

Case Report

# BRCA1 Mutation: An Insidious Enemy with Multiple Facets...

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## Keywords

Hereditary breast and ovarian cancer · Angiosarcoma · PARP inhibitors

## Abstract

Epidemiological studies suggest that around 10% of breast cancers are due to hereditary predisposition. The risk of cancer is exponentially increased in patients harboring *BRCA1* or *BRCA2* mutations. Cumulative breast cancer risk by age 80 is estimated to 72% for *BRCA1* mutation carriers and 69% for *BRCA2*. The cumulative risk estimates for developing ovarian cancer by age 80 are 44% for *BRCA1* mutation carriers and 17% for *BRCA2*. We present here the case of a 59-year-old woman who developed a left breast cancer in 2014 treated by conservative surgery, radiotherapy, and endocrine therapy with letrozole. The diagnosis of *BRCA1* mutation was performed in 2015. In 2018, the patient was referred to our institution for treatment of an aggressive angiosarcoma developed in the same breast. She had undergone radical hysterectomy by the age of 49 years for a benign uterine pathology. In 2020, she developed a tumor in the gastric wall; histological analysis confirmed a serous papillary carcinoma of ovarian origin. She was treated – after gastrectomy and lymphadenectomy – with 6 courses of carboplatin and paclitaxel followed by olaparib therapy. In 2021, she suffered from a chest recurrence of high grade angiosarcoma. New resection with free margins was performed. We discuss the link between angiosarcomas and BRCA mutations, the therapeutic options for angiosarcoma and ovarian cancer of extra ovarian origin and the follow-up modalities.

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## Introduction

Mutations in the *BRCA1* or *BRCA2* genes affect homologous recombination repair. Harmful mutations may produce a hereditary breast-ovarian cancer syndrome.

Breast (high grade invasive ductal carcinoma) and ovarian (papillary serous carcinoma) cancers are the most frequent – but not exclusive – neoplasias associated with *BRCA1* mutations. Preventive strategies have been developed in order to decrease the incidence of these cancers. These strategies are based on chemopreventive treatments (essentially for the breast) and risk reduction surgeries: mastectomies associated with breast reconstructions and adnexectomies for the ovaries. To avoid the side effects induced by premature ovarian failure, some studies are currently investigating the option of partial or total salpingectomy before 50 years. Complementary oophorectomy would take place at the age of natural menopause.

The case we are presenting here illustrates the fact that sometimes risk reduction surgery is unable to prevent the development of ovarian cancer from an extra ovarian origin. It highlights the potential multiple facets of cancers generated by *BRCA1* mutations. The optimal management of such mutated patients remains a complex challenge.

