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OSIMERTINIB-INDUCED TOXIC EPIDERMAL NECROLYSIS – A CASE REPORT

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ABSTRACT

Purpose: To investigate the rare side effects of Osimertinib in a case of toxic epidermal necrosis.

Case Presentation: We report on a case of a 44-year old woman with lung adenocarcinoma harboring an EGFR-sensitizing mutation who was treated with Osimertinib as the second-line treatment. Ten days after Osimertinib initiation, a diffuse erythematous rash rapidly spread over the patient's trunk along with vesicles and purpuric macules; furthermore, she developed erythema and exfoliation on the face and trunk and severe mucositis. Toxic epidermal necrolysis (TEN) is life-threatening dermatologic adverse event, caused by a delayed-type drug hypersensitivity reaction. Although skin toxicity is common during treatment with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), Osimertinib-associated TEN is very rare.

Results: Treatment with systemic steroids and immunoglobulin as well as supportive treatment led to an improvement of her general wellbeing, followed by a remarkable recovery.

Conclusions: Although the clinical use of Osimertinib is becoming widespread, the side effects may not be fully understood. Clinicians should indeed pay more attention to the occurrence of side effects and be prepared to deal with them in timely manner.

Keywords: Osimertinib, EGFR, TEN

INTRODUCTION

Cutaneous drug eruptions are one of the most common types of adverse reaction to medications, with an overall incidence of 2–3 % in hospitalized patients [1]. Drug induced exfoliating dermatitis (ED) includes a group of rare and more severe drug hypersensitivity reactions (DHR) involving skin and mucous membranes and usually occurring from days to several weeks after drug exposure [2]. Erythema multiforme (EM), Stevens–Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) are the main clinical presentations of drug induced ED.

Osimertinib is a well-tolerated third-generation irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) currently used for advanced non-small cell lung cancer (NSCLC) harboring EGFR sensitizing (exon 19 deletions and L858R) mutations or EGFR resistant (T790M) mutation. Osimertinib is generally very well tolerated. Skin toxicity is a common toxicity; however, it is generally mild, with dry skin, acne or rash being most commonly reported (3). Toxic epidermal necrolysis (TEN) is an acute, life-threatening mucocutaneous disorder with an estimated incidence of 0.4-1.9/1,000,000

and a mortality higher than 20%-40% and is mostly drug-related (80% 95%) (4,5). It is clinically characterized by a widespread sloughing of the skin and mucosa on both external and internal surfaces. Histologically, the denuded areas show full thickness epidermal necrosis. Here we present a case of a very severe, potentially life threatening skin complication to Osimertinib.

CASE PRESENTATION

A 44-year-old woman who was previously diagnosed with stage IV NSCLC (adenocarcinoma) was admitted to our hospital in 2020 and treated with initial chemotherapy, a platinum-based regimen. The EGFR19 exon mutation was detected during molecular profiling; thus, she started taking erlotinib (150 mg once daily). No obvious diarrhea or rash occurred. In March of 2024, the patient was admitted to our hospital due to severe headache, nausea, and vomiting. Emergency head CT showed multiple lesions in the brain. Considering she was free of disease for four years; we decided to perform palliative WBI (whole-brain irradiation). Afterward, we switched her to Osimertinib (80 mg QD). On April 5th, which was exactly 10 days after Osimertinib initiation, the patient suddenly developed a widespread eruption including acne-like rash on the trunk, erythema papules on the face and lips, inside the mouth involving the oral mucosa with oral ulcer present as well as conjunctivitis on both eyes (Figure 1). Consequently, the treatment with Osimertinib was immediately discontinued. Even so, the erythema and the macular rash did not alleviate and parenteral prednisolone, antibiotic and antifungal drugs were initiated following consultation. On April 9th, four days after the initiation of prednisolone, diffuse erythema appeared, general epidermal detachment, erosion and loose blisters developed over her entire body including the face. Affection of the mucosal tissue in the respiratory and gastrointestinal tract as well as, particularly notable eye involvement was present. (Figure 2). After consulting fellow dermatologists, the patient was diagnosed with TEN and subsequently transferred to the University Clinic of Dermatology-Skopje. In this institution, intravenous immunoglobulin (IVIg; 15 g/day) was immediately administered for 4 days. On April 23rd the overall condition of the patient greatly improved as a result of this treatment, proving to be lifesaving at the Dermatology Clinic and fourteen days after symptomatic treatment initiation. The erythematous rash on the patient's trunk disappeared and a lot of scar lesions remained with still poor condition of the mucosal tissue (Figure 3). On April 29th furthermore, skin rehabilitation process took place at our Clinic which consisted of a local dressing change, according to the dermatologist's instructions (figure 4). During this hospital stay, the clinical condition of the patient became much better and even blood biochemistry revealed previously elevated tumor markers for lung adenocarcinoma decreasing. On May 7th epidermal detachment, erosion and loose blisters on her face and trunk completely ameliorated

