

Case Report

Esophageal Infiltration by High-Grade Serous Ovarian Carcinoma: A Very Rare Case Report

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Keywords

Case report · Ovarian cancer · Esophageal metastasis

Abstract

Introduction: Esophageal involvement in high-grade serous ovarian carcinoma is a rare phenomenon when advanced systemic disease is detected. Dysphagia is the most common guide symptom. However, diagnosis is often delayed due to its submucosal process that is not early seen in endoscopic initial evaluation, while computerized tomography (CT) scan usually shows concentric thickening of the esophageal layers and gives the suspected diagnosis. **Case Presentation:** We present the case of a patient who died of mediastinitis caused by an esophageal perforated ulceration due to infiltration of high-grade serous ovarian carcinoma. In addition, this is the first case report of severe esophageal candidiasis associated that delayed diagnosis and subsequent oncological treatment. **Conclusion:** Esophageal secondary infiltration must be suspected when a patient has a history of malignancy combined with consistent CT findings.

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Introduction/Background

The intraperitoneal route of dissemination is the most common route in ovarian cancer. However, cancer cells may metastasize through the lymphatic pathway or spread hematogenously elsewhere in the body [1].

Secondary involvement of the esophagus by malignancy is rare, occurring in patients with cancer at an estimated incidence of 1–6%, and is most commonly related to breast and lung cancers [2, 3]. Esophageal metastasis from ovarian cancer is scarcely described in the literature having few case reports published. Here, we report a case of impressive circumferential involvement of the esophageal serosa in high-grade serous ovarian carcinoma with documented histological confirmation.

Case Report

A 65-year-old female was diagnosed with FIGO stage IVB high-grade serous ovarian carcinoma (radiologic pathological cardiophrenic adenopathies) in February 2019. She received four cycles of carboplatin AUC6 and paclitaxel 175 mg/m² chemotherapy as neoadjuvant treatment. The patient achieved clinical and radiological response including remission of cardiophrenic involvement. The Multidisciplinary Committee recommended interval debulking surgery in August 2019. It consisted of total hysterectomy, double adnexectomy, omentectomy, appendicectomy, and wide peritonectomies; lymphadenectomy was not required because of the absence of macroscopic lymph nodes. Surgery was optimal without macroscopic residual disease. Genetic counseling revealed a germinal pathogenic mutation in *BRCA1* gene (c.3770-3771delAG). After surgery, the patient completed three cycles of carboplatin and paclitaxel, finishing the last of the cycles in November 2019. Olaparib (300 mg/m² bid) was initiated as a maintenance therapy. Owing to recurrent grade 3 anemia despite dose reductions, treatment was stopped in December 2020.

The first recurrence was detected in January 2021, when platinum remained still an option. It was located in the peritoneum and mediastinal lymph nodes and was therefore considered unresectable. The patient was enrolled in a clinical trial for second-line treatment with carboplatin AUC5-liposomal pegylated doxorubicin 30 mg/m² +/- antiPDL1, achieving a partial response after three cycles in May 2021, which was maintained after five cycles. In October 2021, she initiated maintenance therapy with niraparib 200 mg daily +/- antiPDL1 until progression of adenopathies in the mediastinum was detected in March 2022.

Third-line treatment consisted of weekly paclitaxel (80 mg/m²) plus biweekly bevacizumab (15 mg/kg) with a partial response in the first CT scan exam. In October 2022, the patient started with non-specific symptoms of epigastralgia and esophagitis initially treated with proton-pump inhibitors as no progression in the mediastinum was detected in the computerized tomography (CT) scan and first esophagogastroscope reported no lesions in the mucosa. In December 2022, clinical symptoms progressed to dysphagia and aphonia, and the Ca 125 levels increased dramatically from 300 UI/mL to 1,500 UI/mL in 2 weeks, and a CT scan showed esophageal thickening, shown in Figure 1.

The patient was admitted to the hospital due to an infectious respiratory condition in January 2023, and as aphonia and mild dysphagia persisted, a second examination with endoscopic ultrasonography (EUS) was performed. The results showed diffuse thickening of the esophageal wall with preserved layered echostructure, at the expense of the more superficial layers (mucosa and submucosa) with whitish/yellowish plaques compatible with extensive esophageal candidiasis.

