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Case Report

Severe esophagitis directly induced by accumulation of crizotinib-residue at the esophageal mucosa proven with polarizing microscope examination

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Crizotinib demonstrates dramatic effects for the patients with *echinoderm microtubule-associated protein-like 4 (EML4)-anaplastic lymphoma kinase gene (ALK)* fusion or *c-ros oncogene 1 (ROS-1)* fusion-positive lung cancer, with some characteristic toxicities. Although several studies reported that serious esophagitis was induced by crizotinib, the detailed mechanisms and ways to ameliorate the esophagitis have not been clarified. In this report, we report two cases with lung cancer who had been treated with crizotinib and developed severe esophagitis. Polarizing microscope examination clearly revealed that the accumulation of crizotinib-residue in the esophageal biopsy samples at the second anatomical narrowing of the esophagus in both cases. Since it seemed that the accumulation of crizotinib-residue in the esophageal mucosa directly caused the esophageal inflammation, we recommended taking crizotinib with a large amount of water (more than 200 ml) and to stay sitting upright for 30 minutes after intake. After that, the esophagitis gradually improved and the patients could continue taking crizotinib without dose reduction or withdrawal. Our experiences suggest that this crizotinib-induced esophagitis could be easily prevented by proper administration of crizotinib.

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Key words: Crizotinib, esophagitis, ALK, ROS-1, polarizing microscopes

Introduction

Molecular targeted therapies for non-small cell lung cancer (NSCLC) have been developed in this decade. Genotype-directed molecular targeted therapies prolong the prognosis of the patients with NSCLC harboring oncogenic driver mutations. To receive the benefit of molecular targeted therapies for the long term, treatment-related adverse events need to be managed appropriately during the treatment.

Crizotinib is known as an ATP-competitive, small-molecule

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inhibitor for multi-receptor tyrosine kinases (RTKs), such as MET, anaplastic lymphoma kinase (ALK), and c-ros oncogene 1 (ROS-1). Crizotinib demonstrates dramatic and durable response for the patients with *echinoderm microtubule-associated protein-like 4 (EML4)-ALK- or ROS-1* fusion-positive lung cancer [1, 2], with some characteristic toxicities. Although previous studies reported that serious esophagitis induced by crizotinib treatment, the detailed mechanisms of the esophagitis have not yet been clarified [3-7].

Herein, we report two cases who experienced severe esophagitis due to accumulation of crizotinib-residue at the anatomical narrowing of the esophagus, pathologically proven with polarizing microscopes.

Case presentation

Case 1

A 59-year-old woman, non-smoker, was diagnosed with NSCLC harboring *EMK4-ALK* fusion and a systemic survey showed stage IVB (cT2aN1M1b) disease with liver metastasis. She received two cycles of cisplatin and irinotecan, followed by two cycles of carboplatin and amrubicin, because neuroendocrine components existed in the tumor. Unfortunately, these treatments did not show sufficient effects, therefore, the treatment with crizotinib was started (250 mg capsule, twice daily) as third line treatment. Performance status (PS) was 1 at this point. Two months later, chest CT revealed that the tumors had shrunk and a partial response was achieved, confirming that crizotinib showed sufficient anti-tumor effect for the patient. However, she developed chest and back pain, which exacerbated gradually, four months after the initiation of treatment with crizotinib. Treatment with a histamine 2 (H2) blocker and a proton pump inhibitor (PPI) did not improve the symptoms and chest CT showed thickening of the middle esophageal wall, suggesting that esophagitis developed. Also, esophagogastroduodenoscopy (EGD) revealed ulcerative esophagitis with white moss (Fig. 1A) at the second anatomical site of narrowing of the esophagus. Pathological findings of esophageal biopsies showed active esophagitis with fibrinopurulent exudate and invasion of inflammatory cells, with a predominantly neutrophilic infiltrate and crystal structures around the inflammatory sites (Figs. 1B and 1C). To elucidate these crystal structures in the inflammatory sites, we made a paraffin-embedded block of crizotinib powder (Fig. 1D) and observed by polarizing microscopy in addition to the biopsy sample because we considered that accumulation of crizotinib-residue might cause the esophageal inflammation. Interestingly, both the crystal structures found in the biopsied esophageal mucosa and the crizotinib powder had very similar positive birefringence on this examination (Fig. 1E). These results suggested that the accumulation of crizotinib-residue in the esophageal mucosa directly induced the esophageal inflammation. Therefore, we recommended to take crizotinib capsule with a large amount of water (200 ml) and stay sitting upright for 30 minutes after intake. Subsequently, her symptoms had improved two weeks after starting the safe coping method and disappeared one month later, and EGD examination confirmed that the esophagitis healed two months later (Fig. 1F).

