposis. Clin Exp Allergy. 2015;45(2):328-346. doi:10.1111/cea.12472
21. Human Nose. Available online: http://pngimg.com/uploads/nose/nose_PNG2.png (accessed on 12 March 2019).
22. Plaza V, Álvarez F, Calle M, et al. Consensus on the asthma-COPD overlap syndrome (ACOS) between the Spanish COPD guidelines (GesEPOC) and the Spanish guidelines on the management of asthma (GEMA). Arch Bronconeumol 2017
23. Fitzpatrick AM, Baena-Cagnani CE, Bacharier LB. Severe asthma in childhood: recent advances in phenotyping and pathogenesis. Curr Opin Allergy Clin Immunol. 2012;12(2):193-201. doi:10.1097/ACI.0b013e32835090ac

EXOSOMES — A NEW WINDOW OF HEALTH FROM DISEASE, TREATMENT, DIAGNOSIS, AESTHETICS, AND LIFESPAN

Migena Gega, Admir Nake, Klerida Shehu, Jonida Stefa, Orgeta Dervishi

Faculty of Medical and Technical Sciences, University of Medicine, Tirana, Albania.

Correspondence E-mail: migenagega@yahoo.com

Abstract

Exosomes are extracellular vesicles (30–200 nm) that come out of every cell. They include micro-vesicles and apoptotic bodies, and they are very important for communication between cells, epigenetic regulation, and sending messages close (paracrine function) or far away (endocrine function). Exosome era targets and promotes therapeutic and research approaches, from early laboratory or imagery biomarkers to monitoring of prognosis, even though they have not received the green light from the FDA (Food and Drug Administration).

Aim. Highlighting the characteristics and the windows that are opened by recent investigations of exosomes in many fields of medicine, diagnosis, laboratory biomarkers, preventive medicine, drug therapies, drug delivery, and cosmetics, including diagnosis and treatment of cancer.

Material and Methods. Recently, articles using words such as exosome, biogenesis, function, and structure, and phrases such as exosome and cancer, exosome and influencing factors", exosome in physiological condition, exosome and diseases, and artificial exosome

Results and Conclusions. Exosomes, as a "mirror of intracellular and membrane life" and "intracellular dynamics," show very early the status of a healthy or disease process happening in the organelles of cells, its "natural and social microenvironment," and are therefore a useful tool" for a new, efficient synergy of evidence-based medicine with personalized medicine, where the focus is not only on the disease but also on improving health status, aesthetics, anti-ageing, and lifespan.

Key words.: exosome, oncosome, nano-therapy, early biomarkers

EKZOZOMET - NJË DRITARE E RE SHËNDETI NGA SËMUNDJET, TRAJTIMI, DIAGNOZA, ESTETIKA DHE JETËGJATËSIA

Abstrakt

Eksozomet janë fshikëza ekstraqelizore, të madhësisë 30-200 nm, që dalin nga çdo qelizë, ku përfshihen gjithashtu mikrofshikëzat dhe trupat apoptotikë, të rëndësishme për komunikimin ndërqelizor, rregullimin epigjenetik dhe përcjelljen afër (funksioni parakrin) dhe në distancë (funksioni endokrin) të mesazheve biologjike, si në kushte normale edhe patologjike. "Era" e

eksozomeve synon dhe promovon shumë terapi dhe qasje hulumtuese nga kapja e hershme laboratorike ose imazherike, deri tek monitorimi prognostik, edhe pse nuk ka ende për to një dritë jeshile miratimi nga FDA.

Qëllimi: Theksimi i karakteristikave të eksozomeve dhe dritareve që hapen nga njohja e thellë dhe e duhur e tyre në fushën mjekësore, diagnostikuese, monitoruese, trajtuese, klinike, laboratorike, eksperimentale, farmaceutike, preventive, referuar studimeve më të fundit të literaturës.

Materiali dhe Metoda: Jane studiuar artikujt më të fundit duke përdorur fjalët "exosome," "biogenesis,"function," "structure" si edhe tog-fjalëshat : "exosome and cancer", "exosome and influencing factors", "exosome in physiological condition", "exosome and diseases", "artificial exosome"

Rezultate dhe Përfundime: Eksozomet "si pasqyrë e jetës qelizore" dhe "dinamizmit ndërqelizor" tregojnë shumë herët statusin e qelizsë së shëndoshë apo të sëmurë, "mikromjedisit nayral dhe social të saj", për rrjedhojë janë instrument i dobishëm për një hop të ri, një ndërthurje sa më efikase të "evidenced based medicine" me mjekësinë e personalizuar, ku fokusi është jo vetëm sëmundja, por edhe përmirësimi i statusit shëndetësor, estetik parandalimi i plakjes dhe jetëgjatësia.

Fjalë kyç. exozome, oncozome, nanoterapi, shenjues të hershëm

Introduction

The term exosome belongs to the beginning of the 1980s, although researched years earlier. Trams in 1981 was the first that used this term for extracellular vesicles, to which he attributed physiological and cellular elimination mechanisms (1). Meanwhile, in 1983, Pan and Johnstone observed the removal of transferrin receptors from reticulocytes, precisely through these extracellular vesicles (2, 3). These extracellular vesicles have a lipid membrane with transmembrane protein structures that, in addition to their structural role, play the role of receptors and messengers (1, 2, 4). Exosomes are formed and placed in homeostatic equilibrium as a result of the synergy between several biochemical pathways, such as the secretory, endocytic, recycling, retrograde, anterograde, and exosome release pathways (2, 5). Exocytosis begins with the activation of the endocytic pathway through two possible ways, well known as the clathrin-dependent pathway or the clathrin-independent pathway (6). Important actors of the exosomal substrate and their fate are also lysosomes, as well as the Golgi apparatus, in concert with the cell membrane that invaginates and ensures the exosomal lipid membrane (7,8).

Rab-5 and GTPases, with a pH presence of 6.5 and phosphatidylinositol, are the key regulators of the formation of what are called early endosomes (3). Rab7 and GTPases contribute to the formation of exosomes in the presence of a pH of 5.5. Also, Rab5-Rab7 actively maintain the biogenesis of endosomes (2,3). As F-actin forms near early endosomes with the help of annexins A2, moesin, and cortactin, the Arp2/3 complex moves on to the next step in making exosomes, which is the formation of mature multivesicular bodies. In this process, lysosomal hydrolases and SNARE proteins also contribute (2, 3). Certainly, this

process cannot be realised without the presence of the ESCRT sorting complex, the elements of which act sequentially. Meanwhile, without the presence of the ESCRT complex, the pathways of their formation, primarily involving ceramides and tetraspanins, also describe themselves (3). On the other hand, membrane fusion enables the formation of endo-lysosomes, which allows functional and structural interaction and the contribution of lysosomes in the further pathway of exosome formation, but also in the formation of what are called endosome-related organelles such as melanosomes into pigmented cells, alpha dense granules into platelets, Prader-Willi bodies into endothelial cells, or the formation of specialised lysosomes like melanocytes (3,4). The endosome-lysosome pathway can be affected by some genetic pathologies such as Chediak-Higashi and Hermansky-Pudlak (3,4). Anterograde and retrograde transport involve dynamic interaction with the Golgi apparatus and late endosomes (multivesicular bodies) (3,4). The aim of our study is highlighting the characteristics and the windows that are open by recent investigation of exosomes in many fields of medicine, diagnosis, laboratory biomarkers, preventive medicine, drug therapies, drug delivery, and cosmetics, including diagnosis and treatment of cancer.

Materials and methods

This is a narrative review, with updating purpose, referred recent literature of international prestigious journals, using title of articles that include words such as exosome, biogenesis, function, and structure, and phrases such as exosome and cancer, exosome and influencing factors", exosome in physiological condition, exosome and diseases, and artificial exosome.

Main including criteria:

1. Article published during two recent years, 2023 and 2024 in prestigious journals and prestigious platforms, such as Frontier Medicine, Elsevier, PubMed 2. Only one reference belongs to 2019 because it is a PhD thesis and include clear surprisingly useful scientific information about exosome.

2. We selected firstly articles that explain terminology of exosome, published in these prestigious journals.

3. Article that realize clarification of relation structure-function and dynamism or "versions of life" of exosome. 4. Article that explain role of exosome in health and disease, and field of dermatology 5. Owing to the aim of this article and title we investigate articles that explain role of exosomes in diagnosis, therapy and lifespan. Asking question if exosome have other attributes we saw their role in contemporary medicine aspects such are attributes of early biomarkers, new drugs or route for therapy. Following this point of view, promptly derive logical questions: Are exosome FDA approved and which is trend of expenses to realize that exosome are really an hot spot and new window of medicine or just only an illusion or just still far from the applied stage?

Excluding criteria:

1. Article before 2023, respecting update purpose

2. At about 100 articles are studied but are excluded because were before 2023, or part of other fields of studies in medicine or our highlighted focus.

Results

Terminology. The size of exosomes, exosome-linked vesicles, and artificial exosomes. Exosomes, from their inception until their incorporation into the target cell, are found with the status of exosomes 30-200 nm, vesicles with sizes of 200-1000, and apoptotic bodies with sizes of 1000-5000 (1- 5). In contrast, ectosomes, unlike exosomes, are vesicles 100-1000 nm in size that exit directly into the extracellular environment, without intracellular interactions, and therefore structurally do not interact and exchange with the Golgi apparatus, lysosomes, or the intracellular environment, having a different structural composition (1-5).

Amphisomes are hybrid organelles resulting from the fusion of autophagosomes with late exosomes at the intracellular level (2, 9-11, 13). Exosomes derived from cancer cells are larger, over 1000-10000 nm, and are called oncosomes (5, 10, 12, 13).

Migrasomes are a variant of exosomes with sizes of 500-3000 nm, with a maximum presence of about 400 min, mainly consisting of structural proteins, RNA, organelles, and a number of smaller vesicles. The formation of migrasomes is influenced by the phosphatidylinositol (3,4) bisphosphate-Rab 35 pathway, as well as by pH and temperature, but also, like exosomes, by some viruses and drugs. The formation, rupture, and release of migrasomes (migracytosis) remain to be studied (10, 11).

Exomers are smaller than 50 nm, and supermers are smaller than 30 nm, and the way they are formed is unknown (10, 11). Artificial exosomes (synthetic nanoparticles) have also become part of the industrial market of exosomes and have seen rapid development in recent decades. These include liposomes, micelles, dendrimers, nanocapsules, nanoemulsions, nanodiamonds, nanosponges, and self-assembled peptides, studied especially for targeted cancer therapy (13- 15).

Actors of exosomes are responsible for completing the structural "puzzle."

Action scenes and the exosomal actors' pathways are the intracellular environment, the extracellular environment, biological fluids (blood, urine, plasma, saliva, cerebrospinal fluid), tumour microenvironment, healthy cells of the body, and cells under pathological conditions, including cancer cells (27, 28, 9, 13-15). So, if we look at exosomes through an electronic microscope, we can see that they are made up of plasma membrane components from the ones that come from inside cells, the Golgi apparatus, and lysosomes, which form vesicles like early and late endosomes (2,3). Also, plasma components anchored to the surface of exosomes are part of their structure and can either speed up or slow down the delivery of their message to the target cell. Therefore, the composition of exosomes depends on the nature of the cell components (membrane, lysosomes, Golgi apparatus) from which they originate, as well as the modulation they undergo during the transition through all stages, from biogenesis to the target cell (host) with extracellular components, as well as plasma components (3, 17, 18). Cells that produce exosomes at the highest rate are cancer cells, called oncosomes (2, 9,18). Among non-cancerous cells are platelets, dendritic cells, T lymphocytes, and B lymphocytes. The rate of exosome production is also studied under

experimental conditions, with cell lines aimed at applying exosome-producing "machines" as therapies, from cancer to cosmetic goals (10, 14).

- Main components of exosomes

RNA, DNA fragments, tetraspanins, annexins, protein biomarkers, transcription factors, metabolites, and different miRNAs make up most of exosomes. Exosomes have heat shock proteins, antigen-presenting proteins, glycoproteins, adhesion molecules, cytoskeletal proteins, ESCRT (endosomal sorting complex required transport), growth factors, and cytokines (2,5). Exosomes also have lipid structures such as cholesterol, phosphatidic acid, ceramide, sphingomyelin, phosphatidylinositol, phosphatidylserine, phosphatidylcholine, phosphatidylethanolamine, and gangliosides. Mitochondria can also be found in exosomes (2, 3).

- Some factors influence the rate of exosome production.

Exosomal and endosomal factors

The promotion of exosome production and their arrival in the target cell is multifactorial. Factors are biological, biochemical, intracellular, or extracellular; natural or unnatural (in experimental artificial conditions) (2,3). A lot of people talk about how important it is for exosome production (initiation) and modulation that contact is blocked, Rab homeostasis, or Ral, especially Rab 27A and Rab 27B, or the dynamic balance between Rab 27 and Rab 7. What makes up exosomes determines whether early endosomes are taken over by lysosomes or move on to become exosomes (2,3). The rate of glycosylation (N-linked glycosylation), the degree of interaction with the Golgi apparatus, and oligomerisation condition the production of exosomes in the respective cell and their transport to the target cells. Therefore, syndecan, heparan sulphates, proteoglycans, and cytoplasmic adaptors such as syntenin play the role of mediators in the biogenesis of exosomes (2,3). Complex lipids such as ceramides, phosphatidylserine, phosphatidylethanolamine, and phosphatidic acid promote exosome production, and through their structural addition or subtraction, exosome homeostasis is also modulated (2,3, 12).

Cholesterol is also an important lipid in the rate of exosome production. Endogenous vesicles play a significant role in the potential exosome production pathway. If they are rich in cholesterol, they enter the exosome production pathway, and if they are poor in cholesterol, they are sequestered by lysosomes (15, 16). Cellular stress, hypoxia, inflammation, and hypoglycemia condition the protein composition and RNA components of exosomes.

Extracellular factors influencing the degree of exosome expression

pH, or Ca++. ionophores, hypoxia, hormonal modulation (it is now accepted that hormones can also be transmitted through exosomes), circadian rhythm hormones, and temperatures are external factors influencing the inhibition or continuation of exosome production (2,3, 17). Important studied hormones that give impact in exosome production are cortisol, while oestradiol stimulates specific miRNA exosomes in breast cancer, and as a synergistic partner, exosomes have circadian rhythm hormones such as melatonin (8, 13).

Discussion

There is still a lot of potential for exosomes and a significant amount of work to be done in order to find as many applications as possible. Nevertheless, it is worth highlighting some modern approaches to them.

- Exosomes, Dermatology, and Longevity

One of the clinical areas that has turned attention to exosomes is dermatology, especially aesthetic dermatology, which is already an important part of it and has developed vigorously, especially during recent years. People now view exosomes as a form of regenerative therapy (8,18,19). For example, various dermatoses can be treated with ointments containing exosomes, which bring re-epithelialization and regulate cutaneous inflammation (20). After clinical cutaneous aspects such as ichthyosis, eruptions, cutis lesions, skin thickening-lipodystrophy, hypopigmentation, hyperpigmentation, and hair loss, the dynamism of exosomes (vesicular trafficking) can be hidden, a consequence of certain genetic alterations (10, 20). Exosomes are seen as very useful for increasing human lifespan; why not for other living beings? For example, various miRNAs, such as miRNA 335 and miRNA-34, modulate the lifespan of mesenchymal cells by inhibiting the action of enzymes such as superoxide dismutase and thioredoxin reductase, enzymes that contribute to oxidative stress, thus the instability of the respective organelles (17, 21, 22) Exosomes are seen as aesthetic dermatological applications; for example, ointments based on exosomes applied with laser therapy are more effective than laser therapy alone, for example, in melanin indexes, skin wrinkles, skin radiance, or photo-ageing (7). Many other diseases in other organs can result precisely from the jeopardized dynamism of exosomes, a consequence of certain genetic alterations (10). Such as hepatosplenomegaly, cardiomyopathies, acute renal failure, tubulopathies, cataracts, retinopathies, and corneal anomalies, may also have genetic alterations as the cause, already studied and confirmed to bring the jeopardizing of exosome dynamics (vesicular trafficking) (10, 13). Studies according to Lang et al. say that SIRT-4 proteins affect mitochondrial homeostasis, and meanwhile miRNA-15b is the one that modulates SIRT-4, influencing lifespan (17, 21, 22).

