Case Reports in Gastroenterology

Case Rep Gastroenterol 2016;10:466–471

DOI: 10.1159/000448070
Published online: August 31, 2016

Case Series

Verrucous Squamous Cell Cancer in the Esophagus: An Obscure Diagnosis

Charlotte Egeland[a] Michael P. Achiam[a] Birgitte Federspiel[b]
Lars Bo Svendsen[a]

[a]Department of Surgical Gastroenterology C, Rigshospitalet, University Hospital of Copenhagen, Copenhagen, Denmark; [b]Department of Pathology, Rigshospitalet, University Hospital of Copenhagen, Copenhagen, Denmark

Keywords
Verrucous carcinoma · Squamous cell carcinoma · Esophagus · Dysphagia

Abstract
Verrucous carcinoma is a rare, slow-growing type of squamous cell cancer. Fewer than 50 patients with verrucous carcinoma in the esophagus have been described worldwide. In 2014, two male patients were diagnosed with verrucous carcinoma in the distal part of the esophagus. The endoscopic examinations showed a similar wart-like, white, irregular mucosa in both cases. The diagnosis was difficult to make since all biopsies taken from the affected area showed no malignancy. This cancer type has a relatively good prognosis when the diagnosis is finally obtained. Both our patients presented with dysphagia, weight loss, and an endoscopically malignant tumor, but surgery was not performed until after 9 and 10 months, respectively, and then in order to get a diagnosis. At the last follow-up, both patients were without any recurrence of the disease.

KARGER

Charlotte Egeland, BSc
Department of Surgical Gastroenterology C, Rigshospitalet
University Hospital of Copenhagen, Blegdamsvej 9
DK–2100 Copenhagen (Denmark)
E-Mail charlotte.egeland@gmail.com

Introduction

Verrucous carcinoma (VC) is a slow-growing cancer type which has been reported in the esophagus, oropharynx, larynx, glans penis, scrotum, vulva, vagina, cervix, endometrium, urinary bladder, anus, and in the sole of the feet [1]. The first 5 cases of esophageal VC ever described were reported by Minielly at al. [2] in 1967. In total, 50 cases have been described worldwide. VC is known to be associated with several medical conditions, such as chronic esophagitis, esophageal diverticular disease, gastroesophageal reflux disease [3], hiatal hernia, achalasia, and caustic injury [4]. Recently, an association with human papilloma virus (HPV) has been hypothesized [5]. Known risk factors include smoking and alcohol abuse [1, 3, 6–8]. VC occurs more frequently in males and has been reported at all ages from 36 to 76 years [4]. The diagnosis is rare and often delayed since initial superficial biopsies usually show nonspecific chronic inflammation and candida infection but only rarely malignancy [6]. The majority of cases follow a similar symptom pattern and have similar endoscopic and histological characteristics. The endoscopic appearance is often described as a shaggy, papillary mucosa with white plaques. Surgery is often done due to progressive wasting.

In 2014, we diagnosed 2 male patients at the Department of Gastrointestinal Surgery and the Department of Pathology, Rigshospitalet, Copenhagen. The 2 cases will be presented in the following to highlight the characteristics of this rare type of carcinoma.

Case 1

Our first patient was a 67-year-old male with a medical history of diabetes mellitus type II, hypertension, and benign polyps in the colon (three polypectomies). The patient had a history of tobacco use during the last 50 years; at the time of reference, he smoked 10 cigarettes daily. He had no alcohol overconsumption. When referred, the patient had suffered from dysphagia for 2 months, and he only consumed fluids. Besides a weight loss of 8 kg (weight at referral 83 kg, weight loss corresponding to 9% of initial body weight), the first physical examination was unremarkable, as were the initial blood tests. The primary endoscopy revealed a mucosa covered with white plaques spreading from 30 to 40 cm from the incisors. In the distal part of the affected area, the mucosa protruded and covered almost 2/3 of the lumen and involved the entire circumference (fig. 1). The finding was thought to be a candida infection. Biopsies showed severe acute inflammation with reactive changes but without dysplasia or malignancy. A computed tomography (CT) scan showed a thickened wall in the distal part of the esophagus. Since no malignancy was found, the patient was discharged.