Case 2

A 32-year-old woman, nonsmoker, was diagnosed with NSCLC harboring *ROS-1* fusion, and a systemic survey showed stage IVB (cT2aN1M1c) disease with liver and brain metastases and a malignant pleural effusion. She received four cycles of cisplatin, pemetrexed, and bevacizumab, followed by one cycle of pemetrexed and bevacizumab maintenance therapy. Although the patient achieved a partial response, the treatment could not continue due to liver toxicity (Grade 3 ALT increased; Common Termiology Criteria for Adverse Events (CTCAE) ver.4.0). Therefore, treatment with crizotinib (250 mg capsule, twice daily) started as second line treatment. PS was 1 at this point. Four days after the initiation of treatment with crizotinib, she developed chest pain, which exacerbated day by day. Four days after the onset of chest pain, EGD was performed and revealed ulcerative esophagitis at the second anatomical narrowing of the esophagus (Fig. 2A). Pathologic findings of esophageal biopsied samples showed active esophagitis with crystal structures (Fig. 2B). Similar to case 1, we examined the biopsy sample with polarizing microscopy and found that the crystal structures at the inflammatory sites had positive birefringence and resembled crizotinib morphologically (Fig 2C). Since we suspected that accumulating crizotinib-residue caused the esophagitis, we recommended to take crizotinib with a large amount of water (200 ml) and stay sitting upright for 30 minutes, in addition to taking a PPI, and her symptoms had started to improve one day after starting the safe coping method and disappeared two weeks later. After that, she could continue taking the same dose of crizotinib without any chest pain, and the esophagitis had not recurred over four months.

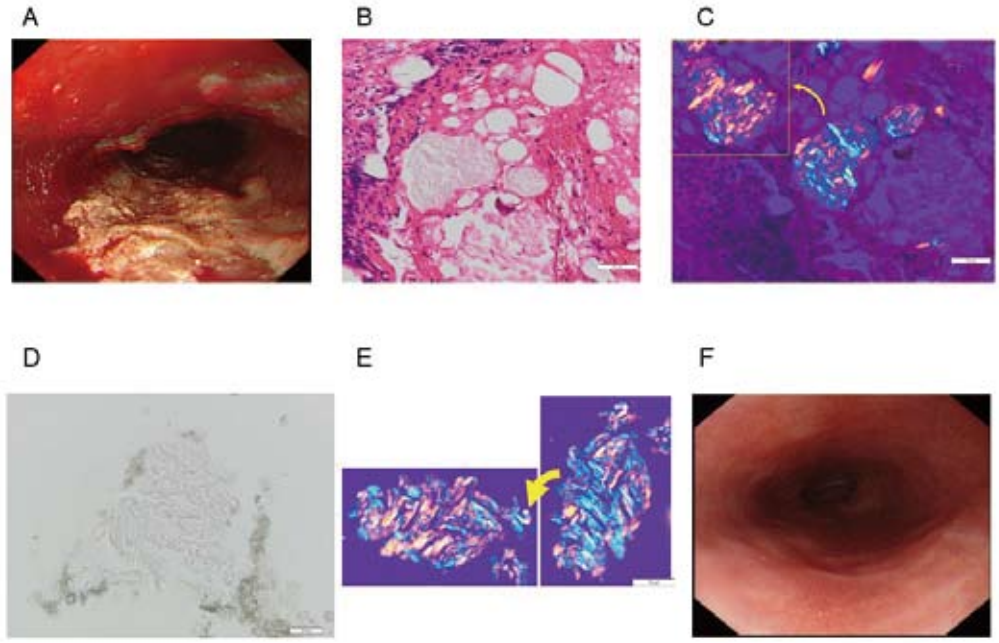

Figure 1. Examinations of Case 1
(A) Endoscopic image of extensive ulcerative esophagitis in the mid-esophagus five days after appearance of chest pain.
(B) Histological image of esophagitis with crystal structures and (C) observation by a polarizing microscope. Bar: 50 μm.
(D) Histological image of paraffin-embedded block of crizotinib powder and (E) observation by a polarizing microscope. Bar: 20 μm (D), 50 μm (E).
(F) Endoscopic image of healed esophagus (two months later).

