

Case Report

Primary Peritoneal Carcinosarcoma in a Breast Cancer Patient Harboring a Germline *BRCA2* Pathogenic Variant: Case Report

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Keywords

Primary peritoneal carcinosarcoma · Germline *BRCA2* pathogenic variant · Case report

Abstract

Malignant mixed müllerian tumor (MMMT) is a rare neoplasm, consisting of carcinomatous (epithelial) and sarcomatous (mesenchymal) components that most commonly arise in the endometrium and more infrequently in the ovaries, fallopian tube, cervix, and vagina. Primary peritoneal carcinosarcoma (PPCS) is an extremely rare extragenital presentation of MMMT. Although the occurrence of breast cancer and epithelial ovarian carcinoma in association with *BRCA* pathogenic variants is firmly established, the etiologic role of these genes in the development of other tumor types is less well known. Here, we present a rare case of PPCS in a 42-year-old Brazilian woman with a *BRCA2* pathogenic variant, c.2808_2811del (NM_000059.3). The patient developed metastatic breast cancer at the age of 37 and underwent a risk-reducing bilateral salpingo-oophorectomy 2 years later. She was then diagnosed with PPCS 3 years after the risk-reducing surgery. She underwent treatment with surgery, chemotherapy, and targeted therapy but passed away almost 5 years after the second primary tumor diagnosis. To our knowledge, this is the first case of peritoneal carcinosarcoma described in a *BRCA2* pathogenic variant carrier, and its report leads to a better understanding of the disease's molecular features and possible therapeutic approaches.

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Introduction

Carcinosarcoma (CS) is a highly aggressive, rare tumor with both carcinomatous (epithelial) and sarcomatous (mesenchymal) components. This tumor often develops in the uterine cavity. Primary peritoneal carcinosarcoma (PPCS) is an extremely rare extragenital presentation of CS of mullerian origin, previously called malignant mixed mullerian tumor (MMMT) [1, 2]. Recent findings suggest that the two histological components, carcinoma and sarcoma, express many similar immunohistochemical markers. CS frequently exhibits copy-number alterations and recurrent somatic mutations resembling features of endometrioid and serous uterine carcinomas [3]. The evolving knowledge of the molecular landscape of these tumors supports the development necessity of new treatment paradigms.

Most hereditary breast and ovarian cancers are associated with germline pathogenic variants in *BRCA1* and *BRCA2* genes [4]. Although the occurrence of breast carcinoma and epithelial ovarian carcinoma in association with *BRCA* pathogenic variants is firmly established, the etiologic role of these genes in the development of other tumor types is less well known [5, 6]. Here, we present a case of a female *BRCA2* pathogenic variant carrier diagnosed with two primary cancers: metastatic breast cancer at age 37 and PPCS at age 42, 3 years after risk-reducing bilateral salpingo-oophorectomy (BSO).

Case Report

A 37-year-old Brazilian woman was diagnosed with stage IV invasive breast carcinoma of no special type, histological grade 2 (Nottingham), estrogen receptor and progesterone receptor positive, HER2 negative (immunohistochemical score 0), with a Ki67 labeling index of 20%. Metastatic bone lesions were found in the clivus and left iliac crest. Germline *BRCA1* and *BRCA2* Sanger sequencing revealed a *BRCA2* pathogenic variant, c.2808_2811del (NM_000059.3).

She underwent upfront right mastectomy and axillary lymph node dissection in 2012. The tumor measured 2.0 cm, and none of the 14 nodes dissected were positive. After surgery, she received six cycles of docetaxel, doxorubicin, and cyclophosphamide and 4 years of adjuvant tamoxifen. Due to oligometastatic disease classification, the multidisciplinary board decided to perform stereotactic radiosurgery for the bone metastases.

In 2014, 2 years after breast cancer diagnosis, the patient underwent prophylactic BSO (uterus was not removed). The pathological examination indicated no malignancy. The specimens were not subjected to SEE-FIM protocol.

