Diseases of the Esophagus (2004) **17**, 187–190

DISEASES OF THE ESOPHAGUS

Case report

Photodynamic therapy and endoscopic metal stent placement for esophageal papillomatosis associated with squamous cell carcinoma

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SUMMARY. **Esophageal squamous papillomatosis is a rare condition associated with human papilloma virus infection and has been complicated by the development of squamous cell carcinoma. Photodynamic therapy using porfimer sodium has been used for the treatment of esophageal cancer but has not been utilized in the treatment of esophageal squamous papillomatosis. We report here the first case of papillomatosis and obstructing squamous cell carcinoma of the esophagus palliated with porfimer sodium photodynamic therapy indicating successful photosensitizer uptake in papilloma-laden tissue. Extensive debulking of papilloma and tumor allowed esophageal recanalization and placement of a self-expanding metal stent for long-term dysphagia palliation. This unique case highlights the combined use of endoscopic techniques for optimal treatment results.**

KEY WORDS: **esophageal cancer, papillomatosis, photodynamic therapy, squamous cell carcinoma.**

INTRODUCTION

Esophageal squamous papillomatosis is a rare condition that has only been reported in approximately 200 cases in the medical literature.[1] These lesions have been associated with viral infection, particularly human papilloma virus (HPV).[2,3] The finding of HPV-associated esophageal papillomatosis appears to be more common in areas with a high incidence of esophageal squamous cell carcinoma such as northern China, Iran and South Africa.[4] Esophageal papillomatosis caused by HPV infection is very uncommon in North America unless associated with sexual transmission from genital HPV lesions.[5] While the development of invasive squamous cell carcinoma of the esophagus is frequently noted in HPV associated disease,[6] the malignant potential of esophageal papillomatosis without demonstrable HPV infection is controversial.[7] There is no established treatment for esophageal papillomatosis although endoscopic therapy with cytosine injection and surgical resection has been reported.[8,9] Photodynamic therapy (PDT) features the combined use of a photosensitizer, light and oxygen to produce target cell toxicity and death.[10] While the combination of light and dyes have been used to treat infections for hundreds of years,[11] this is the first case of esophageal squamous papillomatosis treated with porfimer sodium photodynamic therapy and subsequent placement of a self-expanding metal stent for successful palliation of dysphagia.

CASE REPORT

This report describes the case of an 84-year-old, white man who developed swallowing difficulties in January 2003. His past medical history was significant for severe coronary artery disease with previous four-vessel bypass graft surgery in 1997, insulin-dependent diabetes mellitus, prostatitis, and asymptomatic gallstone disease. Previous exposure to Histoplasmosis was suggested by the presence of calcified diminutive nodules in the lung periphery noted on chest X-ray. Although his brother had previously been treated for acute histoplasmosis infection, there was no sign of active histoplasmosis infection in the current case.

The onset of dysphagia was progressive. The intermittent solid food dysphagia that initially responded to endoscopic dilation worsened over a period of 8 weeks requiring placement of a percutaneous

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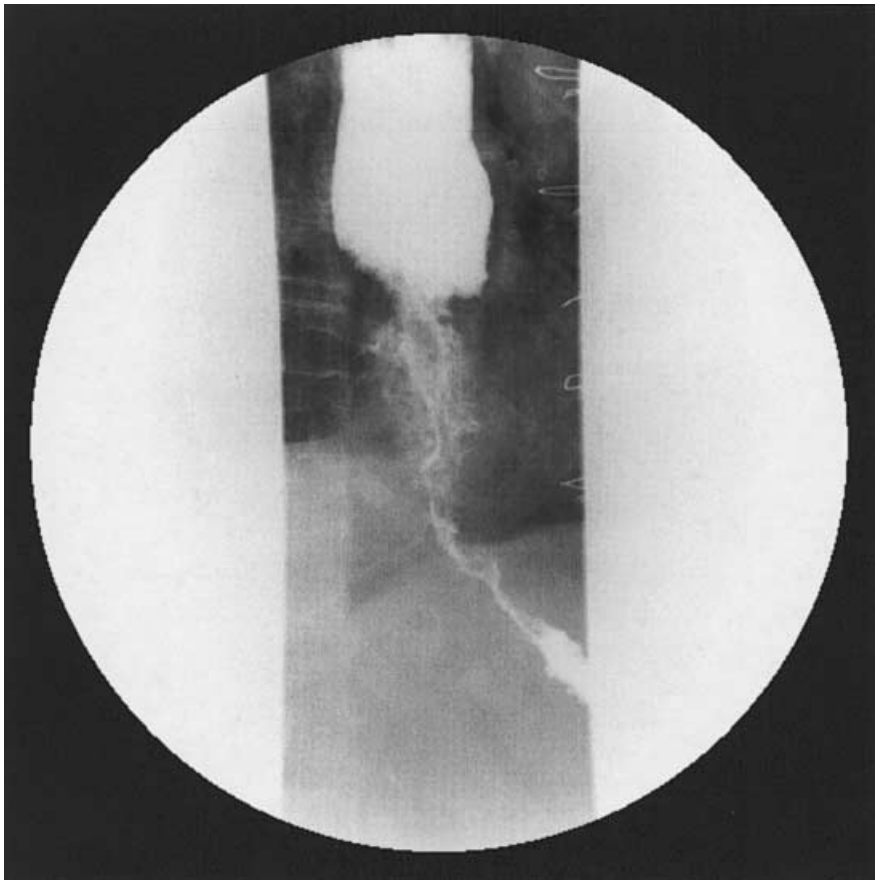

