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Case Report

An unusual mechanism of metastasis in serous carcinoma of the endometrium associated with BRCA1 mutation gene: A case report with clinical and immunohistochemical features

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Summary

The current case report documented a uterine high-grade serous carcinoma in a 48-year-old woman with previous clinical history of breast cancer, BRCA1 gene mutation, and melanoma of the back. Uterine Serous Carcinoma (USC) was minimally invasive with fallopian tubes, ovaries, omentum, peritoneal surface and lymph node biopsy demonstrating no evidence of neoplasm at the time of total abdominal hysterectomy with bilateral salpingo-oophorectomy. In the peritoneal washing cytology and in the lumen of both fallopian tubes there were neoplastic cells which, on immunohistochemical analysis, showed immunoreactivity for p53 and p16 and negativity for WT1, supporting the endometrial origin of these malignant serous neoplastic cells. One year after surgery, the patient presented with recurrent peritoneal neoplastic nodules and metastases into intestinal lymph-nodes. To detect neoplastic USC cells in the fallopian tube lumen and to prove a retrograde trans-tubal spread into the peritoneal cavity, it is mandatory to examine the fallopian tubes in their entirety according to the SEE-FIM (Sectioning and Extensively Examining the Fimbria) protocol. In addition, this case report highlights the importance of the peritoneal cytology and omentectomy during a total abdominal hysterectomy with bilateral salpingo-oophorectomy to establish adequate staging and future patient management, even in cases of minimally invasive serous endometrial carcinoma.

Key words: Uterine serous carcinoma; Peritoneal washing cytology; Sectioning and extensively examining the fallopian tube protocol; Retrograde trans-tubal spread.

Introduction

Uterine Serous Carcinoma (USC) is an uncommon, aggressive type of endometrial carcinoma with a high recurrence rate and a poor survival outcome. Despite its rarity, USC is responsible for a disproportionate number of endometrial cancer deaths [1-2] more often deeply invades the myometrium and has a propensity for peritoneal spread and invasion of the lymphatic and vascular spaces [3].

Frequently, advanced-stage disease or recurrence is common even when USC is apparently only minimally invasive or confined to the endometrium [4-6].

A study by De Jonge *et al*. suggests that USC may be an overlooked component of BRCA1/2-associated hereditary breast and ovarian cancer syndrome. Accordingly, these authors proposed that screening for germline BRCA1/2-pathogenic mutations should be considered in patients diagnosed with USC, especially when there is a first-degree family history of breast and/or ovarian cancer [7].

We report a case of USC in a patient with mutations of the BRCA1 gene and a previous history of breast cancer, featuring an unusual peritoneal metastasis mechanism.

Case Presentation

A 48-year-old woman presented at our institution for abnormal vaginal bleeding. Her past medical history included a quadrantectomy of the left breast for infiltrating ductal carcinoma six years earlier, mutations of the BRCA1 gene, and treatment with chemotherapy and radiotherapy for 18 months. Her family history did not reveal BRCA related malignancies.

Three years prior to this diagnosis, the patient had a nodular malignant melanoma of the back with metastases to the axillary lymph nodes and subcutaneous tissue that was treated with immunotherapy. Her endometrial biopsy revealed USC. As a result, she underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy, peritoneal washing, omentectomy and sentinel lymph node biopsy for the assessment of surgical staging. Although lymphadenectomy is recommended for patients with serous carcinomas according to the criteria suggested by European Society for Medical Oncology (ESMO) and European Society of Gynecological Oncology (ESGO) [8], the patient underwent only sentinel lymph node biopsy because recent studies prove that sentinel node biopsy is a useful option [9, 10].

