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CASE REPORT

ERYTHEMA MULTIFORME-LIKE ERUPTION INDUCED AFTER IMMUNE CHECKPOINT INHIBITOR AND TARGET THERAPY IN A PATIENT WITH MALIGNANT MELANOMA – A CASE REPORT

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Abstract. Introduction. *Erythema multiforme is an acute polyetiological hypersensitivity reaction characterized by polymorphic rashes of the skin and the mucous membranes. The triggering factors for the disease might be viral and bacterial infections, tumors, autoimmune connective tissue diseases, drugs. Immune checkpoint inhibitors are used for the treatment of multiple oncological diseases but they often cause cutaneous immune-related adverse events. Pembrolizumab is a monoclonal antibody that blocks the programmed death 1 receptor and leads to T-cytotoxic lymphocyte activation. Vemurafenib is a BRAF inhibitor which is used for the treatment of metastatic melanomas positive for BRAF V600E mutation and blocks tumor cell proliferation. Both of these agents improve survival of melanoma patients, but the modified immune condition often results in severe side effects.* ***Case presentation.*** *We report a case of a 77-year-old male patient who developed severe erythema multiforme-like eruption associated with Vemurafenib target therapy and Pembrolizumab immunotherapy for metastatic malignant melanoma.* ***Conclusion.*** *Immune checkpoint inhibitors and target therapy prolong the patient's life, resulting in significantly improved patient survival but various immune related cutaneous adverse reactions like erythema multiforme-like eruption or even Stevens–Johnson syndrome and toxic epidermal necrolysis can occur. Dermatologists play an important role in evaluating and managing these cutaneous toxicities. Our case presentation emphasizes the role of physicians in the follow-up of patients with malignant melanoma who must carefully observe general and dermatological status during the melanoma management.*

Key words: *erythema multiforme-like eruption, malignant melanoma, immunotherapy, target therapy, case report*

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INTRODUCTION

Erythema multiforme (EM) is an acute polyetiological hypersensitivity reaction characterized by polymorphic rashes of the skin and the mucous membranes. The triggering factors for the disease are viral and bacterial infections, oncological and autoimmune connective tissue diseases, drugs. Immune checkpoint inhibitors (ICIs) nowadays are key drugs that lead to promotion of anti-tumor activity by the patient's immune system. They are approved for the treatment of many solid tumors – malignant melanoma, merkel cell carcinoma, head and neck squamous cell carcinoma, urothelial carcinoma, renal cell carcinoma, lung and gastrointestinal cancers [1]. The modern therapeutic strategies against metastatic malignant melanoma are presented by target therapy and ICIs. Vemurafenib is a BRAF inhibitor that blocks the tumor cell proliferation and is used for the treatment of BRAF V600E positive melanoma. Pembrolizumab is a monoclonal antibody which connects with the programmed death 1-receptor of the T-cytotoxic lymphocytes, inhibits its function and activates the anti-tumor immune system. Both drugs maintain anti-tumor immunity and prolong the patients' life, but can trigger immune related adverse events (irAEs) affecting multiple organs [2].

We present the case of a patient with metastatic melanoma malignum who developed erythema multiforme-like eruption after treatment with Pembrolizumab and Vemurafenib.

CASE REPORT/CASE PRESENTATION

We present the case of a 77-year-old man who was diagnosed with cutaneous malignant melanoma of the right thoracic wall. A sentinel lymph node biopsy was performed and micro-metastases with positive BRAF V600E mutation in one of the pathologically enlarged lymph nodes, were found. The disease was staged T3aN1aM0, Stage IIIA and therapy with Interferone Alfa-2a injection 3 mln UI three times weekly s.c. was initiated. For 18 months stable course of the disease was achieved.

Two years later metastases in the right gluteus minimus and left tibialis posterior muscles were found using Positron Emission Tomography/Computer Tomography (PET/CT). According to the therapeutic guideline Interferone therapy was stopped and Pembrolizumab immunotherapy 140 mg (2 mg/kg body weight) every 21 days was initiated. After six treatment cycles new metastases were observed – in the left rectus femoris and vastus lateralis muscles.

