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Ovarian metastases reported after adjuvant laparoscopic oophorectomies in breast cancer

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Abstract

Introduction: Ovarian metastases (OM) of breast cancer (BC) can occur with different rates, ranging from 3–30%, being reported after prophylactic, therapeutic ovariectomies or discovered at necropsy. The aim of the study was to review the histopathological aspects of 59 laparoscopic oophorectomies performed in our Department as part of the oncological treatment of premenopausal women with BC. A number of eight (13.55%) patients were histologically confirmed with OM. The initial tumor, node, metastasis (TNM) stage of BC tumors was advanced with no pelvic symptoms or imaging abnormalities associated. Five (62.5%) patients had unilateral ovarian involvement and three (37.5%) bilateral, two of them being associated with primary bilateral BC. The immunohistochemical markers used to confirm the breast origin of metastasis were estrogen receptor (ER), progesterone receptor (PR), gross cystic disease fluid protein 15 (GCDFP15), Wilms' tumor 1 (WT1), cancer antigen-125 (CA-125), cytokeratin 7 (CK7), cytokeratin 20 (CK20). One case showed positive cytoplasmic reaction for thyroid transcription factor-1 (TTF-1). GCDFP15 was positive in all OM and almost all (seven of eight) were noted as non-immunoreactive for WT1. Although six cases of metastatic BC were positive for CK7 and negative for CK20, only four of them retain the same immunoprofile of their primary tumor for the metastatic ovarian lesions. Only one case out of eight showed weak and focal positivity for CA-125. Three cases were positive for mucin 1 (MUC1) and epithelial membrane antigen (EMA). *Conclusions*: The differential diagnosis between OM and primary ovarian cancer can be challenging for the pathologist as well and immunostaining is of help. GCFDP15 is the most specific for breast carcinoma. In contrast with the recent papers published in the literature, we detected TTF-1 cytoplasmic expression in invasive breast carcinoma by SPT24 clone.

Keywords: breast cancer, ovarian metastases, ovariectomy, mastectomy, immunohistochemistry.

Introduction

Ovarian metastases (OM) of breast cancer (BC) can occur with different rates, ranging from 3–30%, being reported after prophylactic, therapeutic ovariectomies or discovered at necropsy [1]. The frequency of BC origin for the metastatic ovarian cancer is higher in Western countries as compared to Asia and Africa population [2].

Ovarian ablation by surgery is an old therapeutic method for BC used for more than 100 years [3–5]. It is still indicated in premenopausal women (which represents about 25% of all BCs), in almost 2/3 of cases because the tumors are expressing hormone receptors [6, 7]. It may be used as adjuvant therapy in patients that are refusing chemo- and hormonotherapy or in addition to those, having a positive effect on disease free and overall survival compared to no adjuvant therapy [8].

Laparoscopic approach has decreased the postoperative morbidity and mortality and speeds postoperative recovery [8].

The purpose of this study was to review the morpho-pathological aspects (gross anatomy, histopathology and immunohistochemistry) encountered in OM in patients with BC that were submitted to laparoscopic surgical ablation of their ovaries as adjuvant treatment. Those data were correlated with clinical aspects and levels of cancer specific markers.

Patients, Materials and Methods

Our study included a group of 59 women between the ages of 28 and 51, hospitalized and diagnosed with BC in the Surgical Clinic of "Colţea" Clinical Hospital, Bucharest, Romania.

Clinical data were extracted from clinical observation files and collected in a database: age at the moment of BC diagnosis, histological type of BC [with tumor, node, metastasis (TNM) staging] and of the OM, uni/bilaterality of the BC and of the OM, time intervals from the BC diagnosis to the detection of the secondary ovarian tumor,

the greatest diameter of the ovarian tumor, the adjuvant therapy, hormone receptors and human epidermal growth factor receptor 2 (HER2)/neu status, preoperative serum cancer antigen-125 (CA-125) concentration, the presence and the location of the synchronous metastases, global survival.

The files from the Department of Pathology regarding the histopathological and the immunohistochemical (IHC) examinations were available both for the primary breast tumor and the OM. The Hematoxylin–Eosin (HE)-stained sections and IHC studies were reviewed by two experienced pathologists.

Results

From January 2010 to January 2014, 59 patients underwent laparoscopic ablation of their ovaries, eight (13.5%) of them had OM confirmed at the histological examination (Table 1).

Clinical data

The age at the time of BC diagnosis ranged from 28 to 51 years (average 42.3 years). In cases with OM, the age ranged between 31 and 49 years (average 38.1 years) at the time of surgical castration. Initial TNM stage of the BC was (according to the 7th edition of *TNM Classification*): stage IIIA – two patients, stage IIIB – one patient, and stage IV – five patients (Table 2). At the moment of oophorectomy, no pelvic symptoms or imaging abnormalities were noted for five of all 59 (8.47%) patients. For the initial BC, six of eight (75%) patients underwent Madden mastectomy, including axillary dissection associated with neo-adjuvant and adjuvant chemotherapy plus Tamoxifen. The other two patients received only oncological treatment including chemotherapy and hormone therapy. Five out of eight patients HER2+ were given Trastuzumab. Almost all patients (five out of six) with Madden mastectomy had positive axillary lymph nodes with a mean value of 5+ nodes of 14 excised. Two of six patients with Madden mastectomy presented perineural invasion at histology, one of them having, in addition, vascular invasion. The histology grade was 1 in two patients, 2 for four patients, and 3 for two patients. Surgical castration was added for all eight cases.

