

AKNEIFORMNA ERUPCIJA IZAZVANA VEDOLIZUMABOM – PRIKAZ SLUČAJA

ACNEIFORM ERUPTION INDUCED BY VEDOLIZUMAB – A CASE REPORT

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Sažetak

Lekovi mogu dovesti do nastanka različitih neželjenih reakcija, uključujući i kožne promene. Razvoj biološke terapije za lečenje inflamatornih, onkoloških i autoimunskih bolesti nosi sa sobom rizik za pojavu novih kožnih neželjenih reakcija. Vedolizumab je humanizovano monoklonsko antitelo koje se vezuje za $\alpha 4\beta 7$ integrin na T-helper limfocitima, selektivno delujući u digestivnom traktu. Koristi se u terapiji ulceroznog kolitisa i Kronove bolesti. Paradoksalno, akne mogu biti izazvane ili pogoršane primenom vedolizumaba. Prikazujemo pacijenta koji je razvio diseminovane eritemne papule i pustule na licu, vratu i grudnom košu tokom terapije vedolizumabom.

Ključne reči: akne; humanizovano monoklonsko antitelo; biološka terapija; neželjene reakcije na lekove; ishod lečenja

Abstract

Medications may induce a wide range of adverse effects, including various cutaneous manifestations. The increasing use of biological therapies in the treatment of inflammatory, oncological, and autoimmune diseases has been associated with the emergence of novel skin reactions. Vedolizumab is a humanized monoclonal antibody that blocks the $\alpha 4\beta 7$ integrin on T-helper lymphocytes, acting selectively in the gastrointestinal tract. It is widely used in the treatment of ulcerative colitis and Crohn's disease. Paradoxically, acne can be triggered or exacerbated by the use of vedolizumab. We report a patient who developed disseminated erythematous papules and pustules on the face, neck, and chest during vedolizumab therapy.

Key words: Acneiform Eruptions; Antibodies, Monoclonal, Humanized; Biological Therapy; Drug-Related Side Effects and Adverse Reactions; Treatment Outcome

Uvod

Lekovi mogu dovesti do nastanka različitih neželjenih reakcija, među kojima su i kožne promene. Neželjene kožne reakcije obično nisu teške, mada u retkim slučajevima mogu biti opasne po život [1]. Razvoj biološke terapije za lečenje inflamatornih, onkoloških i autoimunskih bolesti nosi sa sobom rizik za pojavu novih neželjenih reakcija. Biološka terapija podrazumeva primenu monoklonskih antitela ili fuzionih proteina usmerenih protiv specifičnih trigera – citokina ili drugih molekula uključenih u patogenezu bolesti, čime se

Introduction

Medications may induce a wide range of adverse effects, including various cutaneous manifestations. Adverse cutaneous reactions are usually not severe, however, in rare cases they can be life-threatening [1]. The development of biological therapy for the treatment of inflammatory, oncological and autoimmune diseases carries the risk of new adverse reactions. Biological therapy involves the use of monoclonal antibodies or fusion proteins directed against specific triggers - cytokines or other molecules involved in the pathogenesis of the disease, thus blocking

blokira njihovo dejstvo [2]. Ulcerozni kolitis je hronična, recidivantna inflamatorna bolest creva sa značajnim morbiditetom i smanjenjem kvaliteta života [3]. Etiologija bolesti je i dalje nepoznata. Bolest obično počinje u rektumu i širi se proksimalno, zahvatajući sluzokožu debelog creva. U terapiji se, pored standardnih lekova poput kortikosteroida i imunosupresiva, primenjuje i biološka terapija [4]. Vedolizumab je humanizovano monoklonsko antitelo, koje se vezuje za $\alpha 4\beta 7$ integrin na T-helper limfocitima i selektivno deluje u gastrointestinalnom traktu [5]. Indikovano je za lečenje ulceroznog kolitisa i Kronove bolesti [5]. Iako je dizajniran kao dobro selektivni lek sa povoljnim bezbednosnim profilom, u retkim slučajevima njegova primena može biti povezana sa pojavom ili pogoršanjem akni, što predstavlja paradoksalnu kožnu neželjenu reakciju. Prikazujemo slučaj pacijenta sa akneiformnom erupcijom nastalom tokom terapije vedolizumabom.

