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CASE REPORT | ESOPHAGUS

Esophageal Stricture Resulting from Systemic Chemotherapy for Solid Malignancy

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ABSTRACT

Although dysphagia in patients treated for malignancy is usually related to reflux esophagitis, infectious esophagitis, malignant infiltration, or as a complication of radiation therapy, acute esophageal stricture resulting from chemotherapy is very rare. Only 2 prior cases have been described in the treatment of an adult patient with malignancy. We present a unique case of isolated chemotherapy-induced esophageal stricture in a patient receiving treatment for metastatic testicular seminoma without prior history of gastroesophageal reflux disease, caustic ingestion, or other risk factors for esophageal stricture formation.

INTRODUCTION

Esophageal stricture is a process that is generally categorized as either peptic or nonpeptic in origin. Peptic strictures are the result of longstanding gastroesophageal reflux disease. Causes of nonpeptic strictures include infection, postsurgical complication, tumor, toxic ingestion, or localized radiation exposure.[1] Esophageal stricture secondary to isolated chemotherapy is exceptionally rare. To our knowledge, only 2 other cases are described in adult patients.[2,3] In pediatric patients, it has been identified as a rare complication following induction therapy for acute leukemia.[4]

CASE REPORT

A 34-year-old man with a diagnosis of metastatic testicular seminoma presented to the hospital after left orchiectomy for initiation of chemotherapy. His initial computed tomography (CT) scan of the chest, abdomen, and pelvis was significant for a large abdominal and pelvic mass, narrowing of the ascending colon, duodenal obstruction, and compressive atelectasis with multifocal infiltrates in the lungs concerning for bowel, abdominal, and lung metastases. There was no evidence of esophageal pathology at this time. He was started on full-dose intravenous etoposide 100 mg/m^2 and intravenous cisplatin 20 mg/m^2 (EP chemotherapy) daily and received an initial 5 days of therapy. Due to abnormal pulmonary function tests, he was unable to receive bleomycin. Laboratory monitoring following the initial cycle of chemotherapy showed a response to chemotherapy with a reduction in serum lactate dehydrogenase (LDH). CT also showed a small decrease in size of multiple abdominal and retroperitoneal masses, which indicated tumor response to chemotherapy.

Two weeks after the first cycle of full-dose EP chemotherapy, the patient developed symptoms of dysphagia and odynophagia. He reported difficulty and pain swallowing solids, with a sensation of food getting "stuck in his chest." He was able to tolerate small sips of liquids. The primary team noted oral thrush, which was empirically treated with antifungal therapy for suspected candida esophagitis. The patient had appropriate transport and clearance in the

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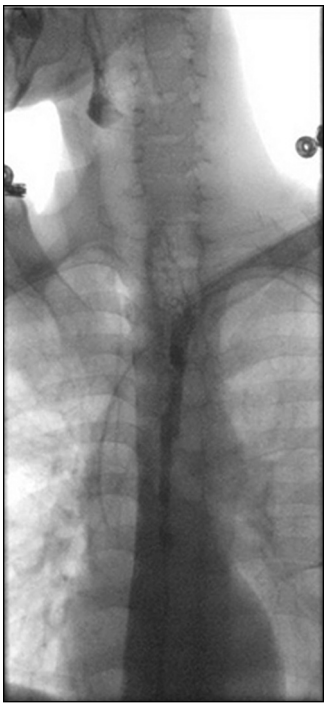

Figure 1. Gastrografin esophogram showing generalized distal narrowing of the distal esophagus.

oral phase and timely initiation of swallow in the pharyngeal phase, with no overt suggestion of aspiration. He complained of soreness during swallow evaluation. Further workup was not pursued, as the patient refused initial endoscopy.

The patient had a good tumor response to 2 full-dose cycles based on a decrease in β-human chorionic gonadotropin (β-hCG) tumor marker level and LDH, but his symptoms of dysphagia and odynophagia persisted throughout the second and third cycles of full-dose EP chemotherapy. He denied any history of acid reflux, abdominal pain, melena, constipation, vomiting, or hematochezia, and he had no prior history of caustic ingestions or radiation therapy. His medication list included ondansetron as needed for nausea and docusate for constipation. Physical exam was grossly unremarkable without evidence of oral thrush or ulceration. Abdominal, cardiac, pulmonary, skin, and neurologic exam were within normal limits. Initial laboratory results were notable for normocytic anemia, with hemoglobin 8.6 g/dL. He had elevations in serum LDH, α-fetoprotein, and β-hCG consistent with his primary malignancy, but these markers had decreased, indicating chemotherapy response. There was no evidence of coagulopathy, and liver function tests were within normal limits.

