An interesting case of likely BRCA2 related bilateral breast cancer with metastasis in the fimbrial part of fallopian tube

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Abstract

Background: In a patient with a germline BRCA2 pathogenic variant with breast cancer, an adnexal mass can represent either a metachronous primary tumor or a metastasis of the breast cancer. A clear distinction between those two possibilities is crucial since treatments differ substantially and so does survival of the patient.

Case presentation: We present a case of a 47-year-old patient with bilateral breast carcinoma with a germline BRCA2 pathogenic variant. The first manifestation of the disease was a lump in her left breast in 1998, histological report was invasive ductal carcinoma, triple-negative. She was treated with surgery, chemotherapy and radiotherapy. In 2011 a new occult carcinoma was found in her right axilla, however the specimen was estrogen receptor (ER) and progesterone receptor (PgR) positive. She was treated as a new primary occult carcinoma of the right breast with surgery, radiotherapy and adjuvant hormonal treatment. In 2016 a mass in the left adnexa was found with imaging techniques. She underwent surgery as if it was primary ovarian cancer, yet histology revealed it was a metastasis of a triple-negative breast carcinoma in the fimbrial part of the left Fallopian tube. She received adjuvant chemotherapy after surgery and is now in complete remission.

Conclusion: We present an interesting and quite rare case of two primary breast carcinomas in a patient with a known BRCA2 pathogenic variant with metastasis in the fimbrial part of the left Fallopian tube. We conclude that there were two primary breast tumours and the one from 2011 spread into the fimbrial part of the left Fallopian tube in 2016. Despite the fact that molecular analyses could not confirm the joint tumour origin, we believe that there was a receptor status conversion over time explaining different receptor status. The possibility of a triple-negative metastasis from the tumour treated in 1998 is less probable. With both of aforementioned possibilities being prognostically unfavourable, the patients’ outcome is so far excellent and she was in complete remission at the time of writing this article.

Keywords: Breast cancer, BRCA2, Oligometastatic, Fimbrial part of fallopian tube, Receptor conversion

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Background
Breast is one of the leading cancer sites in females across the globe. It is also the leading cancer site for females in Slovenia [1]. The presence of BRCA1 or BRCA2 pathogenic variant poses a significant risk of developing breast and ovarian cancer as well as other types of cancer – gastric, colorectal, uterine cancer, melanoma etc. [2]. Since there is no effective screening method for ovarian cancer so far [2], once identified as a BRCA carrier, several preventive measures and implications are suggested by the guidelines [2] for these patients, among which risk-reducing salpingo-oophorectomy is recommended before the age of 40. According to the literature, the so-called occult cancers are found in 2–12% when risk-reducing surgery is performed [2, 3].

In a patient with a history of breast cancer with a positive BRCA1 or 2 pathogenic variant, an adnexal mass can represent either a metachronous primary tumour or a metastasis. Histological examination is necessary. Occult tubo-ovarian cancers are usually smaller and found incidentally in risk-reducing surgery while metastases usually present clinically or are found by imaging techniques, rarely incidentally in the case of prophylactic adnexal removal [3–5]. However, the distinction between the two is clinically important not only from therapeutic, but also from the prognostic point of view: it was shown that if an ovarian mass represents a metastasis of another cancer, the patients’ survival is worse than survival of the patients with primary ovarian cancer [6].

We report a case of a patient with breast cancer with a metastasis into the fimbriae of the left Fallopian tube which was suspected to be a primary ovarian cancer due to her BRCA2 pathogenic variant.

Case presentation
A 47-year-old female presented with a lump in her left breast in December 1998. Her family history was unremarkable and her Ca 15–3 level was normal. Tumorectomy was performed in a regional hospital and revealed a poorly differentiated invasive ductal carcinoma measuring 9 mm in the largest diameter (Fig. 1). Oestrogen receptor (ER) and progesterone receptor (PgR) were tested and were negative. Human epidermal growth factor receptor 2 (Her2) status has not been determined yet in those times. She was sent to our Institute for additional treatment. Since pathologist could not have evaluated the status of excisional margins because of the mechanical tissue damage, the quadrantectomy and axillary dissection were performed in February 1999. One out of 17 resected lymph nodes was metastatic (1/17) with extracapsular infiltration of perinodal fat tissue while quadrantectomy specimen revealed only foci of residual ductal carcinoma in situ (DCIS) and reactive changes from the tumourectomy itself. She was treated with adjuvant chemotherapy and irradiation. She received 6 cycles of CMF (cyclophosphamide, methotrexate and fluorouracil) and 50 Gy on her left breast and additional 10 Gy on the tumor bed. The adjuvant treatment was completed in July 1999 and regular follow up was initiated.