- Exosomes and the spread of diseases in organisms

Exosomes can influence the inhibiting or promoting development of many diseases. Exosomes influence disease spread; for example, viral diseases are more spectacular, and the spread of the cancer process (1, 2, 4, 9, 13). Exosomes during the cancer process influence invasion, metastasis, neovascularisation, and angiogenesis (13).

- Exosome, early and prognostic laboratory biomarkers"

Since the initial mechanisms of the disease serve to find "early biomarkers," an in-depth study of the mechanism of spread directly contributes to finding new therapies and "prognostic biomarkers" (13). Moreover, the intertwining of bioinformatics and artificial intelligence with the latest advances in exosomes aims at applying biosensors for miRNA exosomes, representative with value for capturing early cancer processes (24- 26).

- Exosome Machinery and the Pharmaceutical Industry

On the other hand, the pharmaceutical industry is increasingly developing an "exosome machinery," an exosome industry with continuous and high production rates. According to economic reports on the exosome research market, the trend of predictions for the money spent in function of this industry until 2028 is exponential, from 148 million in 2022 and 169 million in 2023 to 356 million in 2028. As a matter of fact, research studies conducted over the past decade on exosomes have also seen exponential growth (27-31). The current trend is their use in nanotechnology, molecular diagnostics, cardiovascular diseases, pharmaceutical purposes, neurodegenerative diseases, biotechnology, diagnostics, and cancer research (32, 36). The future trend is their use together with artificial intelligence in drug discovery, "point of care" tests, telemedicine, CAR-T cell therapy, nanorobotics, microfluidics, and 3D bioprinting (37-39). The study of partners of exosomes in therapeutic approaches has resulted in many synergistic tangos, such as the potentiation of melatonin-exosome effects in anticancer and anti-inflammatory processes and the slowing of degenerative processes, embryonic development, renal insufficiency, wound healing, and liver lesions (40).

- Exosomes: A New Way for Drug Administration

Moreover, the use of artificial exosomes (synthetic nanoparticles) as an effective and maximally efficient way of transmitting drugs directly to the center of action or target cell is now seen as an optimal and new way of direct bar passage, minimizing the effect of "drug loss," side effects, or complications, as occurs in classic routes such as oral, muscular, or intravenous (40).

Conclusions

Exosomes, as a "mirror of intracellular and membrane life" and "intracellular dynamics," show very early the status of a healthy or disease process happening in the organelles of cells, its "natural and social microenvironment," and are therefore a useful tool" for a new, efficient synergy of evidence-based medicine with personalized medicine, where the focus is not only on the disease but also on improving health status, aesthetics, anti-ageing, and lifespan.

References

1. MacDonald E, Salem N Jr. Dr. Eberhard Trams-The man who coined the name "exosomes"-A prescient but largely forgotten pioneer. J Extracell Vesicles. 2023;12(10):e12370. doi:10.1002/jev2.12370
2. Wang Y, Xiao T, Zhao C, Li G. The Regulation of Exosome Generation and Function in Physiological and Pathological Processes. Int J Mol Sci. 2023;25(1):255. Published 2023 Dec 23. doi:10.3390/ijms25010255
3. Roberta Palmulli. Role of CD63 in the biogenesis and the function of exosomes. Cellular Biology. Université Paris Cité, 2019. English. ffNNT : 2019UNIP5033ff. fftel-03969520f
4. Koh HB, Kim HJ, Kang SW, Yoo TH. Exosome-Based Drug Delivery: Translation from Bench to Clinic. Pharmaceutics. 2023 Jul 29;15(8):2042. doi: 10.3390/pharmaceutics15082042.
5. Kumar MA, Baba SK, Sadida HQ, et al. Extracellular vesicles as tools and targets in therapy for diseases. Signal Transduct Target Ther. 2024;9(1):27. Published 2024 Feb 5. doi:10.1038/s41392-024-01735-1

6. Gupta D, Wiklander OPB, Wood MJA, El-Andaloussi S. Biodistribution of therapeutic extracellular vesicles. Extracell Vesicles Circ Nucl Acids. 2023;4(2):170-190. Published 2023 Apr 19. doi:10.20517/evcna.2023.12
7. Wang CK, Tsai TH, Lee CH. Regulation of exosomes as biologic medicines: Regulatory challenges faced in exosome development and manufacturing processes. Clin Transl Sci. 2024;17(8):e13904. doi:10.1111/cts.13904
8. Ram Kumar RM, Logesh R, Joghee S. Breast cancer derived exosomes: Theragnostic perspectives and implications. Clin Chim Acta. 2024;557:117875. doi:10.1016/j.cca.2024.117875
9. Wang W, Sun H, Duan H, et al. Isolation and usage of exosomes in central nervous system diseases. CNS Neurosci Ther. 2024;30(3):e14677. doi:10.1111/cns.14677
10. Xie J, Zheng Z, Tuo L, et al. Recent advances in exosome-based immunotherapy applied to cancer. Front Immunol. 2023;14:1296857. Published 2023 Nov 7. doi:10.3389/fimmu.2023.1296857
11. Wang J, Yue BL, Huang YZ, Lan XY, Liu WJ, Chen H. Exosomal RNAs: Novel Potential Biomarkers for Diseases-A Review. Int J Mol Sci. 2022;23(5):2461. Published 2022 Feb 23. doi:10.3390/ijms23052461
12. Wang Y, Jiang M, Zheng X, et al. Application of exosome engineering modification in targeted delivery of therapeutic drugs. Biochem Pharmacol. 2023;215:115691. doi:10.1016/j.bcp.2023.115691
13. Reiss AB, Ahmed S, Johnson M, Saeedullah U, De Leon J. Exosomes in Cardiovascular Disease: From Mechanism to Therapeutic Target. Metabolites. 2023;13(4):479. Published 2023 Mar 27. doi:10.3390/metabo13040479
14. Zanirati G, dos Santos PG, Alcará AM, Bruzzo F, Ghilardi IM, Wietholter V, Xavier FAC, Gonçalves JIB, Marinowic D, Shetty AK, et al. Extracellular Vesicles: The Next Generation of Biomarkers and Treatment for Central Nervous System Diseases. International Journal of Molecular Sciences. 2024; 25(13):7371. https://doi.org/10.3390/ijms25137371.
15. Xie J, Zheng Z, Tuo L, et al. Recent advances in exosome-based immunotherapy applied to cancer. Front Immunol. 2023;14:1296857. Published 2023 Nov 7. doi:10.3389/fimmu.2023.1296857
16. Li, J., Wang, J. & Chen, Z. Emerging role of exosomes in cancer therapy: progress and challenges. Mol Cancer **24**, 13 (2025). https://doi.org/10.1186/s12943-024-02215-4
17. Rodriguez C, Porcello A, Chemali M, Raffoul W, Marques C, Scaletta C, Lourenço K, Abdel-Sayed P, Applegate LA, Pelissier Vatter F, et al. Medicalized Aesthetic Uses of Exosomes and Cell Culture-Conditioned Media: Opening an Advanced Care Era for Biologically Inspired Cutaneous Prejuvenation and Rejuvenation. Cosmetics. 2024; 11(5):154. https://doi.org/10.3390/cosmetics11050154
18. Vyas KS, Kaufman J, Munavalli GS, Robertson K, Behfar A, Wyles SP. Exosomes: the latest in regenerative aesthetics. Regen Med. 2023;18(2):181-194. doi:10.2217/rme-2022-0134
19. Li, J., Wang, J. & Chen, Z. Emerging role of exosomes in cancer therapy: progress and challenges. Mol Cancer **24**, 13 (2025). https://doi.org/10.1186/s12943-024-02215-4
20. Wang M, Shu H, Cheng X, et al. Exosome as a crucial communicator between tumor microenvironment and gastric cancer (Review). Int J Oncol. 2024;64(3):28. doi:10.3892/ijo.2024.5616

21. Reiss AB, Ahmed S, Johnson M, Saeedullah U, De Leon J. Exosomes in Cardiovascular Disease: From Mechanism to Therapeutic Target. Metabolites. 2023;13(4):479. Published 2023 Mar 27. doi:10.3390/metabo13040479
22. Sen S, Xavier J, Kumar N, Ahmad MZ, Ranjan OP. Exosomes as natural nanocarrier-based drug delivery system: recent insights and future perspectives. 3 Biotech. 2023;13(3):101. doi:10.1007/s13205-023-03521-2
23. Kumar, M.A., Baba, S.K., Sadida, H.Q. et al. Extracellular vesicles as tools and targets in therapy for diseases. Sig Transduct Target Ther **9**, 27 (2024). https://doi.org/10.1038/s41392-024-01735-1
24. Drula R, Pardini B, Fu X, et al. 17β-estradiol promotes extracellular vesicle release and selective miRNA loading in ERα-positive breast cancer. Proceedings of the National Academy of Sciences of the United States of America. 2023 Jun;120(23):e2122053120. DOI: 10.1073/pnas.2122053120. PMID: 37252969; PMCID: PMC10266002
25. Chu X, Hou M, Li Y, Zhang Q, Wang S and Ma J (2024) Extracellular vesicles in endometriosis: role and potential. Front. Endocrinol. 15:1365327. doi: 10.3389/fendo.2024.1365327
26. Romero-García N, Mas-Bargues C, Huete-Acevedo J, Borrás C. Extracellular Vesicles and Cellular Ageing. Sub-cellular Biochemistry. 2023 ;102:271-311. DOI: 10.1007/978-3-031-21410-3_11. PMID: 36600137.
27. Perpiñá-Clérigues, C., Mellado, S., Català-Senent, J.F. et al. Lipidomic landscape of circulating extracellular vesicles isolated from adolescents exposed to ethanol intoxication: a sex difference study. Biol Sex Differ **14**, 22 (2023). https://doi.org/10.1186/s13293-023-00502-1
28. Perpiñá-Clérigues C, Mellado S, Galiana-Roselló C, et al. Novel insight into the lipid network of plasma extracellular vesicles reveal sex-based differences in the lipidomic profile of alcohol use disorder patients. Biol Sex Differ. 2024;15(1):10. Published 2024 Jan 25. doi:10.1186/s13293-024-00584-5
29. Zeng K, He H, Lv Z, et al. Profiling of circulating serum exosomal microRNAs in elderly patients with infectious stress hyperglycaemia. Clin Transl Disc. 2023; 3:e205. https://doi.org/10.1002/ctd2.205
30. Rasti M, Parniaei AH, Dehghani L, et al. Enhancing the wound healing process through local injection of exosomes derived from blood serum: An in vitro and in vivo assessment. Regen Ther. 2024;26:281-289. Published 2024 Jun 19. doi:10.1016/j.reth.2024.06.004
31. Qi R, Wang Y, Yan F, Zhong J. Exosomes derived from ITGB1 modified Telocytes alleviates LPS-induced inflammation and oxidative stress through YAP1/ROS axis. Heliyon. 2024;10(5):e27086. Published 2024 Mar 8. doi:10.1016/j.heliyon.2024.e27086
32. Martínez-Espinosa I, Serrato JA, Cabello-Gutiérrez C, Carlos-Reyes Á, Ortiz-Quintero B. Exosome-Derived miRNAs in Liquid Biopsy for Lung Cancer. Life. 2024; 14(12):1608. https://doi.org/10.3390/life14121608
33. Metcalf GAD. MicroRNAs: circulating biomarkers for the early detection of imperceptible cancers via biosensor and machine-learning advances. Oncogene. 2024;43(28):2135-2142. doi:10.1038/s41388-024-03076-3
34. Tang, H., Yu, D., Zhang, J. et al. The new advance of exosome-based liquid biopsy for cancer diagnosis. J Nanobiotechnol **22**, 610 (2024). https://doi.org/10.1186/s12951-024-02863-0

35. Shin H, Choi BH, Shim O, et al. Single test-based diagnosis of multiple cancer types using Exosome-SERS-AI for early stage cancers. Nat Commun. 2023;14(1):1644. Published 2023 Mar 24. doi:10.1038/s41467-023-37403-1
36. Li B, Kugeratski FG, Kalluri R. A novel machine learning algorithm selects proteome signature to specifically identify cancer exosomes. Preprint. bioRxiv. 2023;2023.07.18.549557. Published 2023 Dec 20. doi:10.1101/2023.07.18.549557
37. Baghban N, Kodam SP, Ullah M. Role of CD9 Sensing, AI, and Exosomes in Cellular Communication of Cancer. Int J Stem Cell Res Ther. 2023;10(1):079. doi:10.23937/2469-570X/1410079
38. Sharma P, Roy A, Dhamija RK, et al. A comprehensive proteomic profiling of urinary exosomes and the identification of early non-invasive biomarker in patients with coronary artery disease. J Proteomics. 2024;293:105059. doi:10.1016/j.jprot.2023.105059
39. Banavar, G., Ogundijo, O., Toma, R. et al. The salivary metatranscriptome as an accurate diagnostic indicator of oral cancer. npj Genom. Med. **6**, 105 (2021). https://doi.org/10.1038/s41525-021-00257-x
40. Kim, H.I., Park, J., Zhu, Y. et al. Recent advances in extracellular vesicles for therapeutic cargo delivery. Exp Mol Med **56**, 836–849 (2024). https://doi.org/10.1038/s12276-024-01201-6

COLORECTAL CANCER OR INFLAMMATORY BOWEL DISEASE?

IrgenTafaj, Frosilda Kola

Service of Gastroenterology-Hepatology, University Hospital Center "Mother Teresa", Tirana, Albania

Correspondent E-mail: irgentafaj@yahoo.com

Abstract

Introduction: Inflammatory bowel disease can have multiple and atypical endoscopic appearances that sometimes can mimic other types of colitis or even colorectal cancer. Ruling out malignancy in these cases might be challenging.

Case report: A 60 years old, female patient without medical antecedents, presented at ER for severe abdominal pain in the right lower quadrant and recent constipation. Blood tests showed slightly elevated inflammatory markers. Colonoscopy revealed a polypoid lesion in proximal ascending colon, macroscopically compatible with a colon cancer. The ileocecal region was impossible to explore. Multiple biopsies were taken. CT scan showed circumferential thickening of the colon walls in caecum and proximal part of ascending colon, which is contrasted after IV contrast injection, slight densification of locoregional adipose tissue and millimetric locoregional lymph nodes. CA 19-9, CEA were normal. Pathology findings were lympho-plasmocytic inflammation in lamina propria, as well as micro abscesses in the crypts. Reactive changes in some crypts with inflammatory background were observed. No malignancy was detected. Pathology findings are compatible with IBD and the patient was put under treatment by corticosteroid-therapy and 5-ASA. A control colonoscopy was performed 3 months later, biopsies of the remained lesion were taken and the diagnosis of Crohn's disease was reconfirmed.

Conclusion: Atypically short, segmentary, isolated location in the colon of IBD can easily be misdiagnosed as colon cancer. In IBD, therapeutic test, repeated colonoscopies with biopsies take precedence over surgical resection for the diagnosis.

Keywords: Inflammatory bowel disease, atypical Crohn's disease, colorectal cancer

KANCERI KOLOREKTAL APO SËMUNDJA INFLAMATORE E ZORRËS?

Abstrakt

Hyrje: Sëmundja Inflamatore e Zorrës (SIZ) shfaqet me paraqitje endoskopike të larmishme dhe atipike që shpeshherë mund të imitojnë kolitet me etiologji të ndryshme, madje dhe kancerin kolorektal. Përjashtimi i malinjancës në këto raste mund të jetë sfidues.

Rast Klinik: Një paciente femër 60 vjeç, pa të dhëna për probleme shëndetësore të mëparshme, paraqitet në Shërbimin e Urgjencës me ankesat dhimbje abdominale të forta dhe konstipacion prej disa javësh. Ekzaminimet laboratorike paraqesin rritje të lehtë të markuesve të inflamacionit. Pacientja iu nënshtrua kolonoskopisë ku u evidentua një lesion polipoid i kolonit ascendent proksimal, makroskopikisht kompatibël me kancer koloni. Regjioni ileocekal ishte i pamundur të eksplorohej. U morën materiale multiple për biopsi. Në skanerin abdominal u vërejt trashje cirkumferenciale e mureve të kolonit në cekum dhe pjesën proksimale të kolon ascendent, që kontrastohej pas kontrastit intravenoz, densifikim i lehtë i indit adipoz lokoregjional dhe limfonoduj milimetrik lokoregjional. Markuesit tumoralë CA19-9, CEA ishin normal. Në ekzaminimin histopatologjik të mostrës rezultoi inflamacion limfo-plazmocitar i lamina propria, mikroabcese të kripteve, pa atipi qelizore. Të dhënat histopathologjike janë në përputhje me Sëmundjen Inflamatore të Zorrës. Pacientes i fillohet trajtimi me kortikoterapi dhe 5-ASA. Kolonoskopia e rikontrollit u realizua pas 3 muajsh dhe u morën sërisht biopsi multiple, që rikonfirmuan diagnozën e Morbus Crohn.

