Esophageal squamous papillomatosis with dysplasia. Is there a role of balloon-based radiofrequency ablation therapy ?

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Abstract

Esophageal squamous papillomatosis (ESP) is a rare condition, occurring in an estimated 0.01-0.097% in data from upper gastrointestinal endoscopies and autopsy series (1-2). Chronic mucosal irritation and infection with human papilloma virus (HPV) are proposed etiologies (1). Heavy use of tobacco and alcohol are common associations. The premalignant potential of ESP has long been debated in literature. The clinical course is variable, ranging from spontaneous regression to the development of squamous cell carcinoma (3-5). Due to the paucity of reported cases, no generalized therapeutic or surveillance recommendations exist. Photodynamic therapy (PDT) has been successfully used to treat Barrett's esophagus as well as superficial adenocarcinoma (6). However, its safety and efficacy in treating ESP with dysplasia is lacking. Balloon-based radiofrequency ablation using the HALO^{90} Ablation System is designed to remove the diseased cells using controlled heat. In recent clinical trials, it has shown great promise in treating Barrett's esophagus with high-grade dysplasia (7-9). We report the first ever use of balloon-based radiofrequency ablation to treat ESP with dysplasia. Clinical symptoms resolved after the first therapy session, however, ablation therapy was terminated early because squamous cell carcinoma in-situ was detected on surveillance endoscopy prior to the fourth therapy session. Although we failed to treat type 4 ESP with high-grade dysplasia with balloon-based radiofrequency ablation therapy, we believe that it might play a role in treating other localized types of ESP. (Acta gastroenterol. belg., **2009**, 72, **373-376**).

Key words : esophageal squamous papillomatosis, HALO Ablation System, esophageal squamous cell carcinoma.

Case report

A 74-year-old white male presented with chronic heartburn and regurgitation unresponsive to lifestyle and dietary modification, antacid use, over-the-counter H_2 receptor antagonists and proton pump inhibitors. He denied any associated nausea, vomiting, diarrhea, odynophagia, weight loss, dysphagia or other GI symptoms. His past medical history was significant for hypertension, type 2 diabetes mellitus, dyslipidemia and chronic obstructive pulmonary disease. He was an ex-smoker with a 100-pack year cigarette smoking history. Physical examination and routine laboratory studies were normal. Upper endoscopy showed circumferential, white-colored, cobble stoned plaque-like lesions in the distal esophagus extending from 32 to 37 centimeters from the gums (Fig. 1). Histological examination of the esophageal specimens showed inflamed squamous mucosa with papillomatous changes and moderate dysplasia (Fig. 2a). Rare hyphae consistent with candida albicans overgrowth were also noted. He was treated for

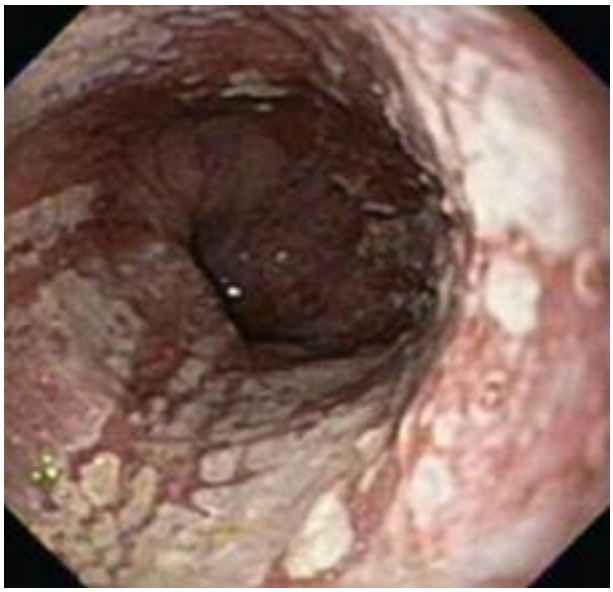

Fig. 1. — Esophageal squamous papillomatosis ; endoscopic view.

fungal esophagitis that did not improve his symptoms or endoscopic findings on repeat examination. Multiple deep cold biopsies were obtained which showed that the squamous epithelium had a disorderly growth pattern with squamous eddies and dyskeratosis, nuclear enlargement, crowding and hyperchromasia involving nearly the full thickness of the epithelium ; features consistent with moderate to severe dysplasia (Fig. 2b). Specialized immunoassays were carried out which showed proliferation by KI-67 mostly limited to basal area. Gomori methenamine silver (GMS) stain was negative for fungal elements but showed heavy bacterial colonization. Further testing with in-situ hybridization for human papilloma virus (HPV) typing was performed and was negative for HPV viral type 6, 11, 16, 18, 31, 33 and 51. Endoscopic ultrasound (EUS) showed mild thickening of the mucosal lining with no extension beyond the submucosa. The muscularis propria layer was intact throughout

