

Early-stage Ovarian High-Grade Serous Carcinoma with Borderline-like Morphology: a Diagnostic Pitfall

Carcinoma Seroso de Alto Grau do Ovário em Estádio Inicial com Morfologia Tipo *Borderline*: um Desafio Diagnóstico

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Abstract

Ovarian serous carcinomas follow distinct developmental pathways that influence their behavior and clinical outcomes. High-grade serous carcinoma (HGSC) typically arises from fallopian tube and is characterized by cytologic atypia, solid growth patterns, and aberrant p53 expression. In contrast, serous borderline tumors exhibit low-grade cytologic features and distinct architectural patterns. Rarely, HGSC may present with morphologic features that mimic serous borderline tumors, representing a significant diagnostic pitfall. We present a rare case of ovarian HGSC with borderline-like morphology in a 75-year-old woman.

Keywords: Ovarian cancer; High-grade serous carcinoma; Serous borderline tumor.

Resumo

Os tumores serosos do ovário apresentam vias de desenvolvimento distintas, que condicionam o seu comportamento e prognóstico. O carcinoma seroso de alto grau surge geralmente de lesões tubárias e caracteriza-se por atipia citológica, padrões de crescimento sólidos e expressão aberrante de p53. No entanto, tumores borderline apresentam características citológicas de baixo grau e padrões arquiteturais distintos. Raramente, o carcinoma seroso de alto grau pode apresentar características morfológicas semelhantes à dos tumores borderline, constituindo um desafio diagnóstico. Descreve-se o caso raro de uma mulher de 75 anos com carcinoma seroso de alto grau com morfológica semelhante à de um tumor *borderline*.

Palavras-chave: Cancro do ovário; Carcinoma seroso de alto grau; Tumor seroso *borderline*.

INTRODUCTION

Ovarian cancer is the third most common gynecological malignancy worldwide and remains one of the leading causes of gynecologic cancer-related mortality, accounting for more than 200.000 deaths annually¹. According to histopathology, immunohisto-

chemistry, and molecular analysis, epithelial ovarian cancers are classified into five major subtypes: high-grade serous carcinoma (HGSC), low-grade serous carcinoma (LGSC), mucinous carcinoma, endometrioid carcinoma, and clear cell carcinoma^{2,3}.

HGSC is the most frequent and aggressive subtype. It typically arises from serous tubal intraepithelial carcinoma and is characterized by tumor protein 53 mutations^{4,5}.

In contrast, LGSC is a distinct clinical and molecular entity that can arise *de novo* or, more commonly, from

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preexisting serous borderline tumors. These tumors have a different molecular profile, characterized by mitogen-activated protein kinase (MAPK) pathway mutations. Women with this subtype are generally diagnosed at a younger age, experience an indolent progression and, consequently, have a higher long-term survival rate^{4,6}.

We present an uncommon early-stage ovarian HGSC presenting as a predominantly cystic lesion with borderline-like morphology. Notably, intraoperative frozen section examination initially suggested a serous tumor with cytological atypia and equivocal stromal invasion, leading to the interpretation that it was at least a serous borderline tumor. However, definitive histology revealed a small solid component with unequivocal features of HGSC and diffuse aberrant p53 expression in both solid and cystic components. There was no evidence of serous tubal intraepithelial carcinoma (STIC) on SEE-FIM (Sectioning and Extensively Examining the FIMbriated End) sampling. This case highlights a real-life diagnostic pitfall with direct implications for intraoperative consultation and patient management, emphasising the limitations of frozen section evaluation in cystic serous tumors.

CLINICAL CASE

We present the case of a 75-year-old female patient with good performance status, referred to our gynecological oncology department due to a suspicious adnexal mass. Her medical history included type 2 diabetes mellitus, ascending aortic aneurysm, dyslipidemia, and a prior episode of thrombophlebitis. The patient's obstetric and gynecological history include two vaginal deliveries and menopause at 52 years of age, with no history of hormonal therapy. Regarding family history, her paternal grandmother had uterine cancer, and her maternal uncle had colorectal cancer.

The patient reported a one-month history of pelvic pain, more intense on the right side, along with abdominal distension. Physical examination revealed a bulky, mobile mass, palpable up to the level of the umbilicus. No enlarged inguinal or supraclavicular lymph nodes were identified.