Fig. 1 Barium esophagram showing marked narrowing with mucosal irregularity extending over a long segment of the distal esophagus and extrinsic compression of the right mid esophagus due to mediastinal lymphadenopathy.

gastrostomy for enteral nutrition. Endoscopic dilations became progressively more difficult and only intermittent swallowing of thin fluids was possible. Endoscopic studies described white-yellow verrucae lesions lining the mucosal surface of the distal esophagus with severe narrowing of the esophageal lumen. Computed tomography previously noted only a thickened esophageal wall without para-esophageal lymphadenopathy or evidence of metastatic disease.

Our evaluation included an esophageal barium X-ray that demonstrated marked narrowing of the lumen with mucosal irregularity extending throughout the esophagus (Fig. 1). Computed tomography with contrast enhancement found a dilated-appearing esophagus with wall thickening and air-fluid level but no mediastinal mass or lymphadenopathy. Endoscopy documented extensive, diffuse esophageal papillomatosis throughout the middle and distal esophagus with relatively normal appearing mucosa lining the dilated proximal esophagus. Biopsies of these verrucae lesions demonstrated a papillary growth pattern with hyperkeratosis, metaplasia, koilocytes and dysplasia similar to genital condylomata with viral-type changes and focal, microinvasive well-differentiated squamous cell carcinoma (Fig. 2). Further testing with in-situ hybridization for human papilloma virus (HPV) typing was performed on esophageal mucosal biopsies and was negative for HPV viral type 6, 11, 16, 18, 31, 33 and 51 with appropriate testing of positive and negative controls.

As endoscopic dilations were increasingly more difficult yet ineffective in sustaining relief of dysphagia, we elected to proceed with endoscopic ablative therapy using photodynamic therapy using methods described previously.[12] Subsequently, the patient underwent infusion of porfimer sodium (2 mg/kg; Axcan Scandipharm, Mont-St-Hilaire, Quebec, Canada) followed by photodynamic therapy with endoscopic delivery of 300–400 J/cm fiber length red light energy (wavelength 630 nm) using a 5-cm length quartz diffusing light fiber powered by a diode laser (Diomed, Andover MA) in divided doses over two treatment sessions. Debridement endoscopy procedures were performed the day following each PDT light application. The previously white frond-like papillomas featured extensive necrosis and blue-black discoloration. After extensive debridement of the necrotic papillomatosis tissue, swallowing improved to allow intake of full liquids and soft solids. While PDT was successful in re-establishing esophageal patency and swallowing

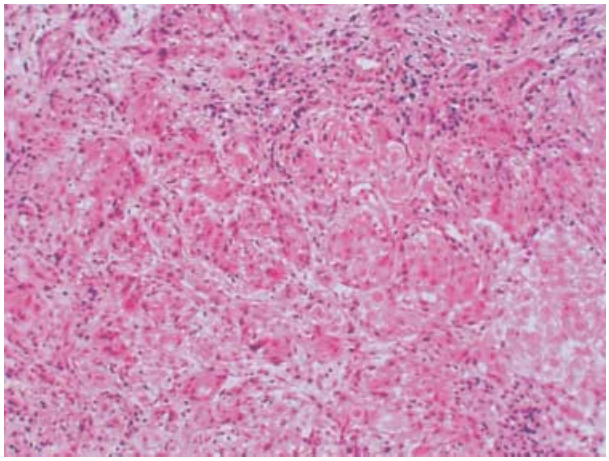

Fig. 2 Endoscopic biopsy of the lower esophagus demonstrating infiltrating squamous cell carcinoma (HE stain, ×100 magnification).