Table 1 – ***OM reported after therapeutic oophorectomies in BC***

Authors	Year	BCs (*n*)	OM (*n*)	Frequency
Curtin *et al.* [9]	1994	20	5	25%
Gagnon & Têtu [10]	1989	64	28	43.75%
Cristian *et al.*	2019	59	8	13.55%

OM: Ovarian metastases; BC: Breast cancer; *n*: No. of cases.

Table 2 – ***Characteristics of the patients with OM***

Case No.	Age at BC diagnosis [years]	Histological type of BC	TNM	BC – uni/ bilaterality	OM – histology and uni/ bilaterality	Time interval BC–OM [months]	ER/PR/Ki67/ HER2/neu expression	CA-125 [U/mL]
1.	31	LIC + DIC	T4dM1* (bone, lung, lumboaortic, liver)	Bilateral	DIC bilateral	9	ER 80%, PR 50%, Ki67 70%, HER2/neu +	↑
2.	42	DIC	T3N2M1 (bone, liver)	Left	DIC left ov.	72	ER 65–70%, PR 80%, Ki67 50%, HER2/neu ++	↓
3.	32	LIC + DIC	T4cN0M0	Left	DIC left ov.	6	ER 55%, PR 60%, Ki67 37%, HER2/neu +	↓
4.	37	DIC	T3N1M0	Right	DIC bilateral	10	ER 50%, PR 45%, Ki67 35%, HER2/neu –	↑
5.	34	LIC	T3N1M0	Left	LIC right	16	ER 40%, PR 35%, Ki67 30%, HER2/neu –	↓
6.	45	LIC	T4dM1* (bone, liver)	Bilateral	LIC bilateral	13	ER 75%, PR 60%, Ki67 55%, HER2/neu +	↑
7.	49	DIC	T4bN3M1 (bone)	Left	DIC left ovary	12	ER 60%, PR 65%, Ki67 65%, HER2/neu +	↓
8.	35	DIC	T3N2M1 (bone)	Left	DIC left ovary	8	ER 65%, PR 65%, Ki67 25%, HER2/neu –	↓

OM: Ovarian metastases; BC: Breast cancer; LIC: Lobular invasive carcinoma; DIC: Ductal invasive carcinoma; TNM: Tumor, node, metastasis; ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2; CA-125: Cancer antigen-125; *Patient not surgically treated.

The ovaries were macroscopically quasinormal in all cases (Figure 1). The mean size value of the ovaries was 3/1.5/1.2 cm. The greatest diameter of tumors was between 1 mm and 8 mm. Multifocality was a pattern met in three of eight (37.5%) cases with OM. All the metastases were solid. Histological types were ductal invasive carcinoma (DIC) in four (50%) patients, lobular invasive carcinoma (LIC) in two (25%) patients and both DIC plus LIC in two (25%) cases (Figures 2–5). For both these latter two cases, the predominant pattern was LIC. Five (62.5%) patients had unilateral ovarian involvement and three (37.5%) had bilateral tumor, two of the latter being associated with primary bilateral BC. Two patients of these eight with OM had a bilateral synchronous BC (Figure 6), the histology for these last two cases being a lobular and a mixed lobular carcinoma plus DIC.

The basic antibody panel of metastatic work-up for identification of BC origin included estrogen receptor (ER),

progesterone receptor (PR), gross cystic disease fluid protein 15 (GCDFP15), Wilms' tumor 1 (WT1), CA-125, cytokeratin 7 (CK7), cytokeratin 20 (CK20). ER and PR status studied on the core-biopsy specimen of the breast was positive for all cases and HER2/neu expression was detected in five out of eight tested cases (Figures 7 and 8). The immunoprofile noted in primary BC for these markers was similar in the metastatic lesion of the ovaries. In addition, GCDFP15 was positive in all OM and almost all (seven of eight) were noted as non-immunoreactive for WT1 (Figure 9). Although six cases of metastatic BC were positive for CK7 and negative for CK20, only four of them retain the same immunoprofile of their primary tumor for the metastatic ovarian lesions (Figure 10). Only one case out of eight showed weak and focal positivity for CA-125 (Figure 11). Three cases were positive for mucin 1 (MUC1) and epithelial membrane antigen (EMA) (Figures 12 and 13). One case showed positive cytoplasmic reaction for thyroid transcription factor-1 (TTF-1) (SPT24 clone, Novocastra/Leica) (Figure 14).

