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KNJIGA SAŽETAKA

NACIONALNI KONGRES
SA MEĐUNARODNIM UČEŠĆEM
KLINIČKE MANIFESTACIJE
AUTOIMUNSKIH BOLESTI

ABSTRACT BOOK

NATIONAL CONGRESS
WITH INTERNATIONAL PARTICIPATION
CLINICAL MANIFESTATIONS
OF AUTOIMMUNE DISEASES

SERBIAN JOURNAL OF THE MEDICAL CHAMBER

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**LEKARSKA KOMORA SRBIJE
REGIONALNA LEKARSKA KOMORA BEOGRADA**

**NACIONALNI KONGRES SA MEĐUNARODNIM UČEŠĆEM
KLINIČKE MANIFESTACIJE AUTOIMUNSKIH BOLESTI**

**NATIONAL CONGRESS WITH INTERNATIONAL PARTICIPATION
CLINICAL MANIFESTATIONS OF AUTOIMMUNE DISEASES**



**KNJIGA SAŽETAKA
ABSTRACT BOOK**

**Dom Vojske, Beograd
29–30. maj 2025. godine**

EDITORIJAL



doc. dr Maja Životić

U okviru **Nacionalnog kongresa sa međunarodnim učešćem**, pod nazivom „**Kliničke manifestacije autoimunskih bolesti**“, koji je održan 29. i 30. maja 2025. godine u organizaciji **Lekarske komore Srbije/ Regionalne lekarske komore Beograda**, istraživao je značaj prepoznavanja, dijagnostike, terapije i rehabilitacije različitih kliničkih manifestacija autoimunskih bolesti u svakodnevnoj medicinskoj praksi. Pažljivo su razmotrene karakteristike autoimunskih lezija u različitim organskim sistemima, uključujući kožu, nervni sistem, kardiovaskularni sistem, respiratorni trakt, hematološki sistem, endokrini sistem, bubrege, jetru i žučne puteve, digestivni trakt, kao i psihijatrijske manifestacije. Posebno smo ponosni što je u program kongresa bila uključena i sesija posvećena savremenim aspektima fizikalne medicine i rehabilitacije, koja ima ključnu ulogu u očuvanju funkcionalne sposobnosti, poboljšanju kvaliteta života i smanjenju invaliditeta kod pacijenata sa autoimunskim bolestima. Ova tema, nažalost često zapostavljena u okviru multidisciplinarnih timova, još jednom je istakla važnost integrisanog pristupa i saradnje različitih specijalnosti u zbrinjavanju ovih pacijenata.

Ključna je bila multidisciplinarna borba protiv autoimunskih bolesti, što uključuje rano prepoznavanje simptoma, pravovremeno postavljanje dijagnoze, primenu odgovarajućih terapijskih modaliteta i adekvatne rehabilitacione strategije. Kongres „Kliničke manifestacije autoimunskih bolesti“ okupio je stručnjake iz različitih oblasti medicine kako bi razmotrili najnovija dostignuća, izazove i perspektive u dijagnostici, lečenju i rehabilitaciji ovih bolesti, doprinoseći time unapređenju kliničke prakse i poboljšanju zdravlja pacijenata. Autoimunske bolesti zauzimaju važno mesto u savremenoj medicini, jer njihova multisistemska priroda značajno utiče na morbiditet, mortalitet i invaliditet, a samim tim i na kvalitet života pacijenata. Ovaj uticaj nije samo medicinski, već ima i veliki ekonomski značaj, s obzirom na povećane troškove lečenja i dugoročne rehabilitacije.

Želimo da se učesnici kongresa rado prisete tema i predavanja koja su im pružila uvid u najnovija dostignuća i izazove u oblasti autoimunskih bolesti. Takođe, želimo da onima koji nisu imali priliku da prisustvuju omogućimo da kroz ove sažetke osete deo atmosfere i bogatstva znanja koje je predstavljeno na ovom značajnom skupu.

Posebnu zahvalnost dugujemo svim predavačima – kako domaćim, tako i stranim – koji su svojim izlaganjima doprineli visokom kvalitetu kongresa, a čija su izlaganja obogatila naučni program i podstakla diskusiju. Vaš entuzijazam i posvećenost od neprocenjivog su značaja za napredak medicinske nauke i prakse.

Odabrani sažeci objavljeni u suplementu Srpskog medicinskog časopisa Lekarske komore prošli su recenziju od strane Naučnog odbora kongresa.

Srdačno,

*Organizacioni odbor Nacionalnog kongresa sa međunarodnim učešćem
„Kliničke manifestacije autoimunskih bolesti“*

EDITORIAL

As part of the **National Congress with International Participation**, titled “**Clinical Manifestations of Autoimmune Diseases**,” which was held on May 29–30, 2025, and organized by the **Serbian Medical Chamber/Regional Medical Chamber of Belgrade**, we explored the importance of recognizing, diagnosing, treating, and rehabilitating various clinical manifestations of autoimmune diseases in everyday medical practice. The characteristics of autoimmune lesions in different organ systems were carefully examined, including the skin, nervous system, cardiovascular system, respiratory tract, hematological system, endocrine system, kidneys, liver and bile ducts, digestive tract, as well as psychiatric manifestations. We are particularly proud that the congress program included a session dedicated to contemporary aspects of physical medicine and rehabilitation, which play a key role in preserving functional capacity, enhancing quality of life, and reducing disability in patients with autoimmune diseases. Unfortunately, this topic is often neglected within multidisciplinary teams, but once again, it underscored the importance of an integrated approach and collaboration among different specialties in caring for these patients.

The congress highlighted the essential role of a multidisciplinary approach in combating autoimmune diseases, encompassing early symptom recognition, timely diagnosis, appropriate therapeutic modalities, and adequate rehabilitation strategies. The “Clinical Manifestations of Autoimmune Diseases” congress brought together experts from various fields of medicine to discuss the latest achievements, challenges, and perspectives in the diagnosis, treatment, and rehabilitation of these diseases, thereby contributing to the improvement of clinical practice and the health of patients. Autoimmune diseases occupy a significant place in modern medicine due to their multisystem nature, which greatly affects morbidity, mortality, and disability, and therefore the overall quality of life of patients. This impact is not only medical but also carries substantial economic significance, considering the increased costs of treatment and long-term rehabilitation.

We hope that the congress participants will fondly remember the topics and presentations that provided them with insights into the latest achievements and challenges in the field of autoimmune diseases. We also hope that those who were unable to attend will, through these abstracts, experience a part of the atmosphere and wealth of knowledge shared at this significant event.

We owe special thanks to all the presenters—both domestic and international—who contributed to the high quality of the congress with their presentations, enriching the scientific program and stimulating discussion. Your enthusiasm and dedication are invaluable to the advancement of medical science and practice.

Selected abstracts published in the supplement of the Serbian Journal of the Medical Chamber were reviewed by the Congress Scientific Committee.

Warm regards,

*Organizing Committee of the National Congress with International Participation
“Clinical Manifestations of Autoimmune Diseases”*

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Nacionalni kongres sa međunarodnim učešćem

KLINIČKE MANIFESTACIJE AUTOIMUNSKIH BOLESTI

National congress with international participation

CLINICAL MANIFESTATIONS OF AUTOIMMUNE DISEASES 13–41

SPECTRUM OF CUTANEOUS LUPUS ERYTHEMATOSUS

Mirjana Gajić Veljić¹¹ Medicinski fakultet, Univerzitet u Beogradu, Beograd, Srbija¹ Faculty of Medicine, University of Belgrade, Belgrade, Serbia

SAŽETAK

Lupus erythematosus (LE) je autoimunska inflamatorna oboljenja koje se karakteriše slomom tolerancije, produkcijom brojnih autoantitela, deponovanjem imunskih kompleksa u zidovima, predominantno malih krvnih sudova, sa posledničnom aktivacijom sistema komplementa koja dovodi do zapaljenja i oštećenja tkiva. Oko 70% pacijenata sa lupusom ima sistemski LE (SLE), oko 15% ima isključivo kutane forme, oko 10% pacijenata sindrom preklapanja sa drugom reumatskom bolešću, a 5-10% pacijenata ima lupus indukovani lekom.

Kutani lupus može da postoji nezavisno ili u sklopu SLE. Deli se na akutni kutani LE, subakutni kutani LE (papuloskvamozni i anularnopoliciklični) i hronični LE koji obuhvata diskoidni (lokalizovani i generalizovani), tumidni, chilblain LE, lupus profundus, lupus panniculitis i lupus erythematosus-lichen planus sindrom preklapanja (LE-LP overlap syndrome).

SLE je hronično, multisistemsko, autoimunska oboljenja nepredvidivog toka i prognoze. Manifestuje se širokim spektrom kliničkih i imunoloških poremećaja i može zahvatiti različite organe i organske sisteme (kožu, zglobove, bubrege, kardiovaskularni, hematopoetski i nervni sistem). Promene na koži u sklopu SLE dele se na specifične (kutani lupus, promene koje imaju specifičan histološki nalaz) i nespecifične (sreću se i kod drugih oboljenja, nemaju specifičnu histologiju). Nespecifične lezije su češće kod SLE i njihovo prisustvo može ukazati na veću aktivnost bolesti. Dele se na one koje predstavljaju kriterijume za klasifikaciju SLE (fotosenzitivnost, ulceracije na oralnoj sluznici, neožiljna alopecija) nespecifične kutane vaskularne reakcije (vaskulitis, vaskulopatija, Raynaud-ov fenomen, urtikarija, urticaria-like vasculitis, palmarni eritem, periungvalne telangiektazije, eritromelalgija, livedo racemosa) i ostale lezije (mucinoza i kalcinoza kože, promene na noktima, stečene bulozne dermatoze povezane sa SLE, kutane manifestacije autoimunskih sindroma preklapanja itd).

Ključne reči: akutni kutani lupus erythematosus, subakutni kutani lupus erythematosus, hronični kutani lupus erythematosus, sistemski lupus erythematosus, specifične kutane promene, nespecifične kutane promene

ABSTRACT

Lupus erythematosus (LE) is an autoimmune inflammatory disease characterized by the breakdown of tolerance, the production of numerous autoantibodies, the deposition of immune complexes in the walls, predominantly of small blood vessels, with the consequent activation of the complement system, which leads to inflammation and tissue damage. About 70% of patients with lupus have systemic LE (SLE), about 15% have exclusively cutaneous forms, about 10% of patients have an overlap syndrome with another rheumatic disease, and 5-10% of patients have drug-induced lupus.

Cutaneous LE can occur as a manifestation of systemic lupus erythematosus (SLE) or independent of SLE. It is divided into acute cutaneous LE, subacute cutaneous LE (papulosquamous and annular polycyclic) and chronic LE which includes discoid (localized and generalized), tumid, chilblain LE, lupus profundus, lupus panniculitis and lupus erythematosus-lichen planus overlap syndrome (LE-LP overlap syndrome).

SLE is a chronic, multisystemic, autoimmune disease with an unpredictable course and prognosis. It is manifested by a wide range of clinical and immunological disorders and can affect different organs and organ systems (skin, joints, kidneys, cardiovascular, hematopoietic and nervous system). Skin changes in SLE are divided into specific (cutaneous lupus, changes that have a specific histological finding) and non-specific (also found in other diseases, without a specific histology). Nonspecific lesions are more common in SLE and their presence may indicate greater disease activity. They are divided into those that represent the criteria for the classification of SLE (photosensitivity, ulcerations on the oral mucosa, non-scarring alopecia), non-specific cutaneous vascular reactions (vasculitis, vasculopathy, Raynaud's phenomenon, urticaria, urticaria-like vasculitis, palmar erythema, periungual telangiectasia, erythromelalgia, livedo racemosa) and other lesions (mucinoses and calcinosis of the skin, changes in the nails, acquired bullous dermatoses associated with SLE, cutaneous manifestations of overlapping autoimmune syndromes, etc.).

Keywords: acute cutaneous lupus erythematosus, subacute cutaneous lupus erythematosus, chronic cutaneous lupus erythematosus, systemic lupus erythematosus, specific skin changes, non-specific skin changes

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Alopecija areata (AA) je autoimunska bolest koju karakteriše neožiljni gubitak dlake na kapilicijumu i ostalim kosmatim regijama. Do samog oboljenja dolazi zbog gubitka imunske privilegije folikula dlake, gde autoreaktivni T ćelijski limfociti i *natural killer* ćelije, uz interferon gama dovode do oštećenja folikula i posledičnog ispadanja dlake.

Iako je učestalost AA u opštoj populaciji oko 2%, teške forme, kod kojih nedostatak dlake prevazilazi 50% površine kapilicijuma, su daleko ređe, sa prevalencijom između 0,01% i 0,09%.

Teške forme AA u velikoj većini slučajeva zahtevaju primenu sistemske imunomodulatorne terapije, a do sada zvanične preporuke i terapijski algoritmi za ovo oboljenje nisu usaglašeni od strane eksperata u ovoj oblasti.

Do sada, ova grupa pacijenata lečena je sistemskim kortikosteroidima, ali i različitim formama *steroid sparing* agenasa, uz velike diskrepance u efikasnosti i održivosti efekata terapije.

Novine u sistemske terapiji teških formi AA predstavlja primena oralnih janus kinaze inhibitora (JAK), koji su prema literaturi i kliničkoj praksi pokazali zadovoljavajuć bezbednosno/efikasni profil.

Na žalost, ova terapija nije široko dostupna u zemljama Evropske Unije, i samim tim uvođenje ovog tipa terapija kod pacijenata u Srbiji je ograničeno.

Naši podaci prikazaće iskustvo lečenja kako odraslih tako i pedijatrijskih pacijenata sa teškim formama AA na Klinici za dermatovenerologiju, Univerzitetskog kliničkog centra Srbije, koji su lečeni intravenskom pulsnom kortikosteoroidnom terapijom sa, ili bez *steroid sparing* agenasa. Uz terapijske algoritme, biće prikazani faktori koji utiču na efikasnost i samu održivost terapije.

Ključne reči: alopecija areata, SALT skor, pulsna kortikosteroidna terapija, klobetazol propionat

ABSTRACT

Alopecia areata (AA) is an autoimmune disease characterized by non-scarring hair loss on the scalp and other hairy barring regions. The disease itself occurs due to the loss of the immune privilege of the hair follicle, where autoreactive T cell lymphocytes and natural killer cells, along with interferon gamma, lead to follicle damage and subsequent hair loss.

Although the incidence of AA in the general population is about 2%, severe forms, in which loss of hair exceeds 50% of scalp, are much more rare, with a prevalence between 0.01% and 0.09%.

