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Synchronous Ovarian Dysgerminoma and Breast Carcinoma in a Patient with Positive Immunostain of BRCA1

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Rezumat

Disgerminom ovarian și carcinom mamar sincron la o pacientă cu imunomarcaj BRCA1 pozitiv

Cancerul mamar este cel mai frecvent proces neoplazic malign şi a doua cauză de deces la sexul feminin. Cancerul ovarian, deşi prezintă o incidență mai mică, constituie însă o cauză importantă de morbiditate şi mortalitate, fiind depistat de obicei în stadii avansate. Prezența ambelor forme de cancer la o pacientă se asociază cu un risc crescut de mutații ale genei BRCA1, acestea fiind responsabilă, împreună cu mutațiile genei BRCA2, de cele mai multe din cancerele mamare şi ovariene familiale. Cazul prezentat este deosebit deoarece aduce în atenție asocierea sincronă, rară, dintre un disgerminom ovarian primar (cu o incidență de sub 1% din cazurile de cancer ovarian) şi un carcinom mamar primar, la o pacientă de 46 de ani. Pentru examenul imunohistochimic s-a utilizat un panel de 5 biomarkeri: receptor estrogenic, receptor progesteronic, Herceptest, p53 si BRCA1. În cazul prezentat am indentificat un status hormonal negativ, absența expresiei HER2/neu dar cu supraexpresia proteinei p53 şi a proteinei BRCA1. Evoluția postoperatorie după fiecare intervenție chirurgicală a fost favorabilă, pacienta fiind externată cu recomandarea de a efectua consult genetic.

Cuvinte cheie: BRCA1, disgerminom ovarian primar, carcinom mamar primar

Abstract

Breast cancer is the most common malignant neoplastic process and the second cause of death for women. Ovarian cancer, despite having a lower incidence, represents an important cause of morbidity and mortality because it is usually discovered in advanced stages. The presence of both forms of cancer in a patient is associated with a high risk of BRCA1 gene mutations, which are responsible, together with BRCA2 gene mutations, for most of the breast and ovarian cancer family. Our case is special because it presents a synchronous and a rare association of a primary ovarian dysgerminoma (with an incidence of less than 1% of ovarian cancers) and a primary breast carcinoma in a patient of 46 years old. Immunohistochemical examination was performed using a panel of five biomarkers: oestrogen receptor, progesterone receptor, Herceptest, p53 and BRCA1. In our case, we identified a negative hormonal status and the absence of HER2/neu expression but a positive immunoexpresion for p53 protein and BRCA1 protein. Postoperative course was favourable for the patient after each surgery, and she was discharged with the recommendation to perform a genetic counselling.

Key words: BRCA1, primary ovarian dysgerminoma, primary breast carcinoma

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Introduction

Compared to breast cancer, with a 30% incidence among females and a 15% mortality rate (1), ovarian cancer presents a lower incidence, of approximately 3%, but continues to represent an important cause for morbidity and mortality, usually both of them being diagnosed in advanced stages (2,3). Synchronous presence of two primary tumours, located at both breast and ovary level, in a patient younger than 60 years old is rare and associated with an approximately 30% risk of presenting mutations of the BRCA1 and BRCA2 genes (Breast Cancer 1/2 Gene) (4). BRCA1/2 are tumour suppression genes, which encode proteins that have a main role in DNA repairing processes and are responsible for the majority of family linked breast and/or ovarian cancers (5,6). The presence of BRCA1 or BRCA2 germinal mutations leads in equal measure to the development of primary breast cancer (60% – 85% of cases) (5). Also, BRCA1 mutations are associated with a 40% – 60% risk to develop contralateral primary breast cancer, and with a risk almost 4 times higher compared to BRCA2 mutations to develop ovarian cancer (35% - 45% for BRCA1 and 10% - 27% for BRCA2) (7).