In September 2011 she had noticed a tumour in her right axilla. An ultrasound of the axillar region revealed 2 × 1 cm pathological lymph node. Cytological examination of the node showed a metastasis of adenocarcinoma. A following magnetic resonance imaging (MRI) of the right breast showed no pathological lesions. Her laboratory blood testing was normal including the Ca 15–3 level, as well as ultrasound of the abdomen and X-ray of the chest. Right axillar dissection was performed in November 2011, 1 out of 19 removed lymph nodes was positive for invasive carcinoma (Fig. 2). This metastasis...
measured 2 cm in the diameter, extracapsular extension was present. ER was 100% positive and PgR was 90% positive, Her-2 was negative and proliferation index (MIB-1) was 10–15%. Due to the difference of biomarker status of the metastasis in the right axilla and the tumour of the left breast in 1999, she was interpreted to have a new primary, occult cancer of the right breast and was treated with adjuvant hormonal treatment (an aromatase inhibitor) and irradiation of right breast and right axillar region with 50 Gy.

Genetic testing for germline variants was performed in April 2016 at our institute with next generation sequencing (NGS) and showed mutation in BRCA2 gene: c.8755-1G > A, heterozygotic, which is currently classified as a pathogenic variant. From the whole blood, DNA was extracted using InnuPREP Master Blood kit (Analytik Jena, Thuringia, D). The coding sequence and exon/intron boundaries on DNA isolated from blood were enriched using Nextera DNA Library Preparation Kit in combination with TruSight Cancer Panel (Illumina, San Diego, USA), according to manufacturer’s protocol. NGS was performed on Illumina MiSeqDx Sequencing System (Illumina). Read alignment and variant calling was performed using MiSeq Reporter software 2.5.1. Variant annotation was performed using Variant Studio software 3.0 (Illumina) and Alamut Visual software 2.11 (Interactive Biosoftware, Rouen, France). Direct Sanger sequencing was performed to confirm mutations detected by NGS. For direct DNA sequencing, the samples were bidirectionally sequenced on an automated ABI 3500 genetic analyzer (Applied Biosystems, Foster City, CA). While still receiving adjuvant hormonal treatment, a mass in the left lower abdomen was found, measuring 6 × 5 cm. The Ca 15–3 level was elevated for the first time (35 kU/l, normal level below 30 kU/l), while the Ca 125 level was normal. Fine needle aspiration sampling was performed twice and revealed only poorly differentiated carcinoma; immunocytochemistry could not have been done due to the lack of material. The tumor board decided for surgical removal of the lesion as if it was a primary ovarian cancer. She underwent surgery in June 2016, combining the risk-reducing (due to known BRCA2 pathogenic variant) and primary ovarian cancer approach - total hysterectomy with bilateral adnexectomy and removal of the regional lymph nodes. The final histological report identified a metastasis of a poorly differentiated carcinoma, which was CK7 and GATA3 positive, and CK20, PAX-8, WT1 negative. ER and PgR as well as Her-2 receptor status were negative. It was clearly concluded that it is a metastasis of a breast carcinoma in retroperitoneal lymph nodes as well as in the fimbrial part of the left Fallopian tube. Metastasis in the fimbrial part of the left Fallopian tube are seen in Figs. 3 and 4. Five out of 11 surgically removed lymph nodes were positive for malignancy. Since metastases of the breast cancer were triple-negative, she received additional 6 cycles of EC chemotherapy (epirubicin, cyclophosphamide). During chemotherapy her Ca 15–3 level returned to normal.