Four months later, the patient was referred again due to a further massive weight loss of 25 kg; at this time he weighed only 58 kg (weight loss corresponding to 36% of initial body weight). Gastroscopy and blood test were performed again, and human immunodeficiency virus, herpes, and HPV infection were ruled out. To rule out achalasia of the esophagus and gastroesophageal junction, a high-resolution impedance manometry examination was performed followed by a positron emission tomography (PET)-CT scan, but neither could explain the condition the patient suffered from. During this period of approximately 4 months, the patient was hospitalized at the Department of Infectious Diseases.

Six months after the first visit, another gastroscopy was performed showing ulceration and a process protruding into the lumen. The biopsy revealed a squamous cell papilloma. In view of the severe weight loss and the poor condition of the patient, an esophagectomy was

offered and accepted. The pathology report described a low-grade verrucous squamous cell carcinoma (fig. 2). There was no dissemination into the lymph nodes or other organs. The patient was discharged after 2 weeks and is presently symptom free.

Case 2

The second patient was a 59-year-old male. He was a heavy smoker (10–15 cigarettes daily since 18 years of age) and had a history of previous alcohol abuse of >168 g pure alcohol per week during a period of 10 years. In addition, he had a hiatal hernia and Barrett's esophagus for which he was treated with a proton pump inhibitor (pantoprazole 40 mg daily). The tumor was found in an upper endoscopy preformed routinely. The initial symptom was dysphagia which he had suffered from intermittently during the last one and a half years. Blood tests and a physical examination showed no abnormalities. An area of a 10-cm, white, irregular mucosa with a 1-cm large polyp-like process was observed at gastroscopy (fig. 3). Biopsies revealed acute and chronic inflammation as well as infection with nonhemolytic streptococcus, *Escherichia coli*, and a few fungal hyphae. The tissue was extended-spectrum β-lactamase positive. The patient underwent a series of gastroscopies without malignant findings, just as the initial CT scan was without suspicion of malignant disease.

Three months later, a biopsy from the esophagus showed a squamous cell papilloma. The following PET-CT scan performed 6 months after the initial visit found tumor growth and a suspicion of malignancy, stage T2N0M0. An endoscopic ultrasonography-guided fine-needle aspiration found no malignant cells. During this period, the patient suffered from dysphagia but had no weight loss, nor was he hospitalized. Despite the lack of malignant findings, the patient was offered an esophagectomy and underwent surgery.

Nine months after the first visit, the pathology report of the resected specimen showed a hyperplastic mucosa with a low-grade VC, a mostly exophytic papillary tumor. The tumor was highly parakeratinized with no dissemination into the lymph nodes or other organs. After a minor pneumonia, for which he received antibiotic treatment, the patient was discharged after 2 weeks. The patient is presently without symptoms.

Discussion

In our 2 cases, as in almost all cases previously described, there has been a considerable delay of diagnosis. For our patients, it took more than 9 months before curative surgery was performed. This seems to be a consistent pattern for this group of patients, including the presence of dysphagia, occasionally a massive weight loss, and a typical endoscopic picture. The mucosa in our 2 cases was white and covered with plaques and wart-like polyps. Furthermore, the mucosa is often described as exophytic, and the description 'a multilobular polypoid mass' has also been used [9]. The only strategy to identify and, moreover, to diagnose and treat this limited group of patients is to be familiar with this typical white, wart-like mucosa and to initiate aggressive treatment already after a few endoscopic examinations. Even if all biopsies are without malignancy, a suspicion of VC should be present just based on the macroscopic appearance.

