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CASE REPORT

Case Report: Borderline tumor and primary peritoneal carcinoma - a rare synchronism [version 1; peer review: 1 approved, 1 approved with reservations]

Mariana Rei ^{1,2}, Sofia Raposo³, Paulo Figueiredo⁴, Rita Sousa³, Luís Sá³

¹Department of Obstetrics and Gynecology, Centro Hospitalar Universitário São João, Porto, Porto, 4200-319, Portugal

²Unit of Obstetrics and Gynecology, Faculty of Medicine, University of Porto, Porto, Portugal

³Department of Gynecology, Instituto Português de Oncologia Francisco Gentil de Coimbra, Coimbra, Portugal

⁴Department of Pathology, Instituto Português de Oncologia Francisco Gentil de Coimbra, Coimbra, Portugal

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Abstract

Ovarian borderline serous tumors present with peritoneal involvement in 20% of cases, either as non-invasive or invasive implants, also known as extraovarian low-grade serous carcinoma. The coexistence of high-grade serous carcinoma is rare, suggesting a synchronous neoplasia with a distinct and independent tumor biology and behavior. We aim to describe a case of a synchronous ovary-peritoneum neoplasia: serous borderline tumor and primary peritoneal high-grade serous carcinoma. A discussion and literature review concerning the optimal diagnostic and therapeutic approach is provided.

Keywords

borderline tumor, ovarian neoplasm, peritoneal neoplasm, high grade serous carcinoma, low grade serous carcinoma

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Approval Status

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version 1 12 Sep 2019	view	view

1. **Carla Bartosch** , Portuguese Oncology Institute of Porto, Porto, Portugal
2. **Maria Dolores Diestro**, La Paz University Hospital, Madrid, Spain

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: Mariana Rei (marianarei@hotmail.com)

Author roles: **Rei M:** Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft Preparation; **Raposo S:** Supervision, Writing – Review & Editing; **Figueiredo P:** Data Curation, Validation; **Sousa R:** Validation, Writing – Review & Editing; **Sá L:** Supervision, Validation, Writing – Review & Editing

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Introduction

Serous borderline tumors/atypical proliferative serous tumors (SBT/APST) are defined as non-invasive tumors displaying greater epithelial proliferation and cytological atypia than their benign counterparts. However, the SBT/APST show less cellular atypia than low-grade serous carcinoma (LGSC)¹. This entity is considered the premalignant lesion of LGSC and usually occurs in women 10 to 15 years younger than those with serous carcinoma. Although there are some similarities in risk-factor associations to high-grade serous carcinoma (HGSC), infertility is more common and there is usually no relation with *BRCA1/BRCA2* mutations^{2,3}.

Peritoneal lesions associated with SBT/APST may occur in 20% of cases and were classically defined as non-invasive or invasive implants based on the capacity to infiltrate the underlying tissue. The non-invasive implants are further subdivided into desmoplastic or epithelial types and have almost no negative influence on the 10-year survival rates. Distinctively, the invasive form behaves like LGSC, featuring a poor prognosis with a 50% recurrence rate and a 35% 10-year survival rate^{2,4,5}.

Therefore, the morphology of the peritoneal implants is the main prognostic factor for patients presenting with stage II-III SBT/APST^{1,5}. However, implants are heterogeneous, different histologic patterns may coexist, and unequivocal invasion may be difficult to establish in some cases. A comprehensive histopathological examination of multiple fragments of peritoneal implants is recommended in order to optimize the differential diagnosis between non-invasive and invasive implants.

Primary peritoneal carcinoma (PPC) resemble low- or high-grade serous ovarian counterpart and occurs in women with a mean age of 62 years. The estimated lifetime risk is 1 per 500 women, and nearly 15% of common epithelial ovarian cancers are in fact PPC¹. Histology and immunohistochemistry (IHC) are virtually indistinguishable from epithelial ovarian carcinoma and the most common histological variant is HGSC, although other histologic types have also been reported. In order to meet criteria for PPC, both ovaries and tubes should be macro- and microscopically normal in size or enlarged by a benign process¹. From a clinical point of view, the clarification of the tumor origin may not be critical, since the oncologic behavior, treatment and prognosis largely overlap their ovarian counterparts and therefore are addressed similarly. Conversely, the distinction between LGSC and HGSC is of utmost importance concerning diagnostic, therapeutic approaches and prognosis.

The coexistence of SBT/APST and HGSC is rare, suggesting a synchronous neoplasia with a distinct and independent tumor biology and behavior. We aim to describe a case of a synchronous ovary-peritoneum neoplasia. A discussion and literature review concerning the optimal diagnostic and therapeutic approach is provided.