Gastrografin esophogram revealed a narrowing in the distal third of the esophagus with no obstruction to liquid contrast (Figure 1). There was no evidence of contrast extravasation, and no ulcerations were noted. CT scan of the chest, abdomen, and pelvis revealed esophageal distension to the gastroesophageal junction with a mildly thickened esophagus and no extrinsic compression. Prior to esophagogastroduodenoscopy (EGD), the patient declined a therapeutic dilatation due to concern regarding the risk of perforation. On EGD, the upper third of the esophagus was erythematous and friable with contact (Figure 2). A 1 cm x 9 mm site of moderate stenosis found 29 cm from the incisors was traversed with mild resistance (Figure 2). An additional site of stenosis found 30 cm from the incisors was traversed with sloughing of cells. A severe stenosis with a luminal diameter of 3 mm found at 36 cm from the incisors was not traversed (Figure 2). A pediatric endoscope was used due to the severity of stenosis. The stenotic area appeared ulcerated at the top. Cells for cytology from within the stricture were obtained by brushing, and biopsies were taken with cold forceps for viral culture and histology. Histopathologic examination revealed nonspecific esophagitis. Cytology and biopsy results were negative for malignancy and revealed cells typical of acute inflammation. No fungal elements were noted. Biopsy revealed fragments of granulation tissue with acute and chronic inflammation.

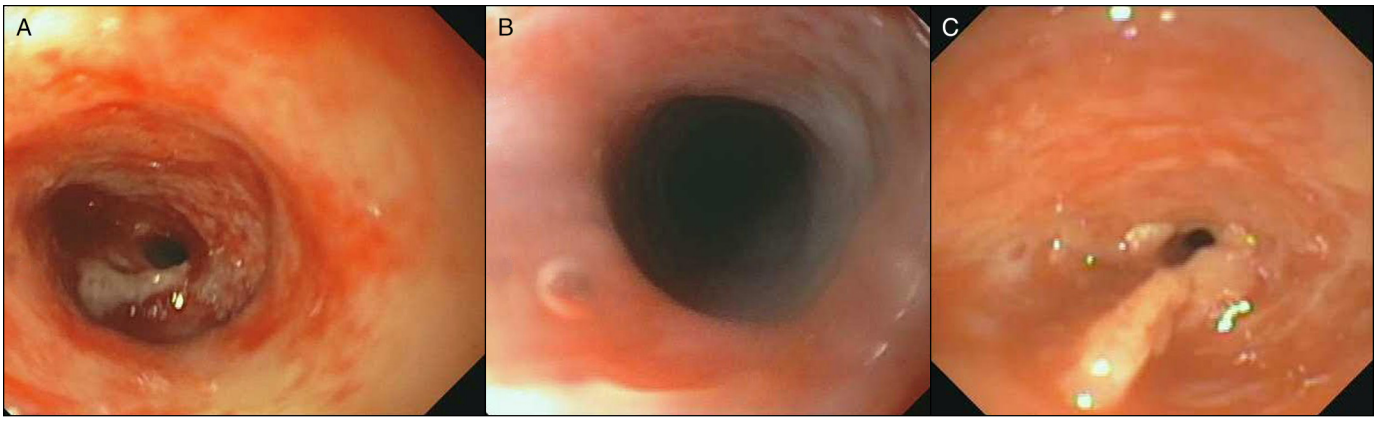

Figure 2. Endoscopy of the esophagus revealing (A) a stricture and friable mucosa, (B) a 1 cm x 9 mm moderate stenosis 29 cm from incisors, and (C) a severe stenotic stricture 36 cm from incisors measuring 3 mm in inner diameter.

The patient's symptoms continued, but he refused endoscopic dilation. He was continued on a thin liquid diet and eventually treated with laparoscopic percutaneous endoscopic gastrostomy (PEG) tube placement and parenteral feeding to optimize nutrition. He was seen 6 weeks after PEG tube placement in the oncology clinic. Though his disease shows response to chemotherapy, he still requires parenteral feeding and remains hesitant regarding endoscopic dilation. The acute onset of esophageal stricture, without any prior radiation treatment or secondary cause of dysphagia, led to the diagnosis of esophageal stricture secondary to the use of systemic EP chemotherapy.

