Diseases of the Esophagus (2004) **17**, 345–347

DISEASES OF THE ESOPHAGUS

Case report

Esophageal papillomatosis complicated by squamous cell carcinoma in situ

J. Reynoso,[1] R. E. Davis,[1] W. W. Daniels,[2] Z. T. Awad,[1] Z. Gatalica,[2] C. J. Filipi[1]

Departments of [1]Surgery and [2]Pathology, Creighton University School of Medicine, Omaha, Nebraska, USA

SUMMARY. **We present a case of esophageal papillomatosis with underlying squamous cell carcinoma in situ. An esophageal lesion resected from a 74-year-old woman demonstrated histological findings characteristic of squamous cell papilloma (fibrovascular core and numerous finger-like projections covered with hyperplastic squamous epithelium) and severe dysplasia characteristic of squamous cell carcinoma. The relation of squamous papilloma and squamous cell carcinoma is discussed. It is suggested that esophageal squamous cell papilloma is a premalignant lesion.**

KEY WORDS: **esophageal papillomatosis**, **squamous cell carcinoma.**

CASE REPORT

A 74-year-old woman with a history significant only for ovarian dermoid cyst presented with a 6-month history of coughing and intermittent dysphagia for solids. The patient denied heartburn, regurgitation, weight loss, emesis and melanotic or bloody stools. Upper endoscopy with biopsy demonstrated a circumferential, pearly, friable, exophytic growth between 20 and 30 cm from the incisors (Fig. 1). Multiple biopsies were non-diagnostic for cancer and presumptive treatment for fungal esophagitis did not improve her dysphagia. A biopsy obtained at rigid endoscopy demonstrated squamous papilloma with areas of hyperkeratosis, inflammation and atypia (Fig. 2). Due to the dysphagia and the concern of occult squamous cell carcinoma, the patient underwent laparoscopic transhiatal esophagectomy with cervical gastroesophageal anastomosis.

The resected esophageal specimen contained papillomas with in-situ squamous carcinoma showing foci of microinvasion into the lamina propria (Fig. 3). Dysplasia was observed primarily in the lower half of the papillomatous squamous epithelium. Resection margins were free of malignancy, as were eight regional lymph nodes. Immunohistochemical staining for herpes virus was negative. Human papillomavirus (HPV) DNA of both low risk (types 6,11,42,43,44) and high risk (types 16,18,31,33,35,39,45,51,52,56, 58,68,70) were not identified by in-situ hybridization.

Address correspondence to: Dr Charles J. Filipi, M.D., Department of Surgery, Creighton University Medical Center, 601 N 30th Street, Omaha, NE 68131, USA. Email: cjfilipi@creighton.edu

DISCUSSION

Papillomas of the uterine cervix,[1] anogenital region,[2] and larynx are thought to be premalignant lesions.[3] The association of HPV with malignant transformation in these areas has been well demonstrated. Esophageal squamous cell papillomatosis (ESP) and esophageal squamous cell carcinoma (ESCC) have also been associated with HPV. However, the progression of ESP to ESCC and the association of HPV with this malignant transformation are subject to debate. We found two reports of esophageal squamous papillomatosis with malignant degeneration, one of which had concomitant HPV infection.[4,5]

Esophageal squamous papillomatosis is a rare lesion that is usually found incidentally on upper endoscopy or at autopsy. The reported incidence of this lesion at endoscopy varies widely, from 0.077% to 0.35%.[6,7] Esophageal papillomas are usually solitary small lesions, measuring 2–6 mm in diameter.[8,9]

A study of ESP and ESCC from China and South Africa found HPV in seven of 11 papillomas and 19 of 63 esophageal carcinomas.[10] In 'high risk' areas, evidence of HPV infection, especially with types 6, 11, 16 and 18, is often found in about half of analyzed cases of ESP and ESCC.[10–14] Conversely, in 'low-risk' areas such as France, Italy, Finland

and the United Kingdom, the incidence of HPV infection is low in both ESP and ESCC.[6,7,15,16] One exception to this pattern is reported by Lavergne *et al*. who found evidence of HPV infection in seven of 11 cases of ESP in Europe.[10] Previously unknown types of HPV have been demonstrated in ESP and ESCC, and it should be noted that still unknown strains could remain undetected in lesions that test negative for more common HPV types.[10] This could explain why lesions that have a histologic appearance characteristic of HPV infection test negative for HPV by polymerase chain reaction (PCR) or in-situ hybridization.