Case report

We present the case of a 52-year-old postmenopausal woman with no relevant medical history, referred to an oncologic center due to a voluminous adnexal mass. She clinically presented with metrorrhagia, asthenia and anorexia with a significant weight loss. Serum tumor markers Ca125, HE4 and Ca 72.4 were significantly increased (1058 U/mL, 1795 pmol/L and 9.5 U/mL, respectively). Pelvic ultrasonography revealed a large heterogeneous multicystic adnexal mass, with multiple papillae and irregular intern contour. Thoraco-abdominal-pelvic computerized tomography (CT) scan revealed a vascularized heterogeneous adnexal mass measuring 190×100 mm; no ascites or unequivocal signs of peritoneal carcinomatosis or distant dissemination were observed. The validated preoperative diagnosis models ROMA, LR2 and ADNEX were calculated, presenting, respectively, a 34.8%, 72.8% and 85.8% risk of malignancy^{6–9}.

Within two weeks, the case was discussed in the multidisciplinary gynecologic oncology tumor board, advising for laparotomy with frozen section of the suspicious lesions. The patient was then submitted to exploratory laparotomy, revealing a frozen pelvis and peritoneal carcinomatosis: the right ovary was transformed into a voluminous neoplasia; independently, a large tumor mass involving omentum and the transverse portion of colon, apparently not surgically resectable; the left ovary was macroscopically normal. Intraoperative frozen section of the right ovary revealed a borderline tumor, whereby cytoreductive surgery was performed, including hysterectomy, double adnexectomy, omentectomy and resection of the peritoneal implants. The final cytoreduction was complete for the pelvis but incomplete for the superior abdomen, with over 2 cm of residual disease (R2). The final histology with hematoxylin and eosin staining revealed two synchronous tumors: BST of the right ovary and HGSC of probably primary peritoneal origin, FIGO stage IIIC (Figure 1A–C). The left ovary did not show any signs of either malignancies. The IHC was crucial for the final diagnosis, showing positivity for PAX8, WT-1 and p53, while calretinin and CD10 staining were negative.

The post-operative CT scan performed four weeks later revealed rapid peritoneal disease progression, with high-volume ascites and hydronephrosis, resulting in an important decline on clinical status and death before initiating palliative chemotherapy.

Discussion

The dualistic model of ovarian carcinogenesis recognizes two distinct categories in epithelial ovarian carcinomas: the more common aggressive type II tumors and the less common slow-growing type I tumors¹⁰. A revised model takes into account the current histopathologic classification, providing a bridge into the future by integrating emerging molecular genetic findings⁵. Type I tumors arise mostly from borderline tumors and include endometriosis-related tumors, LGSC, mucinous carcinomas and malignant Brenner tumors. Distinctively, type II tumors

Figure 1. Synchronous ovarian serous borderline tumor and primary peritoneal high-grade serous carcinoma. (A) Hematoxylin-eosin staining, magnification 10x. High-grade serous carcinoma (HGSC) in a peritoneal implant, of presumably primary peritoneal origin. (B) Hematoxylin-eosin staining, magnification 10x. SBT/APST of the right ovary. Left ovary with no evidence of malignancy. (C) Hematoxylin-eosin staining, magnification 10x. Invasive peritoneal implant of the parietocolic gutter, suggestive of HGSC.

seem to develop from tubal intraepithelial carcinomas (STICs) that disseminate as carcinomas involving ovary and extraovarian sites, in most cases corresponding to HGSC. This two-tier system subdivides serous carcinomas into low- and high-grade, implying independent pathogenesis and displaying distinct morphology, IHC and molecular biology^{2,5,11}.

Histopathologically, SBTs are characterized by a hierarchical papillary or micropapillary pattern, low-grade nuclear atypia and low mitotic activity. Most SBTs and LGSCs show PAX2 expression but no aberrant p53 expression and p16 overexpression. The molecular genetic analysis frequently demonstrates *KRAS* or *BRAF* mutation but *TP53* mutation is rare. In contrast, HGSCs present an invasive growth pattern, high-grade nuclear atypia and intense mitotic activity. Aberrant p53 expression, p16 overexpression and high MIB-1 labeling index are common; molecular studies frequently reveal *TP53* mutation, but *KRAS/BRAF* mutation is infrequently reported^{12,13}.

Nevertheless, it is still not clear whether some type II tumors develop from type I tumors. Dehari *et al.*¹⁴ studied the clonality of six cases of HGSC closely related to SBT/APST and invasive micropapillary LGSC from a cohort of 210 ovarian serous tumors. A morphologic continuum between the high-grade and the low-grade tumors was observed in four cases; the same *KRAS* mutations were found in both the SBT/APST and HGSC component of the tumor, indicating a clonal relationship and suggesting that in rare cases, HGSC may arise from SBT/APST¹⁴.

