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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. Oslobađanjem 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 dermatoza, 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) ihibitor 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) ihibitor 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 (Guillian-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 indirektne 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, dijagnostikovanog 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 spongiosis or subepidermal detachment with eosinophils, in combination with direct or indirect immunofluorescence reveling 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, ekskorijacije, 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, izazvanog 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 metilprednizolonom 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 prednizonom 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

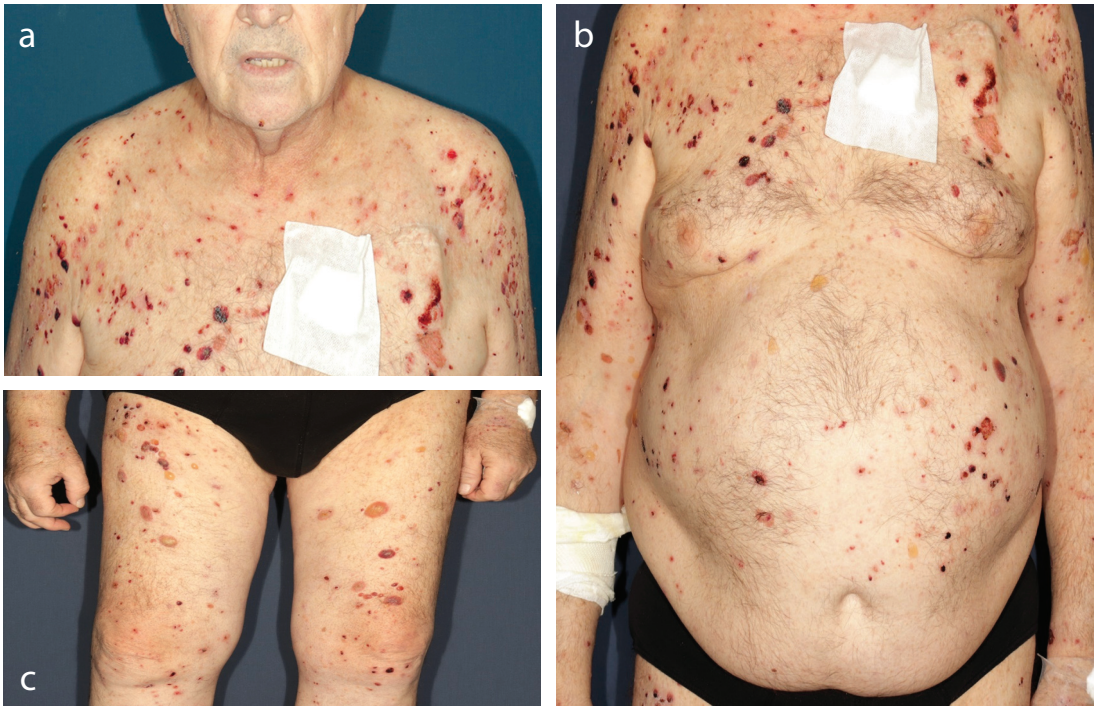
We report the case of 74-year-old male diagnosed with stage IV melanoma of unknown primary origin, following complete right axillar lymph node dissection and excision of a subcutaneous metastatic deposit of the right scapular region. Histopathological analysis confirmed metastatic melanoma, and genetic 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).**

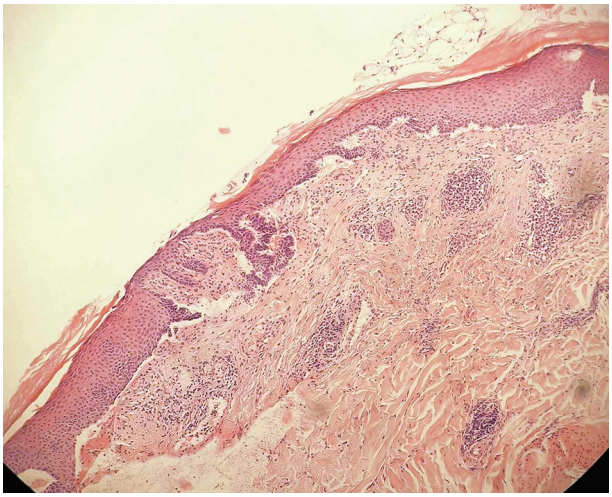
These findings confirmed the diagnosis of BP induced by anti-PD1 inhibitor therapy, classified as grade 3, in accordance with the classification and grading of dermatologic




***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 subepidermalnu bulu sa površinskim dermalnim infiltratom sastavljenim od limfocita, histiocita i eozinofila*
**Figure 2.** Haematoxylin-eosin stain showing a subepidermal 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, tampered 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 ekskorijacija 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-*mab), 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 zavoja 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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