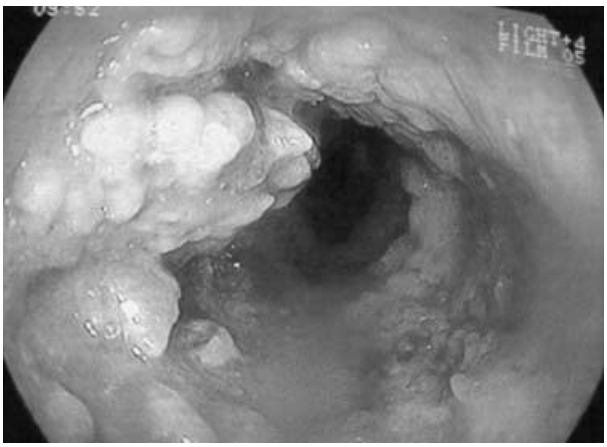

Fig. 1 Endoscopic view of the legion, a circumferential growth, which extended from 20 to 30 cm from the incisors.

Fig. 2 A biopsy obtained at rigid esophagoscopy demonstrated squamous papilloma.

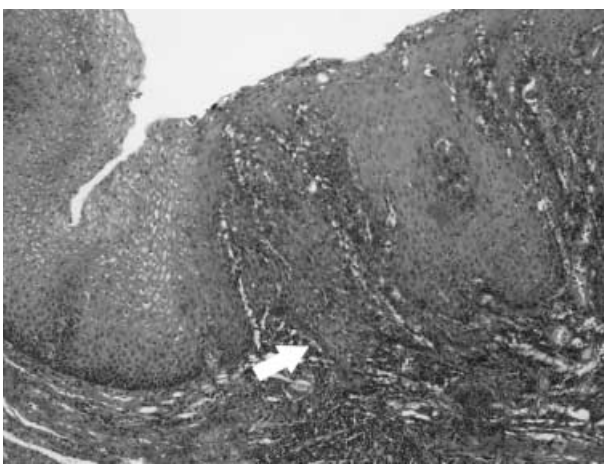

Fig. 3 The resected esophageal specimen contained squamous carcinoma with microinvasion (arrow) into the lamina propria.

The natural history of ESP is variable. Several cases in the literature describe esophageal papillomas that spontaneously regress or remain static with minimal treatment.[8,17–19] ESP has also been reported to cause esophageal stricture.[20] One report describes papillomatosis of the distal esophagus that, over the course of two years, spread through the bronchial tree and ultimately caused the patient's death.[21] Adenocarcinoma of the esophagus has been found within a squamous papilloma that was removed at flexible endoscopy.[22] We found two reported cases of ESCC in association with esophageal papillomatosis.[4,5]

Several etiologies have been proposed for ESP. The high incidence of papillomas in the lower esophagus raises suspicion that chronic irritation due to esophageal reflux could be a cause. However, ESP has also been found in the upper third of the esophagus.[9] Many investigators feel that a viral etiology is likely, given the lesion's similar appearance to viral papillomas in other locations. However, viral DNA is not consistently recovered from ESP, even with very sensitive molecular analysis techniques such as PCR.[7,10]

The premalignant potential of ESP has long been debated in the literature. The first histological description of ESP by Adler *et al*., in 1959, is accompanied by four other cases in which lesions that were initially believed to be ESP were later found to be an unspecified type of 'carcinoma.'[23] Syrjanen *et al*. first demonstrated HPV in association with ESP in 1982.[11] Since then several studies have detected HPV in ESP as well as ESCC.[10,12–14,24,25] However, on other occasions investigators have failed to find HPV infection in ESC and in ESCC.[6,26] This disparity suggests that although HPV has been shown to be associated with these lesions, other factors are involved. Other viruses such as herpes simplex virus, cytomegalovirus and Epstein-Barr virus have also been implicated in ESCC.[27]

