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A Surprising Diagnosis in a Breast Lump: The First Case Report of Uterine Carcinosarcoma Presenting as Breast – Only Metastasis

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ABSTRACT

Extra-mammary breast malignancies are rarely the source of a metastatic breast mass. Uterine carcinosarcoma (UCS) is a rare disease with aggressive features and poor survival due to late presentation and advanced stage at diagnosis. Peritoneal seeding and cancer dissemination are not uncommon, but metastasis to the breast is extremely rare. Here we report a case of metastatic carcinosarcoma of uterus with unusual presentation as a breast lump without gynecological symptoms. Tissue biopsy and immunostaining confirmed the diagnosis. Few cases have been reported in the literature, mainly of serous type with the development of metastatic disease at multiple sites. To date, this is the only reported case of uterine carcinosarcoma metastasizing to the breast only, without intrabdominal dissemination, peritoneal carcinomatosis or another distant metastasis. We discuss presentation, diagnosis, methods of differentiation, and the up-to date treatment recommendations.

Keywords

Breast malignancies, Carcinoma, Malignant tumors, Endometrial cancer.

Introduction

Primary mammary carcinoma is the most common malignancy of the breast, accounting for at least 98% of all breast malignancies. In very rare cases, accounting for 0.3-2 % only, a breast lump can be a secondary malignancy, metastatic from extra-mammary malignant tumors [1-3]. To date, less than 500 cases of extra-mammary cancer were reported to have a secondary involvement of the breast [2,4]. Most of those breast metastases are originating from melanoma and lung cancer [4,5], other primaries include gastrointestinal tract, thyroid, kidney, sarcomas of different origins, and endometrial malignancies [6,7].

Endometrial cancer is the most common gynecologic cancer, affecting 417,367 women worldwide and causing 97,370 deaths in 2020 as per Global cancer statistics [8]. Most of endometrial cancer are of endometrioid type that occur at an early stage with favorable prognosis. Carcinosarcoma is a rare entity with aggressive features causing majority of cancer related deaths along with serous and clear cell histology. Non-endometrioid type endometrial cancer tend to occur at an advanced stage with tumor dissemination in over half of cases. Unfortunately, recurrence is very high even with aggressive surgery and adjuvant chemotherapy. Recurrences are usually local at vault but in serous histology relapse most often occur at peritoneum and intrabdominal cavity [3,9]. Pattern of spread of endometrial cancer is usually through direct extension and lymphatic channels. Hematogenous spread is rare and mainly to lung, bone, liver, and brain. Metastasis to breast is extremely rare especially in the absence of widely metastatic disease with few cases reported at literature [10]. Uterine carcinosarcoma (UCS) is a rare and invasive un-differentiated neoplasm that constitutes both an epithelial and a stromal component (sarcoma) arising from a single malignant epithelial clone. it represents less

than 5% of all uterine tumors but accounts for 15% of all deaths caused by uterine malignancy [11]. the prognosis of UCS is often very poor, with 30–40% of cases having extrauterine involvement at the time of presentation, include regional lymph nodes, ovaries, fallopian tubes, and omentum, and over 10% of patients already developed distant metastasis [12]. To our knowledge this is the first case of carcinosarcoma of uterus presenting as a breast lump to be reported in history. The management approach for UCS is mostly similar to the invasive endometrial carcinoma; surgery, adjuvant chemotherapy, and radiotherapy. Due to late presentation, rapid spread, high recurrence rate, and poor prognosis of the UCS, there is a need for clinical trials on the early detection of the disease, as well as targeted therapy on immunohistochemical markers.

Case Report

Presentation: A 61 years old lady with good performance status and chronic history of medication- controlled hypertension, she was referred by her primary care physician with a biopsy proven triple negative invasive mammary carcinoma of the right breast. The patient initially presented with right breast painful mass of three-months duration. She denied any previous history of breast lumps, skin discoloration or nipple discharge. She denied history of weight loss or loss pf appetite. She is menopausal for 3 years with no history of postmenopausal bleeding. She reported menstrual irregularities at the past, that was not investigated. She denied any history of hormonal treatment or exposure to radiation, but reported family history of uterine cancer at her mother and breast cancer at her sister.