Case report

M.P., female, 46 years old, residing in an urban area, with no significant personal or family history, non-smoker, with 3 pregnancies and 3 births until present, was admitted to the Constanța County Emergency Hospital, after presenting to the Emergency Unit for diffuse abdominal pain and the presence of a tumoral mass in the upper-inner quadrant of the left breast. The clinical examination performed at admission showed an abdomen very expanded in volume, moderately diffusely tender, with no signs of peritoneal irritation. Pelvi-abdominal CT exam revealed the presence of a large medial-abdominal and hypogastric mass, with a semi-solid aspect, which appears to form a joint body with the uterus; no secondary processes present in the liver.

A two-stage surgical intervention is decided for. In the first stage, after the appropriate preoperative preparation and under general anaesthesia with oro-tracheal (GA-OTI) intubation in place, a median subumbilical incision is made, displaying a large tumour developed outside the pelvis, next to the left ovary and fallopian tube, not adherent to the uterus. Hysterectomy with bilateral adnexectomy and pelvic peritonectomy with reductive omentectomy are performed. The resection pieces were sent to the Department of Clinical Pathology for a histopathology exam. Subsequently, one week after the intervention, a second operation is decided for. Under GA-OTI, Madden type radical left mastectomy and excision of numerous large, hard, conglomerated lymph nodes from all the axillary lymph stations are performed. Under haemostasis control, the surgical wound is sutured and the piece is submitted to a histopathology exam.

Two years later, the patient is readmitted for the presence of a tumoral mass in the upper-outer quadrant of the right breast, for which she was submitted to 4 sessions of radiotherapy. A surgical intervention for Madden type right mastectomy with right axillary lymphadenectomy under GA-OTI was performed. The patient's positive evolution allowed for her to be discharged 5 days later, under the recommendations of hygienic-dietary regime, surgical check-up, outpatient oncology treatment and genetic counselling.

Histopathologic exam

Macroscopic aspect:1) Left adnexal tumour – gigantic cystic mass, with a slightly irregular external surface. After sectioning, the tumour appears to be solid in over 75% of its volume, yellowish in colour, with translucid areas and necrotic areas. The rest of the tumour presents cystic cavities with serous-citrine content, slightly viscous (Fig. 1). 2) The radical left mastectomy specimen displays in the upper-inner and central quadrants a nodular tumoral mass, with a maximum diameter of 5 cm, grey-yellowish in colour, with high consistency imprecise limits (Fig. 2). Numerous nodes are identified within the axillary extension, with sizes ranging from 0.5 to 2 cm, white-greyish in colour, with high consistency. 3) The right radical mastectomy specimen – after sectioning of the upper-outer quadrant, a star-like tumoral mass, with a maximum diameter of 3.2 cm, white in colour, with high consistency is revealed.

Microscopic aspect: 1) Left adnexal tumour – malignant neoplastic proliferation, with monomorphic polygonal and round cells, bearing a granular aspect, with mitoses and nuclear atypical characteristics suggestive for poorly differentiated disgerminoma (Fig. 3). 2) The radical left mastectomy specimen - poorly differentiated infiltrating ductal carcinoma-not otherwise specified (IDC-NOS) and high lymphocyte infiltrate (Fig. 4); capillaries presenting tumour emboli; striated muscle tissue with neoplastic invasion. Lymph node metastases present in all 10 lymph nodes analysed. 3) The right radical mastectomy specimen - poorly differentiated