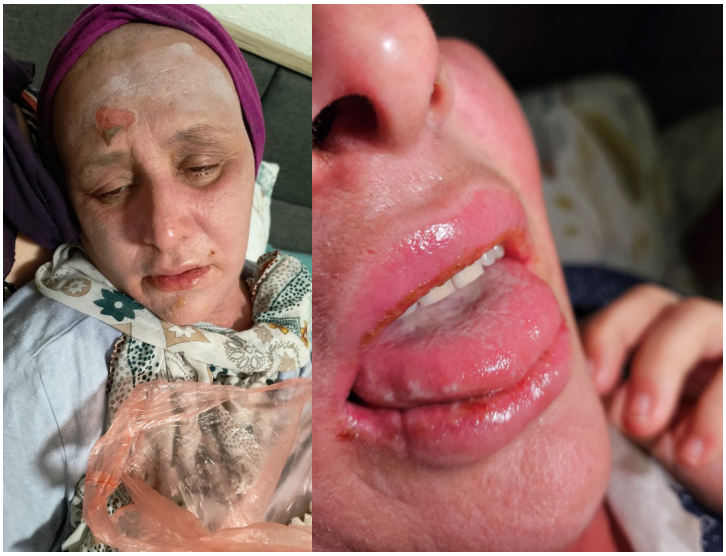

Figure 1. *First skin and mucosal manifestation of Osimertinib, April 5th*

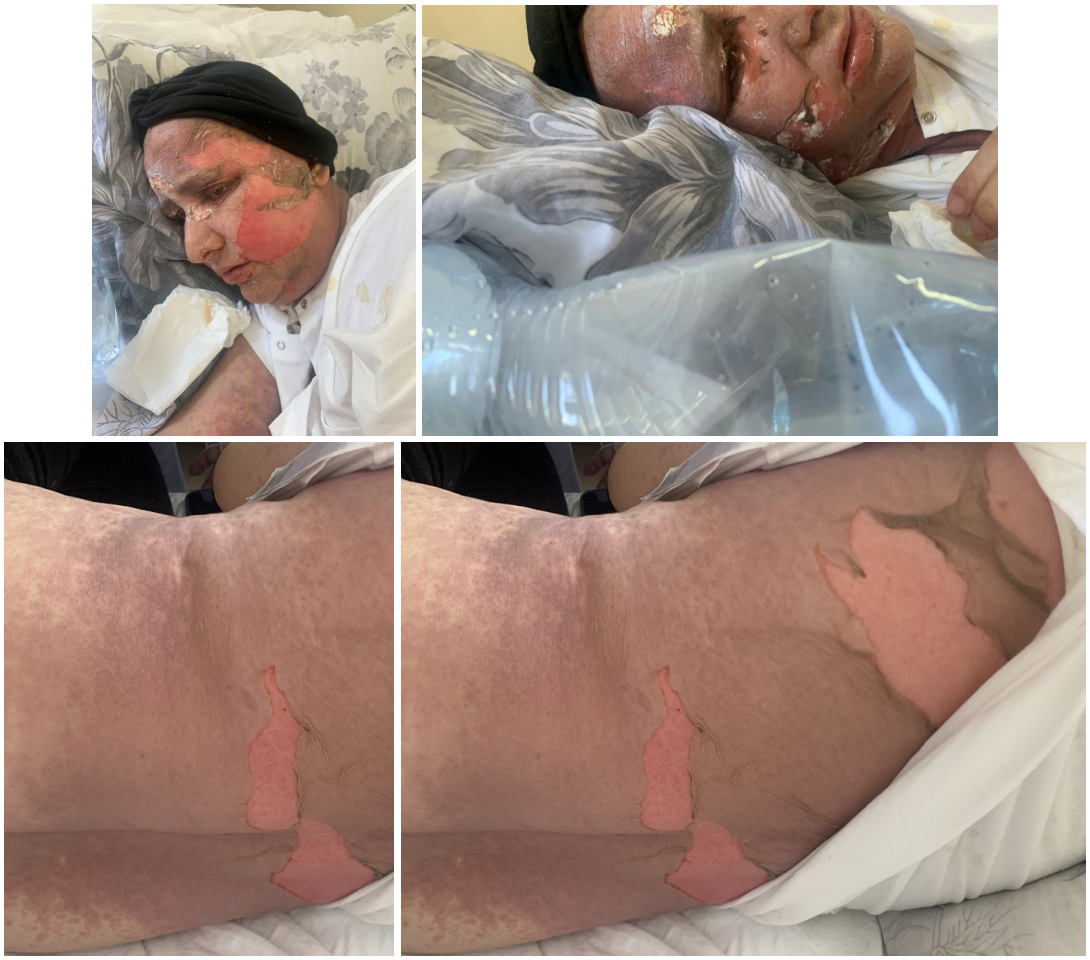

Figure 2. *April 9th, four days after the initiation of prednisolone and Osimertinib discontinuation*