Severe forms of AA require systemic immunomodulatory therapy, and up until now, official recommendations and therapeutic algorithms for this disease have not been universally accepted by experts in this field.

Until now, these patients have been treated with systemic corticosteroids, but also with different forms of steroid sparing agents, with great discrepancies in the effectiveness and sustainability.

A novelty in the systemic therapy of severe AA is the application of oral Janus kinase inhibitors (JAK), which according to the literature and clinical practice have shown a satisfactory safety/effectiveness profile.

Unfortunately, this therapy is not widely available in the countries of the European Union, and therefore administration of this therapy in Serbia is limited.

Our data will show the experience of treating both adult and pediatric patients with severe forms of AA at the Clinic for Dermatovenerology, University Clinical Center of Serbia, who were treated with intravenous pulse corticosteroid therapy with or without steroid sparing agents. Along with the therapeutic algorithms, the factors that influence effectiveness and sustainability of the therapy will be presented.

Keywords: alopecia areata, SALT score, pulse corticosteroid therapy, clobetasol propionate

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AUTOIMMUNE ENCEPHALITIDES AND PARANEOPLASTIC SYNDROMES

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SAŽETAK

Autoimunski encefalitis (AE) predstavljaju imunski posredovane bolesti mozga koje nastaju usled pada imunske tolerancije na antigene sopstvenog nervnog tkiva. Karakterišu se heterogenom kliničkom prezentacijom sa predominantnom kognitivnom i psihijatrijskom simptomatologijom, udruženo sa novonastalim epileptičkim napadima. Patogeneza AE je rasvetljena otkrivanjem specifičnih autoantitela usmerenih prema intracelularnim ili površnim antigenima neurona u likvoru i/ili serumu ovih pacijenata. Pored dijagnostičkog značaja, pomenuta antitela su važna za klasifikaciju AE, prema kojima se oni dele u dve patogenetski heterogene grupe, na AE sa antitelima usmerenim prema intracelularnim antigenima neurona (Hu, Ma₂, CV₂/CRMP₅, GAD, amfifizin) i AE sa antitelima usmerenim prema površnim antigenima neurona (LGI₁, CASPR₂, NMDA, AMPA, GABA_A, GABA_B, mGluR, DPPX). Prva grupa oboljenja je veoma često udružena sa malignitetima i ima loš tok i prognozu. Sa druge strane, kod AE sa antitelima usmerenim prema površnim antigenima neurona prisustvo tumora je ređe, a prognoza bolesti značajno bolja sa postizanjem oporavka kod dve trećine obolelih. Pomenuta antitela determinišu specifičnosti u kliničkom ispoljavanju AE, kao i tip tumora koji se nalazi u osnovi neurološkog ispoljavanja, usled čega se kod pacijenata sa AE u zavisnosti od nalaza antitela usmerava dalje dijagnostičko ispitivanje. U skladu sa ovim, danas postoje jasno definisani protokoli za skrining na malignitete kod ovih bolesnika. Pored kliničke slike i laboratorijskog nalaza u postavljanju dijagnoze AE važni su i rezultati dopunskih ispitivanja, pregleda likvora, elektroencefalografije i MR endokranijuma. Savremeni terapijski koncept podrazumeva primenu različitih modaliteta imunoterapije udruženo sa simptomatskim lečenjem. Kod pacijenata sa malignitetom neophodan je i hirurški i onkološki tretman prema protokolima za odgovarajuće tumore.

Ključne reči: autoimunski encefalitis, dijagnostika, autoantitela, lečenje

ABSTRACT

Autoimmune encephalitis (AE) are immune-mediated brain diseases caused by the loss of immune tolerance to antigens of the central nervous tissue. They are characterized by a heterogeneous clinical presentation with predominant cognitive and psychiatric symptomatology, often associated with new onset epileptic seizures. The pathogenesis of AE has been elucidated through the discovery of specific autoantibodies directed against intracellular or surface neuronal antigens found in the cerebrospinal fluid and/or sera of these patients. These autoantibodies are also crucial for the classification of AE, dividing them into two pathogenetically distinct groups: AE with autoantibodies directed against intracellular neuronal antigens (Hu, Ma₂, CV₂/CRMP₅, GAD, amphiphysin) and AE with autoantibodies directed against surface neuronal antigens (LGI₁, CASPR₂, NMDA, AMPA, GABA_A, GABA_B, mGluR, DPPX). The first group of diseases is frequently associated with malignancies and generally has a poor prognosis. On the other hand, in AE with autoantibodies directed against surface neuronal antigens, the presence of tumors is less common, and the prognosis of the disease is significantly better, with recovery achieved in two-thirds of affected individuals. These autoantibodies determine the specific clinical manifestations of AE, as well as the type of tumor underlying the neurological presentation, which guides further diagnostic evaluations. Accordingly, well-defined protocols for malignancy screening in these patients are available today. In addition to the clinical picture and laboratory findings, the results of supplementary investigations, including cerebrospinal fluid analysis, electroencephalography, and brain MRI, are crucial for diagnosing AE. Therapeutic approaches involve the use of various immunotherapy modalities combined with symptomatic treatment. In patients with malignancies, surgical and oncological treatments are also necessary according to protocols for the specific tumors.

Keywords: autoimmune encephalitis, diagnosis, autoantibodies, treatment

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SAŽETAK

Multipla skleroza (MS) je hronično autoimuno, zapaljensko i neurodegenerativno oboljenje mozga, kičmene moždine i optičkog nerva. Klinički simptomi i znaci MS izuzetno su raznovrsni. Velika raznolikost u kliničkim manifestacijama na početku i tokom bolesti odražava predilekciona mesta za demijelinizacione plakove. Motorni, senzitivni, vizuelni, kao i simptomi i znaci oštećenja moždanog stabla i malog mozga predstavljaju najčešće kliničke manifestacije MS. Osim toga poremećaji mokraćne bežike i creva, kao i poremećaji seksualnih funkcija, zamor, kognitivni i psihijatrijski poremećaji su takođe često prisutne karakteristike koje veoma utiču na onesposobljenost kod osoba sa ovom bolešću. Oboleli od MS takođe mogu imati stereotipne, repetitivne, paroksizmalne simptome i znake. Bilo koja od gore navedenih manifestacija može biti početni simptom MS ili se može javiti kasnije tokom bolesti. Potrebno je naglasiti da su kliničke manifestacije koje se mogu javiti kao i klinički tok nepredvidljivi. Brojni simptomi MS mogu negativno uticati na aktivnost svakodnevnog života, fizičko, emocionalno i psihološko funkcionisanje i na kvalitet života obolelih, a neki od njih mogu dovesti do teške onesposobljenosti. Pojedine manifestacije su često barem na početku, neprepoznate od samih pacijenata. Od ogromnog značaja je prepoznavanje uzroka simptoma i znakova MS, tj. da li su oni posledica lezija unutar centralnog nervnog sistema (CNS), izazvane ovom bolešću (primarni), da li su nastali zbog funkcionalnog deficita (sekundarni), ili određenog komorbiditeta. Posebno je važno razmatranje komorbiditeta koji može dovesti do pojave smetnji koje se preklapaju ili se pogrešno pripisuju MS, naročito kada su u pitanju određene kliničke manifestacije koje su atipične za ovu bolest.

Ključne reči: multipla skleroza, simptomi, znaci, komorbiditeti, kvalitet života

ABSTRACT

Multiple sclerosis (MS) is a chronic autoimmune, inflammatory, and neurodegenerative disease affecting the brain, spinal cord, and optic nerve. The clinical symptoms and signs of MS are extremely diverse. The wide variety of clinical manifestations at the beginning and during the course of the disease reflect the predilection sites for demyelinating plaques. Motor, sensory, visual, as well as symptoms and signs of brainstem and cerebellar damage are the most common clinical manifestations of MS. Additionally, bladder and bowel disorders, sexual dysfunction, fatigue, cognitive and psychiatric disorders are also common features that significantly affect the disability of individuals with this disease. MS patients can also have stereotypical, repetitive, paroxysmal symptoms and signs. Any of the aforementioned manifestations can be the initial symptom of MS or may appear later in the disease. It is important to emphasize that the clinical manifestations that may occur and the clinical course are unpredictable. Numerous symptoms of MS can negatively impact daily life activities, physical, emotional, and psychological functioning, and the quality of life of patients, and some of them can lead to severe disability. Some manifestations are often, at least initially, unrecognized by the patients themselves. It is of great importance to identify the cause of the symptoms and signs of MS, i.e., whether they are the result of lesions within the central nervous system (CNS) caused by this disease (primary), due to functional deficits (secondary), or a certain comorbidity. It is particularly important to consider comorbidities that can lead to overlapping or misattributed disturbances, especially when certain clinical manifestations are atypical for this disease.

Keywords: multiple sclerosis, symptoms, signs, comorbidities, quality of life

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VASCULAR MANIFESTATIONS OF AUTOIMMUNE DISEASES

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SAŽETAK

Različite bolesti autoimunske etiologije mogu imati i vaskularne manifestacije. One se prezentuju širokim spektrom kliničkih pojava i sindroma koji mogu biti posledica bolesti *per se*, ali i posledica dugotrajne primene imunosupresivne terapije. U patofiziološkom smislu, ispoljavanja vaskularnih manifestacija autoimunskih bolesti podrazumevaju sledeće mehanizme: inflamacija, disfunkcija endotela, vaskulitis / aortitis, taloženje imunskih kompleksa u zidu krvnih sudova. Didaktički i suštinski, vaskularne manifestacije autoimunskih bolesti mogu se prezentovati kao: vaskulitisi, antifosfolipidni sindrom, ateroskleroza, hipertenzija i *Rejnoov* fenomen. Navedene kliničke manifestacije pojedinačno ili sadejstvom više različitih, mogu dovesti do krajnjih posledica. One se mogu ogledati u formiranju arterijskih aneurizmi sa mogućim komplikacijama, trombozama arterijskih i venskih krvnih sudova, te ishemiji i potencijalno ireverzibilnom oštećenju ciljnih organa.

Bolesti koje mogu imati implikacije na funkciju krvnih sudova mogu biti klasične reumatske autoimunske bolesti kao što su reumatoidni artritis, sistemski lupus, sistemska skleroza, ankilozirajući spondilitis, relapsirajući polihondritis, Behçet-ova bolest, ali i hronične inflamatorne bolesti multifaktorijske etiologije kao što su *Takayasu* arteritis i gigantocelularni arteritis.

Ključne reči: autoimunske bolesti, vaskularne manifestacije, aortitis, ateroskleroza, antifosfolipidni sindrom

ABSTRACT

Various autoimmune diseases may present with vascular manifestations. These manifestations encompass a wide spectrum of clinical features and syndromes, which may arise either as a direct consequence of the underlying disease or as a result of prolonged immunosuppressive therapy. From a pathophysiological perspective, vascular involvement in autoimmune diseases may occur through several mechanisms: inflammation, endothelial dysfunction, vasculitis/aortitis, and immune complex deposition within the vessel walls.

Didactically and fundamentally, vascular manifestations of autoimmune diseases can be categorized into the following clinical entities: vasculitides, antiphospholipid syndrome, atherosclerosis, hypertension, and Raynaud's phenomenon. These manifestations, individually or in combination, may lead to significant complications, such as the formation of arterial aneurysms with associated risks, arterial and venous thromboses, ischemia, and potentially irreversible damage to target organs.

Diseases that can impair vascular function include classic rheumatic autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, ankylosing spondylitis, relapsing polychondritis, and Behçet's disease, as well as chronic inflammatory diseases of multifactorial etiology such as *Takayasu* arteritis and giant cell arteritis.

Keywords: autoimmune diseases, vascular manifestations, aortitis, atherosclerosis, antiphospholipid syndrome

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THERAPY OF CARDIAC DISEASES IN PATIENTS WITH AUTOIMMUNE DISEASES

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SAŽETAK

Uvod: Autoimune bolesti (AB) kao što su reumatoidni artritis, sistemski eritematozni lupus, sistemska skleroza i Sjogrenov sindrom, pokazuju povišene stope kardiovaskularnog morbiditeta i mortaliteta. Pacijenti sa infarktom miokarda i AB imaju veći rizik od mortaliteta, rekurentnog infarkta miokarda, srčane insuficijencije, i potrebe za koronarnom reintervencijom tokom praćenja u poređenju sa pacijentima bez AB. Prepoznavanje kardiovaskularnog rizika povezanog sa autoimunim bolestima i procena uočenog rizika od KVB je ključna za skrining kako bi se rano otkrili rizični pacijenti i na taj način potencijalno poboljšala dugoročna prognoza brzom intervencijom. Cilj ispitivanja je analizirati učestalost autoimunih bolesti u populaciji bolnički lečenih kardioloških pacijenata i terapijskih pristup u navedenim stanjima.

Metode i rezultati: Retrospektivno je analizirano 19 pacijenata koji su lečeni u Klinici za kardiologiju VMA tokom 2024. godine. 7 (37%) pacijenata je imalo SLE, 5 (26%) sistemska sklerozu, 4 (21%) reumatoidni artritis, 2 (11%) ankilozirajući spondilitis i 1 (5%) sistemska bolest vezivnog tkiva. U grupi pacijenata je bio 6 (32%) muškaraca i 13 (68%) žena. Prosečna starost pacijenata je bila 65 godina ($SD \pm 9,848$). Prosečan broj dana bolničkog lečenja je bio 7 dana ($SD \pm 7,231$). Hipertenziju je imalo 17 (90%) pacijenata, ishemijsku bolest srca 10 (53%), diabetes melitus 8 (42%) pacijenata, bubrežnu slabost 5 (26%) pacijenata, 2 (11%) HFrEF, 11 (58%) HFpEF i 6 (32%) normalnu EF leve komore. U laboratoriji 11 (58%) pacijenata je imalo povišen BNP, 11 (58%) je imalo HDL ispod 1 mmol/L. Kod analize kardioloških bolesti 7 (37%) je imalo ishemijsku bolest srca, 4 (21%) plućnu hipertenziju, 2 (11%) kardiomiopatiju, 2 (11%) urođenu srčanu manu, 2 (11%) hipertenziju, 1 (5%) fibrilaciju pretkomora i 1 (5%) akutnu plućnu tromboemboliju. Od kardioloških lekova najzastupljeniji su bili beta blokatori (15-79%) i acetilsalicilna kiselina (15-79%). Pacijenti su lečeni lekovima (17-90%), perkutanom koronarnom intervencijom (1-5%) i balon plućnom angioplastikom plućnih arterija (BPA) (1-5%). Tokom bolničkog lečenja ovih pacijenata nije bilo umrlih.

