Case Report

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Crizotinib-associated erythema multiforme in a lung cancer patient

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Summary **Crizotinib is an oral small-molecule anaplastic lymphoma kinase (ALK) tyrosine-kinase inhibitor for the treatment of ALK-positive non-small-cell lung cancer (NSCLC). A 63-year old woman with postoperative relapsed ALK-positive NSCLC was treated with crizotinib. Erythema multiforme (EM) occurred one week after initiation of crizotinib therapy. Skin biopsy specimen showed compatible drug eruption. The discontinuation of crizotinib improved her eruption within one week. This report presented the first case of crizotinib-associated EM, which is the preclinical stage of Stevens-Johnson syndrome. Although crizotinib is clinically available, we should be aware of its potential severe skin adverse event.**

Keywords: Lung cancer, crizotinib, drug eruption

1. Introduction

Crizotinib is an oral small-molecule anaplastic lymphoma kinase (ALK) tyrosine-kinase inhibitor for the treatment of non-small-cell lung cancer (NSCLC) patients with echinoderm microtubule-associated protein-like 4 (EML4)/ALK rearrangements (*1,2*). ALK is a validated tyrosine kinase target in several cancers including NSCLC, and ALK rearrangements are found in approximately 5% of cases of NSCLC (3). Crizotinib is superior to standard chemotherapy in patients with ALK-positive NSCLC (*3*).

Common adverse events were visual dysfunction, gastrointestinal disorders, and pitting edema. While the incidence of skin complaints is 11% (*2*), there is no detailed case report on the progress of the drug eruption. We report the first case of erythema multiforme (EM) associated with crizotinib.

2. Case Report

A 63-year old woman with ALK-positive NSCLC underwent right upper lobectomy in 2009. After four years of her surgery, computed tomography showed right upper mediastinal lymphadenopathy and multiple nodular shadows in both lung fields. Thus, because of postoperative recurrence, she was treated with crizotinib (250 mg twice a day). One week after the initiation of crizotinib therapy, she was aware of asymptomatic cutaneous lesions. Physical examination revealed erythema multiforme on the trunk and extremities (Figure 1). There was no enanthema on the oral mucosa. She had no obvious symptoms including fever, vision disorder, and general fatigue. Laboratory examinations revealed that the percentage of eosinophils was increased (15.3%) although white blood cell count was normal (3,600/μL). Skin biopsy specimen showed spongiosis (Figure 2A) and perivascular lymphocytic/eosinophilic infiltrates (Figure 2B) in the upper dermis. According to these results, she was diagnosed as having crizotinib-associated EM. EM has the possibility that develops into Stevens Johnson syndrome, one of the severe drug eruptions. Therefore, crizotinib was discontinued and topical clobetasol ointment was undertaken. Her eruption almost improved within one week.

3. Discussion

Crizotinib is well tolerated, and severe adverse event

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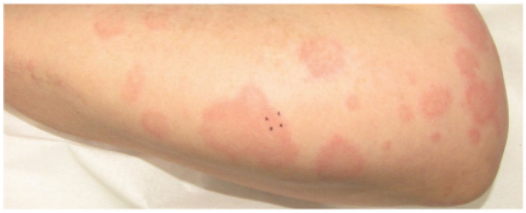

Figure 1. Erythema multiforme were detected on the left arm.

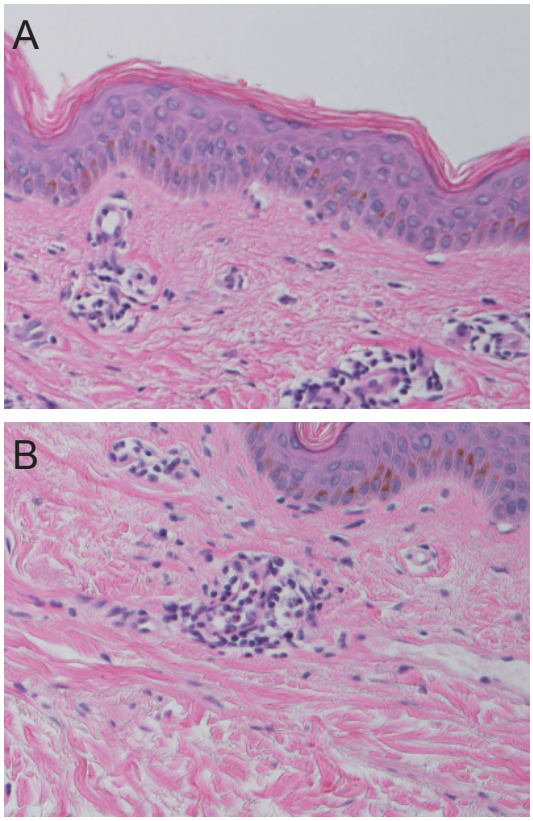

Figure 2. Histopathological findings. (A) Spongiosis and **(B)** perivascular lymphocytic/ eosinophilic infiltlates in the upper dermis (original magnification, ×400).

is comparatively rare. In 172 ALK-positive NSCLC patients, the common adverse events were mild (grade 1-2) gastrointestinal disorders (nausea (55%), vomiting (47%), diarrhea (60%), or constipation (42%)), vision disorder (60%), and edema (31%) (*3*). Regarding severe adverse events associated with crizotinib, there were diffuse alveolar damage (*4*) and esophageal ulcer (*5*). To our knowledge, our case is the first report of crizotinib-associated EM.

EM has a varied etiology including drug and infection. In this case, she had no symptom such as an indication of infection. In fact, from the initiation of crizotinib treatment, her eruption became progressively worse. And discontinuation of crizotinib resulted in improvement of EM. She didn't take newly started drug except crizotinib. On ground of such clinical courses, we diagnosed her with EM induced by crizotinib. EM sometimes develops into Stevens Johnson syndrome, which has the possibility of critical organ damage and potentially deadly risk. We should carefully examine the patient developing EM caused by novel agents whose adverse events have never been reported.

In conclusion, although crizotinib is a clinically available ALK inhibitor, we should be aware of its potential skin adverse event. Further accumulation of adverse events is necessary in future.

References

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