In March 2017, almost 5 years after the initial diagnosis, a routine abdominal scan revealed a mass near the rectum and colon with an increased uptake in the 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) (Fig. 1a). The patient underwent exploratory laparotomy and segmental rectosigmoid resection. The pathological findings revealed carcinoma with extrinsic involvement of the intestinal wall, from the adipose tissue to the submucosa, represented by three nodules, measuring 2.5 cm, 0.6 cm, and 5.8 cm, respectively. Two of nine pericolic lymph nodes were positive. This tumor was poorly differentiated and composed of epithelioid cells with a high nuclear-cytoplasmic ratio, vesicular nuclei, and conspicuous nucleoli (Fig. 2a). Immunohistochemical profile is shown in Table 1. The tumor was CDX2 negative, cytokeratin 7 positive, and cytokeratin 20 negative, excluding the potential of a primary intestinal tumor, and positive for GATA-3 (Fig. 2b); however, there was no estrogen or progesterone receptor expression, whereas they were highly expressed in the primary breast tumor. Based on this expression profile, we could not exclude the possibility of breast metastasis with loss of

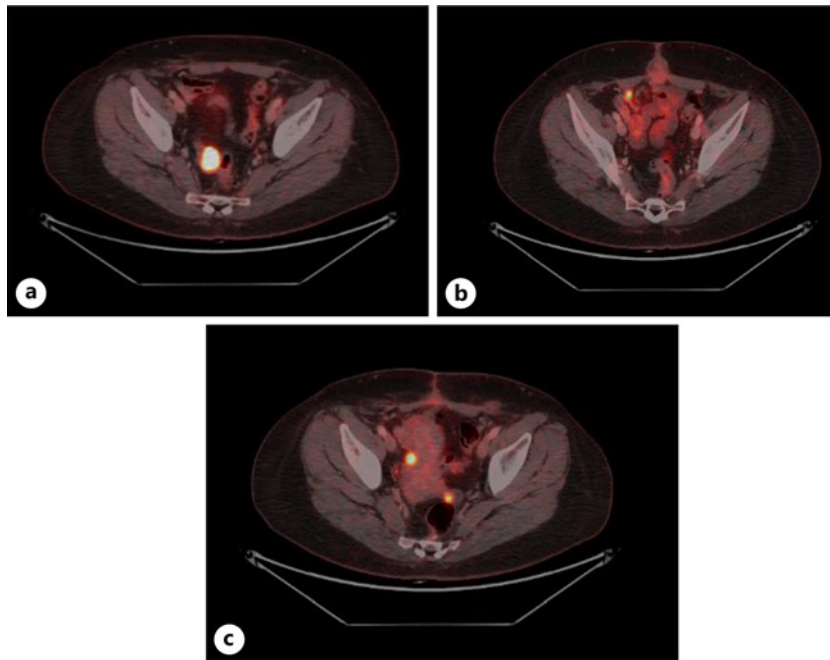


Fig. 1. Image exams. **a** March 2017 – PET scan: hypermetabolic lesion in the peritoneum near the sigmoid rectum. **b** August 2019 – PET scan: increased peritoneum disease. **c** December 2019 – PET scan: increased peritoneum disease.

differentiation in the progression of the disease; therefore, we assumed that the disease could be a breast cancer recurrence. She then started carboplatin and paclitaxel for six cycles. Re-evaluation after the sixth cycle did not show any lesions.

