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CASE REPORT

# Severe contact esophagitis in a patient taking crizotinib: A case report

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## INTRODUCTION

Anaplastic lymphoma kinase (*ALK*), a gene rearrangement, is responsible for around 5% of non-small cell lung cancers (NSCLCs), accounting for around 60,000 new cases each year worldwide. *ALK*-positive disease generally affects younger patients and demonstrates an aggressive clinical course when compared with other NSCLCs.[1] Crizotinib, an orally available tyrosine kinase inhibitor that targets *ALK* (and other tyrosine kinases), was introduced in 2011 for use in advanced *ALK*-positive NSCLC.[2]

## CASE REPORT

A 61-year-old Caucasian female was referred with advanced lung adenocarcinoma on the background of surgically resected stage I disease five years ago. The patient also had a history of gastroesophageal reflux disease and was taking esomeprazole (40 mg daily). She commenced carboplatin, vinorelbine and later, pemetrexed, for the treatment of her NSCLC, but was initiated on crizotinib (250 mg twice daily) three months later once the *ALK* gene rearrangement was detected.

Within two months of commencing crizotinib, the patient reported symptomatic improvement, and a computed tomography scan demonstrated a partial response to therapy. However, five months later, multiple cerebral metastases were discovered and crizotinib was withheld while she received whole brain radiotherapy, as crizotinib is a potent radiosensitizer. Dexamethasone was given for reduction of cerebral edema during radiotherapy treatment and subsequently weaned. Crizotinib recommenced two weeks after radiotherapy was completed. Within one month of resuming crizotinib, the patient developed odynophagia, with a significant reduction in oral intake and 4 kg weight loss. Her dose of esomeprazole was then increased to 40 mg twice daily, and ranitidine (150 mg at night), with lignocaine viscous and an antacid (Mylanta, Johnson & Johnson Pacific Pty Ltd, Australia) also added to the regimen. Her condition deteriorated requiring hospitalization, as she was unable to swallow because of the pain. At this time, crizotinib was ceased and the patient commenced parenteral opioids and ketamine for pain management.

A gastroscopy at this time demonstrated a diffuse esophagitis (initially thought to be most likely secondary to reflux) (see Figure 1). There was no evidence of muco-

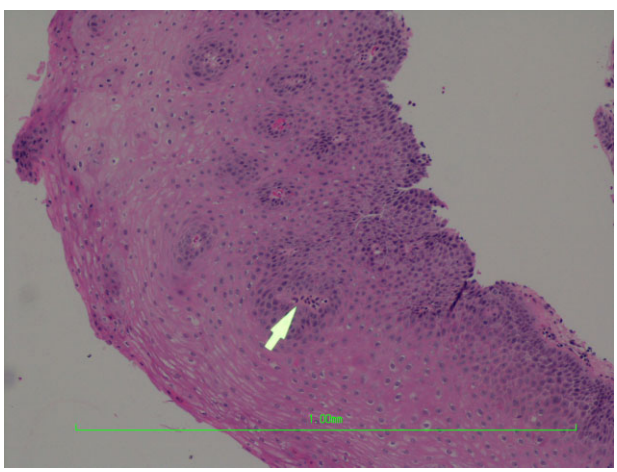

**Figure 1** Inflammatory infiltrate containing lymphocytes consistent with esophagitis.

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cutaneous *Candida* infection and herpes simplex and cytomegalovirus testing were negative. Unfortunately, no endoscopy photos were obtained at this time. Given the severity of her symptoms, the patient's condition necessitated nasogastric feeding for two weeks to supplement her poor oral intake. Her symptoms improved within seven days of stopping crizotinib.

Further questioning of the patient found that she had changed the way she administered the drug after completing radiotherapy. Upon recommencing crizotinib, she took the drug either while semi-recumbent or supine, with little regard to concomitant fluid intake. Prior to her discharge (two weeks after her admission for esophagitis), she was successfully rechallenged with crizotinib at 250 mg daily in addition to esomeprazole. She was counseled to take the medication with a glass of water while in an upright position and to stay upright for at least 30 minutes after the dose. No further esophagitis was experienced and therapy was reestablished at full dose. She continued to respond to crizotinib for 24 months, where upon progression of her disease she was changed to ceretinib, a second-line orally available tyrosine kinase inhibitor for the treatment of *ALK*-positive NSCLC. The patient was counseled to take ceretinib in the same manner as crizotinib to avoid the development of esophagitis on the drug, given their similar mechanism of action.

## DISCUSSION

Crizotinib's approval for use in NSCLC was preceded by two single-arm trials[3,4] and a phase III trial, which demonstrated superiority in terms of response rates, progression-free and overall survival.[1] In the latter trial, the most commonly reported adverse effects were visual disorders (60%) with gastrointestinal disorders such as diarrhea, nausea and vomiting (47–60%) also reported in high numbers. Esophageal disorders were not recorded in these studies.[1]

Since its approval, there have been five cases of esophagitis reported in patients taking crizotinib, which have been attributed to "pill esophagitis" in two cases[5] and unknown causes in the other three cases.[6–8] In three of these cases,[5] crizotinib was not recommenced or was recommenced, and maintained, at a lower dose. The case described in this report differs in that *diffuse* inflammation was seen at gastroscopy, consistent with contact esophagitis (rather than focal "pill esophagitis"), and the patient was then able to recommence her original crizotinib dose with medication counseling. The latter observation importantly supports this hypothesis, rather than an etiology such as reflux or a stress reaction, which would not improve with medication counseling.

Contact esophagitis is often described when patients ingest tablets without adequate liquid, with multiple ulcerations usually seen across a large area at endoscopy.[9] This phenomenon has been described in relation to bisphosphonates, whereby patients experience worsening "reflux" symptoms and diffuse ulceration is seen at endoscopy.[9] Importantly, this is described when patients inappropriately administer the drug, and resolves with medication counseling, where patients are advised to take the medication with a large glass of water and to remain upright for 30 minutes after the dose.[9] The authors of this case postulate that a similar mechanism may occur with crizotinib, and that dose reduction beyond the acute period is therefore not required for patients who develop esophagitis while taking the medication.

Post-marketing surveillance continues to inform product information (PI) content for medications. The current United Kingdom PI for crizotinib advises that the capsules should be swallowed whole, preferably with water, and should not be crushed, dissolved or opened.[10] Despite the rarity of documented cases of esophagitis, the authors propose that all patients should be counseled to remain upright for at least 30 minutes after the dose in addition to these recommendations.

In summary, the case presents another example of severe esophagitis in a patient taking crizotinib, highlighting the need for ongoing post-marketing surveillance and vigilance among prescribers, particularly in regards to administration advice.

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