For the purpose of this article, the molecular analyses of the tumor tissue were done to find out whether this has been the same tumour all along. The DNA samples extracted from formalin-fixed paraffin embedded tumor tissue (FFPE) were used. DNA was extracted using GeneRead DNA FFPE Kit (Qiagen GmbH, Hilden, Germany) from manually macro-dissected areas annotated by a pathologist by scraping directly off unstained standard glass slides (10 μm). Hematoxylin-eosin staining of the first sectioned slide was performed to visualize the presence of tumour cells, and to guide macro-dissection on unstained duplicate slides and to determine the area of the tissue cores. The coding sequence and exon/intron boundaries
The survival of those with primary ovarian cancer, the occurrence in 15% of patients with metastases into ovaries is worse than to 33% of cases of ovarian metastases. Since the survival et al. [7] shows that breast is the primary site in 1.8% up to 33% of cases of ovarian metastases. Since the survival of patients with metastases into ovaries is worse than the survival of those with primary ovarian cancer, the distinction between the two is critically important to understand [6].

Looking from the other point of view, BRCA2 carriers are more likely to develop a metachronous ovarian cancer than the general population. An Italian group analyzed risk-reducing surgery specimens in the 18 years observation period for either BRCA1 and BRCA2 carriers, non carriers or patients with unknown BRCA1 and BRCA2 status. 75% of women had a history of breast cancer and when performing a risk-reducing salpingo-oophorectomy, 3.6% of patients had an occult cancer, while only two out of 411 patients had a breast cancer metastasis in the uterine adnexa, alluding that a metastasis in the fimbrial part of the Fallopian tube is a rare event [3]. Rabban published a review with the comparison of histological features of primary ovarian cancer and breast cancer metastases into the uterine adnexa [4]. Only 1% of BRCA1 and BRCA2 positive patients in their series had a breast cancer metastasis into the uterine adnexa, again confirming the rarity of the event [4]. These data show that our case is interesting yet rare and not often described in the literature. However, late metastases in BRCA2 positive patients are not uncommon. Regarding the interval from the first disease occurrence in 1999 it is very unusual for a triple-negative breast cancer to have such a long and slow course. In the literature, there are reports of a receptor conversion through time [8]. The meta-analysis by Aurilio et al. showed that the rates of discordance of primary tumor and metastasis for ER and PgR were 20 and 33% [13]. They also noted that the conversion to negative receptor status at recurrence was seen more frequently than the positive conversion with rates of 24% vs. 14% for ER status and 46% vs. 15% for PgR status [13], which can be greatly attributed to the treatment given that select subclones with different phenotypes to emerge. For the purpose of this article a molecular analyses of all three samples were done using TST 170 gene panel and no common mutation was found. As this gene panel includes a limited set of genes, we cannot definitively exclude the possibility that the tumors are of the same origin. However, based on histological results, we conclude that it is more likely that there was a receptor status conversion over time due to hormonal treatment the patient was receiving after 2011 and that the metastasis in the fimbrial part of the left Fallopian tube was a metastasis of a 2011 tumour rather than a metastasis of a triple-negative cancer from 1998. Knowing that the conversion of receptor status is known to be associated with a worse prognosis [8], our patient is still in complete remission and continues her regular follow-up.

**Conclusions**

This is an interesting case of BRCA2 positive patient with bilateral primary breast cancer having a different receptor expression with a very long interval from
Table 1: Variants detected in three different tumor samples of the same patient. In the table are included only variants reported in whole GnomAD population (ALL) or European or Non-Finish population (NFE) with frequencies < 1%. Variants classified as benign in ClinVar database were removed from the report.

