GE – Portuguese Journal of Gastroenterology

Clinical Case Study

GE Port J Gastroenterol 2026;33:566–571
DOI: 10.1159/000553165

Received: April 12, 2026
Accepted: June 8, 2026
Published online: June 18, 2026

Verrucous Carcinoma of the Esophagus: A Deceiving Entity with an Uncertain Etiology – Case Report

Isabel Malta Carvalho[a] Tânia Gago[a] Luís Relvas[a] Margarida Portugal[a] Jesus Cadilla[b] Bruno Peixe[a]

[a]Gastroenterology Department, Unidade Local de Saúde do Algarve, Faro, Portugal;
[b]Pathology Department, Unidade Local de Saúde do Algarve, Faro, Portugal

Keywords
Verrucous carcinoma · Esophageal neoplasm · Malignant stenosis · Case report

Abstract
Verrucous carcinoma of the esophagus is an extremely rare malignancy, described as a well-differentiated variant of esophageal squamous cell carcinoma, typically exhibiting exophytic/verrucous growth and intraluminal involvement that is often rich in inflammation and hyperkeratosis, which hampers histologic diagnosis and consequently delays treatment. We report the case of a 58-year-old woman with progressive dysphagia and a circumferential, verrucous esophageal lesion, without histologic confirmation despite multiple biopsies and endoscopic resections, showing only focal p16 positivity. After further evaluation with CT, endoscopic ultrasound, and FDG-PET/CT, a presumptive diagnosis of locally advanced verrucous carcinoma of the esophagus was assumed, and palliative chemotherapy was initiated, followed by a sustained endoscopic and radiologic response. This case highlights the importance of multidisciplinary discussion when verrucous carcinoma of the esophagus is suspected and the unexpected, sustained response despite unresectability.

Carcinoma verrucoso do esófago: uma entidade enganadora com uma etiologia incerta – caso clínico

Palavras Chave
Carcinoma verrucoso · Neoplasia esofágica · Estenose maligna · Caso clínico

Resumo
O carcinoma verrucoso do esófago é uma neoplasia extremamente rara, descrita como uma variante muito bem diferenciada do carcinoma de células escamosas do esófago, com típico crescimento exofítico/verrucoso e invasão endo-luminal exuberante com inflamação e hiperqueratose, o que torna as biópsias superficiais frequentemente não diagnósticas e consequentemente atrasa o tratamento. Apresentamos o caso de uma doente de 58 anos, com disfagia progressiva, com uma lesão circunferencial, verrucosa do esófago, sem diagnóstico histológico apesar de múltiplas biópsias e ressseções endoscópicas com ansa, salientando-se apenas positividade focal a p16. Após estadiamento com TC, EUS e PET-FDG, foi assumido diagnóstico presuntivo de carcinoma verrucoso do esófago localmente avançado,

karger@karger.com
www.karger.com/pjg

Correspondence to:
Isabel Malta Carvalho, isamalta_c16@hotmail.com

tendo iniciado quimioterapia paliativa com posterior resposta endoscópica e radiológica sustentada. Este caso realça a importância da discussão multidisciplinar na suspeita de carcinoma verrucoso do esófago e enfatiza a resposta sustentada inesperada, apesar de irressecável.

Introduction

Verrucous carcinoma of the esophagus (VCE) is an extremely rare variant of squamous cell carcinoma first described by Minielly in 1967 [1]. Approximately 80 cases have been described in the literature [2]. VCE is typically a slow-growing, well-differentiated, locally invasive tumor with uncommon nodal metastases. Although its exact etiology remains unknown, most reported cases have been associated with prolonged chronic inflammatory or irritative conditions, including tobacco exposure, reflux esophagitis, alcohol use, and achalasia. More recently, human papillomavirus (HPV) infection has been proposed as a potential contributor [3]. VCE predominantly affects males (approximately 2:1) with reported ages ranging from 36 to 79 years [4].