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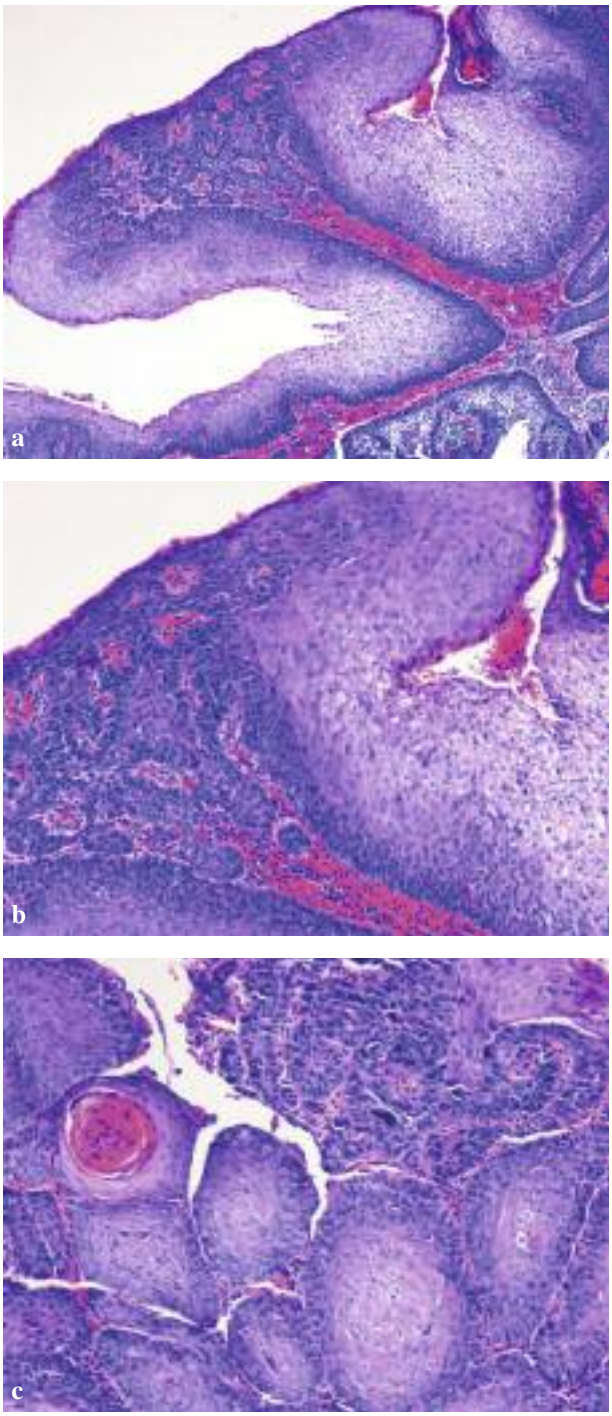

Fig. 2. — a) Esophageal squamous papillomatosis ; hematoxylin and eosin stain ×100, b) Focal moderate to severe dysplasia ; hematoxylin and eosin stain ×400, c) High-power view showing focal carcinoma in-situ ; hematoxylin and eosin stain ×400.

(Fig. 3). After discussion with the patient, he decided to undergo balloon-based radiofrequency ablation therapy with surveillance endoscopy and biopsies every three months. Using a Halo^{90} catheter, 68 ablations at an energy setting of 40 Watts and 12 j/cm^2 were performed in a stepwise fashion every three months. A total of three