On examination her ECOG was 0, BMI 25. Head and neck examination were negative. Breast examination was intact with no palpable masses and no axillary or supraclavicular lymphadenopathy. Abdominal, groin and pelvic examination all were unremarkable.

Repeated breast mammogram and ultrasound at our hospital revealed a 1.3 x 0.7 cm round, circumscribed hypoechoic homogenous mass, with well-defined border and no calcifications at 5 o'clock position of the right breast. No suspicious axillary lymph nodes could be detected (Figure 1). A repeated ultrasound guided Tru-cut biopsy revealed the presence of malignant epithelial cells consist with high grade carcinoma with scattered lymphoid aggregates and No background breast tissue is seen in the material. The distribution of the lymphatic aggregates suggests the possibility of sampled intramammary lymph node. Immunobistocbemical stains performed show that the tumor cells were positive for PAX8, while negative for ER, PR, HER2, GATA-3, mammoglobin and GCDFP15, in keeping with metastatic poorly differentiated extra-mammary carcinoma (Figure 2).

In search for the primary extra-mammary malignancy, a PET/CT 18F-FDG whole body scan was done and revealed a single right breast FDG avid lesion corresponding to known metastatic lesion along with Intense bulky uterus and bilateral adnexal lesions worrisome for malignancy. A Pelvic MRI showed an enlarged uterus, measuring 10.1x7.5x7.8cm, full of multiple subserosal, submucosal and intramural fibroids along with thickened endometrium and bilateral enlarged ovaries with complex masses (Figure 3).

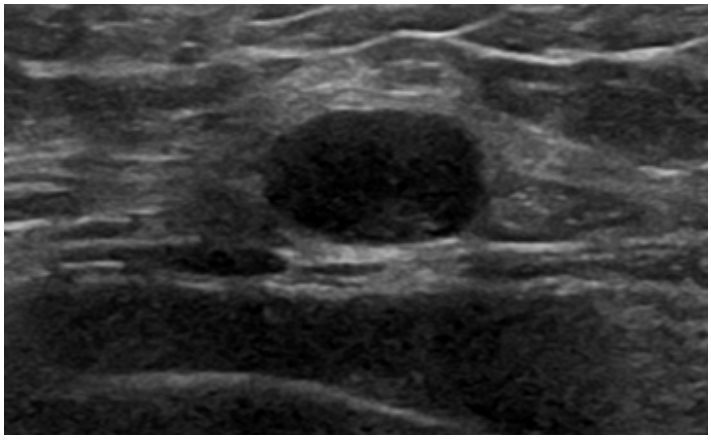

Figure 1: Targeted right breast ultrasound demonstrating a 1.3 x 0.7 cm well circumscribed hypoechoic homogenous mass at 5 o'clock of the right breast.

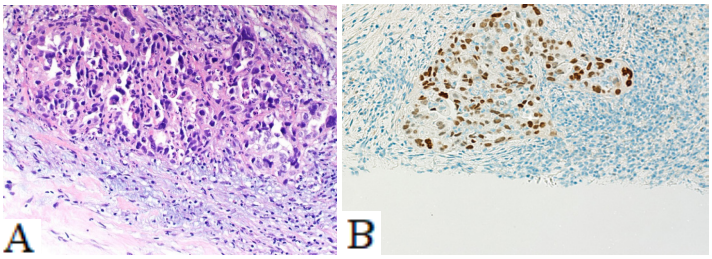

Figure 2: Histology images of the tru-cut biopsy of right breast mass: (A) Hematoxylin and eosin (H&E) stain of demonstrate foci of malignant epithelial structures, marked cytologic atypia and xanthopanulomatous reaction and scattered lymphatic aggregates. (B) Immunobistocbemical stains show tumor cells positive for PAX8, while negative for ER, PR, HER2, GATA-3, mammoglobin and GCDFP15 markers.