Clinically, patients may present with symptoms typical of esophageal malignancy, most commonly dysphagia, weight loss, and odynophagia, while cough and hematemesis have also been described. Owing to its slow growth, the clinical course can be relatively indolent [4]. Macroscopically, VCE often appears as an exophytic, verrucous, wart-like lesion. Due to the proliferative nature of these lesions, superficial biopsies frequently capture only the hyperkeratotic surface and associated inflammatory changes. For this reason, repeated endoscopic biopsies may be nondiagnostic, and definitive diagnosis may require deep sampling or complete tumor resection [5].

Case Report

A 58-year-old woman with no relevant past medical history was referred to a gastroenterology consultation due to a 2-month history of gradually progressive dysphagia and mild odynophagia. She denied tobacco exposure, alcohol use, or reflux symptoms, but reported recent frequent consumption of large amounts of very hot liquids. On physical examination, the patient appeared emaciated, with no other remarkable findings. Routine laboratory tests were unremarkable, including negative tumor markers (CEA, CA 19.9, and SCC antigen), which were obtained as part of the initial nonspecific malignancy workup. An upper gastrointestinal endoscopy revealed circumferential verrucous wart-like lesions, followed by circumferential exophytic papillary lesions extending from 20 to 30 cm from the incisors, which were highly suspicious for esophageal carcinoma (shown in Fig. 1a,b). Multiple biopsies showed hyperplastic squamous mucosa with chronic inflammation, without dysplasia or invasive carcinoma in the sampled tissue (shown in Fig. 2). Over the course of 3 months, three additional upper gastrointestinal endoscopies were performed. Multiple standard and jumbo biopsies were obtained, followed by wider and deeper snare-assisted resections during subsequent procedures to improve diagnostic yield; however, all specimens remained nondiagnostic. During this period, there was progressive worsening of the stenosis, considered most likely related to disease progression (shown in Fig. 1c,d). Endoscopic ultrasound-guided tissue acquisition was not feasible due to the near-complete stenosis, inability to traverse the lesion, and concern regarding procedural safety, particularly the risk of perforation, with limited expected additional diagnostic yield after multiple previous deep biopsies. Tissue studies for acid-fast bacilli, CMV, HPV, and other less common microorganisms were negative. Immunohistochemistry demonstrated focally positive p16. Several expert gastrointestinal pathologists from three different centers reviewed the specimens, without definitive evidence of malignancy. Contrast-enhanced CT demonstrated a long-segment thoracic esophageal mass extending below the carina, causing marked luminal stenosis with upstream dilation, associated with regional mediastinal adenopathy and no distant metastases (shown in Fig. 3a).

Endoscopic ultrasonography was limited by the insurmountable stenosis at 30 cm from the incisors. Nevertheless, concentric hypoechoic thickening involving the full esophageal wall up to the adventitia was identified, with multiple suspicious locoregional lymph nodes, corresponding to at least uT3N2 disease (shown in Fig. 3b).

FDG-PET/CT demonstrated intense uptake in the mid-esophageal lesion and regional lymph nodes, without evidence of distant metastatic disease. Based on the unique endoscopic findings, p16 positivity (despite negative HPV testing), progressive clinical deterioration, and imaging compatible with locally advanced disease, a presumptive diagnosis of stage III verrucous carcinoma