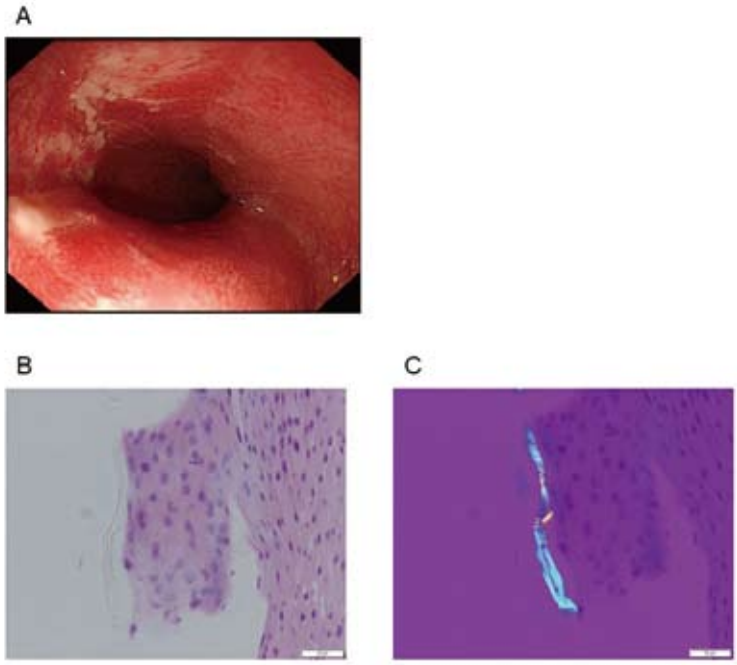

Figure 2. Examinations of Case 2
(A) Endoscopic image of esophagitis in the mid-esophagus four days after the initiation of treatment with crizotinib.
(B) Histological image of esophagitis with the crystal structures and (C) observation by a polarizing microscope. Bar: 50 μm.

Discussion

In this case study, we report that accumulation of crizotinib-residue at the anatomical narrowing sites of the esophagus caused direct injure to esophageal mucosa, and the esophagitis may be easily recovered without crizotinib withdrawal or dose reduction by taking crizotinib with a large amount of water and by sitting upright for 30 minutes.

Crizotinib is approved not only for *EML4-ALK*-positive lung cancer, but also for *ROS-1* fusion-positive lung cancer in Japan and many countries. Although the second or third-generation ALK inhibitor has been reported to show higher efficiency and less toxicity than crizotinib, the role of crizotinib is still important in the treatment for the patients with lung cancer due to the approval of crizotinib against *ROS-1* fusion-positive lung cancer. Despite the dramatic response, several severe toxicities associated with crizotinib have been reported, including abdominal disorders. In a phase I/II/III study of crizotinib, 20 cases (1.1%) of esophagitis and six cases (0.3%) of esophageal ulcers were reported in 1796 patients [8], however, the detailed mechanisms of the esophagitis have not revealed yet.

Previous studies reported that pills could be trapped and adhere to the esophageal mucosa, as the result, several drugs could induce esophagitis. The large size of capsules and tablets, inadequate fluid intake with drug administration, and altered esophageal anatomy were reported as risk factors for pill esophagitis. Especially, a lightweight and large capsule like crizotinib is associated with delayed esophageal transit time that could cause esophagitis, compared with a heavy capsule [9] [3].

In the present study, accumulation of crizotinib-residue was found in esophageal mucosa by observation with a polarizing microscope. Accumulation of crizotinib-residue at the esophagus could induce inflammation of the esophagus, because high concentration of crizotinib could inhibit cell proliferation and cell viability in normal cells, suppressing many functions of RTKs, such as ALK, MET, ROS-1, AXL, TRK. Further investigations are required to clarify the exact and detailed molecular mechanisms of inflammation induced by crizotinib at the esophageal mucosa.

As demonstrated by the present cases, the esophagitis may occur at any time during treatment with crizotinib when the capsule is trapped at the esophagus. In support of this hypothesis, it was reported that the duration of onset and the improvement of symptoms after initiating crizotinib varied from several days to nine months or later [10]. Although several reports have suggested that PPIs or H2 blockers were slightly effective for the esophagitis, they might not improve the inflammation of the esophagitis directly [5]. Also, a chest CT revealed thickening of the middle esophageal wall in case 1. If crizotinib-induced esophagitis is suspected, we recommend a CT scan to pick the esophagitis up as a screening, an EGD check for confirmation of pill esophagitis, taking crizotinib with 200 ml of water, and remaining the patients in the sitting position for 30 minutes after administration. Since the esophagitis could be healed by appropriate instruction easily, dose reduction or withdrawal of crizotinib due to the esophagitis could be avoided.

Conclusion

In this case study, we report that accumulation of crizotinib-residue induced severe pill esophagitis in two cases, and crizotinib-residue could be found in esophageal mucosa by examination with polarizing microscopes in both cases. This drug-induced esophagitis could improve with appropriate drug administration and instruction by medical staffs. These results indicate that physicians should carefully instruct their patients on the method of taking crizotinib capsules.

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