Histologic changes characteristic of documented HPV infection in other body sites have been demonstrated in esophageal papillomas as well as esophageal squamous cell carcinoma.[24,28] These characteristics include koilocytosis (vacuolated cells with clear cytoplasm or perinuclear halos and nuclear pyknosis), cytologic atypia (giant cells, multinucleate cells and koilocytosis combined with anisonucleosis), maturation and keratinization disturbances in squamous epithelium (hyperkeratosis,

acanthosis, papillomatosis, and dyskeratosis) and over-morphologic patterns (differing types of elevated, flat or inverted verrucous or papillary-type lesions).[24]

The recovery of HPV nuclear material from both ESP and ESCC, especially in 'high risk' areas such as China and South Africa, strongly indicates an association between HPV infection and both clinical entities. This association may be similar to that seen in the cervix, anogenital region and larynx, where HPV-mediated progression from papilloma to carcinoma is well accepted. Such a progression may be in effect in the esophagus as well, possibly mediated by environmental factors that are present more often in 'high risk' areas. In Scottish upland cattle, ESP caused by HPV infection transforms to ESCC when bracken fern is present in the diet.[29]

The association between ESP, HPV and the risk of ESCC is less obvious in 'low risk' areas such as Europe and the United States. Clinicians in these 'low risk' areas faced with ESP have managed these lesions conservatively, even in some cases where the lesions were large or multiple.[18,20,25] Conversely, the literature contains one report of adenocarcinoma and two reports of SCC in ESP treated with esophagectomy in 'low risk' areas.[4,5,22]

We present a case of squamous cell carcinoma in situ within a large squamous papilloma of the esophagus, diagnosed after esophagectomy. To our knowledge this is the third such reported case in a 'low risk' area. Patients with large or multiple squamous papillomas should be advised that these lesions have malignant potential.

