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ORIGINAL ARTICLES

Onihomikoze kod pacijenata obolelih od hronične venske insuficijencije

Onychomycosis in patients with chronic venous insufficiency

CASE REPORTS

Eczema herpeticum kao komplikacija eritrodermiskog pemphigus foliaceus-a – prikaz slučaja

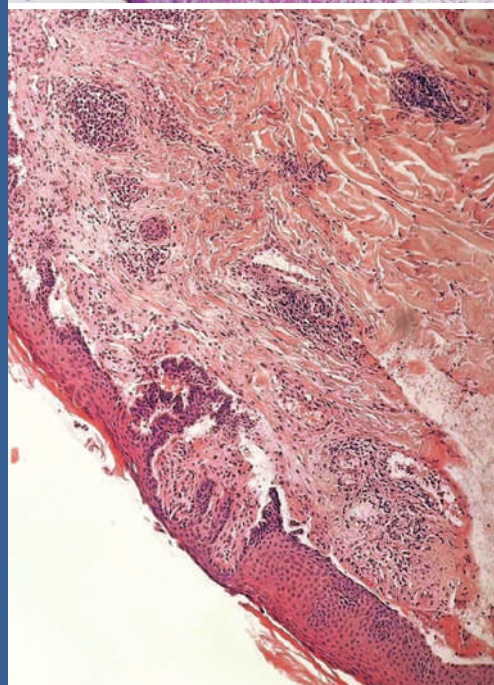
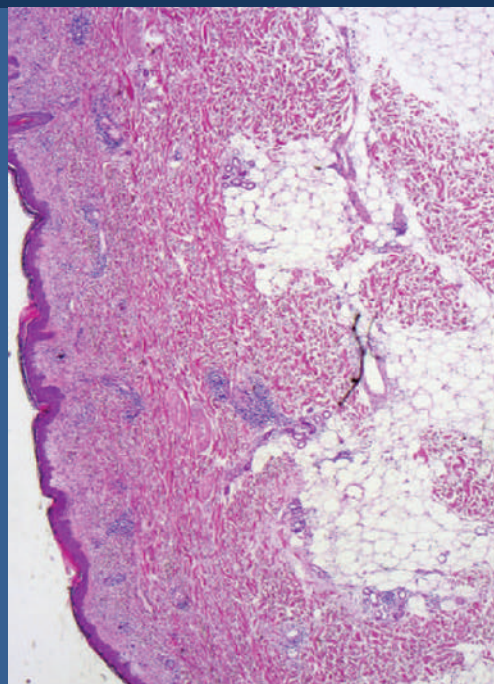
Eczema herpeticum as a complication of erythrodermic pemphigus foliaceus – Case report

Klinički amyopatski dermatomiozitis sa progresijom u klasičan dermato miozitis – dijagnostički i terapijski izazov – prikaz slučaja

Clinically amyopathic dermatomyositis progressing into classic dermatomyositis – diagnostic and therapeutic challenge – Case report

Bulozni pemfigoid kao neželjeni efekat terapije nivolumabom – prikaz slučaja

Bullous pemphigoid as an adverse event of checkpoint inhibitor therapy – Case report





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SADRŽAJ

Serbian Journal of Dermatology and Venereology 2024; 13 (2):59-106.

ORIGINALNI RADOVI

- 63 ONIHOMIKOZE KOD PACIJENATA OBOLELIH OD HRONIČNE VENSKE INSUFICIJENCIJE**
*Jelena BANJAC, Aleksandra MATIĆ, Danilo KUZMAN, Dunja VESKOVIĆ,
Miloš ĐURĐEVIĆ, Đurđa CVJETKOVIĆ NIKOLETIĆ, Milan MATIĆ*

PRIKAZI SLUČAJEVA

- 79 ECZEMA HERPETICUM KAO KOMPLIKACIJA ERITRODERMIJ- SKOG PEMPHIGUS FOLIACEUS-a – PRIKAZ SLUČAJA**
Jovana PAVLICA, Željko MIJUŠKOVIĆ, Lidija KANDOLF, Miroslav DINIĆ
- 87 KLINIČKI AMIOPATSKI DERMATOMIOZITIS SA PROGRESIJOM U KLASIČAN DERMATO MIOZITIS – DIJAGNOSTIČKI I TERAPIJSKI IZAZOV – PRIKAZ SLUČAJA**
*Danilo KUZMAN, Ljuba VUJANOVIĆ, Dunja VESKOVIĆ, Jelena BULAJIĆ,
Aleksandra Fejsa LEVAKOV, Aleksandra MATIĆ*
- 97 BULOZNI PEMFIGOID KAO NEŽELJENI EFEKAT TERAPIJE NIVOLUMABOM – PRIKAZ SLUČAJA**
*Jelena RADOSAVLJEVIĆ, Igor SALATIĆ, Željko MIJUŠKOVIĆ, Nenad PETROV,
Miroslav DINIĆ, Lidija KANDOLF*

CONTENTS

Serbian Journal of Dermatology and Venereology 2024; 13 (2):59-106.

ORIGINAL ARTICLES

- 63 ONYCHOMYCOSIS IN PATIENTS WITH CHRONIC VENOUS INSUFFICIENCY**
Jelena BANJAC, Aleksandra MATIĆ, Danilo KUZMAN, Dunja VESKOVIĆ,
Miloš ĐURĐEVIĆ, Đurđa CVJETKOVIĆ NIKOLETIĆ, Milan MATIĆ

CASE REPORTS

- 79 ECZEMA HERPETICUM AS A COMPLICATION OF ERYTHRODERMIC PEMPHIGUS FOLIACEUS – CASE REPORT**
Jovana PAVLICA, Željko MIJUŠKOVIĆ, Lidija KANDOLF, Miroslav DINIĆ
- 87 CLINICALLY AMYOPATHIC DERMATOMYOSITIS PROGRESSING INTO CLASSIC DERMATOMYOSITIS – DIAGNOSTIC AND THERAPEUTIC CHALLENGE – A CASE REPORT**
Danilo KUZMAN, Ljuba VUJANOVIĆ, Dunja VESKOVIĆ, Jelena BULAJIĆ,
Aleksandra Fejsa LEVAKOV, Aleksandra MATIĆ
- 97 BULLOUS PEMPHIGOID AS AN ADVERSE EVENT OF CHECKPOINT INHIBITOR THERAPY – CASE REPORT**
Jelena RADOSAVLJEVIĆ, Igor SALATIĆ, Željko MIJUŠKOVIĆ, Nenad PETROV,
Miroslav DINIĆ, Lidija KANDOLF

ONIHOMIKOZE KOD PACIJENATA OBOLELIH OD HRONIČNE VENSKE INSUFICIJENCIJE

ONYCHOMYCOSIS IN PATIENTS WITH CHRONIC VENOUS INSUFFICIENCY

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Sažetak

Onihomikoza je najčešća gljivična infekcija noktiju na svetu koja uzrokuje promenu boje i zadebljanje zahvaćenih noktiju. Češće se javlja kod pacijenata sa hroničnom venskom insuficijencijom ili perifernom vaskularnom bolešću zbog različitih faktora, uključujući starenje populacije. Razne vrste gljivica, posebno dermatofiti kao što su *T. rubrum* i *T. mentagrophytes*, glavni su uzročnici onihomikoze, koja može zahvatiti i nokte na rukama i nogama. Klinička prezentacija je različita, pri čemu je distalna lateralna subungvalna onihomikoza najčešći oblik. Dostupne su različite dijagnostičke metode za onihomikozu, pri čemu se direktna mikroskopija i kultivacija gljivica smatraju zlatnim standardom. Tačna i pravovremena dijagnoza mora biti potvrđena mikološkim ispitivanjem pre nego što se započne terapija, jer je reinfekcija česta, a teži slučajevi su manje podložni odgovoru na lečenje. Topička terapija se generalno preporučuje kao prvi izbor lečenja kod starijih pacijenata. Kada je sistemska terapija neophodna, terbinafin bi trebalo da bude lek prve linije zbog manjeg rizika od interakcija sa drugim lekovima. Nedavna istraživanja su istakla značajnu povezanost između hronične venske insuficijencije i onihomikoze, ali ograničen broj studija ukazuje na potrebu za daljim unapređenjem pridržavanja smerica za lečenje onihomikoze kod pacijenata sa hroničnom venskom insuficijencijom.

Ključne reči: onihomikoza; venska insuficijencija; hronično oboljenje; nokti; periferno vaskularno oboljenje; mikoze; terapija

Abstract

Onychomycosis is the most common fungal infection of the nails globally, characterized by discoloration and thickening of the affected nail plate. It is more frequently observed in patients with chronic venous insufficiency or peripheral vascular disease, due in-part to age-related changes and impaired circulation. A variety of fungi, predominantly dermatophytes such as *T. rubrum* and *T. mentagrophytes*, are the primary causative agents, affecting both fingernails and toenails. The clinical presentation is polymorphic, with distal lateral subungual onychomycosis being the most prevalent subtype. Several diagnostic methods are available, with direct microscopy and fungal culture remaining the gold standard. Confirming the diagnosis through mycological examination is essential prior to initiating treatment, as reinfection is common and advanced cases often show poor therapeutic response. In elderly patients, topical therapy is generally preferred as the first-line treatment. When systemic therapy is indicated, terbinafine is the agent of choice due to its lower risk of drug interactions. Recent research has demonstrated a significant association between chronic venous insufficiency and onychomycosis; however, the limited number of studies emphasizes the need for improved guideline adherence in managing onychomycosis in this patient population.

Key words: Onychomycosis; Venous Insufficiency; Chronic Disease; Nails; Peripheral Vascular Diseases; Mycoses; Drug Therapy

Uvod

Hronična venska bolest (HVB) i onihomikoza noktiju na stopalima (OM) predstavljaju značajne zdravstvene probleme čija učestalost raste sa godinama, često negativno utičući NA kvalitet života pacijenata [1]. Brojne studije su potvrdile da se promene na noktima stopala često javljaju kod pacijenata sa HVB, pri čemu su takve promene zabeležene kod više od 83% obolelih, a onihomikoza je potvrđena u većini slučajeva [1–3]. Manifestacije hronične venske insuficijencije (HVI) na noktima često mogu imitirati promene karakteristične za onihomikozu, uključujući zadebljale nokte tamne boje sa prisutnom hiperplazijom ležišta nokta i čestom pojavom onihogrifoze. Pored toga, s obzirom na to da su i onihomikoza i venska insuficijencija češće u starijoj populaciji, nije retkost da se kod pacijenata sa HVI potvrdi prisustvo gljivične infekcije noktiju [2].

Onihomikoza je gljivična infekcija odgovorna za oko 50% svih bolesti noktiju [4, 5]. Globalna prevalencija iznosi 5,5%, dok se procenjuje da je u Sjedinjenim Američkim Državama između 2% i 14%, dok u Evropi varira od 0,5% do 24% [6, 7]. Infekcija može zahvatiti bilo koju komponentu nokatne jedinice, uključujući nokatnu ploču, matriks i posteljicu, kao i okolnu kožu [8, 9]. Ova bolest je hronična, ne prolazi spontano i karakteriše se zadebljanjem, lomljivošću, diskoloracijom i odvajanjem nokatne ploče [10–12]. Progresivne mikroangiopatske promene kapilara nokta usled HVI mogu doprineti razvoju onihomikoze [13].

Procena je da HVI pogađa oko 15% odrasle populacije, dok većina studija navodi raspon između 10% i 30%, pri čemu učestalost značajno raste kod starijih osoba [13]. Ova bolest obuhvata širok spektar kliničkih manifestacija, od varikoznih vena i hroničnog bola u donjim ekstremitetima do edema, kožnih promena i ulceracija [2]. Rizik od razvoja venskog ulkusa tokom života iznosi oko 1% kod opšte populacije, dok je prevalencija do tri puta veća kod osoba starije dobi [1]. U kliničkoj praksi je primećeno da ovi pacijenti često imaju promene na noktima koje ukazuju na prisustvo onihomikoze [14]. Lečenje onihomikoza stopala može biti izazovno zbog sporog rasta noktiju, što zahteva produženo lečenje, smanjene penetracije topikalnih preparata i visokog rizika od recidiva bolesti [10].

Introduction

Chronic venous disease (CVD) and toenail onychomycosis (OM) are prevalent and clinically significant conditions that increasingly affect the aging population, often compromising quality of life [1]. Numerous studies have reported a high frequency of toenail abnormalities among patients with CVD, with over 83% exhibiting such changes, and onychomycosis confirmed in the majority of cases [1–3]. The nail alterations associated with chronic venous insufficiency (CVI) may closely resemble those seen in onychomycosis, including thickened and darkened nails, hyperplastic nail bed, and onychogryphosis. Given that shared risk factors – particularly advanced age – coexistence of fungal infections in toenails of patients with CVI is not uncommon [2].

Onychomycosis accounts for approximately 50% of all nail disorders [4, 5], with a global prevalence of 5.5%. Prevalence rates vary widely, ranging from 2-14% in the United States and 0.5-24% in Europe [6, 7]. The infection may involve any component of the nail unit – nail plate, matrix, bed – as well as adjacent skin [8, 9]. Onychomycosis is a chronic, non-self-limiting condition, clinically characterized by thickening, brittleness, discoloration, and onycholysis (separation of the nail plate) [10–12]. In patients with CVI, progressive microangiopathic changes in the nail capillaries may further contribute to susceptibility to fungal nail infections [13].

CVI affects approximately 15% of the adult population, with reported prevalence ranging from 10-30% in most studies, and significantly increasing with age [13]. The clinical spectrum of CVI includes varicose veins, chronic leg pain, edema, skin changes, and venous ulcers [2]. The lifetime risk of venous ulceration is approximately 1% in the general population but can be up to three times higher among the elderly [1]. Clinical observations suggest that patients with CVI frequently present with nail changes suggestive of onychomycosis [14]. Treatment of toenail OM is often challenging due to slow nail growth, prolonged treatment duration, limited penetration of topical agents, and a high recurrence rate [10].

Although onychomycosis is a benign and treatable condition, it can substantially affect

Iako je onihomikoza benigna i izlečiva bolest, može značajno uticati na svakodnevni život pacijenata. Pregledni članak studija o njenom uticaju na kvalitet života je pokazao da ova infekcija može uzrokovati fizičko oštećenje, ograničenu funkcionalnost, bol ili nelagodnost, kao i socijalnu stigmatizaciju, pri čemu su psihološki i psihosocijalni uticaj za beleženi kod čak 92% kod obolelih pacijenata [17].

Etiopatogeneza i faktori rizika

Patogeni mikroorganizmi

Prema aktuelnim istraživanjima, mikološkim ispitivanjem je potvrđeno da približno 4% pacijenata, bez obzira na prisustvo karakterističnih kliničkih manifestacija, ima onihomikozu noktiju stopala uzrokovanu dermatofitima [10]. Uzročnici onihomikoze uključuju dermatofite, nedermatofitne plesni (NDP) i kvasnice. Većinu dermatofitnih infekcija noktiju (60–70%) izazivaju *Trichophyton rubrum* i *Trichophyton mentagrophytes*, dok nedermatofitne buđi uključuju vrste kao što su *Scopulariopsis brevicaulis*, *Acremonium spp.*, *Aspergillus spp.*, *Fusarium spp.*, *Alternaria alternata* i *Neoscytalidium* [9, 15, 16]. Onihomikoza izazvana kvasnicama je najčešće uzrokovana vrstama roda *Candida* [15]. NDP vrste nisu sposobne da razgrade keratin, te infekcija obično nastaje traumom, direktnim kontaktom sa zemljom i biljkama ili kao sekundarna infekcija [4].

Kod dermatofitne onihomikoze, *tinea pedis* se najčešće javlja kao predisponirajući faktor, a Zaias i saradnici su 1996. godine opisali porodični obrazac prenošenja infekcije, ističući genetsku predispoziciju za razvoj bolesti [17]. Nedermatofitne onihomikoze su oportunističke infekcije i tipično se karakterišu odsustvom interdigitalne infekcije. Izloženost NDB može dovesti do razvoja onihomikoze u prisustvu brojnih predisponirajućih faktora, kao što su visoke temperature i vlažna sredina, zatvorena obuća, hiperhidroza, deformiteti noktiju i povrede noktiju koje se klinički manifestuju kao asimetrični obrasci hoda koji utiču na nokatnu jedinicu [9, 18].

Faktori rizika

Brojni faktori rizika doprinose razvoju onihomikoze (**Slika 1**). Predisponirajući faktori se

patients' quality of life. A systematic review assessing its impact found that it contributes to physical impairment, functional limitations, pain or discomfort, and social embarrassment, with psychological and psychosocial distress reported in up to 92% of patients [17].

Etiopathogenesis and risk factors

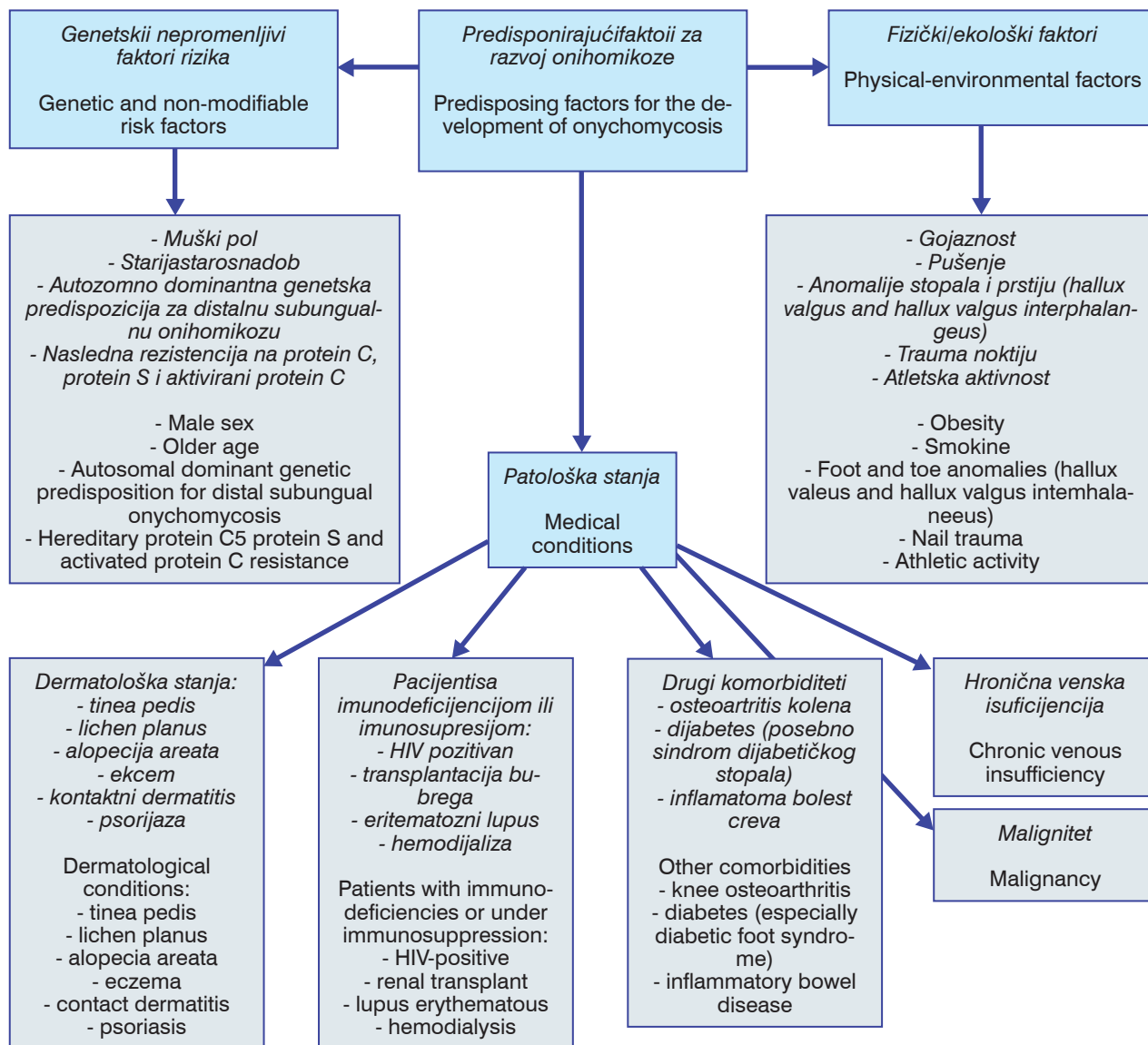
Pathogenic organisms

Current research indicates that approximately 4% of patients – whether or not they exhibit typical clinical signs – are confirmed to have toenail onychomycosis due to dermatophytes based on mycological testing [10]. The main causative agents of onychomycosis are dermatophytes, non-dermatophyte molds (NDM), and yeasts. Among dermatophytes, *Trichophyton rubrum* and *Trichophyton mentagrophytes* are responsible for 60–70% of infections. Other pathogens include NDMs such as *Scopulariopsis brevicaulis*, *Acremonium spp.*, *Aspergillus spp.*, *Fusarium spp.*, *Alternaria alternata*, and *Neoscytalidium* [9, 15, 16]. Yeast-related onychomycosis is most commonly caused by *Candida spp.* [15]. NDMs are typically considered opportunistic pathogens, as they lack the ability to degrade keratin. Infections caused by NDMs are usually acquired via trauma, contact with soil or plants, or develop as secondary infections [4]. Unlike dermatophyte infections, NDM onychomycoses are rarely associated with concurrent interdigital tinea pedis. Risk of infection by NDMs increases with exposure to high temperatures, humidity, hyperhidrosis, occlusive footwear, and nail deformities – manifesting clinically as asymmetric gait nail unit signs [9, 18].