Management

The final provisional diagnosis of metastatic carcinoma to breast from gynecological origin seemed more likely. The patient was referred to Gynecology oncology clinic, and was discussed in both, the Breast and the gynecology oncology multidisciplinary tumor boards (MDT). The board decision was to perform the least invasive surgical procedures to establish the accurate diagnosis. Accordingly, the patient underwent an ultrasound guided excision of the right breast metastatic intramammary lymph node (Figure 4), and diagnostic laparoscopy with examination under anesthesia and endometrial biopsies. Intraoperative findings were suggestive of bulky uterus of 22-week size with bilateral ovarian masses and no peritoneal carcinomatosis or upper abdomen disease. Intraperitoneal survey was negative for carcinomatosis or extra-uterine spread other than bilateral ovarian masses.

Pathology report of breast confirmed the presence of metastatic serous carcinoma of the endometrium, and endometrial biopsy confirmed the presence of carcinosarcoma with IHC as follow:

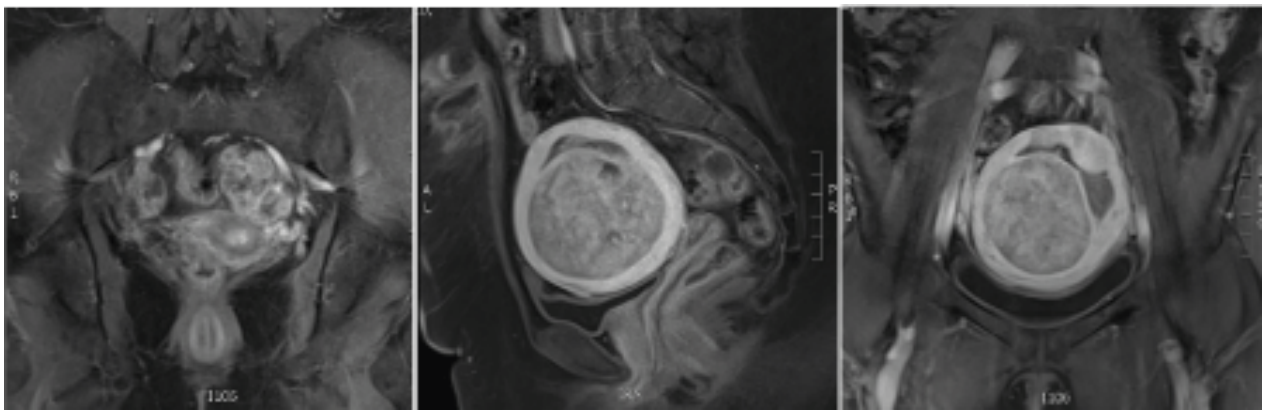

Figure 3: Sagittal (Right) and axial (middle) and coronal (left) MRI images of the abdomen and pelvis demonstrate a markedly enlarged and heterogeneous uterus with a complex bilateral adnexal mass.