Transvaginal ultrasound showed a large multilocular cyst with low-level internal echoes in the right pel-

vis, measuring 120 × 90 × 81 mm. Evaluation of the uterus and left adnexa revealed no significant abnormalities, and no free fluid was observed. An abdominal-pelvic computed tomography (CT) scan confirmed a large multilocular cyst with thin septa and no solid component in the right ovary. No lymphadenopathy or ascites was noted. The thoracic CT scan was unremarkable. Tumor marker values (cancer antigen 125 and 19-9) were within normal limits.

Due to the suspicious features and the patient's postmenopausal status, a laparotomy was recommended to allow comprehensive staging. Regarding intraoperative findings, the right ovary was enlarged due to a cystic lesion measuring approximately 12 cm, with smooth and intact surface (twisted pedicle), and there was no evidence of peritoneal dissemination. The uterus and left adnexa showed no apparent macroscopic alterations. Right adnexectomy was initially performed, an intraoperative frozen section suggested a serous tumor with cytological atypia and equivocal stromal invasion, leading to an interpretation of at least a serous borderline tumor pending permanent sections. Therefore, total hysterectomy with left adnexectomy and an infra-colic omentectomy were subsequently performed according to pathological results and current staging recommendations. The postoperative course was uneventful.

Pathological examination of the right ovary revealed a 150 mm multilocular cystic ovarian lesion with smooth inner walls and no capsular rupture, containing a discrete solid white-yellowish nodule, firm, measuring 16mm. Histopathological examination showed a neoplasm composed mainly of cystic structures with areas of low cellularity and mild architectural complexity, features that closely resembled a serous borderline tumor. In contrast, the solid component displayed features of HGSC, with solid and glandular growth patterns, marked nuclear atypia, frequent atypical mitotic figures, and focal areas of necrosis. (Figure 1 and 2)

Immunohistochemical analysis showed neoplastic cells positive for P16, WT1, PAX8, and demonstrated diffuse aberrant p53 expression in both the solid and borderline-like areas, supporting the diagnosis of HGSC. (Figure 3) Extensive sampling of the fallopian tubes, performed according to the SEE-FIM protocol, revealed no evidence of serous tubal intraepithelial carcinoma (STIC). (Figure 4) Based on the histopathological

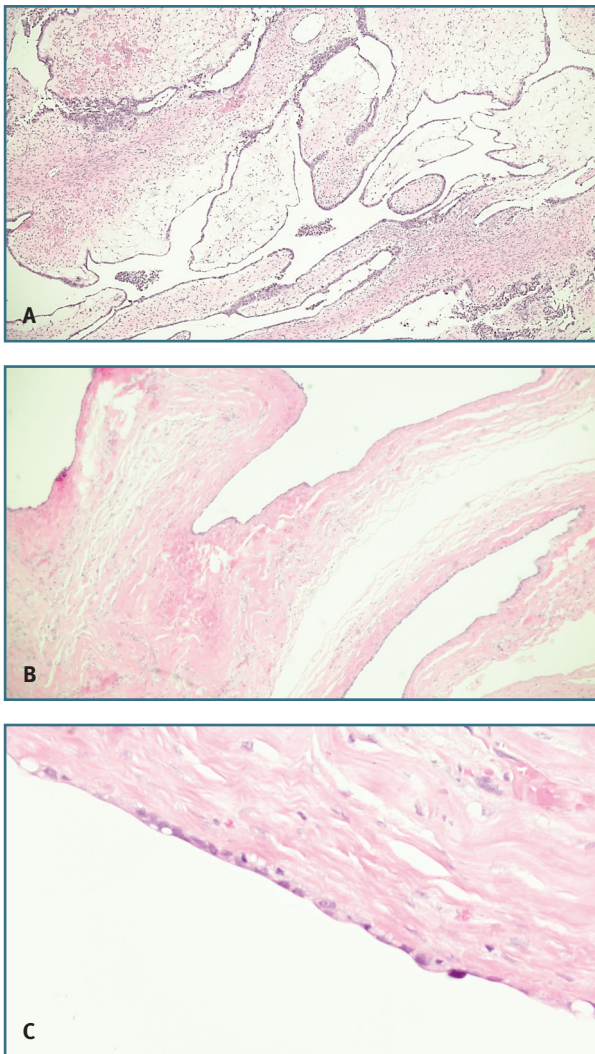


FIGURE 1 (A, B, C). Borderline-like morphology. Histological section from the cystic component showing areas of low cellularity and mild architectural complexity, with features mimicking a serous borderline tumor (A and B- H&E $\times 50$ A eB; C- H&E- $\times 400$).

and immunohistochemical findings, a diagnosis of ovarian HGSC was established. According to the clinical and pathological evaluation, the tumor was classified as stage I disease.