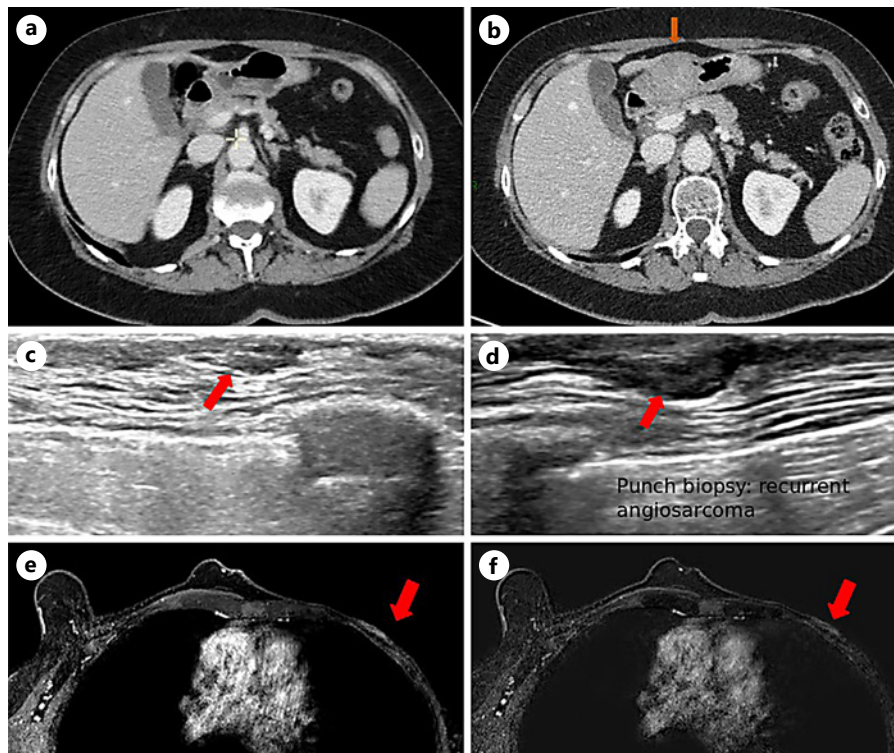
## Case Report

We here present the case of a 59-year-old woman. The medical history of the patient revealed only hypertension. The patient had 3 pregnancies and 3 children. By the age of 49 years, she had hysterectomy and adnexectomy for a benign uterine pathology. She did not take any hormone replacement therapy. In 2014, she developed a left breast cancer. The characteristics of the tumor were an invasive ductal carcinoma grade II/III of 15 mm, no lymph node involved out of the 9 removed. The prognostic indicators were estrogen receptor: 7/8, progesterone receptor: 6/8, and HER2: 0 and KI67: 15% – the lesion was classified as pT1cN0M0. The patient was treated by lumpectomy, radiotherapy, and endocrine therapy with letrozole.

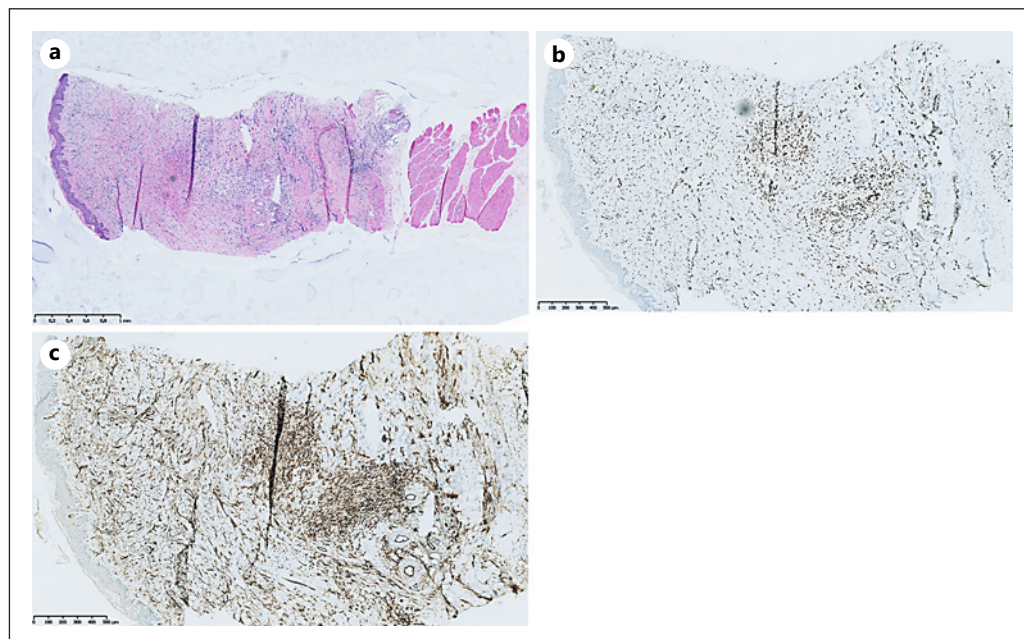
In 2015, genetic testing was performed because the daughter of the patient developed an aggressive triple-negative breast cancer at the age of 35 years. The patient and her daughter were found to be *BRCA1* mutation carriers (c. 1892 duP p Ser632Ly sfs). The patient continued her endocrine therapy.

