



Cetuximab-Induced Small Intestine Stricture in Metastatic Squamous Cell Carcinoma of the Oral Cavity

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ABSTRACT

Cetuximab is an epidermal growth factor receptor (EGFR) inhibitor, which is used to treat patients with metastatic head and neck cancer. Dermatological reactions are the most serious adverse events associated with cetuximab treatment including an acne-like rash, xerosis, and pruritus. Other adverse effects include infections, hypomagnesemia, mucositis, conjunctivitis, nausea, and diarrhea. Mucositis is not only restricted to the oral mucosa, however, can affect any part of the gastrointestinal tract. The duration of treatment-related mucositis has been associated with stricture formation. We describe a case of chronic duodenal and jejunal strictures attributed to cetuximab use.

INTRODUCTION

Cetuximab is an epidermal growth factor receptor (EGFR) inhibitor, which is used to treat patients with metastatic colorectal cancer and head and neck cancer.¹ Dermatological reactions are the most serious adverse events associated with cetuximab treatment including an acne-like rash, xerosis, and pruritus.² Other adverse effects include infections, hypomagnesemia, mucositis, conjunctivitis, nausea, and diarrhea.³ Mucositis is a common adverse effect associated with the use of EGFR inhibitors, and its incidence has not been thoroughly reported in the literature. We report a case of a patient on cetuximab who developed chronic small intestine strictures in the duodenum and jejunum that are attributed to cetuximab.

CASE REPORT

A 59-year-old man with squamous cell carcinoma of the left floor of mouth and right alveolar ridge with metastasis to the hilar lymph nodes and lungs, initially diagnosed in December 2015, was on concurrent chemoradiation for 15 months then underwent salvage surgical resection. Unfortunately his disease progressed after the surgical resection despite the chemoradiation, and subsequently he was switched to paclitaxel and cetuximab in February 2017. Paclitaxel was discontinued in July 2018 because of worsening neuropathy, and he was continued on cetuximab. The patient underwent a gastrostomy tube placement for dysphagia at the time of initial diagnosis of the cancer by interventional radiology, which was later changed endoscopically to the gastrojejunostomy tube because of intolerance to gastric feeding in March 2017. On the initial endoscopic examination in March 2017 (1 month after starting the cetuximab), the patient was found to have severe mucositis of the gastric and duodenal mucosa, and no strictures were seen at that time. The patient was on a proton pump inhibitor and a mixture of diphenhydramine, viscous lidocaine, magnesium hydroxide/aluminum hydroxide, and nystatin for oral mucositis. Laboratory data showed normal hemoglobin, normal inflammatory markers, and mild hypoalbuminemia, which was attributed to chronic illness and malignancy. Computed tomography of the abdomen and pelvis as a part of the cancer surveillance was negative for distal small intestinal strictures. He underwent several percutaneous endoscopic gastro jejunostomy (PEGJ) exchange due to tube malfunction during which he was found to have strictures of the duodenal bulb, third part of the duodenum, and proximal jejunum (2.5 years after the initial placement of PEGJ and 3 years after the initiation of cetuximab) (Figure 1). The patient had progressive severe duodenal and jejunal strictures that required intermittent balloon dilation to replace his PEGJ tube over the period of 4 years. Biopsies were not performed on the strictures. In addition, the patient suffered from continuous leaking around the gastrostomy site which resolved with exchange of the jejunostomy tube from 18 to 16 FR, which is attributed to the fact that a larger tube caliber may have caused intermittent partial obstruction at the level of narrowest stricture in the duodenum with retention of gastric secretions that led to leaking around the gastrostomy site.

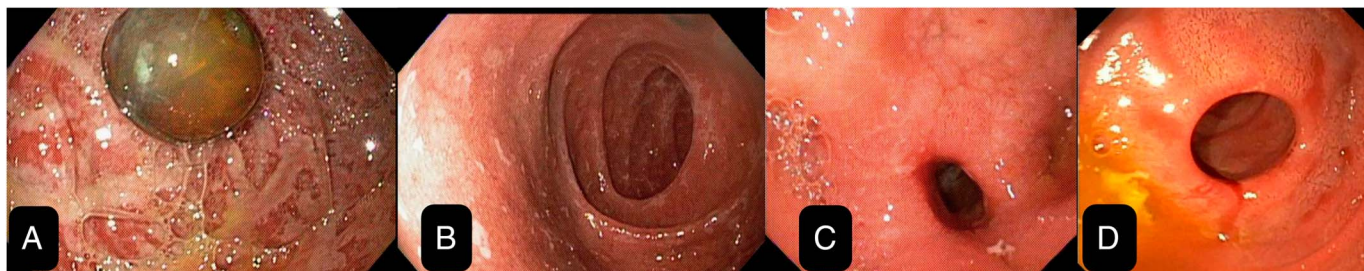


Figure 1. Shows gastric mucositis (A), duodenal bulb mucositis (B), duodenal bulb diaphragmatic-like stricture (C), and proximal jejunal diaphragmatic-like stricture (D).

DISCUSSION

Oral and gastrointestinal mucositis associated with the use of cetuximab can present with painful ulcerations, dysphagia, diarrhea, and gastrointestinal bleeding. Mucositis in this population is not only restricted to the oral mucosa, however, and can affect any part of the gastrointestinal tract.⁴ The proposed pathophysiology of EGFR inhibitor-associated mucositis is direct cellular DNA damage, reactive oxygen species effect, and proinflammatory cytokines that lead to mucosal inflammation, in addition to the loss of epidermal growth factor effect, which plays an important role in cell migration, increase in blood flow, and repair of the basal membranes.⁵ Although there is no clear evidence to why stricture complicates EGFR inhibitor-associated mucositis, however, the proposed mechanism is that prolonged mucosal ulceration leads to fibrosis and scarring formation.⁶ Mucositis can be severe, affect the quality of life, and may lead to treatment interruption and discontinuation. Gastrointestinal strictures associated with the use of cetuximab or any other EGFR inhibitor have not been reported in the literature according to our search in PubMed. There was a report of intestinal obstruction attributed to the use of gefitinib with resolution of symptoms on discontinuation of gefitinib.⁷ It has been reported in the oncology literature that the duration of treatment-related mucositis has been associated with stricture formation.⁶ Apart from oral mucositis, there are limited data on the management of gastrointestinal mucositis in patients receiving targeted therapies (EGFR inhibitors). Antioxidants (vitamin E, zinc), anti-inflammatory (pentoxifylline), and sucralfate have been studied and used in mucositis related to radiation therapy and chemotherapy. However, there is no strong evidence to recommend those medications in EGFR inhibitor-associated mucositis.⁸ The case we describe had no history of Crohn's disease, long-term use of nonsteroidal anti-inflammatory medications, a second malignancy or abdominal metastases to explain the strictures, or previous abdominal surgeries. Although the distal end of the jejunostomy tube is beyond the distal stricture, we have low suspicion that a 16 FR feeding tube would exert significant pressure to cause ischemia and subsequent stricture formation. Therefore, it was concluded and hypothesized that the duodenal and jejunal strictures were associated with the EGFR inhibitor cetuximab. Monitoring of gastrointestinal symptoms in patients on a

long-term EGFR inhibitor is therefore advised with consideration of standard endoscopic dilation treatment when clinically indicated.

DISCLOSURES

Author contributions: M. Eisa is the article guarantor. All authors contributed equally to this manuscript.

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Informed consent was obtained for this case report.

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