

## Severe Ulcerative Esophagitis Induced by Crizotinib Therapy

Ala' A Abdel Jalil, MD, FACP<sup>1</sup>, Jamie Craig, PharmD<sup>2</sup>, Rajesh Bajaj, MD<sup>3</sup>, and Timothy Spurling, MD<sup>4</sup>

<sup>1</sup>Internal Medicine Department, McLeod Regional Medical Center, Florence, SC

<sup>2</sup>Pharmacy Department, McLeod Regional Medical Center, Florence, SC

<sup>3</sup>Division of Hematology/Oncology, McLeod Regional Medical Center, Florence, SC

<sup>4</sup>Division of Gastroenterology and Hepatology, McLeod Regional Medical Center, Florence, SC

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### Abstract

Crizotinib is an oral tyrosine-kinase inhibitor that inhibits anaplastic lymphoma kinase (ALK) in gene-rearranged non-small cell lung cancer (NSCLC). In 2011, the Food and Drug Administration approved crizotinib for treatment of locally advanced or metastatic ALK-positive NSCLC. The crizotinib adverse events profile included esophageal disorders in 11% of patients treated during trial phases I, II, and III, but none of them had severe events. We describe the development of severe ulcerative esophagitis secondary to crizotinib therapy and the re-introduction of therapy at a lower dose without recurrence of esophageal symptoms.

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### Introduction

In 2011, the Food and Drug Administration (FDA) approved the Vysis ALK Break-Apart FISH Probe Kit for the detection of anaplastic lymphoma kinase (ALK) gene rearrangements in non-small cell lung cancer (NSCLC), while concurrently granting approval for an agent directed at this target. Crizotinib was granted accelerated approval by the FDA for the treatment of locally advanced or metastatic NSCLC testing positive for the ALK rearrangement. The approval of crizotinib was based on 2 single-arm studies. Within both studies, the most commonly reported adverse reactions included visual disturbance, nausea, vomiting, diarrhea, constipation, and edema. Currently available studies have not specifically reported on the incidence of esophagitis associated with crizotinib treatment.<sup>1,2</sup> Severe esophagitis attributed to crizotinib was reported by Srivastava et al earlier this year; however, crizotinib therapy was not re-introduced to that patient due to tumor progression.<sup>3</sup> The current report describes the development of severe esophagitis secondary to crizotinib therapy and the re-introduction of therapy at a decreased dose.

### Case Report

A 74-year-old Caucasian male, a never smoker, presented to his primary care provider complaining of right hip and back pain for few months and cough for few weeks. Chest imaging was obtained and showed a left upper lobe mass with multiple additional masses within the lungs. Further imaging by PET scan revealed extensive disease with bone and lymph node metastasis. A biopsy of left scalene lymph node showed metastatic well-differentiated mucinous carcinoma of pulmonary origin. The tumor cells were 68% positive for ALK rearrangement. The patient was started on crizotinib 250 mg capsules twice per day.

The patient did well initially, but within 1 week started to complain of progressive dysphagia. He denied odynophagia, fever, or chest pain. During the second week of crizotinib therapy, he presented to the emergency room

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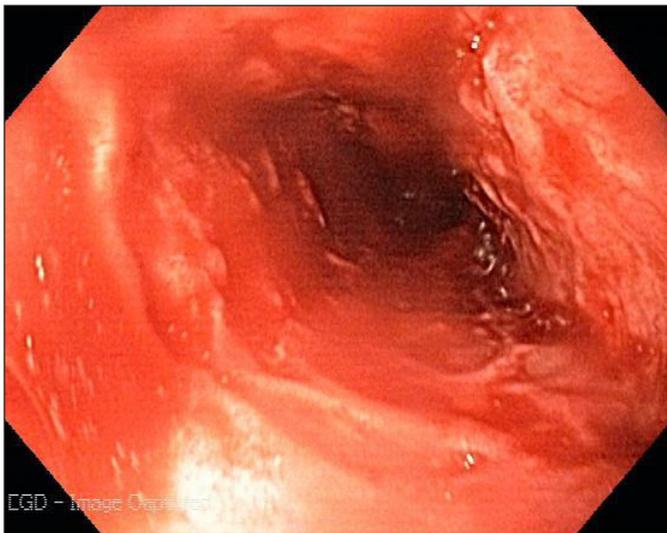
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**Correspondence:** Ala' A Abdel Jalil, MD, FACP, Assistant Professor, Internal Medicine Department, McLeod Regional Medical Center, 555 E. Cheves Street, Florence, SC 29506 (Ala79md@yahoo.com).

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with severe dehydration, weakness, poor oral intake, and 2 days of small volume hematemesis. The patient was admitted to the hospital, and crizotinib treatment was held. Supportive care with intravenous fluids and pantoprazole drip was started. Hemoglobin level at presentation was 12.0 g/dL and decreased to 9.8 g/dL within 2 days. Esophagogastroduodenoscopy (EGD) demonstrated a diffusely ulcerated esophagus from the cricopharyngeus to the gastroesophageal junction, with blood actively oozing from the entire esophagus secondary to severe ulcerations (Figure 1 and Figure 2). Biopsy was deferred because of active esophageal bleeding. The patient was started on total parenteral nutrition to allow the esophagus to heal. His swallowing started to improve 1 week after crizotinib was held, and within 2 weeks of his presentation he was able to resume oral intake.