Prikaz slučaja

Muškarac starosti 26 godina upućen je u našu dermatološku kliniku zbog promena na koži lica, vrata i grudnog koša unazad tri meseca. Pacijentu je dijagnostikovano ulcerozni kolitis 2018. godine a na biološkoj terapiji je vedolizumabom poslednjih devet meseci. Prethodno je primao infliksimab i adalimumab, koji su obustavljeni zbog neefikasnosti. Kožne promene su se pojavile 5-6 meseci nakon započinjanja terapije vedolizumabom. Pri dermatološkom pregledu, uočeno je prisustvo eritema lica, diseminovanih papula i pustula na koži lica, vrata i grudnog koša, mestimično prekrivenih žućkastim krustama (**Slika 1 A, B**). Pacijent je bio afebrilan i bez subjektivnih tegoba. Na osnovu kliničkog pregleda postavljena je dijagnoza akneiformne erupcije. Pacijent je lečen sistemskom i lokalnom antibiotikom terapijom (azitromicin 500mg per os triput nedeljno i sol. eritromicin 2%) i kratkotrajnom sistemskom kortikosteroidnom terapijom (prednizon). Gastroenterolog je konsultovan zbog procene uticaja antibiotika na osnovnu inflamatornu bolest creva. Zbog pojave akneiformnih promena, kao i neefikasnosti same biološke terapije, vedolizumab je obustavljen iz dalje terapije. Nakon dve nedelje od primenjene terapije dolazi do postepenog povlačenja promena (**Slika 2 A, B**) sa kompletnim povlačenjem nakon četiri nedelje od početka

their action [2]. Ulcerative colitis is a chronic, relapsing inflammatory bowel disease associated with significant morbidity and reduced quality of life [3]. The etiology of the disease remains unknown. The disease usually begins in the rectum and spreads proximally, involving the mucosa of the large intestine. In addition to standard treatments such as corticosteroids and immunosuppressive agents, biological therapy is also used in disease management [4]. Vedolizumab is a humanized monoclonal antibody that binds to the $\alpha 4\beta 7$ integrin on T-helper lymphocytes and acts selectively in the gastrointestinal tract [5]. It is used in the treatment of ulcerative colitis and Crohn's disease [5]. Although it was designed as a gut-selective drug with a favorable safety profile, in rare cases its use may be associated with the development or worsening of acne. In this paper, we present the case of a patient with an acneiform eruption during vedolizumab therapy.

