Int J Clin Exp Med 2018;11(4):4317-4323
www.ijcem.com /ISSN:1940-5901/IJCEM0032535

Case Report

Primary extraskeletal myxoid chondrosarcoma with adenofibroma of the breast: a case report and literatures review

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Received May 21, 2016; Accepted August 9, 2016; Epub April 15, 2018; Published April 30, 2018

Abstract: Primary extraskeletal myxoid chondrosarcoma (EMC) of the breast has been rarely reported. In the present study, the clinical feature, imaging result, pathology, treatment and prognosis of a patient with primary EMC and adenofibroma of the breast were analyzed. A 50-year-old menopausal woman presented at hospital with complaints of the masses in her breasts. Breast ultrasound revealed several masses were found in bilateral breasts. The largest one located at lower outer quadrant in right breast with a clear boundary, irregular shape, uneven echo and blood flow signals, which was 3.3 cm in diameter. Mammography showed multiple nodules were found in bilateral breasts, and most of the boundaries were clear. The largest mass located in the outer quadrant measured 3.0 cm × 3.1 cm in the right breast. After sufficient preparation, the patient received mastectomy in right breast and sentinel lymph node biopsy. Microscopic examination confirmed the largest tumor located in the lower outer quadrant of the right breast was EMC and the tumors in the right outer and upper quadrant were adenofibroma with calcification. The nipple and lymph nodes were not involved. Immunohistochemical staining indicated the EMC were positive for vimentin, S-100 protein, P53 (+80%), Ki67 (+40%), and focal positive for epithelial membrane antigen, cytokeratin, but negative for cytokeratin 5/6, cytokeratin-H, cytokeratin-L, P63, calponin, smooth muscle actin, estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2. Post operation, the patient did not receive any other treatment and followed up for 18 months, no tumor recurrence and distant metastasis was found.

Keywords: Breast, chondrosarcoma, extraskeletal myxoid, therapeutics

Introduction

Extraskeletal chondrosarcoma was first described by Stout and Verner in 1953 [1]; however, it was not until 1972 that extraskeletal myxoid chondrosarcoma (EMC) was histopathologically defined as its own entity [2]. EMC is a relatively rare but well-characterized tumor that accounts for <2% of all soft tissue sarcomas [3]. Approximately 80% of these tumors occur in the extremities, with 20% located in the trunk. The male to female ratio of EMC is 2:1, with a peak occurrence in the fifth and sixth decades [3]. EMC occurred in breast was extremely rare and it was the rarest among the breast sarcomas [4]. To our knowledge, limited data are available due to the rarity of the disease. Between 1967 and 2017, only 20 cases of primary EMC of the breast were reported, and 18 cases of them were available for review (**Table 1**).

In the present study, we report a case of primary EMC with adenofibroma of the breast. The clinical feature, imaging result, pathology, treatment and prognosis of this patient were analyzed.

Case report

A 50-year-old menopausal woman presented at Yantai Yuhuangding Hospital (Yantai, Shandong, China) on 2014-06-23 with complaints of the masses in her bilateral breasts through ultrasound. She had a previous history of hypertension for 2 years. In 2001, she received surgical treatment because of ovarian cyst and uterine fibroids in changdao county people's hospital. The patient's menarche occurred at 15 years old with regular menstrual periods. She was married at 25-year-old and had one child. Her father was suffering from colon cancer, cerebral infarction and diabetes.