Because of the severity of the inflammation and ulcerations on EGD, a clinical decision was made to re-introduce crizotinib therapy at half dose (250 mg daily) and monitor the patient closely for recurrence of esophagitis. The patient reported tolerating therapy at a follow-up visit after 3 months. Endoscopy was not repeated given the resolution of patient's symptoms.

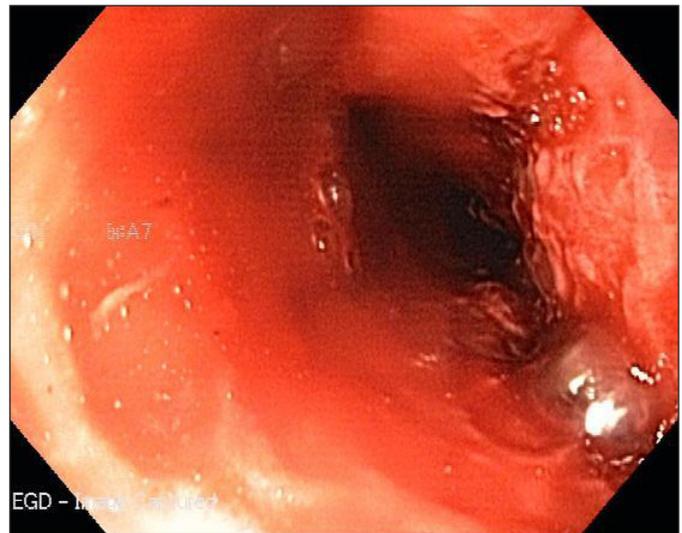


**Figure 1.** Severe ulcerations in whole esophagus.

## Discussion

Camidge et al presented an updated analysis of the phase I crizotinib study with regards to its activity and safety. Gastrointestinal and visual events, with the majority grade 1 or 2, were reported as some of the more frequently occurring adverse events. Overall, crizotinib was reported to be well-tolerated, with no reports of esophagitis.<sup>2</sup>

Treatment emergent esophageal disorder—widely defined as dyspepsia; dysphagia; epigastric discomfort, pain, or



**Figure 2.** Ulcerations in esophagus with active oozing of blood.

burning; esophagitis; esophageal obstruction, pain, spasm, or ulcer; gastroesophageal reflux; odynophagia; and reflux esophagitis—was reported in 20% of patients in both trials, leading to the approval of crizotinib. Only half of these incidences were categorized as treatment related, and no grade 3 or 4 toxicity occurred.

A recent phase III study by Shaw et al compared crizotinib therapy with standard chemotherapy in 347 patients with ALK-positive NSCLC. The adverse effects profile seen was similar to previously reported studies. Gastrointestinal effects were reported as similar to previous findings with no specific cases of esophagitis reported.<sup>4</sup>

Park et al described 2 cases of esophagitis associated with crizotinib therapy, attributing the incidences to pill-induced esophagitis.<sup>5</sup> These cases differ from our case in that the ulceration was confined to mid-esophagus, which supports the diagnosis of pill esophagitis compared to the diffuse disease in our patient.

Our case describes the development of EGD-proven severe ulcerative and diffuse esophagitis within 2 weeks of the initiation of crizotinib. Given the timing of initiation of therapy and the onset of symptoms, the severe esophagitis was attributed to the initiation of crizotinib therapy. Treatment was discontinued, and the patient's symptoms of esophagitis resolved. Additionally, the patient tolerated re-introduction of a half dose of crizotinib therapy.

Although an infectious etiology could not be excluded with absolute certainty in our patient without obtaining biopsies, the clinical presentation and endoscopic examination were not supportive of such etiology. Most patients with infectious

esophagitis present with odynophagia in addition to dysphagia. EGD was not consistent with typical findings of infectious esophagitis. Cytomegalovirus (CMV) and *Candida* are 2 commonly identified causes of esophagitis. However, CMV most commonly causes multiple, deep ulcers at the lower esophageal sphincter, and *Candida* infection results in white mucosal plaque-like lesions.<sup>6,7</sup> The patient was not felt to be immunosuppressed enough to place him at increased risk of these infections. Herpes simplex virus infection usually affects the distal esophagus with well-circumscribed ulcers and normal-appearing intervening mucosa.<sup>8</sup> Our patient had superficial, diffuse ulcerations of esophagus with no white mucosal lesions.

Camidge et al describe the role of ALK in the development of gut and visual systems of other organisms. While the role and function of ALK is not well-known in humans, they suggest the predominance of gastrointestinal and visual side effects seen with crizotinib therapy may be accounted for by the anti-ALK effects within these tissues.<sup>2</sup>

Given the severity of disease experienced by our patient and the high percentage of ALK expression in the tumor cells, we postulate that the severity and diffuse nature of the esophagitis represents an on-target anti-ALK phenomenon.

## Disclosures

Author contributions: A. Abdel Jalil and J. Craig acquired, analyzed and interpreted the data. A. Abdel Jalil, J. Craig, R. Bajaj, and T. Spurling drafted and critically revised the manuscript for important intellectual content. AA Abdel Jalil is the article guarantor.

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Informed consent was obtained for this case report.

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