The immunotherapy was switched to target therapy with Vemurafenib tablets 240 mg in daily dosage 960 mg (480 mg twice per day). Three days after the beginning of the last therapy generalized exanthema of the body appeared and the patient was admitted to the Department of Dermatology and Venereology. The rash first appeared on the extensor surfaces of the upper limbs and then affected the trunk. There were no pathological changes in the somatic status. The pathological skin changes affected symmetri-

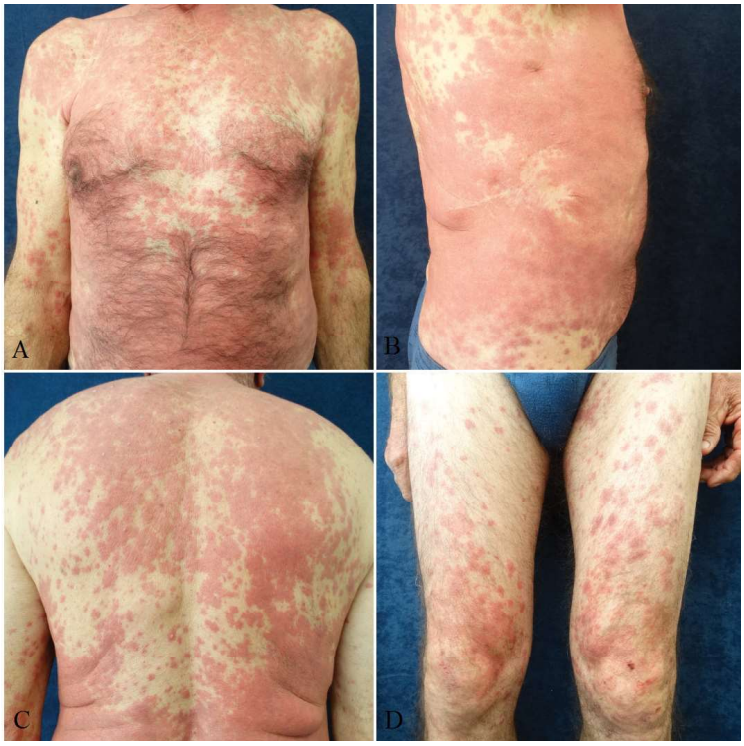

Fig. 1A-D. Multiple erythematous maculopapular and annular lesions with central area of hemorrhage coalescing on the trunk, upper and lower extremities. (A) Postlesional cicatrix on the right thoracic wall

cally the face, neck, trunk and the extensor surfaces of the upper and lower extremities. They were presented by multiple erythematous macules, urticarial and annular lesions with central area of hemorrhage and vesicles, surrounded by pale region. The lesions coalesced on the trunk as shown in Fig. 1 A-D.

A few erosive lesions in the mucous membrane of the mouth were found. The routine blood count, biochemistry and urine analysis were within the reference ranges, except for high erythrocyte sedimentation rate (ESR), high glucose level, high leukocyte count, high C-reactive protein (CRP), urea and creatinine levels. Immunological examination was within the normal range. Microbiological examinations from pathologically changed skin were negative. Histopathological examination of lesional skin showed apoptotic keratinocytes, hydropic degeneration of basal keratinocytes and intercellular edema in the epidermis, edema and moderate perivascular lymphocytic infiltrate in the papillary dermis shown in Fig. 2.

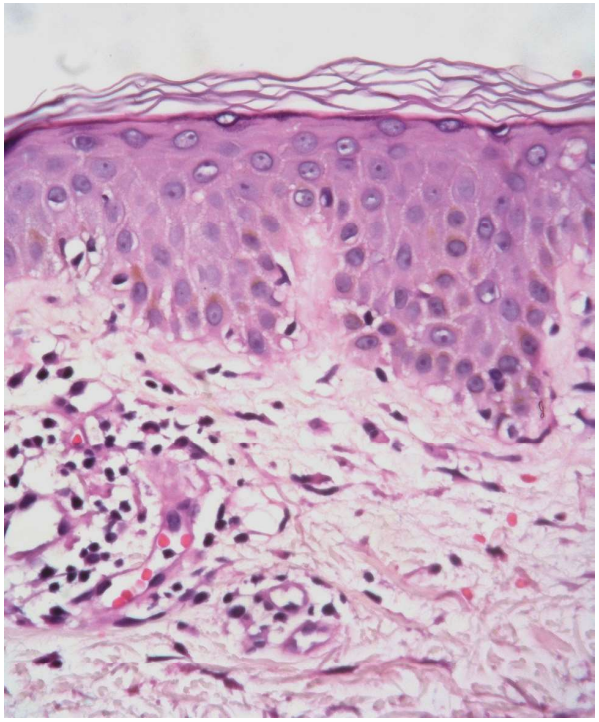

Fig. 2. Histopathological examination of the skin lesions (HEx100) Epidermis – apoptotic keratinocytes, hydropic degeneration with intercellular oedema of basal keratinocytes; Papillary dermis – oedema and moderate perivascular lymphocytic infiltrations