In 2018, she complained of a bluish cutaneous lesion and an induration in the treated breast. A biopsy revealed an angiosarcoma of grade III. She was referred to our institution for the treatment of this aggressive angiosarcoma of the left breast. The patient underwent complementary mastectomy plus partial resection of the pectoralis major. Because of insufficient margins (the lesion measured 11 × 10 cm), she underwent a second resection and a skin closure with cutaneous graft. No adjuvant therapy was proposed because she already received irradiation (Fig. 1c, d, 2). In 2019, the patient requested a contralateral risk reduction mastectomy.

In 2020, during the follow-up by CT-scan, a lesion in the gastric wall was identified (Fig. 1a, b). The patient underwent a laparoscopy which did not reveal any abnormality in the pelvis and no peritoneal carcinomatosis. The proposed treatment was a gastrectomy plus lymphadenectomy, and the analyses were in favor of a serous papillary carcinoma of ovarian origin with 11/37 positive nodes (Fig. 3, 4). The patient received 6 courses of chemotherapy with carboplatin and paclitaxel. After the end of the chemotherapy, a maintenance therapy with olaparib (PARP inhibitor) was initiated. In May 2021, physical examination revealed a blue palpable lesion on the left chest wall and the diagnosis of recurrent high grade angiosarcoma was made with a biopsy. The lesion measured 50 mm on magnetic resonance imaging (Fig. 1e, f).

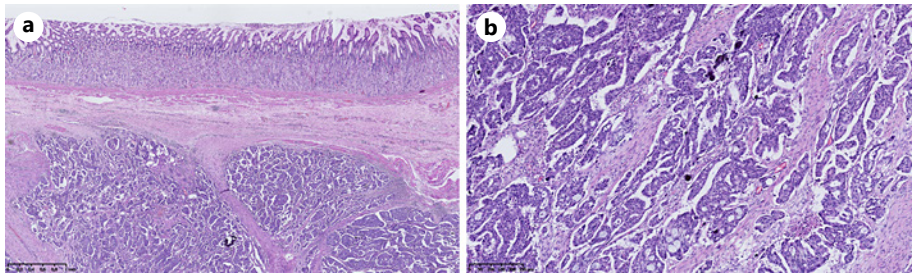


**Fig. 1.** a, b Lesion in the gastric wall. c–f Bluish skin lesion at the left mastectomy site and breast MRI. MRI, magnetic resonance imaging.