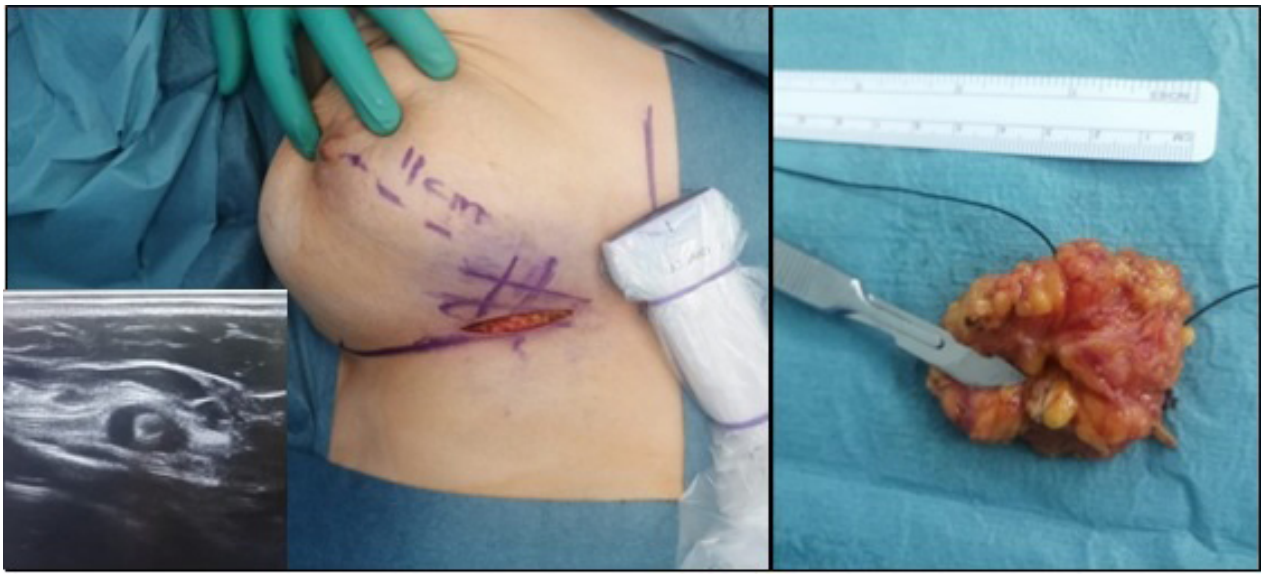

Figure 4: Ultrasound- guided wide local excision of right breast lesion (Left), lesion shows at the tip of the blade with surrounding surgical margins (right).

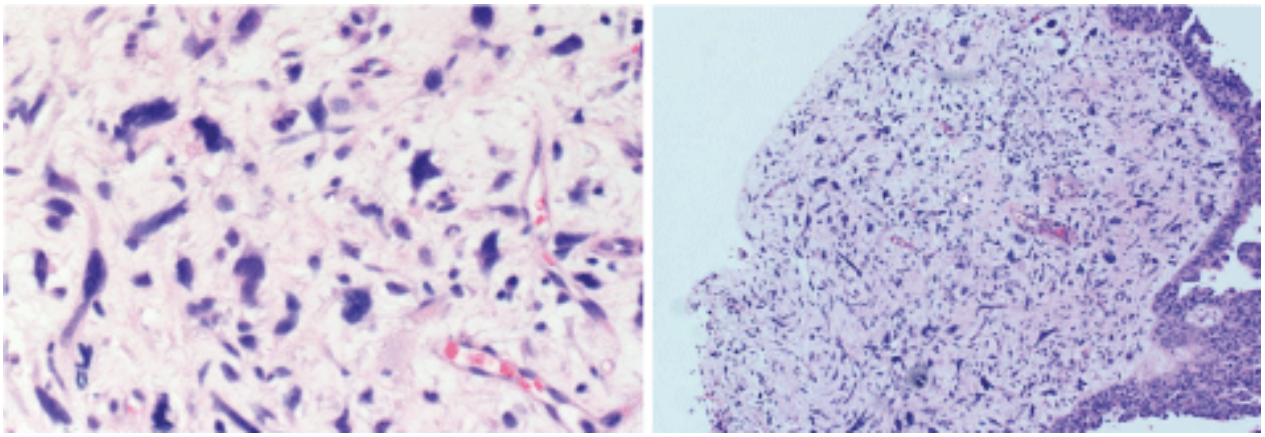

Figure 5: (H&E) stain from endometrial curettage demonstrates the carcinosarcoma with spindle cell component and large volume area of pleomorphic neoplastic cells and necrosis.

P53 and CK7 diffusely positive, WT1 weakly and patchy positive (Figure 5).