DISCUSSION

Dysphagia in the immunocompromised patient is typically the result of opportunistic infection caused by *Candida albicans*, herpes simplex virus, or cytomegalovirus. Reflux esophagitis, caustic ingestion, esophageal webs, and foreign bodies can cause dysphagia in both immunocompromised and immunocompetent individuals. The patient had no historical features to suggest such an etiology for his symptoms, and endoscopic and histopathologic findings excluded them. Esophageal strictures are a known complication following radiation therapy, but the patient had no history of radiation therapy. Isolated chemotherapy-induced strictures are rare, especially in adults.

Two large retrospective studies evaluated the prevalence of esophageal stricture in pediatric patients treated for malignancy. In both studies, all patients had prolonged follow-up to include delayed toxicity. Of the several thousand cases, included in these studies, only 2 cases of esophageal stricture were found in patients receiving chemotherapy alone.[4,5] In the adult population, only 2 patients have been previously identified who developed stricture during treatment with systemic chemotherapy.[2,3] In both of these cases, symptoms began within 3 weeks of initiation of systemic chemotherapy, as in our case. However, the previously reported causative chemotherapeutic agents were different from our case. One patient had received 5-fluorouracil- (5-FU)-based chemotherapy for rectal cancer. Her symptoms initially improved following endoscopic dilation therapy, but she required monthly endoscopy secondary to the development of new strictures at the proximal and distal ends of the stents.[3] She had no evidence of esophageal malignancy on repetitive endoscopy with multiple biopsies, and cross-imaging confirmed the benign process. The second patient received idrarubucin and cytarabine chemotherapy for acute myelogenous leukemia. She had symptoms 12 days after induction therapy and responded to esophageal dilation without recurrence of symptoms. Although the causative chemotherapy agents differed, etoposide, 5-FU, and cytarabine similarly inhibit the *S* phase of the cell cycle, which disrupts DNA replication leading to significant mucosal damage throughout the gastrointestinal tract. Prior studies have suggested that both etoposide and cisplatin can exacerbate radiation effects on the esophagus.[6,7] Because our patient never received radiation therapy, and given the rarity of chemotherapy-induced stricture, it is difficult to determine which agent is responsible for the adverse outcome.

Mucositis and esophagitis are known complications of many chemotherapeutic agents. Stricture formation is extremely rare and largely absent in the literature. In this case, we suspect the patient's esophageal stricture was a complication of systemic chemotherapy as the patient had no history of long-standing acid reflux or known exposure to established non-peptic causes of stricture. This unexpected adverse outcome is likely caused by an interplay of mucosal damage associated with chemotherapy and the rapidly proliferating cells that line the gastrointestinal tract. It is interesting to note its severity in the absence of concomitant radiation toxicity. These findings should prompt further investigation into the pathways of injury, potentially involved genetic mutations, and the risk factors of such a rare isolated injury.

DISCLOSURES

Author contributions: All authors contributed equally to the manuscript. D. Sedhom is the article guarantor.

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Informed consent was obtained for this case report.

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REFERENCES

1. Spechler SJ. AGA technical review on treatment of patient with dysphagia caused by benign disorders of the distal esophagus. *Gastroenterology*. 1999;117(1):233.
2. Yata K, Yamada O, Iwato K, et al. Acute myelogenous leukemia associated with severe esophageal stricture after chemotherapy (in Japanese). *Rinsho Ketsueki*. 2002;43:41–3.
3. Chala E, Cheesman A, Hammami M, Taylor JR, Poddar N, Garrett RW, Alkaade S. A unique case of a patient with rectal cancer who developed benign esophageal stenosis after localized rectal radiation and systemic chemotherapy. *Case Rep Gastroenterol*. 2015;9:44–8.
4. Kelly K, Storey L, O'Sullivan M, et al. Esophageal strictures during treatment for acute lymphoblastic leukemia. *J Pediatr Hematol Oncol*. 2010;32:124–7.
5. Ellenhorn J, Lambroza A, Lindsley KL, et al. Treatment-related esophageal stricture in pediatric patients with cancer. *Cancer*. 1993;71:4084–90.
6. Umsawasdi T, Valdivieso M, Barkley HT, et al. Esophageal complications from combined chemoradiotherapy (cyclophosphamide + Adriamycin + cisplatin + XRT) in the treatment of non-small cell lung cancer. *Int J Radiat Oncol Biol Phys*. 1985;11:511–9.
7. Giever R, Heusinkveld R, Manning M, Bowden G. Enhanced radiation reaction following combination chemotherapy for small cell carcinoma of the lung. *Int J Radiat Onc Biol Phy*. 1982;8:921–5.