Zaključak: Kardiovaskularni sistem, a posebno srčani mišić, su organi koji su često zahvaćeni u sklopu autoimunih bolesti, što značajno utiče na opterećenje kardiovaskularnog sistema i prognozu bolesti srca. Zato je kod pacijenata sa autoimunim bolestima tokom dijagnostike potrebno uvek uraditi i kardiološki skrining i po potrebi započeti pravovremeno lečenje.

Ključne reči: autoimune bolesti, kardiovaskularni sistem, lečenje

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ABSTRACT

Introduction: Autoimmune diseases (ADs) such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis and Sjogren's syndrome show elevated rates of cardiovascular morbidity and mortality. Patients with myocardial infarction and ADs have a higher risk of mortality, recurrent myocardial infarction, heart failure, and the need for coronary reintervention during follow-up compared with patients without ADs. Recognition of cardiovascular risk associated with autoimmune diseases and assessment of perceived CVD risk is crucial for screening to detect at-risk patients early and thereby potentially improve long-term prognosis through prompt intervention. The aim of the study is to analyze the frequency of autoimmune diseases in the population of cardiology patients treated at the hospital and the therapeutic approaches in the mentioned conditions.

Methods and results: 19 patients who were treated at the Cardiology Clinic of the Military Medical Academy during 2024 were retrospectively analyzed. 7 (37%) patients had SLE, 5 (26%) systemic sclerosis, 4 (21%) rheumatoid arthritis, 2 (11%) ankylosing spondylitis, and 1 (5%) systemic connective tissue disease. There were 6 (32%) men and 13 (68%) women in the group of patients. The average age of the patients was 65 years ($SD \pm 9.848$). The average number of days of hospital treatment was 7 days ($SD \pm 7.231$). Hypertension was present in 17 (90%) patients, ischemic heart disease in 10 (53%), diabetes mellitus in 8 (42%) patients, renal failure in 5 (26%) patients, 2 (11%) HFrEF, 11 (58%) HFpEF and 6 (32%) normal left ventricular EF. In the laboratory, 11 (58%) patients had elevated BNP, 11 (58%) had HDL below 1 mmol/L. When analyzing cardiac diseases, 7 (37%) had ischemic heart disease, 4 (21%) pulmonary hypertension, 2 (11%) cardiomyopathy, 2 (11%) congenital heart defect, 2 (11%) hypertension, 1 (5%) atrial fibrillation and 1 (5%) acute pulmonary thromboembolism. Of the cardiac drugs, the most common were beta blockers (15-79%) and acetylsalicylic acid (15-79%). Patients were treated with drugs (17-90%), percutaneous coronary intervention (1-5%) and balloon pulmonary angioplasty (BPA) (1-5%). There were no deaths during the hospital treatment of these patients.

Conclusion: The cardiovascular system, and especially the heart muscle, are organs that are often affected as part of autoimmune diseases, which significantly affects the workload of the cardiovascular system and the prognosis of heart disease. That's why in patients with autoimmune diseases, during diagnosis, it is always necessary to perform cardiac screening and, if necessary, start timely treatment.

Keywords: autoimmune diseases, cardiovascular system, treatment

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OTORHINOLARYNGOLOGICAL MANIFESTATIONS OF GRANULOMATOSIS WITH POLYANGIITIS AND EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS

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SAŽETAK

Uvod/Cilj: Granulomatoza sa poliangiitisom (Granulomatosis with polyangiitis – GPA; ranije poznata kao Wegenerova [Wegener] granulomatoza) i eozinofilna granulomatoza sa poliangiitisom (Eosinophilic granulomatosis with polyangiitis – EGPA; ranije poznata kao Čardž-Štrausov sindrom [Churg-Strauss syndrome]) su autoimune bolesti koje karakteriše prisustvo nekrotizujućih granuloma. Dok u GPA dominira sistemski vaskulitis sa dominacijom neutrofilnih granulocita, EGPA se karakteriše prisustvom eozinofilnih granuloma. Ukoliko se ne reaguje na vreme, obe bolesti vode letalnom ishodu. Zahvaćenost delova otorinolaringološke (ORL) regije je visoko zastupljena kod obe bolesti. Rad treba da ukaže na etiopatogenezu, kliničke karakteristike, dijagnostičke procedure i modalitete lečenja ova dva teška klinička entiteta.

Metode: Pregledni rad sa prikazima slučajeva.

Rezultati: Kod obe bolesti su zahvaćeni mali i srednje veliki krvni sudovi gornjeg i donjeg disajnog puta. Nosna šupljina i paranazalni sinusi su u GPA zahvaćeni u 85-100% slučajeva u formi akutnog i hroničnog rinosinuzitisa, atrofičnog rinitisa sa formiranjem krstoznih naslaga u nosnoj šupljini, perforacijom nosnog septuma i deformacijom nosne piramide. Srednje i unutrašnje uvo su zastupljeni u 20-70% slučajeva u formi akutnog zapaljenja srednjeg uva i senzorineuralnog oštećenja sluha sa ili bez vrtoglavice. Kasnije su zahvaćeni pluća i bubrezi. Za postavljanje dijagnoze je važno detektovati citoplazmatska anti-neutrofilna antitela (c-ANCA), dok se definitivna dijagnoza postavlja na osnovu histopatološke potvrde vaskulitisa, granulomatozne inflamacije i nekroze tkiva. EGPA je daleko ređe oboljenje. U početnom stadijumu se može manifestovati simptomima i znacima alergijskog rinitisa, hroničnog rinosinuzitisa sa nosnim polipima i astme, dok se kasnije ispoljavaju hipereozinofilija, polineuropatija i sistemski nekrotizujući vaskulitis. Srednje uvo je često zahvaćeno u formi eozinofilnog zapaljenja, dok se zahvatanje unutrašnjeg uva manifestuje senzorineuralnim oštećenjem i vrtoglavicom. Za dijagnozu su takođe važni serološki testovi (anti-MPO-ANCA i anti-PR3-ANCA). Nažalost, u većini slučajeva se bolest prepoznaje veoma kasno, a za definitivnu dijagnozu je potrebna histološka potvrda eozinofilnih granuloma. Kortikosteroidna i imunosupresivna terapija su zlatni standardi lečenja za oba klinička entiteta, dok u terapiji EGPA dobre rezultate daje i biološka terapija.

Zaključak: Oblici sekundarnog hroničnog rinosinuzitisa se mogu ispoljiti kroz dva različita klinička entiteta, GPA i EGPA. Oba zahtevaju multidisciplinarni pristup, kako u dijagnostici, tako i u lečenju.

Ključne reči: granulomatoza sa poliangiitisom, otitis medija, nosni polipi, rinitis, sinuzitis

ABSTRACT

Introduction/Aim: Granulomatosis with polyangiitis (GPA; previously known as Wegener's granulomatosis) and eosinophilic granulomatosis with polyangiitis (EGPA; previously known as Churg-Strauss syndrome) are autoimmune diseases characterized by the presence of necrotizing granulomas. While GPA is dominated by systemic vasculitis with a predominance of neutrophilic granulocytes, EGPA is characterized by the presence of eosinophilic granulomas. If not treated in time, both diseases lead to death. Involvement of parts of the otorhinolaryngological (ENT) region is highly prevalent in both diseases. The work should indicate the etiopathogenesis, clinical characteristics, diagnostic procedures and treatment modalities of these two difficult clinical entities.

Methods: Review paper with case reports.

Results: Small and medium-sized blood vessels of the upper and lower respiratory tract were affected in both cases. The nasal cavity and paranasal sinuses are affected in GPA in 85-100% of cases in the form of acute and chronic rhinosinusitis, atrophic rhinitis with the formation of crusted deposits in the nasal cavity, perforation of the nasal septum and deformation of the nasal pyramid. The middle and inner ear are represented in 20-70% of cases in the form of acute inflammation of the middle ear and sensorineural hearing impairment with or without vertigo. Later, the lungs and kidneys were affected. To establish the diagnosis, it is important to detect cytoplasmic anti-neutrophil antibodies (c-ANCA), while the definitive diagnosis is established on the basis of histopathological confirmation of vasculitis, granulomatous inflammation and tissue necrosis. EGPA is a much rarer disease. In the initial stage, it can be manifested by symptoms and signs of allergic rhinitis, chronic rhinosinusitis with nasal polyps and asthma, while later hypereosinophilia, polyneuropathy and systemic necrotizing vasculitis are manifested. The middle ear is often affected in the form of eosinophilic inflammation, while the involvement of the inner ear is manifested by sensorineural damage and dizziness. Serological tests (anti-MPO-ANCA and anti-PR3-ANCA) are also important for diagnosis. Unfortunately, in most cases the disease is recognized very late, and a definitive diagnosis requires histological confirmation of eosinophilic granulomas. Corticosteroid and immunosuppressive therapy are the gold standards of treatment for both clinical entities, while biological therapy also gives good results in the treatment of EGPA.

Conclusion: Forms of secondary chronic rhinosinusitis can manifest through two different clinical entities, GPA and EGPA. Both require a multidisciplinary approach, both in diagnosis and treatment.

Keywords: granulomatosis with polyangiitis, otitis media, nasal polyp, rhinitis, sinusitis

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SAŽETAK

Sarkoidoza predstavlja hronično granulomatozno oboljenje nepoznate etiologije. Klinički tok može biti asimptomatski, akutni, kada se naziva Lofgrenov sindrom i obuhvata poliartritis predominantno donjih ekstremiteta, medijastinalnu limfadenopatiju i eritema nodosum (specifične promene po koži potkolenica), ili hronični, čiji simptomi zavise od zahvaćenosti organa. Najčešće zahvaćeni organi su limfni čvorovi medijastinuma sa plućima, te prva dijagnostička procedura treba da bude radiografija grudnog koša. Specifični biomarkeri, za dijagnostiku i praćenje pacijenata su ACE, hitotriozidaza i Ca u 24-časovnom urinu, ali treba napomenuti da tumačenje markera zavisi od drugih faktora, prevashodno kliničke slike pacijenta. „Zlatni standard“ za dijagnozu sarkoidoze predstavlja patohistološka verifikacija, obzirom da veliki broj bolesti može da imitira sarkoidozu, pre svega druge granulomatoze (tuberkuloza, histiocitoza) i maligniteti (maligniteti pluća, hematopoeznog tkiva, sekundarni depoziti). Sarkoidoza ima tendenciju spontane remisije, ali ukoliko su prisutni simptomi, hroničan tok, ili ekstrapulmonalna zahvaćenost, potrebno je uvesti u terapiju imunomodulatornu terapiju, u prvoj liniji oralnu kortikosteroidnu terapiju. Iako u najvećem broju slučajeva sarkoidoza ima povoljan tok, pacijenti sa hroničnom plućnom sarkoidozom, sarkoidozom srca ili neurosarkoidozom mogu imati značajno narušen kvalitet života, te je neophodan multidisciplinarni pristup u njihovom lečenju.

Ključne reči: sarkoidoza, granulomatoza, ACE, hitotriozidaza, medijastinalna limfadenopatija

ABSTRACT

Sarcoidosis is a chronic granulomatous disease of unknown etiology. The clinical course can be asymptomatic, acute, when it is called Lofgren's syndrome and includes polyarthritis of lower extremities, mediastinal lymphadenopathy and erythema nodosum (specific changes on the skin of the lower legs), or chronic, whose symptoms depend on the involvement of the organs. The most frequently affected organs are the lymph nodes of the mediastinum with the lungs, so the first diagnostic procedure should be a chest radiography. Specific biomarkers for diagnosis and monitoring of patients are ACE, chitotriosidase and Ca in 24-hour urine, but it should be noted that the interpretation of markers depends on other factors, primarily the clinical picture of the patient. The "gold standard" for the diagnosis of sarcoidosis is pathohistological verification, given that a large number of diseases can mimic sarcoidosis, primarily other granulomatosis diseases (tuberculosis, histiocytosis) and malignancies (lung and hematopoietic malignancies, secondary deposits of other malignancies). Sarcoidosis has a tendency for spontaneous remission, but if symptoms are present, if it has a chronic course, or if there is extrapulmonary involvement, it is necessary to introduce immunomodulatory therapy, primarily oral corticosteroid therapy. Although in the majority of cases sarcoidosis has a favorable course, patients with chronic pulmonary sarcoidosis, cardiac sarcoidosis or neurosarcoidosis may have significantly impaired quality of life, and a multidisciplinary approach is necessary in their treatment.

Keywords: sarcoidosis, granulomatosis, ACE, chitotriosidase, mediastinal lymphadenopathy

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SAŽETAK

Autoimunska hemolizna anemija (AIHA) je retka (incidencija 1-3/100 000 stanovnika) stečena bolest koju karakteriše imunski posredovana destrukcija autologih eritrocita. Osnovni test za dijagnostiku AIHA je pozitivan direktan Coombs-ov test, i klasifikacija AIHA se vrši na osnovu seroloških i termalnih karakteristika detektovanih antitela (At). Kod AIHA uzrokovana toplim antitelima (wAIHA) koja je najčešći tip (60-70% slučajeva) prisutna su poliklonska At klase IgG koja se vezuju na antigene (Ag) na membrani eritrocita (Er) na temperaturi 37°C. Najčešći tip AIHA uzrokovane hladnim At (cAIHA) je Bolest hladnih aglutinina koja čini 20% svih AIHA i uzrokovana je monoklonskim IgM autoAt koja reaguluju na 4°C i snažno aktiviraju komplement. Najređi oblik AIHA (<1%) je Paroksizmalna hemoglobinurija na hladnoću koju karakteriše prisustvo bifazičnih Donath-Landsteinerovih At. Kod 5-10% bolesnika postoje karakteristike i tople i hladne AIHA, kada govorimo o mešovitoj AIHA.

U patogenezi AIHA ulogu ima gubitak centralne i periferne tolerancije, disbalans između C8+ i CD4+ limfocita, kao i CD4+ Treg, Th2 i Th17 imunofenotipa. Klirens obloženih Er zavisi od vrste autoAt i stepena aktivacije komplementa. Kada se snažno aktivise komplement dolazi do intravaskularne hemolize, hemoglobinemije i hemoglobinurije. Kod ekstravaskularne hemolize fagocitoza opsonizovanih Er vrši se u slezini (wAIHA) ili jetri (cAIHA). Prva terapijska linija wAIHA su kortikosteroidi i rituksimab, a cAIHA utopljavanje i plazmafereze. Kako je više od 50% svih AIHA sekundarna, uz lečenje AIHA neophodno je istovremeno lečiti osnovnu bolest. Tok AIHA je nepredvidiv sa četim relapsima, i značajno umanjuje kvalitet života. Najčešću uzroci smrtnosti su infekcije, akutna bubrežna slabost, trombot-ski događaji.