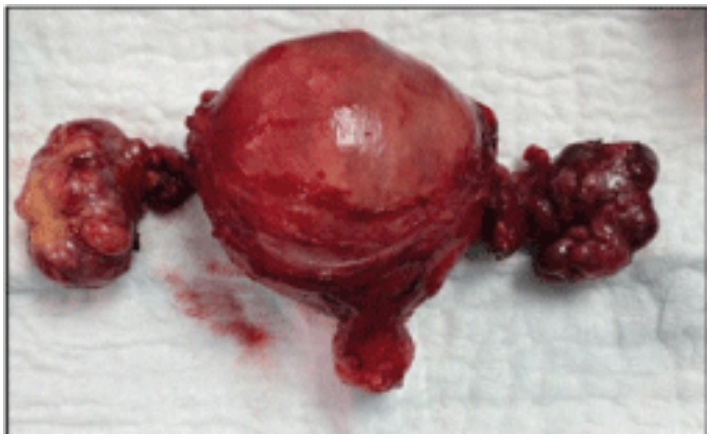

Figure 6: The specimen showing bulky uterus with multiple bilateral mixed solid and cystic ovarian masses.

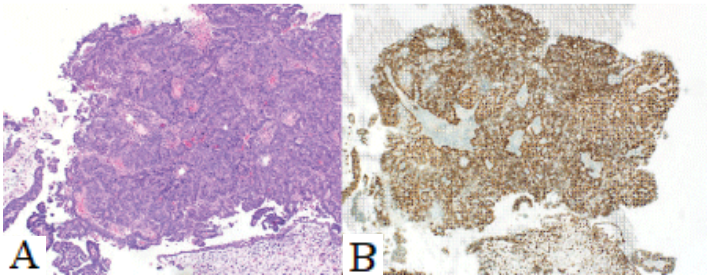

Figure 7: (A) section showed carcinosarcoma, the malignant epithelial component (carcinoma) is 90% of serous type consist of variable sizes of solid nests, tubeculae and tubule-papillary structure. (B): Immunohistochemical stains: positive for p53 and panCK in the carcinoma while Vimentin is positive in the sarcomatous component.

Based on these findings, the decision was made for upfront primary cytoreductive surgery where she underwent total abdominal hysterectomy bilateral salpingoopherectomy, infracolic omentectomy and resection of peri-umbilical nodule and right iliac node, complete debulking surgery with no macroscopic disease at the end of surgery. Intraoperative findings showed bulky uterus with bilateral solid cystic ovarian masses (Figure 6), bulky right external iliac node, nodular omentum and no carcinomatosis with clear upper abdomen and peritoneal surfaces. final pathology report revealed a uterine carcinosarcoma, tumor size 7.3 cm, 70% myometrial invasion, with serosal deposits, negative LVSI and nodes, positive peri-umbilical nodule, positive omentum, both tubes and ovaries all positive for carcinosarcoma of the uterus with positive peritoneal cytology. IHC as follow: P53 Mutant, P16 Diffusely positive, PR positive, Ki67 expressed, Her2 negative, ER, Napsin A and WT1 Negative. The assigned FIGO stage was stage 4B Carcinosarcoma of uterus (Figure 7).

Follow up course: Patient recovered very well after her surgery, she received 6 cycles of adjuvant chemotherapy (carboplatin and paclitaxel). However, she relapsed 6 months later at her vaginal vault, abdominal cavity and pelvic peritoneum. Relapse was confirmed by CT Chest, abdomen, and pelvis. The case was discussed at the MTD meeting and the options were given to the patient of secondary cytoreductive surgery versus second line chemotherapy, she opted for chemotherapy

Discussion

Metastasis to breast from Mullerian origin is extremely rare especially from uterine cancer. It is a rare event with incidence of 0.2-1.3% [12]. Usually, it is associated with widespread disease that has a dismal prognosis with an average survival of 16 months. The incidence of breast metastasis from ovary is 0.03-0.6 % and from uterus is much lower. Histology is always serous and left upper outer quadrant of breast is usually the most common site due to its higher vascularity, indicating that the underlying route of dissemination is via blood stream as speculated by some authors [13]. On the contrary to this, our patient developed the metastasis in the lower inner quadrant which is the least vascularized part of the breast indicating that the route of metastasis was not hematogenous in this case. The Hematogenous metastases has tendency to be multiple and results in bilateral lesions that colonized around the main breast blood supply. On the other hand, most of the lymphatic metastases will present as solitary round lesions with rapid growth that is well-circumscribed with clearly defined borders in radiological images along with diffuse skin and trabecular thickening because of obstruction of draining lymphatics [14].