We report a case of a rare synchronism of neoplasms with distinct carcinogenesis pathways: SBT/APST of the right ovary with preserved contralateral ovary and HGSC identified in peritoneal implants. Peritoneal involvement could be related to multiple origins: non-invasive implants of SBT/APST, invasive implants or extraovarian LGSC, coexistence of other ovarian or secondary malignancy. An accurate histopathological and immunohistochemical analysis is of utmost importance in order to better delineate treatment and prognosis.

In this case, the ovarian tumor showed positivity for PAX8 and WT1. PAX8 is expressed in ovarian and endometrial neoplasias, whereas WT1 is expressed in ovarian serous tumors and is useful to support ovarian origin. Estrogen receptor expression was also positive. On the other hand, both progesterone receptors and CD10 were not present on IHC analysis.

TP53 mutations integrate the molecular carcinogenesis pathway of STIC and are ubiquitous in HGSC, therefore optimizing the differential diagnosis between HGSC and LGSC. p53 is widely used as a surrogate for *TP53* mutation; a recent study showed that it can approach 100% specificity for *TP53* mutation, and its high negative predictive value is clinically useful to exclude the possibility of a LGSC^{2,12}. In the current report, peritoneal implants stained positive for this marker, excluding the diagnosis of non-invasive implants of SBT/APST or LGSC and reinforcing the coexistence of HGSC. Identification of HGSC in peritoneal implants with a preserved contralateral ovary and tube strongly suggests a primary peritoneal origin.

The diagnosis of peritoneal carcinomatosis related to HGSC majorly impacts therapeutic approach. While there is no evidence to recommend neoadjuvant or adjuvant chemotherapy in SBT/APST, the diagnosis of HGSC with a high peritoneal cancer index (PCI) might have altered the course of the surgical approach in favor of chemical cytoreduction with neoadjuvant chemotherapy.

Nearly 15 to 20% of HGSC are associated with *BRCA1/BRCA2* germline mutations¹⁵. Its presence impacts therapy and prognosis, since these tumors are highly sensitive to poly (ADP-ribose) polymerase inhibitors, showing improved survival comparing to non-carriers¹³. Hence, there is now strong evidence to recommend genetic testing to all women affected with high-grade epithelial non-mucinous ovarian/tubal/peritoneal cancer¹⁵.

The diagnosis of a borderline tumor with peritoneal implants imposes the challenging differential diagnosis between non-invasive implants, LGSC and the rare coexistence of HGSC of ovarian or extraovarian origin. This last entity presents a distinct tumor biology and carcinogenesis profile, with strong implications in therapeutic approach and prognosis. Whenever unresectable disease is strongly suspected, adnexectomy or ovarian biopsy in association with peritoneal implants biopsy would allow an accurate diagnosis of a synchronous neoplasia. A peritoneal disease with high tumor burden due to HGSC could impact the optimal therapeutic approach, namely the possibility of neoadjuvant chemotherapy and interval surgery.

The discrepancy between tumor markers, imaging criteria and malignancy scores should raise the clinical suspicion for the coexistence of a synchronous neoplasia with a more aggressive oncologic behavior.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Consent

Written informed consent for publication of clinical details and images was obtained from a relative of the patient.

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Maria Dolores Diestro

Gynecologic Oncology Unit, IdiPAZ (Hospital La Paz Institute for Health Research), La Paz University Hospital, Madrid, Spain

From the point of view and optics of Oncological Gynaecology, it would highlight the originality of the clinical case presented.

The presentation of clinical and surgical data is adequate and meticulous and translates a good level of background knowledge of the author.

Good writing, clarity in the presentation and good structuring of the discursive dialogue of the discussion.

Perhaps there would be a short synthesis at the end of the article with the background of the case and a small conclusion.

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 05 Nov 2019

Mariana Rei, Centro Hospitalar Universitário São João, Porto, Portugal

Thank you for your kind reply and consideration of the manuscript "Borderline tumor and primary peritoneal carcinoma: a rare synchronism" for revision. The reviewers' comments were highly appreciated and were thoroughly taken into consideration.

1. Additional clinical details were provided in order to demonstrate the pathological diagnosis in which the case relies on, namely regarding the morphological and immunohistochemical features and a new set of histologic images.

2. In the last paragraph of the Discussion section we display a final summary of the main findings and their implications for the clinical practice, while trying to be clear and concise. Thank you in advance for your encouraging and inspiring review. We hope that the manuscript is now appropriate for being considered for publication. Please do not hesitate to contact me if any further information is needed.

Kind regards,
Mariana Rei, MD

Competing Interests: No competing interests were disclosed.