Tinea pedis is often a precondition to dermatophyte onychomycosis. In 1966, Zaias et al. described a possible hereditary component, suggesting a genetic predisposition to fungal nail infection [17].

Risk factors

Numerous risk factors contribute to the development of onychomycosis (**Figure 1**). These can be broadly grouped into three categories: genetic and non-modifiable risk factors, physical and environmental factors, and medical conditions [19].



Slika 1. Faktori rizika za razvoj onihomikoze

Figure 1. Risk factors contributing to the development of onychomycosis

moгу svrstati u tri glavne kategorije: genetski i nepromenljivi faktori rizika, fizički i ekološki faktori, kao i razna patološka stanja [19].

Među faktorima rizika, vaskularna oboljenja kao što su hronična venska insuficijencija i periferna vaskularna bolest (PVB) smatraju se nezavisnim prediktorima onihomikoze (OM) [2, 13, 20]. Veruje se da progresivne mikroangiopatske promene u kapilarima noktа doprinose nastanku OM [20]. Rezultati novijih studija takođe potvrđuju povezanost između onihomikoze i razvoja ulkusa kože kod

Among these, vascular diseases, including chronic vascular insufficiency (CVI) and peripheral vascular disease (PVD), are considered independent and significant predictors of onychomycosis (OM) [2, 13, 20]. Progressive microangiopathic changes in nail capillaries due to vascular compromise are believed to promote fungal colonization and infection [20]. Recent studies have also demonstrated a strong association between onychomycosis and the development of skin ulcers in patients with CVI, identifying fungal nail infections as an

pacijenata sa HVI, ukazujući na njen značaj nezavisno od već dobro uspostavljenih faktora rizika poput vaskularnih bolesti, neuropatije i postojanja kožnih bolesti [21, 22]. Ipak, postoji mali broj radova u literaturi koji proučavaju učestalost onihopatije i onihomikoze kod ovih pacijenata. Saez de Ocariz i saradnici ispitujući onihomikozu i negljivične onihopatije pacijenata sa venskim ulkusima nogu, potvrdili su da je onihomikoza češće dokazana [3].

Etiopatogeneza onihomikoze kod pacijenata sa HVI

Etiopatogeneza kožnih i promena na noktima je kompleksna kod pacijenata sa HVI. Venska hipertenzija uzrokuje smanjenje protoka krvi kroz kapilare i smanjenje njihovog broja, što rezultira patološkim promenama u njihovim zidovima [1]. Hemodinamički poremećaji mogu nastati kao posledica valvularne insuficijencije ili venske opstrukcije [2]. Hipoperfuzija donjih ekstremiteta uzrokuje suboptimalnu oksigenaciju i oslabljenu razmenu hranljivih materija u stopalima [14]. Nedostatak hranljivih materija i ishemija verovatno su glavni uzroci povećane smrti ćelija i smanjene regeneracije tkiva [1]. Oslabljen dotok krvi i lokalna hipoperfuzija dovode do makroangiopatije, mikroangiopatije, neuropatije i ulceracija [10, 23]. Venska staza, edem i promene na koži koje prate CVI i periferne vaskularne bolesti takođe mogu narušiti prirodnu zaštitnu barijeru kože i noktiju, omogućavajući lakšu penetraciju gljivica. Smanjen protok krvi dodatno kompromituje lokalni imunski odgovor u pogođenim područjima, olakšavajući kolonizaciju i opstajanje gljivica u nokatnoj jedinici [24]. Gljivični enzimi sa proteolitičkom, keratinolitičkom i lipolitičkom aktivnošću pomažu u razgradnji keratina u nokatnoj ploči i pospešuju invaziju gljivica u nokat [8]. Ovi faktori povećavaju verovatnoću gljivične infekcije i smanjuju uspeh antimikotične terapije [23].

Saez de Ocariz i saradnici su izvestili da je prevalencija onihomikoze nožnih noktiju kod pacijenata sa CVI iznosila 36,11%, što je više u odnosu na opštu populaciju [3]. Dokazana je značajna korelacija između venskih i perifernih vaskularnih bolesti i onihomikoze, što je u skladu sa prethodnim istraživanjima. U studiji preseka iz 2005. godine koja je uključivala

important contributing factor – independent of other well-established risks such as vascular disease, neuropathy, and existing skin disease [21, 22]. However, the literature remains limited regarding the frequency and distribution of both onychopathy and onychomycosis in this population. In a study by Saez de Ocariz et al., which investigated fungal and non-fungal nail changes in patients with venous leg ulcers, onychomycosis was confirmed in over a half of the evaluated cases [3].

Etiopathogenesis of onychomycosis in patients with CVI

The development of skin and toenail abnormalities in CVD is complex. Venous hypertension reduces blood flow through the capillaries and decreases capillary density, ultimately causing pathological changes in vessel walls [1]. These hemodynamic disruptions may arise from valvular insufficiency or venous obstruction [2]. Impaired perfusion of the lower limbs leads to suboptimal oxygenation and diminished nutrient exchange, particularly in the feet [16]. Nutrient deficiency and ischemia likely contribute to increased cellular apoptosis and impaired tissue regeneration [1]. This compromised blood supply and regional hypoperfusion can result in macroangiopathy, microangiopathy, neuropathy, and ulceration [10, 20]. In addition to circulatory impairment, venous stasis, edema, and skin barrier damage – all characteristic of CVI and PVD – disrupt the skin and nails' natural defenses, facilitating fungal invasion. The reduction in local blood supply also compromises immune surveillance, enabling fungi to persist within the nail bed [29]. Fungi contribute to this process through the secretion of proteolytic, keratinolytic, and lipolytic enzymes, which degrade the nail plate's keratin structure and promote deep invasion [30, 31]. These pathophysiological mechanisms not only increase susceptibility to fungal infections but also reduce the effectiveness of antifungal treatments [20].

In a study by Saez de Ocariz et al., toenail onychomycosis was diagnosed in 36.11% of patients with CVI, a prevalence notably higher than that observed in the general population [3]. A significant association between venous and peripheral vascular disease and onychomycosis has been consistently report-

42 ambulanta pacijenta sa onihomikozom i 39 kontrolnih ispitanika, venska insuficijencija je bila češća u grupi pacijenata sa onihomikozom nego u kontrolnoj grupi [13]. Takođe prospektivna epidemiološka studija iz 2000. godine sprovedena na 254 pacijenta u vaskularnoj ambulanti pokazala je značajnu povezanost između onihomikoze i periferne vaskularne bolesti [25].

Klinička slika

Hronična ponavljana mikrotrauma nokta dovodi do subungualne hiperkeratoze, oniholize, paronihije, Beauovih linija, onihomadeze i onihomikoze [23, 26]. Progresivne mikroangiopatske promene u kapilarama nokta izazvane HVI, koje dovode do zadebljanja i zamućenja noktiju, mogu doprineti razvoju onihomikoze [27]. Uobičajeni klinički znaci OM uključuju promenu boje nokta (žuta, bela, gde je gljivica gusta, braon ili mešavina svih boja), odvajanje nokta od nokatne ploče (oniholiza), lomljivost, zadebljanje nokta i subungvalno nakupljanje keratinskog materijala [9, 10, 18]. Infekcije izazvane NDP i kvasnicama izgledaju kao žutobela promena boje praćena upalom i gnojnim iscetkom, dok bakterijske pseudomonas infekcije mogu izazvati zelenu prebojenost nokta [28]. Inficirani nokti, posebno u slučaju sekundarnih bakterijskih infekcija, mogu izazvati lokalni bol i paresteziju, što može imati značajne psihosocijalne posledice [7].

Klinička klasifikacija

Na osnovu obrasca zahvaćenosti nokatne jedinice, onihomikoza se može klasifikovati u pet podtipova: distalna lateralna subungvalna onihomikoza (DLSO), superficijalna bela/crna onihomikoza (SO), proksimalna subungvalna onihomikoza (PSO), endoniks onihomikoza (EO) i totalna distrofija noktiju (TD) [16, 19]. Pored toga, pacijenti mogu imati mešovite oblike onihomikoze, najčešće sa DLSO i SO, kao i sekundarnu onihomikozu [4, 16, 29]. Najčešći oblik onihomikoze je distalna subungvalna forma, koja se češće javlja na noktima nožnih prstiju. Ukoliko se ne leče, svi ovi oblici mogu dovesti do totalne distrofije nokta [30]. Primeri različitih tipova onihomikoza su prikazani na **Slici 1a–c**.

ed in previous studies. In a 2005 cross-sectional study of 42 outpatients with onychomycosis and 39 control subjects, venous insufficiency was significantly more frequent in the affected group [13]. Similarly, a 2000 prospective epidemiological study of 254 patients assessed in a vascular clinic confirmed a strong correlation between onychomycosis and PVD [32].

Clinical presentation

Chronic and repetitive microtrauma to the nail can result in a variety of nail changes, including subungual hyperkeratosis, onycholysis, paronychia, Beau's lines, onychomadesis, and ultimately onychomycosis [23, 26]. Progressive microangiopathic alterations in nail capillaries due to CVI contribute to nail thickening, increased opacity, and may facilitate fungal infection [27]. The typical clinical features of OM include nail discoloration (ranging from yellow, white, and brown to mixed shades, depending on the fungal load), onycholysis (separation of the nail plate from the nail bed), brittleness, thickening of the nail plate, and subungual scaling and debris accumulation [9, 10, 18]. Infections caused by NDM and yeast often manifest as yellow-white nail discoloration, accompanied by inflammatory changes and sometimes purulent discharge. In contrast, bacterial infections – most notably by *Pseudomonas aeruginosa* – can give the nail a greenish hue [28]. In cases complicated by secondary bacterial infections, patients may experience pain, paresthesia, and notable psychosocial impacts [7].

Clinical classification

Onychomycosis is clinically classified into five main subtypes based on the pattern of nail unit involvement: distal lateral subungual onychomycosis (DLSO) – the most common type, especially on toenails, superficial white/black onychomycosis (SO), proximal subungual onychomycosis (PSO), endonyx onychomycosis (EO), and total dystrophic onychomycosis (TDO) [16, 19]. In addition, patients may present with mixed patterns of onychomycosis (MPO), most frequently combining DLSO and SO, or with secondary onychomycosis [4, 16, 29]. If left untreated, all subtypes may progress to total nail dystrophy



Slika 1. Klinička prezentacija onihomikoze (a. Distalna lateralna subungualna onihomikoza, b. Totalna distrofijska onihomikoza, c. Distalna onihomikoza)

Figure 1. Clinical presentation of onychomycosis (a. Distal lateral subungual onychomycosis, b. Total dystrophic onychomycosis, c. Distal onychomycosis)

Dijagnoza i diferencijalna dijagnoza

Dijagnoza onihomikoze se može postaviti na osnovu medicinske i socijalne anamneze pacijenta, faktora rizika, kliničkog pregleda i dermoskopije, ali ovi podaci sami nisu dovoljni za konačnu dijagnozu [7, 16]. Dijagnostički postupak uključuje mikološke testove uzoraka koristeći konvencionalne metode poput mikroskopije i kulture, kao i molekularne tehnike [30]. Istraživanja pokazuju da prevalencija onihomikoze može varirati u zavisnosti od korišćene dijagnostičke metode [10]. Antifungalni lekovi

[30]. Examples of various clinical forms of onychomycosis are shown in **Figure 1a-c**.

Diagnosis and differential diagnosis

Diagnosing onychomycosis requires a comprehensive approach that includes patient medical history, risk factor assessment, clinical examination, and dermoscopy. However, these methods alone are insufficient for a definitive diagnosis [7, 16]. Confirmation relies on mycological testing using convention-

se mogu zadržati u subungvalnim ostacima i nokatnoj ploči, potencijalno prelazeći u kultivacioni medijum, što može inhibirati rast gljivica i uticati na druge dijagnostičke testove [4, 7].

Mikroskopija kalijum-hidroksidom

Gljivice se mogu uočiti mikroskopskim ispitivanjem strugotina nokta tretiranih 5–40% kalijum-hidroksidom (KOH) [7, 31]. KOH rastvara keratin i ostatke, čineći gljivične strukture poput hifa vidljivijim [7, 8]. Iako ova metoda potvrđuje dijagnozu, ne pravi razliku između gljivica niti identifikuje specifični patogen [16]. Ovaj test niskog troška daje odmah rezultate, sa senzitivnošću 48–60% i specifičnošću između 38% i 78% [8, 31].

Kultura na gljivice

Mikološka kultura je jedina metoda koja identifikuje mikroorganizam i potvrđuje njegovu vitalnost. Sabouraudov dektrozni agar, sa cikloheksimidima ili bez njih, koristi se u laboratoriji za rast dermatofita i NDP [7]. Glavni nedostaci su duže vreme kultivacije i sporiji proces identifikacije patogena [30]. Kulture gljivica imaju do 40% lažno negativnih rezultata, posebno kada su delimično primenjeni antifungalni tretmani [9, 31]. Iako su kulture vrlo specifične (83–100%), njihova osetljivost je niska (60–65%), skupe su, a rezultati se čekaju 2–4 nedelje [8, 31, 32].

Histopatologija

Iako se mikroskopija i mikološka kultura smatraju zlatnim standardom za dijagnostiku onihomikoze, njihov visok procenat lažno negativnih rezultata doveo je do primene preciznijih metoda poput histologije i PCR [9]. Histopatologija može otkriti kvasnice, spore, hife i pseudohife, ali ne može identifikovati organizam niti odrediti njegovu vitalnost. PAS bojenje (Periodic acid schiff) ili bojenje Grokotovim metenamin-srebrom zlatni su standardi za detekciju gljivičnih elemenata, dok PCR i kultura gljivica identifikuju gljivicu [7, 16]. Osetljivost se kreće 82–88%, ali kombinovanjem PAS boje i kulture osetljivost raste na 96% [8].

PCR test

PCR testiranje omogućava brzo i specifično amplifikovanje fragmenta gljivične DNK

al methods, such as microscopy and fungal culture, in addition to more advanced molecular techniques [30]. The diagnostic yield can vary significantly depending on the method employed [10]. Importantly, prior antifungal therapy may cause drug residue to accumulate in the subungual debris and nail plate, potentially interfering with culture growth and other diagnostic tests [4, 7].

Potassium hydroxide (KOH) microscopy

KOH microscopy is a widely used initial diagnostic tool. Nail scrapings are treated with 5–40% potassium hydroxide (KOH), which dissolves keratin and debris, enhancing the visibility of fungal structures such as hyphae under the microscope [7, 8, 31]. While this method confirms the diagnosis, it cannot distinguish between types of fungi or identify the specific pathogen [16]. This low-cost screening test provides immediate results, with reported sensitivity ranging from 48–60%, and specificity between 38–78% [8, 31].

Fungal Culture

Fungal culture is the only method that can identify the specific organism and confirm its viability. Sabouraud dextrose agar is used for dermatophytes, while media without cycloheximide are preferred to isolating non-dermatophyte molds (NDM) [7]. The drawbacks include long cultivation period (results may take 2 to 4 weeks) [30]. Fungal cultures have up to 40% false-negative rates, especially when antifungal treatments have been partially used [9, 31]. While cultures are highly specific (83–100%), their sensitivity is low (60–65%), and they cost more than KOH microscopy [8, 31, 32].

Histopathology

Although fungal culture and microscopy are considered the diagnostic gold standard, their false-negative rates justify the use of histology and PCR [9]. Histology enables the detection of yeast, spores, hyphae, and pseudohyphae, although it cannot assess organism viability or determine the exact species. While the Periodic acid-Schiff (PAS) or Grocott methenamine-silver (GMS) staining are the gold standards for detecting fungal elements, PCR and

[8]. Molekularna dijagnostika nudi veću osetljivost i brže rezultate u poređenju sa tradicionalnim kulturama gljivica [32]. Međutim, rezultati zasnovani na PCR-u se mogu razlikovati u zavisnosti od tipa testa, kao što su konvencionalni PCR ili real-time PCR (qPCR) [10]. Zbog visokih troškova i ograničene dostupnosti, ove tehnike se ne koriste široko u opštoj praksi [8, 30].

Dermoskopija nokta

Dermoskopija noktiju je brza, neinvazivna i efikasna metoda za razlikovanje onihomikoze od drugih bolesti noktiju [8, 33]. Najčešći dermoskopski obrazac je nazubljeni proksimalni rub sa šiljcima u području oniholize [6, 8]. Takođe, može pomoći u identifikaciji optimalnog mesta za uzimanje uzorka tokom mikološkog ispitivanja [8].