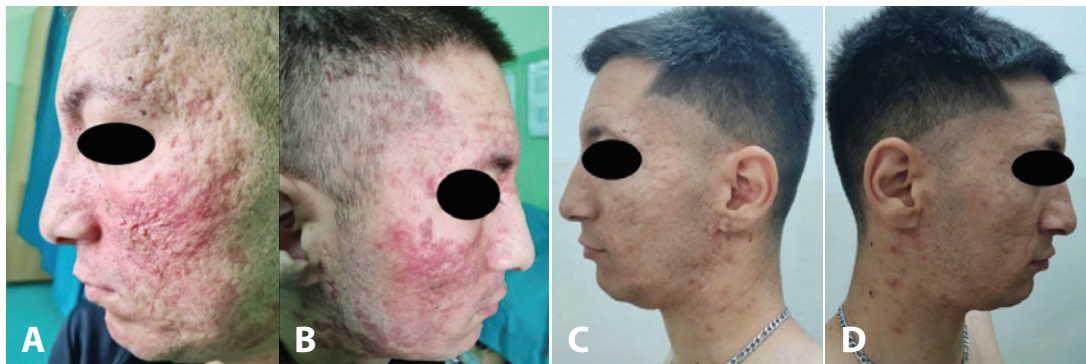
Case Report

A 26-year-old male was referred to our dermatology clinic with a three-month history of skin lesions involving the face, neck, and chest. He had been diagnosed with ulcerative colitis in 2018 and had been receiving biological therapy with vedolizumab for the last 9 months. Prior treatments included infliximab and adalimumab, both of which were discontinued due to lack of efficacy. The cutaneous lesions appeared approximately 5–6 months after initiation of vedolizumab therapy. Dermatological examination revealed facial erythema, disseminated papules and pustules on the skin of the face, neck and chest, partially covered with yellowish crusts (**Figure 1 A, B**). The patient was afebrile, without symptoms. Based on the clinical presentation alone, a diagnosis of acneiform eruption was established. The patient was treated with systemic and topical antibiotic therapy (azithromycin 500 mg orally three times weekly and erythromycin 2% solution), along with short-term systemic corticosteroid therapy (prednisone). A gastroenterologist was consulted to evaluate the potential impact of antibiotic treatment on the underlying inflammatory bowel disease. Additionally, vedolizumab was discontinued due to the development of acneiform eruption and the lack of therapeutic efficacy. After two weeks of therapy, gradual regression of the skin lesions was observed (**Figure 2 A, B**) while complete resolution of the skin lesions was achieved by the fourth week of therapy (**Fig-**



Slika 1 (A, B). Klinički prikaz vedolizumab-indukovane akneiformne erupcije

Figure 1 (A, B). Initial clinical presentation of vedolizumab-induced acneiform eruption



Slika 2. Regresija promena posle 2 (A,B) i 4 nedelje (C,D) od terapije

Figure 2. Regression of skin lesions after 2 (A,B) and 4 weeks (C,D) of therapy

terapije (**Slika 2 C, D**). Pacijent je podvrgnut hirurškom lečenju kolektomiji sa ilestomijom zbog progresije ulceroznog kolitisa.

ure 2 C, D). The patient subsequently underwent surgical treatment consisting of colectomy with ileostomy due to progression of ulcerative colitis.

Diskusija

Vedolizumab je humanizovano monoklonosko IgG1 antitelo koje selektivno inhibira interakciju između integrina $\alpha 4 \beta 7$, eksprimiranog na površini T-limfocita, i njegovog liganda MAdCAM-1 (mucosal addressin cell adhesion molecule-1).

Discussion

Vedolizumab is a humanized monoclonal IgG1 antibody that selectively inhibits the interaction between integrin $\alpha 4 \beta 7$, expressed on the surface of T-lymphocytes, and its ligand MAdCAM-1 (mucosal addressin cell adhesion molecule-1).

molecule-1), koji je dominantno prisutan na endotelnim ćelijama krvnih sudova gastrointestinalnog trakta [6]. Ova inhibicija sprečava adheziju i transmigraciju leukocita u crevnu sluznicu, čime se postiže ciljano smanjenje inflamatornog odgovora u gastrointestinalnom traktu, bez sistemske imunosupresije. Vedolizumab je indikovano za lečenje umereno do teških formi inflamatornih bolesti creva ulceroznog kolitisa i Kronove bolesti refraktornih na standardnu terapiju [6].

U kliničkim ispitivanjima, uključujući GEMINI studije dugoročne bezbednosti, većina pacijenta imala je neželjene reakcije na lek koje su uglavnom blage do umerene težine [7-10]. Dermatološke neželjene reakcije, poput akni i akneiformnih erupcija, retko su opisane u dostupnoj literaturi, što ukazuje na njihovu nisku učestalost, ali i na njihovu potencijalnu nedovoljnu prepoznatljivost ili prijavljivanje u kliničkoj praksi. U tom kontekstu, prikaz ovakvih neželjenih reakcija može doprineti boljem razumevanju bezbednosnog profila vedolizumaba, posebno imajući u vidu njegovu sve širu primenu.