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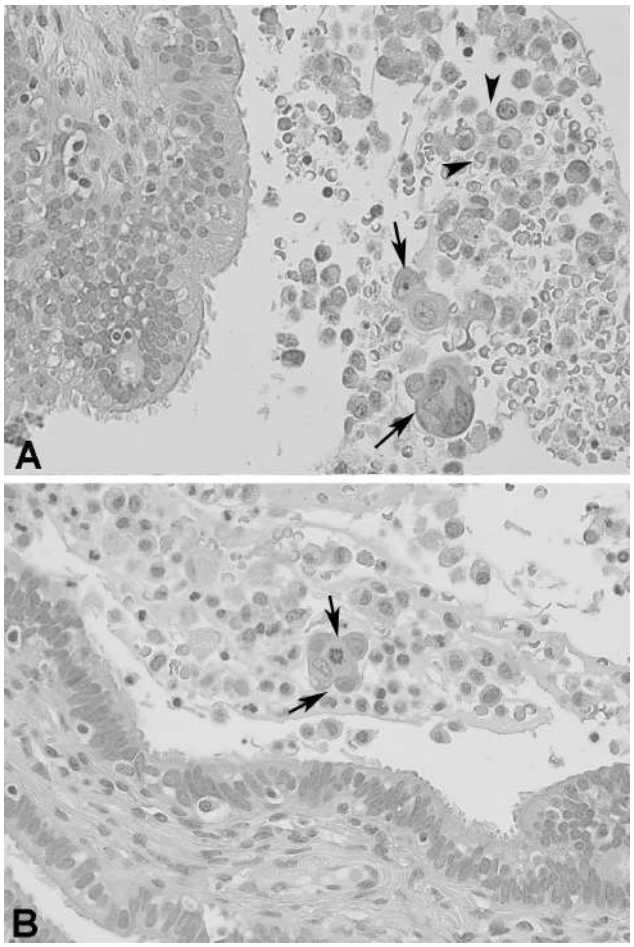

Figure 1. — Hysterectomy specimen with bilateral salpingo-oophorectomy showing small papillary groups of neoplastic cells with severe nuclear atypia admixed with red cells and macrophages (A: Hematoxylin and Eosin ×400, arrows neoplastic cells, heads of arrows macrophages) in the lumen of the fallopian tubes. Also note mitosis (B: Hematoxylin and Eosin ×400, arrows mitosis).

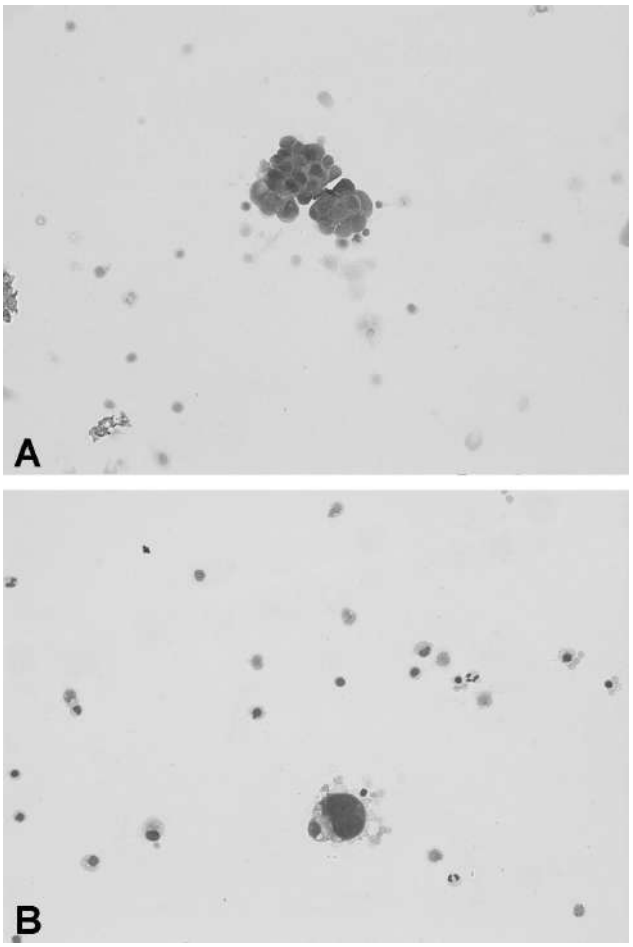

Figure 2. — The same neoplastic elements present in the lumen of the fallopian tubes were also observed in samples of peritoneal washings as small papillary groups (A: Papanicolaou stain ×200) and single cells (Giemsa ×200). Note severe nuclear atypia.

A thorough examination of the omentum and the entire peritoneal surface during the abdominal hysterectomy revealed no gross metastatic implants. The fallopian tubes were examined in their entirety according to SEE-FIM (Sectioning and Extensively Examining the Fimbria) protocol [11] to exclude concomitant intra-epithelial and invasive serous tubal carcinomas. In addition, sentinel lymph nodes were embedded in paraffin and cut at 150 μ intervals; then half of the sections were assessed by immunohistochemical reaction for cytokeratin to detect metastasis [12].