Konkluzion: Sëmundja Inflamatore e Zorrës me prekje segmentare, të shkurtër, atipike të kolonit mund të ngatërrohet lehtësisht me kancerin kolorektal. Në SIZ, testi terapeutik, kolonoskopitë e përsëritura me biopsi kanë përparësi në raport me rezeksionin kirurgjikal për vendosjen e diagnozës.

Fjalë kyçe: Sëmundja inflamatore e zorrës, Morbus Crohn atipik, Kanceri kolorektal

Introduction

Inflammatory bowel diseases (IBD) are chronic immune-mediated diseases with their onset usually during young adulthood and a lifelong course characterized by periods of remission and relapse. The two main forms of IBD are Crohn’s Disease (CD) and Ulcerative Colitis (UC). Crohn’s disease can involve any part of the gastrointestinal tract, but most commonly the ileum and proximal colon. It is represented histologically by chronic discontinuous inflammatory infiltrates with transmural involvement. In contrast, ulcerative colitis, despite having significant shared genetic risk with Crohn’s disease, is characterized primarily by continuous inflammatory lesion that is limited to the submucosa and is restricted to involvement of the colon alone, often with its onset in the rectum and more proximal extension (1). Crohn's disease is a form of IBD with multifactorial pathogenesis involving genetic predisposition, defects in the gut epithelial barrier, dysregulated immune response, and environmental factors. In Crohn's disease, the inflammatory process has a transmural extension that is associated with involvement of the serosa and peri-intestinal adipose tissue (2). It can affect any part of the gastrointestinal tract from the mouth to the anus; 30% of patients present with strict involvement of the small intestine, 20% with involvement of the colon alone, and 50% with involvement of both the small and the large intestine. Crohn’s disease is most commonly seen in the Western developed world. Its incidence has a bimodal distribution with the onset occurring most frequently between ages 15 to 30 years and 40 to 60 years old, more prominent in urban than rural areas (3).

IBD presents with endoscopic appearances of various, atypical forms that can often be confused with colorectal cancer (CRC) (4). Sometimes Crohn's disease and colon cancer might have very similar endoscopic characteristics and it becomes a real challenge for the

clinician to make the right diagnosis (5). Epidemiological and pathological data also indicate that Crohn's disease is associated with a high risk of dysplasia and colorectal cancer, further complicating the differential diagnosis of whether it is a "de novo" malignancy or malignant transformation of Crohn's disease (6).

In this report, an atypical case of Crohn's disease will be described, detailing the clinical course of a female patient, who presented with persistent abdominal pain and constipation.

Case Report

A 60 years old, female patient without medical antecedents, presented at the Emergency Department for severe abdominal pain in the right lower quadrant and recent constipation. She has tried antispasmodic treatment, without effect. The abdominal ultrasound was normal. Colonoscopy performed 3 days later showed a polypoid lesion in proximal ascending colon, macroscopically compatible with a colon cancer. The ileocecal region was impossible to explore, because of this stenotic lesion. Multiple biopsies were taken. The rest of the colon was normal. The necessary laboratory examinations were done and showed slightly elevated inflammatory markers, level of fecal calprotectin 270.79mg/kg, tumor markers CEA, CA19-9 were normal.

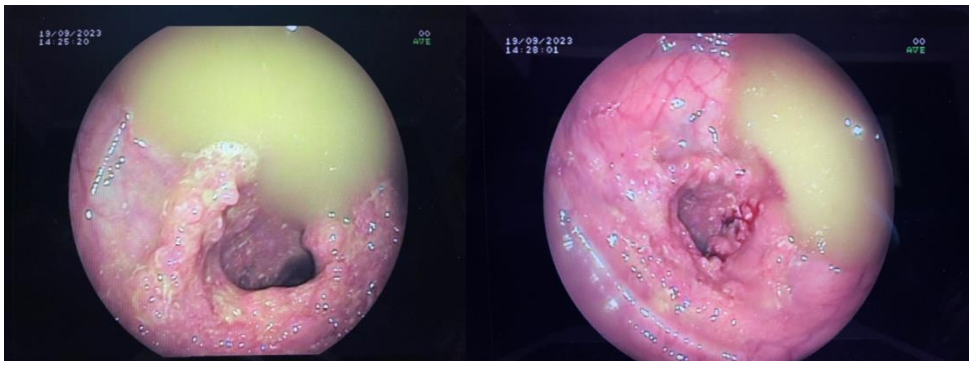


Figure 1. Colonoscopy 1: Polypoid lesion in proximal ascending colon, macroscopically compatible with colon cancer.

CT scan showed circumferential thickening of the colon walls in caecum and proximal part of ascending colon, which enhances after IV contrast injection, slight densification of locoregional adipose tissue and millimetric locoregional lymph nodes. The rest of the colon is normal. Histological description of the biopsy shows lympho-plasmocytic inflammation in lamina propria, as well as micro abscesses in the crypts. Reactive changes in some crypts with inflammatory background were observed. No malignancy was detected. Pathology findings are compatible with IBD and the patient was put under treatment by corticosteroid-therapy and 5-ASA.



Figure 2. CT scan: circumferential, regular thickening of the colon walls of the cecum and proximal ascending colon, with contrast enhancement and densification of locoregional adipose tissue.

A control colonoscopy was performed 3 months later. The lesion has transformed into a short fibrotic stricture, which allows the passage of the endoscope and the exploration of the ileocecal region. The terminal ileum was normal, but linear and cicatricial lesions were found in the caecum. Biopsies of the remained lesion were taken and the histological description shows fragments of the colonic mucosa with irregular cryptic architecture, focally mild dysplasia but without evidence of invasive or “in situ” malignancy.



Figure 3. Fibrotic stricture of ascending colon.



Figure 4. Cicatricial lesions of caecum

Based on the results of the examinations and the clinical and endoscopic response to the treatment, the diagnosis of Crohn's colitis, was reconfirmed. After ruling out any possibility of malignancy, the patient was put under treatment with immunosuppressors and regular follow-up was suggested to her.

Discussion

Crohn's disease and colorectal cancer are colon diseases, that sometimes are difficult to distinguish from one another, not only clinically but also from the macro-endoscopic appearance.

Microscopically, Crohn's disease is characterized by transmural inflammatory thickening of the caecum with inflammatory infiltrates composed mainly of lymphocytes and plasma cells (2).

Macroscopically, it is characterized by inflammatory mucosal lesions interrupted by areas of normal mucosa. The mucosa of inflammatory lesions presents with diverse forms such as mucosal hyperemia, superficial erosions, ulcerations, thickening of the mucosal folds, strictures, fibrosis, fistulas. Ulcers are morphologically described as aphthous, linear, or stellate. Small aphthous ulcers often found near lymphoid follicles coalesce to form larger, deeper linear ulcers with hanging mucosal margins, creating the characteristic "cobblestone appearance" of the mucosa (7). Over time, healing of the ulcers may leave fibrotic scars and, as in ulcerative colitis, inflammatory polyps may form. In complex cases, fissures and fistulous tracts, and intermural or abdominal abscesses, may develop, which are a typical feature of Crohn's disease. In atypical forms, Crohn's disease presents as a vegetative lesion, with circular, fibrotic, bleeding strictures (8). Among the various presentations of Crohn's disease, "pseudopolypoid" CD is a rare occurrence. The exact frequency or prevalence of this form is not well documented in the medical literature due to its rarity (9).

This atypical subtype presents as localized mass within the gastrointestinal tract, often mimicking the appearance of colorectal carcinoma. The main characterizing features behind the pathophysiology of tumefactive, pseudopolypoid Crohn's disease, are cyclical periods of flares and remissions in which inflammation is a key factor. As a result of remitting clinical course, with repeating episodes of exacerbations and remissions, post-inflammatory polyps (pseudopolyps) develop in approximately 10–20% of IBD patients. Pseudopolyps can present as solitary or multiple, of various sizes, and either localized or diffuse in terms of distribution. Pseudopolyposisis usually associated with more severe and longer duration of IBD (9).

In Crohn's disease, patients have a three-fold higher risk of colorectal cancer than the normal population as a result of chronic mucosal inflammation, expressed regeneration of epithelial cells and expressed sporadic mutations (9). The molecular pathway leading to colorectal cancer in IBD appears to differ from the *adenoma-to-CRC* sequences. These cancers appear to arise from either flat dysplastic tissue or dysplasia-associated lesions or masses. The risk of CRC for patients with IBD increases by 0.5-1% yearly, 8-10 years after diagnosis (11).

The case of our patient is one of the rare forms of presentation of Crohn's disease, the polypoid form of Crohn's colitis. The short polypoid, stenotic, bleeding lesion, limited to the right colon, in a patient with no previous medical history are elements in favor of colorectal cancer diagnosis. The histological examination in this case was crucial in the diagnosis and it made a surprising plot twist. It showed fragments of the colonic mucosa with pronounced lympho-plasmocytic inflammation in the lamina propria as well as pronounced micro-abscesses in the crypts, reactive changes of some crypts in the background of inflammation, but without cellular atypia, suggesting the diagnosis of Crohn's disease. The histological examination was reconfirmed a second time and repeated endoscopic examination were performed to exclude any possibility of malignancy. The therapeutic test was also in favor of atypical form of Crohn's disease, the lesion changed dramatically under anti-inflammatory drugs, leaving inflammatory scars in the caecum, characteristic of remission phase in inflammatory bowel disease.

Based on the data of clinical case similar studies and the scientific literature, in patients with a short clinical history of inflammatory disease, with a segmentary lesion limited to the right colon, should exclude the possibility of a "de novo" malignancy or on pre-existing inflammatory disease (10). To achieve this challenging differential diagnosis, a detailed

evaluation of clinical features, laboratory, imaging, endoscopic and histological examinations by a multidisciplinary medical team is required.

Conclusion

Crohn's disease has different endoscopic presentations, including atypical forms. Atypically short, segmentary, isolated location in the colon of inflammatory bowel disease can easily be misdiagnosed as colon cancer. The case highlights the importance of considering pseudopolypoid Crohn's colitis in the differential diagnosis of patients presenting with abdominal pain and what appears to be a colonic mass. In inflammatory bowel disease, therapeutic tests, repeated colonoscopies with biopsies take precedence over surgical resection for the diagnosis.

Conflict of interest: None

References

1. Timothy C. Wang, M.Camilleri, B.Lebwohl, K.K. Wang, - Yamada's Textbook of Gastroenterology, 7th Edition/1232
2. Sleisenger and Fordtran's Gastrointestinal and Liver -- Mark Feldman MD, Lawrence S_ Friedman MD, Lawrence J_ Brandt -- 11, 2020 – Elsevier/1897
3. Baumgart DC, Sandborn WJ. Crohn's disease [published correction appears in Lancet. 2013 Jan 19;381(9862):204]. Lancet. 2012;380(9853):1590-1605. doi:10.1016/S0140-6736(12)60026-9
4. Crohns colitis foundation.org/education-resources/ibd-mimics-most-common-conditions-misdiagnosed-ibd-Jan 2020
5. Chen, W., Chao, S., & Wang, M. (2016). A Right Colon Adenocarcinoma Case Mimicking Crohn's Disease: A Case Report. https://doi.org/10.14309/00000434-201610001-01332
6. Ankouz A, Majdoub KI, Ousadden A, Mazaz K, Taleb KA. Colonic adenocarcinoma revealing Crohn's disease: a case report. J Med Case Rep. 2010;4:167. Published 2010 Jun 1. doi:10.1186/1752-1947-4-167
7. American Society for Gastrointestinal Endoscopy Standards of Practice Committee. Shergill AK, Lightdale JR, Bruining DH, Acosta RD, Chandrasekhara V, Chathadi KV, Decker GA, Early DS, Evans JA, Fanelli RD, et al. The role of endoscopy in inflammatory bowel disease. Gastrointest Endosc. 2015;81:1101–1121.e1-13.
8. Annese V, Daperno M, Rutter MD, Amiot A, Bossuyt P, East J, Ferrante M, Götz M, Katsanos KH, Kießlich R, et al. European evidence based consensus for endoscopy in inflammatory bowel disease. J Crohns Colitis. 2013;7:982–1018
9. Politis DS, Katsanos KH, Tsianos EV, Christodoulou DK. Pseudopolyps in inflammatory bowel diseases: Have we learned enough?. World J Gastroenterol. 2017;23(9):1541-1551. doi:10.3748/wjg.v23.i9.1541
10. Ansari AZ, Razzak S, Patibandla S, Kumar S, Hafeez S, Kratz K. Tumefactive Crohn's Disease Mimicking Colon Carcinoma in a Young Female: A Case Report. Cureus. 2024;16(1):e52221. Published 2024 Jan 13. doi:10.7759/cureus.52221
11. Bernstein D, Rogers A. Malignancy in Crohn's disease. Am J Gastroenterol. 1996;91(3):434-440.

PULMONARY HYPERTENSION IN A GERIATRIC PATIENT WITH ANEMIA FROM HEREDITARY HEMORRHAGIC TELANGIECTASIA: CASE REPORT

Irida Kecaj[1], Rizvan Myrtaj [1], Ergita Nelaj[1], Ilir Gjermeni[1], Ina Refatllari[2], Kei Xhixhabesi[3], Margarita Gjata[1]

[1]*Department of Internal Medicine, UHC "Mother Teresa", Tirana, Albania*
[2]*Department of Cardiology, UHC "Mother Teresa", Tirana, Albania*
[3]*Faculty of Medicine, University of Medicine, Tirana, Albania*

Corresponding E-mail: irida.kecaj@yahoo.com

Abstract

Introduction: Hereditary Hemorrhagic Telangiectasia (HHT) is a rare autosomal dominant disorder causing mucocutaneous telangiectasia and arterial-venous malformations (AVMs) in various organs. Pulmonary AVMs cause right-to-left shunting, causing hypoxemia, paradoxical embolisms, and other complications. In contrast, hepatic AVMs can result in high-output heart failure due to the left-to-right shunting. About 10% of HHT patients develop pulmonary arterial hypertension (PAH), caused by small artery remodeling leading to elevated vascular resistance. This case report describes a 74-year-old woman with HHT as the cause of pulmonary hypertension, right heart failure, and anemia.

Case presentation: A 74-year-old female hospitalized at Internal Medicine due to a two-week history of dyspnea, edema of the inferior sides, and recurrent spontaneous epistaxis. On physical examination, we found telangiectasias on her hands and ears. The patient previous medical history included HHT, diabetes mellitus type 2, arterial hypertension, and chronic atrial fibrillation untreated for the last 10 days due to epistaxis. Laboratory results revealed anemia with hemoglobin at 7 g/dL, altered liver tests, elevated D-Dimer and NT-proBNP. Echocardiography showed a normal left ventricular function (FE 61%), dilated right heart chambers, tricuspid regurgitation, and PAP of 60 mmHg, abdominal ultrasound revealed dilated hepatic veins and portal vein measuring 16mm (7-13mm). These findings raise the suspicion of pulmonary thromboembolism, which was ruled out. Pulmonary arterial hypertension and signs of right heart failure resulted from HHT, which improved under diuretic therapy, and topical treatment for epistaxis.

Conclusion: This case highlights the complex and intricate multiorgan complications of HHT, such as anemia from recurrent nosebleeds and right heart failure brought on by elevated pulmonary artery pressures. Management in geriatric patients with HHT requires careful consideration of comorbidities such as atrial fibrillation and pulmonary embolism, particularly concerning anticoagulation strategies and bleeding risks associated with the respective treatments.

Keywords: hereditary hemorrhagic teleangioectasia, pulmonary hypertension, hepatic arteriovenous malformation.