Pretragom dostupne literature pronađena su dva opisana slučaja akneiformnih erupcija koje su, slično kao kod našeg pacijenta, pokazale dobar terapijski odgovor na antibiotsku terapiju [11,12]. Magdaleno-Tapia J. i saradnici [11] opisali su pacijentkinju sa akneiformnom erupcijom kod koje je postignut dobar odgovor na sistemska primenu doksiciklina u kombinaciji sa lokalnim ivermektinom. Uprkos prisutnoj erupciji, terapija vedolizumabom je nastavljena zbog dobre kontrole osnovne bolesti. U prikazu Gilhulija (Gilhooley E.) i saradnika [12], pacijent sa nodulocističnim aknama ostvario je dobar odgovor na sistemska terapiju limesiklinom, nakon čega je terapija vedolizumabom nastavljena uz dobru toleranciju. Nasuprot tome, Blankenship (Blankenship K.) i saradnici [13] prikazali su pacijenta sa fulminantnim aknama kod koga nije postignut zadovoljavajući odgovor na sistemska antibiotska terapiju (trimetoprim-sulfametoksazol i amoksicilin-klavulonska kiselina), dok je dobar odgovor zabeležen nakon dugotrajne primene sistemskih kortikosteroida i retinoida (izotretinoin). Terapija vedolizumabom je prekinuta zbog razvoja teških i brzo progresivnih fulminantnih akni, koje nisu reagovala na standardnu antibiotsku terapiju i pokazivale su jasno vremensko pogoršanje u odnosu na ponovljene infuzije leka [13].

hesion molecule-1), which is predominantly present on the endothelial cells of blood vessels of the gastrointestinal tract [6]. This inhibition prevents the adhesion and transmigration of leukocytes into the intestinal mucosa, thereby achieving a targeted reduction in the inflammatory response in the gastrointestinal tract, without systemic immunosuppression. Vedolizumab is indicated for the treatment of moderate to severe forms of inflammatory bowel disease, ulcerative colitis and Crohn's disease refractory to standard therapy [6].

In clinical trials, including the GEMINI long-term safety studies, most patients experienced adverse drug reactions that were generally mild to moderate in severity [7-10]. Dermatological adverse reactions, such as acne and acneiform eruptions, are rarely described in the available literature, which indicates their low frequency, but also their potential under-recognition or under-reporting in clinical practice. In this context, the presentation of such adverse reactions may contribute to a better understanding of the safety profile of vedolizumab, especially considering its increasingly widespread use.

A review of the available literature identified only two cases of acneiform eruptions that, similar to our patient, showed a good therapeutic response to antibiotic therapy [11,12]. Magdaleno-Tapia J. et al. [11] reported a patient with an acneiform eruption who had a good response to systemic doxycycline in combination with topical ivermectin. Despite the present eruption, vedolizumab therapy was continued due to good control of the underlying disease. Furthermore, in the report by Gilhooley et al. [12], a patient with nodulocystic acne achieved a favorable response to systemic therapy with lymecycline, after which vedolizumab treatment was continued with good tolerability. In contrast, Blankenship K. et al. [13] presented a patient with fulminant acne in whom a satisfactory response to systemic antibiotic therapy (trimethoprim-sulfamethoxazole and amoxicillin-clavulonic acid) was not achieved, while a good response was noted after long-term administration of systemic corticosteroids and retinoids (isotretinoin). Vedolizumab therapy was discontinued due to the development of severe and rapidly progressive fulminant acne, which did not respond to standard antibiotic therapy and showed a clear worsening over time in association with repeated infusions of the drug [13].