Diferencijalna dijagnoza

Onihomikoza može da imitira druge benigne promene, uključujući promene na noktima u sledećim stanjima: *Onychodystrophia traumatica*, *Psoriasis*, *Lichen planus*, *Paronychia chronica*, *Pityriasis rubra pilaris*, *Pachyonychia congenita*, *Trachyonychia*, *Onychogryphosis*, *Onycholysis idiopathica*, *Onychodystrophia medialis*, *Melanonychia striata*, *Exostosis subungualis*, *Verruca*, *Onychomatricoma*, *Scleroderma*, *Lupus erythematosus*, *Pruritus*, *Tungiasis*, *Infectioides bacteriales*. Diferencijalna dijagnoza takođe uključuje maligna stanja kao što su karcinom skvamoznih ćelija, kao i subungualni i amelanotični melanom [7, 8]. U ovim slučajevima, empirijska antifungalna terapija povećava rizik od nepotrebnih neželjenih efekata, ne dolazi do poboljšanja, može ga čak pogoršati i povećati morbiditet i mortalitet [7].

Terapija onihomikoze

Onihomikoze je teško lečiti zbog ograničene dostupnosti antifungalnih lekova, potrebe za dugotrajnom terapijom i lošeg poverenja pacijenata [34]. Među svim dermatomikozama, ona je najteža za lečenje, uglavnom zbog anatomije nokta i teškoće prodora lekova u zaraženo područje [23]. Obavezna je preporuka potvrde dijagnoze pre početka lečenja, posebno sistemskom terapijom [35–37]. Empirijski oralni antifungalni lekovi

can identify the fungus [7, 16]. Sensitivity ranges from 82–88% when used alone, but combining PAS stain and fungal culture can raise sensitivity to 96% [8].

PCR

PCR enables the rapid and specific amplification of fungal DNA fragments [8]. Compared to traditional fungal cultures, molecular diagnostics provide higher sensitivity and faster turnaround times [32]. However, PCR results may vary depending on the specific method used, such as conventional PCR or real-time PCR (qPCR) [10]. Despite their advantages, high costs and limited accessibility restrict their use in routine clinical practice [8, 30].

Nail Dermoscopy

Nail dermoscopy is a noninvasive, quick, and effective technique for differentiating onychomycosis from other nail disorders [8, 33]. The most characteristic dermoscopic finding is a jagged proximal edge with spikes extending in the onycholytic area [6, 8]. Dermoscopy also facilitates precise sample collection by identifying optimal areas for mycological sampling [8].

Differential diagnosis

Onychomycosis can mimic other benign conditions, including nail changes in traumatic onychodystrophy, psoriasis, lichen planus, chronic paronychia, pityriasis rubra pilaris, pachyonychia congenita, trachyonychia, onychogryphosis, idiopathic onycholysis, median nail dystrophy, melanonychia striata, subungual exostosis, verruca, onychomatricoma, scleroderma, lupus erythematosus, scabies, tungiasis, and bacterial infections. Differential diagnosis also includes malignant conditions such as squamous cell carcinoma, and subungual and amelanotic melanoma [7, 8]. Empirical antifungal treatment in such cases may not only be ineffective but also delay proper diagnosis and management, potentially increasing morbidity and mortality [7].

Treatment approach for onychomycosis

Onychomycosis remains one of the most difficult dermatomycoses to treat, primarily

su pokazali otpornost kod nekih pacijenata [16, 38]. Najčešći ishodi u studijama o onihomikozi su kliničko i mikološko izlječenje. Kliničko izlječenje odnosi se na normalan nokat bez znakova gljivične infekcije, što je najvažnije za pacijente. Izlječenje podrazumeva negativnu kulturu i negativnu direktnu mikroskopiju. Potpuno izlječenje obuhvata oba, a lekari ga često uopotrebljavaju za procenu uspešnosti lečenja [16].

Topikalna antimikotična terapija

Topikalna antifungalna terapija uključuje lakove za nokte, rastvore i druge topikalne preparate [39]. Nokti su generalno prodorniji za antifungalne lekove u vodenim formulacijama, a lak za nokte ne ometa značajno prodor, što omogućava pacijentima da sakriju onihomikozu tokom lečenja. Topikalni tretmani nude nisku sistemsku izloženost i minimalne nuspojave, ali obično imaju nisku efikasnost, bilo da se koriste samostalno ili kao adjuvantna terapija [8, 16]. Koncentracija leka u tkivu zavisi u velikoj meri od propustljivosti topičkog sredstva, zbog čega je poboljšanje transungualnog isporučivanja ključno za razvoj novih tretmana [17]. Pridržavanje terapije može biti problem zbog dugog trajanja lečenja (48 nedelja) i čestih aplikacija [40]. Nuspojave su minimalne i obično se svode na lokalne reakcije poput crvenila ili peckanja [31].

Broj FDA odobrenih topikalnih antifungalnih lekova je bio ograničen zbog poteškoća u penetraciji kroz nokatnu ploču. Do 2014. godine, ciklopiroks 8% lak je bio jedini odobren topički tretman za OM [16]. Godine 2014. FDA je odobrila efinaconazol 10% i tavaborol 5% rastvore, koji su pokazali bolji prodor u nokat nego ciklopiroks. Metaanaliza je pokazala da je efinaconazol imao najveću verovatnoću izlječenja, u poređenju sa oralnim itraconazolom [16].

Sistemska antimikotična terapija

Sistemska terapija se često koristi za lečenje onihomikoze zbog njihove dostupnosti, visoke efikasnosti i relativno niske cene [9, 19]. Međutim, koncentracija leka koja dospeva do inficiranog mesta je ograničena zbog loše cirkulacije krvi do nokatnog ležišta [41]. Oralne terapije se smatraju zlatnim standardom za umerenu do tešku onihomikozu, jer pružaju

due to limited drug penetration through the nail plate, slow nail growth, which prolongs treatment duration, and poor patient adherence to long-term therapy protocols [23, 34]. Given these challenges, confirming the diagnosis before initiating therapy, especially systemic treatment, is strongly recommended [35–37]. Empirical use of oral antifungals can lead to resistance with some patients [16, 38]. The primary goals of treatment are clinical and mycological cures. Clinical cure refers to restoration of normal-appearing nail with no visible signs of fungal infection, which is often the most relevant outcome for patients. Mycological cure implies negative findings on both culture and direct microscopy. Complete cure is a combination of both clinical and mycological cure, typically used as the endpoint in clinical trials and to assess overall treatment success [16].

Topical antifungal treatment options

Topical antifungal therapies include nail lacquers, solutions, and other external agents designed to act locally on the infected nail unit [39]. Water-based formulations are generally more effective due to better nail permeability, and the use of cosmetic nail polish does not significantly impede antifungal penetration, allowing for aesthetic concealment during therapy. Topical treatments are associated with low systemic absorption and minimal side effects, but their efficacy is limited whether used alone or as an adjuvant [8, 16]. Drug concentration in the tissue depends heavily on the permeability of the topical agent, making improved transungual delivery a key focus for developing new treatments [17]. One major drawback is the lengthy treatment duration – typically 48 weeks – and the need for frequent applications, which can negatively affect patient adherence [40]. Side effects are usually mild and localized, such as erythema or burning sensations [31].

Until 2014, ciclopirox 8% nail lacquer was the only FDA-approved topical treatment for OM [16]. Subsequently, efinaconazole 10% solution and tavaborole 5% solution were approved, offering superior nail penetration and improved efficacy. A recent meta-analysis found efinaconazole to have the highest cure probability among topical agents, with efficacy comparable to oral itraconazole [16].

najefikasniji tretman. Tri osnovna oralna leka su terbinafin, itrakonazol i flukonazol. Često je potrebno produženo korišćenje zbog njihove ograničene bioraspoloživosti i izazova u održavanju adekvatnih koncentracija leka u nokatnom krevetu [31].

Terbinafin

Terbinafin se dozira u količini od 250 mg dnevno za šest nedelja u slučaju infekcija na rukama i 12 nedelja za infekcije na stopalima [16, 19]. Stope potpunog izlečenja su 59% i 38%, a stope mikološkog izlečenja su 79% i 70% [9]. Potencijalne nuspojave su blage i uključuju glavobolje, osipe, gastrointestinalne simptome, a retko i hepatotoksičnost [19, 42]. Terbinafin se može primeniti kao pulsna terapija kao off-label opcija za lečenje onihomikoze, što može biti isplativo i poboljšati pacijentovu usklađenost sa terapijom [7, 43]. Kontinuirana terapija terbinafinom ima sličnu efikasnost kao i pulsna terapija, iako su neka istraživanja pokazala superiornost kontinuirane terapije u odnosu na pulsnu za onihomikozu noktiju na stopalima [8].

Pregledni članak iz 2020. godine koji je analizirao 30 studija upoređujući kontinuirane i pulsne režime terbinafina, nije pronašao značajne razlike u stopi mikološkog izlečenja [44]. Takođe, Cochrane metaanaliza iz 2017. godine kojom je obuhvaćeno 48 randomizovanih kontrolisanih ispitivanja sa 10.200 učesnika zaključila je da terbinafin dovodi do viših stopa kliničkog i mikološkog izlečenja u poređenju sa drugim terapijskim opcijama za onihomikozu stopala [8].

Itrakonazol

Itrakonazol se obično dozira u pulsnom režimu (jedna nedelja sa 400 mg dnevno, nakon čega sledi tri nedelje pauze), osam nedelja za onihomikozu noktiju na rukama i 12 nedelja za onihomikozu na stopalima [25]. Itrakonazol se može primeniti i u kontinuiranom režimu od 200 mg dnevno tokom 12 nedelja. Studije koje su ocenjivale oralnu primenu itrakonazola pokazale su stopu izlečenja 46–69% [16]. Potencijalne nuspojave uključuju glavobolju, infekcije gornjih respiratornih puteva, gastrointestinalne simptome, hipertrigliceridemiju, povišene transaminaze, a retko i perifernu neuropatiju i hepatitis [9, 19].

Oral antifungal treatment options

Systemic antifungal agents remain the gold standard for treating moderate to severe onychomycosis due to their availability, superior efficacy, and affordability [9, 19]. However, the drug concentration that reaches the infected site is limited by poor vascularization of the nail bed [41]. The three most commonly used oral antifungals are terbinafine, itraconazole, and fluconazole. Because bioavailability is limited, long treatment courses are often required to achieve adequate drug concentrations in the nail bed [31].

Terbinafine

Terbinafine is typically administered at 250 mg daily for 6 weeks (fingernails) and 12 weeks (toenails) [16, 19]. The complete cure rates are 59% for fingernails and 38% for toenails, and the mycologic cure rates are 79% for fingernails and 70% for toenails [9]. Potential side effects are generally mild and include headache, rash, gastrointestinal disturbances, and rare hepatotoxicity [19, 42]. Pulse therapy with terbinafine, though off-label, is sometimes used to reduce cost and improve compliance [7, 43]. While some studies suggest continuous regimens may be more effective, particularly for toenail infections, overall outcomes are similar [8].

A 2020 systematic review of 30 studies found no significant differences in mycological cure rates between continuous and pulsed terbinafine regimens [44]. Likewise, a 2017 Cochrane meta-analysis involving 48 randomized controlled trials and 10,200 participants concluded that terbinafine yielded higher clinical and mycological cure rates than other oral antifungals for toenail onychomycosis [8].

Itraconazole

Itraconazole is administered either as pulse therapy (400 mg/day for 1 week, followed by 3 weeks off, repeated for 8 weeks for fingernails and 12 weeks for toenails), or as continuous therapy (200 mg/day for 12 weeks) [25]. Clinical studies have reported mycological cure rates between 46% and 69% [16]. Itraconazole is generally well tolerated, although potential side effects include headache, upper respiratory tract infections, gas-

Metaanaliza iz 2019. godine koja je obuhvatila 26 randomizovanih kontrolisanih ispitivanja ($n = 8.136$) pokazala je da kontinuirana primena oralnog terbinafina ili itraconazola imaju značajno višu stopu mikološkog izlečenja u poređenju sa topikalnim preparatima [45]. U randomizovanoj studiji sa jednom slepom probom koja je obuhvatila 101 pacijenta starijeg od 60 godina, kontinuirani terbinafin kao i pulsni itraconazol postigli su više od 60% izlečenja i kliničke efikasnosti nakon 18 meseci, bez značajnih razlika između grupa [7]. Ostale metaanalize ukazuju da terbinafin (250 mg dnevno) i pulsni itraconazol (400 mg) nadmašuju oralni flukonazol i druge lokalne terapije, pri čemu je oralni terbinafin najefikasniji [16, 45].

Flukonazol

Flukonazol je odobren za lečenje onihomikoze u Evropi i Kini, dok se u SAD koristi off-label [9, 19]. Doza je 150 mg nedeljno tokom 6–9 meseci, odnosno 12–18 meseci. Zbog kratkotrajne koncentracije leka u noktima, neophodna je duža primena terapije [7].

Terapija laserom

Većina lasera koristi princip selektivne fototermolize [8]. Od 2012. godine FDA je odobrila četiri sistema lasera (1064 nm Nd:YAG laseri, kako kratkopulsni tako i Q-switched laseri, ugljen-dioksidni laseri i diodni laseri 870, 930 nm) i koriste se zbog kratkog vremena tretmana i manji broj tretmana koji je potreban [9, 16]. Međutim, kliničke studije nisu pokazale značajno bolje rezultate od trenutnih lokalnih i sistemskih antifungalnih terapija u potpunom izlečenju onihomikoze [16]. Laser terapije su sigurne, ali skupe, i mogu se razmotriti kod pacijenata kod kojih su sistemski antifungalni lekovi kontraindikovani ili kao deo kombinovane terapije [46].

Proceduralni tretmani

Procedure poput debridmana, skraćivanja inficiranih noktiju, avulzije ili matriksektomije mogu se razmotriti kod pacijenata sa recidivom onihomikoze [16]. Keratolitički agensi kao što su urea, salicilna kiselina, mlečna kiselina i papain mogu poboljšati unos topikalnih antifungalnih agensa u nokte [8]. Studije koje su

trointestinal disturbances, hypertriglyceridemia, elevated transaminases, and rarely, peripheral neuropathy and hepatitis [9, 19].

A 2019 meta-analysis of 26 randomized controlled trials ($n = 8,136$) concluded that oral terbinafine and oral itraconazole result in significantly higher mycological cure rates than topical therapies [45]. Additionally, a single-blind, randomized trial of 101 elderly patients (≥ 60 years) showed that both continuous terbinafine and pulse itraconazole achieved $>60\%$ mycological cure and clinical efficacy at 18 months, with no statistically significant differences between groups [7]. Other meta-analyses confirm that terbinafine (250 mg daily) and pulsed itraconazole (400 mg/day) outperform oral fluconazole and topical therapies, with terbinafine considered the most effective oral agent overall [16, 45].

Fluconazole

Fluconazole is approved for treating onychomycosis in Europe and China, while it is used off-label in the US [9, 19]. The typical regimen is 150 mg weekly for 6–9 months (fingernails) and 12–18 months (toenails). Due to its short residual concentration in the nail, prolonged treatment durations are required to achieve therapeutic efficacy [7].

Laser therapy

Most lasers use the principle of selective photothermolysis [8]. Since 2012, the four FDA-approved laser systems (1064 nm Nd:YAG lasers (short-pulsed and Q-switched), carbon dioxide lasers, and diode lasers (870 and 930 nm) have been utilized due to short treatment sessions and fewer total treatments [9, 16]. However, clinical studies have not demonstrated superior efficacy compared to conventional topical or oral antifungal therapies for complete resolution of onychomycosis [16]. Laser therapy is considered safe but expensive, and may be suitable for patients cannot tolerate systemic antifungal agents or as part of combination therapy [46].

Procedural treatments

Procedural interventions such as nail debridement, trimming of infected nail plates, partial or total avulsion, and matrixectomy can

upoređivale terbinafin kao monoterapiju vs. prethodni debridman, pokazale su bolje rezultate sa debridmanom noktiju na stopalima [7]. Studija koja je istraživala efekte debridmana u poređenju sa debridmanom uz topičku antifungalnu terapiju, pokazala je da kombinovana terapija dovodi do značajnog mikološkog izlječenja od 76,7%, dok nije bilo mikološkog izlječenja samo sa debridmanom [16].

Specifičnosti terapije kod starijih odraslih

Hronična venska insuficijencija koja je povezana sa onihomikozom, često se javlja u starijim populacijama, a njena učestalost raste sa godinama [18]. Postoji mali broj navoda u literaturi koji procenjuju efikasnost i sigurnost antifungalnih lekova kod starijih pacijenata [8, 34]. Sistematska terapija ima ograničenu efikasnost kod ovih pacijenata, a komorbiditeti zahtevaju razmatranje alternativnih tretmana poput keratolitika. Itrakonazol je pokazao stopu izlječenja od svega 25%, u poređenju sa uobičajenih 60–70%, što je verovatno rezultat deformacija noktiju koje otežavaju penetraciju leka. Stoga, pre nego što se započne antimikotična terapija onihomikoze kod pacijenata sa HVI, posebno kod starijih osoba, važno je priznati mogućnost suboptimalnih rezultata [2]. Ovi pacijenti imaju specifične faktore rizika koji ih predodređuju za loš odgovor na antifungalnu terapiju, uključujući spor rast noktiju, rekurentnu onihodistrofiju i povećanu prevalenciju PVB [7]. Zbog toga, topikalni i sistemski antifungalni lekovi treba da se koriste u opštoj populaciji, ali terapija treba da traje duže. Lokalna terapija se preporučuje kao prva linija lečenja za starije pacijente sa ograničenim zahvatanjem noktiju. Za pacijente kojima je potrebna sistemska terapija, terbinafin je lek izbora zbog nižeg potencijala za interakcije sa lekovima, dok se itrakonazol može primeniti za kandidijalnu onihomikozu, uzimajući u obzir moguće interakcije. U određenim situacijama, hemijska avulzija nokta ili mehanički debridman mogu biti prikladniji [34].

Zaključak

Onihomikoza je gljivična infekcija nokta koja uzrokuje promenu boje i zadebljanje zahvaćenih noktiju. Studije pokazuju povezanost između površinske venske insuficijencije i onihomikoze. Ona je češća kod pacijenata sa HVI ili PVB zbog nekoliko faktora koji doprinose

be effective adjuncts, especially in cases of onychomycosis recurrence [16]. The use of keratolytic agents, including urea, salicylic acid, lactic acid, and papain, has been shown to enhance topical antifungal penetration into the nails [8]. Studies comparing terbinafine monotherapy to terbinafine proceeded by debridement have shown improved therapeutic outcomes with the addition of debridement [7]. Furthermore, one clinical trial demonstrated that combined debridement and topical antifungal therapy achieved 76.7% mycological cure, whereas debridement alone yielded no significant mycological cure [16].