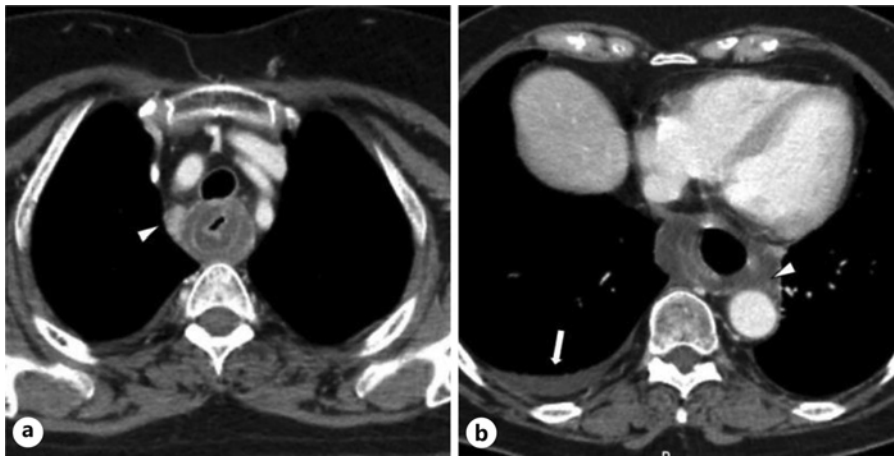


Fig. 1. Axial planes from same CT scan at upper thoracic esophagus level (**a**) and lower thoracic esophagus level (**b**) show miliary involvement of the esophageal serosa with diffuse and regular thickening of all layers of the wall of the thoracic and abdominal esophagus. It is associated with enlarged mediastinal lymph nodes (**a**, arrowhead), a slight amount of periesophageal fluid (**b**, arrowhead), and a right pleural effusion (**b**, arrow).

Biopsies were performed, reporting severe candidiasis; no malignant cells were identified at that moment. Fluconazole (400 mg/day) was administered for 21 days, and the oncological treatment was stopped because of active infectious disease.

After completing treatment with antifungals, the patient continued with progressive dysphagia until it became complete for solids and partially for liquids. The patient was admitted to the hospital again in early February 2023 because disease progression was suspected. The patient presented with clinical signs of deterioration and malnutrition. The differential diagnosis at that time was progressive disease with esophageal infiltration versus fluconazole-resistant candidiasis; however, a CT scan showed increasing esophageal thickening and Ca 125 levels continued to increase at 4,500 UI/mL. We considered to repeat esophagogastroscopy, which revealed a fibrinated ulcer measuring 15 mm with an ovoid morphology compatible with fistulation to the mediastinum, as shown in Figure 2. A nasogastric feeding tube was then inserted.

The patient's clinical evolution worsened with signs of sepsis due to mediastinitis with progressive respiratory failure until the patient died despite antibiotic and supportive treatment. Pathological reports have described infiltration by high-grade serous carcinoma consistent with disease progression, as shown in Figure 3. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000534702>).

Discussion

Esophageal extrinsic stricture secondary to direct extension by malignancies of contiguous organs, especially in the mediastinum, is a complication seen at a low frequency in the esophagus [3]. Despite being estimated to occur in 1–6% of patients with cancer, metastases to the esophagus from a distant organ are even less frequent [2].

Most patients present with progressive dysphagia to solids and liquids, associated with weight loss, months or years after the diagnosis and treatment of their original primary malignancy. Its clinical occurrence is uncommon, resulting in a delay in diagnosis [3, 4].

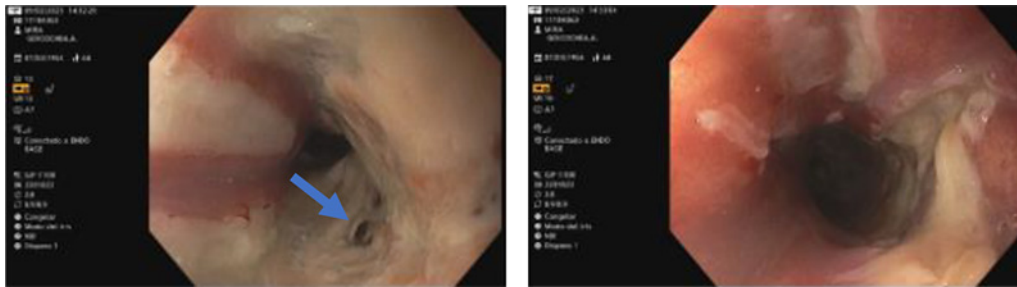


Fig. 2. Endoscopic picture shows deep excavated ulcerations with whitish exudate suggestive of infiltrative etiology associated with candidiasis throughout the esophagus lumen. Perforation to the mediastinum (blue arrow). Normal stomach and duodenum.

We have performed a literature review and compared our case report with other published studies focusing on ovarian cancer. We found very few cases of ovarian cancer reported in the literature published several years ago.