For postoperative staging and treatment planning, positron emission tomography integrated with CT (PET/CT) scan was performed, showing no metabolically active disease. After discussion of the case in the tumor board meeting, the patient initiated adjuvant chemotherapy with carboplatin alone (paclitaxel was omitted due to thrombocytopenia), completing six cycles. The patient

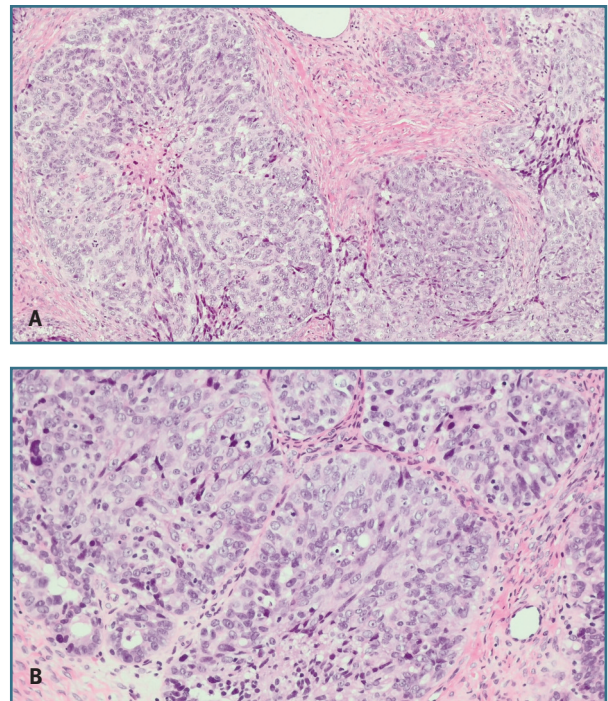


FIGURE 2. Solid component – high-grade serous carcinoma. The solid nodule displays unequivocal features of high-grade serous carcinoma, with solid and glandular growth patterns, marked nuclear atypia, frequent atypical mitotic figures, and focal areas of necrosis (A-H&E $\times 100$, BH&E $\times 200$).

remains asymptomatic and follow-up at 18 months showed no evidence of recurrence or metastasis.

DISCUSSION

This case report describes a patient with high-grade serous carcinoma exhibiting extensive borderline-like serous morphology, which initially led to consideration of a possible association with a serous borderline tumor.

The dualistic model of epithelial ovarian carcinogenesis classifies these tumors in two main categories (Type I and Type II) based on distinct pathogenetic pathways and clinical behavior.

Type I tumors, including low-grade serous carcinoma, arise from benign precursors such as borderline tumors, are generally indolent, and tend to be genetically stable. In contrast, Type II tumors, including high-grade serous carcinoma, are clinically aggressive and

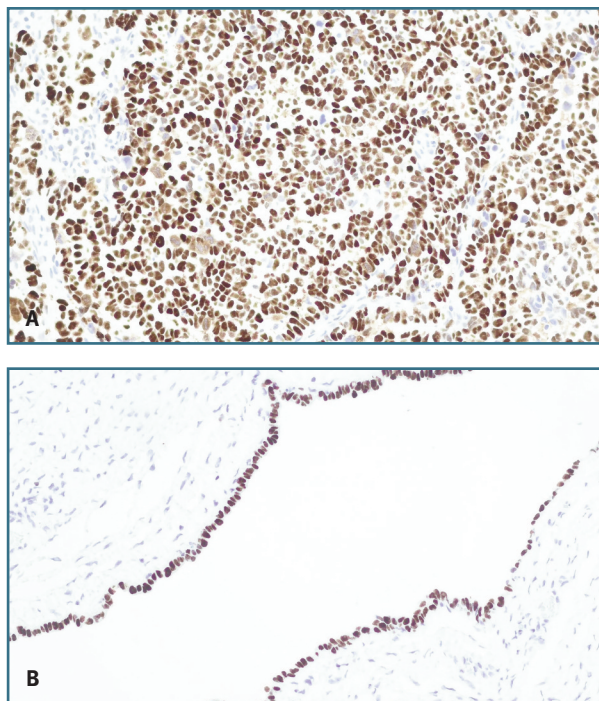


FIGURE 3. p53 immunohistochemistry. Diffuse aberrant p53 expression is observed in both the solid high-grade component (A) and the borderline-like cystic areas (B), supporting the diagnosis of high-grade serous carcinoma (p53 immunohistochemistry, $\times 200$).

exhibit marked chromosomal instability, typically associated with *TP53* mutations^{4,7,8}.