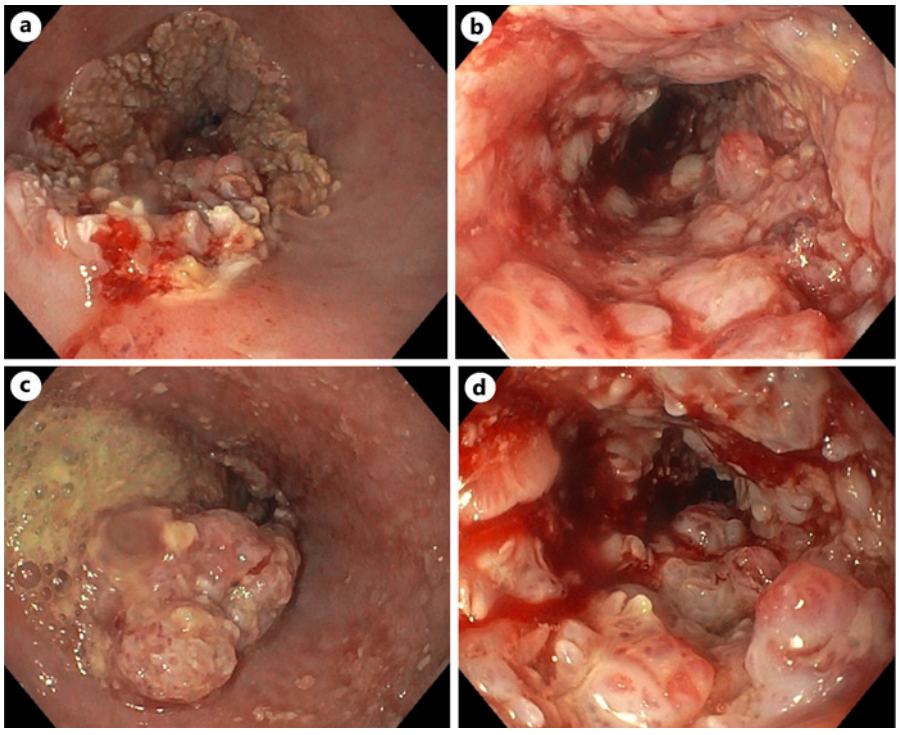

Fig. 1. Initial and progressive endoscopic appearance of the esophageal lesion. **a** Initial appearance of the verrucous lesion beginning at 20 cm from the incisors. **b** Circumferential exophytic papillary extension of the lesion. **c** Progressive circumferential exophytic lesion with luminal compromise. **d** Worsening luminal stenosis with near-complete obstruction.

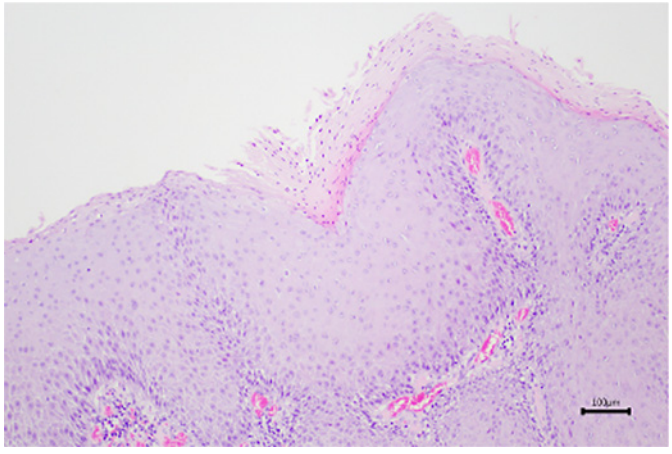

Fig. 2. Histopathologic findings. Hyperplastic and hyperkeratotic squamous epithelium with marked chronic inflammatory infiltrate, without evidence of dysplasia or invasive carcinoma in the biopsy specimens.

of the esophagus was made (u/cT3N+M0). The patient underwent neoadjuvant chemoradiotherapy with carboplatin and paclitaxel and subsequently underwent exploratory thoracoscopy. Surgical resection was initially considered; however, thoracoscopy demonstrated locally advanced unresectable disease with mediastinal involvement, precluding curative surgery. Palliative chemotherapy was initiated with FOLFOX, aiming to achieve rapid cytoreduction and symptom control in the context of progressive dysphagia and unresectable disease. Due to worsening oral intake involving both liquids and solids, a percutaneous endoscopic gastrostomy (PEG) tube was placed, resulting in subsequent clinical improvement, weight gain, and improved quality of life (ECOG performance status 0).

After 8 cycles of chemotherapy, approximately 12 months after the first endoscopy, a repeat endoscopy was performed to assess local response, which demonstrated no visible tumor (shown in Fig. 4). Considering the unexpected endoscopic findings, FDG-PET/CT was repeated, demonstrating diffuse thoracic esophageal uptake (SUVmax 4.9), interpreted as likely posttreatment inflammatory change, although residual disease could not be excluded. No other sites of suspected neoplasia were identified.