Therapeutic considerations in elderly patients

Chronic venous insufficiency (CV), a condition increasingly prevalent in aging populations, is frequently associated with onychomycosis [18]. However, limited data are available regarding the efficacy and safety of antifungal therapy in the elderly [8, 34]. Systemic antifungal treatment in this population is often complicated by comorbidities, necessitating consideration of alternative treatments such as keratolytics. Itraconazole showed only 25% cure rate in elderly patients, compared to the typical 60–70% observed in younger populations, likely due to nail deformities impeding drug penetration. Therefore, it is essential to acknowledge the potential for suboptimal outcomes before initiating antifungal treatment for onychomycosis in patients with CVI, particularly older individuals [2]. These patients have specific risk factors predisposing them to poor response to antifungal therapy, including slow nail growth, recurrent nail dystrophy, and increased prevalence of PVD [7]. Therefore, topical and systemic antifungals should be used in the general population, but therapy should be extended. Topical therapy is preferred as the first line treatment in older adults with limited nail involvement. When systemic therapy is required, terbinafine is favored over azoles due to its lower risk of drug-drug interactions. Itraconazole may still be considered for candida-associated infections, though careful monitoring is essential. In selected cases, chemical nail avulsion or mechanical debridement may be more suitable [34].

nastanku bolesti. Dermatofiti su najčešći gljivični uzročnici onihomikoze. Mikroskopija i mikološke kulture se smatraju zlatnim standardom u dijagnostici onihomikoze, iako visoki nivoi lažno negativnih rezultata zahtevaju upotrebu preciznijih metoda. Uprkos hroničnom i benignom kliničkom toku, onihomikoze karakterišu visoke stope reinfekcija i recidiva čak i nakon dugotrajnog lečenja. Značajan broj starijih pacijenata koristi višestruke terapije lekovima zbog različitih komorbiditeta. Zbog toga je topička terapija obično preferisana opcija lečenja za ovu specifičnu grupu. Kada je sistemsko lečenje neophodno, oralni terbinafin treba da bude izbor prvog reda, jer nosi manji rizik od interakcije sa drugim lekovima u poređenju sa azolima.

Dostupne preporuke za lečenje onihomikoze kod pacijenata sa HVI nude vrlo ograničen uvid u ovakve specijalne slučajeve. Nedostaju dobro kontrolisane studije koje bi pomogle u donošenju odluka o lečenju u ovakvim grupama, pa je potrebno dalje istraživanje kako bi se procenila povezanost između onihomikoze noktiju i HVI. Buduća istraživanja trebalo bi da se fokusiraju na uspostavljanje robustno dizajniranih kliničkih ispitivanja u različitim populacijama pacijenata, kako bi se dalje istražile nove terapije i utvrdile optimalne i standardizovane smernice za kombinovanu terapiju.

Conclusion

Onychomycosis is a common fungal nail infection characterized by discoloration and thickening of the affected nail plate. Studies indicate a correlation between superficial venous insufficiency and onychomycosis. It is more frequently observed in patients with CVI or PVD due to multiple contributing factors. Dermatophytes remain the predominant causative agents. While microscopy and fungal culture are still the gold standard for diagnosis, their limitations in sensitivity have encouraged the adoption of more advanced diagnostic modalities. Despite its benign appearance, onychomycosis is associated with high reinfection and recurrence rates even after prolonged treatment. Due to frequent comorbidities and polypharmacy, topical therapy is generally the first-line option in this specific group. Oral terbinafine should be considered when systemic treatment is necessary, as it poses a lower risk of drug-drug interactions compared to azoles.

Current treatment recommendations specific to OM in CVI patients are limited. The lack of large, well-controlled clinical trials prevents definitive guidance for managing this subgroup. Future research should prioritize robust clinical studies in diverse populations, with the aim of identifying effective combination therapies and establishing evidence-based, standardized treatment protocols.

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ECZEMA HERPETICUM KAO KOMPLIKACIJA ERITRODERMIJSKOG PEMPHIGUS FOLIACEUS-a – PRIKAZ SLUČAJA

ECZEMA HERPETICUM AS A COMPLICATION OF ERYTHRODERMIC PEMPHIGUS FOLIACEUS – CASE REPORT

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Sažetak

Uvod. Eritrodermijski pemfigus foliaceus predstavlja autoimunske bulozne oboljenja uzrokovane autoantitela na proteine dezmozoma. Oštećenje epidermalne barijere i imunosupresija su faktori rizika za razvoj ekcema herpeticum.

Prikaz slučaja. Žena, 70 godina, sa eritrodermijom kože i brojnim erozijama, ranije lečena od ekcema, a 2019. godine učinjena je histerektomija usled maligne neoplazme uterusa. Histopatološki nalaz biopsije kože leđa: hronični spongiotični dermatitis. Direktnim imunofluorescentnim pregledom uočeni su intraepidermalni, intercelularni depoziti IgG i C3. U krvi su detektovana pemfigusna antitela, eozinofilija i povišena koncentracija IgE. MSCT pretrage i tumorski markeri su bili uredni. Usled neefikasnosti terapije metilprednizolonom, ordinirana je pulsna kortikosteroidna terapija, nakon čega se uočava pojava vezikula i žučkastokrkih krusti na koži leve polovine lica. Klinički je dijagnostikovano ekcema herpeticum i ordinirana parenteralna terapija aciklovir amp. (500 mg/8 h tokom 14 dana) i levofloksacin amp. (1 g tokom 10 dana) sa potpunom regresijom promena. **Zaključak.** Parenteralna i promptna terapija aciklovirom je osnova lečenja.

Ključne reči: pemfigus; autoimuna oboljenja; ekcem; Kapošijeva variceliformna erupcija; dijagnoza; faktori rizika; terapija

Abstract

Introduction. Erythrodermic pemphigus foliaceus is a rare autoimmune blistering disease characterized by autoantibodies targeting desmosomal proteins. Eczema herpeticum affects individuals with impaired skin barriers or immunosuppression, often complicating pre-existing skin conditions. **Case Report.** We present a case of a 70-year-old woman with erythroderma and skin erosions, previously treated for generalized eczema. Her medical history included hysterectomy for uterine neoplasia in 2019. Skin biopsy revealed chronic spongiotic dermatitis, and direct immunofluorescence demonstrated intracellular and intradermal IgG and C3 deposits. Serological analysis confirmed pemphigus antibodies, along with eosinophilia, and elevated IgE levels. Computed tomography and tumor markers excluded underlying malignancy. After inadequate response to methylprednisolone, the patient underwent pulse corticosteroid therapy. Subsequently, vesicles and crusts developed on her face, leading to a diagnosis of eczema herpeticum. She was treated with intravenous acyclovir (500 mg every 8 hours for 14 days) and oral levofloxacin (1 g daily for 10 days), resulting in complete resolution of the lesions. **Conclusion.** Prompt recognition and treatment of eczema herpeticum with intravenous acyclovir are essential for favorable outcomes.

Key words: Pemphigus; Autoimmune Diseases; Eczema; Kaposi Varicelliform Eruption; Diagnosis; Risk Factors; Drug Therapy

Uvod

Pemphigus foliaceus (PF) je autoimunske oboljenje koje se karakteriše pojavom bula i erozija na eritematoznoj osnovi od kojih su pojedine pokrivene krustama najpre na koži skalpa, lica,

Introduction

Pemphigus foliaceus (PF) is a rare autoimmune blistering disease characterized by the development of superficial blisters, erosions, scaling, and crusting on an erythema-

gornjih delova trupa, a kasnije tokom diseminacije i na ostalim delovima tela sa terminalnim razvojem ekfolijativne eritrodermije. Zahvaćenost sluznica je veoma retka, a promene su često praćene osećajem peckanja i bola. Pemphigus erythematosus (PE) ili Sener-Usher syndrom predstavlja podtip PF koji odlikuje pojava erozija prekrivenih ljušpama i krustom u fotoeksponiranim zonama (skalp, lice, gornji delovi trupa). Ali, istovremeno sa razvojem ovih lezija mogu biti prisutne i lezije nalik lupusu. Sve navedene promene se pogoršavaju prilikom fotoekspozicije, a 80% pacijenata sa PE mogu imati pozitivan lupus band test [3]. Incidencija PF-a u Aziji, Evropi, Severnoj Americi i Južnoj Africi iznosi od 0,5–1/100.000, dok je značajno viša u delovima Južne Amerike i Severne Afrike [4]. Pojava bolesti u porodicama je retka, ali je uočena veća prevalencija u određenim etničkim grupama, naročito među Aškenazi Jevrejima, što je povezano sa genetskim faktorima, posebno HLA DRB1*0402 genotipom [1]. U patogenezi PF-a ulogu imaju autoantitela protiv komponenti dezmozoma, što dovodi do akantolize, formiranja subepidermalnih rascepa i bula. Kod PF-a dominantna su autoantitela za dezmozoglein 1 (Dsg 1), što rezultira lezijama uglavnom na koži, dok je zahvatanje sluznica izuzetno retko zbog niske koncentracije Dsg 1 u mukoznim tkivima. Dijagnoza se potvrđuje histopatološkim pregledom, koji pokazuje supkornealnu akantolizu, direktnom imunofluorescencijom, koja otkriva intercelularne intraepidermalne depozite IgG i C3 pretežno u površinskim slojevima epidermisa i serološkim testovima koji određuju titar pemfigusnih antitela [1, 2]. Pemfigus pripada grupi dermatozata sa oštećenjem epidermalne barijere, a uobičajene komplikacije su bakterijske i virusne infekcije kože. Termin Kapošijeva varičelijiformna erupcija obuhvata vezikulozne erupcije kože izazvane herpes simplex virusom tip 1 i 2, Varicela zoster virusom (VZV), Cocksackie A16 i poksvirusima kod pacijenata sa hroničnim dermatozama. Termin eczema herpeticum se odnosi na virusne superinfekcije uzrokovane HSV kod pacijenata sa atopijskim dermatitisom [5].

Veoma retko, kao komplikacija eritrodermijskog pemfigusa, može se javiti Kapošijeva varičelijiformna erupcija (eczema herpeticum). Ovo je potencijalno životno ugrožavajuće stanje koje se uglavnom javlja u detinjstvu, ali su zabeleženi slučajevi i kod odraslih. Najčešće se javlja na koži sa oštećenjem epidermalne barijere, a opisana je kao komplikacija atopijskog dermatitisa, dermatitis herpetiformis-a, mycosis fungoides-a,

tous base. The disease typically begins on the scalp, face, and upper trunk, with subsequent progression to other parts of the body, potentially culminating in exfoliative erythroderma. Mucosal involvement in PF is uncommon, and patients often report burning sensations and pain associated with skin lesions [1, 2]. A distinct variant of PE - also known as Sener-Usher syndrome - is defined by erosions covered with scales and crusts, predominantly in sun-exposed areas such as the scalp, face, and upper trunk. In some cases, discoid lupus erythematosus-like lesions may coexist. These lesions typically worsen with ultraviolet exposure, and up to 80% of patients with PE may demonstrate a positive lupus band test [3]. The disease usually manifests in individuals between the fourth and sixth decades of life. The incidence of PF ranging from 0.5 to 1 per 100,000 people in Asia, Europe, North America, and South Africa, but is significantly higher in parts of South America and North Africa [4]. While familial clustering is rare, PF shows increased prevalence among certain ethnic groups, particularly Ashkenazi Jews, attributed to genetic predisposition - most notably the HLA DRB1*0402 genotype [1].

The pathogenesis of PF involves autoantibodies directed against desmosomal - primarily desmozoglein 1 (Dsg 1) - leading to acantholysis, subepidermal cleft formation, and blisters. Due to the low concentration of Dsg 1 in mucosal epithelium, mucosal involvement is extremely rare. Diagnosis is confirmed by histopathological examination revealing subcorneal acantholysis, direct immunofluorescence showing intercellular IgG and C3 deposits in the upper epidermis, and serological assays that detect pemphigus antibodies [1, 2].

Because PF disrupts the epidermal barrier, affected individuals are susceptible to secondary skin infections, including both bacterial and viral etiologies. Kaposi's varicelliform eruption (KVE) refers to a vesiculopustular viral superinfection occurring in the context of underlying dermatoses. It is caused by viruses such as herpes simplex virus (HSV) types 1 and 2, varicella-zoster virus (VZV), Cocksackievirus A16, and various poxviruses. A specific subtype of eczema herpeticum denotes HSV infection superimposed of atopic dermatitis [4].

Darierove bolesti, Hejli-Hejli bolesti, Groverove bolesti, iritantnog kontaktnog dermatitisa i opekotina [6]. Najčešće se EH viđa kod atopijskog dermatitisa (oko 3% pacijenata), dok je u jednoj studiji opisan kod jedne trećine pacijenata sa pemphigus foliaceusom [7, 8]. Eczema herpeticum se manifestuje pojavom vezikula, hemoragičnih erozija i krusti. U slučaju sistemske infekcije, EH može dovesti do malaksalosti, groznice, keratokonjuktivitisa, encefalitisa i sepse. Promene na koži su obično lokalizovane na glavi, vratu i trupu i traju u proseku 2–6 nedelja. Terapija izbora je intravenska primena aciklovira i širokospektralnih antibiotika radi prevencije sekundarnih kožnih infekcija. Neadekvatno prepoznavanje i lečenje EH nosi rizik od smrtnog ishoda usled sistemske diseminacije, zahvatanja više organa i sepse.

Prikaz slučaja

Žena, starosne dobi od 70 godina javlja se u Kliniku u suberitrodermiji sa mnogobrojnim erozijama po koži, na koži trupa i ekstremiteta (Slike 1–4).

Pacijentkinja navodi da se deset godina unazad lečila od generalizovanog ekcema, koji nije



Slika 1. Erozijske sa sitnom skvamom na eritematoznoj osnovi u regijama lica, vrata, trupa i gornjih ekstremiteta

Figure 1. Diffuse macular erythema with fine adherent scales and small skin erosions involving the face, neck, décolletage, and upper extremities.
Legenda. Prisutne su eritematozne makule sa tankom adherentnom skvamom, u regiji lica, vrata, dekoltea i gornjih ekstremiteta, međusobno slivene sa prostorima neizmenejene kože između

Legend. The patient presents with erythematous macules, thin adherent scales, and small erosions scattered across the décolleté, trunk, and proximal upper extremities, interspersed with areas of unaffected skin

Although extremely rare, KVE (eczema herpeticum) can complicate erythrodermic pemphigus foliaceus. This potentially life-threatening condition typically affects children but has also been documented in adults. It usually develops in areas of compromised skin barrier and has been reported in association with atopic dermatitis, dermatitis herpetiformis, mycosis fungoides, Darier disease, Hailey-Hailey disease, Grover disease, irritant contact dermatitis, and burns [6]. While EH occurs in approximately 3% of patients with atopic dermatitis, one study reported its occurrence in up to one-third of patients with PF [7, 8]. Clinically, EH presents with vesicles, hemorrhagic erosions, and crusts, predominantly affecting the head, neck, and trunk. In systemic dissemination, symptoms may include malaise, fever, keratoconjunctivitis, encephalitis, and sepsis. Lesions typically persist for 2 to 6 weeks. Intravenous acyclovir remains the treatment of choice, often combined by systemic antibiotics to prevent secondary bacterial infections. Delayed or missed diagnosis can result in severe complications, including multiorgan failure and sepsis.



Slika 2. Erozijske kože, od kojih su pojedine pokrivene krustama na koži donjih ekstremiteta

Figure 2. Erosions with scaling and crusts on an erythematous base in the lower extremities
Legenda 2. Kod pacijentkinje se vide erozijske kože sa tankom adherentnom skvamom na eritematoznoj osnovi od kojih su pojedine pokrivene krustama u regiji donjih ekstremiteta.

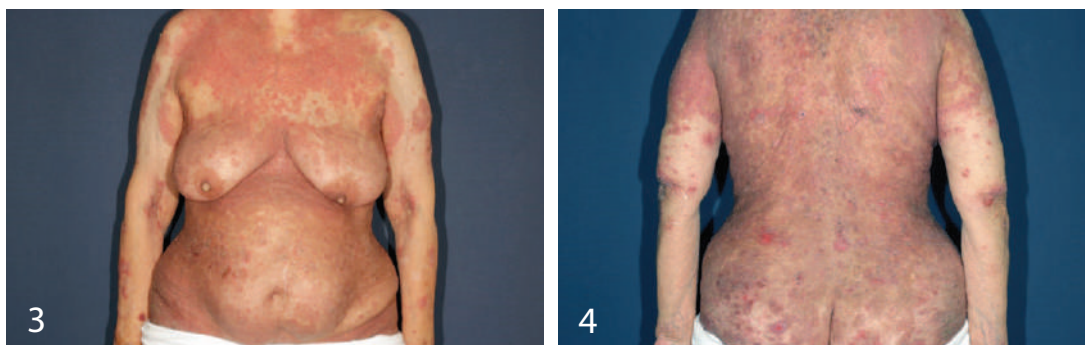
Legend 2. The patient presents with erosions on the lower extremities, with several lesions entirely covered by crusts.

potvrđen biopsijom kože i drugim ispitivanjima. Do decembra 2023. godine lečena je anti-histaminicima, sistemskim i lokalnim kortikosteroidima u drugim ustanovama, uz delimično poboljšanje. Godine 2019. učinjena je histerektomija sa adnektomijom zbog maligne neoplazme uterusa, koja je sada u remisiji. Biopsija kože sa leđa pokazala je histopatološke nalaze epiderma sa znacima blage do umerene iregularne psoriasiformne hiperplazije sa očuvanim granularnim slojem, dok je u kornealnom sloju uočena parakeratoza, fibrinski eksudat i neutrofilne supkornealne mikropustule. U papilarnom dermisu primećen je blagi perivaskularni limfocitni i histiocitni infiltrat. Direktnom imunofluorescencijom uočeni su intraepidermalni, intercelularni depoziti IgG i C3. Indirektnom imunofluorescencijom detektovana su pemfigusna antitela u titru 1:80. Krvne analize su ukazale na povišene eozinofile (632/ μ L) i povećanu koncentraciju IgE ($p > 3.000$ IU/ml), dok su ostali imunski parametri (ANA, ENA skrining) bili u granicama referentnih vrednosti. Pacijentkinja je ispitivana i u pravcu postojanja neoplazije te su učinjeni CT grudnog koša, abdomena i male karlice i tumorski markeri za tumore želuca, pluća, jetre i kolona koji su bili u referentnim vrednostima. Pacijentkinji je dijagnostikovano eritrodermijski pemfigus foliaceus, započeta sistemska kortikosteroidna terapija (1 mg/kg metilprednizolona), a usled neefikasnosti ordinirana je i pulsna kortikosteroidna terapija (1 g/dan me-

Case presentation

A 70-year-old woman presented to our clinic with suberythroderma and numerous erosions affecting the skin of the trunk and extremities (**Figures 1–4**).

The patient had a 10-year history of presumed generalized eczema, though this diagnosis had never been confirmed by biopsy or other diagnostic procedures. Prior to December 2023, she received antihistamines and both topical and systemic corticosteroids at various institutions, resulting in only partial improvement. Her past medical history was notable for a hysterectomy with adnexectomy in 2019 due to a malignant uterine neoplasm, currently in remission. A skin biopsy was performed from a lesion on the back. Histopathological analysis revealed mild to moderate irregular psoriasiform epidermal hyperplasia and a preserved granular layer. The stratum corneum exhibited parakeratosis, fibrin exudate, and a subcorneal micropustule rich in neutrophils. A mild perivascular lymphohistiocytic infiltrate was noted in the papillary dermis. Direct immunofluorescence demonstrated intraepidermal intercellular deposits of IgG and C3, while indirect immunofluorescence revealed pemphigus antibodies at a titer of 1:80. Laboratory tests showed elevated eosinophils (632/ μ L) and markedly increased IgE level ($p > 3,000$ IU/ml). Antinuclear anti-



Slika 3 i 4. Erozije kože, od kojih su pojedine pokrivena krastama na koži grudnog koša, abdomena i leđa

Figures 3 and 4. Erosions with scaling and crusts on an erythematous base involving the chest, abdomen, and back

Legenda. Pacijentkinja sa izraženim erozijama, praćenim deskvamacijom i formiranjem krusta na eritematoznoj osnovi na koži grudnog koša, abdomena i leđa, uz zahvatanje značajne površine kože. Na osnovu svih do sada prezentovanih prikaza, može se zaključiti da pacijentkinja ispoljava stanje suberythrodermije kože.