References

1 Kistner R W, Hertig A T. Papillomas of the uterine cervix; their malignant potentiality. Obstet Gynecol 1955; 6: 147–61.
2 zur Hausen H. The role of papillomaviruses in anogenital cancer. Scand J Infect Dis Suppl 1990; 69: 107–11.
3 Toso G. Epithelial papillomas – benign or malignant? Interesting findings in laryngeal papilloma. Laryngoscope 1971; 81: 1524–31.
4 Waluga M, Hartleb M, Sliwinski Z K, Romanczyk T, Wodolazski A. Esophageal squamous-cell papillomatosis complicated by carcinoma. Am J Gastroenterol 2000; 95: 1592–3.
5 Van Cutsem E, Geboes K, Visser L, *et al.* Squamous papillomatosis of the oesophagus with malignant degeneration and demonstration of the human papilloma virus. Eur J Gastroenterol Hepatol 1991; 3: 561–6.
6 Chang F, Janatuinen E, Pikkarainen P, Syrjanen S, Syrjanen K. Esophageal squamous cell papillomas. Failure to detect human papillomavirus DNA by in situ hybridization and polymerase chain reaction. Scand J Gastroenterol 1991; 26: 535–43.
7 Talamini G, Capelli P, Zamboni G *et al.* Alcohol, smoking and papillomavirus infection as risk factors for esophageal squamous-cell papilloma and esophageal squamous-cell carcinoma in Italy. Int J Cancer 2000; 86: 874–8.
8 Orlowska J, Jarosz D, Gugulski A, Pachlewski J, Butruk E. Squamous cell papillomas of the esophagus. report of 20 cases and literature review. Am J Gastroenterol 1994; 89: 434–7.
9 Franzin G, Musola R, Zamboni G, Nicolis A, Manfrini C, Fratton A. Squamous papillomas of the esophagus. Gastrointest Endosc 1983; 29: 104–6.
10 Lavergne D, de Villiers E M. Papillomavirus in esophageal papillomas and carcinomas. Int J Cancer 1999; 80: 681–4.
11 Syrjanen K, Pyrhonen S, Aukee S, Koskela E. Squamous cell papilloma of the esophagus: a tumour probably caused by human papilloma virus (HPV). Diagn Histopathol 1982; 5: 291–6.
12 Yamada Y, Ninomiya M, Kato T *et al.* Human papillomavirus type 16-positive esophageal papilloma at an endoscopic injection sclerotherapy site. Gastroenterology 1995; 108: 550–3.
13 Chang F, Syrjanen S, Shen Q, Wang L, Wang D, Syrjanen K. Human papillomavirus involvement in esophageal precancerous lesions and squamous cell carcinomas as evidenced by microscopy and different DNA techniques. Scand J Gastroenterol 1992; 27: 553–63.
14 Chang F, Syrjanen S, Shen Q *et al.* Human papillomavirus involvement in esophageal carcinogenesis in the high-incidence area of China. A study of 700 cases by screening and type-specific in situ hybridization. Scand J Gastroenterol 2000; 35: 123–30.
15 Morgan R J, Perry A C, Newcomb P V, Hardwick R H, Alderson D. Human papillomavirus and oesophageal squamous cell carcinoma in the UK. Eur J Surg Oncol 1997; 23: 513–17.
16 Benamouzig R, Jullian E, Chang F *et al.* Absence of human papillomavirus DNA detected by polymerase chain reaction in French patients with esophageal carcinoma. Gastroenterology 1995; 109: 1876–81.
17 Di Ciommo V, Ferrario F, Boldrini R, Bosman C. A case of squamous papilloma of the esophagus: spontaneous disappearance? J Clin Gastroenterol 1993; 17: 264–5.
18 Sandvik A K, Aase S, Kveberg K H, Dalen A, Folvik M, Naess O. Papillomatosis of the esophagus. J Clin Gastroenterol 1996; 22: 35–7.
19 Dumot J A, Vargo J J, Zuccaro G Jr. Esophageal squamous papilloma causing dysphagia. Gastrointest Endosc 2000; 52: 660.
20 Narayani R I, Young G S. Recurrent proximal esophageal stricture associated with dysplasia in squamous cell papillomatosis. Gastrointest Endosc 2002; 56: 591–4.
21 Hording M, Hording U, Daugaard S, Norrild B, Faber V. Human papilloma virus type 11 in a fatal case of esophageal and bronchial papillomatosis. Scand J Infect Dis 1989; 21: 229–31.
22 Reed P A, Limauro D L, Brodmerkel G J Jr, Agrawal R M. Esophageal squamous papilloma associated with adenocarcinoma. Gastrointest Endosc 1995; 41: 249–51.
23 Adler R H, Carberry D M, Ross C A. Papilloma of the esophagus: Association with hiatal hernia. J Thorac Surg 1959; 37: 625–35.
24 Winkler B, Capo V, Reumann W *et al.* Human papillomavirus infection of the esophagus. A clinicopathologic study with demonstration of papillomavirus antigen by the immunoperoxidase technique. Cancer 1985; 55: 149–55.
25 Politoske E J. Squamous papilloma of the esophagus associated with the human papillomavirus. Gastroenterology 1992; 102: 668–73.
26 Loke S L, Ma L, Wong M, Srivastava G, Lo I, Bird C C. Human papillomavirus in oesophageal squamous cell carcinoma. J Clin Pathol 1990; 43: 909–12.
27 Chang F, Syrjanen S, Wang L, Syrjanen K. Infectious agents in the etiology of esophageal cancer. Gastroenterology 1992; 103: 1336–48.
28 Syrjanen K J. Histological changes identical to those of condylomatous lesions found in esophageal squamous cell carcinomas. Arch Geschwulstforsch 1982; 52: 283–92.
29 Jarrett W F, McNeil P E, Grimshaw W T, Selman I E, McIntyre W I. High incidence area of cattle cancer with a possible interaction between an environmental carcinogen and a papilloma virus. Nature 1978; 274: 215–17.