A case of crizotinib-induced esophageal ulcers

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We report a case of crizotinib-induced esophageal ulcers in a 45-year-old woman with metastatic anaplastic lymphoma kinase-positive non-small-cell lung cancer after 10 weeks of therapy. Endoscopic and pathologic findings were consistent with active inflammation with mid-esophageal ulceration and consistent with drug-induced esophagitis. Crizotinib was held and had a complete clinical and radiographic resolution of her symptoms. Patient was started on treatment with another anaplastic lymphoma kinase-targeted agent alectinib and has been tolerating it well without evidence of recurrence of esophagitis.

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Practice points

- Crizotinib is an oral anaplastic lymphoma kinase-tyrosine kinase inhibitor and is the first-line treatment for non-small-cell lung cancer.
- Patient developed endoscopic and radiographic evidence of esophagitis associated with ulceration after 10 weeks of therapy with crizotinib.
- Esophageal ulceration is a rare adverse event of crizotinib.
- Crizotinib therapy was stopped, alectinib was initiated, with complete resolution of symptoms.

Crizotinib is an oral anaplastic lymphoma kinase (ALK)-tyrosine kinase inhibitor that is a US FDA approved first-line treatment for ALK-rearranged non-small-cell lung cancer (NSCLC) [1]. Crizotinib is generally well tolerated with reported adverse events like nausea, vomiting, diarrhea, constipation, transaminitis, mild visual disturbances and peripheral edema [2]. Crizotinib-induced esophagitis was not reported in clinical trials with crizotinib and there was only one previous case described in the literature [3]. We report a case of crizotinib-induced esophagitis associated with ulceration which promptly resolved after switching treatment to alectinib.

Case

A 45-year-old woman with metastatic ALK-positive NSCLC was started on treatment with crizotinib (one 250 mg capsule, twice daily). Two weeks after initiation of crizotinib, she started experiencing mild odynophagia and epigastric discomfort with oral intake. She was started on esomeprazole. She continued to have progressive dysphagia and odynophagia. An esophagogastroduodenoscopy done after 8 weeks of therapy was normal and did not show any evidence of

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Figure 1. Esophageal ulcer (white) with surrounding erythema.

esophagitis or ulceration. Following this procedure she progressed to developing severe retrosternal chest pain and decreased oral intake due to odynophagia leading to hospitalization. A CT scan of her chest done at 10 weeks of therapy revealed diffuse circumferential thickening of the proximal to mid esophageal wall, representing esophagitis. An esophagogastroduodenoscopy done the next day revealed two nonbleeding superficial esophageal ulcers (Figure 1). Crizotinib was discontinued and esomeprazole (40 mg twice daily) was continued. Histopathological examination of the ulcer edge showed active inflammation with ulcer and granulation tissue (Figure 2). No evidence of dysplasia or malignancy was noted on pathology. Immunohistochemical stains

for cytomegalovirus, herpes simplex virus and fungal organisms was negative. Other etiologies including peptic ulcerations and parasitic infections were considered but the histologic features and the location of the ulcerations were consistent with drug-induced esophageal ulcerations. Her symptoms resolved completely within 1 week of stopping crizotinib. She was started on alectinib 600 mg twice daily and has been tolerating it well without recurrence of esophagitis. Subsequent CT scan done 7 weeks after discontinuing crizotinib showed significant decrease in esophageal wall thickening, suggestive of resolving esophagitis and ulceration.

Discussion

Clinical trials with crizotinib treatment show extended survival and improved response rates, along with limited toxicity. We describe in this report a case of esophagitis with associated ulceration that has not been reported in clinical trials with crizotinib. Medication-induced esophageal ulceration typically presents with retrosternal chest pain, dysphagia and odynophagia. This case not only raises physician awareness of this uncommon adverse event, but also encourages vigilance in evaluating esophagitis symptoms in patients treated with crizotinib. Additionally, our patient has tolerated alectinib therapy since discontinuation of crizotinib without evidence of recurrence of esophagitis. A recent study has demonstrated prolonged performance status and

Figure 2. Active esophagitis (panel A H&E low power) with ulcer, granulation tissue with fibrinopurulent debris (panel B) and squamous epithelium with neutrophilic infiltrates (panel C).

favorable adverse event profile of alectinib when compared with crizotinib [4]. Patients with ALK-positive NSCLC have the option of switching to alectinib if patients do not tolerate crizotinib.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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