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Esophageal Squamous Papilloma in the Pediatric Population

*Neha Malhotra, †Nuphar Lendner, ‡Christina Gagliardo, §Keith Breglio, ‖Niv Mor, and *Graciela Wetzler

Abstract: Esophageal squamous papillomas (ESP) are rare benign tumors of the esophagus, which occur mostly in the adult population. Few cases have been reported in children and due to the low incidence, the pathogenesis of ESP is not entirely understood and the management is not standardized. It is thought that mucosal irritation from underlying inflammation, perhaps from GERD, trauma or human papilloma viruses can play a role in the formation of ESP. This report describes 4 cases of pediatric ESP from a single center and discusses the management of these lesions, including the use of antacids and the human papilloma viruses vaccine as treatment modalities. Given the limited data on ESP in the pediatric population, this report aims to describe the management of this condition in 1 center.

Key Words: esophageal squamous papilloma, upper endoscopy, human papilloma virus, esophagogastroduodenoscopy, human papilloma virus, gastroesophageal reflux disease

INTRODUCTION

Esophageal squamous papilloma (ESP) is a rare benign epithelial tumor of the esophagus with a prevalence of 0.01%–0.43% in patients undergoing upper endoscopy (1). They are benign epithelial lesions, found incidentally on mucosal examination and occur mostly in the adult population. ESPs are not thought to cause any significant symptoms of dysphagia, pain, or otherwise. They are often found as solitary, small, sessile lesions, although may also be found in a diffuse manner. The pathogenesis of ESP is uncertain but two theories have been proposed: mucosal irritation due to underlying inflammatory conditions such as gastroesophageal reflux disease (GERD) and human papilloma virus (HPV) associated epithelial changes (1). This report will discuss ESP in the pediatric population from a single center, discuss pathology findings, and provide a description of treatment modalities utilized in these patients.

MATERIALS AND METHODS

Case 1

A 3-year-old female presented with a 1-week history of cough, intermittent fevers, rhinorrhea, decreased appetite and 4-month history of intermittent dysphagia. Physical exam showed an erythematous oropharynx and an elongated uvula with cystic swelling at the tip. She failed to improve after a course of antibiotics.

Due to persistent uvula swelling, a microdirect laryngoscopy was completed and revealed an uvular lesion and a pedunculated laryngeal lesion on a vascular stalk. Both were excised completely with biopsy forceps, and histopathologic review confirmed an uvular epidermoid cyst and a laryngeal squamous papilloma. Immunohistochemistry showed HPV-subtype 6/11. The patient's mother had no history of HPV, she underwent a PAP smear 1 year before the patient's presentation and did not have any abnormal lesions. HPV testing was not performed on the mother, since she did not have any abnormal lesions.

Treatment with histamine receptor antagonist (H2RA) was initiated, and a follow-up laryngoscopy a month later showed a new postcricoid mass with extension into the esophagus. She underwent a triple combined procedure of a microdirect laryngoscopy, bronchoscopy, and esophagogastroduodenoscopy (EGD). The cricoid mass was removed and pathology again confirmed a squamous papilloma. The EGD revealed diffuse, pale and pink, pedunculated esophageal lesions with flowery borders extending to the gastroesophageal junction (see Fig. 1). The largest lesion measured approximately 5 mm, and two smaller lesions were present. All three of the lesions were removed completely with pediatric biopsy forceps, with one single attempt for each lesion.

Sections of the esophageal lesion demonstrated benign, undulating squamous epithelium (Fig. 2A). The exophytic, polypoid growth pattern seen during the EGD (see Fig. 1) is the result of true papillary growth, where epithelium lines a fibrovascular core (black arrows in Fig. 2B, C). The finger-like epithelial-lined projections of an esophageal squamous papilloma are identified (Fig. 2B). Immunohistochemistry for low-risk HPV DNA (genotypes 6, 11) showed nuclear expression within squamous cells (Fig. 2D).