The lymphatic spread of Mullerian malignancies is usually to the regional lymph nodes surrounding the organ of origin. Lymphatic metastasis from ovarian cancer is very commonly to involve the abdominal (47%), para-aortic (38%), mediastinal (29%), and pelvic (17%) lymph nodes [15,16]. There are reports of certain malignancies that present with metastasis to lymph nodes located away from the original tumor. Those may present with the Troisier sign which is the finding of an enlarged left supraclavicular lymph node, or what is called “Virchow's node”. This finding was first described in 1848 by German pathologist Rudolf Virchow as a sign of metastatic cancer mainly from gastric origin [17]. In 1889, French pathologist Charles-Emile Troisier reported this enlarged left supraclavicular lymph node linked to metastatic spread of other malignancies including GI, kidneys, testes, and ovaries [18]. Virchow's node is the thoracic duct end node. It receives afferent lymphatic drainage from the left head, neck, chest, abdomen, pelvis, and bilateral lower extremities, which eventually drains into the jugulo-subclavian venous junction via the thoracic duct [19]. Which explains the Troisier sign. However, we found no reports in the literature of secondary malignancy metastasizing to an intramammary lymph node, as seen in our patient.

Most of the reported cases in the literature are patients who developed asymptomatic metastatic lesion within the breast, growing slightly and discovered during the metastatic work up (CT scan or PET CT scan) of an already known primary extra-mammary tumor [2]. However, in our case, the metastatic breast

lump was the first presenting symptom and sign of the hidden mysterious extra-mammary primary, which is here, of mullerian origin.

The early differentiation between a primary breast lesion and a metastatic lesion from an extra-mammary origin is very crucial in the management. Images can guide the diagnosis. Primary breast tumors present as a hypoechoic mass with calcifications and speculated margins or as a diffuse lesion with significant surrounding desmoplastic reaction. Conversely, metastatic lesions tend to be well-circumscribed with clearly defined borders and lack surrounding inflammatory changes and may often mimic benign breast lesions. Interestingly, calcifications have rarely been reported in breast metastases, apart from High grade serous ovarian cancer (HGSOC) [20].

Primary breast cancer immunostaining includes Ki-67, estrogen and progesterone receptor status, HER-2/neu oncoprotein, GATA 3, gross cystic fluid protein 15 and mammaglobin [21-23]. High-grade serous tumors of the gynecologic tract most commonly display a pattern of positivity for PAX-8, p53, p16, CK7, WT-1 and variable estrogen receptor and Ki-67 expression [22,24]. Our patient was initially misdiagnosed with a primary breast cancer due to the presence of the lesion inside the breast. The phenotype of the tumor was determined to be triple negative after staining negative for ER, PR and Her2 neu receptors, due to the fact that it was not from breast origin. Accurate histopathological and IHC interpretation was the key to discover the correct diagnosis.

Throughout literature we found that the overall incidence of primary gynecologic tumor metastasis to the breast was only 0.17% of all breast metastasis, most of these cases were related to primary ovarian carcinoma, more specific to serous ovarian carcinoma in few BRCA mutant patients [25].

Ten cases of uterine cancer metastasizing to breast only have been reported in the literature including five leiomyosarcomas, three endometrioid, one endometrial stromal sarcoma and one undifferentiated carcinoma [26-28].

Management of secondary metastatic breast cancer is still not known. Limited retrospective data demonstrates an improved survival with resection of the breast tumor plus systemic therapy versus systemic therapy alone. In respect to uterine cancer specifically, a large body of retrospective literature demonstrates improved survival with complete cytoreduction in patients with extra pelvic disease [29].