Ključne reči: autoimunska hemolizna anemija, direktan Coombs-ov test, autoantitela, komplement, lečenje

ABSTRACT

Autoimmune Hemolytic Anemia (AIHA) is a rare (incidence 1–3 per 100,000 population) acquired disorder characterized by immune-mediated destruction of autologous red blood cells (RBCs). The diagnostic hallmark of AIHA is a positive direct Coombs test, and classification of AIHA is based on the serological and thermal characteristics of the detected antibodies (Abs). In warm AIHA (wAIHA), which is the most common type (60–70% of cases), polyclonal IgG Abs bind to antigens on the RBC membrane at 37°C. The most common type of cold AIHA (cAIHA) is Cold Agglutinin Disease, accounting for about 20% of all AIHA cases. It is caused by monoclonal IgM Abs that react at 4°C and strongly activate the complement system. Paroxysmal Cold Hemoglobinuria, a very rare form of AIHA (1% of all AIHA cases) is characterized by the presence of biphasic Donath-Landsteiner Abs. In 5–10% of patients, features of both warm and cold AIHA are present—this is referred to as mixed AIHA. The pathogenesis of AIHA involves loss of central and peripheral immune tolerance, and an imbalance between CD8+ and CD4+ T lymphocytes, and CD4+ Tregs and Th17 immune phenotypes. The clearance of Ab-coated RBCs depends on the type of autoAb and the extent of complement activation. Strong complement activation leads to intravascular hemolysis, with resulting hemoglobinemia and hemoglobinuria. In extravascular hemolysis, phagocytosis of opsonized RBCs occurs in the spleen (wAIHA) or liver (cAIHA). First-line treatment for wAIHA includes corticosteroids and rituximab, while for cAIHA, management involves warming measures and plasmapheresis. Since more than 50% of AIHA cases are secondary, it is essential to treat the underlying disease concurrently with AIHA management. The clinical course of AIHA is unpredictable, often marked by frequent relapses, and significantly impairs quality of life. The most common causes of mortality include infections, acute kidney injury, and thrombotic events.

Keywords: autoimmune hemolytic anemia, direct Coombs test, autoantibodies, complement, treatment

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SAŽETAK

Neutropenija je smanjenje broja neutrofila u krvi na vrednosti $< 1.5 \times 10^9/L$. Deli se na neutropenije izazivane intrinzičkim defektom u mijeloidnim ćelijama ili njegovim prekusorima i sekundarne neutropenije koje nastaju na terenu sistemskih oboljenja, virusnih infekcija, primene lekova, usled hipersplenizma ili deficita hematinika. Autoimuna neutropenija je neutropenija koja nastaje kao posledica prisustva antitela usmerenih protiv neutrofila vodeći njihovoj destrukciji ili T limfocita koji dovode do inhibicije neutrofila ili njihovih prethodnika. Autoimune neutropenije se mogu podeliti na akutne i hronične. Akutne nastaju nakon virusnih infekcija i primene lekova. Sekundarne nastaju u okviru infekcija, hematoloških oboljenja, primene lekova itd. Osnovni ciljevi kod svakog bolesnika sa neutropenijom su određivanje uzroka neutropenije, primena antibiotika, granulocitnog faktora rasta, utvrđivanje uzroka infekcije u slučaju njenog razvoja i implementacija protektivnih mera za suzbijanje infekcije. Dijagnostički pristup podrazumeva detaljno uzimanje kliničkih podataka (istorija bolesti, zanimanje, istorija infekcija, uzimanja lekova i sl), testove krvi (virusološke analize, imunološke testove, krvna slika i razmaz periferne krvi, testovi funkcije jetre, imunoglobulini, imunofenotipizacija) i analizu kostne srži (aspiraciona punkcija i biopsija kostne srži, analiza kariotipa). Lečenje podrazumeva lečenje uzroka bolesti i zavisi od etiologije, težine i prisustva infektivnih komplikacija. Primarna AIN Retko zahteva lečenje jer je kod nje pojava infekcija retka. Terapija podrazumeva primenu antibiotika, IVIG, kortikosteroida, imunosupresiva i granulocitnog faktora rasta.

Gljučne reči: neutropenija, autoimunitet, hematološka oboljenja

ABSTRACT

Neutropenia is a decrease in the number of neutrophils in the blood to $< 1.5 \times 10^9/L$. It is divided into neutropenias caused by an intrinsic defect in myeloid cells or its precursors and secondary neutropenias that occur within the clinical picture of systemic diseases, viral infections, drug administration, due to hypersplenism or hematinic deficiency. Autoimmune neutropenia is a neutropenia that occurs as a result of the presence of antibodies directed against neutrophils leading to their destruction or T lymphocytes that lead to the inhibition of neutrophils or their precursors. Autoimmune neutropenia can be divided into acute and chronic. Acute occurs after viral infections and drug administration. Secondary ones arise as a result of infections, hematological diseases, drug administration, etc. The main goals for every patient with neutropenia are to determine the cause of neutropenia, use of antibiotics, granulocyte growth factor, determine the cause of infection in case of its development and implementation of protective measures to control infection. The diagnostic approach involves taking detailed clinical data (history of illness, occupation, history of infections, taking medications, etc.), blood tests (virological analysis, immunological tests, blood count and peripheral blood smear, liver function tests, immunoglobulins, immunophenotyping) and bone marrow analysis (aspiration puncture and bone marrow biopsy, karyotype analysis). Treatment depends on the etiology, severity and presence of infectious complications. Primary AIN rarely requires treatment because infections are rare. Therapy involves the use of antibiotics, IVIG, corticosteroids, immunosuppressants and granulocyte growth factor.

Keywords: neutropenia, autoimmunity, hematological disease

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SAŽETAK

Poznato je da je tip 1 dijabetesa (T1D) autoimunska bolest koja za posledicu ima selektivnu destrukciju ćelija pankreasa koje luče insulin. U fazama koje prethode kliničkoj manifestaciji T1D mogu se detektovati autoantitela na β -ćelijske antigene, ali i poremećaji ćelijskog imuniteta, kao i defekti u insulinskoj sekreciji i senzitivnosti. U tom smislu, moguće je identifikovati osobe sa rizikom za ispoljavanje T1D, na osnovu genetskih, imunoloških i metaboličkih markera rizika. Istovremeno, nedavno je pokazano da je moguće odložiti T1D imunoterapijom u osoba sa visokim rizikom za T1D. Teplizumab, humanizovano anti CD3 monoklonsko antitelo modifikuje/usporeva progresiju bolesti od faze 2 predijabetesa do klinički manifestnog T1D protekcijom β -ćelija. U tom kontekstu, poslednje preporuke Američke asocijacije za dijabetes sugerišu skrining za T1D upotrebom 4 autoantitela (GAD, IA2, IAA, ZnT8 At) uz savet da se osobe sa rizikom monitorizuju i upute u centre koji rade kliničke studije prevencije ili im se omogući primena teplizumaba. Preporuka je da se testiranje vrši u prvih rođaka osoba sa T1D, ali i u osoba iz opšte populacije, prvenstveno sa autoimunskim oboljenjima (celijakija, tiroidne bolesti), genetskim rizikom za T1D, i odraslih osoba sa poremećajem glikozne tolerancije i indeksom telesne mase $< 25 \text{ kg/m}^2$ ili < 35 godina starosti. Dodatno, osobe sa klinički manifestnim T1D često imaju i druge multisistemske autoimune poremećaje, uključujući bolesti štitne žlezde, celijakiju, vitiligo, gastritis, kožne i reumatske bolesti. U tom smislu, neophodan je skrining antitela i za druga autoimunska oboljenja radi rane identifikacije i terapije ovih komorbiditeta, u cilju poboljšanja kvaliteta života osoba sa T1D.

Ključne reči: tip 1 dijabetesa, predijabetes, prevencija, skrining, autoimune bolesti

ABSTRACT

Type 1 diabetes (T1D) is an autoimmune disease that results in the selective destruction of insulin-secreting cells in the pancreas. In the stages preceding the clinical manifestation of T1D, autoantibodies to β -cell antigens and defects in insulin secretion and sensitivity can be detected. Consequently, it is possible to identify individuals at risk for T1D, based on genetic, immune, and metabolic risk markers. At the same time, it has recently been shown that it is possible to delay T1D immunotherapy in people at high risk for T1D. Teplizumab, a humanized anti-CD3 monoclonal antibody, modifies/slows disease progression from stage 2 prediabetes to clinically manifest T1D by β -cell protection. In this context, the latest recommendations of the American Diabetes Association suggest screening for T1D using four autoantibodies (GAD, IA2, IAA, ZnT8 Ab) with the advice that people at risk should be monitored and referred to centers that do clinical prevention studies or be allowed to use teplizumab. It is recommended to test first-degree relatives of people with T1D, but also in people from the general population, primarily with autoimmune diseases (celiac disease, thyroid disease), genetic risk for T1D, and adults with impaired glucose tolerance, and body mass index $< 25 \text{ kg/m}^2$ or < 35 years of age. Finally, people with T1D often have multisystem autoimmune disorders, including thyroid or celiac disease, vitiligo, gastritis, skin and rheumatic diseases. In this regard, antibody screening for other autoimmune diseases is necessary to identify and treat these comorbidities early, to improve the quality of life of people with T1D.

Keywords: type 1 diabetes, prediabetes, prevention, screening, autoimmune diseases

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HISTOPATHOLOGICAL DIAGNOSIS OF AUTOIMMUNE THYROID DISEASES

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SAŽETAK

Prezentacija prikazuje inflamatorna i autoimunska oboljenja štitaste žlezde, sa akcentom na njihovu patohistološku dijagnostiku. Tiroiditisi se klasifikuju na akutne, subakutne i hronične. Subakutni de Quervainov tiroiditis povezan je s prethodnom infekcijom, granulomatoznom inflamacijom i karakterističnim mikroskopskim nalazima.

Najveći fokus stavljen je na Hašimotov tiroiditis, najčešći autoimuni tiroiditis, sa varijantama: nodularnom (onkocitni nodusi), fibrozirajućom i mešovitim formama, koje histološki mogu imitirati tumorske lezije. Obradena je i njegova diferencijalna dijagnoza sa limfomima, karcinomima i drugim benignim entitetima.

Riedelov tiroiditis, redak oblik fibrosklerotične bolesti povezan s IgG4 oboljenjima, prikazan je kao dijagnostički izazov zbog rigidnosti žlezde i atipične infiltracije. Takođe je objašnjen multifokalni sklerozirajući tiroiditis, česta zamka za pogrešnu dijagnozu mikrokarcinoma.

U okviru Gravesove bolesti analizirani su mikroskopski znaci aktivne faze i promene u fazi izgaranja, uključujući formiranje čvorova sa atipijom.

Zaključak ističe značaj razlikovanja benignih od malignih promena, upotrebu imunohistohemije i molekularne dijagnostike, te važnost timskog rada između patologa, endokrinologa i hirurga.

Ključne reči: tiroiditis, Hašimoto, Riedel, autoimunska oboljenja, dijagnoza, štitasta žlezda

ABSTRACT

This presentation outlines inflammatory and autoimmune diseases of the thyroid gland, with a focus on their histopathological diagnosis. It begins by classifying thyroiditis into acute, subacute, and chronic forms. Subacute de Quervain's thyroiditis is associated with a preceding infection, granulomatous inflammation, and characteristic microscopic findings.

The primary emphasis is placed on Hashimoto's thyroiditis, the most common autoimmune thyroiditis, including its variants: nodular (oncocytic nodules), fibrosing, and mixed forms, which can histologically mimic neoplastic lesions. The differential diagnosis is discussed in detail, particularly in distinguishing it from lymphomas, carcinomas, and other benign entities.

Riedel's thyroiditis, a rare form of fibrosing disease associated with IgG4-related disorders, is presented as a diagnostic challenge due to glandular rigidity and atypical infiltration. Multifocal sclerosing thyroiditis is also described as a common diagnostic pitfall that can mimic papillary microcarcinoma.

In the context of Graves' disease, the microscopic features of the active phase and the so-called "burnt-out" phase are analyzed, including the development of nodular changes with atypia.

The conclusion highlights the importance of distinguishing benign from malignant lesions, the use of immunohistochemistry and molecular diagnostics, and the essential role of multidisciplinary collaboration between pathologists, endocrinologists, and surgeons in achieving accurate diagnosis.

Keywords: thyroiditis, Hashimoto disease, Riedel's thyroiditis, autoimmune diseases, diagnosis, thyroid gland

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SAŽETAK

Uvod: Osteoporoza (OP) je jedna od najčešćih ekstraartikularnih komplikacija u mnogim hroničnim autoimunim inflamatornim reumatskim bolestima AIRB (reumatoidnom artritisu (RA), psorijazi (Ps), psorijaznom artritisu (PsA), aksijalnom spondyloartritisu (axSpA), sistemskom eritemskom lupusu (SLE).

Metode: Istraživali smo PubMed, EMBASE, Web of Science, ScienceDirect baze podataka za studije od početka maja 2022 godine

Rezultati: Većina studija kod postmenopausalnih žena sa AIRB pronalazi povezanost između visokog nivoa proinflammatory markera, hronične primene kortikosteroida i povećanog gubitka koštanog tkiva. Procena pacijenta sa AIRB obuhvata anamnezu, klinički pregled, procenu rizika za prelome, laboratorijske analize, kao i osteodenzitometriju. Neprepoznavanje i netretiranje OP je uslovljeno faktorima: nedovoljnim znanjem o osteoporozi i koristi od terapije, zabrinutosti zbog mogućih neželjenih efekata terapije, slabe motivisanosti i loše edukacije pacijenata. Razvijeno je nekoliko različitih metoda za smanjenje propusta u prepisivanju terapije, a među njima se Fracture Liaison Service se pokazao kao najefikasniji. Strategije za upravljanje osteoporozom obuhvataju edukaciju pacijenata, promene životnog stila, prevenciju padova, adekvatnu ishranu, kontrolu aktivnostibolesti, kao i uvođenje lekova za osteoporozu.

Zaključak: Uprkos značajnim naprecima u prevenciji, dijagnostici i tretmanu, prevalenca je visoka i zahteva pravovremeno prepoznavanje i sveobuhvatni pristup. Procena faktora rizika za padove i prelome kosti, kao i za oporavak od velikog je značaja kod pacijenata sa AIRB.