Table 1. Review of the primary chondrosarcoma of the breast reported in the literature between 1967 and 2017

NO.	First author, year (reference)	Gender	Age, years	Size, (cm)	Tumor site	Duration (months)	Method used for diagnosis	Therapy	Immunohistochemistry	ALN Status	Follow up
1	G. Militelloa et al, 2017 [5]	Female	41	3 × 2.5 × 2.5	Right	NA	Ultrasonography, MRI and vacuum-assisted core biopsy (VACB)	Skin-nipple-sparing mastectomy and radiotherapy	vimentin(+), pankeratin (focal +), CK7(-), CK5/6(-), S100(-), ER(-), PR(-), EMA (-) and Her2(-)	Pathologically negative	DFS for 12 months
2	Pasta V et al, 2015 [6]	Female	63	6.5 × 4.5 × 5	Right	NA	Ultrasonography, mammography and core needle biopsy	Quadrantectomy, chemotherapy (epirubicin and ifosfamide for 6 cycles) and radiotherapy	NA	Clinically negative	DFS for 30 months
3	Puneet Kumar Bagri et al, 2015 [7]	Male	65	10.4 × 10.3 × 9.9	Right	5	MRI	Radical mastectomy with grafting	S-100(+), vimentin(+), cytokeratin(-), ER(-) and PR(-)	Pathologically negative	DFS for 3 months
4	A Farahat et al, 2014 [8]	Female	35	19 × 9 × 9	Right	NA	Ultrasonography, core needle biopsy and tumorectomy	Breast conservative surgery	S-100(+), casein kinase(-), calponin(-) and actin(-)	Clinically negative	DFS for 15 months
5	Sinhasan SP et al, 2014 [9]	Female	55	10 × 7	Left	4	Ultrasonography and FNAC	Mastectomy	Vimentin(+), cytokeratin(-) and ER(-)	Clinically negative	DFS for 6 months
6	Errarhay et al, 2013 [10]	Female	24	1.5	Right	5	Ultrasonography, mammography and tumorectomy	Mastectomy	Vimentin(+), AE1/AE3(-), CK7(-), ER(-), PR(-) and HER2(-)	Clinically negative	NA
7	Mujtaba et al, 2013 [11]	Female	40	21 × 19 × 11	Right	10	Mammography	Mastectomy and radiotherapy	Vimentin(+), S-100(+), CKAE1/AE3(-), EMA(-) and CK-7(-)	Clinically negative	NA
8	Badyal et al, 2012 [12]	Male	80	20 × 10	Right	9	FNAC	Mastectomy with axillary sampling and radiotherapy	NA	Pathologically negative	NA
9	Patterson et al, 2011 [13]	Female	52	5.6 × 4.1 × 2.8	Left	12	Mammography, FNAC and core needle biopsy	Mastectomy with sentinel lymph node biopsy and radiotherapy	NA	Pathologically negative	DFS for 12 months
10	Lakshmikant et al, 2010 [14]	Female	42	13 × 10 × 6	Left	6	Core needle biopsy	Mastectomy	NA	Pathologically negative	NA
11	Bhosale et al, 2010 [15]	Female	45	7 × 5	Right	6	Tumorectomy and axillary lymph node FNAC	Modified radical mastectomy, radiotherapy and chemotherapy	S-100(+), ER(-), PR(-) and HER2(-).	Pathologically positive	NA
12	De Padua et al, 2009 [16]	Female	56	18 × 16 × 13	Right	12	FNAC	Mastectomy with axillary nodal sampling and with an excision of the superficial aspect of pectoralis major. radiotherapy	Vimentin(+), S-100(+), Cytokeratin(-), smooth muscle actin(-) and leucocyte common antigen (LCA)(-)	Pathologically negative	NA
13	Gurleyik et al, 2009 [17]	Female	52	5 × 3 × 5	Right	3	Ultrasonography, mammography, FNAC and tumorectomy	Modified radical mastectomy (level I axillary dissection)	ER(-), PR(-) and HER2(-)	Pathologically negative	NA