The average time between primary BC diagnosis and the time of the laparoscopic oophorectomy (which represents the time of detection of the OM) was 18.25 months (range 8–72 months). When laparoscopic oophorectomy was performed, five out of eight (62.5%) patients had other metastatic sites identified and three patients had metastatic tumors clinically and imagistically limited to the ovaries. Liver and bone were the most frequent associated metastatic sites. Hormone receptor status in OM was positive for all cases. The survival after the OM findings was 100%, our period of study being relatively short (four years). Therefore, the follow-up for these patients ranged from six to 48 months.

No relationship was found between the size of the ovaries/metastases and clinically parameters or survival. Preoperative CA-125 serum level concentrations were measured in all patients. Three of eight (37.5%) cases had elevated serum CA-125 concentrations (≥35 U/mL) with a mean value of 53.9 U/mL.

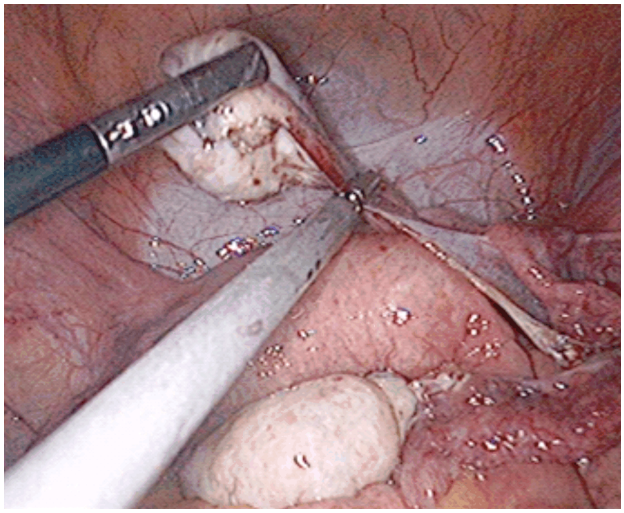

Figure 1 – ***Laparoscopic view: normal appearance of the ovaries in a patient with microscopic OM from BC. OM: Ovarian metastasis; BC: Breast cancer.***

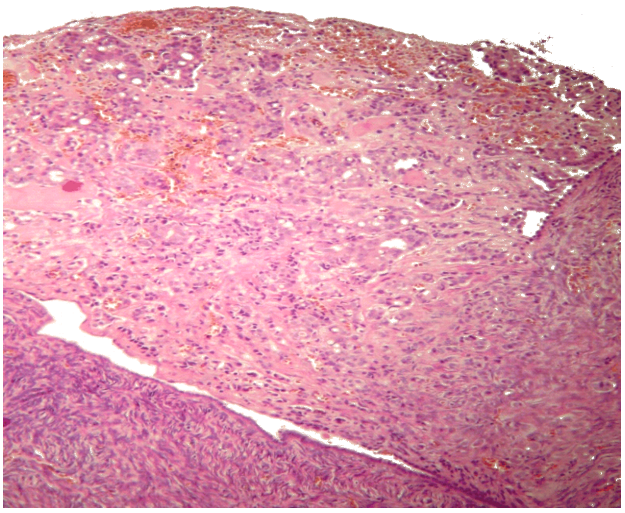

Figure 2 – ***Metastasis of a breast DIC involving the capsule of the ovary (HE staining, ×100). DIC: Ductal invasive carcinoma; HE: Hematoxylin–Eosin.***

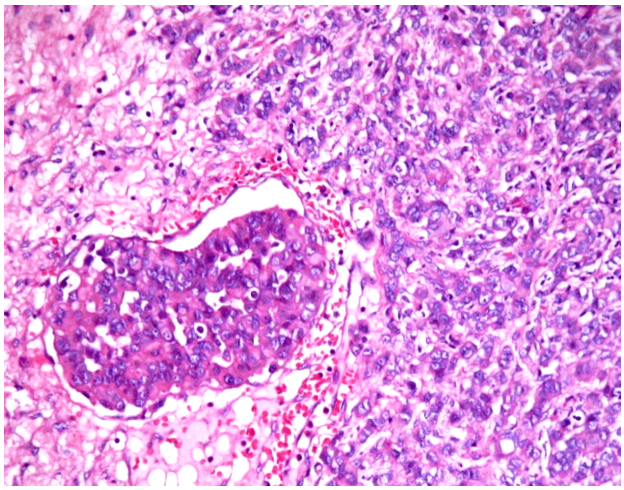

Figure 3 – ***OM of an invasive BC with tumor embolus (HE staining, ×200). OM: Ovarian metastasis; BC: Breast cancer; HE: Hematoxylin–Eosin.***