Despite initial unresectability, the patient demonstrated an unexpectedly favorable course. After 12 cycles of FOLFOX, CT showed near-complete response, and nivolumab maintenance therapy was subsequently introduced. At the last follow-up, approximately 2.5 years after diagnosis, the patient remained clinically stable, with findings limited to a concentric stenosis managed with serial endoscopic dilations and PET uptake considered consistent with residual inflammatory changes.

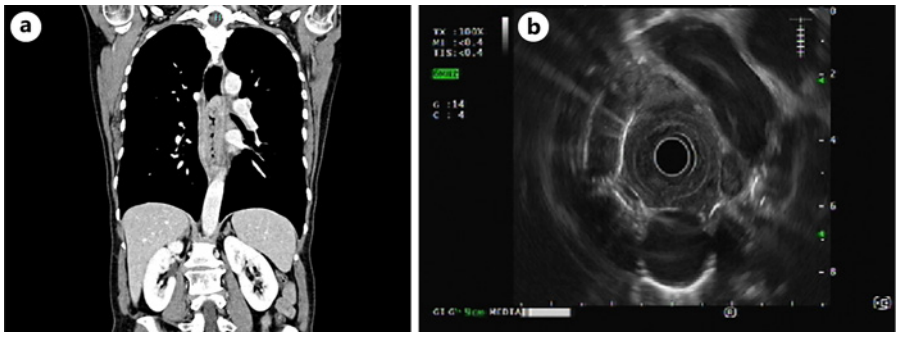

Fig. 3. Radiologic and endosonographic evaluation of the lesion. **a** Contrast-enhanced CT showing a long-segment circumferential esophageal mass with marked luminal stenosis and upstream dilation. **b** Endoscopic ultrasonography demonstrating concentric hypoechoic thickening involving the full esophageal wall up to the adventitia, with suspicious locoregional lymph nodes.

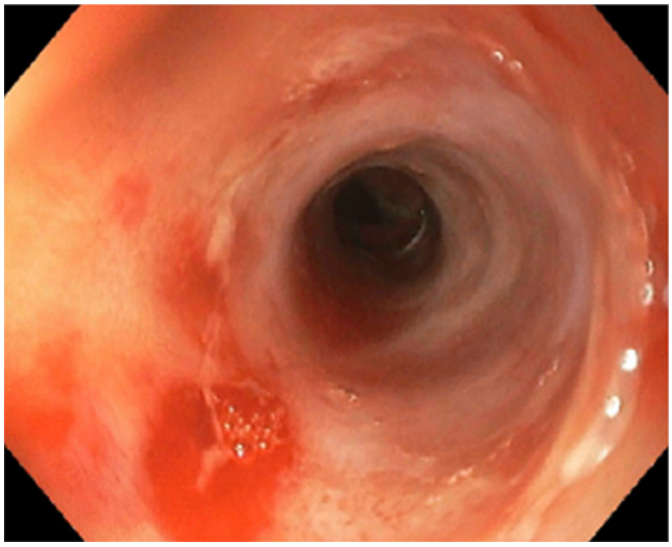

Fig. 4. Posttreatment endoscopic appearance after chemoradiotherapy and palliative chemotherapy. Upper gastrointestinal endoscopy performed after neoadjuvant chemoradiotherapy followed by 12 cycles of palliative FOLFOX, showing complete endoscopic regression of the previously described verrucous lesion, with residual concentric stenosis and no visible tumor.

The patient progressively resumed oral intake after endoscopic dilations and currently maintains combined oral and PEG feeding, with the PEG tube preserved for nutritional safety.