The patient from our report was treated with systemic and local antibiotic therapy, as well as

Naš pacijent je lečen sistemskom i lokalnom antibiotskom terapijom, kao i kratkotrajnom sistemskom primenom kortikosteroida (prednizon), uz dobar terapijski odgovor već nakon dve nedelje i postepeno povlačenje kožnih promena. Zbog nezadovoljavajućeg efekta vedolizumaba na osnovnu bolest, kao i pojave kožnih neželjenih reakcija, lek je isključen iz dalje terapije. Usled neadekvatne kontrole bolesti primenom biološke terapije, pacijent je podvrgnut totalnoj kolektomiji sa ileostomijom. Ostale moguće etiologije akni (steroidom indukovane, pogoršanje postojećih akni, kožne manifestacije inflamatorne bolesti creva ili prethodne terapije) razmotrene su, ali morfologija lezija, vremenska povezanost sa vedolizumabom i povlačenje promena nakon prekida leka ukazuju na verovatnu vedolizumab-indukovanu akneiformnu erupciju.

Pacijenti opisani u prikazima Gilhulija i saradnika [12], kao i Blankenshipa i saradnika [13], prethodno su bili lečeni inhibitorima TNF-alfa, što je bio slučaj i kod našeg pacijenta. Moguće je da je prethodna izloženost inhibitorima TNF-alfa doprinela razvoju ovih neželjenih reakcija, s obzirom da su neželjeni efekti češći kod pacijenta koji su ranije primali ovu grupu bioloških lekova [7]. Ovaj nalaz dodatno ukazuje na potrebu dermatološkog praćenja pacijenata na biološkoj terapiji, naročito onih sa prethodnom izloženošću inhibitorima TNF-alfa.

Promena puta primene leka takođe potencijalno može uticati na pojavu neželjenih kožnih reakcija. Šankar (Shankar Raj) i saradnici [14] opisali su akneiformnu erupciju kod pacijenta sa Kronovom bolešću nakon prelaske sa i. v. na s. c. primenu vedolizumaba, iako je pacijent prethodno dobro tolerisao i. v. terapiju. Ovaj slučaj ukazuje da neželjeni efekti nisu zavisni samo od samog leka, već i od razlika u farmakokinetici i formulaciji [14].

Zaključak

Neželjene kožne reakcije mogu nastati tokom primene različitih lekova, dok su akne indukovane ili pogoršane lekovima relativno retke. Sa uvođenjem novih lekova, neophodno je detaljno dobiti anamnestičke podatke radi blagovremenog prepoznavanja mogućih neželjenih efekata i pravovremenog ukidanja ili zamene terapije.

short-term systemic administration of corticosteroids (prednisone), resulting in a favorable therapeutic response within two weeks, followed by gradual resolution of the skin lesions. Due to the unsatisfactory effect of vedolizumab on the underlying disease and occurrence of cutaneous adverse reactions, the drug was excluded from further therapy. In the setting of inadequate disease control with biological therapy, the patient ultimately underwent total colectomy with ileostomy. Other possible etiologies of acne (steroid-induced, exacerbation of existing acne, skin manifestations of inflammatory bowel disease or previous therapy) were considered, but the morphology of the lesions, their association with vedolizumab, and the resolution of lesions after discontinuation of the drug suggest that the acneiform eruption is likely vedolizumab-induced.

The patients described in the reports by Gilhooly et al. [12] and Blankenship et al. [13] had previously been treated with TNF- α inhibitors, as was the case in our patient. It is possible that previous exposure to TNF- α inhibitors contributed to the development of these adverse reactions, given that adverse effects are more common in patients who previously received this group of biological drugs [7]. This finding further underscores the importance of dermatological monitoring of patients on biological therapy, especially those with previous exposure to TNF- α inhibitors.

Interestingly, the route of drug administration may influence the development of adverse cutaneous reactions. Shankar Raj et al. [14] described an acneiform eruption in a patient with Crohn's disease after switching from IV to SC administration of vedolizumab, despite previous tolerance of intravenous therapy. This case highlights that side effects are not dependent only on the drug itself, but also on differences in pharmacokinetics and formulation [14].

Conclusion

Adverse cutaneous reactions may occur with a wide range of medications; however, drug-induced or drug-exacerbated acne is relatively uncommon. With the increasing use of novel therapeutic agents, obtaining a thorough medical and pharmacological history is crucial for the timely recognition of potential adverse cutaneous effects and for the appropriate discontinuation or modification of therapy.

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