Nodular mucosa in the stomach was observed and the biopsies were consistent with *Helicobacter pylori* gastritis. She was treated with a proton pump inhibitor (PPI) and antibiotics. The bronchoscopy

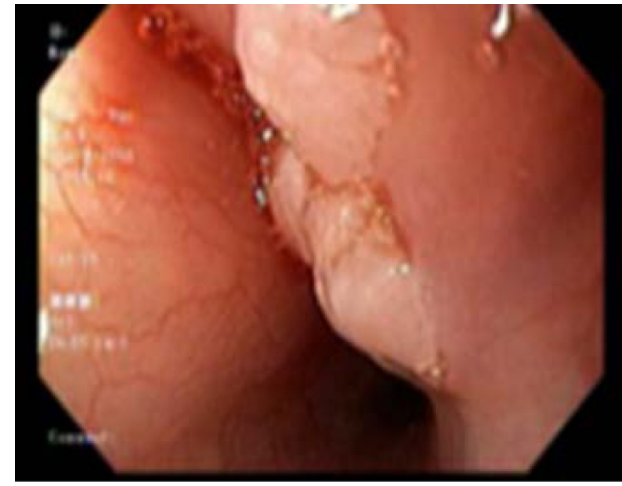

FIGURE 1. Polypoid growth seen on EGD from case 1. EGD = esophogogastroduodenoscopy.

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*Pediatric Gastroenterology, Maimonides Medical Center, Brooklyn, NY; †UH Rainbow Babies & Children's Hospital, Cleveland, OH; ‡Morristown Medical Center, Morristown, NJ; §Stony Brook Children's Hospital, Stony Brook, NY; and ‖SUNY Downstate Health Sciences University, Brooklyn, NY.

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Correspondence: Neha Malhotra, MD, 977 48th Street, Brooklyn, NY 11219. E-mail: nemalhotra@maimonidesmed.org

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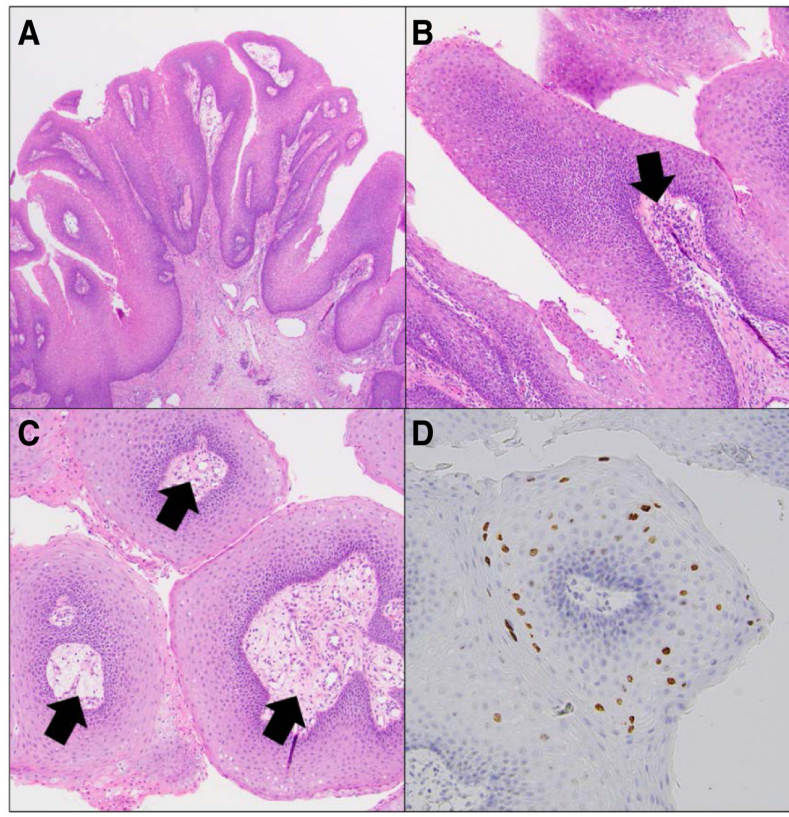

FIGURE 2. Esophageal lesion sections from case 1. A) Benign, undulating squamous epithelium. The exophytic, polypoid growth pattern seen on endoscopy is the result of true papillary growth where epithelium lines a fibrovascular core (black arrows, B and C). Immunohistochemistry for low-risk HPV DNA (genotypes 6, 11) showed nuclear expression within squamous cells (D). HPV = human papilloma viruses.

was normal. At a 1-year follow-up visit, the patient complained of new onset hoarseness.