Ključne reči: osteoporoza, prevalenca, faktori rizika, prelomi, terapija

ABSTRACT

Introduction: Osteoporosis (OP) is one of the most common extra-articular complications in many chronic autoimmune inflammatory rheumatic diseases (AIRDs), including rheumatoid arthritis (RA), psoriasis (Ps), psoriatic arthritis (PsA), axial spondyloarthritis (axSpA), and systemic lupus erythematosus (SLE).

Methods: We searched the PubMed, EMBASE, Web of Science, and ScienceDirect databases for studies starting from the beginning of May 2022.

Results: Most studies on postmenopausal women with AIRDs find a correlation between high levels of pro-inflammatory markers, chronic corticosteroid therapy and increased bone loss. Patient assessment in autoimmune rheumatic inflammatory diseases (AIRDs) includes medical history, clinical examination, fracture risk assessment, laboratory tests, and bone densitometry. The lack of adequate diagnosis and treatment of OP is influenced by factors such as insufficient knowledge about osteoporosis and its therapeutic benefits, concerns about potential side effects of treatment, low motivation, and inadequate patient education. Several different methods have been developed to reduce oversights in prescribing therapy, with the Fracture Liaison Service being the most effective. Strategies for managing osteoporosis include patient education, lifestyle modifications, fall prevention, proper nutrition, disease activity control and the introduction of osteoporosis medications.

Conclusion: Despite significant advances in prevention, diagnosis and treatment, the prevalence of osteoporosis remains high and requires timely recognition and a more comprehensive approach. Assessing risk factors for falls and fractures, as well as recovery potential is crucial in patients with AIRDs.

Keywords: osteoporosis, prevalence, risk factors, fractures, therapy

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ANTI-INFLAMMATORY EFFECTS OF EXERCISE IN AUTOIMMUNE DISEASES

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SAŽETAK

Vežbanje ostvaruje brojne pozitivne efekte na ljudsko zdravlje. Sve je više dokaza da vežbanje ima i antiinflamatorni efekat, što je od potencijalno velikog značaja u prevenciji i lečenju niza hroničnih oboljenja koja u osnovi imaju sistemsku inflamaciju. U tom kontekstu, studije su pokazale poseban značaj vežbanja kod pacijenata sa autoimunim bolestima. U ovom radu, daje se kratak pregled antiinflamatornih efekata vežbanja, naročito u kontekstu autoimunih bolesti, čime se postavlja osnova za promociju redovnog vežbanja kod pacijenata sa autoimunim bolestima u cilju bolje kontrole bolesti i povećanja kvaliteta života.

Ključne reči: fizička aktivnost, autoimune bolesti, inflamacija

ABSTRACT

Exercise has numerous positive effects on human health. There is increasing evidence that exercise also has an anti-inflammatory effect, which is of potential great importance in the prevention and treatment of a number of chronic diseases accompanied by systemic inflammation. In this context, studies have shown the special importance of exercise in patients with autoimmune diseases. In this paper, a brief overview of the anti-inflammatory effects of exercise, especially in the context of autoimmune diseases, is provided, which lays the foundation for the promotion of regular exercise in patients with autoimmune diseases with the aim to achieve better disease control and improve the quality of life.

Keywords: physical activity, autoimmune diseases, inflammation

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REHABILITATION OF PATIENTS WITH MULTIPLE SCLEROSIS

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SAŽETAK

Rehabilitacija pacijenata obolelih od MS jeste kompleksan proces koji podrazumeva procenu funkcionalnih smetnji, aktuelne simptomatologije i ličnih potreba individue, pravljenje racionalnog plana u cilju redukcije posledica bolesti na funkcionalnu sposobnost, ličnu aktivnost i socijalnu participaciju. Praćenjem stepena oporavka, u zavisnosti od funkcionalnog statusa, program rehabilitacije se svakodnevno revidira, proširuje, a u skladu sa dominantnom aktuelnom simptomatologijom i specifično usmerava. Za ostvarenje i praćenje plana i ciljeva rehabilitacije potreban je stručan rehabilitacioni tim

Planiranje rehabilitacionih mera i postupaka zavisi od kliničke forme i faze bolesti u kojoj se pacijent nalazi. Sledeći korak pri odlučivanju o vrsti rehabilitacionog tretmana određen je stepenom funkcionalne onesposobljenosti definisan EDSS skorom a izbor rehabilitacionih mera i postupaka diktiran je u znatnoj meri aktuelnom simptomatologijom. Rehabilitacioni program se zavisno od funkcionalne onesposobljenosti može obavljati u bolničkim uslovima (intra-hospitalno ili ambulantno), u kućnim uslovima i u lokalnoj zajednici.

Terapijski pristupi uglavnom se zasnivaju na kineziterapiji usmerenoj ka restituciji artrokinematike i sticanju motornih veština koje će u najvećoj meri odgovoriti na potrebe pacijenta. Međutim, iako je kineziterapija bezbedna i specifična, ne obezbeđuje uvek visoku efikasnost. Stoga, nametnula se potreba za unapređenjem strategija u oblasti rehabilitacije MS. Noviji terapijski pristupi podrazumevaju primenu intenzivnog, specifičnog, na motorni zadatak orijentisanog pokreta i zavisno od mogućnosti bolesnika ponavljanje ciljanog pokreta oštećenog ekstremiteta tokom treninga. Sticanje novog iskustva kod ovih bolesnika ima značajnu ulogu u sledstvenoj fiziološkoj reorganizaciji i prilagođavanju neoštećenog tkiva mozga.

Adekvatno i na vreme započeto sprovođenje multifokusirane rehabilitacije, smanjuje i usporava napredak funkcionalne onesposobljenost i poboljšava kvalitet života pacijenata sa MS.

Ključne reči: procena pacijenta, cilj rehabilitacije, funkcionalna onesposobljenost, kvalitet života

ABSTRACT

Rehabilitation of MS patients is a complex process involving the assessment of functional impairments, current symptoms, and individual needs. It includes creating a rational plan aimed at reducing the impact of the disease on functional ability, personal activity, and social participation. The rehabilitation program is continuously revised and adjusted based on the patient's recovery progress, functional status, and dominant symptoms. A professional rehabilitation team is essential for planning and monitoring goals.

Rehabilitation strategies depend on the clinical form and stage of the disease. The next step in determining the type of rehabilitation is based on the level of functional disability, typically assessed using the EDSS score, while current symptoms largely dictate the choice of therapeutic approaches. Depending on disability level, rehabilitation can be provided in hospitals (inpatient or outpatient), at home, or in community settings.

Therapeutic approaches mainly rely on kinesiotherapy aimed at restoring joint movement and developing motor skills to meet patient needs. However, despite being safe and specific, kinesiotherapy alone may not always ensure high effectiveness. This has led to the development of improved strategies, including intensive, task-specific motor training and repetitive movement of the affected limb, adjusted to the patient's abilities. Gaining new motor experience supports physiological reorganization and adaptation of undamaged brain tissue.

Timely and comprehensive rehabilitation can slow functional decline and significantly improve the quality of life in MS patients.

Keywords: patient assessment, rehabilitation goals, functional disability, quality of life

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AUTOIMMUNE DISEASES AND KIDNEY TRANSPLANTATION

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SAŽETAK

Zahvatanje bubrega kod bolesnika sa autoimunom bolesti određuje često i preživljavanje ove grupe pacijenata. Promene koje nastaju u bubrezima u velikom broju slučajeva je sa visokim rizikom od razvoja bubrežne slabosti uprkos intenzivnoj terapiji koja uključuje visoke doze kortikosteroida i terapiju imunosupresivima. Ukoliko ovi pacijenti razviju terminalnu slabost bubrega, ESRD, prema svim studijama značaj preemptivne transplantacije je izuzetan. Preemtiv transplantacija je pokazala bolji ishod, preživljavanje ovih bolesnika u odnosu na one koji su bili 6 meseci na nekoj od oblika dijalize. Napredak u imunosupresiji i preživljavanju grafta je poboljšao preživljavanje recipijenata, međutim, zbog dužine davanja imunosupresije, postoji povećan rizik od pojave tumora. Za lekare koji se ne bave transplantacijom i autoimunim bolestima najvažnije je upućivanje ovih pacijenata kod pogoršanja bubrežne funkcije u referentne ustanove radi dalje evaluacije, ali svakako najveći doprinos ovih lekara je upućivanje ovakvih bolesnika na redovne godišnje skrining preglede na maligne bolesti.

U zaključku najvažnije za lekare koji se ne bave transplantacijom, autoimunim bolestima jeste pravovremeno upućivanje ovih pacijenata kod smanjenja bubrežne funkcije u referentne ustanove radi dalje evaluacije, ali svakako najveći doprinos ovih lekara je upućivanje ovakvih bolesnika na redovne godišnje skrining preglede na maligne bolesti.

Ključne reči: autoimune bolesti, transplantacija bubrega, terminalna bolest bubrega, imunosupresija, skrining na maligne bolesti

ABSTRACT

Renal involvement in patients with autoimmune diseases often plays a decisive role in determining overall survival within this patient group. Renal damage frequently leads to a high risk of progression to kidney failure, despite the use of intensive therapy that includes high-dose corticosteroids and immunosuppressive agents. In cases where patients progress to end-stage renal disease (ESRD), numerous studies emphasize the significant benefits of preemptive kidney transplantation.

Preemptive transplantation has been associated with superior outcomes and increased survival compared to patients who underwent dialysis for at least six months prior to transplantation. Advances in immunosuppressive therapy and improved graft survival have further enhanced patient outcomes. However, the prolonged use of immunosuppressive agents increases the risk of malignancy development.

For physicians not directly involved in transplantation or the management of autoimmune diseases, timely referral of patients with declining renal function to specialized centers is of critical importance for further evaluation. Nevertheless, one of the most important contributions these physicians can make is to ensure that such patients are regularly referred for annual cancer screening.

In conclusion, timely referral of patients with autoimmune diseases and impaired renal function to specialized centers is essential. Moreover, the greatest contribution of non-transplant physicians lies in ensuring that these patients undergo routine annual malignancy screening.

Keywords: autoimmune diseases, kidney transplantation, end-stage renal disease, immunosuppression, malignancy screening

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IgA VASCULITIS IN CHILDREN AND ITS ASSOCIATION WITH NEPHRITIS

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SAŽETAK

IgA vaskulitis (IgAV), donedavno poznat kao Henoch Schönlein purpura, je najčešći sistemski vaskulitis kod dece sa tipično akutnom prezentacijom. Procenjuje se da je učestalost ove bolesti 3–27 slučajeva na 100 000 dečje populacije. Glavnu ulogu u patogenezi imaju kompleksi ili agregati IgA. Naime, kod ovih bolesnika u regionu „šarke“ molekula IgA1, iz dosada neobjašnjenih razloga, se nalazi smanjen broj rezidua galaktoze. Takvi molekuli IgA imaju sklonost da stvaraju agregate i da podstiču sintezu autoreaktivnih IgG antitela sa stvaranjem imunih kompleksa. Imuni kompleksi se sistemski deponuju, dovodeći do nekrotičnog vaskulitisa. Nefritis se javlja kod 30–40% obolelih i predstavlja najozbiljniju kliničku manifestaciju bolesti, jer je jedino on povezan sa dugoročnim morbiditetom i mortalitetom, kako kod dece, tako i kod odraslih. Prve urinarne abnormalnosti se obično detektuju unutar 4 nedelje od početka bolesti (80% obolelih), kod preostalih unutar 2 meseca, retko kasnije. Najčešće renalne manifestacije bolesti su: mikroskopska ili makroskopska hematurija, proteinurija bez edema, nefritički sindrom, nefrotski sindrom, ili kombinacija nefrotsko-nefritičkog sindroma. Minimalne urinarne abnormalnosti (izolovana mikroskopska hematurija i neperzistentna blaga ili umerena proteinurija) se najčešće spontano izgube, dok teški slučajevi nefritisa zahtevaju biopsiju bubrega uz primenu renoprotektivne i specifične terapije (kortikosteroidi, ciklosporin A...), zbog moguće progresije u hroničnu bubrežnu bolest. Bez obzira što većina dece sa IgAV nefritisom ima odličnu prognozu, zahvaćenost bubrega je često asimptomatska i zahteva aktivan skrining (hemijski pregled i sediment urina uz merenje krvnog pritiska), jer renalne sekvele ostaju konstantna briga obzirom da je njihov ishod dekadama unazad nepromenjen.

Cljučne reči: Henoch Schönlein purpura, deca, nefritis

ABSTRACT

IgA vasculitis (IgAV), until recently known as Henoch Schönlein purpura, is the most common systemic vasculitis in children with a typically acute presentation. It is estimated that the frequency of this disease is 3–27 cases per 100,000 children. IgA complexes or aggregates play a major role in pathogenesis. Namely, in these patients, in the region of the “hinge” of the IgA1 molecule, for reasons not yet explained, there is a reduced number of galactose residues.

Such IgA molecules have a tendency to form aggregates and to stimulate the synthesis of autoreactive IgG antibodies with the formation of immune complexes. Immune complexes are deposited systemically, leading to necrotizing vasculitis. Nephritis occurs in 30–40% of patients and represents the most serious clinical manifestation of the disease, because it is the only one associated with long-term morbidity and mortality, both in children and in adults. The first urinary abnormalities are usually detected within 4 weeks of the onset of the disease (80% of patients), with the rest within 2 months, rarely later. The most common renal manifestations of the disease are: microscopic or macroscopic hematuria, proteinuria without edema, nephritic syndrome, nephrotic syndrome, or a combination of nephrotic-nephritic syndrome. Minimal urinary abnormalities (isolated microscopic hematuria and non-persistent mild or moderate proteinuria) usually disappear spontaneously, while severe cases of nephritis require a kidney biopsy with the use of renoprotective and specific therapy (corticosteroids, cyclosporin A...), due to possible progression to chronic kidney disease. Despite the fact that most children with IgAV nephritis have an excellent prognosis, kidney involvement is often asymptomatic and requires active screening (chemical examination and urine sediment with blood pressure measurement), because renal sequelae remain a constant concern since their outcome has been unchanged for decades.