HIPERTENSIONI PULMONAR NË NJË PACIENT GERIATRIK ME ANEMI NGA TELEANGIOEKTAZIA HEMORAGJIKE HEREDITARE

Abstrakt

Hyrje: Teleangioektazia Hemoragjike Hereditare (THH) është një çrregullim gjenetik autosomal dominant që shkakton teleangioektazi mukokutane dhe malformacione arterovenoze (MAV) në organe të shumta. MAV pulmonare shkaktojnë shunte gjaku djathtas-majtas, duke sjellë hipoksemi, emboli paradoksale dhe ndërlikime të tjera. Nga ana tjetër, MAV hepatike mund të prodhojnë insuficiencë kardiake me debit të lartë për shkak të shunteve të gjakut majtas-djathtas. Rreth 10% e pacientëve me THH zhvillojnë hipertension arterial pulmonar (HAP), për shkak të rimodelimit të arterieve të vogla duke çuar në rritje të rezistencave vaskulare. Ky rast klinik përshkruan një grua 74 vjeçare me THH, si shkaktare e hipertensionit pulmonar, insuficiencës kardiake të djathtë dhe anemisë.

Prezantimi i rastit: Pacientja 74 vjeçare shtrohet në shërbimin e Mjekësisë Interne, për shkak të historisë dy javore me dispne, edema të anësive inferiore dhe episodeve rekurrente te epistaksis spontan. Në ekzaminimin fizik u gjendën teleangioektazi në pëllëmbët e duarve dhe në veshë. Në historikun mjekësor të pacientes përfshihej THH, diabeti mellitus tip 2, hipertensioni arterial, si dhe fibrilacioni atrial kronik i pa trajtuar në 10 ditët e fundit për shkak të epistaksisit. Analizat laboratorike treguan anemi me hemoglobinë 7g/dL, testet e funksionit hepatik të alteruara, D-Dimer dhe NT-proBNP të rritura. Ekokardiografia tregoi funksion sistolik ventrikular në normë (FE 61%), dhomat e djathta të zemrës të dilatuara, regurgitim trikuspidal, dhe PsAP=60 mmHg. Ekografia abdominale tregoi vena hepatike të dilatuara dhe vena porta me madhësi 16mm (7-13mm). Këto gjetje ngritën dyshimin për tromboemboli pulmonare që u përjashtua. THH rezulton të jetë shkaku i hipertensionit arterial pulmonar dhe insuficiencës kardiake të djathtë, që u përmirësuan me terapinë me diuretike. U aplikua edhe terapia topike për epistaksisin, terapia për diabetin dhe aneminë.

Konkluzione: Ky rast vë në dukje komplikacionet e ndërsjella dhe komplekse të THH, si anemia prej epistaksisit rekurrent dhe insuficienca kardiake e djathtë e shkaktuar nga rritja e presioneve në arteriet pulmonare. Menaxhimi i pacientëve geriatrikë me THH ka nevojë për marrjen në konsideratë të bashkësëmundshmërive si fibrilacioni atrial dhe embolitë pulmonare, veçanërisht për sa i përket antikoagulimit dhe rrezikut për gjakrrjedhje të shoqëruar me trajtimet përkatëse.

Fjalë kyçe: teleangioktazi hemoragjike hereditare, hipertension pulmonar, malformacion arteriovenoz hepatik.

Introduction

Hereditary hemorrhagic telangiectasia (HHT) and pulmonary hypertension (PH) are apparently very different diseases that both affect the pulmonary vascular system. HHT, also known as Rendu-Osler-Webber syndrome, is a rare autosomal dominant disorder causing mucocutaneous telangiectasias and arteriovenous malformations (AVMs) in various organs, which are direct deviations between arteries and veins that lack a capillary bed (1). Pulmonary AVMs cause right-to-left shunting, causing hypoxemia, paradoxical embolisms,

and other complications (2). In contrast hepatic AVMs can result in high-output heart failure due to the left-to-right shunting (1). PH, a typical high-resistance vascular condition that can lead to heart failure, is defined as an increase in mean pulmonary arterial pressure greater than 25 mmHg. About 10% of HHT patients develop pulmonary arterial hypertension (PAH), caused by small artery remodeling leading to elevated vascular resistance (3). In the context of pulmonary vascular diseases, HHT presents an interesting paradoxical situation, where lung involvement can be characterized by pulmonary AVM and PH, which are low-resistance and high-resistance vascular states, respectively.

Case presentation

A 74-year-old female hospitalized at internal medicine department due to a two-week history of dyspnea, edema of the inferior sides, and recurrent spontaneous epistaxis. On physical examination, we found telangiectasias on her hands and ears (Fig. 1,2).





Figure 1. Telangiectasia of the hand

Figure 2. Telangiectasia of the ear

The patient previous medical history included HHT, diabetes mellitus type 2, arterial hypertension, and chronic atrial fibrillation untreated for the last 10 days due to epistaxis.

The laboratory tests performed during hospitalization are summarized in Table 1.

Table 1. Laboratory tests

Laboratory tests	Values	Reference range
RBC (mln / uL)	2.50	4-5.6
Hgb* (g/dL)	7.0	12.1-15
HTC (%)	22.3	37-46
Reticulocytes (<20)	15	
Ferritine (ng/mL)	15.65	5-204
TSH (mU/L)	3.898	0.35-4.94
FT4 (ng/dL)	0.85	0.7-1.48
Uric Acid (mg/dL)	10.5	1.6-6
Blood nitrogen (mg/dL)	46.1	21-43
Total bilirubin (mg/dL)	1.92	0.3-1.2
Direct bilirubin (mg/dL)	1.11	0.1-0.5
AST / SGOT (U/L)	37	5-34
NTproBNP (< 125 pg/mL)	3567.70 pg/mL	< 125
D-dimer (< 0.5 ug/mL)	2.37 ug/mL	< 0.5
* *During hospitalization the patient was given 3 blood transfusions. On discharge Hgb = 9.9 g/Dl*		

Echocardiographic examination showed a severely dilated (basal diameter 50 mm) and hypokinetic right ventricle (TAPSE 10 mm) with severe pulmonary hypertension (PAP >60 mmHg), dilated left atria and a nondilated left ventricle with preserved systolic ejection fraction.

Abdominal ultrasound (not shown) revealed blunt liver edge and dilated hepatic veins and dilated portal vein measuring 16 mm (normal range of 7-13 mm) with blood flow velocity of 9.7 cm/sec (normal value: 19.3 cm/s), suggestive of hypertension portal and it was found the presence of a vascularized lesion which showed multiple dilated peripheral vascular channels, with a flow pattern similar to portal venous flow. No abdominal fluid (ascites) was present, and other abdominal organs were without pathological alterations.

In order to determine the nature of the vascularized hepatic lesion, a contrast-enhanced CT scan of the liver and bile ducts was performed, which revealed a well-defined lobulated isodense lesion with a hypodense center surrounded by multiple dilated tortuous vascular channels in the periphery of the lesion which follow similar contrast enhancement pattern as that of the portal vein in all the phases, with contrast opacification of the portal vein and its branches in the arterial phase, due to arterio-portal shunting (Fig. 3).

Cardiac echo, high d-dimer and atrial fibrillation not regularly treated due to repeated hemorrhagic phenomena, raise the suspicion of pulmonary thromboembolism, which was ruled out with angio-CT. Pulmonary hypertension and signs of right heart failure resulted from HHT, which improved under diuretic therapy. After the hemorrhage was stopped with supportive treatment including pressure, packing without necessity of cauterization in our patient, and anemia was corrected with hemotransfusions and iron supplements were started, it was decided to start anticoagulation with a reduced dose due to the high hemorrhagic risk presented by the patient.



Figure 3. CT Scan in arterial phase

Discussion

HHT is a genetically heterogenous disorder that presents with a series of vascular defects throughout the body. On the molecular level HHT is caused by mutations that affect the TGF-β signaling pathway, which plays a crucial role in vascular development. There are two main mutations, comprising up to 96% of "classic HHT" cases, producing two main forms of the disease. Heterozygous mutations in endoglin (ENG; HHT1) or Activin A receptor type 1-like (ACVRL 1, encoding ALK1; HHT2), which encode transmembrane receptors that, in cooperation with an additional receptor such as BMPR2, bind to soluble bone morphogenetic protein (BMP) ligands to activate transcriptional responses within endothelial cells (4,5). The cellular response to this signal may include both effects on endothelial cell migration, but also the proliferation and recruitment of smooth muscle cells that prevent AVMs (5). HHT predominantly affects the Caucasian population, with a wide geographic distribution, which can also be found in Asiatic, African and Arabic populations. The worldwide prevalence of HHT ranges from 1:5000 to 1:10000 individuals (6). The clinical diagnosis of HHT is based on the Curacao criteria, which include epistaxis, telangiectasia, visceral lesions, and family history. Visceral lesions may occur in the gastrointestinal, pulmonary, hepatic, spinal, or cerebral organs (1). Our patient, in addition to cutaneous hemorrhagic phenomena and epistaxis, she also had a positive and significant family history for HHT (father, daughter, uncle, and cousin).

PH is part of a heterogeneous group of chronic, progressive hemodynamic disorders with different etiologies, characterized by an increase in arterial pressure in the pulmonary artery, which over time can lead to dysfunction of the right side of the heart. The most accurate way of determining PH is between the catheterization of the right side of the heart with an average pulmonary arterial pressure > 20 mmHg at rest (7). PH, in contrast to HHT, has multiple underlying causes. According to the latest ESC/ERS guidelines, pulmonary hypertension is divided into 5 groups distinguished by hemodynamics and the location and type of

pulmonary vascular lesions that cause elevated pressure: Group 1-pulmonary arterial hypertension; Group 2-PH due to left heart disease; Group 3-PH due to lung disease or hypoxia; Group 4-chronic thromboembolic PH); and Group 5-PH due to unclear multifactorial mechanisms (8).

In patients with HHT, PH has been considered primarily to be group 1 (pulmonary arterial hypertension), which is characterized by increased dilatation and vasoconstriction in the pulmonary vascular bed leading to a state of high resistance, low cardiac output, and right heart failure (9). According to genetic concepts, the presence of PAH in patients with HHT is explained by heterozygous mutations in BMPR2, which acts in the same pathway as ACVRL1 and ENG, which account for more than 70% of inherited PAH and 20% of idiopathic PAH (10).

It remains unclear how disruption of the same signaling pathway leads to different phenotypes of dilated pulmonary AVMs (HHT) and proliferative obliterative vasculopathy (PAH).

In patients with HHT, systemic AVMs, particularly in the liver, may cause a state of increased cardiac output leading to increased flow through the pulmonary circuit, elevated pressures, and group 2 PH, or pulmonary venous hypertension (PVH) (11). Liver AVMs can be present in up to 75% of patients with HHT but manifest with clinical signs and symptoms in less than 10% of patients. These AVMs can vary in type depending on the combination of vessels involved in the shunts. Hepatic AVMs can result in three patterns of shunting: hepatic arteries to hepatic veins, hepatic arteries to portal veins, and portal veins to hepatic veins (12). Hepato-portal AVMs can result in portal hypertension and potentially hepatic encephalopathy, although this is extremely rare. Common manifestations of hepatic AVMs include hepatomegaly, auscultatory sounds such as bruits due to the turbulent blood flow in the shunts, and altered liver function tests (11, 12).

HHT appears to be the root cause of the pulmonary hypertension and right heart failure. HHT patients even at relatively young ages have an increased risk of thromboembolic events, in the form of deep vein thrombosis and pulmonary embolisms, despite inflammation not being a prominent disease feature (13, 14). It is believed this result from increased levels of coagulation factor VIII, probably caused by the low levels of iron (15). The findings of the cardiac echo, together with elevated d-dimer levels and atrial fibrillation (untreated due to hemorrhagic phenomena) raised concern for a pulmonary embolism, which in our patient was ruled out through an angio-CT scan. At our patient was excluded the presence of underlying hyperthyroidism, because it should be taken into consideration in patients with pulmonary hypertension, especially in those with high cardiac output, as hyperthyroidism causes systemic vasodilation and increases metabolic demands (16). In our case, since there is a lack of detailed hemodynamic information and relevant genotype data necessary to determine genotype/phenotype correlations to generate mechanistic hypotheses regarding the underlying causes of PH and HHT, based also on hepatic AVMs present in abdominal CT angiography, it was considered PH group 2. The presence of PH, regardless of etiology, is a poor prognostic indicator of disease, including HHT (17). Given the multifactorial etiology of PH in HHT and the distinct prognostic and therapeutic implications of different PH groups, it is important to consider a complete hemodynamic profile in HHT patients with PH. Another discussion during the treatment of our patient was the necessity of using anticoagulation due to atrial fibrillation and active hemorrhagic phenomena (epistaxis). While guidelines do not

contraindicate the use of anticoagulants in HHT patients, there is a fine balance to be found between anticoagulation strategies and bleeding risks associated with the respective treatments and prevention of thromboembolic events. Hence, despite guidelines non contraindicating anticoagulation, decisions must be personalized to fit each patient's unique medical circumstances in a case-by-case basis (1). Thus, after the hemorrhage was stopped with supportive treatment including pressure, packing without necessity of cauterization (18) in our patient, and anemia was corrected with hemotransfusions and iron supplements were started, it was decided to start anticoagulation with a reduced dose due to the high hemorrhagic risk presented by the patient.

Conclusion

This case highlights the complex and intricate multiorgan complications of HHT, such as pulmonary hypertension with different mechanisms and right heart failure brought on by elevated pulmonary artery pressures, or anemia from recurrent nosebleeds. Other potential complications include: strokes, cerebral abscesses, and VTEs. Management in geriatric patients with HHT requires careful consideration of comorbidities such as atrial fibrillation and pulmonary embolism, particularly concerning anticoagulation strategies and bleeding risks associated with the respective treatments. HHT is a quintessential internal medicine condition, requiring a holistic and multidisciplinary understanding and approach, which places the internal medicine specialist in the ideal position for its management.

Conflict of interest: None

References

1. Faughnan ME, Mager JJ, Hetts SW, et al. Second International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia. Ann Intern Med. 2020;173(12):989-1001. doi:10.7326/M20-1443.
2. Mathavan A, Mathavan A, Reddy R, et al. Pulmonary hypertension in hereditary hemorrhagic telangiectasia: A clinical review. Pulm Circ. 2023;13(4):e12301. Published 2023 Oct 19. doi:10.1002/pul2.12301.
3. Bofarid S, Hosman AE, Mager JJ, Snijder RJ, Post MC. Pulmonary Vascular Complications in Hereditary Hemorrhagic Telangiectasia and the Underlying Pathophysiology. Int J Mol Sci. 2021;22(7):3471. Published 2021 Mar 27. doi:10.3390/ijms22073471.
4. Angel CM. Hereditary Hemorrhagic Telangiectasia: Diagnosis and Management. J Clin Med. 2022;11(16):4698. Published 2022 Aug 11. doi:10.3390/jcm11164698.
5. McDonald J, Wooderchak-Donahue W, VanSant Webb C, Whitehead K, Stevenson DA, Bayrak-Toydemir P. Hereditary hemorrhagic telangiectasia: genetics and molecular diagnostics in a new era. Front Genet 2015;6:1.
6. Majumdar S, McWilliams JP. Approach to Pulmonary Arteriovenous Malformations: A Comprehensive Update. J Clin Med. 2020 Jun 19;9(6):1927. doi: 10.3390/jcm9061927. PMID: 32575535; PMCID: PMC7356967.
7. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, et.al., Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1):1801913.

8. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF,et, al.; ESC/ERS Scientific Document Group. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2023 Jan 6;61(1):2200879. doi: 10.1183/13993003.00879-2022. PMID: 36028254..
9. Tuder RM, Archer SL, Dorfmüller P, Erzurum SC, Guignabert C, et.al. Relevant issues in the pathology and pathobiology of pulmonary hypertension. J Am Coll Cardiol 2013;62(25, Suppl):D4–D12.
10. Deng Z, Morse JH, Slager SL, Cuervo N, Moore KJ, Venetos G, et.al. Familial primary pulmonary hypertension (gene PPH1) is caused by mutations in the bone morphogenetic protein receptor-II gene. Am J Hum Genet 2000;67:737–744.
11. Circo S, Gossage JR. Pulmonary vascular complications of hereditary haemorrhagic telangiectasia. Curr Opin Pulm Med 2014;20:421–428.
12. Memeo M, Stabile Ianora AA, Scardapane A, Buonamico P, Sabbà C, Angelelli G. Hepatic involvement in hereditary hemorrhagic telangiectasia: CT findings. Abdom Imaging. 2004;29(2):211–20.
13. Serra MM, Elizondo CM, Alonso M, Peuchot V, Vazquez FJ. Incidence of Thromboembolic Disease in Hereditary Hemorrhagic Telangiectasia (Osler Weber Rendu Syndrome). Blood. 2018;132(Supplement 1):4967. doi:10.1182/blood-2018-99-112945.
14. Shovlin CL, Sulaiman NL, Govani FS, Jackson JE, Begbie ME. Elevated factor VIII in hereditary haemorrhagic telangiectasia (HHT): association with venous thromboembolism. Thromb Haemost. 2007;98(5):1031-1039.
15. Livesey JA, Manning RA, Meek JH, et al. Low serum iron levels are associated with elevated plasma levels of coagulation factor VIII and pulmonary emboli/deep venous thromboses in replicate cohorts of patients with hereditary haemorrhagic telangiectasia. Thorax. 2012;67(4):328-333. doi:10.1136/thoraxjnl-2011-201076.
16. Qaiser KN, Sahay S, Tonelli AR. Pulmonary hypertension due to high cardiac output. Respir Med. 2023;206:107034.
17. Lyle MA, Fenstad ER, McGoon MD, Frantz RP, Krowka MJ, et.al. Pulmonary hypertension in hereditary hemorrhagic telangiectasia. Chest 2016;149:362–371.
18. Mikołajczyk-Solińska M, Leończyk K, Brzezina A, Rossa S,Kasznicki J. Life-threatening anaemia in patient with hereditary haemorrhagic telangiectasia (Rendu-OslerWeber syndrome). Open Medicine. 2020;15(1):134-138.doi:10.1515/med-2020-0020.

A NONTRAUMATIC, RIGHT-SIDED DIAPHRAGMATIC HERNIA, IN AN ADULT, DIAGNOSED DURING AN ASTHMA ATTACK.

Eris Mesonjesi[1], Klea Xhelilaj[2], Denisa Spahiu[3], Albana Gjeli[4], Viola Nushi[2], Etleva Qirko Loloci[1]

[1]Allergology and Clinical Immunology, Department of Internal Medicine, University Hospital Center "Mother Teresa", Tirana, Albania.
[2]Allergology and Clinical Immunology, Private Practice, Tirana, Albania.
[3]Allergology and Clinical Immunology, "Continental" Hospital, Tirana, Albania.
[4]Allergology and Clinical Immunology, Private Practice, Elbasan, Albania.

Correspondent E-mail: erismesonjesi@gmail.com

Abstract

Background: A diaphragmatic hernia is a serious medical condition in which an abnormal opening or defect in the diaphragm allows organs from the abdomen, such as the stomach or intestines, to move into the chest cavity. It can be congenital or acquired. Congenital diaphragmatic hernias are rare and usually occur on the left side (80%) of the diaphragm. Acquired diaphragmatic hernia usually occurs following trauma.

Case report: This is a rare case of a right-sided diaphragmatic herniation of the ascending colon, in a 76-year-old severe asthmatic patient with a non-congenital diaphragmatic hernia, no history of trauma, surgery or radiation. Before the pandemic, this patient needed hospitalization 3-4 times a year for her asthma, but for the last 2 years, the patient was not hospitalized because she was afraid of Covid-19, resulting in a badly controlled asthma with daily symptoms and repeated doses of oral or intravenous corticosteroids, beside her regular combined inhaler with maximal dose of corticosteroids. Due to the persistent cough, chronic steroid use, severe asthma, and advanced age this unusual complication has happened. Computed tomography showed right diaphragmatic hernia of ascending colon without incarceration and hiatal hernia.

Conclusion: Non-traumatic right-sided diaphragmatic hernia involving the colon is an extremely rare condition in adults. In this case, persistent coughing, along with other contributing factors, likely played a role in the development of the hernia. Diagnostic imaging, particularly chest X-rays and CT scans, proved essential in confirming the diagnosis by revealing the herniated colon. Given the rarity of such hernias, they should be included in the differential diagnosis to ensure timely identification and appropriate treatment.

Keywords: diaphragmatic hernia, asthma, cough, non-traumatic, right-sided.

NJË RAST KLINIK DIAGNOSTIKUAR ME HERNIE DIAFRAGMALE JOTRAUMATIKE TË ANËS SË DJATHTË GJATË NJË KRIZE ASTMATIKE.

Abstrakt

Hyrje: Patologjia e hernies diafragmale është një gjendje e rëndë mjekësore në të cilën një defekt në diafragmë lejon që organet nga abdomeni, si stomaku ose intestini të lëvizin brenda në kafazin torakal. Mund të jetë kongjenitale ose e fituar. Herniet diafragmale kongenitale janë të rralla dhe zakonisht ndodhin në anën e majtë (80%) të diafragmës. Hernia diafragmale e fituar zakonisht ndodh pas traumës.

Rasti klinik: Po paraqesim një rast të rrallë me hernie diafragmale të kolonit ashendent në anën e djathtë të diafragmës, në një paciente 76-vjeçare me astma bronkiale të formës së rëndë me një hernie diafragmale jo të lindur, pa histori traume, operacioni apo rrezatimi. Para pandemisë, kjo paciente hospitalizohej 3-4 herë në vit për astmën e saj të rëndë, por 2 vitet e fundit pacientja nuk u shtrua në spital, për shkak të frikës së Covid-19, duke rezultuar në një astmë të pakontrolluar me simptoma të përditshme dhe e mjekuar me kortikosteroidë orale ose intravenoze përveç terapisë inhalatore të kombinuar me dozë maksimale. Për shkak të kollës së vazhdueshme, përdorimit kronik të steroideve, astmës së rëndë dhe moshës ndodhi ky ndërlikim spontan i pazakontë.

Konluzion: Hernia diafragmale jo-traumatike e anës së djathtë e kolonit ashendent është një gjendje jashtëzakonisht e rrallë tek adultët. Në pacienten tonë, kolla e vazhdueshme, së bashku me faktorë të tjerë kontribues, ka patur një rol të rëndësishëm në shkaktimin e hernies. Imazhet diagnostike, veçanërisht grafia pulmonare dhe tomografia e kompjuterizuar, rezultuan thelbësore në konfirmimin e diagnozës duke zbuluar hernien e kolonit ashendent. Duke pasur parasysh raste të tilla, herniet diafragmale duhet të përfshihen në diagnozën diferenciale për të siguruar identifikimin në kohë dhe trajtimin e duhur.

Fjalë kyç: hernie diafragmale, astma, kollë, jo traumatike, djathtas.

Introduction

The diaphragm is a primary respiratory muscle separating the thoracic and abdominal cavities. Its cyclical contractions and expansions facilitate the inhalation and exhalation of air. A diaphragmatic hernia, characterized by the abnormal protrusion of an organ or tissue through a weakened muscle wall, can compromise its functionality and potentially lead to severe health consequences if not addressed promptly (1). There are two main types of diaphragmatic hernia (DH), namely, congenital and acquired (2). A diaphragmatic hernia, though uncommon, can be a complication for individuals with asthma. Spontaneous diaphragmatic hernias are difficult to diagnose, as early symptoms may be absent (3). Additionally, right-sided hernias are rare, with only a few cases reported in the literature.

Case presentation

A 76-year-old woman, a well-known patient to our department, with a 40-year history of severe persistent allergic asthma presented to the emergency department with more than usual respiratory distress. Her symptoms included shortness of breath, a non-productive cough, wheezing, tachypnea, chest tightness, and respiratory failure (Table 1). Despite maximal treatment with inhaled medications and oral corticosteroids over the past two weeks, her condition worsened.

An initial chest X-ray, done at the emergency room, revealed abnormalities in the lower right lung, including a pleural effusion. To further evaluate the extent of lung involvement and guide treatment, a CT scan was scheduled upon hospital admission, while receiving the appropriate treatment for her asthma.

Table 1 Laboratory findings

Arterial Blood Gas (ABG)		
Parameter	**Value**	**Reference Range***
pCO2	37.9 mmHg	35–45 mmHg
pO2	62 mmHg	>80 mmHg
pH	7.43	7.35–7.45
HCO3	25.3 mmol/L	22–26 mmol/L
Base Excess (BE)	1.1 mmol/L	-2 to +2 mmol/L
tHb	12 g/dL	12–16 g/dL
SatO2	92.4%	>95%
O2Hb	91.3%	>95%
COHb	0.5%	<1.5%
MetHb	0.7%	<1.5%
Glucose	150 mg/dL	70–110 mg/dL
NT-proBNP	891.9 pg/mL	high

Summary:

1. Mild hypoxemia is suggested by low pO2, SatO2, and O2Hb levels.
2. NT-proBNP is elevated, potentially indicating cardiac strain or heart dysfunction.
3. Glucose is elevated, possibly reflecting hyperglycemia.

** NT-proBNP reference varies by age, gender, and clinical condition. Typically, values >300–900 pg/mL can be elevated.

Laboratory results, including the complete blood count, inflammatory markers, liver and kidney function tests (urea, creatinine, hepatic enzymes, total bilirubin), troponin, CRP, and D-dimer, are all within normal limits.

Spirometry: resulted with severe obstruction.

CT-scan interpretation: trachea and main bronchi were normal, heart with normal dimensions, no sign of pericardial fluid. Sinister scissuritis. Right diaphragmatic hernia of ascending colon without incarceration and hiatal hernia. No pleural effusion. (Fig.1)

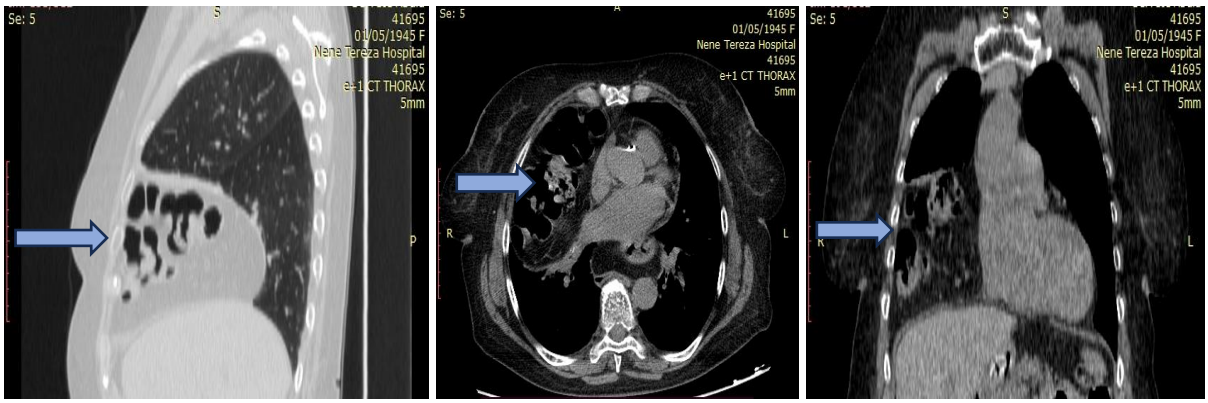


Figure 1: The CT scan revealed that the trachea and main bronchi were normal. It also identified a right-sided diaphragmatic hernia involving the ascending colon, without signs of incarceration.

Echocardiography: left ventricular septal hypertrophy, calcified mitral valve, no other abnormal findings.

Medical history: in skin prick test she was sensitized to Dermatophagoides pteronysinuss and Dermatophagoides farinae (house dust mites), allergic rhinitis, severe persistent bronchial asthma, treated with Beclomethasone dipropionate\formeterol fumarate 100\6mcg, 2x2 puffs and Salbutamol 0.1mg 2pufs as needed. She was a patient who required several hospitalizations each year. However, since the pandemic began, she had refused to visit the hospital, opting instead for home-based treatment, which was insufficient to effectively control her symptoms. She had undergone chest X-rays on previous occasions. We compared the diagnostic imaging available from those instances and found no evidence of these herniations at that time. She also suffered from congestive heart failure NYHA 2 with peripheral edema (Table 1). She had no history of any chirurgical intervention, no malignancies, no radiotherapy.

Discussion

This is a fascinating case, involving an elderly patient from our clinic with a long history of hospitalizations due to unstable asthma.

The diaphragm, is indispensable for the process of respiration. Congenital diaphragmatic hernia (CDH) is a birth defect that occurs when the diaphragm fails to fully develop. This allows abdominal organs to herniate into the chest cavity. CDH affects approximately 1 in 3000 newborns and is associated with significant health problems and a high mortality rate. It often leads to underdeveloped lungs (pulmonary hypoplasia) and high blood pressure in the lungs (pulmonary hypertension). The most common location for a CDH is the left side of the

diaphragm (75-90% of cases), but it can also occur on the right side (10-15%) or both sides (1-2%). Some studies suggest a slightly higher incidence of CDH in male fetuses. The prevalence of CDH does not seem to be related to the mother's age. (4,5) This is not the case for our patient, as she is of advanced age and has undergone numerous chest X-rays and CT scans throughout her life, none of which previously revealed any signs of herniation.

Meanwhile acquired diaphragmatic hernias (ADHs) are typically seen in adults. They can be classified into three main types:

1. *Hiatal Hernia*: This occurs when part of the stomach protrudes through the diaphragm into the chest cavity. While often included in ADH classifications, it's not considered a true diaphragmatic hernia.
2. *Traumatic Diaphragmatic Hernia (TDH):* This type arises from a traumatic event, such as a car accident or a penetrating injury, that causes a tear in the diaphragm. This rupture allows abdominal organs to migrate into the chest cavity. Diaphragmatic rupture is estimated to occur in around 2.1% of blunt trauma cases and 3.5% of penetrating trauma cases.
3. *Iatrogenic Hernia:* This type is caused by a surgical procedure that inadvertently creates a hole in the diaphragm (6,7).

Other causes of adult diaphragmatic hernia include delayed presentation of congenital diaphragmatic hernia, persistent infections such as pneumonia or empyema, and stress on the diaphragm from straining or coughing (8). Spontaneous diaphragmatic rupture following coughing, childbirth, or extensive exercise is very rare (9). We believe this is the case with our patient, who suffered a hernia due to coughing and uncontrolled asthma

Clinically, right-sided diaphragmatic hernias are less common than left-sided ones. The percentages of right and left sided CDH vary, with published incidences ranging from 8 to 24% right-sided CDH, 73%–90% left-sided CDH (10). Additionally, the majority of herniated organs are the omental fat, bowel, spleen, stomach, kidney, and pancreas. The liver and colon as the herniated organ are extremely rare. This may be owing to the protective effect of the liver on the right side (11). Another theory suggests that right-sided hernias rarely occur because the right side of the pleuroperitoneal canal closes earlier (12).

Chronic coughing, a hallmark symptom of asthma, can exert significant pressure on the diaphragm, potentially weakening or tearing it. This weakening may allow abdominal organs to herniate into the chest cavity, leading to respiratory symptoms such as shortness of breath, decreased oxygen levels, and chest pain. The worsening of these symptoms prompted our patient to seek medical care.

Additionally, individuals may experience gastrointestinal symptoms such as abdominal pain, nausea, vomiting, and difficulty swallowing; however, this was not observed in our patient.

Early diagnosis and appropriate treatment are essential to manage symptoms and prevent further complications. To diagnose a diaphragmatic hernia, imaging tests are typically employed. Chest X-rays can reveal displaced abdominal organs or fluid accumulation in the chest cavity. For a more detailed assessment, CT or MRI scans are used to visualize the

hernia, its size, and the organs involved. In some cases, ultrasound may be helpful to evaluate diaphragm movement.

Treatment for diaphragmatic hernia primarily involves surgical repair, particularly when organs are significantly displaced or causing symptoms. Before surgery, stabilizing the patient's condition is crucial, often involving managing asthma symptoms with medications like bronchodilators and corticosteroids (13,14).

After surgery, effective asthma management is essential to prevent recurrence. This includes avoiding triggers and adhering to prescribed medication regimens. With timely surgical intervention and proper asthma management, most patients recover well. However, delayed treatment can lead to complications like lung infections, bowel obstructions, or persistent respiratory issues (13,14).

During this hospitalization, despite being diagnosed with right diaphragmatic hernia, the patient experienced symptom improvement with the treatment provided. After discussing with her family, she declined surgical intervention to repair the hernia.