An old review made in a hospital in Tokyo in 1997 [5] of 1,835 esophagectomies from autopsy records. Metastases to the esophagus occurred at an incidence rate of 6.1%. The lung was the most common primary tumor associated with esophageal involvement. They reported three cases of esophagectomy for secondary carcinoma metastasizing to the ovary, breast, and lungs. In the case of ovarian cancer, they explained a single recurrence to the esophagus after 16 years with complete resection before complementary chemotherapy. Dysphagia was the primary symptom. Histological examination revealed infiltration of the submucosal and deeper layers by serous cancer cells with psammoma bodies which are commonly associated with ovarian cancer without mucosal involvement.

In another review conducted in a referral hospital in Seattle in 2001 [3], they found 6 incident cases between 1972 and 2000; two were lung cancers, four were breast cancers, and none were ovarian cancer. All patients had smooth concentric strictures with normal overlying mucosa on esophagoscopy, while CT images consistently demonstrated marked esophageal wall thickening with no associated extraesophageal masses.

In general, endoscopic biopsy specimens can be negative because the mucosa is not often affected at the beginning of the process [3, 6] as is the case in our patient. However, the esophagus has lymphatics that extend into the lamina propria, as opposed to stopping at the submucosa. These lymphatic channels drain into the thoracic duct, which may act as a portal for metastasis from distant primaries, and mucosal ulceration or polypoidal lesions may be present later if the disease continues to progress in the esophagus [7–9].

When an esophageal stricture with normal mucosa is encountered, a metastatic tumor must be considered, particularly when the patient has a history of malignant tumor [5]. EUS can provide more accurate information with respect to whether lesions are intrinsic or extrinsic to the esophageal wall and act as a guide for obtaining biopsies, while CT studies will demonstrate concentric thickening of the esophageal wall with or without an associated esophageal mass [3, 4, 7].

There are two case reports in the literature describing esophageal involvement in ovarian cancer: a singular case of pseudoachalasia by a metastatic lesion in the gastro-esophageal junction [6] and another case of a single middle esophageal recurrence that was managed with secondary cytoreduction surgery consisting of transhiatal resection with cervical esophago-gastric anastomosis [2].

Local treatment for metastatic lesions in the esophagus usually cannot be justified because such lesions often manifest as active systemic disease or mediastinal carcinomatosis [5]. As most patients with metastasis to the esophagus already have metastasis in other areas,