Keywords: Henoch Schönlein purpura, children, nephritis

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SAŽETAK

Patolog ima važnu ulogu u dijagnozi i praćenju autoimunskih oboljenja bubrega, kao što su lupus nefritis, IgA nefropatija, membranozni glomerulonefritis, ANCA-vaskulitisi i druge bolesti. Ova oboljenja predstavljaju klinički izazov zbog varijabilnosti njihove prezentacije i ishoda. Precizna evaluacija bubrežne biopsije je od suštinskog značaja za postavljanje dijagnoze i izbor terapije. Morfološka analiza biopsije uključuje procenu strukture glomerula, tubula, intersticijuma i krvnih sudova. Patolog primenjuje svetlosnu mikroskopiju, imunofluorescenciju i elektronsku mikroskopiju kako bi identifikovao morfološke promene i depozite imunskih kompleksa. U pedijatrijskoj i adultnoj populaciji ova oboljenja mogu imati različite morfološke obrasce i kliničke ishode. Imunohistohemijska ispitivanja i molekularna analiza doprinose identifikaciji biomarkera povezanih sa progresijom bolesti i terapijskim odgovorom. Uloga patologa uključuje i saradnju sa kliničarima u odlučivanju o terapijskim strategijama. Značaj rada patologa ogleda se u mogućnosti rane dijagnoze i precizne procene težine oštećenja bubrega, čime se poboljšavaju ishodi lečenja i kvalitet života pacijenata.

Ključne reči: autoimunska oboljenja bubrega, patologija

ABSTRACT

A pathologist plays an important role in diagnosing and monitoring autoimmune kidney diseases such as lupus nephritis, IgA nephropathy, membranous glomerulonephritis, ANCA-associated vasculitis, and other conditions. These diseases present a clinical challenge due to the variability in their presentation and outcomes. Accurate evaluation of kidney biopsies is essential for establishing a diagnosis and selecting appropriate therapy. Morphological analysis of biopsies includes the assessment of the structure of glomeruli, tubules, interstitium, and blood vessels. The pathologist utilizes light microscopy, immunofluorescence, and electron microscopy to identify morphological changes and immune complex deposits. In both pediatric and adult populations, these diseases may exhibit different morphological patterns and clinical outcomes. Immunohistochemical studies and molecular analyses contribute to identifying biomarkers associated with disease progression and therapeutic response. The role of the pathologist also involves collaboration with clinicians in determining therapeutic strategies. The significance of the pathologist's work lies in their ability to provide early diagnosis and accurate assessment of kidney damage, thereby improving treatment outcomes and the quality of life of patients.

Keywords: autoimmune kidney diseases, pathology

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SAŽETAK

Autoimuni hepatitis (AIH) je hronično inflamatorno oboljenje jetre koje se karakteriše povišenim vrednostima transaminaza, prisustvom antinuklearnih ili antiglatkomišćinih antitela, povišenim vrednostima imunoglobulina G (IgG) i interfejs hepatitisom/limfoplazmocitnom infiltracijom na patohistološkom nalazu. Epidemiološke studije ukazuju na porast prevalencije AIH širom sveta, sa nešto češćom zastupljenošću kod muških pacijenata. Klinička manifestacija je izuzetno raznolika i može varirati od asimptomatskih oblika, teškog hepatitisa kao i ciroze jetre sa svim karakterističnim komplikacijama. Za postavljanje dijagnoze služimo se validiranim dijagnostičkim scoring sistemima. Cilj lečenja AIH je suzbijanje fibroznih i inflamatornih aktivnosti u jetri kako bi se sprečio napredak bolesti i postigla potpuna remisija. Korikosteroidi i azatioprin su savetovani kao prva linija terapije, dok kod nekompletnog odgovora ili kortikostereoid zavisnih pacijenata savetuje se mikofenolat mofetil kao druga linija terapije. Prognoza je dobra kod pacijenata sa kompletnim biohemijskim odgovorom, mada se savetuje dugoročna terapija održavanja obzirom na česte relapse unutar godinu dana po isključenju imunosupresivne terapije.

Ključne reči: autoimuni hepatitis, autoantitela, fibroza, ciroza

ABSTRACT

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease characterized by elevated transaminase levels, the presence of antinuclear or anti-smooth muscle antibodies, elevated immunoglobulin G (IgG) levels, and interface hepatitis/lymphoplasmacytic infiltration on histopathological examination. Epidemiological studies indicate an increase in the prevalence of AIH worldwide, with a slightly higher frequency among male patients. The clinical manifestation is extremely varied and can range from asymptomatic forms to severe hepatitis and liver cirrhosis with all characteristic complications. For diagnosis, we rely on validated diagnostic scoring systems. The goal of AIH treatment is to suppress fibrotic and inflammatory activities in the liver to prevent disease progression and achieve complete remission. Corticosteroids and azathioprine are recommended as the first line of treatment, while mycophenolate mofetil is advised as the second line of therapy in cases of incomplete response or corticosteroid-dependent patients. The prognosis is good in patients with a complete biochemical response, although long-term maintenance therapy is recommended due to the frequent relapses within one year after discontinuing immunosuppressive therapy.

Keywords: autoimmune hepatitis, autoantibodies, fibrosis, cirrhosis

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AUTOIMMUNE DISEASES OF THE BILIARY TRACT

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SAŽETAK

Primarni sklerozirajući holangitis (PSC) je hronična bolest jetre koju karakteriše progresivnaolestaza sa inflamacijom i fibrozom intrahepatičnih i ekstrahepatičnih žučnih vodova. PSC je hroničnaolestatska bolest jetre koja se javlja pretežno kod mladih ili sredovečnih muškaraca i često je udružena sa inflamatornim bolestima creva. Etiologija za sada nije poznata, smatra se da je u osnovi ovog oboljenja imunološki poremećaj. Progresija bolesti može dovesti do razvoja ciroze jetre i daljih komplikacija u vidu portne hipertenzije i terminalne insuficijencije jetre. Nadalje budući da je u osnovi ove bolesti prisutna inflamacija, mogući je i razvoj holangiocelularnog karcinoma. Budući da je kod ovih pacijenata veoma često prisutna i zapaljenska bolest creva (IBD), najčešće ulcerozni kolitis, to kod ovih pacijenata povećava rizik i od kolorektalnog karcinoma (KRK). Dijagnoza se postavlja na osnovu biohemijskih analiza i magnetne rezonance a u određenim slučajevima i na osnovu biopsije jetre. Trenutno je jedina terapija koja omogućava produžavanje života ovih pacijenata transplantacija jetre. Nakon transplantacije često dolazi do recidiva bolesti. Obzirom na nedefinisano etiologiju potrebna su dodatna ispitivanja koja bi objasnila patofiziološki mehanizam nastanka i progresije bolesti.

IgG4 sklerozirajući holangitis je retkaolestatska bolest jetre koja takođe može biti udružena sa zapaljenskim bolestima creva a najčešće se javlja u sklopu IgG4 posredovane bolesti.

Gljučne reči: autoimunska bolest jetre, primarni sklerozirajući holangitis, IgG4-posredovan holangitis, zapaljenska bolest creva, holangiokarcinom

ABSTRACT

Primary sclerosing cholangitis (PSC) is a chronic liver disease characterized by progressivecholestasis with inflammation and fibrosis of the intrahepatic and extrahepatic bile ducts. PSC primarily affects young to middle-aged men and is frequently associated with inflammatory bowel disease (IBD). Although the exact etiology remains unknown, PSC is believed to be driven by an underlying immune-mediated mechanism.

As the disease progresses, it may lead to liver cirrhosis and subsequent complications such as portal hypertension and end-stage liver failure. Due to persistent inflammation, there is also an increased risk of developing cholangiocarcinoma. In addition, since IBD – most commonly ulcerative colitis – is often present in these patients, there is an elevated risk of colorectal cancer (CRC).

Diagnosis is established through biochemical tests and magnetic resonance imaging (MRI), and in selected cases, liver biopsy. At present, liver transplantation is the only treatment option that significantly prolongs survival in these patients. However, post-transplant recurrence of the disease is not uncommon. Given the unclear etiology of PSC, further studies are required to elucidate the pathophysiological mechanisms underlying its onset and progression.

IgG4-related sclerosing cholangitis is a rarecholestatic liver disease that may also be associated with inflammatory bowel disease, and it typically occurs as part of the IgG4-related disease spectrum.

Keywords: autoimmune liver disease, primary sclerosing cholangitis, IgG4-related cholangitis, inflammatory bowel disease, cholangiocarcinoma

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THE ROLE OF THE PATHOLOGIST IN THE DIAGNOSIS OF AUTOIMMUNE DISEASES AFFECTING THE LIVER AND BILIARY TRACT

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SAŽETAK

Autoimunska oboljenja jetre i žučnih puteva predstavljaju heterogenu grupu bolesti koje uključuju autoimuni hepatitis (AIH), primarnu bilijarnu holangitis (PBC) i primarni sklerozirajući holangitis (PSC). Dijagnoza ovih stanja često predstavlja izazov zbog preklapajućih kliničkih, laboratorijskih i radioloških karakteristika, što čini histopatološku analizu ključnim korakom u dijagnostičkom procesu.

Uloga patologa u ovom kontekstu podrazumeva identifikaciju specifičnih morfoloških karakteristika, kao što su portalni limfoplazmocitni infiltrati kod AIH, destrukcija malih žučnih puteva kod PBC, i fibroinflatorne promene uz fibrozu kod PSC. Poseban izazov predstavlja prepoznavanje preklapajućih (*overlap*) sindroma, gde patolog mora integrisati histološke nalaze sa kliničkim i serološkim podacima kako bi postavio tačnu dijagnozu.

Pored toga, imunohistohemijske i molekularne metode omogućavaju detaljniju karakterizaciju oboljenja, identifikaciju specifičnih biomarkera i isključivanje diferencijalnih dijagnoza poput primarnih ili sekundarnih maligniteta jetre i žučnih puteva. Ishod dijagnostike značajno utiče na kliničko upravljanje, uključujući izbor terapije i prognozu pacijenata.

Kliničko-patološka korelacija je od suštinskog značaja za razumevanje i pravilnu interpretaciju nalaza kod sumnje na autoimunska oboljenja jetre i žučnih puteva. Integracija patoloških nalaza sa kliničkim i laboratorijskim podacima omogućava tačniju dijagnozu, optimizaciju terapijskog pristupa i personalizaciju lečenja. Ovaj multidisciplinarni pristup doprinosi boljem razumevanju bolesti, kao i unapređenju kliničkih ishoda pacijenata.

Ključne reči: autoimuni hepatitis, primarni bilijarni holangitis, primarni sklerozirajući holangitis

ABSTRACT

Autoimmune diseases of the liver and biliary tract represent a heterogeneous group of disorders that include autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC). The diagnosis of these conditions is often challenging due to overlapping clinical, laboratory, and radiological features, making histopathological analysis a critical step in the diagnostic process.

The pathologist's role in this context involves the identification of specific morphological features such as portal lymphoplasmacytic infiltrates in AIH, destruction of small bile ducts in PBC, and fibroinflammatory changes with fibrosis in PSC. A particular challenge is the recognition of overlap syndromes, where the pathologist must integrate histological findings with clinical and serological data to establish an accurate diagnosis.

In addition, immunohistochemical and molecular methods enable more detailed disease characterization, identification of specific biomarkers, and exclusion of differential diagnoses such as primary or secondary malignancies of the liver and biliary tract. The outcome of the diagnostic process has a significant impact on clinical management, including therapy selection and patient prognosis.

Clinicopathological correlation is essential for the understanding and proper interpretation of findings in suspected autoimmune diseases of the liver and biliary tract. The integration of pathological findings with clinical and laboratory data allows for a more accurate diagnosis, optimization of therapeutic approaches, and personalization of treatment. This multidisciplinary approach contributes to a better understanding of these diseases and improved clinical outcomes for patients.

Keywords: autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis

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IgG4-RELATED AUTOIMMUNE DISORDERS OF THE GASTROINTESTINAL TRACT

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SAŽETAK

Bolest udružena sa imunoglobulinom G4 (engl. IgG4-Related Disease, IgG4-RD) predstavlja imunski posredovan fibroinflamatorni poremećaj i kao zaseban kliničko-patološki entitet je opisan u literaturi 2003. godine. Karakteriše se hroničnom inflamacijom, infiltracijom tkiva IgG4-pozitivnim plazma-ćelijama dok se kod 50-70% slučajeva detektuje povišena koncentracija IgG4 u serumu. Histopatološke odlike obuhvataju prisustvo gustog limfoplazmicitnog infiltrata, "storiformne" fibroze, obliterišućeg flebitisa i blage do umerene eozinofilne infiltracije tkiva. Bolest može zahvatiti gotovo svaki organ, a najčešće: pankreas, pljuvačne i suzne žlezde, jetru i žučne puteve, štitastu žlezdu, orbite, bubrege, retroperitoneum, limfne čvorove i aortu. Iako se ranije smatrala retkom, sve veći broj dijagnostikovanih slučajeva ukazuje na to da je verovatno potcenjena, često pogrešno dijagnostikovana kao malignitet, sistemska autoimunska bolest ili je neprepoznata tokom dužeg latentnog (indolentnog) toka. Češće se javlja kod muškaraca u odnosu na žene (odnos približno 8:3), sa pikom incidence u šestoj deceniji života. Klinička prezentacija je varijabilna – od asimptomatskog postojanja solitarne lezije do izraženih sistemskih simptoma i manifestacija multiorganske disfunkcije. Dijagnoza zahteva integraciju kliničke slike, radioloških nalaza (ultrazvuk, kompjuterizovana tomografija, magnetna rezonanca), seroloških markera i karakterističnih histopatoloških kriterijuma. Prva linija terapije su glukokortikoidi, dok se kod relapsa i/ili refraktarnih slučajeva primenjuju imunomodulatorni lekovi (npr. azatioprin, mikofenolat mofetil, ciklofosfamid i dr.). Ciljani biološki lekovi deluju na ključne patogenetske mehanizme – uključujući depleciju B-limfocita, inhibiciju T-limfocitne kostimulacije, blokadu citokina, aktivacije komplementa i prevenciju patološke akumulacije ekstracelularnog matriksa. Rana dijagnoza i pravovremeno lečenje su od ključnog značaja za prevenciju ireverzibilne fibrozne destrukcije zahvaćenih organa.