Consultations with nephrologist, cardiologist and endocrinologist revealed chronic renal insufficiency I degree, hypertensive hearth disease and diabetes mellitus type 1. Orthopedics consultation was scheduled, at which the presence of bone involvement was ruled out and the option of surgical treatment of the metastatic lesions – discouraged. Instead, advice for continuation of systemic anti-tumor therapy according to the guidelines was given. On the basis of the data from the medical history, general and dermatological status, laboratory and instrumental investigations, the diagnosis erythema multiforme-like reaction was established. Systemic treatment with dexamethasone sodium phosphate amp. i.m. and chloropyramine hydrochloride amp. i.v. in tapering doses was conducted. Topical treatment with methylprednisolone aceponate cream and emollients was administered. Therapy for the concomitant diseases was conducted. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The patient was discharged from the hospital in a good condition with decreased erythema and full resorption of the infiltrate demonstrated in Fig. 3 A,B. Immunotherapy with Pembrolizumab was continued. After six treatment cycles new metastatic lesions in lungs, liver and bones were found. The therapy was switched to Dabrafenib + Trametinib but unfortunately the patient developed multiple metastases in internal organs and brain and passed away one year later.

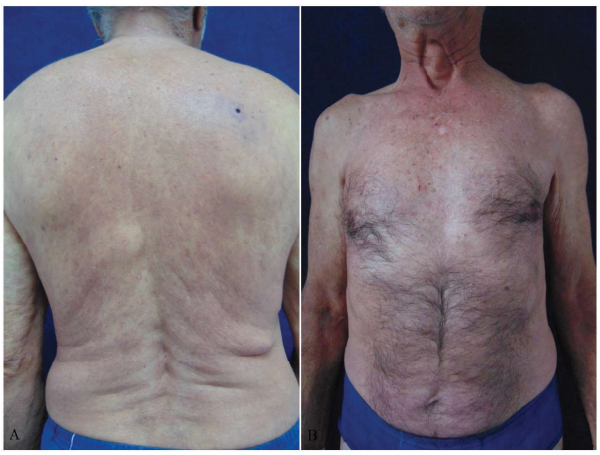

Fig. 3A,B. Decreased erythema and complete resorption of the infiltrate after the treatment

DISCUSSION

Erythema exudativum multiforme was first described by Ferdinand Ritter von Hebra in 1860 [3]. It is an acute polyetiological hypersensitivity reaction characterized by polymorphic rashes of the skin and mucous membranes. Triggering factors for the disease might be viral (herpes simplex virus types 1 and 2) and bacterial (Mycoplasma pneumonia) infections, oncological and autoimmune connective tissue diseases, drugs (anticonvulsants, sulfonamides, nonsteroidal anti-inflammatory drugs, antibiotics, etc.). When drug is the triggering factor, it is

called Erythema multiforme-like reaction, which can progress to serious reactions like Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis, if treatment is continued [4]. According to Braun Falco (2011), the disease has two clinical forms: minor and major. Erythema exudativum multiforme minor is characterized by symmetrical "target" lesions and edematous papules distributed acrally. The major form is presented by lesions of the skin and mucous membranes. EM and SJS were previously thought to be a single spectrum of one disease, but nowadays EM is a distinct entity. There are key differences. Regarding the prodromal symptoms, in SJS several days before the rash, patients suffer from flu-like condition. In EM such symptoms are also possible, but milder. In our case we did not register similar pathological changes. The general condition of patients with SJS is in a deteriorating state with anxiety and considerable pain. In contrast, EM patients are in a relatively good condition. The pathological skin changes in SJS first appear on the trunk and spread to face and limbs rapidly. On the other hand, EM starts from the limbs and spreads to the skin of the trunk. In SJS the involvement of mucous membranes is prominent and severe and at least two different mucosal membranes are affected. The patient, presented by us, had just a few erosive lesions on oral mucous membrane and was able to eat and swallow without severe pain. No other mucous membranes were affected (conjunctive, pharynx, genital, trachea or gastrointestinal). Bullous changes affect more than 10% of body surface area (BSA) in SJS. In our patient much more than 10% of BSA was affected, but the skin was not detached – there were several vesicles on the body and multiple erythematous macules, urticarial and annular lesions with central area of hemorrhage. Regarding the paraclinical examinations, in SJS there is usually leucopenia and lymphopenia. In our case we had leucocytosis and lymphocytosis, which is typical for EM. There are differences in the histopathological changes in both diseases. In SJS the histopathological report shows keratinocyte necrosis, full thickness epidermal/dermal necrosis and minimal inflammation. In EM the reports show edema of the papillary dermis and individual keratinocyte necrosis, like in our case [5, 6]. Pembrolizumab is a high-affinity, human, IgG4 monoclonal antibody that blocks the interaction of PD-1 with PD-ligand 1 between T-lymphocytes and tumor cells. This action leads to suppression of tumor cell differentiation and proliferation. The most common described side effects during treatment with Pembrolizumab are fatigue, itchy rashes, vitiligo, joint and back pain. Autoimmune reactions like immune-mediated pneumonitis, hepatitis, nephritis, etc. often occur. There are studies showing that the drug is still effective up to 12 months after therapy cessation [7]. Vemurafenib is a BRAF inhibitor, used for the treatment of metastatic melanomas positive for BRAF V600E mutation (an amino acid substitution at position 600 in BRAF protein, from valine to glutamic acid). Vemurafenib inhibits selectively the mutated BRAF V600E kinase, and reduces the signals through the aberrant mitogen-activated protein kinase (MAPK) pathway. This leads to stop in the tumor cell proliferation. Vemurafenib use is often linked to various skin reactions like keratosis pilaris-like eruption, photosensitivity, alopecia, erythema multiforme-like reaction, Stevens-Johnson syndrome, toxic epidermal necrolysis [8-10].

The ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients presents a classification defining the rash grade [11]. The Common Terminology Criteria for Adverse Events, version 5.0 determines the cutaneous toxicity as follows: a grade 1 rash covering < 10% of the body surface area (BSA) with or without symptoms; a grade 2 rash covering 10-30% of the BSA with or without symptoms affecting daily living (ADLs) or > 30% of the BSA; a grade 3 rash covering > 30% of the BSA with moderate or severe symptoms affecting ADLs; and a grade 4 rash – life-threatening consequences requiring urgent intervention.

According to Hashimoto et al., erythema multiforme-like eruption is a grade 2 adverse event [12]. They present 12 patients suffering from MM under ICIs treatment with the same irEAs. Similar to their results, in our case the development of EM-like eruption was rapid – 4 days after the start of the therapy. In their study cutaneous irAEs were most commonly associated with the anti-PD-1 antibodies (nivolumab and pembrolizumab), followed by combination of anti-PD-1 and anti-CTLA-4 therapy (nivolumab and ipilimumab).

Many case reports and original articles demonstrate the multiple cutaneous irAEs in patients under target and immunotherapy. The most common reactions are nonspecific maculopapular rash, pruritus, lichenoid reactions, which are easy-to-treat with topical emolient and corticosteroid therapy. Other frequent cutaneous adverse effects include erythema multiforme, psoriasiform reactions, bullous pemphigoid and dermatomyositis. Vitiligo-like depigmentation also occurs in patients who receive anti-PD-1 agents for melanoma [13, 14]. Severe inflammatory eruptions such as Stevens–Johnson syndrome and toxic epidermal necrolysis have also been reported. An interesting fact is that cutaneous irAEs share clinical

and histopathological features with classical inflammatory eruptions [15].

The incidence of inflammatory cutaneous eruptions after immunotherapy with anti-PD-1 and anti-CTLA-4 agents is high, affecting up to 50% of the patients [16]. Most of these events are grade 1-2. Similarly, to the case presented by Nomura et al. [17], our case is a rare description of erythema multiforme-like eruption in a 77-year-old patient with metastatic malignant melanoma, after treatment with Pembrolizumab and Vemurafenib.

CONCLUSION

Immune checkpoint inhibitors and target therapy prolong the patient's live, but various immune related cutaneous adverse reactions like erythema multiforme-like eruption or even Stevens–Johnson syndrome and toxic epidermal necrolysis can occur. Interestingly, inflammatory eruptions induced by immunotherapy and target therapy share similar clinical and histopathological features with classical inflammatory eruptions. Dermatologists play an important role in evaluating and managing these cutaneous toxicities. Our case leads to the conclusion that physicians must carefully observe general and dermatological status during the melanoma management and follow up.

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Statement of Ethics: *Ethical approval is not required for this study in accordance with local or national guidelines. In the event of case report, the Ethical committee of Medical University – Pleven, Bulgaria provides for completion written Informed concent form for publication of medical data signed by the patient and the doctor. We present written informed consent obtained from the patient for publication of the details of their medical case and any accompanying images while he was treated in Clinics of Dermatology and Venereology – Pleven, Bulgaria.*

Conflict of Interest Statement: *Authors declare no conflict of interest.*

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Data Availability Statement: *All data generated or analyzed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author.*

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