Legend. The patient presents with extensive erosions accompanied by scaling and crusting on an erythematous base, visible on the chest, abdomen, and back, covering a large skin surface area. The overall clinical appearance is consistent with suberythroderma.

tilprednizolona tokom tri uzastopna dana). Tokom hospitalizacije, pacijentkinji nisu ordinirani lekovi koji smanjuju potrebu za kortikosteroidima. Nakon završene pulsne kortikosteroidne terapije dolazi do pojave vezikula i žučkastosmeđih krusti u regiji leve periokularne regije, a zatim i leve perioralne regije i duž leve polovine lica (**Slika 5 i 6**).

Na osnovu kliničke slike postavljena je dijagnoza Kaposijeve varičeliformne erupcije i odmah je započeta intravenska antivirusna (aciklovir amp. 500 mg/8 h tokom 14 dana) i antibiotska (levofloksacin amp. 1 g/dan) terapija tokom 10 dana sa potpunom regresijom promena na koži (**Slika 7**).

Diskusija

Pemfigus pripada grupi autoimunih oboljenja koja nastaju kao posledica stvaranja specifičnih autoantitela na komponente dezmozoma. U patogenezi bolesti dominantna autoantitela se stvaraju na proteine dezmozoglein 1 i 3, sa posledičnim razvojem subepidermalnog rascepa i bula [3, 4]. Eritrodermijski pemfigus predstavlja podtip pemfigusa foliaceusa koji se karakteriše prisustvom specifičnih autoantitela pretežno usmerenih na dezmozoglein 1 koji se eksprimira u keratinizujućim tkivima (koža) čime se objašnjava pojava plikova, erozija i krusti na koži uz očuvanost sluznice. Kli-

bodies (ANA) and extractable nuclear antigen (ENA) screening were within normal limits. A thorough malignancy workup - including CT scans of the chest, abdomen, and pelvis, as well as tumor markers for gastric, lung, liver, and colon cancer – yielded no evidence of malignancy. Based on clinical, histopathological, immunofluorescence, and serological findings, the patient was diagnosed with erythrodermic pemphigus foliaceus. Systemic corticosteroid therapy was initiated with methylprednisolone at 1 mg/kg. Due to inadequate response, the patient received pulse corticosteroid therapy (methylprednisolone 1 g/day for 3 consecutive days). No steroid-sparing therapy was initiated during hospitalization. On the 10th day of hospitalization, following pulse therapy, the patient developed vesicles and golden-brown crusts localized to the left periorcular and perioral regions, later spreading to the left hemiface (**Figures 5 and 6**).

Based on the clinical features, a diagnosis of Kaposi's varicelliform eruption (eczema herpeticum) was made. Intravenous antiviral therapy was initiated promptly with acyclovir ampoules at 500 mg every 8 hours, and continued for 14 days. Simultaneously, intrave-



Slika 5 i 6. Vezikule i žučkasto-smeđe kruste u regiji leve polovine lica

Figures 5 and 6. Vesicles and golden-brown crusts localized on the left side of the face
Legenda. Na slikama se uočavaju vezikule i žučkasto-smeđe kruste u regiji leve polovine lica, što klinički ukazuje na eczema herpeticum.

Legend. Vesicular lesions with yellowish-brown crusts are present on the left side of the face, representing a clinical picture consistent with eczema herpeticum.

nički se može manifestovati eritrodermijom, ali to nije uvek slučaj [7]. U seriji slučajeva od šest pacijenata sa eritrodermičnim PF-om, 80% je inicijalno ispoljavalo eritrodermu [7]. Retko se javlja kod dece. Zbog narušenog integriteta epidermalne barijere, uobičajene komplikacije pemfigusa su bakterijske i virusne infekcije kože. Jedna od retkih komplikacija je Kapošijeva variceliformna erupcija, potencijalno fatalna reaktivacija herpes simpleks virusa tipa 1 i 2. Obično se javlja u detinjstvu, verovatno zato što je EH najčešća komplikacija atopijskog dermatitisa kod dece, iako su zabeleženi slučajevi i u starijim uzrasnim grupama [9]. U literaturi je identifikovano nekoliko faktora rizika za razvoj EH: oštećenje epidermalne barijere, imunosupresija, dizbioza kožne flore i stariji uzrast [8, 9]. Kod naše pacijentkinje prisutno je nekoliko navedenih faktora rizika. Eczema herpeticum je češća kod stanja koja uključuju oštećenje epidermalne barijere. Iako se EH najčešće viđa kao komplikacija atopijskog dermatitisa (3% pacijenata), može se javiti i kao komplikacija: ihtioze, opekotina, Sezarijevog sindroma, Darierove bolesti, pemfigusa, benignog porodičnog pemfigusa i kontaktnog dermatitisa [6–8]. Kada se razmatra imunosupresija kao potencijal-



Figure 7. Potpuna regresija ranije prisutnih kožnih promena na levoj polovini lica

Figure 7. Complete regression of the facial skin lesions

Legenda. Uočava se kompletna regresija ranije prisutnih kožnih promena na levoj polovini lica
Legend. Complete regression of the previously observed skin lesions on the left side of the face.

nous antibiotic therapy with levofloxacin was administered at 1 mg/kg for 10 days to prevent secondary bacterial infection. This dual therapy resulted in complete regression of the lesions (**Figure 7**).

Discussion

Pemphigus encompasses a group of autoimmune blistering diseases caused by pathogenic autoantibodies against desmosomal proteins, primarily desmoglein 1 and 3. The binding of these antibodies to their respective targets results in formation of subepidermal clefts and bullae. Erythrodermic pemphigus foliaceus is a rare subtype characterized by autoantibodies targeting desmoglein 1, which is predominantly expressed in the superficial layers of keratinized skin. As a result, patients present with bullae, erosions, and crusting of the skin, typically without mucosal involvement [1, 2]. Although PF can present with erythroderma, it is not a universal feature. In a case series of six patients with erythrodermic PF, 80% initially presented with erythroderma [7]. The disease is rare in children. A major concern in pemphigus is the compromised epidermal barrier, which predisposed patients to secondary bacterial and viral infections. Among these, Kaposi's varicelliform eruption (KVE) – also known as eczema herpeticum (EH) when caused by herpes simplex virus types 1 and 2 (HSV) – represents a potentially life-threatening viral complication. KVE is most frequently seen in pediatric patients with atopic dermatitis, but it can also occur in older age groups [9]. Several risk factors for EH have been identified in the literature, including impaired skin barrier function, immunosuppressive therapy, dysbiosis of skin flora, and advanced age [8, 9]. Our patient presented with multiple such risk factors. Eczema herpeticum is more common in conditions that inherently involve epidermal barrier damage. Although EH is most commonly associated with atopic dermatitis, affecting approximately 3% of patients, it has also been reported in other conditions such as ichthyosis, burns, Sezary syndrome, Darier disease, pemphigus, benign familial pemphigus, and contact dermatitis [6–8]. In a case series of 12 patients with autoimmune blistering dermatoses complicated by EH, three had not received immunosuppressive therapy, specifically those with linear IgA der-

ni faktor rizika, u seriji slučajeva od 12 pacijenata sa autoimunim buloznim dermatozama koji su razvili EH, kod njih troje nije korišćena imunosupresivna terapija, posebno kod pacijenata sa linearnom IgA dermatozom. Kod pacijenata sa pemfigusom razvoj ove komplikacije bio je povezan sa imunosupresijom izazvanom kortikosteroidima, bilo kao monoterapijom ili u kombinaciji sa drugim imunosupresivima [10]. Međutim, u metaanalizi 100 pacijenata, 76% njih nije primilo sistemsku terapiju kortikosteroidima najmanje četiri nedelje pre razvoja EH, što ukazuje da je sistemski imunosupresija samo jedan od faktora rizika [6]. O značaju lokalne imunosupresije kao faktora rizika za razvoj EH govori retrospektivna japanska studija koja pokazuje češću pojavu EH kao komplikacije AD kod pacijenata na lokalnoj kortikosteroidnoj terapiji u odnosu na lokalnu primenu inhibitora kalcineurina, ali pokazuje i korelaciju duže primene lokalnih kortikosteroida sa većim rizikom za razvoj EH (Kapošijeva varičeliformna erupcija je urgentno, životno ugrožavajuće stanje koje zahteva hitno lečenje. Mortalitet kod imunokompetentnih odraslih iznosi 10%, ali može dostići i 50% kod imunokompromitovanih osoba [12, 13]. Dijagnoza se često može postaviti na osnovu anamneze i kliničke slike. Za potvrdu se mogu koristiti Tzanckov bris i bris kože. Lečenje treba započeti odmah. Najzastupljeniji lek, a ujedno i prva linija terapije jeste aciklovir koji se primenjuje intravenski u dozi od 1,5 g dnevno [8]. Uz primarnu antivirusnu terapiju neophodno je sprovesti i intravensku širokospektralnu antibiotsku terapiju u cilju prevencije sekundarne bakterijske infekcije kože. Prema literaturi, propisana terapija obično dovodi do regresije promena na koži nakon 10–14 dana. Međutim, u nekim slučajevima može doći do sistemske diseminacije, zahvatanja više organa, sepse i smrtnog ishoda. S obzirom na to da se imunosupresivni lekovi koriste u lečenju PF-a i drugih dermatosa sa oštećenjem epidermalne barijere, preporučuje se da se u teškim slučajevima EH imunosupresivi (MTX, mikofenolat mofetil i ciklosporin) obustave, a ako je moguće, smanji i doza sistemskih kortikosteroida [14].

Zaključak

Kod hroničnih dermatosa koje u osnovi imaju oštećenje epidermalne barijere, a prisutni su i faktori rizika kao što su starija životna dob i imunosupresija, uz pojavu tipičnih kožnih promena, treba razmišljati u pravcu mogućeg ra-

matosis. The development of this complication in patients with pemphigus was associated with immunosuppression from corticosteroids, either as monotherapy or combined with other immunosuppressants [10]. Notably, a meta-analysis of 100 patients found that 76% had not received systemic corticosteroids within four weeks prior to developing EH, indicating that systemic immunosuppression is just one of the risk factors [6]. Local immunosuppression also plays a role, although a retrospective Japanese study found no statistically significant difference in EH incidence between patients using topical calcineurin inhibitors and those using topical corticosteroids in the treatment of atopic dermatitis [11].

KVE is considered a dermatologic emergency. In immunocompetent adults, the mortality rate is approximately 10%, but this can rise to 50% in immunocompromised individuals [12, 13]. Diagnosis is primarily clinical, based on the medical history and clinical presentation. Supportive diagnostic tools include the Tzanck smear and skin swab. Treatment must be initiated promptly. Intravenous acyclovir remains the first-line therapy, typically administered at 1.5 g per day [8]. In addition to antiviral therapy, systemic broad-spectrum intravenous antibiotics are often necessary to prevent or treat secondary bacterial infections. In most cases, skin lesions regress within 10 to 14 days of treatment initiation. However, in severe cases, systemic viral dissemination, multi-organ involvement, sepsis, and death can occur. In patients receiving immunosuppressive therapy, particularly those with PF and other dermatoses with epidermal barrier damage, it is recommended to discontinue or reduce immunosuppressive agents, such as methotrexate, mycophenolate mofetil, or cyclosporine [14].

Conclusion

In chronic dermatoses characterized by impaired epidermal barrier function, particularly in the presence of risk factors such as advanced age and immunosuppression, the possibility of eczema herpeticum should be considered when typical skin lesions appear. Early recognition and prompt initiation of antiviral therapy, primarily intravenous acyclovir, in combination with antibiotics, are essential to prevent systemic dissemination, secondary

zvoja eczema herpeticum, a zatim i primeniti intravenski aciklovir i antibiotike u cilju sprečavanja moguće sistemske diseminacije, sekundarnih infekcija kože, sepse i smrti.

Skraćenice

EH – *eczema herpeticum*
 PF – *Pemphigus foliaceus*
 PE – *Pemphigus erythematosus*
 VZV – *Varicela zoster virus*
 SLE – *Sistemski eritemski lupus*
 CT – *Kompjuterizovana tomografija*
 IgE – *Imunoglobulin E*
 IgA – *Imunoglobulin A*
 MTX – *Metotreksat*
 H – *Čas*
 G – *Gram*
 mg/kg – *Miligram po kilogramu*
 μL – *Mikrolitar*
 IU/ml – *Internacionalnih jedinica po mililitru*
 Dsg 1 – *Dezmoglein 1*
 DIF – *Direktna imunofluorescencija*

infections, sepsis, and potentially fatal outcomes.

Abbreviations

EH – *Eczema herpeticum*
 PF – *Pemphigus foliaceus*
 PE – *Pemphigus erythematosus*
 KVE – *Kaposi's varicelliform eruption*
 HSV – *Herpes simplex virus*
 VZV – *Varicella-zoster virus*
 SLE – *Systemic lupus erythematosus*
 CT – *Computer tomography*
 IgE – *Immunoglobulin E*
 IgA – *Immunoglobulin A*
 MTX – *Methotrexate*
 H – *Hour*
 G – *Gram*
 mg/kg – *Milligram per kilogram*
 μL – *Microliter*
 IU/ml – *International units per milliliter*
 Dsg 1 – *Desmoglein 1*
 DIF – *Direct immunofluorescence*

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KLINIČKI AMIOPATSKI DERMATOMIOZITIS SA PROGRESIJOM U KLASIČAN DERMATOMIOZITIS – DIJAGNOSTIČKI I TERAPIJSKI IZAZOV – PRIKAZ SLUČAJA

CLINICALLY AMYOPATHIC DERMATOMYOSITIS PROGRESSING INTO CLASSIC DERMATOMYOSITIS – DIAGNOSTIC AND THERAPEUTIC CHALLENGE – A CASE REPORT

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Sažetak

Uvod. Termin klinički amiopatski dermatomiozitis koristi se u slučajevima postojanja kutanih nalaza koji odgovaraju dermatomiozitisu i odsustva kliničkih znakova miopatije. U toku bolesti kod pacijenata se mogu razviti mišićni simptomi te progredirati u klasični dermatomiozitis što se javlja u oko 13% slučajeva. EULAR/ACR kriterijumi klasifikacije za adultne i juvenilne idiopatske inflamatorne miopatije i njihove glavne podgrupe iz 2017. godine imaju ograničenu primenljivost kod pacijenata sa kliničkim amiopatskim dermatomiozitisom. S obzirom na nedostatak randomizovanih kliničkih ispitivanja, preporuke za terapiju oslanjaju se uglavnom na prikaze slučajeva i serije slučajeva. **Prikaz slučaja.** Predstavljamo pacijentkinju starosti 60 godina sa eritematoznim i edematoznim plakovima u periorbitalnoj i centrofacijalnoj regiji i poikilodermom u presteralnoj regiji i spoljašnjem delu leve nadlaktice, bez sistemskih manifestacija i maligniteta. Prethodno je lečena pod dijagnozom kontaktnog dermatitisa. Laboratorijski i elektromiografski parametri nisu pokazali znake zahvatanja mišića, a histopatološka analiza kože je išla u pravcu dijagnoze dermatomiozitisa, međutim, naš pacijent nije ispunio EULAR/ACR kriterijume. S obzirom na to da nije bilo kliničkog odgovora na sistemsku terapiju antimalaricima, ista je zamenjena metotreksatom uz delimičnu regresiju kožnih lezija. Nakon 16 meseci od pojave bolesti i tokom trajanja terapije metotreksatom, pacijentkinja je razvila mišićnu slabost što je potvrđeno EMG-om, ali su mišićni enzimi ostali u referentnom opsegu. Primenjene su visoke doze glukokortikoidne terapije i azatioprin, ali zbog progresije mišićne slabosti i incipientne lezije jetre izazvane lekom, azatioprin je zamenjen ciklosporinom. Ova terapija je rezultirala značajnim poboljšanjem mišićne snage i potpunom regresijom kožnih lezija. **Zaključak.** Naglašavamo ograničenu primenljivost EULAR/ACR kriterijuma klasifikacije kod pacijenata sa klinički amiopatskim dermatomiozitisom i insuficijenciju relevantnih algoritama lečenja. Ističemo da moguća progresija u klasični dermatomiozitis ne mora biti praćena povećanjem mišićnih enzima koji se obično koriste za skrining početka mišićne bolesti. Na kraju, potvrđujemo efikasnost ciklosporina u bolesti rezistentnoj na terapiju.

Ključne reči: dermatomiozitis; klasifikacija; dijagnoza; antimalarici; metotreksat; ciklosporin; ishod lečenja

Abstract

Introduction. Clinically amyopathic dermatomyositis is characterized by cutaneous manifestations consistent with dermatomyositis without clinical signs of myopathy. Muscle involvement may develop over time, progressing to classic dermatomyositis in approximately 13% of cases. The 2017 EULAR/ACR classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups have limited applicability in clinically amyopathic dermatomyositis. Due to the absence of randomized clinical trials, treatment recommendations rely primarily on case reports and case series. **Case report.** We present a 60-year-old female with erythematous and edematous plaques in the periorbital and midfacial regions, along with poikiloderma on the presternal area and the outer aspect of the left upper arm, without systemic involvement or malignancy. Initially misdiagnosed as contact dermatitis, she showed no laboratory or electromyographic signs of muscle involvement, while skin histopathology confirmed dermatomyositis. Despite not meeting EULAR/ACR criteria, clinically amyopathic dermatomyositis was diagnosed. Systemic antimalarial therapy was ineffective, necessitating a switch to methotrexate, which led to partial regression of skin lesions. After 16 months, while on methotrexate, the patient developed muscle weakness confirmed by EMG, though muscle enzyme levels remained within the reference range. High-dose glucocorticoids and azathioprine were initiated, but due to progressive muscle weakness and incipient drug-induced hepatic injury, azathioprine was replaced with cyclosporine, leading to significant muscle strength improvement and complete resolution of skin lesions. **Conclusion.** The case underscored the limitations of the 2017 EULAR/ACR classification criteria in clinically amyopathic dermatomyositis and highlights the absence of standardized treatment protocols. Additionally, we emphasize that possible progression to classic dermatomyositis may occur without muscle enzyme elevation, challenging conventional screening methods. Finally, we confirm the efficacy of cyclosporine in refractory cases.

Key words: Dermatomyositis; Classification; Diagnosis; Antimalarials; Methotrexate; Cyclosporine; Treatment Outcome

Uvod

Dermatomiozitis (DM) je autoimunska bolest vezivnog tkiva koja predstavlja vrstu idiopatske inflamatorne miopatije. Karakteriše se prisustvom različitih kutanih manifestacija koje mogu i ne moraju biti praćene heterogenim sistemskim manifestacijama, uključujući i prisustvo miozitisa [1].

Klinički amiopatski dermatomiozitis (CADM) termin je koji se koristi u slučajevima postojanja kutanih nalaza koji odgovaraju DM-u i odsustva kliničkih znakova miopatije. Procenjuje se da CADM čini oko 20% svih slučajeva DM-a i da se javlja sa većom prevalencijom kod žena [2]. Pacijenti sa CADM mogu razviti mišićne simptome u toku trajanja bolesti te progredirati u klasičan dermatomiozitis (CDM), što je zabeleženo u oko 13% svih slučajeva CADM-a [3].