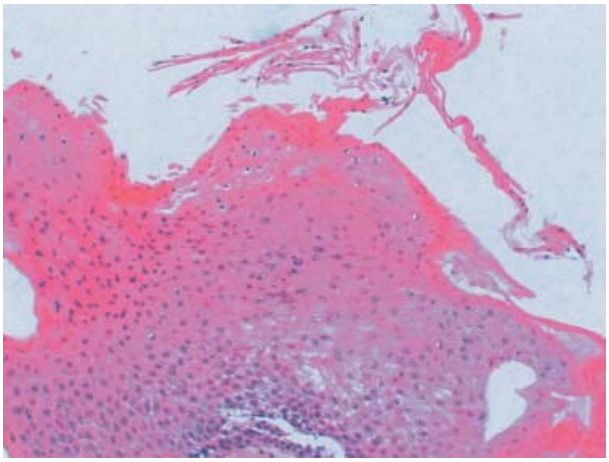

Fig. 3 Endoscopic biopsy of the lower esophagus demonstrating papillomatous squamous proliferation with keratosis and koilocytosis (HE stain, ×100 magnification).

function, the underlying squamous cell carcinoma limited the anticipated palliation provided by PDT. Subsequently therefore an Ultraflex self-expanding metal stent (15 cm length, Boston Scientific, Andover MA) was placed for long-term palliation of dysphagia.

DISCUSSION

Esophageal squamous papillomatosis is a rare condition that has been variably associated with HPV infection and invasive squamous cell cancer.[13–16] In one of the largest studies available, Mosca *et al*. reviewed 7618 consecutive upper endoscopy examinations over a 4-year period and reported finding squamous papillomatosis without HPV infection in nine patients (0.01%).[1] All of these lesions were isolated, small condylomata-like lesions with a mean size of 4 mm. These lesions were generally found in the cervical esophagus, located at 25 cm (mean) from the incisors. All squamous esophageal papillomas were removed and tested for HPV with commercially available kits for in-situ hybridization but none was found. Over a 4-year follow period there was no sign of disease progression and malignant degeneration was not found in any of these patients.

Our patient, however, differs from most cases esophageal papillomatosis reported in the literature in that the squamous papillomatosis was extensive and diffuse with lesions that carpeted the entire middle and lower esophagus. The appearance of these lesions, and the swallowing difficulties associated with them, was rapidly progressive over a period of weeks. These progressive symptoms, however, may have also indicated the development of an underlying invasive squamous cell neoplasm. The appearance of thick-walled esophagus on CT scan indicated that the mucosa was markedly thickened with condylomata-like lesions. While drug therapy has been used for papillomatosis conditions previously, the massive amount of disease in this case suggested that medical therapy might not be effective.[17] Similarly, endoscopic therapy using injection therapy of an antiviral drug or removal by piecemeal polypectomy techniques for esophageal squamous papillomas had been reportedly used only in cases with a limited number of diminutive lesions. The massive amount of papillomatous tissue occluding the esophageal lumen required treatment with an alternative method that could treat a large area of disease and produce rapid necrosis permitting endoscopic debridement to re-establish esophageal patency. For these reasons, we selected treatment with PDT and, based on our review of the literature, we believe that this case is the first successful use of photodynamic therapy, in this instance using the photosensitizer porfimer sodium, for esophageal papillomatosis.

The marked necrosis induced by photodynamic therapy is indicative of successful uptake and absorption of the porphyrin photosensitizer despite the massively thickened esophageal mucosa. The rapid and extensive mucosal necrosis with subsequent endoscopic debridement allowed re-canalization of the esophageal lumen with excellent palliation of dysphagia. We anticipated, however, that this symptomatic improvement would not be long lasting, as this case of esophageal papillomatosis was associated with the development of invasive squamous cell carcinoma. Therefore, approximately 6 weeks after PDT, the patient underwent the endoscopic placement of a self-expanding, covered, wire mesh metal stent.[18] This unique case underscores the importance of optimizing treatment results by combining the use of endoscopic modalities for the long-term relief of dysphagia.[12,19]

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