The pathological findings revealed stage IA USC, which involved less than one half of the myometrium (depth of invasion: 1 mm, myometrial thickness: 20 mm, myometrial invasion: 5%), without lympho-vascular space invasion and with no lymph node metastasis. The mucosa of the fallopian tubes, which were examined in their entirety, were unremarkable. In addition, the ovaries, which were also examined in their entirety, showed no evidence for malignancy.

In contrast, in the lumen of both fallopian tubes, mixed with red cells and macrophages, there were small papillary groups of neoplastic cells with severe nuclear atypia (Figure 1A) and mitoses (Figure 1B). The same neoplastic elements were also observed in samples of peritoneal washings as small papillary groups (Figure 2A) and single cells (Figure 2B). On immunohistochemical analysis, these cells characteristically revealed p16 strong and diffuse positivity (Figure 3A), strong and diffuse nuclear positivity for p53 (Figure 3B), and negativity to WT1. Thus, the final pathological diagnosis was serous carcinoma of the endometrium, Stage pT1a N0 (s), with retrograde transtubal spread. In fact, endometrial malignancy was characterized by the same neoplastic cells present in the fallopian tubes and peritoneal washing that showed severe nuclear atypia, (Figure 4A), diffuse and strong immunoreactivity for p16 protein, (Figure 4B) and diffuse and strong nuclear positivity to p53 (Figure 4C). Although retrograde trans-tubal spread of serous carcinoma was observed and serous carcinoma is classified as high risk of recurrence regardless

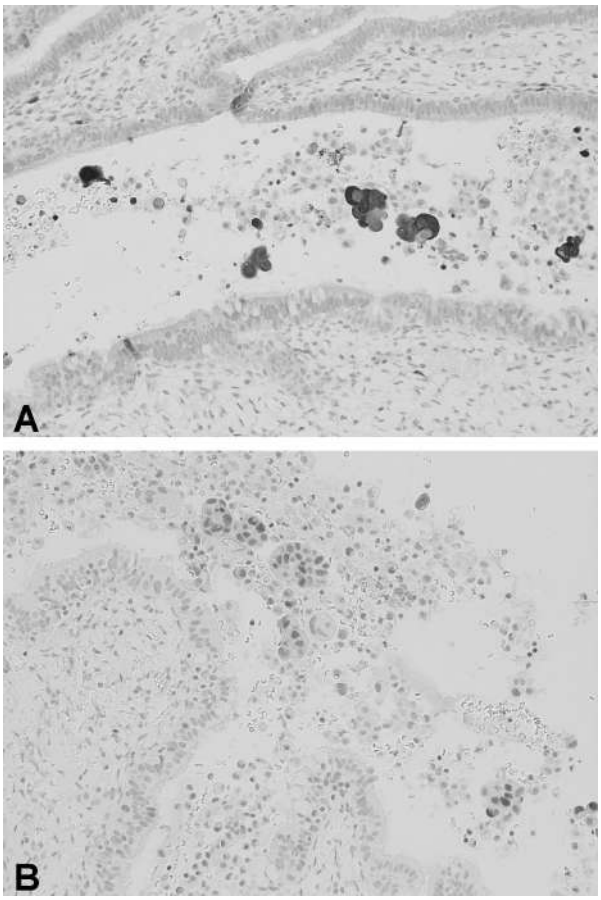

Figure 3. — On Immunohistochemical analysis intra-luminal tubal neoplastic cells showed diffuse and strong immunoreactivity for p16 protein, that involved both its cytoplasms and nuclei (A: ×200) the same neoplastic cells also showed diffuse and strong nuclear positivity to p53 (B: ×200).

of stage by ESMO guidelines, the patient was not treated with chemotherapy in order to avoid bone marrow damage and the resulting negative impact on quality of life, having previously been treated with immunotherapy for advanced melanoma. The patient underwent Computed Tomography (CT), 18F-fluciclovine Positron Emission Tomography/Computed Tomography (PET/CT) and evaluation of serum Cancer Antigen 125 (CA-125), to detect recurrences and metastases of all malignancies affecting this patient. The scans were negative, and the serum CA-125 levels remained undetectable until one year after surgery, when the patient was admitted to our Institution for pelvic pain.