Laryngoscopy revealed extensive recurrent laryngeal lesions with supraglottic papillomatous disease on the endolarynx, epiglottis, and arytenoids causing obstruction of her vocal folds. Treatment was completed with KTP laser ablation of the laryngeal and true vocal cord lesion and debridement of her large respiratory tract lesions. The Gardasil-9 vaccine 3-dose series was also administered as off-label use with shared decision making between the family, the primary care physician and the infectious disease specialist. She remains asymptomatic with resolution of her laryngeal and esophageal lesions on successive endoscopies. Her *H. pylori* infection also resolved.

Case 2

A 14-year-old female presented with chronic abdominal pain, nausea, and emesis. The patient was not sexually active. Laboratory testing and abdominal imaging were normal. An EGD revealed a duodenal ulcer without signs of active bleeding. She was unable to tolerate PPI therapy and was placed on a H2RA medication. A follow-up endoscopy 1 month later revealed an isolated pale papilloma with cauliflower-like appearance in the proximal esophagus, 20 cm from the incisors. The lesion was completely excised with pediatric biopsy forceps. Pathology confirmed ESP with HPV-subtype 16/18 by in situ hybridization. Treatment with PPI therapy was administered. She had completed her Gardasil vaccine series 6 months before presentation. A follow-up endoscopy 6 months later revealed resolution of her esophageal lesion, as well as resolution of her symptoms.

Case 3

A 14-year-old female presented with chronic abdominal pain and nausea. The patient was not sexually active. EGD revealed a small pale, polypoid lesion in the distal esophagus. There was nodularity in the stomach and an ulcer in the duodenal bulb. The esophageal lesion was completely excised with biopsy forceps. Pathology revealed ESP and *H. pylori* gastritis. DNA in situ hybridization confirmed HPV-subtype 6/11 in the ESP. Treatment with PPI therapy and antibiotics was instituted. The patient refused a follow-up EGD. The patient did not receive her HPV vaccine series.

Case 4

A 16-year-old female presented with GERD symptoms and abdominal pain. The patient was not sexually active. An upper endoscopy revealed 2 distinct pale, pedunculated papillary lesions at 25 cm and 32 cm from incisors. The lesions were removed with biopsy forceps and pathology revealed ESP. HPV in situ hybridization was negative. She had completed her Gardasil vaccine series 3 years before her endoscopy. Follow-up EGD revealed no further esophageal lesions. She was also diagnosed with irritable bowel syndrome.

The lesions from cases 2, 3, and 4 were all distinct lesions and appeared as seen in Figure 3. Endoscopy revealed pale papillomatous lesions with a cauliflower-like appearance, and each one was excised completely with biopsy forceps.

An unremarkable esophagus is demonstrated below in Figure 4A. The normal squamous epithelium demonstrates a basal cell layer (white arrow in Fig. 4A) composed of small, round, purple nuclei with scant cytoplasm. As these cells mature, they flatten, accumulate