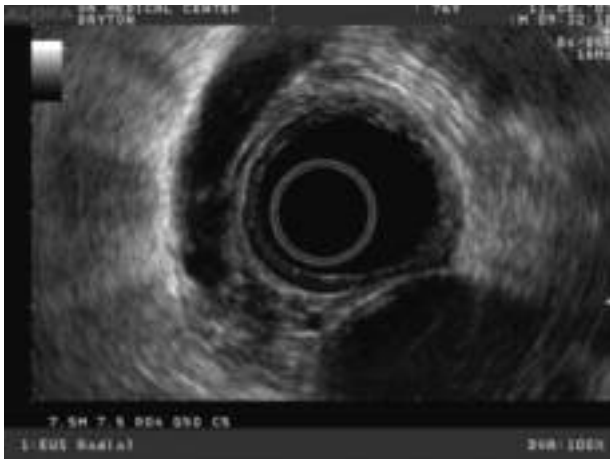

Fig. 3. — EUS showing intact muscularis propria layer

ablation therapy sessions were done. The post-ablation endoscopic images remained satisfactory, clinical symptoms improved and his surveillance biopsies remained negative for any carcinoma. However, prior to the fourth therapy session, his surveillance endoscopy revealed a new focally ulcerated area at about 35 cms from the gums which was biopsied. Histopathology revealed focally invasive moderately differentiated squamous cell carcinoma in biopsies from the ulcerated area (Fig. 2c). Repeat EUS showed a small hypoechoic irregular lesion, infiltrating into echogenic submucosa but did not breach the underlying muscularis layer. A subdiaphragmatic lymph node approximately 1 cm × 0.8 cm was also noted and fine needle aspiration cytology performed showed benign glandular epithelial cells. Positron emission tomography and Computed tomography (CT) of chest, abdomen and pelvis were unremarkable. The esophageal squamous cell carcinoma (ESCC) was staged T1bN0M0 for which the patient underwent esophagectomy. His postoperative course was unremarkable and he remains well on regular follow up in our clinic for the last nine months.

Discussion

ESP is an uncommon benign squamous epithelial tumor that is being diagnosed with increasing frequency. The reported incidence of this lesion varies widely, from 0.01% to 0.04% on autopsy studies and 0.05% to 0.097% in upper endoscopies. The average age for an established diagnosis is usually 50 to 60 years (1,2). ESP is generally thought to be more frequently observed in males, although some authors have described it as a predominantly female disease (10). Patients with ESP rarely have subjective complaints, although chronic heartburn, dyspepsia, early satiety and dysphagia have been reported (11).

Arimura *et al.* (11) classified ESP into 4 groups based on their endoscopic appearance : type 1 – very small,

hemispherical polyp, white in appearance ; type 2 – larger lesion than type1 with sessile appearance ; type 3 – reddish sessile polyp ; type 4 – multinodular or glandular flat elevation. Histologically, type 1-3 show no cellular atypia, and changes in a manner similar to hyperkeratosis or hyperplasia. Neoplastic components dominate type 4 which may co-exist with esophageal carcinoma. According to this classification, our patient had type 4 ESP and was associated with dysplasia and later on squamous cell carcinoma in-situ.

Etiology of ESP is unknown but three hypotheses have been suggested. First, ESP has been induced by chemicals as benzopyrene (12) and nitrosamine (13) in experimental animals. Second, reports from regions with a high incidence of esophageal cancer suggested an association with HPV (14). Third, the most frequently considered cause is chronic irritation and inflammation secondary to gastroesophageal reflux disease (GERD) (10,11). HPV testing using in-situ hybridization was performed in our patient but was negative for HPV viral type 6, 11, 16, 18, 31, 33 and 51. He was, however, a heavy smoker and had severe gastroparesis with long standing GERD. Chemical induction and chronic irritation of esophagus might have induced ESP.

The natural history of ESP is variable. Spontaneous regression (15), remaining static with minimal treatment, esophageal stricture (16), associated adenocarcinoma (17) and progression to squamous cell carcinoma have been reported (11). Surgery and laser therapy, supplemented by interferon alfa and retinoic acid are the primary treatment modalities for respiratory squamous papillomatosis. In contrast, no generalized therapeutic or surveillance recommendations exist for ESP due to paucity of reported cases.

Tumor infiltration into the esophageal wall is the only reliable differentiating factor between ESP and ESCC. chest CT is not a sensitive enough tool for surveillance for ESCC. Conventional endoscopic esophageal biopsies also appear to be inadequate for monitoring these patients for malignancy. Endoscopic biopsies usually sample only the most superficial portions and therefore can miss invasive growth in deeper portions of the affected tissue. EUS is ideally suited to the TNM classification for tumor staging as it can accurately assess the depth of tumor penetration, the presence of regional nodal metastases and can even detect vascular invasion. EUS-guided FNA biopsy allows for cyto-pathological diagnosis of malignant primary tumors and is superior to other imaging modalities for confirmation of nodal metastases (18-20). We used a combination of EUS and surveillance biopsies every three months leading to early diagnosis of transformation of severe dysplasia to a clinical and pathological T1 carcinoma. There is growing body of literature on chromoendoscopy using Lugol solution and endoscopic fluorescence techniques for defining the superficial extent of the disease. EUS has a reported sensitivity and specificity of 97% and 87% respectively for detecting the invasion of muscularis mucosa (21). A combined approach using chromoendoscopy along with EUS and surveillance biopsies may offer a better approach in malignancy screening. However, more prospective studies need to be conducted before this can become a standard approach.