Postavljanje dijagnoze CADM-a decenijama je predstavljalo klinički izazov. Prve kriterijume za klasifikaciju amiopatskog dermatomiozitisa predložio je Sontheimer (Sontheimer) 2002. godine [4]. Načesto korišćeni kriterijumi za klasifikaciju adultnih i juvenilnih idiopatskih inflamatornih miopatija i njihovih glavnih podgrupa su u današnje vreme kriterijumi Evropske alijanse asocijacija za reumatologiju Američkog koledža za reumatologiju (EULAR/

Introduction

Dermatomyositis (DM) is an autoimmune connective tissue disease that represents a type of idiopathic inflammatory myopathy. It is characterized by distinctive cutaneous manifestations, which may or may not be accompanied by heterogeneous systemic involvement, including myositis [1].

Clinically amyopathic dermatomyositis (CADM) refers to cases of DM-consistent cutaneous findings but without clinical signs of myopathy. It is estimated that CADM accounts for approximately 20% of all DM cases, with a higher prevalence in females [2]. While CADM may remain non-progressive, about 13% of cases eventually develop muscle involvement, transitioning to classic dermatomyositis (CDM) [3].

Diagnosing CADM has long been a clinical challenge. The first classification criteria for amyopathic dermatomyositis were proposed by Sontheimer in 2002 [4]. Currently, the most widely used classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups are the 2017 European Alliance of Associations for Rheumatology/ American College of Rheumatology (EULAR/ACR) classification criteria.

ACR) iz 2017. godine, ali njihova primenljivost kod pacijenata sa CADM-om ostaje ograničena [5, 6]. Predložena terapija za kožnu komponentu DM-a uključuje fotoprotektivne mere uz topikalne kortikosteroide ili inhibitore kalci- neurina. Međutim, većina pacijenata zahteva sistemsku terapiju radi kontrole bolesti, pri čemu su hidrosiklorokvin i metotreksat naj- češće upotrebljavani lekovi. Terapija prvog izbora za mišićnu komponentu DM-a je prime- na sistemskih glukokortikoida u različitim te- rapijskim režimima, sa imunospresivima ili bez njih kao što su metotreksat i azatioprin, pri čemu se pacijenti koji ne reaguju adekvatno smatraju rezistentnim na terapiju [7].

S obzirom na nedostatak randomizovanih ili kontrolisanih kliničkih ispitivanja, terapijski pristup za CADM nije jasno utvrđen u poređe- nju sa CDM-om. Ne postoji konsenzus o te- rapiji prvog izbora za CADM jer su preporuke za terapiju pretežno zasnovane na prikazima i serijama slučajeva. Sistematska analiza spro- vedena 2018. godine imala je za cilj da utvrdi koji su terapijski modaliteti korišćeni za odrasle pacijente sa CADM-om, pri čemu nije utvr- đen jedinstveni tretman koji bi bio odgovara- jući za sve pacijente [8].

Prikaz slučaja

Prikazujemo 60-godišnju ženu koja je prethodno lečena sistemskim antihistaminici- ma, glukokortikoidima i topikalnim steroidima pod dijagnozom kontaktnog dermatitisa zbog bilateralnog eritema i edema gornjih kapaka i periorbitalne regije unazad pet meseci, bez poboljšanja. Upućena je dermatologu koji je detektovao pojedinačne i slivene, nejasno ograničene, eritematozne i edematozne pla- kove na koži lica, pretežno u periorbitalnoj i centralnofacijalnoj regiji i preporučio hospita- lizaciju. Takođe, primećeni su pojedinačni pla- kovi sa znakovima poikiloderme na koži pre- sternalne regije i spoljašnjeg dela leve nad- laktice (**Slike 1–3**). Klinički je postavljena sumnja na DM pri čemu je inicijalni skor aktiv- nosti bolesti Indeks raširenosti i težine kožnih promena kod dermatomiozitisa (CDASI) izno- sio osam [8]. Eritemski lupus je razmatran kao glavna diferencijalna dijagnoza.

Prilikom prijema, pacijentkinja je bila u dobrom opštem stanju, kardiopulmonalno kompenzovana, afebrilna i bez drugih kliničkih znakova osim kožnih lezija otkrivenih fizikalnim

However, their applicability to CADM remains limited [5, 6].

Management of DM skin involvement typically includes photoprotection, topical corticosteroids, and calcineurin inhibitors, though most patients require systemic therapy. Hydroxychloroquine and methotrexate are the most commonly used systemic agents. For muscle involvement, systemic glucocorticoids – alone or in combination with immunosuppressants such as methotrexate or azathioprine – are the first-line treatment. Patients with inadequate responses are classified as therapy-resistant [7].

Due to the absence of randomised or controlled clinical trials, treatment guidelines for CADM are less defined than those for CDM. No consensus exists on the optimal first-line therapy, and recommendations are largely based on case reports and case series. A 2018 systematic review examined various treatment modalities in adult CADM patients but found no single therapy universally effective [8].

Case Report

We present a 60-year-old Caucasian female previously treated with systemic antihistamines, glucocorticoids, and topical steroids under the diagnosis of contact dermatitis. She had bilateral erythema and edema of the upper eyelids and periorbital region persisting for five months without improvement. A dermatologist noted both solitary and confluent, poorly defined, erythematous, and edematous plaques predominantly in the periorbital and midfacial region, as well as solitary poikilodermic plaques on the presternal region and the outer aspect of the left upper arm (**Figures 1–3**). Clinical suspicion of DM was raised, with an initial Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) activity score of 8. Lupus erythematosus was considered the primary differential diagnosis.

Upon admission, the patient was afebrile, cardiopulmonary compensated, and in good general condition, with no systemic symptoms beyond the skin lesions. She denied cardiovascular, respiratory, gastrointestinal, urinary, musculoskeletal, or dermatologic complaints. Her medical history included Hashimoto's thyroiditis (treated with levothy-



Slika 1. Klinički aspekt pacijentkinje koji pokazuje heliotropni osip, eritem centrofacijalne regije i V znak

Figure 1. Clinical aspect of the patient showing heliotrope rash, erythema in the midfacial region and the V sign

pregledom. Negirala je tegobe u vezi sa kardiovaskularnim, respiratornim, digestivnim, urinarnim, mišićno-koštanim i drugim sistemima organa, kao i bilo kakve tegobe u vezi sa kožnim lezijama. Od ranijih bolesti navodi Hashimoto tireoiditis zbog čega uzima levotiroksin i totalnu histerektomiju zbog uterinih mioma.

Laboratorijski nalazi, uključujući kompletnu krvnu sliku sa leukocitarnom formulom, markere inflamacije, nivoe mišićnih enzima, analize jetre i bubrega, tumor-markere (CEA, Ca-125, Ca 15-3, Ca 19-9, AFP, beta-2 mikroglobulin), serologiju za HIV, Hepatitis B i C virus, kao i test na okultno krvarenje u tri uzorka stolice bili su u referentnim vrednostima ili negativni. Imunski parametri uključujući C3 i C4 komponente komplementa, imunoglobuline klase IgG, IgA i IgM, anti-dsDNA antitela i ANCA bili su negativni ili u referentnom opsegu osim ANA na Hep-2 ćelijama koja je pokazala pozitivnu nukleoplazmu homogenog tipa i granično pozitivnog ANA-8-Screen-a. Planirani profil miozitisa sa anti-Jo1 i anti-Mi-2 antitelima nije bio dostupan za analizu. Radio-



Slika 2. Kutane lezije na licu – detalj

Figure 2. Facial skin lesions – detail

roxine) and total hysterectomy for uterine myomas.

Laboratory tests, including a complete blood count, inflammatory markers, muscle enzymes, liver and renal function, tumor markers (CEA, CA-125, CA 15-3, CA 19-9, AFP, beta-2 microglobulin), serology for HIV, hepatitis B and C, and fecal occult blood test in three samples, were within reference ranges or negative. Immunological findings, including complement levels (C3, C4), immunoglobulins (IgG, IgA, IgM), anti-dsDNA and ANCA, were also unremarkable, except for a nucleoplasm-positive ANA on Hep-2 cells (homogeneous pattern) and borderline positive ANA-8-Screen. Myositis-specific antibodies (anti-Jo1, anti-Mi-2) were unavailable for analysis. Imaging studies (chest x-ray, abdominal ultrasound, gynecological ultrasound, ECG) showed no significant abnormalities. EMG of the upper and lower extremities revealed cervicobrachial and lumbosacral polyradiculopathy without muscle involvement.

Skin biopsy revealed atrophic and focally hyperkeratotic epidermis with parakeratosis, patchy perifollicular and perivascular lymphocytic infiltrates extending into the dermis

grafija pluća i srca, ultrasonografija gornjeg abdomena, ginekološki ultrazvuk i EKG nisu pokazali značajne promene. EMG gornjih i donjih ekstremiteta pokazao je cervikobrahijalnu i lumbosakralnu poliradikulopatiju bez znakova mišićne zahvaćenosti.

Histopatološkim pregledom kože je registrovan atrofičan i fokalno hiperkeratotičan epidermis sa znacima parakeratoze. Primećen je mrljast perifolikularni i perivaskularni, dermalni i hipodermalni limfocitni infiltrat. Takođe, inflamatorni infiltrat je fokalno zahvatao i epidermis. Adneksi kože su bili atrofični i redukovani a znojne žlezde okružene novoformiranim kolagenom (**Slika 4**). Ovi nalazi su ukazivali na klinički postavljenu dijagnozu DM-a. S obzirom na odsustvo subjektivnih, kliničkih, laboratorijskih i elektromiografskih znakova mišićne bolesti u tom trenutku, biopsija mišića nije sprovedena.

Pacijentkinji je postavljena dijagnoza CADM-a i ordinirana je sistemska terapija hidroksihlorokvinom u dozi od 200 mg dva puta dnevno i kortikosteroidima (metilprednizolon u dozi od 1 mg/kg) uz prelazak na oralnu terapiju prednizonom i postepeno smanjenje doze. S obzirom na odsustvo poboljšanja nakon četiri meseca terapije, hidroksihlorokvin je zamenjen metotreksatom u dozi od 12,5 mg jedanput nedeljno uz povećanu dozu prednizona na 0,5 mg/kg. S obzirom na uočenu parcijalnu regresiju kožnih lezija, bez prisustva sistemskih tegoba, terapija kortikosteroidima je prekinuta nakon šest meseci.

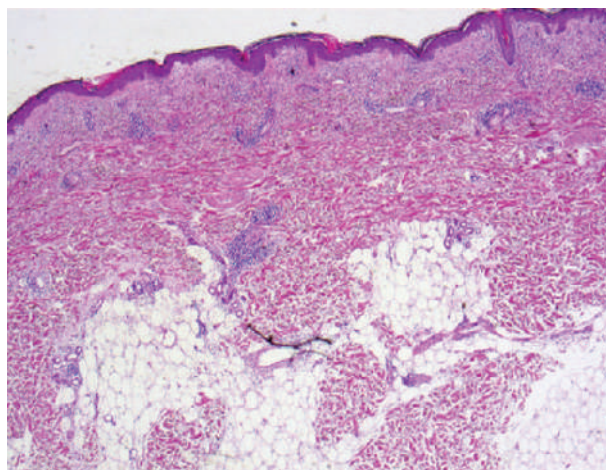
Šesnaest meseci od pojave kožnih lezija i pet meseci nakon obustave sistemske terapije kortikosteroidima, kod pacijentkinje se pojavila novonastala proksimalna mišićna slabost u gornjim i donjim ekstremitetima, koja se manifestovala poteškoćama pri hodanju i gutanju čvrste hrane. Metotreksat je zamenjen azatioprinom u dozi od 2 mg/kg dnevno uz 1 mg/kg prednizona. Međutim, nakon mesec dana je verifikovan dvostruki porast nivoa transaminaza uz nastavak progresije mišićne slabosti do te mere da je pacijentkinja morala da koristi invalidska kolica, što je dovelo do rehospitalizacije i prekida primene azatioprina.

Ponovljeni laboratorijski nalazi uključujući mišićne enzime i tumor-markere bili su u fiziološkim granicama, radiografija pluća i srca, ultrazvuk gornjeg abdomena i štitaste žlezde, CT toraksa i abdomena nisu pokazali znake okultnog maligniteta niti intersticijalne



Slika 3. Kutane lezije na gornjem delu grudnog koša sa znacima poikiloderme

Figure 3. Skin lesions on the upper chest showing signs of poikiloderma



Slika 4. Histopatološka analiza uzorka kože koja prikazuje hiperkeratozu sa atrofijom epidermisa, znake interface dermatitisa i dermalni i hipodermalni perivaskularni limfocitni infiltrat. HE, x25

Figure 4. Histopathology of the skin specimen showing hyperkeratosis with epidermal atrophy, signs of interface dermatitis, and dermal and hypodermal perivascular lymphocytic infiltrate. HE, x25

bolesti pluća. Test gutanja sa barijumskim kontrastom bio je uredan, ezofagogastroduodenoskopija je pokazala znakove gastroezofagealne refluksne bolesti, a EMG nalazom je potvrđena aktivna faza miozitisa u proksimalnim mišićima gornjih i donjih ekstremiteta. Ciklosporin je započeo u dozi od 2,5 mg/kg što je dovelo do značajnog poboljšanja mišićne snage (pacijentkinja je sposobna da hoda uz pomoć štapa) i potpune regresije kožnih lezija, pri čemu je CDASI skor aktivnosti bolesti nakon tri meseca iznosio 1. U daljem toku su doze kortikosteroida i ciklosporina postepeno smanjivane i kod pacijentkinje nije uočen recidiv bolesti niti je otkriven malignitet na osnovu skrininga u skladu sa uzrastom tokom perioda praćenja u trajanju od godinu dana.

Diskusija

Pacijenti sa DM-om mogu imati različite kožne promene koje se tradicionalno klasifikuju kao patognomonične, karakteristične, kompatibilne, manje česte, retke i nespecifične [9]. Heliotropni osip se smatra patognomoničnim i predstavlja ljubičasti eritem kapaka i periorbitalne kože koji može biti praćen edemom. Neki pacijenti mogu imati rasprostranjenije eritematozne promene na licu ili centrofacijalnoj regiji, što je bio slučaj kod naše pacijentkinje. Takođe su primećeni znaci poikiloderme, tj. promene u pigmentaciji, telangiektazije i atrofija kože gornjeg dela grudnog koša (V znak) i lateralne strane nadlaktice, što se smatra ključnom dijagnostičkom karakteristikom DM-a, dok drugi kutani znaci kod naše pacijentkinje nisu uočeni [10].

Diferencijalna dijagnoza, između ostalog, može uključivati airborne ili alergijski kontaktni dermatitis što je i bila inicijalna dijagnoza pacijentkinje pre prijema na našu kliniku. Međutim, prisustvo dodatnih kožnih lezija poput onih na presternalnoj regiji i lateralnom delu nadlaktice kod naše pacijentkinje, ukazivalo je na dijagnozu DM-a. Najčešći problem kod pacijenata sa CADM-om i fotosenzitivnom erupcijom je diferencijalna dijagnoza eritemskog lupusa. Prisustvo ljubičaste boje i patognomoničnih znakova poput heliotropnog osipa bi trebalo da ukažu na dijagnozu DM-a [10]. Sistemski i kutani eritemski lupus takođe su isključeni kod naše pacijentkinje korelacijom sa sprovedenim laboratorijskim i imunskim analizama.

and hypodermis, and atrophic skin appendages and sweat glands surrounded by newly formed collagen (**Figure 4**). These findings supported the clinical diagnosis of DM. Due to the absence of subjective, clinical, laboratory and negative EMG findings for muscle disease, a muscle biopsy was not performed.

The patient was diagnosed with CADM and started on hydroxychloroquine (200 mg twice daily) and methylprednisolone (1 mg/kg), later transitioned to oral prednisone with gradual tapering. After four months without clinical improvement, hydroxychloroquine was replaced with methotrexate (12.5 mg weekly), and prednisone was increased to 0.5 mg/kg. Partial regression of skin lesions was observed, and corticosteroids were discontinued after six months.

Sixteen months after the onset of skin lesions and five months after corticosteroid discontinuation, the patient developed new-onset proximal muscle weakness in both upper and lower extremities, presenting as difficulty walking and swallowing solid food. Methotrexate was replaced with azathioprine (2 mg/kg daily) alongside prednisone (1 mg/kg). However, after one month, transaminase levels doubled, and muscle weakness progressed to the extent that she required a wheelchair, prompting rehospitalization and azathioprine discontinuation.

Repeated laboratory tests, including muscle enzymes and tumor markers, remained within normal limits. Imaging studies (chest x-ray, abdominal ultrasound, thyroid ultrasound, CT scans of the chest and abdomen) showed no evidence of occult malignancy or interstitial lung disease. A barium swallow test was normal, and esophagogastroduodenoscopy revealed only gastroesophageal reflux disease. EMG confirmed active-phase myositis in the proximal muscles of the upper and lower limbs. Cyclosporine (2.5 mg/kg) was initiated, leading to significant improvement in muscle strength (allowing ambulation with a walking stick) and complete resolution of skin lesions, with a CDASI activity score of 1 after three months. Corticosteroid and cyclosporine doses were gradually tapered. During a one-year follow-up, the patient remained relapse-free, and age-appropriate malignancy screening was unremarkable.

Histopatološki nalaz biopsije kože kod naše pacijentkinje bio je u skladu sa dijagnozom DM-a, uključujući hiperkeratozu, atrofiju epidermisa, znake interfejs dermatitisa i perivaskularni limfocitni infiltrat, dok zadebljanje bazalne membrane, inkontinencija pigmenta, dermalni edem i depoziti mucina nisu uočeni [11]. U slučaju ovakvih nalaza, detaljan pregled kože uz kliničko-histopatološku korelaciju je ključan za potvrdu dijagnoze budući da se se histopatološke promene ne mogu razlikovati od onih kod eritemskog lupusa [12].

Pored kožnih lezija, pacijenti mogu imati različite sistemske manifestacije poput pulmonalne, kardijalne, vaskularne i gastrointestinalne zahvaćenosti. Stoga, detaljna procena simptoma i pažljiv fizikalni pregled treba da usmere kliničara ka mogućim dodatnim dijagnostičkim procedurama. Pored toga, prisustvo određenih antitela specifičnih za miozitis može pomoći kliničaru u predviđanju toka bolesti, ali pošto ista nisu bila dostupna za analizu, sprovedena je detaljna dijagnostička obrada pri kojoj nisu pronađeni znakovi sistemske zahvaćenosti kod naše pacijentkinje [1].

Iako postoji nekoliko dijagnostičkih kriterijuma za CADM, jedini validirani su EULAR/ACR kriterijumi iz 2017. godine, koji za klasifikaciju pacijenata bez zahvatanja mišića zahtevaju dva od tri kutana znaka – Gottronov znak, Gottronove papule i heliotropni osip [13]. Pacijenti koji imaju samo jedan od tri navedena kutana znaka neće ispuniti kriterijume te se dijagnoza CADM-a može prevideti. Procena je da se ovo dešava kod oko 25% pacijenata, dok je retrospektivnom studijom iz 2021. godine to zabeleženo čak u 32,8% slučajeva [6, 13]. Ovo je takođe bio slučaj sa našom pacijentkinjom, ali je progresija u CDM dodatno potvrdila našu dijagnozu. Stoga su potrebna dalja ispitivanja i unapređenje postojećih kriterijuma kako bi se povećala senzitivnost i specifičnost klasifikacije pacijenata sa CADM-om [13].