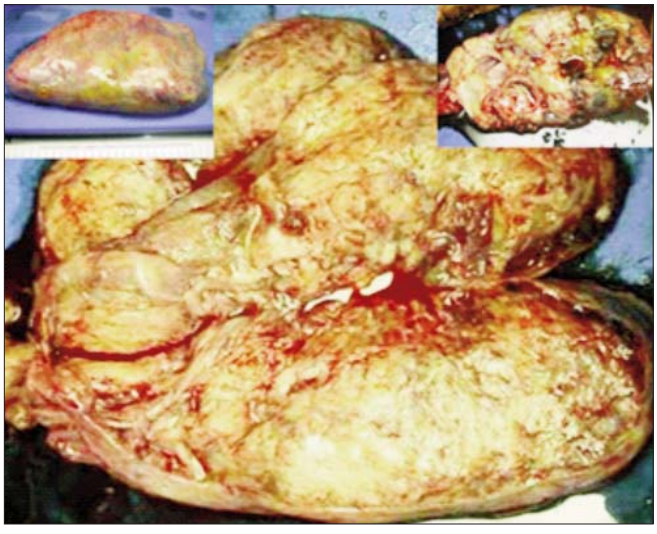

Figure 1. *Image 1 Left adnexal tumorectomy specimen - cystic mass, with cystic areas and solid areas upon sectioning, with lobulated aspect, yellowish in colour*

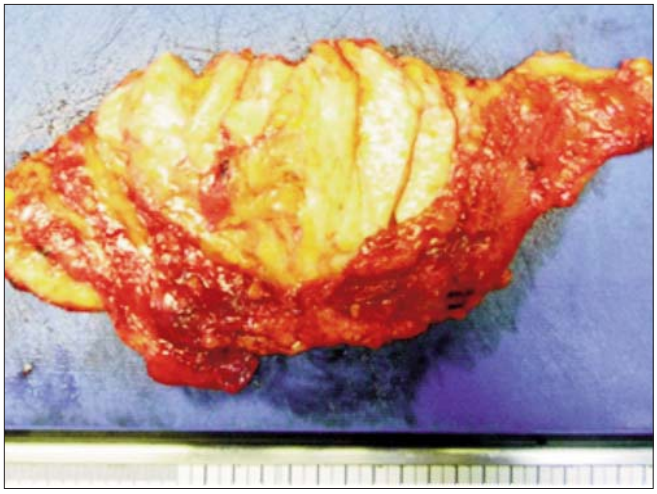

Figure 2. *Left mastectomy specimen – nodular lesion, imprecisely delimited, with a 5 cm maximal diameter, white-yellowish in colour, slightly high consistency*

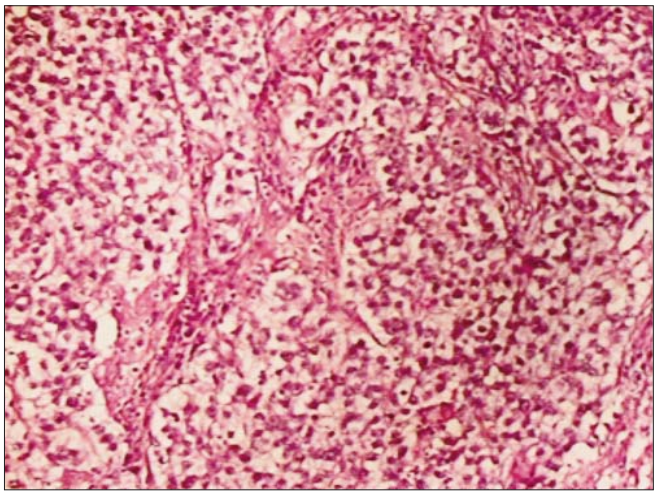

Figure 3. *Dysgerminoma histopathologic aspect – monomorphic cell proliferation, arranged in nests separated by thin connective trabeculae with high inflammatory lymphocyte infiltrate (HE 10x coloration)*