Ključne reči: fibroinflamatorni poremećaj, storiformna fibroza, obliterišući flebitis, glukokortikoidi, imunomodulatorna terapija, biološka terapija

ABSTRACT

Immunoglobulin G4-Related Disease (IgG4-RD) is an immune-mediated fibroinflammatory disorder first described in the literature as a distinct clinicopathological entity in 2003. It is characterized by chronic inflammation, infiltration of tissues by IgG4-positive plasma cells, and elevated serum IgG4 concentrations in 50–70% of cases. Histopathological features include a dense lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis, and mild to moderate tissue eosinophilia. The disease can affect virtually any organ, most commonly the pancreas, salivary and lacrimal glands, liver and biliary tract, thyroid gland, orbits, kidneys, retroperitoneum, lymph nodes, and aorta. Although initially considered rare, the increasing number of reported cases suggests that it is likely underrecognized, frequently misdiagnosed as malignancy or systemic autoimmune disease, or overlooked during a prolonged indolent phase. It is more common in males than females (approximately 8:3 ratio), with peak incidence in the sixth decade of life. Clinical presentation is variable – ranging from asymptomatic solitary organ lesions to pronounced systemic symptoms and manifestations of multi-organ dysfunction. Diagnosis requires integration of clinical features, imaging findings (ultrasound, computed tomography, magnetic resonance imaging), serological markers, and characteristic histopathological criteria. First-line treatment involves glucocorticoids, while immunomodulatory agents (e.g., azathioprine, mycophenolate mofetil, cyclophosphamide) are used in relapsing and/or refractory cases. Targeted biologic therapies act on key pathogenic mechanisms – including B-cell depletion, T-cell costimulation inhibition, cytokine blockade, complement activation, and prevention of pathological extracellular matrix accumulation. Early diagnosis and timely treatment are crucial for preventing irreversible fibrotic organ damage.

Keywords: fibroinflammatory disorder, storiform fibrosis, obliterative phlebitis, glucocorticoids, immunomodulatory drugs, biologic therapy

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RADIOLOGICAL PRESENTATION OF INFLAMMATORY BOWEL DISEASES

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SAŽETAK

Savremene radiološke metode poput CT enterografije (CTE), MR enterografije (MRE) i ultrasonografije (US) predstavljaju ključne alate u dijagnostici i praćenju inflamatornih bolesti creva (IBD), posebno Kronove bolesti (CD). Ove neinvazivne tehnike omogućavaju detaljnu evaluaciju digestivnog trakta, identifikaciju aktivnosti bolesti, procenu terapijskog odgovora i detekciju komplikacija kao što su striktura, fistule i apscesi. CTE i MRE imaju visoku senzitivnost (74–100%) u detekciji CD-a, pri čemu MRE kao nejonizujuća tehnika se posebno ističe u proceni aktivnosti bolesti i diferencijaciji fibroznih od inflamatornih striktura, dok je US efikasan u evaluaciji ileuma. Kod pacijenata sa CD, radiološki pregledi pružaju ključne informacije u tri kliničke faze: inicijalnoj dijagnostici, tokom perioda terapije i u post terapijskom/operativnom praćenju. Radiološki nalaz obuhvata: muralne promene (zadebljanje zida, stratifikaciju, intramuralni edem, hipervaskularizacija), komplikacije (striktura fibrozna ili inflamatorna, fistule, apscesi), mezenterijalne promene („znak češlja“, limfadenopatiju, fibromasna proliferaciju) i ekstraintestinalne manifestacije (sakroileitis, primarni sklerozirajući holangitis, venska tromboza).

Standardizovani skorovi poput MaRIA (Magnetic Resonance Index of Activity) i Clermont score omogućavaju kvantifikaciju aktivnosti bolesti i koreliraju sa endoskopskim nalazima. Posebno su važne nove tehnike kao što su MR elastografija i MR transfer magnetizacije (MTI) koje pružaju dodatne informacije o stepenu fibroze u intestinalnim strikturama.

Perspektivno, primena veštačke inteligencije i radiomike otvara nove mogućnosti u analizi slika, omogućavajući precizniju dijagnostiku i personalizovani pristup lečenju. Iako postoje izazovi u standardizaciji protokola i validaciji AI alata, radiološki imidžing će i dalje igrati ključnu ulogu u kompleksnom menadžmentu IBD-a, pružajući objektivne i ponovljive parametre za praćenje bolesti.

Ključne reči: Kronova bolest, MR enterografija, CT enterografija, fibroza, veštačka inteligencija

ABSTRACT

Modern radiological techniques including CT enterography (CTE), MR enterography (MRE), and ultrasonography (US) serve as essential tools for diagnosing and monitoring inflammatory bowel diseases (IBD), particularly Crohn's disease (CD). These non-invasive methods enable comprehensive evaluation of the digestive tract, assessment of disease activity, monitoring of treatment response, and detection of complications such as strictures, fistulas, and abscesses. CTE and MRE demonstrate high sensitivity (74-100%) in CD detection, with MRE - as a non-ionizing technique - being particularly valuable for assessing disease activity and differentiating between fibrotic and inflammatory strictures, while US proves effective for ileal evaluation. In CD patients, radiological examinations provide critical information across three clinical phases: initial diagnosis, treatment monitoring, and post-therapeutic/surgical follow-up. Key radiological findings include: mural changes (wall thickening, stratification, intramural edema, hypervascularization), complications (fibrotic or inflammatory strictures, fistulas, abscesses), mesenteric alterations (“comb sign,” lymphadenopathy, fibrofatty proliferation), and extraintestinal manifestations (sacroiliitis, primary sclerosing cholangitis, venous thrombosis).

Standardized scoring systems such as the Magnetic Resonance Index of Activity (MaRIA) and Clermont score enable quantitative assessment of disease activity and correlate well with endoscopic findings. Emerging techniques like MR elastography and magnetization transfer imaging (MTI) provide additional insights into the degree of intestinal stricture fibrosis.

Looking ahead, artificial intelligence and radiomics offer promising advancements in image analysis, facilitating more precise diagnostics and personalized treatment approaches. While challenges remain in protocol standardization and AI tool validation, radiological imaging will continue to play a pivotal role in comprehensive IBD management by providing objective, reproducible parameters for disease monitoring.

Keywords: Crohn's disease, MR enterography, CT enterography, fibrosis, artificial intelligence

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HISTOPATHOLOGICAL FEATURES OF AUTOIMMUNE DISEASES OF THE GASTROINTESTINAL TRACT

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SAŽETAK

Autoimunska oboljenja gastrointestinalnog trakta predstavljaju heterogenu grupu poremećaja u kojima imunski sistem reaguje na neodgovarajući način na komponente sopstvenih tkiva, dovodeći do hronične inflamacije i oštećenja organa. Najznačajnija oboljenja među njima su celijakija, autoimuni gastritis, kao i inflamatorne bolesti creva – Kronova bolest i ulcerozni kolitis.

Histopatološka analiza predstavlja ključnu komponentu u dijagnostici ovih oboljenja, omogućavajući preciznu procenu stepena i distribucije inflamacije, prisustvo specifičnih morfoloških promena i isključivanje drugih etiologija. Takođe, histopatološka analiza ima značajnu ulogu u praćenju terapijskih efekata i proceni rizika za nastanak malignih tumora.

Histološki nalazi variraju u zavisnosti od lokalizacije i vrste autoimunskog procesa. Autoimuni metaplastični atrofični gastritis je lokalizovan isključivo u korpusnoj sluznici. Karakterišu ga gubitak korpusnih žlezda uz pojavu pseudopilorične i intestinalne metaplazije. U slučaju celijakije, dominantna je atrofija crevnih resica, hiperplazija kripti i infiltracija pokrovnog epitela i lamine proprije sluznice limfocitima. Kod inflamatornih bolesti creva, Kronova bolest i ulcerozni kolitis se razlikuju prema lokalizaciji zapaljenja, obimu i tipu hronične inflamacije. I pored toga što se karakteristične morfološke promene javljaju naježće u određenim autoimunskim i imunski posredovanim bolestima gastrointestinalnog trakta, one najčešće nisu same po sebi dovoljne za postavljanje histopatološkog zaključka i definitivne dijagnoze. Za tačnu dijagnozu je neophodno poznavanje kliničkih i laboratorijskih parametara, kao i endoskopskog nalaza. Kombinacija morfološke i kliničke procene ostaje osnov za pouzdano dijagnostikovanje i adekvatno lečenje ovih stanja.

Ključne reči: autoimuni metaplastični atrofični gastritis, celijakija, inflamatorne bolesti creva, gastrointestinalni trakt

ABSTRACT

Autoimmune diseases of the gastrointestinal tract represent a heterogeneous group of disorders in which the immune system responds inappropriately to components of the body's own tissues, leading to chronic inflammation and organ damage. The most significant among them include celiac disease, autoimmune gastritis, and inflammatory bowel diseases – Crohn's disease and ulcerative colitis. Histopathological analysis is a key component in the diagnosis of these diseases, enabling precise assessment of the degree and distribution of inflammation, identification of specific morphological changes, and exclusion of alternative etiologies. Furthermore, histopathology plays an important role in monitoring therapeutic effects and evaluating the risk of malignant transformation. Histological findings vary depending on the location and type of autoimmune process. Autoimmune metaplastic atrophic gastritis is exclusively localized in the corpus mucosa and is characterized by the loss of oxyntic glands with the appearance of pseudopyloric and intestinal metaplasia. In celiac disease, the dominant features include villous atrophy, crypt hyperplasia, and infiltration of the surface epithelium and lamina propria with lymphocytes. In inflammatory bowel disease, Crohn's disease and ulcerative colitis differ in terms of the localization, extent, and type of chronic inflammation. Although characteristic morphological changes frequently occur in specific autoimmune and immune-mediated gastrointestinal diseases, they are often insufficient on their own for establishing a definitive histopathological diagnosis. Accurate diagnosis requires integration of clinical and laboratory parameters, as well as endoscopic findings. The combination of morphological and clinical assessment remains the cornerstone of reliable diagnosis and appropriate management of these conditions.

Keywords: autoimmune metaplastic atrophic gastritis, celiac disease, inflammatory bowel diseases, gastrointestinal tract

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SAŽETAK

Uvod: Vaskulitis je kliničko-patološki entitet koji se karakteriše zapaljenjem i oštećenjem zida krvnih sudova. Klasifikacija iz 2012. godine definiše posebnu grupu vaskulitisa malih krvnih sudova povezanih sa antineutrofilnim citoplazmatskim antitelima (ANCA), takozvani ANCA-asocirani vaskulitisi (AAV). AAV mogu biti primarni i sekundarni (indukovani lekom ili infekcijom). AAV dovode do nekrotizujuće inflamacije malih/srednjih krvnih sudova sa malo ili bez depozitovanih imunskih kompleksa. Primarnim AAV pripadaju: mikroskopski poliangiitis (MPA), granulomatoza sa poliangiitisom (GPA) i eozinofilna granulomatoza sa poliangiitisom (EGPA).

Metode: Perinuklearna pANCA specifična za mijeloperoksidazu ima dobru senzitivnost i specifičnost za MPA, dok citoplazmatska cANCA specifična za proteinazu 3 ima dobru senzitivnost i specifičnost za GPA.

Rezultati: Spekter kliničkih manifestacija je širok, od nespecifičnih simptoma do znakova oštećenja različitih organa (koža, bubrezi, pluća, gornji disajni putevi, gastrointestinalni, nervni sistem). Imajući u vidu preklapanje entiteta unutar grupe AAV, uvedeni su 2022. godine klasifikacioni kriterijumi koji boduju definisane kliničke, laboratorijske, patohistološke i imidzing nalaze. Za MPA analizira se 6 parametara i potreban je zbir od minimum 5 bodova za postavljanje dijagnoze. Za GPA analizira se 10 parametara i potreban je zbir od minimum 5 bodova za postavljanje dijagnoze. Za EGPA analizira se 7 parametara i potreban je zbir od minimum 6 bodova za postavljanje dijagnoze. Lekom (propylthiouracil, penicilamin, levamizol) i infekcijom (subakutni bakterijski endokarditis, tuberkuloza) indukovani AAV imaju bolju prognozu, ako se na vreme dijagnostikuju.

Zaključak: Detekcija ANCA ubrzava postavljanje dijagnoze i poboljšava prognozu AAV, posebno kod renopulmonalnih prezentacija. Danas se AAV uspešno leče kombinacijom kortikosteroida, imunosupresiva, biološkom terapijom (rituximab) i plazmaferezom, kod najtežih formi.

Ključne reči: ANCA-udruženi vaskulitisi, mikroskopski poliangiitis, granulomatoza sa poliangiitisom, eozinofilna granulomatoza sa poliangiitisom

ABSTRACT

Introduction: Vasculitis is a clinical-pathological entity characterized by inflammation of the vessels wall. The 2012 classification defined group of small vessel vasculitides associated with antineutrophil cytoplasmic antibodies (ANCA), so-called ANCA-associated vasculitides (AAV). AAVs can be primary or secondary (drug or infection-induced). AAV are characterized by necrotizing inflammation of small/medium size vessels, with little or no immune-complex deposits. Primary AAVs are: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA).

Methods: Perinuclear pANCA specific for myeloperoxidase has good sensitivity/specificity for MPA, while cytoplasmic cANCA specific for proteinase 3 has good sensitivity/specificity for GPA.

Results: The spectrum of manifestations is wide, from non-specific symptoms to signs of damage to various organs (skin, kidneys, respiratory, gastrointestinal, nervous system). Considering the overlap within the AAV group, classification criteria were introduced in 2022 that score defined clinical, laboratory, pathohistological and imaging findings. For MPA, 6 parameters are analyzed and a total of at least 5 points is required to establish a diagnosis. For GPA, 10 parameters are analyzed and a sum of at least 5 points is required to establish a diagnosis. For EGPA, 7 parameters are analyzed and a sum of at least 6 points is required to make a diagnosis. Drug (propylthiouracil, penicillamine, levamisole) and infection (subacute bacterial endocarditis, tuberculosis) induced-AAV have a better prognosis.

Conclusion: The detection of ANCA accelerates the diagnosis and improves the prognosis of AAV. AAV are successfully treated with a combination of corticosteroids, immunosuppressants, biological therapy (rituximab) and plasmapheresis, in the most severe forms.