In March 2019, patient was asymptomatic with normal serum CA 15-3, CEA, and CA125, but a peritoneal disease recurrence was detected on FDG PET/CT. From April to August 2019, she was treated with olaparib, given the possibility of breast metastasis in a patient with a *BRCA2* pathogenic variant. But in August 2019, FDG PET/CT showed enlarged peritoneal lesions compatible with disease progression (Fig. 1b). On account of the lack of tumor response to olaparib, in September 2019, two pelvic implants (pelvic wall/retrouterine and right pelvic wall) and an omentum segment (without neoplasia) were removed by laparoscopy. The pathological examination indicated adenocarcinoma, and the morphology of the lesions was similar to the previous peri-intestinal lesion. The retrouterine neoplasm also had a sharply juxtaposed mesenchymal component (Fig. 2c). The immunohistochemical profile was similar to the previous pelvic lesions, but the tumor showed PAX-8 expression (Fig. 2d). Staining for cytokeratins of 40, 48, 50, and 50.6 kDa (AE1/AE3) showed diffuse positivity in the adenocarcinoma component but no expression in the sarcoma component (Fig. 2e). Vimentin was positive in isolated cells of the adenocarcinoma component and diffusely positive in the sarcoma component (Fig. 2f). The final diagnosis was CS, possibly resulting from evolution of primary peritoneal adenocarcinoma. Although mullerian origin could not be excluded, the co-expression of GATA-3 and PAX-8 raised the possibility of mesonephric differentiation (Table 1).

In December 2019, FDG PET/CT showed recurrence of peritoneal disease (Fig. 1c). The patient was treated with six cycles of carboplatin, gemcitabine, and bevacizumab. Subsequent scans revealed partial response and maintenance therapy with bevacizumab was administered until September 2020, when FDG PET/CT showed increased uptake in the pelvic lymph nodes and in the right iliac fossa nodule. The patient then received

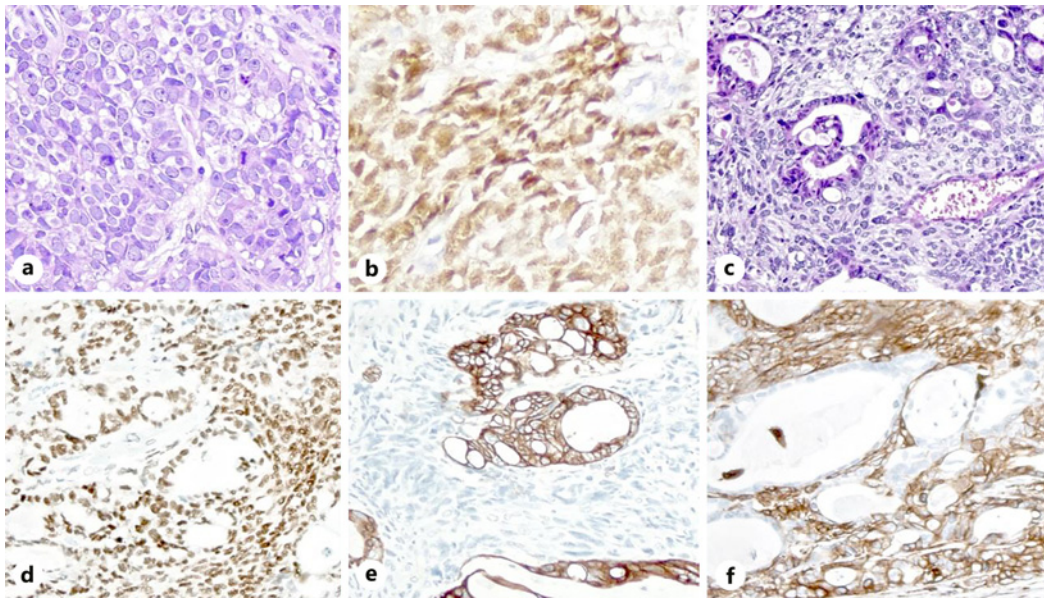


Fig. 2. Poor differentiated neoplasia in rectosigmoid wall composed by epithelioid cells with vesicular nuclei, numerous mitosis (a), and strong expression of GATA-3 (b); recurrence of neoplasia in peritoneum of retrouterine region with biphasic pattern: glandular spaces sharply juxtaposed with solid spindle and epithelioid cells (c), both positive to PAX-8 (d); glandular component of neoplasia with strong expression of cytokeratins, while sarcomatous component was negative (e) and inverse pattern with vimentin, diffusely positive in the sarcomatous component (f).

carboplatin, liposomal doxorubicin, and bevacizumab for three cycles, but FDG PET/CT in January 2021 showed volumetric and FDG uptake in the pelvic lymph nodes and peritoneal nodules.