A German study including 15 patients with VC in the esophagus from 1999 to 2011 [7] and an American study including 11 patients from 1995 to 2010 [8] have been published. Besides these studies, only 25 individual case reports have been published. How many un-

derdiagnosed cases of VC exist remains unknown, but an awareness of this type of carcinoma is certainly desirable in a worldwide context. The resected specimen often shows a relatively low-grade tumor and rarely dissemination into the lymph nodes or other organs, which indicates a generally good prognosis. Unfortunately, the patients often suffer from a long period of undiagnosed illness and may, as a consequence, be in such a poor condition that curative treatment is no longer an option.

The etiology of this carcinoma is still unknown, but different causes, such as chronic inflammatory conditions, have been proposed. Our patients displayed some of the known risk factors. Both patients were heavy smokers, and one of them had a hiatal hernia. However, neither of our patients had an HPV infection in the mucosa. In the literature, the carcinoma is often localized in the distal part of the esophagus, which was also the case in our patients. The endoscopic appearance was very similar to the typical findings described earlier – a white, irregular, exophytic mucosa covered with plaques and wart-like polyps, and all biopsies taken from the area were without malignancy. Due to the exophytic nature of the VC and the bland appearance of the epithelial cells, it is extremely difficult to obtain biopsies that are sufficiently deep to visualize the invasive part of the tumor. Therefore, biopsies are often false-negative and only show nonspecific inflammatory changes or changes compatible with squamous cell papilloma.

In conclusion, VC has a very characteristic pattern of symptoms but also a typical endoscopic appearance. Thus, when clinical suspicion is raised and disseminated disease has been ruled out, the patient should be considered a candidate for potential curative treatment despite negative biopsies. Furthermore, the diagnosis and treatment require a close collaboration between specialists including pathologists, radiologists, and surgeons.

Statement of Ethics

As corresponding author I certify that all authors have participated sufficiently in the planning of the study, intellectual content, and the writing of the work to take public responsibility for it.

Disclosure Statement

The authors declare that they have no conflicts of interest.

References

1 Ahmed K, Timmerman G, Meyer R, Miller T, Mazurczak M, Tams K, Atiq M: Verrucous carcinoma of the esophagus: a potential diagnostic dilemma. Case Rep Gastroenterol 2013;28:498–502.
2 Minielly JA, Harrison EG Jr, Fontana RS, Payne WS: Verrucous squamous cell carcinoma of the esophagus. Cancer 1967;20:2078–2087.
3 Kavin H, Yaremko L, Valaitis J, Chowdhury L: Chronic esophagitis evolving to verrucous squamous cell carcinoma: possible role of exogenous chemical carcinogens. Gastroenterology 1996;110:904–914.
4 Osborn NK, Keate RF, Trastek VF, Nguyen CC: Verrucous carcinoma of the esophagus: clinicopathophysiologic features and treatment of a rare entity. Dig Dis Sci 2003;48:465–474.
5 Tonna J, Palefsky JM, Rabban J, Campos GM, Theodore P, Ladabaum U: Esophageal verrucous carcinoma arising from hyperkeratotic plaques associated with human papilloma virus type 51. Dis Esophagus 2010;23:E17–E20.

6 Ramani C, Shah N, Nathan RS: Verrucous carcinoma of the esophagus: a case report and literature review. World J Clin Cases 2014;16:284–288.
7 Behrens A, Stolte M, Pech O, May A, Ell C: Verrucous oesophageal carcinoma: single case report and case series including 15 patients – issues for consideration of therapeutic strategies. Viszeralmedizin 2014;30:346–352.
8 Sweetser S, Jacobs NL, Wong Kee Song LM: Endoscopic diagnosis and treatment of esophageal verrucous squamous cell cancer. Dis Esophagus 2014;27:452–456.
9 Brandalise A, Lorenzetti C, Aranha NC, Brandalise NA: Verrucous carcinoma of the esophagus involving the entire esophagus. Arq Bras Cir Dig 2015;4:293.