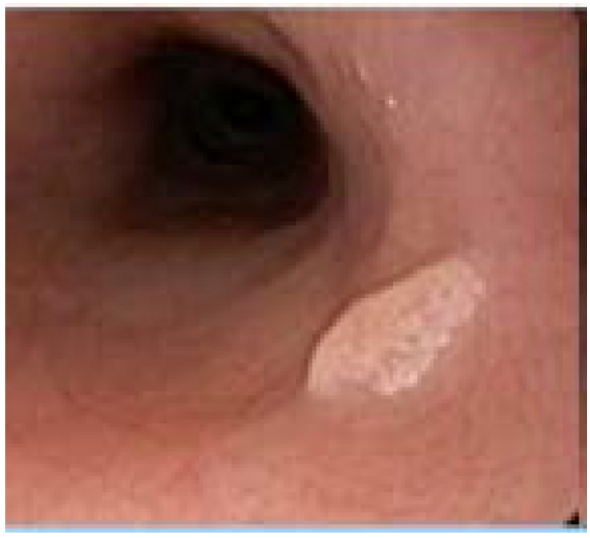

FIGURE 3. Solitary lesion seen in Cases 2, 3, and 4.

more eosinophilic cytoplasm, and migrate to the luminal surface of the esophagus. Esophagus squamous papillomas are lined by similar maturing, benign squamous epithelium that surrounds polypoid fibrovascular cores (block arrows, Fig. 4B) creating the pale, cauliflower-like exophytic lesion typically seen on endoscopy.

DISCUSSION

ESPs are typically solitary lesions identified incidentally when patients undergo an EGD for gastrointestinal symptoms. We observed 4 pediatric patients with ESPs, one of whom had diffuse disease. Three out of the 4 cases of ESP identified at our institution were positive for HPV in situ hybridization. Chronic mucosal irritation due to GERD or HPV is thought to be the most common cause of ESP, and numerous studies have repeatedly demonstrated the presence of HPV in a subset of ESP. The literature reports that they are most commonly associated with HPV-subtype 16/18, although reports of subtype 6–11 are also documented (1,2).

HPVs are double stranded DNA viruses which infect epithelial tissue. HPV initially infects the basal epithelial layer of the surface through minor excoriation (3). They are classified into cutaneous or mucosal type. Mucosal HPVs are further classified into low-risk and high-risk sub-types based on their epidemiologic association with cancer. Low-risk types 6 and 11 are often associated with recurrent respiratory papillomatosis, conjunctival papillomas, and condylomata acuminata. High-risk types 16 and 18 are associated with cervical and oropharyngeal cancer (4). In ESP, prior studies as well as our own have shown that both low-and high-risk types of HPV may be identified in these lesions. While HPV-mediated pathogenesis from papilloma to carcinoma is well known in the cervix, anogenital region, and larynx, the role of HPV in the progression of esophageal squamous cell carcinoma is conflicting and inconclusive (5–7).

In our series, one young patient had diffuse esophageal papillomas that expressed low-risk HPV, similar to the patients who present with HPV-related respiratory papillomatosis. The mode of transmission for HPV in the pediatric population may occur through direct contact of the fetus with maternally infected cells during infant passage though the vaginal canal. In utero infections may also occur through ascending infection from the maternal genital tract. It is also important to note that HPV infection of the fetus can still occur in cases of subclinical cervical HPV in the mother (8). It is unclear how our patient may have acquired HPV, but she experienced resolution of her lesions post-KTP laser ablation and vaccination.

Three additional teenage patients had solitary ESP. Two of the three patients also had HPV by *in situ* hybridization, one low-risk and one high-risk. Neither of these patient went on to have diffuse disease after excision and vaccination. Incidentally, 2 of the 4 cases were simultaneously diagnosed with HPV-related ESP and *H. pylori* gastritis and were treated with antibiotics as well as PPI. There has been 1 additional case report of ESP associated *H. pylori* gastritis, but the HPV test was negative (9). The presence of *H. pylori* in our 2 cases may have been the underlying inflammatory condition and could be considered a risk factor for ESP development.

Treatment of ESP depends on the solitary or diffuse nature of the disease. Small esophageal lesions can be managed by excisional biopsy; however, conservative management is advised when the disease is extensive to avoid mucosal scarring and stenosis. Excision or laser ablation therapy has shown promise for laryngeal lesions.