A new peritoneal biopsy sample was then obtained and confirmed the diagnosis of CS (Fig. 2). A next-generation sequencing was performed using a commercial platform (TruSight Oncology 500 [TSO500]; Illumina, San Diego, CA), which revealed pathogenic alterations in seven genes (Table 2), including the known germline *BRCA2* variant (the panel did not discriminate between somatic and germline alterations). The tumor mutational burden was low (7 mutations/Mb), and microsatellite instability was not detected. RNA analysis indicated no alterations. Loss of heterozygosity (LOH) was not assessed. Mutational signature analysis using the Web-based application Musica (6) aimed to visualize the somatic mutational profile but did not reveal a type 3 signature, which is indicative of *BRCA*-deficient tumors but cannot confirm LOH status.

As the tumor was positive for PD-L1 (SP-142) (IC >1%) and due to the scarcity of available treatments, after a multidisciplinary discussion, the patient started treatment with lenvatinib plus pembrolizumab in February 2021. After 6 months, she had a new progression in the lung, vagina, and para-aortic nodes. She was then treated with weekly paclitaxel for 4 months followed by topotecan after progression. In January 2022, she started treatment with etoposide alongside ifosfamide but progressed in lung, liver, and lymph nodes in May 2022. Her treatment changed to gemcitabine and vinorelbine; however after two cycles, the patient was hospitalized due to malignant bowel obstruction and passed away at the beginning of June 2022, almost 5 years after the second primary tumor diagnosis. The case's events timeline is summarized in Figure 3. The therapies dosage and protocols are succinctly outlined in the online supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000534179>).

Table 1. Immunohistochemical profile of the peritoneal recurrences

Marker	Expression in tumor
March 2017 – rectosigmoid tumor	
CDX2	Negative
Cytokeratin 7	Positive
Cytokeratin 20	Negative
GATA-3	Positive
Estrogen receptor	Negative
Progesterone receptor	Negative
TTF-1	Negative
WT-1	Negative
p53	Strongly positive
PD-L1 (SP-142)	Positive (>1% IC)
September 2019 – pelvic lesions	
Cytokeratin 7	Positive (isolated cells)
Cytokeratin 20	Positive (isolated cells)
GATA-3	Positive (multiple foci)
PAX-8	Positive
Calretinin	Positive in some cells
Cytokeratins 40, 48, 50, 50.6 kDa (AE1/AE3)	Diffuse positivity (adenocarcinoma component) No expression (sarcoma component)
Vimentin	Isolated cells positive (adenocarcinoma component) Diffusely positive (sarcoma component)
Mismatch repair proteins (MLH1, MSH2, MSH6, PMS2)	Expressed (proficiency)

Discussion

The pathogenesis of gynecological CS tumors is unclear, but it has been theorized that they arise from metaplastic differentiation of a carcinoma [7]. We believe this theory could describe this case since it presented first as a poorly differentiated adenocarcinoma and in the recurrence, there were areas of sarcomatous differentiation, which was confirmed by morphology and immunohistochemical profiling.

The annual incidence of uterine CS in Europe is 0.4 per 100,000 and that of ovarian CS is 0.14 per 100,000 [8]. CSs are not usually included in inherited cancer syndromes. However, there are some case reports describing CSs in the context of a cancer predisposition syndrome [9–12].

The risk of ovarian, fallopian tube, or peritoneal cancer in BRCA1 pathogenic variant carriers is 39% and that in BRCA2 pathogenic variant carriers is 10–17% [13, 14]. Patients with a genetic predisposition to breast and ovarian cancer are more likely to develop serous ovarian cancer [15, 16]. The lifetime risk of primary peritoneal cancer among such patients has been estimated to be 1.3–1.5% [17, 18]. The occurrence of gynecological CSs has been described in hereditary breast and ovarian cancer-susceptible families with BRCA1/2 germline pathogenic variants [19].

