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Case Report
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Acute Esophageal Necrosis Complicated by Severe Upper Gastrointestinal Bleeding in Association with Bosutinib Treatment for Chronic Myelogenous Leukemia

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Abstract

Acute Esophageal Necrosis (AEN), also known as "Black Esophagus", is a rare life threatening condition with unknown cause. We present a case of AEN in an 82 years-old male on Tyrosine Kinase Inhibitor (TKI) for Chronic Myelogenous Leukemia (CML). While TKI is known to cause GI toxicity, this is the first case, to our knowledge, reporting AEN.

Introduction

AEN is an uncommon clinical entity caused by variety of factors. It was first described by Goldenberg et al in 1990 [1]. The diagnosis is based on endoscopic appearance after excluding ingestion of corrosive agents. In most patients, the resolution of endoscopic findings occurs with supportive care [2]. Mortality is high and it is largely due to the underlying disease rather than being directly attributable to complications of acute esophageal necrosis.

We report a case of AEN in a patient with CML. Although the main cause of AEN is unknown, our case was temporally associated with treatment of CML with a TKI, bosutinib. At first it was thought that the effect of TKI at the molecular mechanism level appears to comprise only a targeted approach in blocking tyrosine kinases. However, this should not be misleading as many closely interconnected signaling pathways are involved. TKIs are a new modality of anti-cancer-therapy amending classical cytotoxic regimes. TKIs are of substantial benefit in terms of efficacy with a tolerable safety profile. However, long-term safety issues might not be fully elucidated at present and, thus, cannot be finally judged upon.

Bosutinib is an oral TKI for a philadelphia chromosome positive (Ph+) CML. In general, TKIs are associated with gastrointestinal toxicity, however, bosutinib has higher degree of gastrointestinal adverse effects. Bosutinib gastrointestinal adverse effect profile included diarrhea, vomiting, nausea, and abdominal pain [3]. Currently, available studies have not specifically reported on esophageal adverse effect associated with bosutinib treatment.

Case Report

An 82-year-old male with a history of chronic phase CML presented with four days' of hematemesis and melena followed by an episode of syncope. The TKA, Bosutinib 300mg oral daily, had been started two weeks prior to presentation. In addition, he had a past medical history of hypertension, and gastroesophageal reflux disease.

On physical examination, he was found to be hypotensive with blood pressure of 90/55mmHg and tachycardiac with heart rate of 110 beats per minute. Three black tarry loose bowel movements were witnessed in the emergency room. He was resuscitated with Intravenous crystalloid and started on intravenous PPI. Although the blood pressure has dropped in our patient, we opt to follow the restrictive transfusion strategy with a transfusion threshold of 70g/L. The restrictive transfusion has better outcome in patients with upper gastrointestinal bleeding. This strategy reduces the risk of further bleeding, the need for rescue therapy, and the complication rate, all while improving the survival rate [4].

Laboratory investigations revealed initial hemoglobin of 141 g/L, falling to a nadir of 128 g/L. There was evidence of acute kidney injury with urea of 22.8 mmol/L and creatinine of 185 umol/L. Upper endoscopy was performed within 2 hours of arrival at our hospital and revealed a confluent

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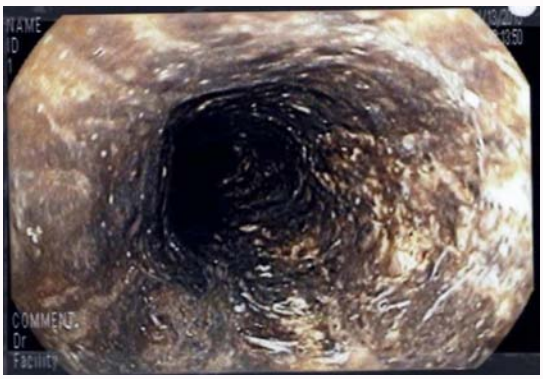

Figure 1: Black esophageal necrosis consistent with mucosal necrosis endoscopically.

black esophageal mucosa, consistent with mucosal necrosis, with a distinct transition to normal mucosa at the gastroesophageal junction. In addition, a non-bleeding visible vessel was seen just proximal to the gastroesophageal junction was seen. This was treated with application of a single clip.