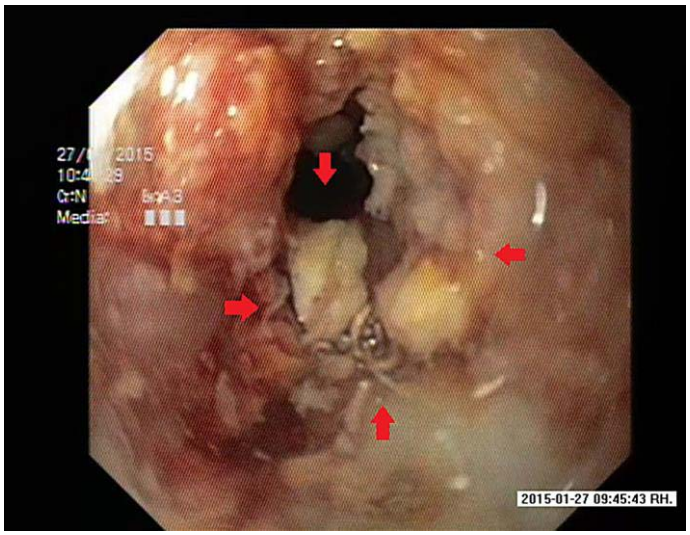

Fig. 1. Upper endoscopy showing a whitish, mostly exophytic mucosa protruding into the lumen. The arrows indicate the tumor area.

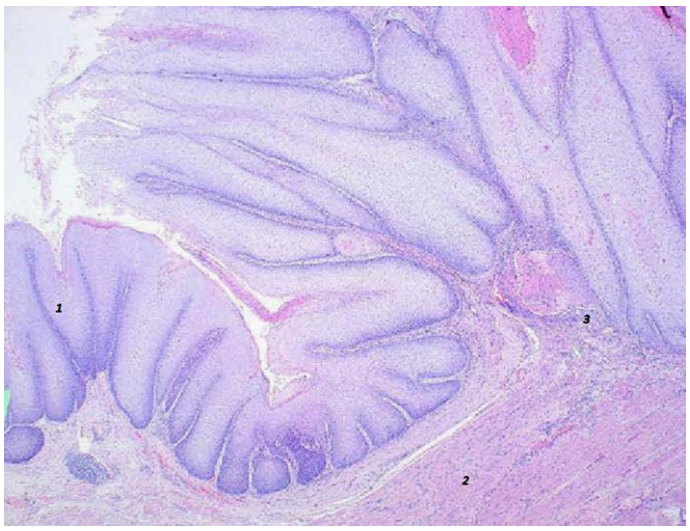

Fig. 2. Histological appearance (original magnification ×20). Note the exophytic growth pattern and the bland epithelium. However, invasion is seen into the muscularis propria (bottom right). 1 = Hyperplastic squamous epithelium; 2 = muscularis propria; 3 = invasion into the muscularis propria.

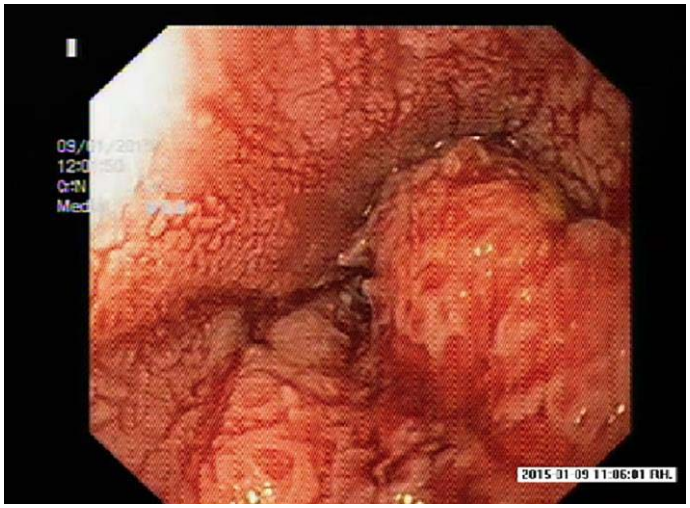

Fig. 3. Upper endoscopy showing the esophagus completely covered with white plaques.