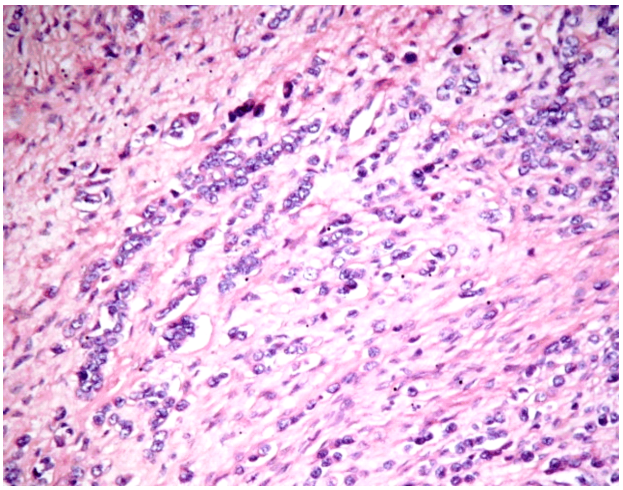

Figure 4 – ***Metastatic breast LIC to the ovary (HE staining, ×200). LIC: Lobular invasive carcinoma; HE: Hematoxylin–Eosin.***

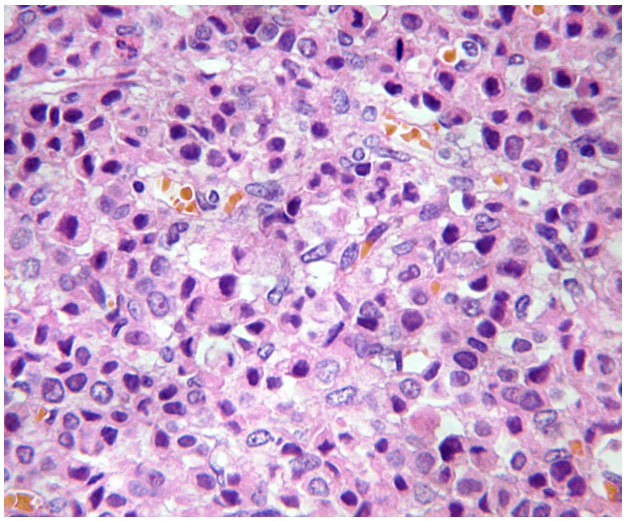

Figure 5 – ***Metastasis of a lobular DIC to the ovary (HE staining, ×400). DIC: Ductal invasive carcinoma; HE: Hematoxylin–Eosin.***

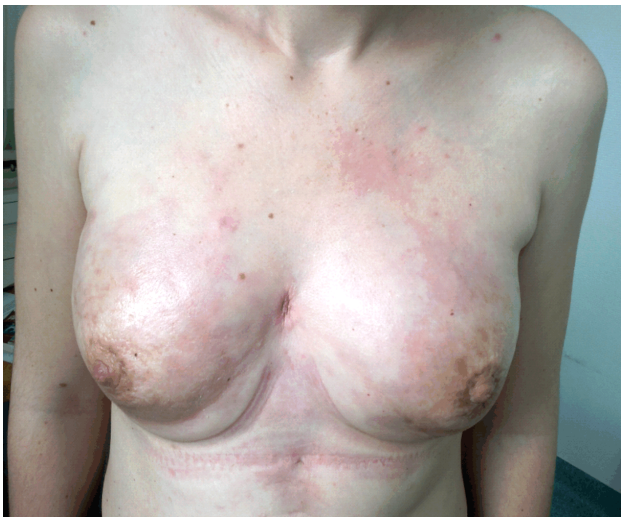

Figure 6 – ***Bilateral BC before laparoscopic oophorectomy in a 32-year-old female (bilateral OM at histology). BC: Breast cancer; OM: Ovarian metastasis.***

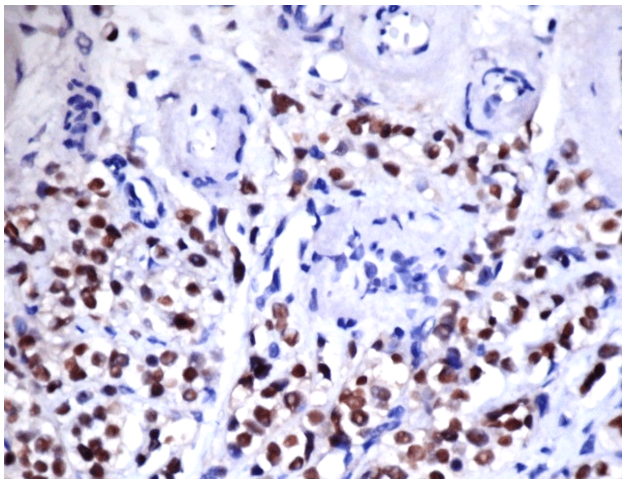

Figure 7 – ***Immunochemistry: OM of invasive BC with positive cytoplasmic reaction for ER (Anti-ER antibody immunomarking, ×200). OM: Ovarian metastasis; BC: Breast cancer; ER: Estrogen receptor.***