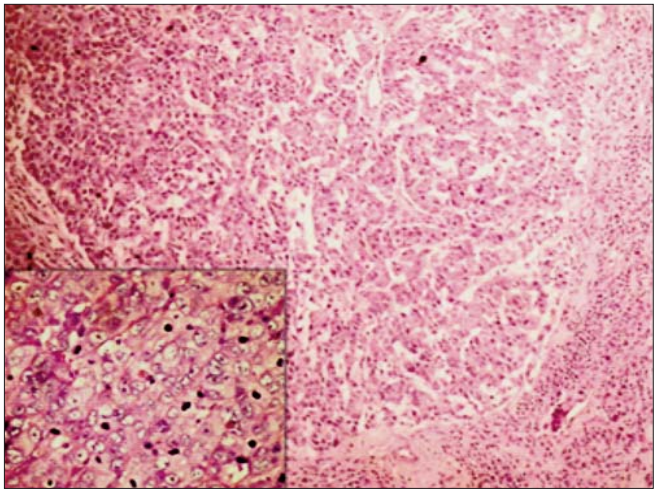

Figure 4. *Histopathologic aspect of IDC-NOS, poorly differentiated, with "pushing" type tumoral margins and high peritumoral inflammatory lymphocyte (HE 4x coloration); (in the case - high mitotic index IDC-NOS, HE 20x coloration)*

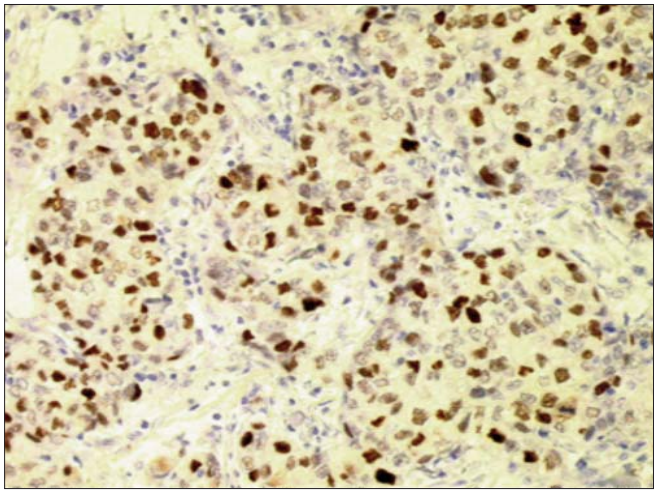

Figure 5. *P 53 immunohistochemical exam – intensely positive nuclear immunostain*

IDC-NOS. Out of all 9 lymph nodes analysed, two present neoplastic invasion.

Immunohistochemical exam was performed on the most suggestive slice from the left mastectomy specimen, using a panel of five biomarkers. Immunohistochemical expression of hormone receptors (oestrogen receptor – OR, progesterone receptor – PR), of type 2 human growth factor (HER2/neu), overexpression of protein P53 (secondary to the mutation of gene p53) and of protein BRCA1 were evaluated. Positive immunostain was obtained only for p53 (intensely positive at nuclear level) and for BRCA1 (diffusely positive at cytoplasm level) (Fig. 6).

Discussions

Although new genetic testing technologies are efficient, they

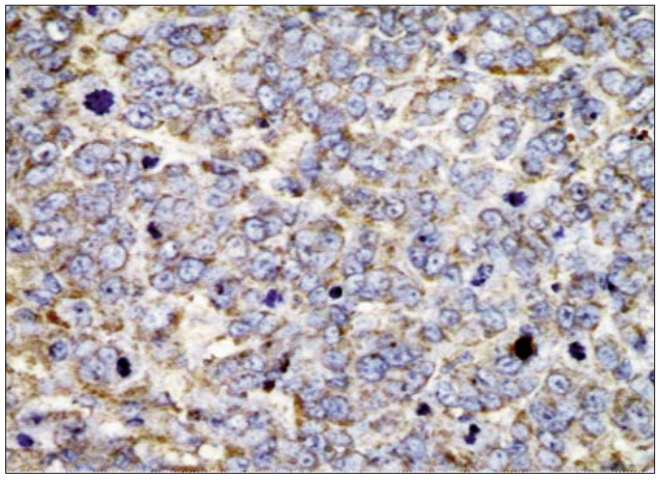

Figure 6. *BRCA1 immunohistochemical exam – positive diffuse immunostain, at cytoplasm level*

