Case Reports in Gastroenterology

Case Rep Gastroenterol 2013;7:498–502

DOI: 10.1159/000357303
Published online: November 28, 2013

1662–0631/13/0073–0498$38.00/0
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Verrucous Carcinoma of the Esophagus: A Potential Diagnostic Dilemma

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Key Words
Esophagus · Verrucous carcinoma · Human papillomavirus

Abstract
Verrucous carcinoma of the esophagus is a rare variant of squamous cell carcinoma associated with human papillomavirus. We report the case of a 58-year-old female who presented with ongoing symptoms of dysphagia. On previous endoscopies she had been noted to have a large polyp-like mass involving the esophagus, with negative biopsies for malignancy. Repeat endoscopy with concurrent endoscopic ultrasound showed a large semi-pedunculated polyp in the distal esophagus and a hypoechoic, irregular mass involving the gastroesophageal junction with esophageal thickening. Deep layer biopsies showed pseudoepitheliomatous hyperplasia with immunohistochemical staining positive for human papillomavirus. The patient was subsequently treated with chemo-radiation followed by esophagectomy.

Introduction

Verrucous carcinoma of the esophagus (VCE) is a rare malignant epithelial tumor representing a variant of squamous cell carcinoma [1]. It was first reported in 1967 by Minielly et al. [2]. Since then, only a small number of cases of this entity have been described in the literature. Other sites of verrucous carcinoma include the oropharynx, larynx, genitalia, cervix, urinary bladder, anus and the soles of the feet [3, 4].

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VCE is usually seen in the middle-aged population, affecting mainly the lower esophagus, with higher prevalence in males [5]. Symptomatically, it commonly presents with an insidious onset of dysphagia and weight loss, with delayed diagnosis ranging from months to years [6]. Grossly, in most cases it is an exophytic slow-growing mass emerging as papillary or warty-like, with extensive superficial growth pattern. Under the microscope well-differentiated squamous cells with minimal to low atypia are seen. In addition, hyperkeratosis, nonspecific inflammation and obvious acanthosis can be seen [1, 6]. Endoscopically, hypoechoic wall thickening is seen from nodular to concentric in appearance, penetrating from the mucosa to the submucosa, with frequent invasion into the muscularis propria layer [3–5, 7].

Risk factors associated with VCE include smoking, alcohol intake, chronic inflammation, achalasia, caustic exposure, and as recently speculated human papillomavirus (HPV) infection [6]. The role of HPV in carcinogenesis is contemplated to be secondary to overexpression of p53, MDM2, ErcB2 and loss of p21 [8, 9]. The diagnosis is difficult, often requiring a high clinical suspicion with multiple repeat endoscopic biopsies, preferably with large-capacity spike forceps [4, 6, 7]. Due to its rarity, treatment modalities are unclear at this point. However, surgery is usually preferred in the early stages, as VCE has a low potential for metastasis and lymph node involvement [6, 7].

Case Presentation

A 58-year-old female with a past history of squamous cell carcinoma of the larynx, treated with radiation therapy and surgery 13 years earlier, presented with dysphagia and weight loss of approximately 10 pounds; symptoms had started almost 2 months before. At the time of presentation, she was able to tolerate a liquid diet only and was referred to us for further diagnostic workup after two prior gastroscopy studies. Previous evaluation had revealed a large polyp-like mass involving the mid and distal esophagus. However, repeat biopsies from this lesion had been negative for malignancy. On repeat esophagogastroduodenoscopy, a large semi-pedunculated polyp was seen in the distal esophagus (fig. 1). The polyp stalk seemed to blend into a background of nodular-appearing mucosa involving the distal esophagus with the gastroesophageal junction. On endoscopic ultrasound, a hypoechoic, irregular mass was found, involving the gastroesophageal junction with associated esophageal thickening, measuring 20 mm in thickness. There was sonographic evidence suggesting invasion into the deep adventitia layer (fig. 2). Biopsies using large-capacity forceps demonstrated pseudoepitheliomatous hyperplasia, raising the suspicion of VCE. p16 immunohistochemical staining was positive for HPV.

Initial positron emission tomography (PET) and computed tomography (CT) evaluation was consistent with an increase in hypermetabolic soft tissue fullness at the gastroesophageal junction. After discussion at the multidisciplinary conference, the decision was made to proceed with chemo-radiation with preoperative carboplatin and Taxol. Repeat PET/CT after 3 months demonstrated significant interval reduction in the size and metabolic activity of the distal esophagus near the gastroesophageal junction, consistent with a positive response to radiation therapy. Clinically, the patient had significant improvement in symptoms after initiation of chemo-radiation therapy. Afterwards, she underwent interval Ivor-Lewis esophagectomy with no residual mass seen on gross specimen. Final histology did not reveal any viable tumor (fig. 3).