Several methods such as electrocoagulation, argon plasma coagulation, photodynamic therapy, lift and cut resection, cap assisted aspiration and band ligation mucosectomy, and endoscopic submucosal dissection have been used for endoscopic resection removal or ablation of esophageal superficial tumors (22). Photodynamic therapy (PDT) is a treatment that uses a red laser light through the endoscope and porfimer sodium as a photosensitizer (6). When photosensitizers are exposed to a specific wavelength of light, they produce a form of oxygen that kills nearby cells. Porfimer sodium is approved to relieve symptoms of esophageal cancer when the cancer obstructs the esophagus and for the treatment of precancerous lesions in patients with Barrett's esophagus. However, to date no studies have been done to assess its safety and efficacy in treating ESP with dysplasia.

Balloon-based radiofrequency ablation using a Halo ablation system is a leading-edge therapy that provides uniform and controlled ablative therapy at a consistent depth, which can remove Barrett's cells and allows the regrowth of normal cells. The ability to provide a controlled amount of ablative therapy to diseased tissue significantly reduces the risk of complications normally associated with other forms of ablation therapy. To date, balloon-based radiofrequency ablation therapy has been successfully used to ablate intestinal metaplasia with high-grade dysplasia (IM-HGD) (23,24). However, prospective trials to assess its safety and efficacy to treat ESP with dysplasia are lacking.

After reviewing all treatment options, our patient opted for balloon-based radiofrequency ablation therapy and was closely followed with EUS and surveillance biopsies every three months. Although his clinical symptoms improved significantly after the first session, the ablation therapy was terminated because squamous cell carcinoma in-situ was detected on surveillance endoscopy prior to the fourth therapy session. According to the Arimura *et al.* classification, our patient had type 4 ESP with moderate to high-grade dysplasia prior to ablation therapy. Although we failed to treat type 4 ESP with high-grade dysplasia with balloon-based radiofrequency ablation therapy, we estimate that it might play a role in treating other localized types of ESP. In future, more prospective studies need to be conducted to assess the safety and efficacy of balloon-based radiofrequency ablation therapy in patients with ESP.

References

1. SANDVIK A.K., AASE S., KVEBERG K.H., DALEN A., FOLVIK M., NAESS O. Papillomatosis of the esophagus. *J. Clin. Gastroenterol.*, 1996, **22** : 35-37.