The AEN was managed conservatively with oral PPI, discontinuation of bosutinib and advancing the diet as tolerated. He was discharged from hospital four days later. However, four days later he presented again with a massive upper GI bleed, with hematemesis, melena and hematochezia, complicated by significant hypotension requiring ICU admission. Upper endoscopy was repeated, showing resolving esophageal necrosis, but an active bleeding visible vessel again just above the gastroesophageal junction. Hemostasis was achieved after injection of epinephrine (1:10,000 concentration) and placement of another clip.

Discussion

AEN, also known as "Black Esophagus", is a rare life threatening condition with an incidence ranging between 0.01 to 0.28% [4]. It affects males more than females in a 4:1 ratio, with a peak incidence in the 6th decade of life [2]. Mortality ranges from 15% up to 36% with only less than 10% of cases have been reported as a cause of death due to esophageal disease itself [5-8].

The exact etiology is unknown but it is thought to be a result of multiple pathological insults. These include local ischemia, corrosive acid exposure and decreased esophageal clearance. Risk factors that identified in the literature include, but not limited to, shock, hypoperfusion, infection, hyperglycemia, underlying malignancy, and irradiation.

The most common presentation of AEN is upper GI bleeding. Other manifestations include retrosternal discomfort, epigastric pain and dysphagia [9,10]. It can be complicated by esophageal perforation in less than 7% while esophageal strictures may occur in more than 10% of patients. The black discoloration with a sharp transition to normal mucosa of the gastroesophageal junction is the hallmark of diagnosing AEN endoscopically. Although biopsy is needed to rule out other causes of black esophagus, the resolution of the endoscopic finding on repeated scope confirmed the diagnosis of AEN in our patient.

Similar to reported cases in the literature, the exact etiology of AEN is unknown in our patient. Hypotension was common found amongst those with AEN. It has been hypothesized that acute circulatory compromise may contribute to the esophageal ischemic necrosis. However, it is difficult to differentiate whether it is the cause, or the effect from the bleeding. We propose the two-hit hypothesis whereby bosutinib, the first "hit", predisposes the esophageal mucosa to ischemic compromise via an unknown mechanism. Thereafter, the second "hit", acute hypotension, precipitates the esophageal necrosis. Given the recent start of the TKI, bosutinib, and the absence of other significant potential causes, it seemed reasonable to implicate the drug in this case of AEN. The safety profile of bosutinib was assessed and it was found that gastrointestinal toxicity is more common in boustinib compared to other tyrosine kinases inhibitors. Gastrointestinal adverse effects that were associated with bosutinib include transient nausea, vomiting, diarrhea, and increased aminotransferases [11].

It is known that TKI are indicated for Gastrointestinal Stromal Tumors (GIST) and there is emerging literature suggesting that EGFR TKI can be useful in esophageal cancers. Indeed, both normal squamous mucosa and carcinoma of the esophagus express EGFR. Interestingly in a mouse model of Candida esophagitis EGFR has been implicated in mucosal defense. Furthermore, another TKI, crizotinib, has been well associated with esophagitis, though this drug acts on the anaplastic lymphoma kinase tyrosine kinase receptor, in contrast to bosutinib, which inhibits the EGFR tyrosine kinase. In the literature, there are cases where TKI was reported to be associated with Gastric Antral Vascular Ectasia (GAVE) [12,13]. However, to our knowledge, no other similar cases of AEN have been reported in association with TKI. To the best of our knowledge, this is the first reported case of AEN attributable to a TKI, specifically bosutinib.

In summary, we have reported the first case of AEN in association with the TKI, bosutinib, used to treat CML. Clinicians should be aware of possible esophageal toxicity with these agents, as the presence of AEN has a high association with a poor outcome, and even mortality. Our patient did well with expectant treatment and PPI therapy, though did suffer from severe recurrent upper GI bleeding. Early endoscopy can identify this severe form of esophageal injury and then lead to cessation of possible offending agents.

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