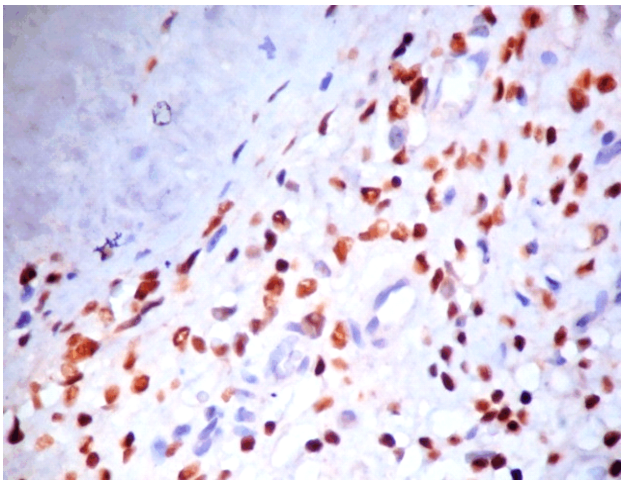

Figure 8 – ***Immunochemistry: OM of invasive BC with positive cytoplasmic reaction for PR (Anti-PR antibody immunomarking, ×200). OM: Ovarian metastasis; BC: Breast cancer; PR: Progesterone receptor.***

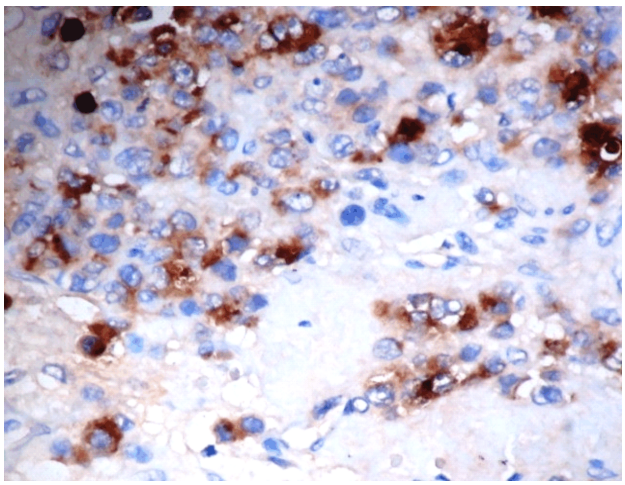

Figure 9 – ***Immunochemistry: positive cytoplasmic reaction for GCDFP15 (Anti-GCDFP15 antibody immunomarking, ×200). GCDFP15: Gross cystic disease fluid protein 15.***

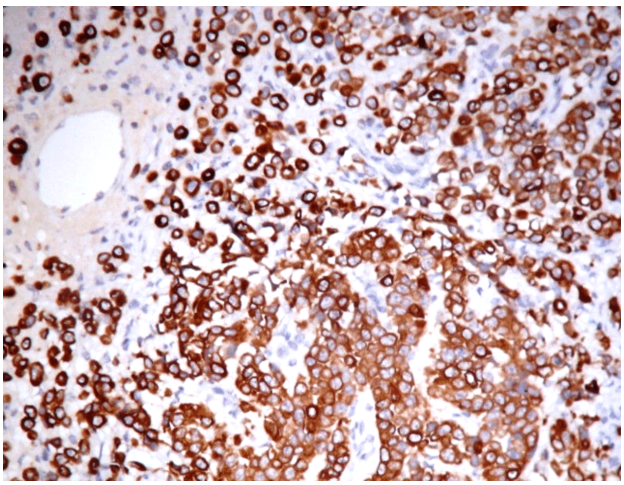

Figure 10 – ***Immunochemistry: OM of invasive BC with positive cytoplasmic reaction for CK7 (Anti-CK7 antibody immunomarking, ×200). OM: Ovarian metastasis; BC: Breast cancer; CK7: Cytokeratin 7.***

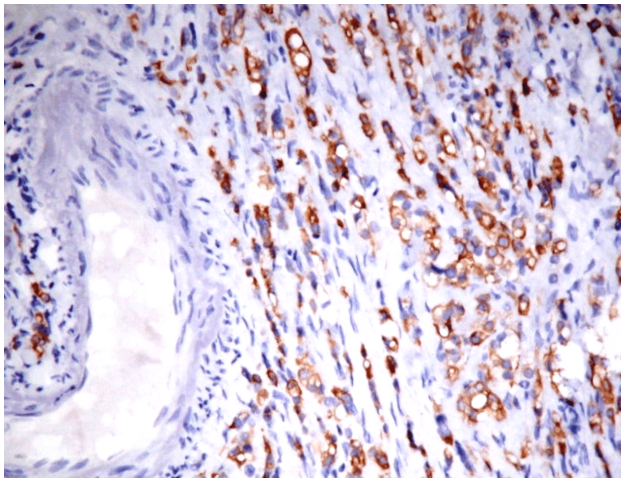

Figure 11 – ***Immunochemistry: OM of invasive BC with positive cytoplasmic reaction for CA-125 (Anti-CA-125 antibody immunomarking, ×100). OM: Ovarian metastasis; BC: Breast cancer; CA-125: Cancer antigen-125.***