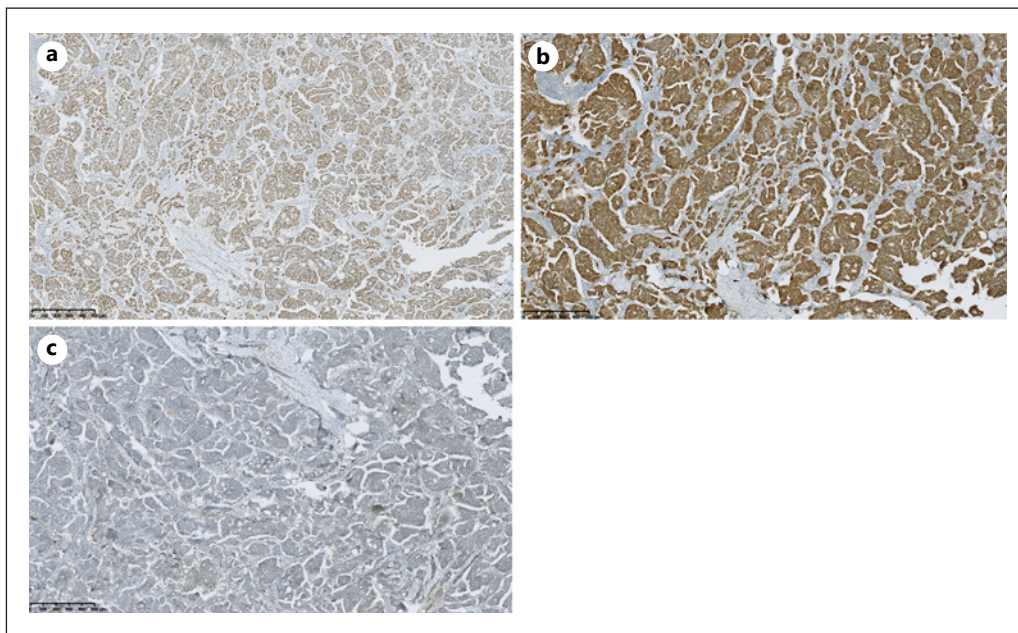


**Fig. 2.** Hematoxylin and eosin. a The biopsy specimen of the left breast displayed infiltrative single neoplastic cells invading both the dermis and subcutis, without invasion of the underlying muscular tissue. The immunohistochemistry, CD31 (b) showed an intense and diffuse nuclear immunoreactivity in the neoplastic cells whereas ERG (c) showed an intense and diffuse cytoplasmic immunoreactivity.





**Fig. 3. a, b** Hematoxylin and eosin. The gastrectomy specimen harbored a micropapillary neoplastic lesion scattered with psammoma bodies which infiltrated the gastric wall down the submucosa. The cells of this lesion had irregular and enlarged nuclei with inconspicuous nucleoli. The overlying mucosa was intact.



**Fig. 4.** Immunohistochemically, the neoplastic cells showed nuclear immunoreactivity for PAX8 (a) and cytoplasmic immunoreactivity for WT1 (b), they did however not show any immunoreactivity for GATA3 (c).

No distant lesions were observed and the patient underwent a resection of the lesion (free margins of more than 50 mm) and skin closure with a new skin graft. No new adjuvant treatment was proposed at the multidisciplinary concentration and olaparib was continued.

### Discussion

*BRCA1* mutation carriers exhibit an increased risk of developing any kind of invasive cancer in addition to the normal risks of developing cancer (and other diseases) associated with increased age, smoking, alcohol consumption, lack of exercise, obesity, etc. When our patient was diagnosed with left breast cancer, the *BRCA1* mutation was not known in the family. She was therefore treated with a conservative approach. Nevertheless, in patients carrying *BRCA1/2* mutations, the international perception is that breast conservation could be an inadequate strategy because of the high risk of new primary cancers [1, 2]. There is

therefore an increased trend toward bilateral mastectomy as the most appropriate strategy for surgical management of newly diagnosed breast cancers in these patients [2], despite remaining unanswered questions concerning a survival advantage [3, 4]. More recent studies indicate that breast conserving therapy is associated with an increased risk of locoregional recurrence compared to mastectomy, but these recurrences do not seem to adversely impact on survival. This means that a personal approach is allowed and that *BRCA1/2* mutation carriers should be informed regarding all surgical options following breast cancer diagnoses [1, 2].

Angiosaromas are a relatively rare histological subtype of sarcomas and represent approximately 1% of all sarcomas. Estimated incidence of treatment associated breast angiosarcomas is 0.002–0.05% per year with a cumulative incidence of 0.27% at 10 years [5, 6].

Among *BRCA1/2* mutation carriers, the risk of angiosarcomas is estimated at 0.43% per year and should not be considered in treatment decisions regarding mastectomy versus breast conserving therapy and irradiation. The etiology of postradiation angiosarcomas may be related to double-strand DNA damage induced by radiation which results in genome instability that may lead to sarcoma [7–9].

The cornerstone of angiosarcomas treatment remains surgical resection with large free margins. Recurrence rates are known to be highly elevated [10]. Because secondary angiosarcomas are related to radiation, no adjuvant irradiation is proposed.

In the literature, for *BRCA1/2* carriers, some authors propose adjuvant therapies with PARP inhibitors and chemotherapy with platinum-based regimens. Our patient had received 6 courses of chemotherapy with carboplatin and taxanes and was on olaparib administered as maintenance treatment for her ovarian cancer. Despite these treatments, she developed a recurrence of angiosarcoma. Other drugs for the treatment of secondary angiosarcomas remain mostly experimental.