Antacid therapy can be considered as well as administration of the HPV vaccine series—as this could have a role in decreasing the mucosal inflammation from HPV. Acid suppression may decrease ongoing inflammation—which is thought to be a risk factor for the development of ESP. Interestingly, a recent study failed to identify

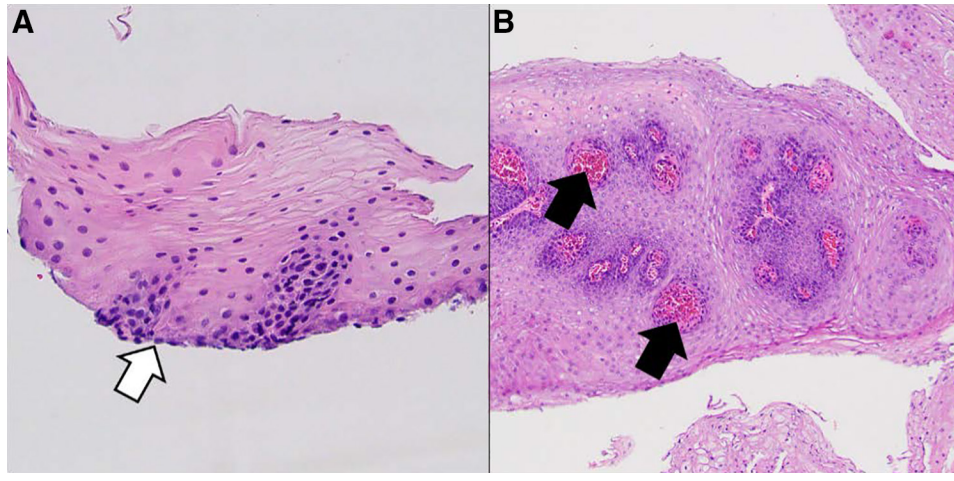

FIGURE 4. A, Normal esophagus with basal layer (white arrow), (B) ESP with a polypoid fibrovascular core (black arrows). ESP = esophageal squamous papillomas.

a relationship between the prevalence of HPV and the occurrence of ESP in pediatric patients. They concluded that reflex testing via in situ hybridization for HPV may not be beneficial or cost effective (10). We did identify HPV in a majority of our ESP cases, and feel there could be a benefit in reflex texting for HPV, which could help direct management and treatment such as the consideration of HPV vaccination.

The role of HPV vaccines as treatment modalities is not yet well understood. The vaccine is based on recombinant HPV cell-coated particles, L1 (11). The Gardasil vaccine contains inactive L1 proteins that trigger an immune response within the host that results in antibody formation that confers primary immunity. The antibodies protect against L1 HPV virion particles from adhering to the host cellular interface (8). Some studies suggest that a higher immune response is mounted in children who are vaccinated as compared to children with HPV exposure. Thus, vaccinating children with active HPV infection could theoretically increase the immune response and potentially aid in clearance of lesions caused by the disease (12). In children under 9 years of age, HPV vaccination would be considered "off label" and potential risks and benefits must be discussed with primary care physicians, infectious disease specialist, patients and families with shared decision making before administration. In addition to our young patient, an additional paper demonstrated that vaccination using an off-label indication for an already approved drug can induce clinical remission (13).

Overall, we present 4 distinct cases of pediatric ESP. Although these lesions were identified, it is unclear if the patient's symptoms were secondary to the lesions or if these were also incidental findings. Symptoms were present in all 4 of the patients, but 2 of them had concomitant *H. pylori* gastritis, one patient had a duodenal ulcer and the last patient was also eventually diagnosed with irritable bowel syndrome. With HPV identified in 75% of our cases, we would recommend HPV testing for pediatric ESP as well as consideration of vaccine administration as possible preventative and therapeutic measure for this lesion.

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Informed patient consent and assent as appropriate were obtained for publication of the details of each case from the parents of case 1, 3, and 4. All attempts were exhausted in trying to contact the parents/guardians of case 2 for the purpose of attaining their consent to publish the details for their cases for this brief report.

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