Uterine carcinosarcoma is a mysterious tumor throughout history that defined the pathophysiology between 3 main domains: collision, combination, and conversion. In a study of 1192 cases of UCS, multivariate analysis showed High-grade/heterologous (5-year rate, 34.0%, $P = 0.024$) and high-grade/homologous (45.8%, $P = 0.017$) but not low-grade/heterologous (50.6%, $P = 0.089$) were independently associated with decreased progression-free survival (PFS) compared with low-grade/ homologous (60.3%). 1096 metastatic sites showed that carcinoma components tended to spread lymphatically, while sarcoma components tended to spread loco-regionally ($P < 0.001$) [30].

Recent advances in the treatment of uterine carcinosarcoma have been emerged due to better understating of tumor pathology, biology, and behavior. Molecular classification using The Cancer Genome Atlas (TCGA) system- 2017 has included carcinosarcoma and clear cell carcinoma. Those tumors have frequent P53 mutations. UCS demonstrate a varied degree of epithelial-mesenchymal transition. Micro RNA expression is under epigenetic control. These fascinating features and biochemical markers make uterine carcinosarcoma attractive for different targeted therapy. There is no standard of care in treating metastatic uterine carcinosarcoma due to rare disease entity. Most of suggested treatments are based on retrospective data and case reports. Complete cytoreductive surgery showed a promising result at many retrospective studies. One of the studies conducted by Edward J Tanner included 44 cases with advanced stage carcinosarcoma stage 3C-4B showed better survival with those who underwent cytoreductive surgery without residual disease. Complete gross resection was associated with a median OS of 52.3 months versus 8.6 months in patients with gross residual disease [31]. However, surgical resection of the primary tumor is not enough to prevent recurrence of such aggressive disease that has high tendency to hematogenous and lymphatic spread even for early-stage disease, therefore, adjuvant therapy is needed. In a study of 300 cases led by Clayton Smith et al, adjuvant radiation therapy increased 5-year survival rates from 33.1% to 42.4%. Radiotherapy (vaginal vault brachytherapy or external beam pelvic radiation) was found to decrease local recurrences and improve both overall and uterine-specific survival in women stages I–IV, with the greatest impact on Stage IV disease [32].

For more promising outcome, combination of different adjuvant therapy including chemotherapy regimen and radiotherapy were added to the treatment plan and showed significant role in minimizing both local and distal treatment failure with survival benefit [33]. Unfortunately, due to rarity of this tumor type and lack of data on efficacy, uncertainties remain about the most optimal adjuvant treatment modality, i.e. type of chemotherapy and mode of radiotherapy (vaginal vault brachytherapy or external beam pelvic radiation). No stage-specific guidelines have yet been established [34].

Multiple adjuvant chemotherapy agents were used, however, survival remained poor. Thus, the Gynecologic Oncology Group (GOG) has activated a series of phase II trials to identify potentially active cytotoxic agents for the treatment of advanced or recurrent uterine carcinosarcoma. Lots of agents have been evaluated including piperazinedione, cisplatin, etoposide, ifosfamide, mitoxantrone, diaziquone, amonafide, aminothiadiazole, paclitaxel, trimetrexate, and topotecan. Best response rate (RR) was 32 % with ifosfamide, doxorubicin 19 %, paclitaxel 18%, cisplatin 8 % [35] and thus, those agents have been evaluated in subsequent phase III trials. So far, Ifosfamide plus paclitaxel is the regimen of choice as it shows great improvement in all three

parameters, recurrence rate, progression-free survival, and overall survival based on the randomized phase III trial (GOG), and is currently the standard arm for upcoming trials in the GOG to support further development of novel regimens [36].

Conclusion

Metastatic diseases to breast are very rare especially from mullerian origin. Distinguishing between primary and metastatic breast cancer is crucial as primary treatment and survival is significantly different. The recognition of unusual presentation of aggressive malignancies like UCS is important for early diagnosis and treatment. In the era of precision medicine, the characterization of genetic and molecular markers may play a role in offering new promising targeted therapies. More studies should be conducted to predict and treat recurrence.

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