Keywords: ANCA associated vasculitides, microscopic polyangiitis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis

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RHEUMATOID ARTHRITIS – CONTEMPORARY DIAGNOSIS AND THERAPY

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SAŽETAK

Reumatoidni artritis (RA) je najčešća zapaljenska bolest zglobova čija se prevalencija kreće 0,5-1%. Etiologija RA još uvek nije potpuno poznata. Smatra se da RA nastaje kod genetski predisponiranih osoba delovanjem različitih faktora rizika iz spoljašnje sredine. Najraniji događaj u patogenezi RA je aktivacija urođenog imunskog odgovora, koji podrazumeva aktivaciju dendritičnih ćelija egzogenim i autolognim antigenima. U sinovitisu ključnu ulogu ima široka citokinska mreža koja deluje proinflamatorno i podstiče oštećenje tkiva. Značajan serološki marker RA je reumatoidni faktor (RF), međutim antitelo koje ima veću specifičnost je antitelo na citrulinisane peptide i proteine (ACPA). Glavno obeležje RA je simetrični, periferni poliartritis koga odlikuje otok sinovijalnog zgloba, značajna jutarnja ukočenost i palpatorna osetljivost. Reumatoidni artritis kao sistemska bolest može dovesti do brojnih vanzglobnih manifestacija. Iako nema dijagnostičkih kriterijuma, u upotrebi su ACR/EULAR 2010. klasifikacioni kriterijumi koji uključuju kliničke manifestacije i serološke testove i koji su razvijeni za ciljnu populaciju koja ima najmanje jedan otečen zglob. Lekovi koji se koriste u lečenju RA su nesteroidni antiinflamatorni lekovi (NSAIL), glukokortikoidi (GK) i lekovi koji modifikuju tok bolesti (LMTB). EULAR-ove preporuke iz 2022.g. sugerišu da lečenje RA treba započeti primenom MTX uz kratkotrajno davanje GK, a zatim ako postoji neefikasnost dodati ili zameniti terapiju drugim sintetskim LMTB. Međutim, ukoliko postoje nepovoljni prognostički markeri treba uvesti biološke LMTB. Cilj lečenja je remisija ili niska aktivnost bolesti. Da bi lečenje bilo efikasno od velike važnosti je rano postavljanje dijagnoze s obzirom da se radi o progresivnom, erozivnom poliartritisu koji dovodi do invaliditeta i skraćuje životni vek bolesnika.

Ključne reči: reumatoidni artritis, dijagnoza, terapija

ABSTRACT

Rheumatoid arthritis (RA) is the most common inflammatory joint disease, with a prevalence of 0.5-1%. The etiology of RA is not completely known. It is believed that RA occur in genetically predisposed individuals due to the action of various factors from the external environment. The earliest event in the pathogenesis of RA is the activation of the innate immune response, which involves the activation of dendritic cells by exogenous and autologous antigens. A broad cytokine network plays a key role in synovitis, which acts pro-inflammatory and promotes tissue damage. An important serological marker of RA is the rheumatoid factor (RF); however, an antibody with greater specificity is antibody to citrullated peptides and proteins (ACPA). The main feature of RA is symmetrical, peripheral polyarthritis characterized by synovial joint swelling, significant morning stiffness, and palpable tenderness. Rheumatoid arthritis, as a systemic disease, can lead to various extra-articular manifestations. Although no diagnostic criteria exist, the ACR/EULAR 2010 classification criteria are in use. These include clinical manifestations and serological tests, and were developed for a target population with at least one swollen joint. Drugs used in the treatment of RA are nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCs), and disease-modifying antirheumatic drugs (DMARDs). The EULAR 2022 recommendations suggest that treatment of RA should be initiated with MTX and short-term administration of GC, then, if there is ineffectiveness, add or replace therapy with other synthetic DMARDs. However, if there are unfavourable prognostic markers, a biological DMARDs should be introduced. The goal of treatment is remission or low disease activity. For the treatment to be effective, early diagnosis is of great importance, as it is a progressive, erosive polyarthritis that leads to disability and shortens the patient's life.

Keywords: rheumatoid arthritis, diagnosis, treatment

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SAŽETAK

Više sindroma centralnog nervnog sistema može biti praćeno simptomima psihoze: limbički i N-metil-D-aspartat receptor encefalitis, neuropsihijatrijski sistemski eritemski lupus, Hashimoto encefalopatija ili encefalopatija reaktivna na steroid povešana sa autoimunskim tiroiditisom, antifosfolipidni sindrom, Šegrenov sindrom, skleroderma ili vaskulitis povešan sa antineutrofilnim citoplazmatskim antitelima. Opsežne analize studija mogućih asocijacija ukazuju na zajedničke prezentacije perniciozne anemije, pemfigoida, psorijaze, celijakije i Gravesove bolesti sa psihozom, a isključuju istovremeno javljanje sa ankilozirajućim spondilitisom i reumatoidnim artritisom. Potvrđen je manji rizik za pojavu shizofrenije kod osoba sa tipom 1 diabetes melitusa. U eri pandemije i virusnih infekcija, ali i zbrinjavanja njihovih brojnih posledica, koncepti autoimunosti i psihotičnosti se mogu dovesti u vezu. Sličnost im je multifaktorska etiopatogeneza, predisponiranost sa specifičnim precipitirajućim faktorom, što sliči teoriji „dva udara“ u shizofreniji. Faza osetljivosti autoimunskih procesa odgovara specifičnim premorbidnim karakteristikama ličnosti pacijenata sa shizofrenijom. Inicijacija i progresija je mnogo sporija nego ona viđena kod reakcija na patogene organizme, sve dok se ne pređe prag, što odgovara prodromu shizofrenije. Mogu se povući paralele između kontrolnih mehanizama oporavka i privremenog uspostavljanja tolerancije i remisije u shizofreniji. Oba ova poremećaja imaju hronični tok. Neophodno je razmotriti dinamiku javljanja psihotičnih simptoma i posebno uzeti u obzir polimorfnu psihopatologiju, ali i pridruženu somatsku problematiku neuroloških ispada, infektivnog sindroma i hiperpireksije, disfunkcionalnosti autonomnog nervnog sistema, onkoloških bolesti itd. Atipične prezentacije mogu biti refraktarne na klasičnu psihotropnu medikaciju ili uz izražena neželjena dejstva posle njene primene. Kauzalni pristup u najvećoj meri je onaj koji razrešava, pa se sve više predlažu imunoterapijske strategije, uz restriktivniju primenu antipsihotika.

Ključne reči: autoimunost, psihotičnost, shizofrenija, imunoterapija, antipsihotici

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ABSTRACT

Several central nervous system syndromes can present with symptoms of psychosis, including limbic encephalitis, N-methyl-D-aspartate receptor encephalitis, neuropsychiatric systemic lupus erythematosus, Hashimoto's encephalopathy and steroid-responsive encephalopathy associated with autoimmune thyroiditis, antiphospholipid syndrome, Sjögren's syndrome, and scleroderma or vasculitis linked to antineutrophil cytoplasmic antibodies. Extensive analyses of potential associations indicate that conditions such as pernicious anemia, pemphigoid, psoriasis, celiac disease, and Graves' disease may commonly present with psychosis. However, these studies exclude a co-occurrence with ankylosing spondylitis and rheumatoid arthritis. Research has confirmed that individuals with type 1 diabetes mellitus have a lower risk of developing schizophrenia. In the context of pandemics and viral infections, as well as their various consequences, the connections between autoimmunity and psychotic symptoms become relevant. Both conditions share similarities in their multifactorial origins and the concept of a specific precipitating factor occurring in vulnerable circumstances, which aligns with the "two hits" theory of schizophrenia. The susceptibility phase of autoimmune processes corresponds to certain premorbid personality traits observed in patients with schizophrenia. The initiation and propagation of symptoms is much slower compared to the reactions seen in response to pathogenic organisms until a certain threshold is reached, which corresponds to the prodromal phase of schizophrenia. Similarities exist between the recovery control mechanisms and the temporarily restoring self-defense, akin to those observed during schizophrenia remission. Both disorders tend to follow a chronic course. It is important to consider the dynamics of psychotic symptom appearance and to take into account polymorphic psychopathology, as well as associated somatic issues such as neurological signs, infectious syndromes, hyperpyrexia, dysfunction of the autonomic nervous system, oncological diseases, etc. Atypical presentations may resist traditional psychotropic medications, and their usage can lead to significant side effects. The causal approach is typically the most effective, which is why immunotherapy strategies are increasingly being proposed alongside a more cautious use of antipsychotics.

Keywords: autoimmunity, psychosis, schizophrenia, immunotherapy, antipsychotics

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SAŽETAK

Uvod/cilj: Smatra se da osnovni mehanizmi koji dovode do poremećaja iz spektra autizma (PSA) uključuju neurobiološke, imunološke i faktore sredine, te njihovu međusobnu povezanost. Ovaj pregled rezimira ulogu poremećaja imunog sistema kod PSA.

Metode: Pregled literature.

Rezultati: Kod PSA se često primećuju abnormalnosti imunog sistema, prvenstveno uključujući povišene proinlatorske citokine, izmenjene frekvencije imunih ćelija i neregulirane mehanizme supresije imuniteta. Konkretno, studije pokazuju da varijacije u odgovorima imunih ćelija, posebno među podgrupama T i B ćelija, doprinose različitim fenotipovima kod PSA. Neuroinlatorski markeri se takođe često identifikuju kod PSA, a specifične imunološke promene značajno korelišu sa ozbiljnošću simptoma.

Pokazano je i da imuni razvoj fetusa i uticaj majčinih autoantitela na razvoj mozga fetusa mogu izazvati ponašanja slična PSA. Neke studije ističu imunološku aktivaciju majke kao ključni faktor u razvoju ASD-a kod potomaka, odražavajući međusobnu povezanost genetskih predispozicija i imunološke disfunkcije. Na dalje, varijacije u ekspresiji imunih gena su usko povezane sa neurorazvojnim procesima, posebno tokom kritičnih prenatalnih i perinatalnih perioda. Pored toga, osovina creva-mozak igra značajnu ulogu, pri čemu disbioza utiče na imunološke i nervne funkcije, te doprinosi simptomatologiji PSA. Izraziti mikrobni profili kod osoba sa PSA odražavaju preovlađujuću disbiozu, potencijalno izazivajući neuroinlatorsku, disregulaciju neurotransmitera i oštećenu neuralnu funkciju.

Zaključak: Iako se kod PSA primećuju različite abnormalnosti imunog sistema, smatra se da ukrštanja između genetskih i imunoloških faktora, kritičnog uticaja okoline majke tokom trudnoće, važnosti sistema neurotransmitera u manifestacijama ponašanja i veze creva i mozga povezana sa neuroinlatorskom mogu predstavljati osnovne mehanizme koji dovode do PSA, te da su to potencijalni terapijski ciljevi.

Ključne reči: autoimunost, antitela, neuroinlatorska, autizam

ABSTRACT

Background/Aim: The underlying mechanisms leading to autism spectrum disorder (ASD) are thought to involve neurobiological, immunological, and environmental factors, and their interrelationship. This overview summarizes the role of immune system dysregulations in ASD.

Methods: Literature overview.

Results: Immune system abnormalities are frequently observed in ASD, primarily involving elevated pro-inflammatory cytokines, altered immune cell frequencies, and dysregulated immune suppression mechanisms. Specifically, studies show that variations in immune cell responses, particularly among T and B cell subsets, contribute to the diverse phenotypes observed in ASD. Neuroinlatorski markers are also commonly identified in ASD, and specific immune alterations significantly correlate with ASD symptom severity.

Maternal influences, such as fetal immune development and the impact of maternal autoantibodies on fetal brain development, may provoke ASD-like behaviors. Some studies highlight maternal immune activation as a key factor in the development of ASD in offspring, reflecting the interplay between genetic predispositions and immune dysfunction. Further, variations in immune gene expression are closely linked to neurodevelopmental processes, especially during critical prenatal and perinatal periods. Additionally, the gut-brain axis plays a significant role, with dysbiosis affecting immune and neural functions and contributing to ASD symptomatology. Distinct microbial profiles in individuals with ASD reflect prevalent dysbiosis, potentially triggering neuroinlatorska, neurotransmitter dysregulation, and impaired neural function.

Conclusion: Although observed various abnormalities of the immune system, the intersections between genetic and immune factors, the critical influence of the maternal environment during gestation, the importance of neurotransmitter systems in behavioral manifestations, and the gut-brain connection linked to neuroinlatorska may constitute the underlying mechanisms leading to ASD and potentially therapeutic goals.

Keywords: autoimmunity, antibodies, neuroinlatorska, autism

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PSYCHIATRIC MANIFESTATION OF AUTOIMMUNE DISEASES

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SAŽETAK

U autoimunim bolestima, kao multisistemskim oboljenjima, zahvaćeni mogu biti centralni, periferni i autonomni nervni sistem. Učestalost javljanja psihijatrijskih manifestacija razlikuje se u pojedinim autoimunim bolestima sa najčešćim javljanjem u sistemskom lupusu (do 80% pacijentata). Simptomi mogu nastati kao direktna ili indirektna posledica autoimunih bolesti (inflamatorne, trombotičke i metaboličke promene kao i infekcija). Takođe se mogu dovesti u vezu i sa terapijom samih oboljenja (kortikosteroidi, biološka terapija), a mogu biti posledica psihološkog distresa zbog tegoba/lečenja autoimune bolesti. Kod pojedinog pacijenta psihijatrijske komplikacije mogu se javiti u formi pojedinačnih simptoma ili sindroma. Najčešći simptomi koji se javljaju su anksioznost, kognitivni poremećaji, emocionalna nestabilnost, poremećaji raspoloženja i spavanja, oštećenja memorije, depersonalizacija, derealizacija, poremećaji senzorijuma, delirijum i psihotični poremećaji. Prepoznavanje i adekvatna dijagnoza psihijatrijskih poremećaja predstavlja izazovan zadatak za svakog kliničara. Lečenje uključuje tretman neželjenih dejstava kauzalne terapije za samo autoimuno oboljenje, uvođenje ciljane psihijatrijske terapije, psihoterapijske intervencije, edukaciju i podršku pacijentu i porodici.

Ključne reči: autoimunost, imunološki sistem, liason psihijatrija, mentalna oboljenja

ABSTRACT

In autoimmune diseases, as multisystem diseases, the central, peripheral and autonomic nervous systems can be affected. The frequency of psychiatric manifestations differs in individual autoimmune diseases, with the most frequent occurrence in systemic lupus (up to 80% of patients). Symptoms may reflect as a direct or indirect consequence of autoimmune diseases (inflammatory, thrombotic and metabolic changes as well as infection). They can also be related to the therapy of the diseases themselves (corticosteroids, biological therapy), and consequence of psychological distress due to problems/treatment of autoimmune diseases. In an individual patient, psychiatric complications can occur in the form of individual symptoms or syndromes. The most common symptoms that occur are anxiety, cognitive disorders, emotional instability, mood and sleep disorders, memory impairment, depersonalization, derealisation, sensorial disorders, delirium, and psychotic disorders. Recognition and adequate diagnosis of psychiatric disorders is a challenging task for every clinician. Treatment includes addressing the side effects of therapy for the autoimmune disease itself, introduction of targeted psychiatric therapy, psychotherapeutic interventions, education and support for the patient and family.

Keywords: autoimmune, immune system, liaison psychiatry, mental illnesses

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