Table 2. NGS (TSO 500 illumina) tumor genomic profiling of peritoneal biopsy dated from December 2000

Gene	Alteration in DNA level	Alteration in protein level	MAF
<i>ARID1A</i>	c.5161C>T	p.(Arg1721Ter)	40.7%
<i>BRCA2</i>	c.2808_2811del	p.(Ala938ProfsTer21)	58.3%
<i>ID3</i>	c.82dup	p.(Arg28ProfsTer8)	3.4%
<i>KRAS</i>	c.35G>T	p.(Gly12Val)	44.0%
<i>PRKN</i>	c.155del	p.(Asn52MetfsTer29)	50.7%
<i>RECQL4</i>	c.1543_1544insACTTGCCACCAGCTCC	p.(Pro515HisfsTer30)	21.6%
<i>TP53</i>	c.524G>A	p.(Arg175His)	44.9%

DNA, deoxyribonucleic acid; MAF, mutation allele frequency.

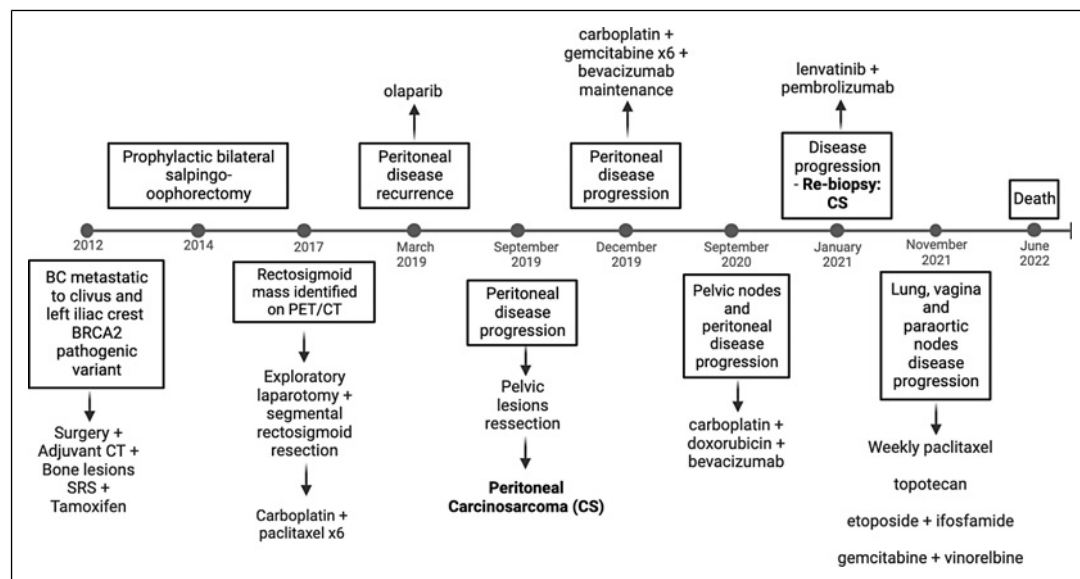


Fig. 3. Case report timeline.

CSs are assumed to be mullerian tumors, although mesonephric and mesonephric-like lesions have been described [2, 3]. Our case showed characteristics of mullerian (PAX-8) and mesonephric (GATA-3) origins. Uterine tumors with both characteristics may represent mesonephric-like mullerian tumors, although true mesonephric carcinomas cannot be excluded [4].

In this case, the first manifestation of the disease was the rectosigmoid tumor. As considered initially, although a rare phenomenon, gastrointestinal metastasis originating from breast cancer can develop. These metastatic occurrences are typically observed within the stomach and are predominantly associated with lobular carcinoma. Nevertheless, occurrences in other sections of the intestine, such as the duodenal bulb, have also been documented. The diagnosis and subsequent management of these cases present considerable challenges [20, 21].