| Gene     | Variant type               | cHGVS                        | pHGVS                        | AF (%) in sample 01 | AF (%) in sample 02 | AF (%) in sample 03 | variant status (germline/somatic) | Frequencies in different population in GnomAD database |
|----------|----------------------------|------------------------------|------------------------------|---------------------|---------------------|---------------------|----------------------------------|--------------------------------------------------------|
| BRCA2    | missense_variant           | NM_000059.3:c.978C > A      | NP_0000502.2:p.(Ser326Arg)   | 16.96               | 24.69               | 15.98               | confirmed germline variant       | ALL:0.090% - NFE:0.14%                                |
| FGF5     | 3_prime_UTR_variant        | NM_004464.3:c.1139T > C     | NP_0001323.3:p.(Ser57leu)    | 39.17               | 40.88               | 81.8                | likely germline variant          | ALL:0.089% - NFE:0.082%                               |
| FGFR2    | missense_variant           | NM_000141.4:c.170C > T      | NP_0004554.4:p.(Pro315=)     | 40.64               | 50                  | 88.62               | likely germline variant          | ALL:0.045% - NFE:0.31%                                |
| STK11    | synonymous_variant         | NM_000455.4:c.945G > A      | NM_000455.4:p.(Pro315=)      | 70.77               | 40.5                | 80.77               | confirmed germline variant       | ALL:0.072% - NFE:0.073%                                |
| BCL6     | splice_region_variant     | NM_001706.4:c.1356-3T > C   | p.?                           | 483                 | 30.6                | 42.9                | likely germline variant          | ALL:0.24% - NFE:0.18%                                 |
| AR       | synonymous_acceptor_variant | NM_000059.3:c.8755-1G > A  | p.?                           | 723                 | 72.6                | 81.2                | confirmed germline variant       | Not known to gnomAD                                   |
| RPS6KB1  | synonymous_variant         | NM_00172043.1:c.621G > A   | NM_00172043.1:p.(Gly207=)    | 899                 | nd                  | nd                  | somatic variant                  | Not known to gnomAD                                   |
| PDGFRB   | missense_variant           | NM_002609.3:c.1312G > T    | NP_002600.1:p.(Gly438Cys)    | nd                  | 33.2                | nd                  | somatic variant                  | Not known to gnomAD                                   |
| CTNNB1   | synonymous_variant         | NM_001904.3:c.765C > A     | NM_001904.3:p.(Ala255=)      | nd                  | nd                  | 77.66               | somatic variant                  | Not known to gnomAD                                   |
| ERBB4    | missense_variant           | NM_005235.2:c.670C > A     | NP_0052261.2:p.(Pro224Thr)  | nd                  | nd                  | 23.68               | somatic variant                  | Not known to gnomAD                                   |
| FGFR1    | missense_variant           | NM_00175929.2:c.4G > A     | NP_00175929.2:p.(Val22le)    | nd                  | nd                  | 37.15               | somatic variant                  | ALL:0.00040%                                        |
| NF1      | missense_variant           | NM_000267.3:c.7086C > G    | NP_0002581.1:p.(Asn236Lys)   | nd                  | nd                  | 34.25               | somatic variant                  | Not known to gnomAD                                   |
| TP53     | missense_variant           | NM_000546.5:c.844C > T     | NP_0005537.3:p.(Arg282Trp)   | nd                  | nd                  | 73.6                | somatic variant                  | ALL:0.00040% - NFE:0.00090%                          |
| TSC1     | missense_variant           | NM_000368.4:c.967C > A     | NP_000368.4:p.(Pro323Thr)    | nd                  | nd                  | 32.35               | somatic variant                  | ALL:0.00040% - NFE:0.00090%                          |

AF allele frequency of nucleotide variant in the sample, nd not detected, cHGVS variant description on coding DNA reference sequence according to Human Genome Variation Society, pHGVS variant description on protein reference sequence according to Human Genome Variation Society.

*the variant was confirmed on DNA isolated from patient blood sample, **variant was classified as likely germline if the frequency in populations reported in GnomAD database were > 0.005, ***variants not reported in GnomAD or reported in GnomAD with the frequency < 0.005 in different populations.
primary disease occurrence and metastasis into the fimbrial part of the Fallopian tube. We conclude that there were two primary breast tumours and the one in 2011 spread into the fimbrial part of the Fallopian tube in 2016. Despite the fact that molecular analyses could not confirm the joint tumour origin, we believe that there was a receptor status conversion over time explaining different receptor status. However, after all the treatment received, the patient has a good quality of life and she is in complete remission at the time of writing this article.

Abbreviations
CMF: Cyclophosphamide, methotrexate and fluorouracil; DCIS: Ductal carcinoma in situ; EC: Epirubicin, cyclophosphamide; ER: Estrogen receptor; PgR: Progesteron receptor; MIB-1: Proliferation index; MRI: Magnetic resonance imaging.

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Non applicable.

Authors’ contributions
LB gathered the data and wrote the main text. GG wrote pathological part of the manuscript and provided the pictures. VS performed the molecular analyses, SN interpreted the results and wrote the text regarding molecular pathology in risk-reducing salpingo-oophorectomies from women with BRCA mutations, emphasizing the differential diagnosis of occult primary and metastatic carcinoma. Ann J Surg Pathol. 2009;33(8):1125–36.
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