14	Verfaille et al, 2005 [4]	Female	77	3	Right	NA	Ultrasonography, mammography and Trucut needle biopsy	Mastectomy and sentinel nodes biopsy	NA	Pathologically negative	DFS for 12 months
15	Gupta et al, 2003 [18]	Female	46	12 × 8 × 4	Left	8	FNAC	Neoadjuvant chemotherapy (CAF, Cyclophosphamide, Adriamycin and 5-FU for 3 cycles, partial response). Modified radical mastectomy	ER(-), PR(-)	Pathologically negative	DFS for 12 months
16	Beltaos et al, 1979 [19]	Female	51	5 × 5 × 5.5	Left	4	Tumorectomy	Radical mastectomy, chemotherapy (doxorubicin hydrochloride 60 mg/m^2; high doses of cyclophosphamide, actinomycin, and vincristine sulfate)	NA	Pathologically negative	Lung metastasis 2 months later, and then cutaneous metastases, survival for 9 months and died in congestive heart failure
17	Beltaos et al, 1979 [19]	Female	73	15 × 20 × 25	Left	96	Mammography and tumorectomy	Mastectomy	NA	Clinically negative	Overall survival for 10 months, the reason of death was unknown, possible hepatic metastasis 1 month postoperation
18	Kennedy T et al, 1967 [20]	Female	77	12.5	NA	9	NA	Mastectomy	NA	Clinically negative	Died from cerebral haemorrhage 9.5 years later. No recurrence

FNAC, fine-needle aspiration cytology; NA, not available; ALN, axillary lymph node; DFS, disease free survival.

Physical examination had established bilateral nipple retraction, a 5.0 cm × 3.0 cm firm mass with irregular margin in the lower outer quadrant of the right breast. No mass was palpable in the opposite breast or in the bilateral axillaries and supraclavicular fosses.

Auxiliary examination revealed the tumor biomarkers (tumor special growth factor, cancer embryo antigen, carbohydrate antigen 15-3, carbohydrate antigen 125 and ferritin) and routine hematological and biochemical parameters were all in normal range. Chest X-ray showed right breast calcification, and no abnormal sign was found. Abdominal ultrasound revealed left renal cyst.

Breast ultrasound revealed several masses in bilateral breasts. The largest one located at lower outer quadrant in right breast with a clear boundary, irregular shape and uneven echo (3.3 cm × 2.1 cm). CDFI revealed blood flow signals were seen in the largest mass in right breast (**Figure 1**). No significantly enlarged lymph node was seen in bilateral axillaries. The BI-RADS classification of lower outer quadrant mass in right breast was 4A, and other masses were 3.

Mammography showed multiple nodules with different sizes were found in bilateral breasts, and most of the boundaries were clear, and popcorn calcification was seen in one nodule. The largest mass located in the outer quadrant measured 3.0 cm × 3.1 cm in the right breast. Sand-like calcification was not seen in bilateral breasts. The BI-RADS classifications were 4B in bilateral breasts (**Figure 1**).

After sufficient preparation, the patient received mastectomy in right breast and sentinel lymph node biopsy because of diagnosis of malignant tumor through intraoperative frozen section. Axillary lymph node dissection was ignored owing to negative sentinel lymph node. Grossly, the cut surface of the largest tumor located in the lower outer quadrant of the right breast was gray and translucent with capsule measuring 3.2 cm × 2.8 cm. The tumor located in the right outer quadrant was gray, tenacious, with a diameter of 1.3 cm × 0.8 cm. The tumor located in the right upper quadrant of the breast was a hard calcified nodule with a diameter of 1.5 cm. Microscopic examination confirmed the largest tumor was EMC and the tumors in the right outer and upper quadrant were adenofibroma with calcification. The nipple and deep resection plane were not involved. Immunohistochemical staining performed by standard indicated the EMC were positive for vimentin, S-100 protein, P53 (+80%), Ki67 (+40%), and focal positive for epithelial membrane antigen, cytokeratin, but negative for cytokeratin 5/6, cytokeratin-H, cytokeratin-L, P63, calponin, smooth muscle actin, estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2.

Post operation, the patient did not receive any other treatment and was followed up for 18 months, no tumor recurrence and distant metastasis was found.

