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Osimertinib-induced Stevens-Johnson syndrome in a patient with EGFR T790M mutation-positive non-small cell lung cancer

To the Editor,

Stevens-Johnsons syndrome (SJS) is a rare but life-threatening cutaneous adverse reaction mainly elicited by exposure to certain drugs. Here, we present a rare case of osimertinib-induced SJS that occurred when treating lung adenocarcinoma, with the SJS being confirmed by history, histopathology, and *in vitro* drug causality assessments.

A 57-year-old lady with stage IV lung adenocarcinoma was treated with gefitinib due to epidermal growth factor receptor (EGFR) exon 19 deletion from March 2016 to April 2018. Tumor resolution was observed, but tumor relapse was observed on a follow-up computed tomography scan 2 years later. A wedge resection was performed, and EGFR T790M mutation was detected. After discussion with the patient, osimertinib 80 mg daily was administered beginning on April 3, 2018. Twenty-two days later, on April 25, 2018, she began experiencing a tingling sensation in her eyes with excessive tearing, which was soon followed by painful oral ulcers and a severe generalized itchy skin rash with central vesicles. She was referred to our dermatology clinic immediately. On examination, we noted numerous atypical target lesions with central erosions and vesicles scattered on the face, trunk, genitalia, and limbs (Fig. 1a). Mucosal involvement of multiple oral ulcers and crusted erosion on the lips were also noted. Osimertinib was thus discontinued under the clinical suspicion of SJS [1]. The patient's drug history was reviewed in detail, and we adopted the algorithm of drug causality for epidermal necrolysis (ALDEN) score [2] to determine the drug causality. Of all the drugs the patient had taken, osimertinib had the highest score (3, possible case), and no other possible culprit was found. A skin biopsy was performed, and the histopathology showed interface dermatitis with prominent basal vacuolar degeneration, numerous apoptotic keratinocytes, dermal-epidermal separation, and subepidermal vesicle formation (Fig. 1b). Serum antibodies for herpes simplex virus and *Mycoplasma pneumoniae* were all negative. The ophthalmologist confirmed the diagnosis of ocular involvement of SJS. After hospitalization, the ruptured blisters converged into patchy skin detachment with positive Nikolsky sign. The erosions gradually re-epithelialized and the mucosal ulcers gradually healed under intensive wound care and intravenous glucocorticoid treatment.

Patch tests [3] and a lymphocyte transformation test (LTT) [4] were performed 2 months later after all the lesions had healed. The patch tests of osimertinib tested in 10%, 30%, and "as is" were all negative. Nevertheless, the LTT was positive for osimertinib (stimulation index > 2) [4]. Osimertinib-induced SJS was thus confirmed.

Osimertinib is a third-generation EGFR-tyrosine kinase inhibitor (TKI) approved by the U.S. Food and Drug Administration for the treatment of metastatic, EGFR T790M mutation-positive non-small cell lung cancer with superior efficacy, together with a good tolerance and safety profile compared to standard EGFR-TKIs [5]. Dermatologic adverse events (dAE) resulting from its use, including rash, xerosis, pruritus, and paronychia, are less severe and less frequent than those resulting from first- and second-generation EGFR-TKIs [6]. Among the rare dAEs of EGFR-TKIs or EGFR inhibitors, SJS, also known as toxic epidermal necrolysis (TEN) in severe variants, is one of the most devastating, requiring for medication cessation, and has been reported to have resulted from treatment with gefitinib, cetuximab and afatinib [7–9]. SJS/TEN is characterized by acute and progressive painful lesions of the skin and mucous membranes that develop into blisters, erosions, and detachment of the epidermis with constitutional symptoms [1]. Drug exposure is the most common etiology, and SJS/TEN is recognized as a delayed drug hypersensitivity reaction with a median latent period of 21 days after administration [1]. The underlying mechanism of EGFR inhibitors, which can enhance inflammatory responses and decrease the survival of epithelial cells, may also contribute to the development of SJS/TEN [10]. The identification of the culprit drug is crucial; however, the different modalities for such identification, including the ALDEN score, *in vivo* patch test, and *in vitro* LTT, all have limitations [2–4]. Therefore, the integration of multiple tests enhances the diagnostic accuracy and helps to better determine the drug causality, especially in cancer patients with simultaneous exposure to multiple drugs or exposure to new or orphan medications [2–4]. Osimertinib-induced SJS was first reported in July 2018 under clinical suspicion [11]. Our case is the first case with confirmed drug causality tests. In conclusion, although osimertinib is associated with less severe and less frequent dAEs, severe cutaneous drug reactions, including SJS, are possible, and any such reactions warrant early clinical recognition, prompt medication discontinuation, and further drug causality testing carried out for confirmation.

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Disclosures

None declared

Conflicts of interest

We declare that we have no conflicts of interest in the authorship or publication of this contribution.

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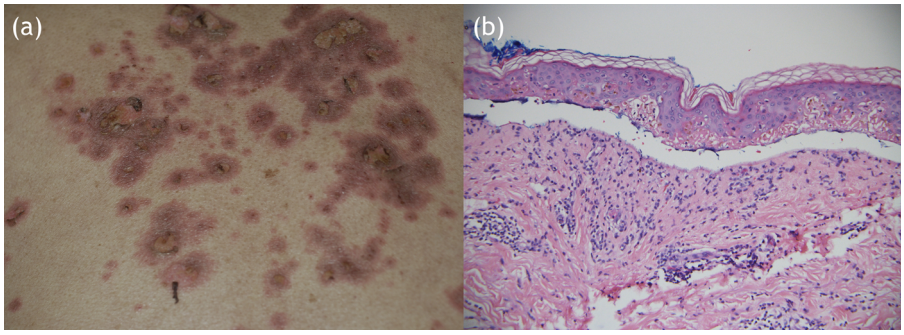

Fig. 1. Clinical and histopathological features.
(a) Atypical target lesions with central erosions on the trunk.
(b)Histopathology showing interface dermatitis with prominent basal vacuolar degeneration, numerous apoptotic keratinocytes, and dermal-epidermal separation (200X).

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