Despite a radical hysterectomy and adnexectomy 15 years before, our patient developed a serous papillary carcinoma in the gastric wall corresponding to an ovarian cancer. A new and complete histological review of her previous radical hysterectomy was performed to reexamine the tubes and ovaries but absolutely no atypical lesion was observed in the examined samples. Ovarian cancer can be prevented by risk-reducing salpingo-oophorectomy in 95% of the cases [3].

Despite numerous studies, the original lesion that gives rise to ovarian cancer remains controversial [11]. The longstanding dogma is that ovarian cancer originates from the surface epithelium layer of the ovary [12]. The surface cells involute and form cysts. The process of cyclic ovulation probably leads to repeated rupture and repair of ovarian surface epithelial cells and due to the accumulation of genetic mutations, the cells turn cancerous and an ovarian tumor is generated [13]. This theory is unable to explain the complex histopathological heterogeneity of the disease. More recent studies confirm that ovarian cancer is a complex disease that originates from multiple sites which are mostly outside of the ovaries [11, 12, 14]. This finding supports the hypothesis of an extraovarian origin of ovarian cancers. The omentum and visceral fat are other possible sites of ovarian cancer initiation. Nieman demonstrated that omental adipocytes – via the secretion of interleukines – can induce homing, attraction, and invasiveness of ovarian cancer cells. Several authors [15–17] demonstrated that adipocytes microenvironment could induce cancer stem cell pathways. This theory could explain that the omentum and the stomach for our patient may not only be sites of metastasis but also possible sites of primary origin for ovarian cancer. Nevertheless, the stomach appears to be an exceedingly rare site for the development of an ovarian lesion.

In women with a diagnosis of advanced ovarian cancer, a combination of cytoreductive surgery and systemic treatment with carboplatin-based chemotherapy remains the standard of care. Unfortunately, a great number of patients relapse within 3 years of completing therapy. Over the last decade, research has focused on introduction of maintenance therapy, such as

PARP inhibitors. PARP inhibitors target the PARP enzyme family (PARP-1, PARP-2, PARP-3) which is involved in DNA repair. After encouraging results in phase II trials, SOLO2, a phase III trial, was the first trial which demonstrated survival benefits among patients with recurrent ovarian cancer receiving olaparib in maintenance therapy [18]. Currently, our patient is still free of recurrence of ovarian cancer, but olaparib as previously explained was unable to avoid recurrence of angiosarcoma.

## Conclusion

This case highlights the difficulties in medical management of *BRCA1* mutation carriers who develop different types and unusual forms of cancers. It also illustrates the failure of “preventive” adnexal surgery and the exceptional localization of a primary ovarian cancer at the gastric level. The potential benefits of PARP inhibitors in the prevention of angiosarcoma recurrence are not confirmed and the need for new therapies to fight this aggressive tumor is more than never necessary.

## Acknowledgments

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## Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. According to the recommendations of our Ethics Committee (Comité d’Ethique Hospitalo-Facultaire Saint-Luc/UCL, number 403), an informed consent was asked to the patient. The completed consent form is available to the editor if requested. This review of patient data did not require ethical approval in accordance with local and national guidelines.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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## Author Contributions

P. Godin: original draft, patient data extraction investigation, and writing. F. Duhoux: supervision, writing, and review editing. F. Mazzeo interpretation, analysis, and supervision. M. Rojas, E. Bollue: resources, review of the literature and investigation. A. François, C. Galant:

patient data extraction, analyses of data, and writing. J. Coulie, M. Coyette, A. Lentini, Y. Deswissen: patient data extraction and interpretation and analysis of the data. V. Perlepe: resources, analysis of data, and writing. L. Fellah, I. Leconte: resources, investigation review of the literature. M. Berliere: original draft, writing, review, and editing.

### Data Availability Statement

All data generated or analyzed are included in this article. Further enquiries can be directed to the corresponding author.

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