Dijagnoza CADM-a ne mora biti konstantna za vreme trajanja bolesti i kod pacijenata se može desiti progresija u CDM ukoliko se razviju mišićni simptomi. Ovo je bio slučaj sa našom pacijentkinjom koja je razvila kliničke znakove miopatije 16 meseci nakon početka kožne bolesti. Iako se nivoi mišićnih enzima tipično koriste kao skrining razvoja zahvaćenosti mišića kod pacijenata sa CADM-om, isti mogu ostati u referentnim granicama uprkos pojavi miopatije. Ovo je bio slučaj sa našom

Discussion

Dermatomyositis (DM) presents with various cutaneous features characterized as pathognomonic, characteristic, compatible, less common, rare, or non-specific [9]. Heliotrope rash, a hallmark of DM, manifests as violaceous erythema of the eyelids and periorbital region, often with edema. Some patients exhibit more widespread facial or mid-facial erythema, as seen in our case. Additionally, poikiloderma – characterized by pigmentary changes, telangiectasia, and skin atrophy – was present on the upper chest (V sign) and lateral upper arm, a critical diagnostic feature of DM, with no other cutaneous features detected in our patient [10].

The differential diagnosis included airborne or allergic contact dermatitis, which was initially suspected in our patient. However, the presence of additional skin lesions on the presternal and lateral upper arm areas supported the diagnosis of DM. Moreover, distinguishing CADM from lupus erythematosus can be challenging, particularly in patients with photosensitive eruptions. The violaceous hue and pathognomonic findings such as heliotrope rash favor DM over lupus [10]. Systemic and cutaneous lupus erythematosus were excluded in our patient based on laboratory and immunological findings.

Histopathological examination supported the diagnosis of DM, revealing hyperkeratosis, epidermal atrophy, interface dermatitis, and perivascular lymphocytic infiltrate, while features such as basement membrane thickening, pigment incontinence, dermal edema, and mucin deposits were absent [11]. Given the potential histopathological overlap between DM and lupus, clinicopathological correlation is essential for an accurate diagnosis [12].

DM can involve multiple organ systems, including pulmonary, cardiac, vascular, and gastrointestinal manifestations. Therefore, a comprehensive clinical evaluation is crucial to guide additional diagnostic testing. Furthermore, myositis-specific antibodies aid in prognostication but were unavailable in our patient. Extensive workup revealed no systemic involvement [1].

The 2017 EULAR/ACR classification criteria for DM require the presence of at least two out of the three hallmark cutaneous features (Göttron sign, Göttron papules, heliotrope rash) for CADM diagnosis [13]. Patients

pacijentkinjom čiji su nivoi mišićnih enzima ostali uredni tokom celog toka bolesti, što je u skladu sa dostupnim podacima iz literature. Progresija u CDM je uočena kod 37 slučajeva (13%) od 281 pacijenta sa CADM-om u sistematskom pregledu koji je sproveo Gerami sa saradnicima dok je povišen CK pronađen samo kod 14 pacijenata u trenutku prelaska u CDM što se desilo u periodu između 15 meseci i 6 godina nakon početka kožnih lezija [3]. Uz to, u novijoj retrospektivnoj studiji iz 2021. godine navodi se šest slučajeva (9%) progresije u CDM od 64 pacijenta sa CADM-om sa medijanom od 10,5 meseci za razvoj mišićne slabosti [6].

Prilikom pregleda dostupne literature o CADM-u, autori nisu pronašli konsenzus u vezi sa lečenjem istog. Ovo razilaženje u mišljenjima je razumljivo imajući u vidu nesklad između odgovora mišićne i kožne komponente na trenutne terapijske modalitete za DM, gde kožna komponenta često predstavlja veći terapijski izazov. Kao rezultat toga, i dalje postoji potreba za algoritmom lečenja pacijenata sa CADM-om [8, 14].

Antimalarici se najčešće propisuju kao sistemski lekovi u terapiji prvog izbora za CADM. Međutim, oni su efikasni u kontroli kožne bolesti samo kod malog procenta pacijenata - samo 11,4% kako su izvestili Pinar (Pinar) i saradnici. Kao rezultat toga, imunosupresivna terapija se često daje u kombinaciji sa hidroklorokinom ili u vidu monoterapije [15]. U sistematskom pregledu u vezi sa lečenjem CADM-a, Kolander (Callander) sa saradnicima navodi da je 35% pacijenata prestalo da prima antimalarike zbog nemogućnosti smanjenja doze glukokortikoida ili nedostatka kliničkog odgovora [8].

Sistemski glukokortikoidi se ne primenjuju rutinski kod pacijenata sa CADM-om, a posebno ne u vidu monoterapije budući da ovaj pristup često nije efikasan. Međutim, primena kure srednjih do visokih doza kortikosteroida se može razmotriti radi ublažavanja tegoba, a ovaj pristup je korišćen kod naše pacijentkinje [16, 17]. Najčešće primenljivani imunosupresivni lekovi su metotreksat i mikofenolat mofetil ili mikofenolna kiselina, kao i intravenski imunoglobulini [17, 18]. Odlučili smo da primenimo metotreksat sa kojim je uspešno postignuta parcijalna regresija kožnih lezija. Međutim, u daljem toku bolesti je naša pacijentkinja razvila mišićne simptome uprkos primeni meto-

exhibiting only one of these features may fail to meet the criteria, leading to underdiagnosis of CADM in up to 25 - 32.8% of cases [6, 13]. Our patient initially did not fulfill the criteria but later progressed to CDM, confirming the diagnosis. Therefore, further evaluation and improvement of existing criteria are needed to increase the sensitivity and specificity of classifying CADM patients [13].

CADM is not always a static diagnosis as patients may transition to CDM upon developing muscle symptoms. This occurred in our patient 16 months after the onset of skin lesions. While muscle enzyme levels are commonly used to monitor for myopathy, they may remain within normal limits despite disease progression, as seen in our patient, whose muscle enzymes remained normal during the entire course of the disease, which is consistent with the available literature data. A systematic review by Gerami et al. reported that 37 cases (13%) out of 281 CADM patients transitioned to CDM, with elevated CK levels in only 14 cases at the time of conversion (which happened between 15 months and 6 years after the onset of skin lesions) [3]. Similarly, a 2021 retrospective study found that 6 out of 64 (9%) CADM patients progressed to CDM, with a median onset of muscle weakness at 10.5 months [6].

Currently, no standardized treatment algorithm for CADM exists due to the discordance between muscle and skin response to therapy. The skin manifestations of DM often pose a greater therapeutic challenge [8, 14].

Antimalarials are commonly prescribed as first-line systemic medications for CADM, but their efficacy in controlling skin disease – is limited (11.4% response rate as reported by Pinar et al.). As a result, switch to immunosuppressants as monotherapy or combined with hydroxychloroquine is required [15]. Moreover, a systematic review of CADM treatment by Callander et al. reported that 35% of patients stopped getting antimalarials as glucocorticoid dose reduction was impossible, or the clinical response was poor [8].

Systemic glucocorticoids are not routinely administered for CADM as monotherapy, as their efficacy is often inadequate. However, a course of medium-to-high dose corticosteroids may be considered to provide relief, as in our patient [16, 17]. Methotrexate and mycophenolate mofetil or mycophenolic

treksata. Shodno tome, terapija je zamenjena azatioprinom uz visoke doze prednizona a u skladu sa preporukama za terapiju CDM [19].

S obzirom na inicijalnu leziju jetre potvrđenu laboratorijskim nalazima i dalje pogoršanje mišićnih simptoma, razmotrili smo opcije lečenja koje se koriste kod DM-a rezistentnog na terapiju uključujući primenu rituksimaba, intravenskih imunoglobulina, inhibitora kalcineurina i ciklofosfamida. Iako se rituksimab preporučuje kao prva terapijska linija u lečenju teraporezistentnog DM-a, primena istog nije bila moguća s obzirom da trenutno nije odobren u našoj zemlji za pacijente koji boluju od DM-a. Stoga smo se odlučili za ciklosporin koji je uspešno kontrolisao miozitis i doveo do potpune regresije kožnih lezija [7].

Procenjeno je da prevalencija malignih bolesti kod odraslih pacijenata sa DM-om iznosi 20%, pri čemu je rizik najveći tokom prve godine bolesti [16], ali ostaje povišen čak i nakon pete godine, kako navode Kjang (Qiang) i saradnici u metaanalizi [20]. Imajući to u vidu, planiramo da nastavimo sa skriningom na malignitete u skladu sa uzrastom i skriningom vođenim simptomima, kao i sa radiološkim imidžingom celog tela jedanput godišnje.

Zaključak

U zaključku naglašavamo ograničenu primenljivost EULAR/ACR kriterijuma klasifikacije za adultne i juvenilne idiopatske inflamatorne miopatije, posebno kod pacijenata sa kliničkim amio-patskim dermatomiozitisom. Takođe, insuficijencija relevantnih terapijskih algoritama predstavlja značajan izazov u lečenju. Ističemo mogućnost progresije kliničkog amio-patskog dermatomiozitisa u klasičan dermatomiozitis i ukazujemo da razvoj subjektivnih i kliničkih znakova zahvaćenosti mišića ne mora biti praćen povećanjem nivoa mišićnih enzima koji se obično koriste za skrining početka mišićne bolesti. Na kraju, potvrđujemo efikasnost ciklosporina kod pacijenata koji nisu adekvatno odgovorili na sve prethodno primenjene terapijske modalitete.

Skraćenice

DM – Dermatomyositis
CADM – Clinically amyopathic dermatomyositis
CDM – Classical dermatomyositis

acid, as well as intravenous immunoglobulin, are frequently used immunosuppressants [17, 18]. Methotrexate initially achieved partial regression of the skin lesions in our patients, but failed to prevent disease progression in terms of muscle involvement. Consequently, azathioprine with high-dose prednisone was introduced, following CDM treatment recommendations [19].

The initial hepatic injury confirmed by laboratory tests and worsening of muscle symptoms necessitated reconsideration of treatment strategies. Options for refractory DM include rituximab, intravenous immunoglobulin, calcineurin inhibitors, and cyclophosphamide. Although rituximab is recommended as a first-line agent for refractory DM, it was unavailable in our country. Thus, we opted for cyclosporine, which successfully controlled myositis and led to complete skin lesion resolution [7].

The estimated malignancy prevalence in adult DM patients is 20%, peaking within the first year of diagnosis [16] but persisting beyond five years, as reported in a meta-analysis by Qiang et al. [20]. Given this risk, continued age-appropriate and symptom-targeted malignancy screening and annual whole-body imaging are planned for long-term surveillance.

Conclusion

This case highlights the limitations of EULAR/ACR classification criteria for adult and juvenile idiopathic inflammatory myopathies, particularly in diagnosing CADM. The absence of standardized treatment algorithms poses a significant therapeutic challenge. Additionally, we underscore the possible progression of CADM to CDM, noting that muscle involvement may develop without a corresponding increase in muscle enzyme levels, which are commonly used for disease monitoring. Finally, our case confirms the effectiveness of cyclosporine in a patient who failed to respond adequately to multiple prior treatment modalities.

Abbreviations

DM – Dermatomyositis
CADM – Clinically amyopathic dermatomyositis
CDM – Classical dermatomyositis

EULAR/ACR – European Alliance of Associations for Rheumatology/American College of Rheumatology
CDASI – Cutaneous Dermatomyositis Disease Area and Severity Index

EULAR/ACR – European Alliance of Associations for Rheumatology/American College of Rheumatology
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BULOZNI PEMFIGOID KAO NEŽELJENI EFEKAT TERAPIJE NIVOLUMABOM – PRIKAZ SLUČAJA

BULLOUS PEMPHIGOID AS AN ADVERSE EVENT OF CHECKPOINT INHIBITOR THERAPY – CASE REPORT

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Sažetak

Inhibitori kontrolnih tačaka, anti-PD-1 antitelo nivolumab i anti-CTLA-4 antitelo ipilimumab, revolucionirali su lečenje raka u protekloj deceniji. Oslobođanjem kočnica imunskog sistema, dovode do aktivacije antitumorskog ćelijskog imuniteta, što dovodi do dugotrajnih odgovora kod nekoliko vrsta tumora, uključujući metastatski melanom, karcinom renalnih ćelija, skvamozni i metastatski nesitnoćelijski karcinom pluća. Međutim, nespecifična aktivacija imunskog sistema često dovodi do neželjenih efekata koji mogu zahvatiti sve organske sisteme, ali najčešće kožu. Najčešće kutane neželjene reakcije su makulopapularni osip i svrab. Retke, ali ozbiljne, po život opasne reakcije, poput buloznih dermatozna, uključujući bulozni pemfigoid, takođe se mogu javiti. Predstavljamo slučaj buloznog pemfigoida tokom lečenja metastatskog melanoma nivolumabom i ipilimumabom. Prepoznavanje i rano lečenje imunski posredovanih neželjenih efekata od suštinskog su značaja za ograničavanje trajanja i težine neželjenih efekata i za sprečavanje prekida kontinuiteta lečenja, te uspostavljanja i održavanja efikasnosti terapije.

Ključne reči: bulozni pemfigoid; neželjeni efekti i neželjene reakcije na lekove; inhibitori kontrolnih tačaka; nivolumab; ipilimumab; melanom; metastaze

Abstract

Checkpoint inhibitors, such as the anti-PD-1 antibody nivolumab and the anti-CTLA-4 antibody ipilimumab, have revolutionized cancer treatment over the past decade. By releasing immune checkpoints, they enhance anti-tumor cellular immunity and have shown durable responses in several malignancies, including metastatic melanoma, renal cell carcinoma, and both squamous and non-squamous non-small-cell lung cancer. However, the non-specific activation of the immune system frequently leads to immune-related adverse events, which may affect any organ system, most commonly the skin. The most frequent cutaneous adverse events are maculopapular rash and pruritus, while rare but severe life-threatening toxicities, such as blistering diseases like bullous pemphigoid, may also occur. We present a case of bullous pemphigoid in a patient treated with combination of nivolumab and ipilimumab for metastatic melanoma. Early recognition and prompt management of immune-related adverse effects are critical to minimizing their severity and duration, ensuring treatment adherence, and preserving the therapeutic efficacy of immune checkpoint inhibitors.

Key words: Pemphigoid, Bullous; Drug-Related Side Effects and Adverse Reactions; Immune Checkpoint Inhibitors; Nivolumab; Ipilimumab; Melanoma; Neoplasm Metastasis

Uvod

Nivolumab je imunoglobulin G4 (IgG4) inhibitor kontrolne tačke antitelo koje prekida inte-

Introduction

Nivolumab is the first-in-human immunoglobulin G4 (IgG4) monoclonal antibody

rakciju PD-1 receptora sa njegovim ligandima PD-L1 i PD-L2, čime se aktivira ćelijski imunski odgovor (1). Ipilimumab je humani imunoglobulin G1 (IgG1) inhibitor kontrolne tačke antitelo koje inhibira citotoksični T-limfocitni antigen-4 (CTLA-4), tako blokirajući inhibitorne signale poreklom od efektorskih T-ćelija, dopuštajući kostimulatornu signalizaciju i generisanje T-ćelijskog antitumorskog odgovora [2]. Oba leka su odobrena za lečenje melanoma, karcinoma renalnih ćelija, skvamoznog karcinoma pluća i metastatskog nemikrocelularnog karcinoma pluća. Međutim, imunoterapija može dovesti i do imunske intolerancije i izazvati imunski posredovane neželjene reakcije (engl. immune-related adverse events – irAE) kroz nespecifičnu aktivaciju imunskog sistema, koje se mogu javiti u bilo kom trenutku: na početku, tokom terapije ili nakon prekida terapije. Najčešće su kožne irAE (makulopapulozni osip, svrab, psorijaza, lezije nalik vitiligu) koje se javljaju do 34% pacijenata na terapiji PD-1 inhibitorima, ali gotovo svi organi mogu biti zahvaćeni: gastrointestinalni trakt (kolitis, ileitis, pankreatitis, gastritis), endokrini sistem (hipofizitis, adrenalna insuficijencija, hipertireoidizam i hipotireoidizam), pluća (pneumonitis, pleuritis, granulomatoza nalik sarkoidozi), nervni sistem (encefalitis, periferna neuropatija, Gilen-Bareov (Guillain-Barré) sindrom, aseptični meningitis), jetra (hepatitis), hematološke ćelije, srce, bubrezi, oči i mišićno-skeletni sistem [3]. Većina kožnih neželjenih reakcija su blage do umerene, ali u retkim situacijama opisan je teški stepen kožne toksičnosti uključujući autoimunske bulozne bolesti i toksičnu epidermalnu nekrolizu. Bulozni pemfigoid (BP) je ozbiljna i retka neželjena reakcija na nivolumab, koja može biti opasna po život [4–6]. Bulozni pemfigoid se najčešće manifestuje bulama napetog krova preko urtikarijalnih plakova na trupu i ekstremitetima, praćenih intenzivnim svrabom. Dijagnoza se potvrđuje histopatološki, gde se uočava eozinofilna spongioza ili subepidermalno odvajanje sa eozinofilima, i putem direktne ili indirektno imunofluorescencije, gde se detektuju depoziti IgG i/ili C3 u zoni bazalne membrane [7].

Prikaz slučaja

Prikazujemo slučaj 74-godišnjeg muškarca sa melanomom IV stadijuma, nepoznatog primarnog porekla, dijagnostikovano nakon kompletne disekcije limfnih čvorova desne aksile i ekscizije supkutanog metastatskog depozita desne

targeting the programmed cell death protein 1 (PD-1) receptor. By disrupting the interaction between PD-1 and its ligands, PD-L1 and PD-L2, nivolumab reactivates the cellular immune response [1]. Ipilimumab, a human immunoglobulin G1 (IgG1) monoclonal antibody, targets cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), blocking inhibitory signals to effector T cells and enabling costimulatory signaling essential for robust antitumor T-cell activation [2]. Both agents are approved for the treatment of melanoma, renal cell carcinoma, squamous cell lung cancer, and metastatic non-small-cell lung cancer (NSCLC). While checkpoint inhibitors (ICIs) offer significant therapeutic benefits, they can also lead to immune intolerance and trigger immune-related adverse events (irAEs) due to non-specific immune activation. These adverse events may emerge early during treatment, throughout therapy, or even after discontinuation. Cutaneous irAEs are among the most common, affecting up to 34% of patients receiving PD-1 inhibitors, and include maculopapular eruption, pruritus, psoriasis, vitiligo-like lesions. However, irAEs may involve nearly any organ system, including: the gastrointestinal tract (colitis, ileitis, pancreatitis, gastritis), the endocrine system (hypophysitis, adrenal insufficiency, hyper- and hypothyroidism), lungs (pneumonitis, pleuritis, sarcoid-like granulomatosis), the nervous system (encephalitis, peripheral neuropathy, Guillain-Barré, aseptic meningitis), liver (hepatitis), hematological cells, heart, kidneys, eyes, and musculoskeletal system [3]. Although most cutaneous toxicities are mild to moderate, rare but severe dermatological complications such as autoimmune bullous diseases and toxic epidermal necrolysis have been reported. Among these, bullous pemphigoid (BP) is a rare but serious immune-mediated skin condition associated with nivolumab therapy and may be life-threatening [4–6]. BP typically presents with tense blisters on urticarial plaques, often affecting the trunk and extremities, and is commonly associated with intense pruritus. Diagnosis is based on histopathological findings of eosinophilic spongiolysis or subepidermal detachment with eosinophils, in combination with direct or indirect immunofluorescence revealing IgG and/or C3 deposits at the basement membrane zone [7].

skapularne regije. Histopatološka analiza odgovarala je metastatskom melanomu, dok je genetska analiza pokazala odsustvo BRAF V600 mutacije. Nakon CT pregleda celog tela, potvrđeni su metastatski depoziti u plućima, mozgu, desnoj parijetalnoj kosti i medijastinalnim limfnim čvorovima. Nakon postavljanja dijagnoze, od juna 2023. do februara 2024. godine, pacijent je lečen kombinovanom imunoterapijom sa četiri ciklusa nivolumaba (480 mg) i ipilimumaba (100 mg) na svake tri nedelje, nakon čega je nastavljeno sa monoterapijom nivolumabom (480 mg) na svake četiri nedelje, što je dovelo do delimične regresije prema RECIST (sistem kriterijuma koji prati odgovor tumora na terapiju, engl. Response Evaluation Criteria In Solid Tumors).