Reviewer Report 14 October 2019

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Carla Bartosch

Department of Pathology, Portuguese Oncology Institute of Porto, Porto, Portugal

This is an interesting case report, presenting the rare finding of a serous borderline ovarian tumor with a synchronous high grade serous carcinoma in the peritoneum. The introduction and discussion are well written. The case report itself, essentially relies on the pathological diagnosis, which in my opinion is insufficiently demonstrated.

My comments and remarks are the following:

Abstract:

- “either as non-invasive or invasive implants, also known as extraovarian low-grade serous carcinoma.” – change to “the latter also known...”

Introduction:

- “In order to meet criteria for PPC, both ovaries and tubes should be macro- and microscopically normal in size or enlarged by a benign process” – This is not entirely correct. If the tube has, for example, STIC, the tumor should be considered of tubal origin, yet it may have a perfectly normal size.
- “largely overlap their ovarian counterparts” – change to “tubal and ovarian counterparts”

Case report:

- The ovarian tumor is large (19cm), was an adequate sampling done to exclude an invasive component?
- In the presence of a HGSC in the peritoneum, total inclusion of the adnexa, particularly the tube following the SEE-FIM protocol, should be done to exclude a tubal primary – was this done? Were there any precursor lesions in the Fallopian tube epithelia? The case reports a “frozen pelvis” – weren’t the tubes involved by the tumor?
- HGSC can architecturally simulate LGSC in the peritoneum. The two basic criteria to distinguished HGSC and LGSC are the nuclear atypia and mitotic index (as emphasized in manuscript reference 11), but none of which are mentioned in the case description.
- HGSC may also simulate a BST architecture in the ovary, but the cytological features and immunohistochemical profile are very different. Please provide the morphological description (including architectural patterns, cytological features, mitotic index) as well as the immunohistochemical profile of both neoplasias to support the diagnosis.
- p53 should be report as wild type or aberrant (null or diffusely positive). Variable p53 positivity occurs in wild type patterns. Aberrant p16 overexpression and a very high proliferation index (Ki-67) would also support the differential diagnosis between HGSC and LGSC.
- Were there any lesions in the hysterectomy specimen, namely in the endometrium?
- Histological pictures are all low-power. A and C show similar aspects. Legend mentions the left ovary, which is not shown – consider deleting this from the legend as it is already in the case report text. I suggest making a panel with low and high power magnifications showing the architectural and cytological features, plus p53 expression, of both neoplasias.
- Was any genetic study performed, namely for BRCA1/2 or BRAF mutations?

Discussion:

- First paragraph – Kurman’s dualistic model and Malpica’s two tier system are different concepts. Thus, the last phrase can not start with “this”.
- Estrogen and progesterone expression is mentioned in the discussion, but is not in the case report description. Provide the extension of ER and PR expression in both tumors. PR

expression was negative in the BST?

Is the background of the case's history and progression described in sufficient detail?

No

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

No

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Gynecologic pathology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 05 Nov 2019

Mariana Rei, Centro Hospitalar Universitário São João, Porto, Portugal

Reply to Reviewers

Thank you for your kind reply and consideration of the manuscript "Borderline tumor and primary peritoneal carcinoma: a rare synchronism" for revision. Your comments were highly appreciated and were thoroughly taken into consideration, as following:

1. Additional clinical details were provided in order to demonstrate the pathological diagnosis in which the case relies on.
2. Regarding the diagnosis of the SBT in the right ovary, multiple tissue blocks from the ovarian tumor were examined in the microscopy exam and none identified invasive component. Both adnexa were totally included and analyzed according to the Sectioning and Extensively Examining the Fimbriated End Protocol (SEE-FIM) and no precursor lesions in the fallopian tube epithelia were found.
3. More detailed information regarding the morphological and immunohistochemical features of both tumor specimens was provided, allowing to distinguish between SBT and HGSC and to rule out LGSC. Regarding IHC, p16 was not performed in either specimen, therefore we could not provide that data.
4. The molecular genetic analysis was not performed, therefore we could not provide that set of data.
5. The concepts of ovarian tumor carcinogenesis models described in the first paragraph of

the discussion, namely Kurman's dualistic model and Malpica's to tier system, were further clarified.

6. Finally, the legend of the histological pictures was modified accordingly and an additional set of images with higher power magnifications plus p53 expression of both tumors was provided.

NOTE: The major revision work-up is noticed in the third, fourth and fifth paragraphs of the Case Report section and in the first paragraph of the Discussion section.

Thank you in advance for your encouraging and inspiring review. We hope that the manuscript is now appropriate for being considered for publication.

Kind regards,
Mariana Rei, MD

Competing Interests: No competing interests were disclosed.

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