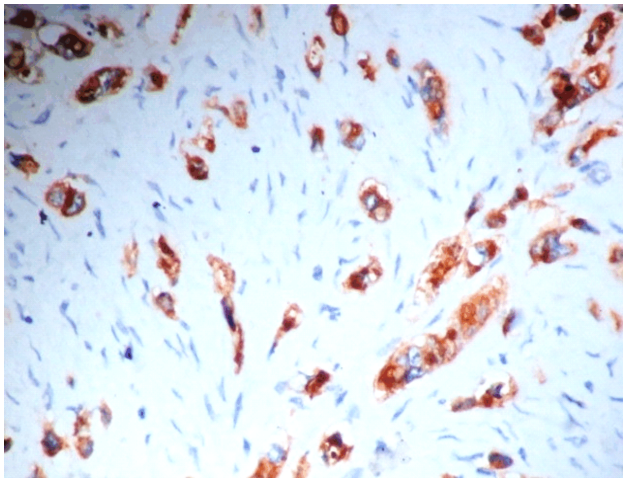

Figure 12 – ***Immunochemistry: OM of invasive BC with positive cytoplasmic reaction for MUC1 (Anti-MUC1 antibody immunomarking, ×200). OM: Ovarian metastasis; BC: Breast cancer; MUC1: Mucin 1.***

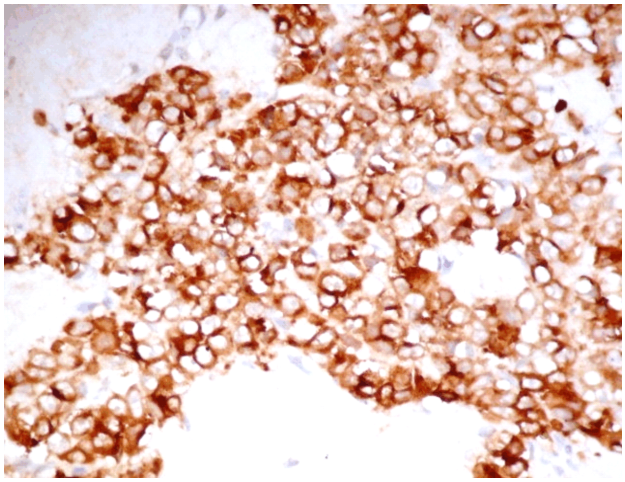

Figure 13 – ***Immunochemistry: OM of invasive BC with positive membranar reaction for EMA (Anti-EMA antibody immunomarking, ×200). OM: Ovarian metastasis; BC: Breast cancer; EMA: Epithelial membrane antigen.***

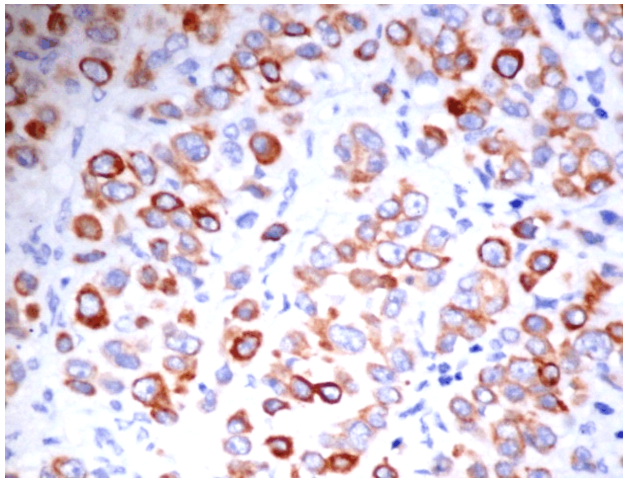

Figure 14 – ***Immunochemistry: OM of invasive BC with positive cytoplasmic reaction for TTF-1 (SPT24 clone) (Anti-TTF-1 antibody immunomarking, ×400). OM: Ovarian metastasis; BC: Breast cancer; TTF-1: Thyroid transcription factor-1.***

Discussions

As compared to the other secondary lesions discovered at autopsies or as an incidental finding in routine surgery, our study data concerns the OM were diagnosed after therapeutic oophorectomies, in premenopausal young women and as a manifestation of a late stage disease [9–11]. In our series, the median age was 38.1 years, in opposition with the median age of diagnosis reported in the literature (which ranges between 48.6 and 52.8 years) [11]. In other studies, the mean time-interval from the BC diagnosis to the detection of the secondary ovarian tumor was 11.5 to 104 months [11], compared to ours, in which the mean value was 18.25 months. In one particular case, this period was increased because of a good clinical response to Tamoxifen plus chemotherapy for a long period of time and therefore the oophorectomy was performed at 72 months. Longer time-intervals are associated with better survival rates, probably due to less aggressive tumor biology [12]. Because of the limited number of studies on this issue, the prognostic factors for the patients with OM after BC are not known [11].