Abdomino-pelvic Computed Tomography (APCT) showed the presence of free fluid in the pelvic cavity associated with thickening of the peritoneum. In addition, small nodules were observed in the peritoneal adipose tissue in the left hypochondrium and along the homolateral side as well as extending into the adipose tissue of the transverse colon. Another peritoneal nodule, measuring 9 × 11 mm, was detected in the right anterior abdominal wall. Serum

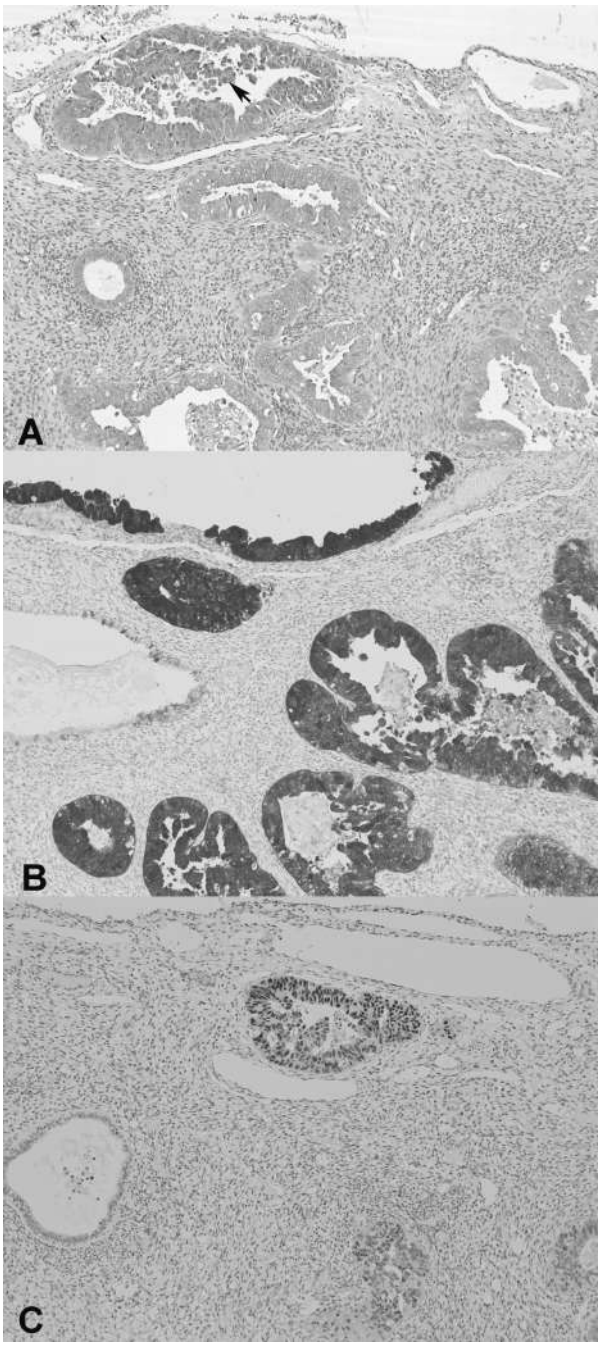

Figure 4. — Hysterectomy specimen with bilateral salpingo-oophorectomy showing uterine serous carcinoma infiltrating superficially the myometrium (Hematoxylin and Eosin ×100). Note the presence of the same neoplastic cells with severe nuclear atypia, present in the fallopian tubes and peritoneal washing neoplastic cells (A: Hematoxylin and Eosin ×100 arrow) with diffuse and strong immunoreactivity for p16 protein, that involved both its cytoplasms and nuclei (B: ×100) diffuse and strong nuclear positivity to p53 (C: ×100).

cancer antigen 125 (ca-125) was increased, measuring up to 440 U/mL, which was spicious of recurrent peritoneal and abdominal metastases of serous carcinoma.

PET-CT revealed abnormal hypermetabolic lesions in the pelvic region and abdominal wall. The patient underwent surgical excision of all the peritoneal lesions and the transverse colon. The frozen and permanent pathological findings confirmed metastatic USC, including in the lymph nodes dissected from the adipose tissue of the intestinal tract. After the second debulking surgery, the patient received three cycles of chemotherapy with Carboplatin-Taxol. Eight months from diagnosis of recurrence the patient remains disease free and with a negative CA125.

Discussion

Advanced-stage disease or recurrence is common even when USC is apparently only minimally invasive or confined to the endometrium alone (Stage I A) [4-6].

Many mechanisms have been proposed to explain why USC often coexists with intra-peritoneal dissemination even in cases with a pT1a stage of development.

These mechanisms include capillary lymphatic embolization and extra-uterine multifocal neoplastic transformation [13-16].