Her medical history includes two vaginal deliveries, no malignancies, no history of trauma, and no prior surgical interventions. In this case, the most plausible explanation for the herniation of the colon is persistent coughing in the context of advanced age, chronic steroid use, and severe asthma.

Conclusions

Non-traumatic, right-sided diaphragmatic hernia of the colon in adults is extremely rare. Persistent coughing, along with other predisposing factors in this patient, likely contributed to the development of the hernia. Chest X-rays and CT scans were instrumental in making the diagnosis. Rare hernias like this should be considered during differential diagnosis to ensure timely and accurate treatment.

Conflict of interests. None

References:

1. Spellar K, Lotfollahzadeh S, Gupta N. Diaphragmatic Hernia. 2024 Jul 23. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 30725637
2. Tabrizian P, Jibara G, Shrager B, Elsabbagh AM, Roayaie S, Schwartz ME. Diaphragmatic hernia after hepatic resection: case series at a single Western institution. J Gastrointest Surg. 2012 Oct;16(10):1910-4. doi: 10.1007/s11605-012-1982-7. Epub 2012 Aug 1. PMID: 22851338.
3. Rashid F, Chakrabarty MM, Singh R, Iftikhar SY. A review on delayed presentation of diaphragmatic rupture. World J Emerg Surg 2009; 4: 32.
4. Kosiński P, Wielgoś M. Congenital diaphragmatic hernia: pathogenesis, prenatal diagnosis and management - literature review. Ginekol Pol. 2017;88(1):24-30. doi: 10.5603/GP.a2017.0005. PMID: 28157247.
5. Kanazawa A, Yoshioka Y, Inoi O, Murase J, Kinoshita H. Acute respiratory failure caused by an incarcerated right-sided adult bochdalek hernia: report of a case. Surg Today. 2002;32(9):812-5. doi: 10.1007/s005950200156. PMID: 12203061.

6. Giuffrida M, Perrone G, Abu-Zidan F, Agnoletti V, Ansaloni L, Baiocchi GL, et.al. Management of complicated diaphragmatic hernia in the acute setting: a WSES position paper. World J Emerg Surg. 2023 Jul 26;18(1):43. doi: 10.1186/s13017-023-00510-x. PMID: 37496073; PMCID: PMC10373334.
7. Rosati C. Acute traumatic injury of the diaphragm. Chest Surg Clin N Am. 1998 May;8(2):371-9. PMID: 9619310.
8. Lund EP, Bergenfeldt M, Burcharth F. Traumatic abdominal hernia caused by cough, presenting with intestinal obstruction. Hernia. 2004 Dec;8(4):399-401. doi: 10.1007/s10029-004-0249-y. PMID: 15221646.
9. Barclay-Buchanan CJ, Herzog ES. Spontaneous Valsalva-Associated Right-Sided Diaphragmatic Rupture. J Emerg Med. 2017 May;52(5):e203-e205. doi: 10.1016/j.jemermed.2016.12.006. Epub 2017 Jan 16. PMID: 28104356.
10. Slavotinek AM, Warmerdam B, Lin AE, Shaw GM. Population-based analysis of left- and right-sided diaphragmatic hernias demonstrates different frequencies of selected additional anomalies. Am J Med Genet A. 2007 Dec 15;143A(24):3127-36. doi: 10.1002/ajmg.a.32100. PMID: 18008313.
11. Goh BK, Teo MC, Chng SP, Soo KC. Right-sided Bochdalek's hernia in an adult. Am J Surg. 2007 Sep;194(3):390-1. doi: 10.1016/j.amjsurg.2006.09.039. PMID: 17693288.
12. Gale ME. Bochdalek hernia: prevalence and CT characteristics. Radiology. 1985 Aug;156(2):449-52. doi: 10.1148/radiology.156.2.4011909. PMID: 4011909.
13. El-Yakub AI, Bello UM, Sheshe AA, Naaya HU. Delayed Presentation of Posttraumatic Diaphragmatic Hernia Masquerading as Recurrent Acute Asthmatic Attack. Case Rep Med. 2017;2017:5037619. doi: 10.1155/2017/5037619. Epub 2017 Sep 19. PMID: 29056971; PMCID: PMC5625800.
14. Fiordaliso M, Consoli A, Ahmad S, Kore D, Ngjelina J, Karaorman M, Chiesa PL. Non traumatic right Bochdalek hernia with loss of Domain in adults. Our experience and review of literature. Ann Ital Chir. 2023 Sep 5;12:S2239253X23039877. PMID: 37814503.

DISSEMINATED TUBERCULOSIS (POTT'S DISEASE AND BILATERAL TUBERCULOUS PLEURAL EFFUSION) ASSOCIATED WITH PULMONARY THROMBOEMBOLISM

Eugerta Dilka[1,2], Klara Ziu[1], Amarilda Dyrmishi[1], Silva Tafaj[1], Amela Hasa[1]

[1]*University Hospital "Shefqet Ndroqi", Tirana, Albania*
[2] *Faculty of Medicine, University of Medicine, Tirana, Albania*

Correspodent E-mail: eugerta @yahoo.com

Abstract

Background. Spinal tuberculosis, also known as Pott's disease, is diagnosed generally based on clinical and radiographic signs. There are rare reports of the association of Pott's disease with Pulmonary thromboembolism (PTE) worldwide.

Methodology. For the patient presented in this study, we faced the difficulty of diagnosing Pott's disease. To confirm the diagnosis, several examinations were used, such as Computed Tomography (CT scan) with contrast of the thoracic and abdominal region to detect pulmonary thromboembolism, bony destruction of the vertebral bodies, and bilateral pleural effusion; pleural fluid examination to establish the diagnosis of pleural effusion; and scientific literature was also consulted to determine the patient's diagnosis.

Case report. We report a case of Pott's disease with bilateral tuberculous pleural effusion in a 55-year-old male (Z.M) who presented with chest pain, cough, persistent fever, weight loss, and night sweats over 2 months. He also had progressive lower back pain, the classical kyphosis deformity of the dorsal spine, legs weakness with changes in posture and gait for more than 2 years. He was mistakenly diagnosed with cancer of the spine with destruction of L1, and L2. The interferon-γ release assay QuantiFERON®-TB Gold and the tuberculin skin test was negative. The fluid was an exudate with lymphocytes 80%, an adenosine deaminase 83.50 U/L, Xpert MTB/RIF positive. A CT scan with contrast of the thoracic and abdominal region and was obtained which showed PTE of right pulmonary artery, bilateral pleural effusion, bony destruction of the T12-L1-L2 vertebral bodies. After ruling out all the other thrombosis causes, we concluded that disseminated TB led to PTE in this case.

Conclusion. Pott's disease should be suspected in the diagnosis of spinal pain in patients with the presence of signals like a prolonged history of progressive back pain, and constitutional symptoms. CT scan with contrast of the chest should be done to exclude PTE in disseminated tuberculosis.

Keywords: Pulmonary thromboembolism; disseminated tuberculosis, spinal tuberculosis (Pott's disease)

TUBERKULOZI I DISEMINUAR (SËMUNDJA POTT DHE VERSAMENT PLEURAL BILATERL TUBERKULAR) SHOQËRUAR ME TROMBEMBOLI PULMONARE

Abstrakt

Hyrje. Tuberkulozi spinal, i njohur gjithashtu si sëmundja e Pott-it diagnostikohet përgjithësisht në bazë të shenjave klinike dhe radiografike. Ka raportime të rralla në mbarë botën të shoqërimit të sëmundjes Pott me Trombembolinë Pulmonare.

Metodologjia. Për pacientin e paraqitur në këtë studim u përballëm me vështirësinë e diagnozës të sëmundja e Pott. Për të konfirmuar diagnozën u përdorën disa egzaminime si: tomografia e kompjuterizuar (CT scan) me kontrast të rregjionit torakal dhe abdominal për të zbuluar trombembolinë pulmonare, destruksionin kockor të trupave vertebralë, versamentin pleural bilateral; egzaminimi i likidi pleural për vendosjen e diagnozës se likidit pleural. Gjithashtu u konsultua literatura shkencore për të përcaktuar diagnozën e pacientit.

Raportim rasti. Ne po paraqesim një rast me sëmundjen Pott's me versament pleural bilateral tuberkular në një pacient 55 vjec i cili u paraqit me dhimbje kraharori, kollë, temperaturë persistente, rënie në peshë, djersitje natën për një periudhë 2 mujore. Ai kishte gjithashtu dhimbje progresive në pjesën e poshtme të shpinës dhe deformim klasik i kifozës së shtyllës kurrizore dorsale, dobësi të këmbëve me ndryshime në posturë dhe ecje për më shumë se 2 vjet. Ai u diagnostikua gabimisht me kancer të shtyllës kurrizore me destruksion të L1, L2. Analiza e çlirimit të interferon-γ QuantiFERON®-TB Gold dhe testi i lëkurës së tuberkulinës ishte negativ. Likidi pleural ishte eksudat me limfocite 80%, adenosinë deaminasë 83.50 U/L, Xpert MTB/RIF pozitive. CT torakal dhe abdominal me kontrast tregoi Trombemboli pulmonare në arterien pulmonare të djathtë, likid pleural bilateral, destruksion kockor të trupave vertebrale T12-L1-L2. Pasi përjashtuam të gjithë shkaqet e tjera të trombozës, arritëm në përfundimin se TB i disiminuar ka shkaktur Trombembolinë pulmonare në këtë rast.

Konkluzioni. Sëmundja e Pott duhet të dyshohet në diagnozën e dhimbjes kurrizore në pacientët me prani të të dhënave si një histori e zgjatur e dhimbjes progresive të shpinës, simptomat konstitucionale. CT scan me kontrast duhet të bëhet për të përjashtuar PTE në tuberkulozin e diseminuar.

Fjalë kyçe. Embolia pulmonare, tuberkuloz i diseminuar, tuberkulozi spinal (sëmundja Pott)

Introduction

Spinal tuberculosis, also known as Pott's disease or tuberculous spondylitis, results from the hematogenous spread of Mycobacterium Tuberculosis (MT) bacteria from an extra-spinal focus to the spine or through lymphatic channels from the paravertebral lymph nodes or pleural space (1,2,3). Tuberculous spondylitis is the most dangerous type of skeletal tuberculosis, as it can lead to deformity of the spine and cause neurological deficits or

pulmonary insufficiency (4). The diagnosis of Pott disease is generally based on clinical and radiographic signs (5).

TB is considered a risk factor for Pulmonary thromboembolism (PTE) and there are rare reports of TB with PTE worldwide. Which TB patients are more susceptible to PTE is still not clear. As a chronic infectious disease, TB is also associated with PTE. Further studies showed that pulmonary TB induced a systemic hypercoagulable state (1).

Case presentation

We report a case of tuberculosis spondylitis (Pott's disease) with bilateral pleural effusion in a 55-year-old male who presented with chest pain, dyspnea, cough, persistent fever, weight loss, night sweats, and anorexia over approximately 2 months. He also had progressive lower back pain with local tenderness, the classical kyphosis deformity of the dorsal spine, and leg weakness with changes in posture and gait for more than 2 years. He was mistakenly diagnosed with cancer of the spine with destruction of L1, L2 and surgical intervention was recommended two years ago. He was a non-smoker. Cardiovascular and neurological examinations were clinically normal. He was normotensive and not tachypneic or tachycardic. On auscultation of the chest, there were decreased breath sounds in bilateral basal regions. The pulse oximeter reading was 96% on air. Pulmonary X-Ray imaging showed bilateral pleural effusion and cultures of sputum were negative for tuberculosis.



Figure 1. Spinal deformity, a significant feature of spinal tuberculosis.

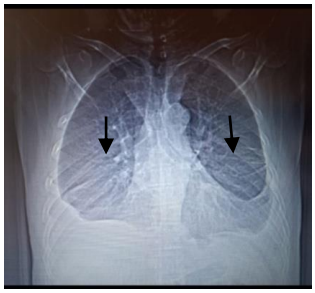


Figure 2. Chest x-ray PA view shows bilateral pleural effusions.

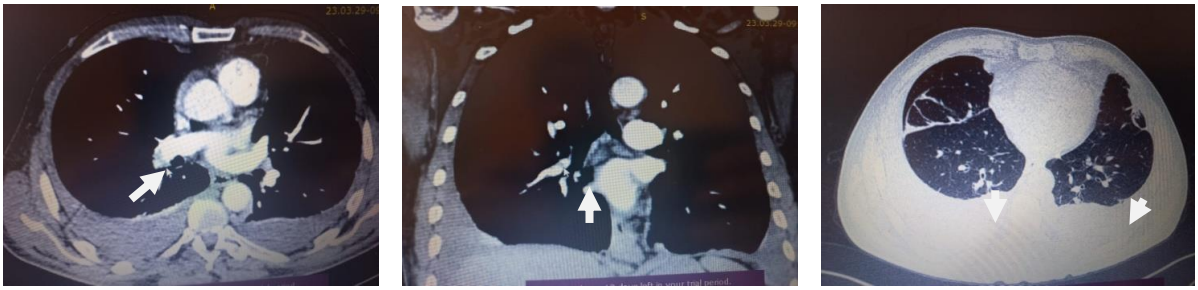


Figure 3. A CT scan with contrast of the chest and lumbar region: thromboembolism of bifurcation of right pulmonary artery with bilateral pleural effusion.



Figure 4.Computed tomography coronal view of the thoracic spine from the initial visit shows significant worsening bony destruction of the T12-L1-L2 vertebral bodies with paravertebral soft tissue extension and a stenosis of the intervertebral disc space.

Laboratory studies showed markedly increased inflammatory activity (CRP 8.5 mg/dL), but a normal white blood count of 8,700/μL. HIV serology was negative. Remarkably, the interferon-γ release assay QuantiFERON®-TB Gold In-Tube was negative (IFN 0.17 IU/mL) and the tuberculin skin test (TST) was negative (0 mm). The initial diagnosis was tuberculosis pleuritis. The pleural effusion was investigated by thoracentesis. The fluid was an exudate with a clear predominance of lymphocytes (80%), and an adenosine deaminase (ADA) value of 83.50 U/L, Xpert MTB/RIF positive. A Computed Tomography (CT) scan with contrast of the chest, lumbar, and spine region was obtained which showed thromboembolism of bifurcation of the right pulmonary artery with bilateral pleural effusion, significant worsening bony destruction of the T12-L1-L2 vertebral bodies with paravertebral soft tissue extension and stenosis of the intervertebral disc space (spondylodiscitis). The patient was a poor surgical candidate for an open biopsy of the lesion.

D-dimer was 13.17 mg/L. Serum protein C, protein S, antithrombin, and factor V levels were normal, and Antinuclear Antibodies (ANA) and antiphospholipid antibodies APLA profile were negative, also. The bilateral limb and lower limb color Doppler scan were negative for any thrombus. After ruling out all the other thrombosis causes, we concluded that disseminated TB led to PTE in this case.

Neurosurgery declined operative medicine due to the patient was without advanced neurological deficits. The patient was initiated on anti-coagulation and weight-based anti-

tubercular therapy (ATT). The patient was started on a four-drug antitubercular treatment regimen of oral rifampin 600 mg/day, isoniazid 300 mg/day, pyrazinamide 500 mg thrice/day, and ethambutol 1200 mg/day (RIPE). Therefore, LMWH was prescribed as anticoagulant.

Discussion

Although it is well known that MT can be pathologic to any organ system, its manifestations can be so variable that sometimes it becomes a challenge for the clinician to identify or even consider it as the cause of the patient's symptomatology (6).

Extra pulmonary tuberculosis (EPTB), defined when the tuberculosis mycobacterium invades areas outside the pulmonary parenchyma, has nonspecific clinical findings developing insidiously mimicking other noninfectious conditions. It requires a high clinical suspicion and carries a long period from the initial symptoms to the final diagnosis. Clinical presentation will vary according to the organ system involved and more than one organ could be involved at the same time. The initial step in early identification is having knowledge of its findings in the proper clinical setting and including them within the differential diagnosis (6).

The diagnosis and treatment of EPTB are challenging. Most cases show constitutive symptoms such as fever, weight loss, night sweats, or malaise with specific systemic symptoms based on the organ affected (7). The sensitivity and specificity of various tests used to diagnose EPTB are highly variable; in most cases, clinical disease presentation should be considered in choosing and interpreting a specific diagnostic test (7).