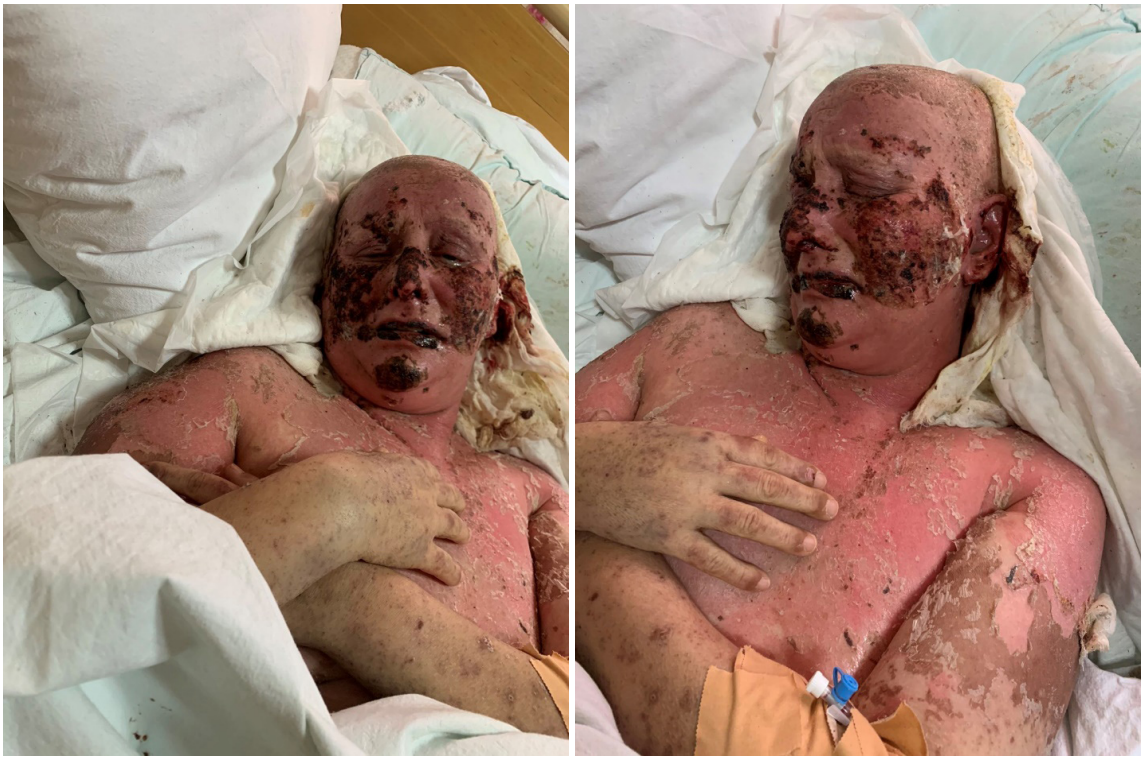

Figure 3. *April 23rd - image shows the condition of the patient during her treatment at the Dermatology Clinic, fourteen days after starting supportive treatment.*

Figure 4. *April 29th, rehabilitation process including local dressing change, day 19 post event*

Figure 5. *May 7th, general epithelialization including independent swallowing and breathing, day 27, post event*

with clearly visible epithelialization including independent and good swallowing and breathing. Problems with her eyes, especially dry eye, were the most difficult to remedy, despite basic fibroblast growth factor eye drops and tobramycin eye drops (Figure 5).

To summarize, because of the emergence of this life-threatening side effect (TEN), the drug Osimertinib was decided to be permanently discontinued with the patient starting a new protocol, this time containing immune check point inhibitor, pembrolizumab. So far we have had positive results during this five-month period of immunotherapy treatment, as the patient is in good overall condition.

DISCUSSION

The central role in the pathogenesis of the drug induced against exfoliate dermatitis (ED) is played by CD8+ lymphocytes and natural killer (NK) cells. Even though there is not a significant increase in the number of T cells infiltrating the skin in toxic epidermal necrolysis (TEN), it was elucidated that their role is crucial, even more than HLAs types. In fact, it was demonstrated that the specificity of the T cell receptor (TCR) is a prerequisite condition for the auto-immune reaction to occur. A specific T cell clonotype was present in the majority of patients with carba-