2. ODZE R., ANTONIOLI D., SHOCKET D., NOBLE-TOPHAM S., GOLDMAN H., UPTON M. Esophageal squamous papillomas, a clinicopathologic study of 38 lesions an analysis for human papilloma virus by polymerase chain reaction. *Am. J. Surg. Pathol.*, 1993, **17** : 803-812.
3. ORLOWSKA J., JAROSOZ 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.
4. 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.
5. DUMOT J.A., VARGO J.J., ZUCCARO G. JR. Esophageal squamous papilloma causing dysphagia. *Gastrointest. Endosc.*, 2000, **52** : 660.
6. WOLFSEN H.C., HEMMINGER L.L., GEIGER X.J., KRISHNA M., WOODWARD T.A. Photodynamic therapy and endoscopic metal stent placement for esophageal papillomatosis associated with squamous cell carcinoma. *Dis. Esophagus.*, 2004, **17** : 187-90.
7. ROSCH T. BARRx for total Barrett's eradication – the new super weapon ? 2008, **40** : 393-4.
8. HUBBAR N., VELANOVICH V. Endoscopic endoluminal radiofrequency ablation of Barrett's esophagus in patients with fundoplications. *Surg. Endosc.*, 2007, **21** : 625-8.
9. DUNKIN B.J., MARTINEZ J., BEJARANO P.A., SMITH C.D., CHANG K., LIVINGSTONE A.S., MELVIN W.S. Thin-layer ablation of human esophageal epithelium using a bipolar radiofrequency balloon device. *Surg. Endosc.*, 2006, **20** : 125-30.
10. JAVDAN P., PITMAN E.R. Squamous papilloma of esophagus. *Dig. Dis. Sci*, 1984, **29** : 317.
11. YUKI T., KAWANO S., OGIHARA T., SATO N., OKAMOTO S., SATO K., KAMADA T., TAKADA N., FURUKAWA J., OKAMURA J. Esophageal squamous cell papilloma, suspected of squamous cell carcinoma. *Internal medicine*, 1993, **32** : 773-776.
12. DUNHAM L., SHEETS R. Effects of esophageal constriction on benzopyrene carcinogenesis in human esophagus and fore stomach. *J. Natl. Cancer Inst.*, 1974, **53** : 875.
13. NAKAMURA T., MATSUYAMA M., KISHIMOTO H. Tumors of esophagus and duodenum induced in mice by oral administration of N-ethyl-N-nitro-N-nitrosoguanidine. *J. Natl. Cancer Inst.*, 1974, **52** : 519.
14. SYRJÄNEN K., PYRHÖNEN S., AUKEE S., KOSKELA E. Squamous cell papilloma of oesophagus : A tumor probably caused by human papilloma virus (HPV). *Diagnostic Histopathology*, 1982, **5** : 291.
15. KATO H., ORITO E., YOSHINOUCHI T., UEDA R., KOIZUMI T., YOSHINOUCHI M., MIZOKAMI M. Regression of esophageal papillomatous polyposis caused by high-risk type human papilloma virus. *J. Gastroenterol.*, 2003, **38** : 579-583.
16. NARYANI R.A.J., YOUNG G.S. Recurrent proximal esophageal stricture associated with dysplasia in squamous cell papillomatosis. *Gastrointest. Endosc.*, 2002, **56** (4) : 591-4.
17. REED P.A., LIMAURO D.L., BRODMERKEL G.J. JR., AGRAWAL R.M. Esophageal squamous papilloma associated with adenocarcinoma. *Gastrointest. Endosc.*, 1995, **41** (3) : 249-51.
18. RAMPADO S., BOCUS P., BATTAGLIA G., RUOL A., PORTALE G., ANCONA E. Endoscopic ultrasound : accuracy in staging superficial carcinomas of the esophagus. *Ann. Thorac. Surg.*, 2008, **85** : 251-6.
19. CHEMALY M., SCALONE O., DURIVAGE G., NAPOLEON B., PUJOL B., LEFORT C., HERVIEUX V., SCOAZEC J.Y., SOUQUET J.C., PONCHON T. Miniprobe EUS in the pretherapeutic assessment of early esophageal neoplasia. *Endoscopy*, 2008, **40** : 2-6.
20. MC DONOUGH P.B., JONES D.R., SHEN K.R., NORTHUP P.G., GALYSH R.L., HERNANDEZ A., WHITE G.E., KAHALEH M., SHAMI V.M. Does FDG-PET add information to EUS and CT in the initial management of esophageal cancer ? A prospective single center study. *Am. J. Gastroenterol.*, 2008, **103** : 570-4.
21. MURATA Y., SUZUKI S., MITSUNAGA A., IIZUKA Y., UCHIYAMA M., UCHIDA K., NAKAMURA S., HAYASHI K., YOSHIDA K., TOKI F., IDE H. Endoscopic ultrasonography in diagnosis and mucosal resection for early esophageal cancer. *Endoscopy*, 1998, **30** Suppl 1 : A44-6.
22. DEPREZ PH., AOUATTAH T., PIESSEVAUX H. Endoscopic removal or ablation of oesophageal and gastric superficial tumours. *Acta Gastroenterol. Belg.*, 2006, **69** : 304-11.
23. GANZ R.A., OVERHOLT B.F., SHARMA V.K., FLEISCHER D.E., SHAHEEN N.J., LIGHTDALE C.J., FREEMAN S.R., PRUITT R.E., URAYAMA S.M., GRESS F., PAVEY D.A., BRANCH M.S., SAVIDES T.J., CHANG K.J., MUTHUSAMY V.R., BOHORFOUSH A.G., PACE S.C., DEMEESTER S.R., EYSSELEIN VE., PANJEHPOUR M., TRIADAFILOPOULOS G., U.S. MULTICENTER REGISTRY. Circumferential ablation of Barrett's esophagus that contains high-grade dysplasia : a U.S. Multicenter Registry. *Gastrointest. Endosc.*, 2008, **68** : 35-40.
24. GONDRIE J.J., POUW R.E., SONDERMEIJER C.M., PETERS F.P., CURVERS W.L., ROSMOLEN W.D., KRISHNADATH K.K., TEN KATE F., FOCKENS P., BERGMAN J.J. Stepwise circumferential and focal ablation of Barrett's esophagus with high-grade dysplasia : results of the first prospective series of 11 patients. *Endoscopy*, 2008, **40** : 359-69.