Discussion

This case highlights several relevant aspects of VCE: (1) the diagnostic challenge posed by repeatedly negative superficial biopsies despite a highly characteristic endoscopic appearance; (2) the possibility of regional nodal involvement, which is uncommon; and (3) the need for cautious interpretation of p16 positivity in this setting. A hallmark of VCE is the frequent mismatch between its characteristic macroscopic appearance and nondiagnostic histology. Superficial biopsies often yield only hyperkeratotic, inflammatory changes, delaying definitive diagnosis and potentially postponing treatment [6]. In such cases, surgical resection may be required to demonstrate tumor presence. A review of 56 published VCE cases showed a 27% diagnostic rate on first biopsy, while many other cases remained nondiagnostic after repeated biopsies, with malignancy being ultimately confirmed only on examination of the resected specimen [7].

Unlike the most commonly described presentation of VCE as a locally invasive tumor with rare metastatic spread, our patient had radiologic evidence of nodal disease. In fact, nodal metastases are infrequent, as demonstrated in the series by Cappellesso et al. [8], where synchronous nodal metastasis occurred in only 1 case and was associated with adverse molecular features (TP53 mutation, high EGFR, and low E-cadherin), supporting the concept that metastatic potential, while rare, should not be excluded. In the systematic review by Li et al. [9], lymph-node metastases were present in only 5% of pathologically staged cases.

The role of HPV in esophageal squamous carcinogenesis has been debated since early reports and later comprehensive reviews, including those by Syrjänen [10]. However, evidence specifically supporting an HPV-driven pathway in VCE remains inconsistent. In the series by Cappellesso et al. [8], HPV was not detected using multiple molecular techniques. Nevertheless, isolated case reports have described HPV detection in VCE, including HPV type 51 [2]. In this context, p16 positivity in our case – despite negative HPV testing – should be interpreted as a nonspecific marker of cell-cycle dysregulation rather than definitive proof of HPV-related oncogenesis, a possibility also raised by Rocco et al., possibly reflecting activation of cellular

tumor-suppressor pathways in response to uncontrolled proliferation.

Our patient also reported frequent ingestion of very hot liquids. While this exposure has not been specifically established as a risk factor for VCE, repeated thermal injury is possible as a chronic irritant. The International Agency for Research on Cancer (IARC), part of the World Health Organization, classifies consumption of beverages above 65°C as "probably carcinogenic to humans" (group 2A) [11] based on epidemiologic associations with esophageal cancer, likely mediated by chronic mucosal injury and inflammation.

Finally, the subsequent clinical course was unexpectedly favorable for a presumed unresectable, locally advanced disease, with marked endoscopic/radiologic response to systemic therapy and durable stability on surveillance. Although the absence of definitive malignant histology is an important limitation, alternative tissue acquisition strategies were considered. However, severe luminal stenosis, inability to traverse the lesion, repeated nondiagnostic deep biopsies, and concern regarding procedural safety and diagnostic yield limited additional invasive approaches. Nevertheless, the combination of the characteristic endoscopic phenotype, transmural wall thickening on endoscopic ultrasound/CT, FDG-avid disease at presentation, and treatment-responsive course supports the likelihood of a true neoplastic process. To our knowledge, this is one of the very few reported cases of presumed verrucous carcinoma of the esophagus in which treatment was initiated and maintained without definitive histologic confirmation. These findings support the need for multidisciplinary decision-making and close follow-up in diagnostically challenging cases.

Conclusion

Verrucous carcinoma of the esophagus should be suspected when a characteristic verrucous lesion remains repeatedly nondiagnostic despite multiple deep biopsies. In selected cases, multidisciplinary assessment may justify presumptive treatment even in the absence of histologic confirmation. Our case also suggests that prolonged response to systemic therapy may occur despite initially unresectable disease.

The authors completed the CARE checklist for this case report, which is available as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000553165).

Statement of Ethics

Ethical approval was not required in accordance with local/national guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images, and can be provided upon request.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study received no specific funding.

Author Contributions

Isabel Malta Carvalho, Tânia Gago, Luís Relvas, and Margarida Portugal contributed to data acquisition, interpretation, and wrote the manuscript. Jésus Cadillá performed histologic analysis of samples. Bruno Peixe critically reviewed the manuscript. All authors approved the final version of this paper.

Data Availability Statement

The complete data of this study are not publicly available due to the patient's privacy, but are available from the corresponding author upon reasonable request.

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