are tedious and expensive. This is why an attempt was made to use the immunohistochemical exam as a method of detecting BRCA1 mutations, it being considered a reliable, practical method, which can aid at least in selecting patients for genetic testing. Studies conducted have demonstrated that a positive BRCA1 status is associated with characteristic histopathologic and immunohistochemical features (8-10), and a positive immunostain for BRCA1 protein can predict the presence of BRCA1 gene mutations with 100% sensitivity and 80% specificity (11). Thus, in the present case we tested the presence of any mutation at exon 1 level of the BRCA1 gene, with the help of GLK-2 (DAKO) monoclonal antibody, which highlighted the presence of protein-BRCA1 at cytoplasm level through a brown coloration (12).

Mutations of the BRCA1 gene determine the development of cancer at a usually young age (13), tumours generally being detected in advanced stages (III/IV) (14-18). From a histopathologic point of view, breast carcinomas are the most frequent type of NOS-IDC (19,20), usually without an identifiable in situ component (8). The only histopathologic characteristics that have proved to be important and able to predict a positive BRCA1 status are: high mitotic index, "pushing" type well-delimited tumour margins that compress the adjacent tissues and the presence of a high lymphocyte infiltrate (21). In the case of ovarian tumours, a high frequency of epithelial carcinomas, especially poorly differentiated serous papillary adenocarcinoma was observed (14), although there are studies infirming these results (22). Among the histopathologic types of ovarian cancer associated more seldom with BRCA1 mutations there is also a case of primary ovarian dysgerminoma mentioned (23). 80% of cases are encountered between the second and third age decades (24), and prognosis in these cases is good, with a 5-year survival rate of 75%- 90% (25).

Establishing the hormone status (OR and PR), as well as evaluating the expression of Her2/neu by means of the immunohistochemical exam are important predictive and prognosis factors (26). In the case of positive BRCA1 tumours, it was observed that these are 4.8 times more frequently negative for hormone receptors compared to sporadic breast cancer, while the expression of OR and PR in patients with BRCA2 mutations is similar to that encountered in sporadic cancers (8,28). Oncogene c-erbB2 or HER 2/neu plays an important role in cellular proliferation, and amplification of the gene or immunohistochemical overexpression of protein HER2 is identified in 20-30% of sporadic breast cancer cases. A 3+ immunohistochemical score (intense membrane positivity, complete in over 30% of tumour cells) is an indication for Herceptin (Traztuzumab) monoclonal antibody therapy. In cases presenting BRCA1mutations, HER2/neu immunostain is present in up to 3.7%, much less than in cases of sporadic breast cancer (29). In ovarian cancers the immunohistochemical expression of HER2 is no different among BRCA1 and BRCA2 cases, nor between these and sporadic cancers (9). In the present case, both the expression of hormone receptors and that of HER2/neu were negative, in according with previous studies (27,29).

Tumour suppressive gene p53 encodes a 53kD nuclear fetoprotein, involved in the regulation of the cellular cycle, in DNA repairing and in apoptosis. In breast cancers secondary to BRCA1 mutations, a higher incidence of gene p53 mutations compared to sporadic cancer and to BRCA2 tumours (for which the absence of this mutation is characteristic) was demonstrated (30). The intensely positive immunostain for p53 obtained in our case is in according with the immunohistochemical profile of BRCA1 positive breast carcinomas. Also, studies previously conducted have demonstrated that ovarian tumour present an immunohistochemical expression of protein p53 far greater that sporadic ovarian cancer (35%), both in BRCA1 tumours (77%) and in BRCA2 ones (45%), without there being a statistically significant difference between them (17,31).

In conclusion, the case presented is special due to the rare, synchronous association of a primary ovarian dysgerminoma and a primary invasive breast cancer, poorly differentiated. This association, together with histopathologic findings and with the immunohistochemical profile obtained led to the suspicion of a mutation at BRCA1 gene. The immunohistochemical exam showed the overexpression of protein BRCA1, but a genetic testing for BRCA1 gene mutations is required for diagnostic certainty.

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