The predilection of BC for developing OM is probably related to a favorable local hormonal environment in young patients with BC [13, 14]. Occurrence during the course of a breast primary carcinoma represents a negative prognostic factor for the patient, the five-year survival rate being less than 10% and the mean survival rate ranges from 16 to 50 months [11, 15, 16]. At the moment of the OM diagnosis, the disease has usually a polymetastatic progression, therefore this could be an explanation of the poor prognosis [17]. Even if at the moment of oophorectomy there are no metastases outside the pelvis, in the following year the risk of development of an extrapelvic secondary lesion is 65% [1]. Otherwise, the initial stage and the histology of the BC have no impact on the survival rate after the discovery of a metastasis [11, 17]. However, primary BC was in an advanced stage for all the patients of our study (at least pT3N1). For the initial BC, vascular invasion is considered as an independent poor prognostic

factor, especially when combined with positive axillary lymph nodes, and has a major role in the dissemination of malignant cells outside the primary tumor site, including even the ovaries [18].

Microscopically, almost all metastases resemble infiltrating ductal or lobular carcinoma and are easily recognized as metastatic from the breast. In our series, the proportion of lobular pattern, single (25%) or in association with the ductal one (25%), was lower than in the series of Bigorie *et al.* (43%) and similar to the series of Eitan *et al.* (22%). The rate of lobular carcinoma metastases to the ovary is higher than ductal carcinoma but as ductal cancer is significantly more frequent in population, the most part of the diagnostic challenges are posed by lesions with a ductal pattern [11, 19]. In the case of an equal number of forms, the probability of development of a second lesion in ovary is three out of five times higher in lobular carcinomas, as compared to ductal carcinomas [19]. The preference of lobular carcinoma to metastasize in the endocrine organs, including ovary, is well known suggesting the hormone regulation for this process [11].

The secondary ovarian lesions are usually small and bilateral, having a solid non-cystic pattern in small-sized ovaries [11, 12]. Bilaterality was met in 37.5% of cases in our series, a significantly lower percentage than other studies, which also consider it to be indicative of metastatic ovarian tumors [18, 12]. The bilateral involvement of the ovaries may also be proof of an aggressive extension of the disease, which is related to a bad prognosis. This is also the best-known feature of ovarian tumors that should increase the suspicion for a metastasis rather than a primary ovarian cancer [11, 17, 19].

The frequency of the microscopic BC metastases in ovaries is about 24–31% [11]. In these cases, the metastases are asymptomatic and incidentally discovered as we've seen in our material as well. Evaluation of the tumors' size in the primary *versus* metastatic distinction concluded that larger tumors are much more likely to be primary [20]. The absence of specific symptoms associated with a high rate of OM in premenopausal women, with BC in different series flagged the issue of the screening of the OM as early as possible [18, 21]. Gastrointestinal symptoms, visualization of solid tumors at ultrasonography or the use of ^{18}F-fluorodeoxyglucose–positron emission tomography (^{18}F-FDG/PET) may sometimes lead to the diagnoses of OM in BC [18]. Elevation of CA-125 in BC is not specific for the positive diagnosis of OM in BC but may conduct to imagistic study of the ovaries in order to identify any abnormalities [11].

In approximately 50% of cases, the macroscopic features of the ovaries are normal, as we encountered in our series as well [10, 11]. Polypoid or papillary formations are rarely met [19]. In about one third of cases, gross findings may also include surface nodularity or several nodules on sectioning [19, 22].

The cellular pattern of the OM is related to the cellular type of the primary tumor. Therefore, the lobular carcinoma infiltrates the ovarian stroma in a diffused manner; otherwise, the usually ductal cancer variants are characterized by a cribriform pattern, nests or small clusters [11, 19, 22]. In addition, nests observed in lobular carcinoma contain uniform cells and can mimic other tumors with an insular pattern [19]. Thin cords aspect is more specific and more suggestive for the metastatic breast origin in cases of lobular as compared to ductal cancer [15]. Admixtures of the patterns and undifferentiated tumors may be seen thus resulting in a real challenge among diagnosis of an ovarian secondary lesion with breast pattern [10, 11, 19, 22].

In order to increase the sensitivity and specificity of the breast metastasis diagnosis, specific IHC markers were studied. GCDFP15 is positive in 52–77% of BC and in 43–71% of OM from BC and usually negative in the cases spread from gastrointestinal cancers or melanoma or in primary ovarian cancer [11, 15, 19, 23]. Only isolated cases of primary ovarian cancer with positive GCDFP15 have been reported, however this marker is used as part of an antibody panel for the discrimination between metastatic breast and ovarian cancer [15, 19]. In BC patients, it is sometimes difficult to differentiate OM from primary ovarian cancer; therefore, a combination of IHC stainings was evaluated in order to facilitate the differential diagnosis. Sometimes, both tumors can have a similar and nonspecific histology and a battery of immunostainings consisting of WT1, CA-125 and GCDFP15 may be helpful [15]. Metastatic BC is usually CK7 positive and CK20 negative, and it may show nuclear staining for ER and PR [15, 16, 19, 23]. The positivity of ER and PR in both OM and primary ovarian cancer make them unusable in the differential diagnosis but, on the other hand, may suggest an important role of hormone regulation in the development of the OM in young premenopausal women [15, 16, 18, 24].

