A Unique Case of a Patient with Rectal Cancer Who Developed Benign Esophageal Stenosis after Localized Rectal Radiation and Systemic Chemotherapy

Elie Chahla, MD
Division of Gastroenterology and Hepatology, Department of Internal Medicine
Saint Louis University School of Medicine
St. Louis, MO 63110 (USA)

E-mail: elie.chahla@gmail.com

Key Words
Rectal cancer • Benign esophageal stenosis • Localized rectal radiation • Systemic chemotherapy

Abstract
Acute esophagitis and esophageal strictures typically occur after local radiation therapy to the thoracic field. Toxicity is usually limited to the field of radiation and potentially augmented by concomitant use of chemotherapy, however esophageal stricturing due to chemotherapy alone is exceedingly rare. Gastrointestinal toxicity has been previously reported in the setting of 5-fluorouracil (5-FU)-based chemotherapy with abnormal thymidylate synthase or dihydropyrimidine dehydrogenase activities. We present a unique case of isolated chemotherapy-induced esophageal stricture in the setting of stage IIIa rectal adenocarcinoma which presented shortly after initiation of treatment with 5-FU-based chemotherapy in a patient with normal thymidylate synthase and dihydropyrimidine dehydrogenase assays. These findings prompt further investigation of pathways and potential risk factors leading to esophageal toxicity in patients treated with 5-FU-based chemotherapy.

© 2015 S. Karger AG, Basel
Introduction

Acute esophagitis and esophageal strictures are relatively common adverse effects related to radiation therapy in the setting of head, neck and thoracic malignancies with an incidence rate ranging from 22 to 37% [1]. Toxicity is usually dose-dependent [2–4], occurs within 2–3 weeks after the initiation of radiation therapy and is primarily related to disruption of the basal epithelial layer of the esophagus [5]. Subsequent inflammation and scar formation within the esophageal muscularis result in stricture formation, typically seen 3–6 months after completion of radiotherapy [6, 7]. Esophageal strictures secondary to radiation therapy are usually located within the field of radiotherapy and potentially augmented by concomitant use of chemotherapy. However, esophageal strictures due to isolated chemotherapy use are extremely rare [8]. To our knowledge, only one case of isolated chemotherapy-induced esophageal stricture has been reported in the adult population, involving a patient with acute myelogenous leukemia [9]. No cases have been identified while undergoing adjuvant chemotherapy for solid tumors. We present the case of a patient receiving adjuvant chemotherapy for rectal cancer who subsequently developed a benign but severe recurrent esophageal stricture.

Case Report

A 55-year-old female was diagnosed with stage IIIa (cT2N0M0, uT2N1M0) rectal adenocarcinoma. She was treated with neoadjuvant chemotherapy with capecitabine (1,250 mg/m² twice daily, days 1–14 of cycle) and localized radiation therapy (50.4 Gy in 28 fractions) to the rectum for 2 months. She subsequently underwent laparoscopic-assisted rectal resection, with pathology revealing moderately differentiated adenocarcinoma with negative margins, colonic J-pouch with diverting ileostomy, and adjuvant chemotherapy with modified FOLFOX-6 (oxaliplatin 85 mg/m², 5-fluorouracil [5-FU] bolus 400 mg/m², leucovorin 400 mg/m² and 5-FU infusion 1,200 mg/m²/day for 2 days) for 2 cycles.

Three weeks after initiation of adjuvant chemotherapy, the patient was hospitalized for management of new-onset dysphagia and odynophagia. Her symptoms persisted despite discontinuation of chemotherapy and empirical treatment with antifungal therapy for suspected Candida esophagitis. An esophagogram and a computed tomography (CT) of the chest revealed irregular long narrowing in the mid and distal esophagus (fig. 1, fig. 2). Upper endoscopic evaluation revealed an 11-cm-long esophageal stenosis with mucosal erythema and friability starting 25 cm from the incisors (fig. 1). Repeat biopsies and imaging studies failed to reveal an infectious or neoplastic etiology. The patient had no history of dysphagia prior to adjuvant chemotherapy and during the period when she received neoadjuvant concurrent chemotherapy and radiation, and her esophagus had been normal-appearing on two previous CT scans performed 2 months before adjuvant chemotherapy administration. The patient’s symptoms improved after endoscopic dilation therapy, but she required repeated endoscopic therapy on a monthly basis including intralesional steroid injections. A fully covered esophageal stent was placed twice with short-term improvement in symptoms. Unfortunately, the patient also had secondary development of new esophageal strictures at the proximal and distal ends of the stent. The esophageal stents were ultimately removed and the patient’s symptoms were controlled with repeat endoscopic dilation of the benign stricture every 4–6 weeks. She had no evidence of esophageal malignancy on repetitive endoscopy with multiple biopsies or cross-sectional imaging for 18 months since diagnosis, further confirming the benign process.
Discussion

Esophageal strictures are a known complication of radiation therapy especially during treatment of head, neck and thoracic malignancies. Injury to the esophagus results in severe fibrosis, mucosal atrophy, ischemic ulcerations and esophageal strictures [10, 11]. Isolated chemotherapy-induced esophageal strictures are a very rare entity and have only been described in the pediatric literature, specifically in the management of acute leukemias. Yata et al. [9] reported the only other existing case in adults, pertaining a 41-year-old woman who developed a 6-cm-long lower esophageal stricture 12 days after re-induction therapy for acute myelogenous leukemia.

Our patient received 28 sessions of low-dose localized radiation therapy to the rectum with concurrent neoadjuvant capecitabine chemotherapy without any gastrointestinal complications. Esophageal toxicity and stricturing did not occur until systemic adjuvant chemotherapy with modified FOLFOX-6 (oxaliplatin, 5-FU bolus and leucovorin) was provided. It is highly unlikely that localized radiation therapy to the rectum would be responsible for the esophageal findings described.

Severe gastrointestinal toxicities of 5-FU-based chemotherapy can be more pronounced in patients with evidence of polymorphisms in the thymidylate synthase (TS) or dihydroorotate dehydrogenase (DPD) genes [12]. Low levels of TS expression are associated with toxicity to 5-FU. When DPD enzyme activity is low, the gastrointestinal mucosal involvement can be severe and, in rare cases, fatal. Surprisingly, our patient’s DPD and TS enzymatic activity levels were both within normal limits.

Esophageal strictures secondary to isolated use of systemic chemotherapy are an exceedingly rare complication. We suspect that this unexpected but dramatic adverse event is caused by mucosal damage limited to the esophagus due to the chemotherapeutic agents, since our patient did not receive localized radiation to the esophageal field.

In conclusion, we report a very unusual and rare case of acute gastrointestinal toxicity limited to the esophagus after initiation of systemic oxaliplatin and 5-FU-based chemotherapy in a patient with normal TS and DPD assays. The possibility of other genetic mutations leading to this complication should be further investigated in future studies.

References


Fig. 1. a Spot image taken during fluoroscopic esophagogram. A long stricture segment (11 cm) is noted in the mid to distal esophagus with associated mucosal irregularity (arrows). S = Stomach. b Endoscopic visualization in the middle third of the esophagus demonstrating very friable, erythematous and hyperemic mucosa with a stricture noted 25 cm from the incisors (between the two arrows).
Fig. 2. Contrast-enhanced CT of the chest. a Sagittal reformatted image demonstrating mild distention of the upper thoracic esophagus (asterisk) and long stricture segment of the mid and distal esophagus (arrows). b Axial CT through the upper thoracic esophagus demonstrating normal wall thickness with mild distention (arrow). c Axial CT through the strictured segment showing significant esophageal wall thickening and luminal narrowing (arrow).