Discussion

EMC occurred in breast was extremely rare. Most of the reported cases had an age preference towards above 50 years [13], of course, there was young patient [10] and male patient [7]. There also had a report of a case of EMC that metastasized to the breast [21]. The lesions exhibit low density on CT, low signal intensity on T1-weighted MRI scans and a high signal intensity on T2-weighted MRI scans [22]. Microscopically, the tumors are characterized by a proliferation of ovoid and bipolar cells that are enmeshed in a prominent myxoid matrix rich in chondroitin and keratin sulfate [23]. Immunohistochemically, the neoplastic cells commonly stain with antibodies to vimentin and S-100 protein. Some studies have shown that they may also be positive for Leu-7 and epithelial membrane antigen. Uniformly, they are negative for keratin, smooth muscle actin and desmin [24, 25].

A unique feature of EMC is nonrandom reciprocal chromosomal translocation [26]. The most common reciprocal translocation is t(9;22)(q22;q12), which leads to juxtaposition of the gene EWSR1 on chromosome 22 and NR4A3 on chromosome 9 [27]. Other translocations being t(9;17)(q22;q11) and t(9;15)(q22;q21) [28]. Another translocation, t(9;22)(q22;q11) is associated with EMC-producing neuroendocrine secretions [29].

Surgical resection of primary EMC remains the cornerstone treatment. The aim is to have microscopic tumor free resection margins at