Despite their distinct pathogenesis, a few cases have been described in the literature in which HGSC coexists with LGSC or a serous borderline tumor. Additionally, high-grade serous carcinoma has been diagnosed in rare cases of recurrent low-grade serous carcinoma⁹⁻¹². Up to 60% of LGSC are characterized by mitogen-activated protein kinase (MAPK) pathway mutations (such as *KRAS*, *BRAF* and *NRAS*), and genomic analysis may help clarify the diagnosis when low-grade and high-grade components are present¹². Serous borderline ovarian tumors represent an intermediate pathological and clinical entity. Certain variants, including the micropapillary pattern, are associated with a poorer prognosis and an invasive progression rate ranging from 11% to 21%^{13,14}.

It is well established that most HGSC arises from serous tubal intraepithelial carcinoma; however, approximately 40% are not derived from the fallopian tube.

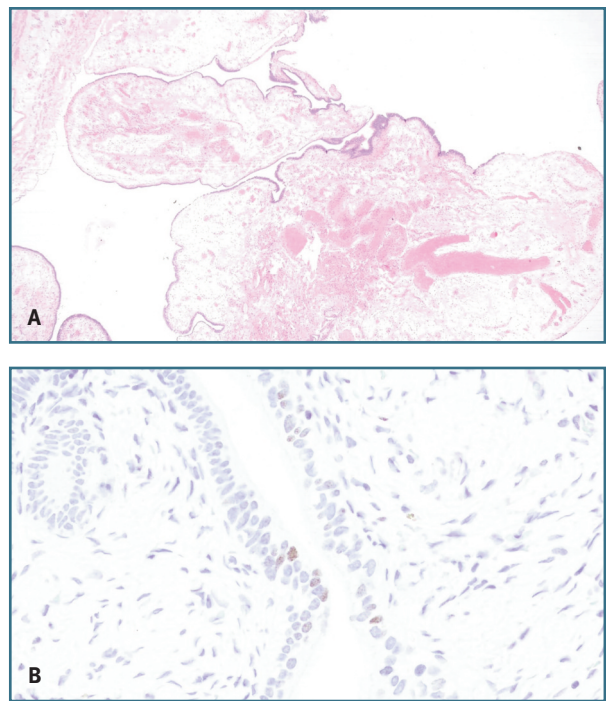


FIGURE 4 (A and B). Fallopian tube (SEE-FIM). Representative section of the fallopian tube processed according to the SEE-FIM protocol, showing no evidence of serous tubal intraepithelial carcinoma (STIC) (A- H&E, $\times 50$; B- p53 immunohistochemistry-wild type pattern $\times 400$).

Some authors suggest that these tumors may originate from the ovarian surface epithelium or from transformation of serous borderline tumors or LGSC¹⁵.

HGSC of the ovary is classically characterized by marked nuclear atypia, high mitotic activity, solid growth patterns, and ubiquitous *TP53* mutations, typically reflected by aberrant p53 immunohistochemical expression. In contrast, serous borderline tumors exhibit hierarchical papillary architecture, mild to moderate cytologic atypia, low proliferative activity, and a wild-type p53 staining pattern. Despite these well-established criteria, rare cases of HGSC may present with unusual morphologic features that closely mimic serous borderline tumors, creating a significant diagnostic pitfall⁴.

The present case illustrates an uncommon presentation of ovarian HGSC with a predominantly cystic and multiloculated architecture, smooth cyst walls, and a small solid component. Notably, the diagnostic challenge was already evident at intraoperative frozen section analysis, where the lesion was interpreted as a serous

tumor with cytologic atypia and equivocal stromal invasion. While the cystic areas showed borderline-like morphology with low cellularity, the solid nodule demonstrated unequivocal high-grade features, including solid and glandular architecture, frequent atypical mitoses, and necrosis. These findings, together with diffuse aberrant p53 expression in both the solid and borderline-like areas, were decisive in establishing the diagnosis of HGSC.