Given that the peritoneum was the primary site from the rectosigmoid tumor, and there were no mesonephric remnants, we believe that this tumor could be originated as endometriosis of the rectosigmoid wall. Tumors that originate as endometriosis can present as a mesonephric-like pattern [4] and frequently harbor ARID1A mutations, which were identified by genomic sequencing in our case. Patient had a previous history of endometriosis.

The ovarian and peritoneal epithelia share a common embryonal (mesonephric) origin and are histologically similar to the müllerian epithelium. That said, primary ovarian, epithelial, tubal, and peritoneal cancers are all müllerian in origin [7]. Conversely, there are three main theories related to CS histogenesis [2]. The collision theory assumes synchronous but independent etiologies for the carcinoma and sarcoma components, whereas the combination and conversion theories suggest a common precursor with divergent and metaplastic differentiation, respectively.

Another possibility for CS development could be radiation-associated sarcoma. Our patient underwent stereotactic radiosurgery in the pelvis for left iliac crest bone metastasis 2 years before the peritoneal cancer diagnosis. The estimated incidence of radiation-associated sarcoma is 0.03–0.2% in the 5 years post-treatment [22]. Further, Kadouri et al. [23] reported a twofold increase in the radiation-associated sarcoma risk among BRCA1 or BRCA2 pathogenic variant carriers.

The patient underwent prophylactic BSO 36 months before the peritoneal CS diagnosis. Due to the heightened susceptibility to ovarian cancer, the incorporation of BSO constitutes a pivotal component within the multimodal strategy for patients carrying *BRCA* pathogenic variants. This intervention has been demonstrated to improve disease-free survival and overall survival outcomes [24].

Primary peritoneal cancer is an aggressive malignancy that cannot be diagnosed early with screening tests [25, 26]. Among *BRCA* pathogenic variant carriers, primary peritoneal cancer can be found many years after prophylactic BSO, and it usually presents at advanced stages [26–29].

As the patient was a *BRCA2* pathogenic variant carrier, we considered the treatment with olaparib reasonable. Olaparib therapy for PPCS has not yet been reported. Nagamata et al. [30] reported a significant response to olaparib in a patient with a PPCS, although neither germline nor somatic genetic testing was performed to assess *BRCA* status. In the present case, the patient had a *BRCA* germline pathogenic variant, but the mutational signature was discordant. Although it was not possible to assess tumor LOH in the *BRCA2* locus, it raises the possibility that this tumor carcinogenesis was not related to the *BRCA2* pathogenic variant.

In conclusion, we describe a rare case of primary CS in the peritoneum in a *BRCA2* pathogenic variant carrier after risk-reducing BSO. Treatment remains a challenge for this type of neoplasm. Better understanding of the molecular alterations of these tumors would allow us to assess the causes and perhaps prevent cases of aggressive presentation, such as the one presented here. The CARE checklist has been completed by the authors for this case report, attached as online supplementary material.

Statement of Ethics

The Ethics Committee of the Hospital Sirio-Libanês approved this case report (Approval Reference Number: 1221 on October 15, 2019). Written informed consent was obtained from the patient before her death for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors declare that they have no potential conflicts of interest related to this publication.

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Author Contributions

Luciana Beatriz Mendes Gomes contributed with the manuscript writing, review, and submission to the journal. Camila Bragança Xavier, Raquel Midori Koga Matuda, and Zenaide Silva de Souza contributed with the manuscript writing and review. Tatiana Strava Correa and Renata Lazari Sandoval contributed with the genetic data and table construction. Luiz Guilherme Cernaglia Aureliano de Lima, Mariana Petaccia de Macedo, and Filomena Marino Carvalho contributed with the pathology data and figures availability. Daniele Assad Suzuki was the patient main doctor and provided critique and feedback on the manuscript. All authors read and approved the final version of the manuscript.

Data Availability Statement

All data underlying the results are available as part of the article and no additional source data are required. Further inquiries can be directed to the corresponding author.

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