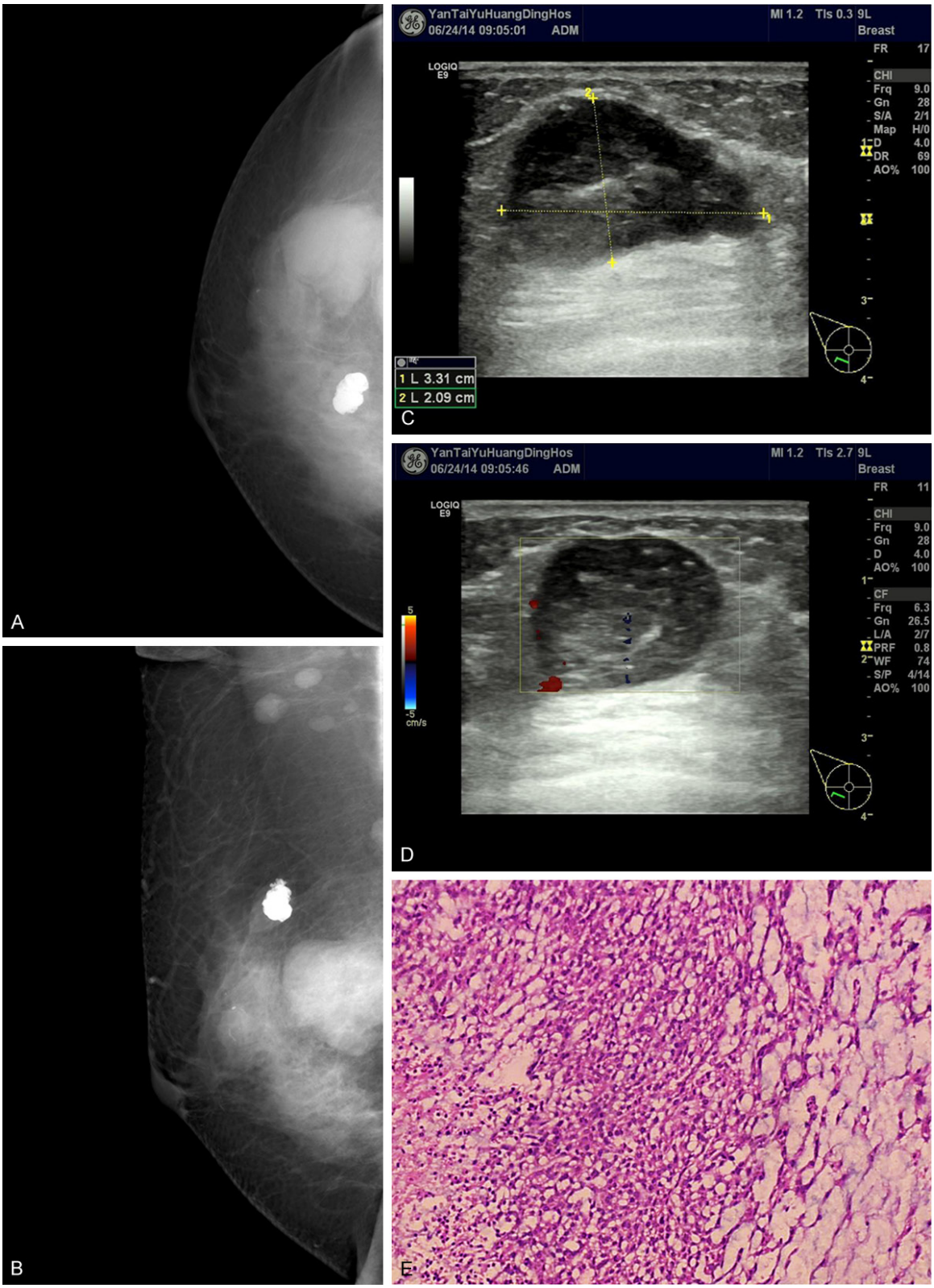

Figure 1. A (Axial) and B (oblique): Mammography findings of the right breast showing multiple nodules with different sizes were found, and most of the boundaries were clear. Popcorn calcification was seen in one nodule. The largest mass located in the outer quadrant measured 3.0 cm × 3.1 cm. C and D: Echography imaging showing the largest mass located at lower outer quadrant in right breast with a clear boundary, irregular shape and uneven echo (3.3 cm × 2.1 cm). CDFI revealed blood flow signals were seen in the mass. E: Extraskeletal myxoid chondrosarcoma of the

breast, characterized by a proliferation of ovoid and bipolar cells that are enmeshed in a prominent myxoid matrix rich in chondroitin and keratin sulfate (Hematoxylin-Eosin stains × 100).

pathological examination. Most of reported cases of EMC of the breast were treated with a radical surgical approach that entailed removal of all breast tissue. Conservative breast surgery in these rare tumors could be a successful approach, especially when no axillary evacuation or adjuvant therapy is required [8]. The role of axillary dissection may be unnecessary because no cases had nodal metastasis through axillary dissection, nodal sampling or sentinel node biopsy.

The role of chemotherapy and radiotherapy is not yet established because of the limited number of cases reported. In the published data no chemotherapeutic agent or combination agents have demonstrated efficacy in the treatment of EMC [30]. Complete response in 1 patient and partial response in 1 out of 6 patients were seen with the use of multi-agent chemotherapy by McGory et al [31]. However, data regarding the agents used was unavailable. Another report showed anthracycline-based chemotherapy is active in a distinct proportion of EMC patients. In their study, eleven patients treated with anthracycline-based chemotherapy were included (anthracycline as single agent/combined with ifosfamide = 1/10). Overall, best response according to Response Evaluation Criteria in Solid Tumours RECIST was: partial response (PR) = 4 (40%), stable disease (SD) = 3, progressive disease (PD) = 3 cases. Median PFS was 8 (range 2-10) months [32]. In addition, radiotherapy seems beneficial in an adjuvant setting and as palliative therapy for metastatic disease [33].

Due to the ineffectiveness of chemotherapy, few alternative agents have been studied. In one study, sunitinib has been confirmed to have anti-tumor activity in EMC [34]. A recent study revealed that six of ten progressive metastatic translocated EMC patients treated with sunitinib had a PR, two were SD, and two PD. Interestingly, all responsive cases turned out to express the typical EWSR1-NR4A3 fusion, while refractory cases carried the alternative TAF15-NR4A3 fusion [35]. Besides, only a partial response had been observed with the use of interferon alpha 2b [36].

The prognosis of EMC of the breast was not fully known. But there was report that EMC had a high propensity for relapse over 5 years of follow-up. So definitive initial surgery and careful monitoring for a prolonged period are still important [33].

Acknowledgements

Supported by key project of research and development plan of yantai city (No.2017YD007).

Disclosure of conflict of interest

None.

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