Positive WT1 and CA-125 expression with loss of GCDFP15 represents the most predictive combination for primary ovarian cancer, especially in women with BReast CAncer (*BRCA*) gene mutations. Lack of WT1 and CA-125 expression and expression of GCDFP15 are considered to be the most specific combination for metastatic breast carcinoma to the ovary [15, 16, 19]. The primary ovarian cancer is more frequently positive for CA-125 (92%) than the metastatic lesion of the BC to the ovary [19].

Almost all ovarian carcinomas, primary breast carcinomas and metastatic breast carcinomas to ovary are positive for MUC1. In opposition, MUC2 is sometimes positive for these tumors, with a frequency that ranges from 8% to 30% [15, 16]. However, both MUC1 and MUC2 immunomarkers are not useful for the differential diagnosis of these tumors. The carcinoembryonic antigen (CEA) glycoprotein has also a variable positivity among the studied tumors, therefore its diagnostic significance is low [15]. Metastatic BC is generally negative for ovarian carcinoma-125 (OC-125) and paired-box gene 8 (PAX8) [15–17].

Due to the prolonged Tamoxifen treatment, ovarian benign cysts formation may occur by a direct action on the ovaries with subsequent stimulation of the excessive growth of ovarian follicles. Torsion or necrosis of these cystic lesions may pose a diagnostic dilemma in patients at risk of OM from BC or of primary ovarian cancer [25]. It is still controversial whether Tamoxifen increases the risk of developing ovarian primary cancer or ovarian secondary lesions with breast origin [25]. Otherwise,

during the course of a BC the frequency of the development of a primary ovarian cancer is significantly higher than the rate of the OM [11, 19].

Recent experimental studies have found breast tumor cells have cancer stem cell properties resembling a progenitor cell and being involved in the development of the secondary lesions at distance [26]. *HER2* regulates these stem cells and therefore increases the proliferation, mitosis and survival of the primary tumor. *HER2* gene encodes the receptor tyrosine kinase HER2 and is often overexpressed in BC. HER2 also stimulates the motility of cells, decreases the apoptosis process and modulates the adhesion of these distantly migrated cells, and therefore its role in the tumor progression and evolution of the metastasis is important [26]. Current research programs are focused on identification and characterization of this stem/progenitor cell-like, and on the possibility of therapeutically targeting its functions in order to prevent HER2+ BC progression [11, 26].

TTF-1 is a nuclear transcription factor, which is considered a reliable marker for lung or thyroid adenocarcinoma [27, 28]. Its expression has been also reported in gastric, colon, ovarian, endometrial, endocervical or renal small cells carcinomas. In opposition to lung cancer, BC usually shows positivity for ER and no immunostaining for TTF-1 and napsin A (Nap-A), thus resulting in a useful panel of markers for differentiating BC from lung cancer [29, 30]. Otherwise, TTF-1 may be positive in approximately 3% of primary BC, being associated with negative prognostic factors [29]. TTF-1 expression in non-small cell breast carcinoma has been detected with 8G7G3/1 and SPT24 clones [27, 28, 31]. Nuclear staining pattern for TTF-1 detected by 8G7G3/1 clone is common for BC. In opposition, some authors detected TTF-1 nuclear expression in invasive breast carcinoma by SPT24 clone [28, 31]. Recently, cytoplasmic expression of TTF-1 was identified in invasive breast carcinoma and this was made by 8G7G3/1 clone and not by SPT24 clone [27]. The latest paper on the issue concluded that a positive TTF-1 immunostaining does not prove that a metastasis located in a non-pulmonary site, as the ovary, has a lung or thyroid origin. Cytoplasmic reaction for TTF-1 in OM from BC represents a very rare, if not exceptional, situation. In the present series, TTF-1 expression was identified by SPT24 clone, in a case with a primary invasive BC. Cytoplasmic reaction for TTF-1 in non-pulmonary sites has usually been reported in some studies with 8G7G3/1 clone but not with SPT24 clone, as we encountered in our series [27]. Cytoplasmic reaction in BC was associated with a high TNM stage and a worse outcome and further investigations are needed to establish if TTF-1 expression in OM from BC plays a role in tumor aggressiveness [27].

Conclusions

Although micrometastases in the ovaries originating from BC have already been reported, additional descriptive data on this issue is needed for a better understanding of histological and clinical features of these tumors. No prospective studies on this topic have been published yet even in the recent literature. Frequently, OM are asymptomatic and the gross features of ovaries are non-specific therefore the OM are identified only microscopically on HE-stained sections after surgical ablation. In addition, the oncologist is not generally focused on the pelvic region during follow-up, therefore malignant foci cells in the ovaries may be discovered at the time of laparoscopic oophorectomy. During the evolution of an advanced BC, the differential diagnosis between OM and primary ovarian cancer can be challenging for the pathologist as well and a specific battery of immunostainings has come along to aid in this problem. Apart from these markers, GCFDP15 is the most specific for breast carcinoma. In contrast with the recent papers published in the literature, we detected TTF-1 cytoplasmic expression in invasive breast carcinoma by SPT24 clone.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contribution

Daniel Alin Cristian, Florin Andrei Grama and Gabriel Becheanu had equal contribution to the paper.

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