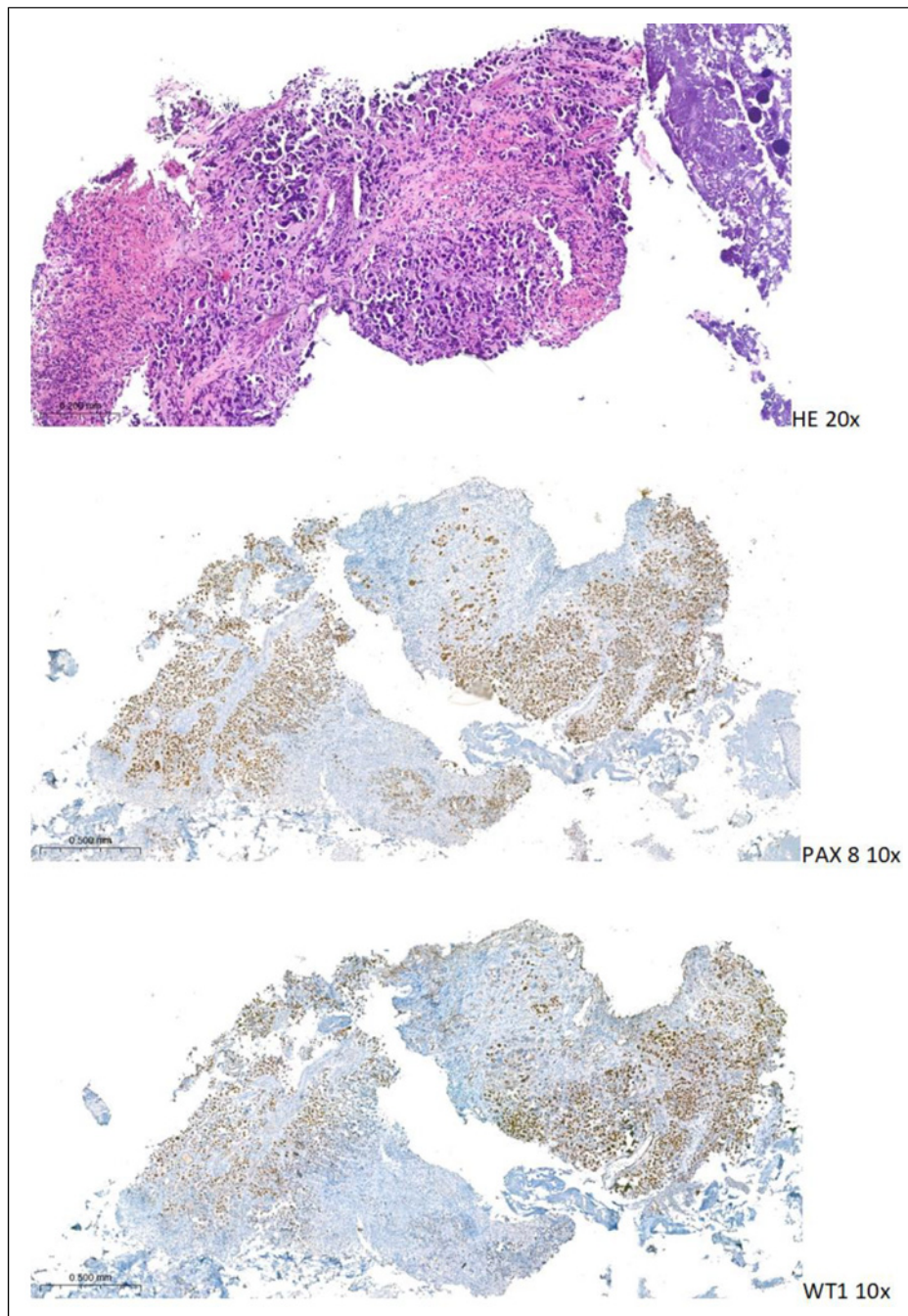


Fig. 3. Fragments of squamous mucosa infiltrated by atypically marked neoplastic cells expressing PAX8 and WT1.

the treatment of choice is usually palliative chemotherapy and/or radiotherapy combined with palliative endoscopic dilatation or stent placement but should be approached with caution as perforation has been described [3, 4, 10].

Surgical resection is difficult and not exempt from serious complications; therefore, it is limited to oligometastatic disease with large recurrence intervals [1, 2, 5]. To our knowledge, this is the first case report of severe esophageal candidiasis that could have delayed diagnosis. Chemotherapy, radiotherapy, and the presence of malignant diseases by itself may contribute

to the development of this disease by inducing immunosuppression. In addition, processes that cause local lesions (metastasis) in the esophageal upper cortex as happened in our patient, can lead to the proliferation and colonization of *Candida*. Furthermore, the destruction of local defense mechanism and systemic factors including application of antibiotics endocrine disorders and nutritional factors contribute to the occurrence of this disease [11].

Diagnosis is made by endoscopy, which confirms the presence of white/yellow plaques or exudates that are adherent to the esophageal mucosa and cannot be washed away with water irrigation. Histological confirmation always helps identify the predominance of neutrophils, fungal spores, and pseudohyphae. Occasionally, mucosal breaks or ulcerations may occur. The treatment of choice is short-term fluconazole 200 mg–400 mg/day for up to 14–21 days [11]. Complications include esophageal stricture or perforation with fistula formation in the mediastinum or bronchial tree. This was the case in our patient after treatment with fluconazole failed. However, we considered tumor infiltration to be the cause of candidiasis and ulceration, and not vice versa, as chemotherapy had been stopped weeks before.

Conclusions

Esophageal secondary infiltration by a distant primary malignancy is often underdiagnosed because of predominantly submucosal involvement until significant complications arise. CT usually shows concentric thickening of the esophageal layers and must be suspected when a patient has a history of malignancy. Curative surgical attempt is not indicated in most patients because it is often accompanied by systemic active disease in other organs, whereas palliative chemotherapy and/or radiotherapy are preferred. In our case report, chemotherapy had to be stopped in view of severe esophageal candidiasis and radiotherapy was also contraindicated. We believe that our case report may help elucidate the uncommon paths of dissemination in ovarian cancer.

Statement of Ethics

This manuscript was originally written by the authors and has not been published elsewhere. Written informed consent was obtained from the patient's guardian for the publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal upon request. Patient's identity has been protected and treated confidentially. This retrospective review of patient data did not require ethical approval in accordance with local guidelines.

Conflict of Interest Statement

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this study.

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Author Contributions

Anna Carbó: conceptualization, investigation, writing-original draft, and reviewing and editing. Laura Cerón, Laia Valls, and Cristina Meléndez: investigation, resources, and data curation. Elisabet Bujons: conceptualization and writing-reviewing. Raquel Liñan: conceptualization, investigation, and resources. Maria Pilar Barretina: validation, writing-reviewing and editing, and supervision.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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