Moreover, some researchers have proposed that patients with BRCA1 mutations have a higher risk of developing multifocal papillary serous carcinoma of the peritoneum in addition to breast and ovarian carcinoma [17].

In contrast, Jarboe *et al*. reported genetically related USC with simultaneous adnexal involvement and serous tubal intra-epithelial carcinoma (STIC), raising the question as to whether the fallopian tube might be the site of origin of some USC [18].

In addition, the authors proposed an extensive examination of the salpinx also in intraepithelial serous carcinoma of the endometrium in order to exclude the possibility of peritoneal spread [18].

The present case, which reported a minimally invasive USC in a 48-year-old woman, is unique as it might prove that in a BRCA1 mutated patient with a history of breast carcinoma and subsequent peritoneal metastases, the latter were not related to concomitant ovarian or tubal lesions.

Although the high-grade serous carcinoma in a 48-year-old is rather uncommon, because high-grade serous carcinoma usually occurs in elderly patients, this finding is in accordance with cases of serous carcinoma in patients with BRCA1 mutations [19].

The presence of neoplastic cells in the tubal lumen and peritoneal washing cytology at the time of hysterectomy and the development of multiple peritoneal metastases one year after the diagnosis of primary USC, is compatible with retrograde trans-tubal spread. Nuclear atypia, mitoses and strong and diffuse immunoreactivity for p16 and p53 demonstrate that these elements, which at lower magnification could be mistaken for macrophages, are malignant serous cells.

Moreover, the endometrial origin of these neoplastic cells in the tubal lumen and subsequent peritoneal metastases was supported by immunohistochemical analysis, which revealed negativity to WT1 [20-21].

Although the literature suggests there is little direct evidence of exfoliated neoplastic USC cells accessing the abdominal peritoneum via the fallopian tubes, we believe this to be the most plausible route for the spread in the present case [22-25].

The presence of intraluminal tumor cells in lumen of fallopian tubes, which represents histological marker of transtubal spread, is more common among women with serous subtype of endometrial carcinoma compared to endometrioid carcinoma (Type I) [24-25].

Snyder *et al*. in their study of eighty-seven patients with USC observed the presence neoplastic clusters within the tubal lumen in 16 cases [23].

Stewart *et al*., in examining a large series of patients with uterine carcinoma, observed that the presence of neoplastic cells in the tubal lumen can be correlated with the grade of uterine malignancy (Type II histology, including high-grade serous carcinoma and clear cell carcinoma), the presence of neoplastic cells in fluid cytology and evidence for extra-uterine metastases [24]. In addition, Felix *et al*., in their study of 295 cases of endometrial carcinoma, found neoplastic cells in the tubal lumen in 35 cases and their presence was associated with adverse prognostic features of uterine neoplasms, such as uterine advanced stage, the presence of vascular lymphatic invasion and Type II histology, including high-grade serous carcinoma and clear cell carcinoma [25].

In addition, they found neoplastic cells in the tubal lumen in examples of USC which also was associated with a reduction in survival, even in cases with diagnosis at an early-stage of development [25].

Conclusions

In conjunction with several studies reported in the literature regarding the presence of intraluminal neoplastic cells in the fallopian tube [23-25], the present case suggests that this finding is not an artifact due to manipulation during pathological processing of specimens, but in all probability represents a propensity of trans-tubal dissemination among aggressive sub-types of uterine carcinoma. The retrograde tubal serous spread to the peritoneum is rare; this occurrence can be observed and, as has been demonstrated in the present case, it may also be present in the case of patients with BRCA mutation gene even in the absence of a neoplasm in the fallopian tubes.

Furthermore, to discover intraluminal endometrial serous neoplastic cells, extensive examinations of the fallopian tubes and immunohistochemical analysis with specific markers are mandatory. In addition, peritoneal washing cytology and omentectomy to detect micrometastasis should always be performed and considered as a part of accurate staging and patient management, even in cases of minimally invasive uterine serous carcinoma.

Authors' contributions

Giovanna Giordano conceived of the original idea for the study, interpreted the results, edited the paper. Alessandro Tafuni and Eugenia Marta Martella contributed to the study design and interpretation of the results. Roberto Berretta obtained consent of patient to publish the paper, performed the surgery and provided clinical data.

Ethics approval and Consent to publication

The patient in this report had given consent for publication.

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Conflict of Interest

All authors have stated that they have no competing interests.

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