The initial diagnosis was tuberculosis pleuritis. Diagnosis involves a combination of clinical, radiological, microbiological, and molecular testing (7). Fluid analysis in PLTB is exudate characterized by lymphocytic predominance. It usually presents with more than 80% of lymphocytic predominance (8). Biochemical parameter, ADA levels is monitored in pleural fluid, and elevated level of this marker help pleural tuberculosis diagnosis in high-prevalence or endemic countries. In endemic countries, pleural ADA levels of >40 IU/L have a positive predictive value of 98% (9). In a high prevalence population, an elevated ADA level (>40 U/L) is considered confirmatory with a clear indication for therapy (8). Xpert MTB/RIF can be used as an initial test for adults with EP-TB indications using a pleural fluid sample. The Xpert MTB/RIF and Xpert Ultra sensitivities are 50% and 71% over MRS with 99% and 71% specificity, respectively, for adult pleural fluid (10). The fluid analysis of our patient was an exudate with a clear predominance of lymphocytes (80%), and adenosine deaminase (ADA) levels of 83.50 U/L, Xpert MTB/RIF positive.

Tuberculosis spondylitis (Pott's disease) is an ancient human disease. Because it is rare in high-income, tuberculosis (TB) low-incidence countries, misdiagnoses occur as sufficient clinical experience is lacking (11). Most spinal infections typically come from a pulmonary focus or extra-pulmonary foci (12). Tubercle bacilli reach the spine either hematogenous or through lymphatic channels from the paravertebral lymph nodes or pleural space (3). Reports suggest that most tuberculosis empyema and patients with vertebral bone involvement (Pott's disease) develop after the transport of tubercle bacilli from the pleural spaces to the parasternal and the para-aortic lymph nodes and the breakdown of caseous foci in these nodes (13). Diagnosis of spinal tuberculosis is multifaceted and includes components of clinical history, laboratory results, and imaging findings (7). The diagnosis of Pott's disease is

generally based on clinical and radiographic signs (5). Pott's disease should be considered when patients present with neurological findings suggesting spinal cord compression and spinal deformity (14). Results in pain and stillness early on, then muscle spasms and restriction of spinal movement, local tenderness, and varying degrees of deformity. The pain may be restricted to the affected region or it may radiate in the distribution of the affected segment (3). In advanced stages of the disease, large areas of bone destruction, associated with the collapse of the vertebrae and kyphoscoliosis deformity of the spine constitute the familiar radiological picture. The classical deformity especially in the lesion of the dorsal spine is the (Gibbus) or (Kyphosis) (3). Chronic back pain is sometimes accompanied by muscle spasms and changes in posture and gait. MT infection often presents with constitutional symptoms such as weight loss, fever, and night sweats (especially if disseminated MT is present) (2).

Our patient showed a combination of alarm signals: chest pain, dyspnea, cough, persistent fever, weight loss, night sweats, anorexia over approximately 2 months, progressive lower back pain with local tenderness, the classical kyphosis deformity of the dorsal spine, leg weakness with changes in posture and gait for more than two years, which encouraged us to do further work-up to establish a definite diagnosis. Due to the subtle nature of symptoms, diagnostic evaluations are often not initiated until the process is advanced. However, establishing the correct diagnosis is challenging and misdiagnoses may occur in up to 41% of cases (15).

The CT scan appearance can be highly suggestive of tuberculosis spondylitis (3). CT scan of the spine is considerably more sensitive and should be obtained whenever an infectious process is suspected (16). The disease is located in the vertebral column, and more specifically, in about 3/4 of the cases, in some part of the column between the sixth dorsal and the third lumbar vertebrae, the ninth dorsal vertebra seems to be the one most frequently involved (3). Two types of lesions can be seen: Vertebral, cavity in a vertebral body, erosion of one or more vertebral surface with or without compression and cuneiform, aspect Disk damage with compression and disappearance of the intervertebral space (5). CT with contrast of the chest, abdominal and the spine region of our patient showed thromboembolism of bifurcation of right pulmonary artery with bilateral pleural effusion, significant worsening bony destruction of the T12-L1-L2 vertebral bodies with paravertebral soft tissue extension and a stenosis of the intervertebral disc space (spondylodiscitis).

Fine Needle Aspiration is a valuable method because it reveals tissue fragments for histopathology and culture, leading to diagnosis. It is usually done when the diagnosis is in doubt or when the patient has received medical treatment for a long period enough to show a clinical response (3). Our patient was a poor surgical candidate for an open biopsy of the lesion.

Treatment regimens do not differ from pulmonary and extrapulmonary tuberculosis (3). Occasionally, surgical intervention is recommended, mainly when organ damage is debilitating to the patient (7). Neurosurgery declined operative medicine because our patient was without advanced neurological deficits. The occurrence of thrombosis in TB patients was associated with the severity of TB itself. It’s known that the three major factors causing thrombosis in TB patients are local lesion invasion, venous compression, and hypercoagulability. MT can directly cause vascular endothelial damage and release

chemoattractant such as complement C3a C5a, plasma enzyme activator and kinin releasing enzyme (kallikrein), which can further promote coagulation and thrombosis. Venous compression caused by lymph node tuberculosis could also lead to thrombosis. Hypercoagulability was due to elevated blood fibrinogen with impaired fibrinolysis, reduced thrombin III, protein C binding to thrombin, and platelet aggregation (1). D-dimer was 13.17 mg/L. We ruled out all the other causes of thrombosis and concluded that disseminated TB led to PTE in this case. The patient was initiated on anti-coagulation and weight-based anti-tubercular therapy (ATT).

Conclusion

Pott's disease should be suspicioned in the diagnosis of spinal pain in patients with significant risk factors and the presence of signals like a prolonged history of progressive back pain and constitutional symptoms. PTE should be suspected and investigated with imaging tests whenever serum D-dimer levels are elevated, particularly in those with severe pulmonary or disseminated tuberculosis. A chest CT scan with contrast should be done to exclude PTE in disseminated tuberculosis. Prophylactic use of anticoagulants should be indicated for patients with severe or hematogenous disseminated tuberculosis.

References

1. Huang L, Yin C, Gu X, et al. Severe pulmonary tuberculosis complicated with insidious pulmonary thromboembolism: a case report and literature review. J Thromb Thrombolysis. 2020;49(4):644-650. doi:10.1007/s11239-019-01967-x
2. Risos K, Duggal NA, Kamath S, Wolberg A, Sundaresh KK. A Case of Posttraumatic Pott's Disease. Cureus. 2022;14(6):e26380. Published 2022 Jun 27. doi:10.7759/cureus.26380
3. EL Bashir Gusin Elbari Ahmed, Tag Eldin O. Sokrab. Clinical pattern of Pott's disease of the spine, outcome of treatment and prognosis in adult Sudanese patients. A prospective and longitudinal study. A Thesis submitted in a partial fulfilment of the requirement for the clinical M.D. degree in Clinical Medicine of the University of Khartoum April 1997.
4. Evgenia Kalamara, Evangelos T Ballas, Guergana Petrova. Pott Disease: When Lumbar Pain is Not Innocent. Respir. Med. 2020, 88(6), 608-611; https://doi.org/10.5603/ARM.a2020.0154
5. Nadia Ait-Khaled and Donald A. Enarson. Tuberculosis. A manual for medical students. World Health Organization International Union Against Geneva Tuberculosis and Lung Disease Paris 2005.
6. Onix J. Cantres-Fonseca, William Rodriguez-Cintron, et al. Extra Pulmonary Tuberculosis: An Overview. Submitted: January 9th, 2018 Reviewed: September 4th, 2018 Published: December 10th, 2018. DOI:10.5772/intechopen.81322.
7. Radha Gopalaswamy, V. N. Azger Dusthackeer at al. Extrapulmonary Tuberculosis—An Update on the Diagnosis, Treatment and Drug Resistance. J. Respir. 2021, 1(2), 141-164; https://doi.org/10.3390/jor1020015. Received: 19 April 2021 / Revised: 19 May 2021 / Accepted: 20 May 2021 / Published: 26 May 2021.
8. A. Méndez-Vilas, Ed. The Challenge of Diagnosing Pleural Tuberculosis Infection. Microbial pathogens and strategies for combating them: Science, technology and education. FORMATEX 2013 : http://www.formatex.info/microbiology4/vol3/1950-1956.pdf

9. Lee YC, Rogers JT, Rodriguez RM, Miller KD, Light RW. Adenosine deaminase levels in nontuberculous lymphocytic pleural effusions. Chest. 2001;120(2):356-361. doi:10.1378/chest.120.2.356
10. WHO. WHO Consolidated Guidelines on Tuberculosis Module 3: Diagnosis—Rapid Diagnostics for Tuberculosis Detection. Available online: https://www.who.int/publications/i/ item/who-consolidated-guidelines-on-tuberculosis-module-3-diagnosis---rapid-diagnostics-for-tuberculosis-detection (accessed on 16 April 2021).
11. Ringshausen FC, Tannapfel A, Nicolas V, et al. A fatal case of spinal tuberculosis mistaken for metastatic lung cancer: recalling ancient Pott's disease. Ann Clin Microbiol Antimicrob. 2009;8:32. Published 2009 Nov 20. doi:10.1186/1476-0711-8-32
12. Chen CH, Chen YM. Early diagnosis of spinal tuberculosis. J Formos Med Assoc. 2016, 115:825-36. 10.106/j.jfma.2016.07.001 https://doi.org/10.106/j.jfma.2016.07.001.
13. Burke HE. A new approach to the pathogenesis of extrapulmonary tuberculosis. The British Journal of Tuberculosis and Diseases of the Chest. 1954;48(1):3-11.
14. Turgut M. Spinal tuberculosis (Pott's disease): its clinical presentation, surgical management, and outcome. A survey study on 694 patients. Neurosurg Rev. 2001;24(1):8-13. doi:10.1007/pl00011973.
15. Nussbaum ES, Rockswold GL, at al: Spinal tuberculosis: a diagnostic and management challenge. J Neurosurg. 1995, 83: 243-247. 10.3171/jns.1995.83.2.0243.
16. Joseffer SS, Cooper PR: Modern imaging of spinal tuberculosis. J Neurosurg Spine. 2005, 2: 145-150. 10.3171/spi.2005.2.2.0145.

RAPID DISEASE PROGRESSION IN A RHEUMATOID ARTHRITIS AND SYSTEMIC SCLEROSIS OVERLAP SYNDROME: A CASE REPORT

Valbona Duraj[1], Joana Hankollari[2], Ornela Gelaj[3], Jonida Xhixho[3], Ligea Gjoni[3]

[1]*Service of Rheumatology, University Hospital Center "Mother Teresa", Tirana, Albania*
[2]*Vorë Health Center, Vorë, Albania*
[3]*Resident in the Rheumatology Service*

Correspondent E-mail: valbonaduraj@yahoo.com

Abstract

Background: Rheumatoid arthritis is a chronic systemic inflammatory disease of an autoimmune nature. The small joints of the hands and feet are the primary targets, but it can also be associated with other joints or extra-articular involvement. Autoimmunity, vasculopathy, fibrosis are characteristics of systemic sclerosis, a chronic connective tissue disease. When patients meet diagnostic criteria for both diagnoses, they are considered to have the overlap syndrome. The treatment is individualized and focuses on the current clinical picture.

Case Report: A 57-year-old patient presents to her rheumatologist at her health center with pain in the small joints of the hands, objectively without signs of inflammation; RF, anti-CCP negative; ERS, CPR above normal justified by the viral condition. The patient did not meet the diagnostic criteria for any autoimmune rheumatic diseases. She had osteoarthritis of the hands. After 6-months, the follow-up visit resulted in the diagnosis of rheumatoid arthritis after the criteria were met. Due to mild pulmonary fibrosis, leflunomide 20 mg/day was initiated for treatment. Two months after starting therapy, the patient reported clinical improvement. Objectively, the small joints of the hands were without inflammation. About two months after the last check-up, Raynaud's phenomenon appeared and she left for Italy, where she was diagnosed with overlap syndrome of rheumatoid arthritis with systemic sclerosis, treated with leflunomide 20 mg/day, prednisone 5 mg/day, nifedipine 30 mg/day. When she returned, she was referred for hospitalization to the rheumatology service of University Hospital Center "Mother Teresa", where the same diagnosis was confirmed. She was treated with azathioprine 50 mg/day, prednisone 5 mg/day, and nifedipine 10 mg/day.

Conclusion: Patients with autoimmune rheumatic diseases require frequent monitoring because of the possibility of rapid progression of the disease, poor prognosis, and overlap syndromes.

Keywords: rheumatoid arthritis, systemic sclerosis, overlap syndrome

AVANCIMI I SHPEJTË I SËMUNDJES NË NJË SUBJEKT ME SINDROMËN E MBIVENDOSJES SË ARTRITIT REUMATOID ME SKLERODERIMINË SISTEMIKE: RAPORTIM RASTI

Abstrakt

Hyrje: Artriti reumatoid është një sëmundje inflamatore kronike sistemike me natyrë autoimune. Ai prek kryesisht artikulacionet e vogla të duarve, këmbëve, por mund të prekë dhe artikulacione të tjera apo prekje extra-artikulare. Sklerodermia sistemike është një sëmundje kronike e indit lidhor që karakterizohet nga autoimuniteti, vaskulopatia, fibroza. Sindromi i mbivendosjes së artritit reumatoid me skleroderminë sistemike ndodh në ato raste kur pacienti plotëson kriteret diagnostike për të dyja diagnozat. Trajtimi është i personalizuar dhe përqendrohet në kuadrin klinik mbizotërues.

Raportim rasti: Pacientja 57 vjeç, paraqitet te mjeku reumatolog në qendrën e saj shëndetësore me dhimbje të artikulacioneve të vogla të duarve, objektivisht pa shenja inflamacioni; FR, anti-CCP negativ; ERS, PCR mbinormë të justifikuara nga gjëndja virale. Pacientja nuk plotësonte kriteret diagnostike për asnjë sëmundje reumatizmale, largohet me diagnozën osteoartrozë e duarve. Në vizitën e rikontrollit, pas 6 muajsh, vendoset diagnoza artritit reumatoid pasi tashmë plotësoheshin kriteret dhe filloi mjekimin me leflunomide 20 mg/ditë për shkak të fibrozës së lehtë pulmonare. Dy muaj pas fillimit të terapisë, pacientja referoi përmirësim të klinikës, objektivisht artikulacionet e vogla te duarve pa inflamacion. Rreth dy muaj pas kontrollit të fundit i shfaqet fenomeni Raynaud dhe niset për në Itali, ku u diagnostikua me sindromën e mbivendosjes të artritit reumatoid me skleroderminë sistemike nën mjekim me leflunomide 20 mg/ditë, prednisone 5 mg/ditë, nifedipinë 30 mg/ditë. Kur rikthehet, referohet për hospitalizim në shërbimin e reumatologjisë QSUT, ku konfirmohet e njëjta diagnozë, nën mjekim me azathioprinë 50 mg/ditë, prednizon 5 mg/ditë, nifedipinë10 mg/ditë.

Konkluzione: Pacientët me sëmundje reumatizmale autoimune kanë nevojë për një monitorim të shpeshtë pasi ekzistojnë raste me një ecuri shumë të shpejtë të sëmundjes, prognozë jo të mirë dhe mund të shfaqen sindroma të mbivendosjes.

Fjalët kyçe: artrit reumatoid, sklerodermi sistemike, sindroma e mbivendosjes.

Introduction

Rheumatoid arthritis is a chronic systemic inflammatory disease of an autoimmune nature. The small joints of the hands and feet are the primary targets, but it can also be associated with other joints or extra-articular involvement (1). Based on 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative, In order to diagnose rheumatoid arthritis, a minimum of 6 points of the diagnostic criteria must be met. The criteria are classified into clinical criteria, serological tests, acute phase inflammatory markers, and duration of symptoms. Clinical criteria include the number of affected joints. Serology assesses the positivity of FR and/or ACPA, including anti-CCP. ERS or CPR is measured to evaluate the level of disease activity,

and symptoms must have been present for at least 6 weeks. Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints and first metatarsophalangeal joints are excluded from assessment. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement. Large joints refer to shoulders, elbows, hips, knees and ankles. Small joints refer to the metacarpophalangeal joints, proximal interphalangeal joints, second to fifth metatarsophalangeal joints, thumb interphalangeal joints and wrists. In this category, at least one of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (eg, temporomandibular, acromioclavicular, sternoclavicular, etc.) (2).