U februaru 2024. godine, sedam meseci nakon početka terapije, pacijent je upućen na Kliniku za kožne i polne bolesti zbog pojave bula praćenih svrabom, koje su se pojavile dve nedelje pre prijema. Pacijent je prijavio osip i intenzivan svrab mesec dana pre pojave bula. Kliničkim pregledom uočene su brojne velike, napete bule, ekzorijacije, kao i brojne hemoragične kruste na mestima prethodnih bula na koži trupa, ekstremiteta i glave, klasifikovanih kao gradus 3 (**Slika 1a, b, c**).

Nalaz na vidljivim sluzokožama je bio uredan. Laboratorijski nalazi su pokazali ubrzanu sedimentaciju eritrocita i povišen CRP, kao i eozinofiliju i anemijski sindrom. Urađena je biopsija kože, a direktna imunofluorescencija (DIF) pokazala je linearne, kontinuirane depozite C3 i IgG duž bazalne membrane. Histopatološka analiza je pokazala subepidermalnu bulu i površinski dermalni infiltrat sastavljen od limfocita, histiocita i eozinofila (**Slika 2**).

Ovi nalazi su potvrdili dijagnozu BP, iza zvanog terapijom anti-PD-1 inhibitorima, koji je klasifikovan kao gradus 3 prema klasifikaciji i gradiranju dermatoloških irAE [8, 9]. Obustavljena je terapija nivolumabom, a započeta je intravenska kortikosteroidna terapija metilprednizonomom u dozi od 40 mg (0,5 mg/kg telesne težine) uz lokalnu primenu triamcinolon-acetonid 0,01% krema dva puta dnevno. Tokom mesec dana hospitalizacije nije bilo pojave novih bula i zabeležena je regresija kožnih lezija. Nakon tri nedelje, terapija nivolumabom je nastavljena i pacijent ju je dobro podneo. Nastavljena je terapija prednizonomom u dozi od 20 mg/dan oralno sa postepenim smanjenjem doze. Pacijent je odbio dalji tretman metastatske bolesti i preminuo je dva meseca kasnije, verovatno usled progresije primarne bolesti.

Case report

We report the case of 74-year-old male diagnosed with stage IV melanoma of unknown primary origin, following complete right axillar lymph node dissection and excision of a subcutaneous metastatic deposit of the right scapular region. Histopathological analysis confirmed metastatic melanoma, and genetic testing revealed no BRAF V600 mutation. A whole-body CT scan demonstrated metastatic lesions in the lungs, brain, right parietal bone, and mediastinal lymph nodes. Following the diagnosis, the patient received combination immunotherapy consisting of nivolumab (480 mg) and ipilimumab (100 mg) administered every three weeks for four cycles, followed by nivolumab monotherapy (480 mg every four weeks) from June 2023 to February 2024. This regimen resulted in partial regression of metastatic disease, according to RECIST criteria (Response Evaluation Criteria in Solid Tumors).

In February 2024, approximately seven months after initiation immunotherapy, the patient was referred to the Department of Dermatology for evaluation of new-onset pruritic blistering eruption, which had developed two weeks prior to admission. The patient reported a preceding rash and intense pruritis one month before the appearance of blisters. Clinical examination revealed numerous large, tense bullae, excoriations, and hemorrhagic crusts at the sites of ruptured bullae, affecting the trunk, extremities and scalp (**Figure 1a, b, c**).

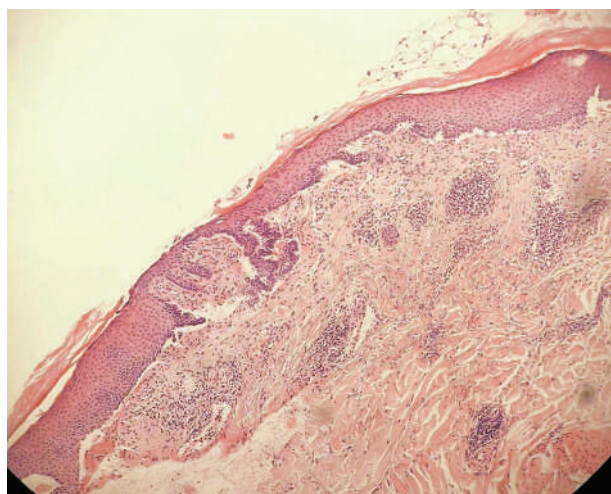
The findings were consistent with grade 3 cutaneous irAEs. Notably, the mucous membranes were not involved. Laboratory findings revealed elevated erythrocyte sedimentation rate (ESR) and elevated C-reactive protein (CRP), eosinophilia and, the anemic syndrome. A skin biopsy was performed. Direct immunofluorescence (DIF) demonstrated linear, continuous deposition of C3 and IgG along the basement membrane zone, while histopathology revealed a subepidermal blister with a superficial dermal infiltrate composed of lymphocytes, histiocytes and eosinophils (**Figure 2**).

These findings confirmed the diagnosis of BP induced by anti-PD1 inhibitor therapy, classified as grade 3, in accordance with the classification and grading of dermatologic



Slika 1. Klinička slika buloznog pemfigoida sa napetim bulama i hemoragičnim krustama na trupu (a), gornjim ekstremitetima (b) i donjim ekstremitetima (c)

Figure 1. Clinical image of bullous pemphigoid showing tense bullae and hemorrhagic crusts on the trunk (a), upper extremities (b), and lower extremities (c)



Slika 2. Hematoksilin-eozin bojenje prikazuje sub-epidermalnu bulu sa površinskim dermalnim infiltratom sastavljenim od limfocita, histiocita i eozinofila
Figure 2. Haematoxylin-eosin stain showing a sub-epidermal blister with superficial dermal infiltrate composed of lymphocytes, histiocytes, and eosinophils

irAE [8, 9]. Immunotherapy with nivolumab was temporarily suspended, and the patient was started on intravenous methylprednisolone (40 mg daily; 0.5 mg/kg body weight), along with topical triamcinolone acetonide 0.01% cream applied twice daily. During a one-month inpatient stay, no new lesions appeared, and regression of existing lesions was observed. After three weeks, nivolumab therapy was resumed and was well tolerated. The patient was discharged on oral prednisone 20 mg/day, tapered gradually. However, the patient refused further oncological treatment, and unfortunately, died two months later, likely due to progression of the underlying malignancy.

Discussion

Bullous pemphigoid (BP) is a rare but severe immune-related adverse event (irAE) associated with immune checkpoint inhibitors (ICIs), particularly those targeting PD-1/PD-L1. While a few cases of BP have been linked to anti-CTLA-4 therapy (e.g., ipilimu-

Diskusija

Bulozni pemfigoid je retka i ozbiljna neželjena reakcija na imunoterapiju. Do sada je prijavljeno nekoliko slučajeva BP-a povezanih sa PD-1/PD-L1 inhibitorima, za razliku od slučajeva povezanih sa anti-CTLA-4 inhibitorom ipilimumabom, što sugeriše da je ovaj irAE specifičniji za anti-PD-1/PD-L1 terapiju. Međutim, kada se nivolumab i ipilimumab koriste u kombinaciji, primećena je povećana stopa kutane toksičnosti u poređenju sa kutanom toksičnošću bilo kojeg od ovih lekova kada se primenjuju pojedinačno [10]. Medijana vremena do pojave BP-a bila je 6–8 meseci (31 nedelja) nakon primene nivolumaba u prijavljenim slučajevima, što je takođe vreme koje je bilo potrebno da se BP razvije kod našeg pacijenta. Manji broj pacijenata razvio je BP nakon 1–1,5 godina od početka primene nivolumaba [4, 11, 12]. Kod jednog slučaja je prijavljen razvoj BP-a tri godine nakon početka terapije, što predstavlja najkasniji opisani početak BP-a u literaturi. U slučajevima gde postoji značajno kašnjenje između početka terapije i pojave BP-a, uvek treba razmotriti moguću povezanost [13].

Prema retrospektivnoj analizi i podacima iz literature o BP izazvanom inhibitorima kontrolnih tačaka, muškarci češće razvijaju BP, naročito u sedmoj deceniji života, što je bio slučaj i kod našeg pacijenta [4, 14]. Klinička prezentacija BP-a može biti raznolika, što čini postavljanje dijagnoze izazovnim. Svrab je jedan od glavnih prodromalnih simptoma BP-a, koji može prethoditi razvoju bula nedeljama ili mesecima, kao u slučaju prikazanog pacijenta [11, 15]. U nekim slučajevima, svrab može biti dominantan simptom, a bule ili osip mogu se nikada ne razviti. Nažalost, svrab je takođe jedan od najčešćih blagih neželjenih događaja kod primene PD-1 inhibitora, prijavljen kod skoro trećine pacijenata.

Bolest se može dalje klasifikovati u četiri podtipa na osnovu morfologije: (1) klasični BP, karakterisan napetim vezikulama i bulama, otvorenim erozijama sa kolaretama ljuspi; (2) atipični – ekcematozni, koji se manifestuje kao ljuspasti, vlažni plakovi, sa kolaretama ljuspi i potencijalnom krustom od isušene serozne drenaže; (3) atipični – svrab bez drugog nalaza, bez jasnog osipa, ali sa linearnim erozijama usled ekskoriјacija nastalih češanjem; (4) atipični – drugi, koji može predstavljati bilo koju vrstu erupcije na koži koja ispunjava kriterijume na osnovu biopsije i laboratorijskih nalaza [16]. Stoga, u diferenciranju PD-1-indukovanog BP i niskostepenih kožnih toksičnosti, biopsija kože i potvrda dija-

ma), most reports involve anti-PD-1/PD-L1 agents, suggesting that this adverse effect is more specific to anti-PD-1/PD-L1 blockade. When used in combination, nivolumab and ipilimumab have been shown to increase the incidence of cutaneous toxicities compared to monotherapy with either agent [10]. The median time to onset of BP following nivolumab administration is reported to be 6-8 months (approximately 31 weeks), which coincides with the time of onset in our patient. However, delayed presentations are also possible, with some cases appearing after 1-1.5 years and one case reported at three years post-initiation - the most delayed onset of BP described in the literature [4, 11, 12]. Therefore, even in cases with a significant time lapse between treatment initiation and the appearance of BP, a potential relationship should be considered [13].

Retrospective analysis and literature reviews indicate that BP is more frequently observed in men, particularly in their seventh decade of life – demographics that match our case [4, 14]. Clinical presentation of BP is heterogeneous, making diagnosis challenging. Pruritus is often an early symptom, sometimes preceding blister formation by weeks to months, as was observed in our patient [11, 15]. In certain cases, pruritus may remain the sole symptom without visible blisters or rash. This is noteworthy given that pruritus is common low-grade irAE seen in up to one-third of patients receiving PD-1 inhibitors. BP can be classified into four morphological subtypes: (1) classic BP, characterized by tense vesicles and bullae, open erosions with collarettes of scale; (2) atypical-eczematous, presenting with scaly, moist plaques, with collarettes of scale and potential crust from dried serous drainage; (3) atypical-pruritus only, with no clear rash, but may show linear erosions due to scratching; (4) atypical-other, skin eruptions not falling into the previous categories but consistent with BP on biopsy or laboratory evaluation [16]. To distinguish PD-1-induced BP from low-grade cutaneous toxicity, skin biopsy and direct immunofluorescence (DIF) remain the gold standard for diagnosis [11].

The 2020 MASCC (Multinational Association of Supportive Care in Cancer) guidelines for managing severe dermatologic irAE recommend withholding ICI therapy for grade 3

gnoze BP direktnom imunofluorescencijom (DIF) predstavljaju „zlatni standard“ [11].

Preporuke Multinacionalnog udruženja za suportivnu negu u onkologiji (engl. Multinational Association of Supportive Care in Cancer) iz 2020. godine za lečenje teških dermatoloških toksičnosti izazvanih inhibitorima kontrolnih tačaka za gradus 3 (bule na > 30% površine tela uz razdvajanje slojeva kože i pridruženi bolovi ili svrab) su: prekinuti ICI terapiju, zatim započeti metilprednizolon (ili ekvivalent) u dozi 1–2 mg/kg dnevno do poboljšanja, a potom preći na prednizon (ili ekvivalent) u dozi 0,5–1 mg/kg dnevno, uz postepeno smanjenje doze tokom najmanje četiri nedelje [17]. Dugotrajna upotreba sistemskih kortikosteroida može izazvati brojne neželjene reakcije i potencijalno ugroziti efikasnost inhibitora kontrolnih tačaka, pa bi trebalo razmotriti upotrebu nesteroidnih agenasa, kao što su rituksimab (500 mg intravenski, jednom nedeljno tokom četiri nedelje) ili omalizumab (300 mg na svakih četiri nedelje). Lokalna terapija uključuje upotrebu emolijentnih masti i nelepljivih zavojica preko otvorenih erozija. Prema najnovijim izveštajima, dupilumab je uspešno off-label korišćen za lečenje irAE zavisnih od kortikosteroida, sa visokom stopom odgovora [18–20]. Potrebna su dodatna istraživanja kako bi se procenila efikasnost i dugoročna bezbednost dupilumaba. Naš pacijent je imao dobar odgovor na primenjenu terapiju, tako da druge terapijske opcije nisu razmatrane. Primena dapsona je takođe bila razmatrana, ali je bila kontraindikovana usled anemijskog sindroma. Prema prethodnim izveštajima, kod skoro 50% pacijenata imunoterapija je trajno prekinuta nakon razvoja BP [14]. Kod našeg pacijenta, imunoterapija je nastavljena uz kontinuiranu terapiju oralnim kortikosteroidima, bez pogoršanja simptoma. Međutim, pacijent je preminuo verovatno usled progresije primarne bolesti.

Zaključak

Uvođenje inhibitora kontrolnih tačaka u onkološko lečenje dovelo je do razvoja širokog spektra toksičnosti, koje ranije nisu bile prijavljene tokom standardne hemoterapije. Ove imunski posredovane nuspojave najčešće se manifestuju na koži, što ukazuje na ključnu ulogu dermatologa u zbrinjavanju ovih pacijenata. Pravovremena dijagnoza i lečenje su od suštinskog značaja kako bi se izbegli nepotrebni prekidi terapije. Terapija nesteroidnim agensima za dermatološke imunski posredovane nuspojave važna je kako se ne bi kompromitovala efikasnost inhibitora kontrolnih tačaka.

reactions (i.e., blisters >30% BSA, with sloughing and significant pain or pruritus), followed by initiating methylprednisone (or equivalent) 1-2 mg/kg/day, transitioning to prednisone (or equivalent) 0.5-1 mg/kg/day with a taper over at least four weeks [17]. Because prolonged systemic corticosteroid use can lead to significant side effects and may reduce the antitumor efficacy of ICIs, steroid-sparing agents such as rituximab (e.g., 500 mg IV weekly for 4 weeks) or omalizumab (e.g., 300 mg every 4 weeks) are increasingly considered. Topical treatment includes emollient ointments and non-stick bandages for erosions. More recently, dupilumab has shown promise as an off-label treatment for steroid-dependent cutaneous irAEs, with favorable response rates [18–20]. However, further studies are needed to validate its efficacy and long-term safety of dupilumab. In our case, the patient responded well to the applied therapy, so escalation to other therapies was not necessary. The use of dapsone was considered but contraindicated due to anemia. In about 50% of reported cases, immunotherapy is permanently discontinued following the development of BP [14]. However, in our patient, ICI therapy was continued with concurrent corticosteroids, without exacerbation of symptoms. Unfortunately, the patient later succumbed, likely due to progression of the primary malignancy.

Conclusion

The introduction of immune checkpoint inhibitors has significantly expanded the spectrum of dermatologic toxicities encountered in oncology, including immune-mediated diseases such as BP. Dermatologic immune-related adverse events are among the most common and require careful monitoring and timely intervention. Accurate diagnosis and appropriate management are crucial to minimize unnecessary discontinuation of cancer therapy. Steroid-sparing agents play a key role in maintaining checkpoint inhibitor efficacy while controlling cutaneous immune-related adverse events.

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References in the text, tables and legends should be identified by Arabic numerals in parentheses. Number references consecutively in the order in which they are first mentioned in the text. The Vancouver System of referencing should be used. List each author's last name and initials; full first names are not included. List all authors, but if the number exceeds six, give the first six followed by „et al.” National journals, which are not indexed in Index Medicus, should be abbreviated according to the style in the List of Abbreviated Titles of Yugoslav Serial Publications available on <http://vbsw.vbs.rs>. For further information please visit www.ICMJE.org.

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5. Additional Information

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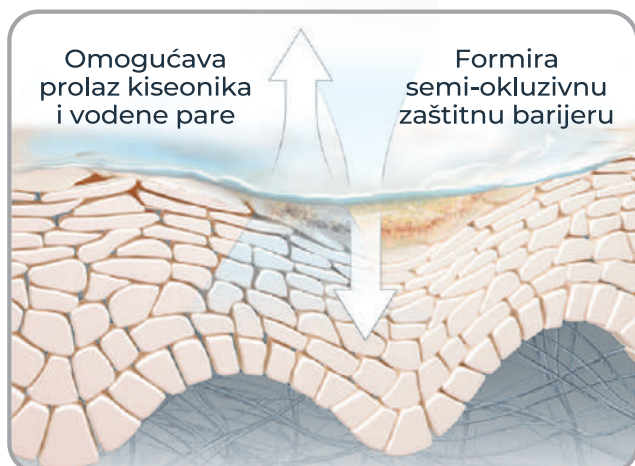
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[1] The low prevalence of allergic contact dermatitis using a petrolatum ointment containing lanolin alcohol, JDD, Oct 2019 [2] AV Rawlings et al., A review on the extensive skin benefits of mineral oils, International Journal of cosmetic science, 2012, 34, 511-518 [3] Draelos et al, Treatment of minor wounds from dermatologic procedures: A comparison of 3 topical wound care ointments using a laser wound model, JAAD supplement March 2011, Vol 64, No