Most HGSCs are currently believed to originate from the fallopian tube epithelium, with serous tubal intraepithelial carcinoma (STIC) recognized as a key precursor lesion². Nevertheless, STIC is not identified in all cases, particularly in early-stage disease^{16,17}. In the present case, extensive sampling of the fallopian tubes according to the SEE-FIM protocol failed to identify STIC, suggesting either an alternative pathway of tumorigenesis or complete overgrowth or regression of a precursor lesion.

In conclusion, this case expands the morphologic spectrum of ovarian HGSC and emphasizes the need for careful evaluation of cystic and borderline-like serous tumors. Recognizing this diagnostic pitfall, ensuring extensive tumor sampling and routine p53 immunohistochemistry, is essential to avoid misclassification and to guarantee appropriate patient management, especially in early-stage disease.

REFERENCES

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229-63.
2. Köbel M, Kang EY. The Evolution of Ovarian Carcinoma Subclassification. *Cancers (Basel)*. 2022;14(2).
3. Höhn AK, Brambs CE, Hiller GGR, May D, Schmoeckel E, Horn LC. 2020 WHO Classification of Female Genital Tumors. *Geburtshilfe Frauenheilkd*. 2021;81(10):1145-53.
4. Vang R, Shih Ie M, Kurman RJ. Ovarian low-grade and high-grade serous carcinoma: pathogenesis, clinicopathologic and molecular biologic features, and diagnostic problems. *Adv Anat Pathol*. 2009;16(5):267-82.
5. Lisio MA, Fu L, Goyeneche A, Gao ZH, Telleria C. High-Grade Serous Ovarian Cancer: Basic Sciences, Clinical and Therapeutic Standpoints. *Int J Mol Sci*. 2019;20(4).
6. Babaier A, Mal H, Alsawi W, Ghatage P. Low-Grade Serous Carcinoma of the Ovary: The Current Status. *Diagnostics (Basel)*. 2022;12(2).
7. Kurman RJ, Shih Ie M. The Dualistic Model of Ovarian Carcinogenesis: Revisited, Revised, and Expanded. *Am J Pathol*. 2016;186(4):733-47.
8. Kurman RJ, Shih Ie M. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. *Am J Surg Pathol*. 2010;34(3):433-43.
9. Dehari R, Kurman RJ, Logani S, Shih Ie M. The development of high-grade serous carcinoma from atypical proliferative (borderline) serous tumors and low-grade micropapillary serous carcinoma: a morphologic and molecular genetic analysis. *Am J Surg Pathol*. 2007;31(7):1007-12.
10. Quddus MR, Rashid LB, Hansen K, Sung CJ, Lawrence WD. High-grade serous carcinoma arising in a low-grade serous carcinoma and micropapillary serous borderline tumour of the ovary in a 23-year-old woman. *Histopathology*. 2009;54(6):771-3.
11. Parker RL, Clement PB, Chervcover DJ, Sornarajah T, Gilks CB. Early recurrence of ovarian serous borderline tumor as high-grade carcinoma: a report of two cases. *Int J Gynecol Pathol*. 2004;23(3):265-72.
12. Chui MH, Song Q, Zhu J, Jiao Y, Wang B, Wang Y, et al. Early Genetic Divergence of High-Grade Carcinomas Originating from Low-Grade Serous Ovarian Neoplasms. *Mod Pathol*. 2025;38(1):100629.
13. Malpica A, Longacre TA. Prognostic indicators in ovarian serous borderline tumours. *Pathology*. 2018;50(2):205-13.
14. Jia SZ, Yao HW, Li N, Yang JJ, Xiang Y, Zheng S, et al. Prognosis and Prognostic Factors of Serous Borderline Tumor-Micropapillary Variant: Retrospective Study of 200 Patients with Long-Term Follow-Up. *J Oncol*. 2022;2022:1655422.
15. Lim D, Oliva E. Precursors and pathogenesis of ovarian carcinoma. *Pathology*. 2013;45(3):229-42.
16. Singh N, Gilks CB, Wilkinson N, McCluggage WG. Assignment of primary site in high-grade serous tubal, ovarian and peritoneal carcinoma: a proposal. *Histopathology*. 2014;65(2):149-54.
17. Kindelberger DW, Lee Y, Miron A, Hirsch MS, Feltmate C, Medeiros F, et al. Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: Evidence for a causal relationship. *Am J Surg Pathol*. 2007;31(2):161-9.

AUTHORS' CONTRIBUTION

All authors contributed equally.

CONFLICTS OF INTEREST

Authors declare they have no conflicts of interest.

PATIENT CONSENT

The patient gave informed consent for publication.

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