Systemic sclerosis is a heterogeneous disorder whose pathogenesis is characterized by 3 features: small-vessel vasculopathy, autoantibody production, and dysfunction of fibroblasts resulting in increased deposition of extracellular matrix. The American College of Rheumatology and European League Against Rheumatism (ACR-EULAR) created a joint proposal for new classification criteria in 2013. The ACR-EULAR classification criteria established that systemic sclerosis can be diagnosed if thickening of the skin of the fingers extends proximal to the metacarpophalangeal joints. Absent this finding, the presence of the following 7 features should be noted and scored: thickening of the skin of the fingers like puffy fingers or sclerodactyly, lesions on the fingertips like ulcers on tip of digits or pitting scars on fingertips, telangiectasia, abnormal nail fold capillaries, interstitial lung disease or pulmonary arterial hypertension, Raynaud phenomenon, and systemic sclerosis-related autoantibodies like presence of ≥1 of the following: Centromere antibody, Scl-70 antibody, RNA polymerase III antibody. Patients with a minimum score of 9 are classified with definite systemic sclerosis (3).

The presence of another rheumatological condition in patients with rheumatoid arthritis is not uncommon (4). Overlap Syndromes have been defined as entities satisfying classification criteria of at least two connective tissue diseases occurring at the same or at different times in the same patient. Connective tissue diseases include systemic lupus erythematosus , rheumatoid arthritis, systemic sclerosis, polymyositis/dermatomyositis, and Sjögren syndrome. Every combination of these disorders has been reported. In a recent study, 6.4% of systemic sclerosis patients studied was identified as having an overlap syndrome. The most frequent systemic sclerosis overlap syndromes reported were myositis in 42.8% and rheumatoid arthritis in 32%. It is known that there is a higher incidence of rheumatoid arthritis in systemic sclerosis patients than in the general population. Therefore, an active search for overlap syndromes should be performed in all patients (5, 6, 7, 8).

Case presentation

A 57-year-old patient presents to our health center with pain of an inflammatory and mechanical nature in the small joints of the hands and radiocarpal joints, which started a month ago. She reports that in the past she has suffered a fracture in the right glenohumeral joint and accidentally damaged the fifth digit of her right hand with a machine. According to her report, she is being treated for arterial hypertension and anxiety. There is no familial history of rheumatoid arthritis. She has performed basic laboratory control tests, which resulted within the norm. There is no record of any previous surgical interventions or drug or

non-drug allergies by her. The patient is experiencing a viral condition. During objective examination, the skin and mucous membranes were well-colored, the heart had rhythmic tones, bilateral vesicular respiration, a soft, palpable abdomen, bilateral negative Giordano test, the inferior extremities were slightly edematous bilaterally, and the vital parameters were normal. Small joints of the hands are not tender to pressure, and there are no signs of inflammation or infiltrations. Crepitation is present in knees during flexion and extension. The articular range of motion of other joints is preserved, but the right glenohumeral articulation is still tender. Normal cervical range of motion. No presence of rheumatoid nodules. Preserved muscular strength. No presence of Raynaud phenomenon, no skin induration. Oral aphthae, dry eyes or mouth, photosensitivity, or psoriatic cutaneous elements in the past or family history were not mentioned. It was recommended to complete the laboratory tests such as RF, anti-CCP, CRP, ERS, uric acid, posterior-anterior and oblique bilateral hand radiography. The hand radiograph showed only changes in favor of osteoarthritis of the hands. RF and anti-CCP were negative, uric acid 5.4 mg/dl, ERS 27 mm/h, CRP 13.6 mg/l. The latter was justified because of the viral condition that the patient was experiencing. She was diagnosed with hand osteoarthritis and treated with piroxicam 20 mg/day for only 10 days and oral hyaluronic acid (9). After two months of persistent pain, she visited a rheumatologist at a private institution. All laboratory tests were repeated, and the diagnosis of osteoarthritis of the hands was reconfirmed.

After 6 months from the first visit to our health center, the patient presented with the same pain, but this time with morning stiffness lasting over an hour, fatigue, body weakness, and knee pain. Our objective examination resulted in the discovery of tenderness, infiltration, and inflammation in the small joints of the hands, such as the proximal interphalangeal, metacarpophalangeal, and radiocarpal. Crepitus was present in her knees. Cervical and lumbar spine were slightly painful during maneuvers. The patient had meanwhile consulted a cardiologist for edema in the inferior extremities, and was recommended to repeat the basic control laboratory tests, ERS, CRP, RF, anti-CCP, uric acid, abdominal ultrasound, venous Doppler ultrasound of the inferior extremities and consult a pulmonologist in case of starting methotrexate therapy. Basic control laboratory tests within the norm, ERS 55 mm/h, CRP 27.71 mg/l, uric acid 2.88 mg/dl, RF slightly positive for the norm of the laboratory where it was performed 18.8 IU/ml, anti-CCP > 1000 U/ml. During a consultation with the cardiologist a few months ago, the patient was diagnosed with stage II arterial hypertension, hypertensive cardiopathy, dyslipidemia, without significant problems of the neck vessels, and was treated with enalapril and bisoprolol. Abdominal ultrasound showed grade II hepatosteatosis and cystitis. The venous Doppler ultrasound of both inferior extremities resulted without thrombosis. The presence of edema in the subcutaneous connective tissue of the bilateral distal thigh was found, with minimal tenosynovial changes in the posterior tibial and bilateral peroneal parts. During the consultation with the pulmonologist, the patient underwent pulmonary x-ray and spirometry. Moderate restriction was found, but it is noted that the patient performed the respiratory test with difficulty. It has been concluded that she has mild pulmonary fibrosis. The diagnosis of seropositive rheumatoid arthritis was made and due to pulmonary fibrosis, the patient started treatment with leflunomide 20 mg/day, she refused prednisone therapy (10). She was recommended to have a follow-up check after 2 months to monitor leflunomide therapy. After two months of treatment, the intensity of the pain has decreased, as well as the edema observed in the objective examination. A very mild normocytic anemia of 11.8 mg/dL and an increase in platelets of 512,000, with a high ERS of

45 mm/h were found. The family doctor was recommended to evaluate thrombocytosis and monitor hemoglobin levels.

After 8 months, she presented for a follow-up and reported that two months after the visit to our health center, she had Raynaud phenomenon when exposed to cold, and wounds for which she had started treatment in Italy, where she was diagnosed with rheumatoid arthritis-systemic sclerosis overlap syndrome and had started treatment with prednisone 5 mg/day, leflunomide 20 mg/day, nifedipine 30 mg/day, colecalciferol, aspirin 100 mg/day, lansoprazole, losartan, fluoxetine. On objective examination, the patient had Raynaud phenomenon, digital wound scars, deformed small hand joints, sclerodactyly, facial telangiectasia, and limited rima oris. In Italy, gastroparesis, mild pulmonary hypertension, and pulmonary fibrosis were also diagnosed. She was sent to the rheumatology service at the University Hospital Center 'Mother Teresa' for a health assessment and treatment. During hospitalization were found the following laboratory test results: anti-CCP 138.1 U/I, CPR 10.46 mg/l, positive ENA screen with positive anti-Scl 70 in ENA profile and normocytic anemia, ANA 1:480. Upon discharge, the diagnosis of overlap syndrome rheumatoid arthritis stage IV with systemic sclerosis (with gastroparesis and pulmonary fibrosis) was confirmed and treatment with azathioprine 50 mg/day, prednisone 7.5 mg/day, nifedipine 10 mg/day was initiated (11, 12, 13). After two weeks, the patient was hospitalized in the Internal Medicine Service at the University Hospital Center “Mother Teresa” due to dyspnea and arrhythmia, and she was discharged with the following diagnoses: anticoagulated paroxysmal atrial fibrillation, NYHA II heart failure, stage II arterial hypertension, systemic sclerosis, depression. After the second discharge, the patient was recommended to continue treatment with azathioprine and prednisone. Her normocytic anemia was probably caused by chronic disease and systemic sclerosis affecting the gastrointestinal tract. She reported that she had no epigastric pain, bleeding, melena, nausea, or vomiting, but only slight dysphagia when eating solid foods. This was the last time the patient came for a health check-up at our health center.

Discussion

According to a study conducted in Centre for Rheumatology, Royal Free Hospital, University College Medical School, London, between September 1999 and February 2007 that included in total, 332 (20%) of 1700 patients with systemic sclerosis (SSc) had overlap syndrome. This comprised myositis (42.8%), rheumatoid arthritis (RA; 32%), Sjögren's syndrome (SS; 16.8%), and systemic lupus erythematosus (SLE; 8.4%). Antinuclear antibody was positive in 96.6% of patients. Anticentromere antibody (ACA) was exclusively present in limited cutaneous systemic sclerosis overlap cases (22%), and more common in systemic sclerosis/Sjögren's syndrome overlap (44.7%), whereas no difference was found in the prevalence of Scl-70 autoantibody between limited cutaneous systemic sclerosis and diffuse cutaneous systemic sclerosis overlap groups. U1RNP was more frequent in SSc/SLE (44%), while Ro antibody was more likely to be found in SSc/SS overlap syndrome (29.8%). ACA was absent and anti-Scl-70 was infrequent in SSc/myositis; polymyositis-scleroderma antibody was more frequent in this group (33.1%). About 50% of patients had raised rheumatoid factor (RF), with no difference between overlap groups irrespective of RF titer. In contrast, anticyclic citrullinated peptide antibody was more frequent in patients with RA features. (7)

As presented in our case, the patient initially met the diagnostic criteria for hand osteoarthritis, within 6 months the typical clinical features of rheumatoid arthritis began and

the diagnostic criteria for seropositive rheumatoid arthritis were met. The overlap syndrome of rheumatoid arthritis with systemic sclerosis was confirmed while the patient manifested typical clinical features of systemic sclerosis. This happened after 5 months of the diagnosis of rheumatoid arthritis. The treatment was carried out in accordance with the patient's manifestations step by step. At the stage of hand osteoarthritis, nonsteroidal anti-inflammatory drugs were used, followed by leflunomide when rheumatoid arthritis was diagnosed due to mild pulmonary fibrosis and with azathioprine, prednisone, and nifedipine after hospitalization in the rheumatology service at the University Hospital Center "Mother Teresa". Such difficult cases with a very rapid course of the disease remind us that patients with autoimmune rheumatic diseases need frequent monitoring as there are cases with a very rapid course of the disease, poor prognosis and overlap syndromes may appear. (14)

Conclusion

Patients with autoimmune rheumatic diseases require frequent monitoring as there are cases with a very rapid course of the disease, poor prognosis, and overlap syndrome may occur. The overlap syndrome of rheumatoid arthritis and systemic sclerosis may require frequent hospitalizations for evaluation of gastrointestinal involvement, evaluation for possible pulmonary hypertension, evaluation of digital wounds, inflammation, and joint deformities, high disease activity and risk of serious cardiac and renal complications that can lead to sudden death.

Conflict of interest: The authors have no conflicts of interest to declare

References

1. Firestein and Kelley's Textbook of Rheumatology, 2:11th edition, Elsevier 2020, p.1181-1283.
2. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative [published correction appears in Ann Rheum Dis. 2010 Oct;69(10):1892]. Ann Rheum Dis. 2010;69(9):1580-1588. doi:10.1136/ard.2010.138461
3. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. Ann Rheum Dis. 2013;72(11):1747-1755. doi:10.1136/annrheumdis-2013-204424.
4. Luca Iaccarino, Mariele Gatto, Silvano Bettio, Francesco Caso, Mariaelisa Rampudda, Margherita Zen, et.al. Overlap connective tissue disease syndromes, Autoimmunity Reviews, 2013, Volume 12, Issue 3.
5. Pinto AS, Santos FC, Dinis SP, Madeira N, Ferreira JF, Vaz C. Systemic sclerosis and rheumatoid arthritis overlap syndrome - management of severe cardiac, pulmonary and articular involvement. Reumatologia. 2023;61(1):55-62. doi:10.5114/reum/161299.
6. Scherlinger M, Lutz J, Galli G, et al. Systemic sclerosis overlap and non-overlap syndromes share clinical characteristics but differ in prognosis and treatments. Semin Arthritis Rheum. 2021;51(1):36-42. doi:10.1016/j.semarthrit.2020.10.009

7. Pakozdi A, Nihtyanova S, Moinzadeh P, et al. Clinical and serological hallmarks of systemic sclerosis overlap syndromes. J Rheumatol 2011; 38: 2406–2409.
8. Jinnin M, Ihn H, Yamane K, et al. Clinical features of patients with systemic sclerosis accompanied by rheumatoid arthritis. Clin Exp Rheumatol 2003; 21: 91–94.
9. Haugen IK, Felson DT, Abhishek A, *et al* 2023 EULAR classification criteria for hand osteoarthritis *Annals of the Rheumatic Diseases* 2024;83:1428-1435.
10. Smolen JS, Landewé RBM, Bergstra SA, *et al* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update *Annals of the Rheumatic Diseases* 2023;82:3-18.
11. Del Galdo F, Lescoat A, Conaghan PG, et al. EULAR recommendations for the treatment of systemic sclerosis: 2023 update. Ann Rheum Dis. Published online October 17, 2024. doi:10.1136/ard-2024-22643
12. Kowal-Bielecka, Otylia et al. "Update of EULAR recommendations for the treatment of systemic sclerosis." *Annals of the rheumatic diseases* vol. 76,8 (2017): 1327-1339. doi:10.1136/annrheumdis-2016-209909
13. Nassar M, Ghernautan V, Nso N, et al. Gastrointestinal involvement in systemic sclerosis: An updated review. *Medicine (Baltimore)*. 2022;101(45): e 31780.
14. Fujiwara, T., Tokuda, K., Momii, K. *et al.* Prognostic factors for the short-term mortality of patients with rheumatoid arthritis admitted to intensive care units. *BMC Rheumatol*. 2020; 4, 64.

Verquvo®
vericiguat

BAYER

Përkeqësimi i insufiçencës kardiake

Jepini pacientëve tuaj një forcë stabilizuese.
Pikërisht kur atyre u nevojitet me shumë.



Verquvo®indikohet tek pacientët adultë me insufçence kardiake simptomatike me reduktim të fraksionit të ejeksionit të cilët janë stabilizuar së fundimi pas një eventi dekompensimi me terapi IV.[1]

Reference: 1. Verquvo (vericiguat). Permbledhja e karakteristikave te produktit (Korrik 2021

PP-VER-AL-0108-1
26 dec 2024

Kerendia®
finerenone

Një lëvizje mund të ndryshojë rezultatin[1]

Për pacientët tuaj me SRK dhe diabet tip 2
Veproni tani duke mundësuar një reduktim të dyfishtë të riskut kardio-renal .



Reduktoni riskun e ngjarjeve kardiovaskulare

Ulni progresin e SRK

Kerendia është i pari dhe i vetmi antagonist selektiv jo-steroidik i receptorëve mineralokortikoid i aprovuar për trajtimin e SRK shoqëruar me diabet tip 2

Pse të ngurrojmë? Veproni tani me Kerendia për ti dhënë pacientëve tuaj mbrojtjen për të cilën ata kanë nevojë

KDIGO = Kidney Disease Improving Global Outcomes; ADA = American Diabetes Association; AACE = American Association of Clinical Endocrinology; ESC= European society of cardiology; SRK=Sëmundja renale kronike;

Reference: 1. Kerendia European Summary of Product Characteristics (SmPC); February 2023. **2.** Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int. March 2022. **3.** American Diabetes Association. Addendum 11. Chronic kidney disease and risk management: Standards of medical care in diabetes-2022. Diabetes Care. 2022; 45 (Suppl 1): S175-S184. **4.** Blonde L, Umpierrez GE, Sethu Reddy S, et al. American Association of Clinical Endocrinology Clinical Practice Guideline: developing a diabetes mellitus comprehensive care plan—2022 update. Endocrine Pract. 2022; (10): 923-1049.**5.** 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes: Developed by the task force on the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC) (https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehad192/7238227?login=true last accessed Sep. 2023 **6.** 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC (https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehad195/7246292?login=true last accessed Sep. 2023)

PP-KER-AL-0345-1
24 Dec 2024

BAYER