mazepine-induced SJS/TEN, and this clonotype was absent in all patients tolerant to the drug who shared the same HLA with the SJS/TEN patients [6, 7].

The introduction of a new target agent in real-world clinical practice is always challenging as new toxicities may arise as the number of patients treated increases. The particularity of our case is that this skin toxicity was induced by a novel drug, Osimertinib, initially reported as less associated with skin toxicity. Further, skin involvement had worsened after the patient was put on carbamazepine for brain metastases, and other antiepileptic drugs, making it difficult to associate Osimertinib with this clinical scenario. It is important to note that skin toxicity can prevail after discontinuation of a target agent. Osimertinib is generally a well-tolerated third generation irreversible EGFR TKI found in the FLAURA trial to improve survival in the first-line setting compared to gefitinib or erlotinib [9]. Skin toxicity is common with TKIs, with 57% of patients receiving Osimertinib experiencing grade 1-2 rash, with only 1% experiencing grade 3-4 [8]. The most common skin manifestations include acneiform rash, erythema, pruritus, skin cracking, and paronychia [9]. Dermatologic toxicity is frequently observed since EGFR TKI will also target EGFR located in skin epithelium; however, they are more frequent in first or second generation EGFR inhibitors [9]. The most common adverse events (AE) associated with Osimertinib therapy reported in the AURA3 trial, comparing Osimertinib with standard chemotherapy, included rash (34%), dry skin (23%), and paronychia (22%); grade 3 rash was rare (1%), and no grade 3 dry skin was reported. Pruritus occurred in 13% of patients with no grade 3 events [10, 11, 12].

Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe mucocutaneous manifestations. The typical clinical features are hemorrhagic erythema of the skin/mucosa blisters and severe epidermal necrolysis. Regarding the affected skin area of the patient, an exfoliation area of less than 10% of the body surface area was evident as SJS, more than 30% as TEN, and between 10% and 30% as SJS/TEN overlap. SJS and TEN are a group of delayed hypersensitivity reactions, and the incidence of TEN is generally believed to be 1.5-2.5 per million [14, 15, 16]. Drugs are the most important (95%) pathogenic factors [17], including non-steroidal anti-inflammatory and analgesic drugs, antiepileptic drugs, allopurinol, etc. [18]. In our patient with a huge body surface area and mucosal involvement, the diagnosis of TEN was made by dermatologist.

Toxic epidermal necrolysis (TEN) includes very rare life-threatening toxic skin reactions to drugs, as previously mentioned. To date, there are several cases of TEN from 2022 Rittberg et al. [18, 19, 20, 21, 22, 23]. In our patient, a biopsy was not completed to definitively rule out TEN, as she was demonstrating clinical improvement. Although a biopsy would have confirmed the underlying skin toxicity, it was felt not necessary by the dermatologist. EGFR TKI re-challenge may be reasonable when no other systemic therapy treatment options are available, if approached cautiously, as recurrence may occur even after a significant dose reduction, and it may be life threatening. In this case, the patient was successfully treated with immunotherapy, but if and when the disease progresses, we could consider re-treatment with, for example, gefitinib.

CONCLUSIONS

Skin toxicity is a very common side effect of EGFR tyrosine kinase inhibitors, more common in first or second generation TKIs, than in third generation TKIs. The most common presentation of skin toxicity in third generation EGFR TKI are grade 1-2 skin toxicities. Here we present a rare case of a severe skin toxicity -TEN to Osimertinib.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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Резиме

ОСИМЕРТИНИБ, ПРЕДИЗВИКАНА ТОКСИЧНА ЕПИДЕРМАЛНА НЕКРОЛИЗА – ПРИКАЗ НА СЛУЧАЈ

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Приказ на случај: Во трудот се презентира 44-годишна болна со аденокарцином на белите дробови, која има докажана мутација на генот EGFR. Кај неа била започната терапија со осимертиниб како второлиниски третман, по прогресија на болеста по 4-годишен успешен третман со прволиниски инхибитор на епидермалниот фактор на раст, ерлотиниб. Десет дена по започнувањето со осимертинибот, кај болната неочекувано се појави дифузен еритематозен осип, кој брзо се шириле и зафати голема површина на трупот, заедно со појава на везикули и пурпурни макули. Дополнително, кај неа се појави ексфолијација на лицето и трупот и тежок мукозитис, кој ги зафати сите слузници, а посебно настрадаа очите. Оваа состојба кај болната, означена како токсична епидермална некролиза (TEN), е дерматолошки несакан настан, опасен за животот, предизвикан поради хиперсензитивност на лек, прикажана како одложена реакција, во овој случај на лекот осимертиниб. Иако токсичноста на кожата е честа појава за време на третманот со првогенерациските тирозин киназа инхибитори на рецепторот на епидермалениот фактор на раст (EGFR-TKIs), појавата на TEN поврзана со третогенерацискиот осимертиниб е исклучително ретка.

Резултати: Третманот со системски стероиди и имуноглобулини, како и супортивен третман, доведоа до подобрување на општата состојба кај болната, проследено со извонредно закрепнување на кожните лезии.

Заклучок: Иако клиничката употреба на осимертинибот станува широко распространета, несаканите ефекти можеби не се целосно објаснети. Лекарите навистина треба да обрнат повеќе внимание на можната појава на овие ретки несакани ефекти за да бидат подготвени навремено да се справат со нив.

Клучни зборови: Осимертиниб, EGFR, TEN