Discussion

VCE can pose a potential diagnostic dilemma because this tumor typically does not show high-grade dysplasia [3, 10]. Therefore, multiple sets of endoscopic biopsies may be required due to the overlying hyperkeratotic layer [3]. Although commonly described as a wart-like lesion, a polypoid mass-like configuration has also been reported [5, 8, 9]. The proximal end of the lesion in our patient started off as a polypoid mass, being contiguous with the distal esophagus as an infiltrating lesion. Two previously attempted biopsies were nondiagnostic. However, the endoscopist's suspicion for a malignant lesion was high. Repeat endoscopic evaluation with concurrent endoscopic ultrasound was suggestive of a malignant process infiltrating through the muscularis propria. Therefore, endoscopic ultrasound may be a useful adjunctive modality in such cases. Furthermore, demonstration of HPV on biopsies and a relevant history of previous squamous cell carcinoma of the larynx was very helpful, raising suspicion for a squamous carcinoma variant involving the esophagus.

In a retrospective analysis of 11 patients with VCE of the esophagus seen at a tertiary referral center over 5 years, about half the patients reported smoking or consuming alcohol on a regular basis. The median time interval from onset of symptoms to diagnosis of esophageal VCE was 2.5 years, with dysphagia being present in all patients. The majority of tumors exhibited a white, warty, plaque-like appearance. Initial pinch biopsies were nondiagnostic in 73% of the patients. In patients treated solely with surgery and who had a preoperative endoscopic ultrasound, the latter tended to overestimate staging of the lesion relative to surgical pathologic staging [6].

In conclusion, a previous history of squamous cell carcinoma, especially with positive HPV staining on biopsies, should raise suspicion of VCE. Since it is a squamous cell variant, chemo-radiation has excellent response, to be followed by surgical resection.

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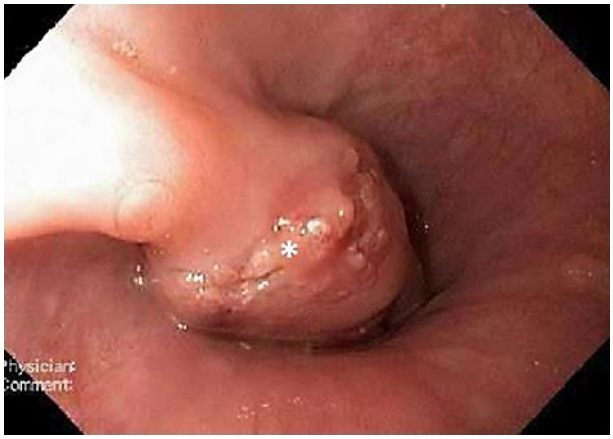

Fig. 1. Proximal end of the large polypoid mass (asterisk) involving the distal esophagus.

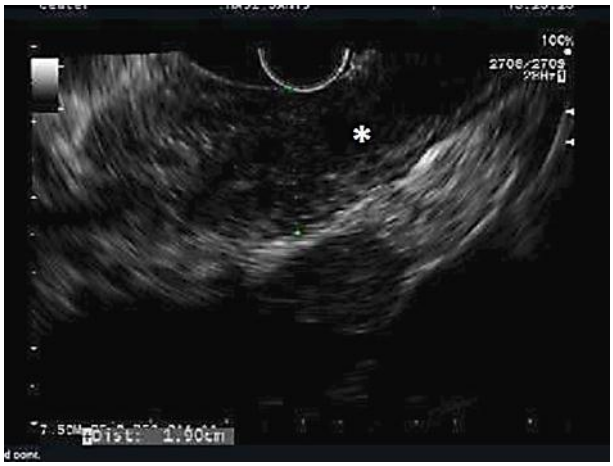

Fig. 2. Hypoechoic mass penetrating through the muscularis propria (asterisk), suggestive of a T3 lesion.

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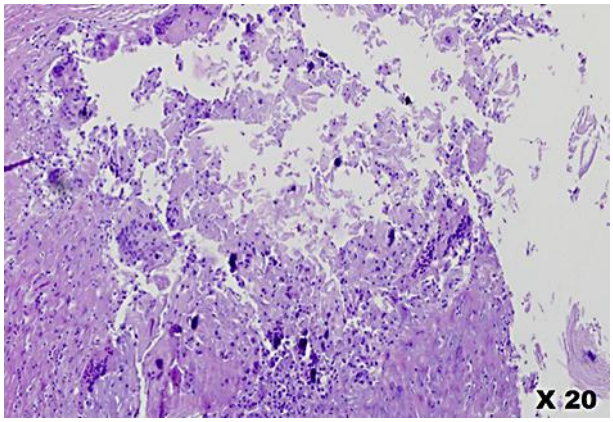

Fig. 3. Esophagectomy specimen (original magnification × 20) post chemo-radiation; giant cell foreign body reaction with keratinaceous debris involving the deep muscularis propria. No definitive viable tumor can be identified.