Primary extraskeletal myxoid chondrosarcoma of the breast: report of a case and literature review

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Summary
Primary extraskeletal myxoid chondrosarcoma (pEMC) of the breast is rare and only a few cases have been reported to date. Herein, we report a case of primary EMC of the breast in a 45-year-old female. The patient presented with a left breast mass for 1 month. Mammogram revealed a fairly circumscribed mass with spicules of calcifications. The core biopsy and resection specimen showed a myxoid soft tissue neoplasm with histologic features of a myxoid chondrosarcoma. Necrosis, hemorrhage, and brisk mitotic activity were present. No malignant epithelial element was identified even after extensive sampling. The tumor cells exhibited immunoreactivity for vimentin, S100, neuron specific enolase, CD99, and synaptophysin, while the epithelial, myoepithelial, and mammary lineage-associated markers were negative. As up to 81% of EMC cases harbor t(9;22)(q22;q12), this results in a fusion of EWS RNA-binding protein 1 gene (EWSR1) at 22q12 to the nuclear receptor subfamily 4, group A, member 3 gene at 9q22. A rearrangement involving the EWSR1 locus was detected in our case. Whole body PET-CT did not reveal any other mass. A diagnosis of pEMC was rendered. The patient received six cycles of 5-Fluorouracil, Cyclophosphamide, and Adriamycin. The patient was in clinical and radiologic remission at the last follow-up (18 months post surgery). PET-CT and brain MRI were negative. In conclusion, surgical pathologists should include EMC in their differential while dealing with a myxoid soft tissue lesion of the breast, particularly in the core needle biopsies. An expeditious diagnosis of EMC of the breast would allow the surgeon to carry out conservative breast surgery instead of more radical approaches taken in cases of other primary malignant mammary neoplasms.

Key words: primary extraskeletal myxoid chondrosarcoma, breast

Introduction
Extraskeletal myxoid chondrosarcoma (EMC) was first described by Stout and Verner in 1953. This constitutes <3% of all the soft tissue sarcomas. EMC is more commonly seen in males (male to female ratio is 2:1) and the median age is 50 years. Only a few rare cases have been reported in children and adolescents. The deep soft tissues of the proximal extremities (thigh being the commonest) and limb girdles are the most common sites of involvement by EMC. The other anatomic locations involved include trunk, head and neck, paraspinal soft tissue, abdomen, pelvis, and foot. Rare tumors have also been reported in the fingers, cranium, ret-
roperitoneum, pleura, bone, and perineum \(^{1-4}\). Primary mammary EMC is exceedingly rare, and only 21 cases of primary EMC of the breast have been reported to date \(^{5-23}\). Moreover, only in a few cases, was adequate IHC and molecular description available. This tumor is an aggressive malignant neoplasm with a high likelihood for local recurrences. Some cases of EMC metastasize with the lungs being the most common site. Interestingly, prolonged survival even in the face of metastatic disease is not uncommon \(^{1-4}\). EMC is classified as a tumor of uncertain differentiation in the most recent edition of the World Health Organization Classification of Tumors of Soft Tissue and Bone, because of the ambiguous line of differentiation of the tumor \(^2\). The most common underlying genetic abnormality (seen in up to 81% of cases) is t(9;22)(q22;q12) results in a fusion of EWS RNA-binding protein 1 gene (EWSR1) at 22q12 to the nuclear receptor subfamily 4, group A, member 3 gene (NR4A3) at 9q22. A subset of cases reveal fusion of the NR4A3 gene with alternative gene partners, namely TATA box binding protein (TBP)-associated factor (TAF15), transcription factor 12 (TCF12) and TRK-fused gene (TFG) \(^{2,3,24}\).

**Case report**

A 45-year-old female presented with a left breast mass of 1 month duration. The mass was not associated with pain, nipple discharge, or any constitutional symptoms. Local examination did not reveal tenderness, edema, cutaneous changes (ulceration or nodularity), or axillary/systemic lymphadenopathy. Systemic physical examination was within normal limits. Personal and family history was not significant for any malignancy. Mammogram showed a 6.0 cm fairly circumscribed spiculated mass (Fig. 1). Core needle biopsy from the left breast mass revealed a

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*Figure 1.* Mammogram showed a 6.0 cm fairly circumscribed spiculated mass in the left breast.
S. Sharma et al.

myxoid soft tissue tumor with chondrosarcomatous areas; interspersed benign breast acini and ducts were present. Based on the morphologic attributes, a metaplastic carcinoma, malignant phyllodes tumor with heterologous elements, a myoepithelial carcinoma, EMC, and metastatic myxoid soft tissue sarcoma were brought into the differential diagnostic consideration. Subsequently, a modified radical mastectomy was performed.

The left modified radical mastectomy specimen measured 28.0 x 18.0 x 6.0 cm with a 15.0 x 7.0 cm portion of grossly unremarkable tan skin. Nipple and areolar complex measured 3.0 x 3.0 cm and was grossly unremarkable. On sectioning, a 6.0 x 5.0 x 4.0 cm tan-white to tan-gray to slate-gray, partly hemorrhagic and partly cystic tumor was present in the central portion of the breast. The tumor was 2.0 cm from the closest margin (inferior margin) and the overlying skin. Multiple tan, ovoid, and rubbery axillary lymph nodes were identified, which ranged from 0.4 cm to 1.5 cm in the maximum dimension. The entire tumor was submitted for histopathologic examination.

The microscopic evaluation revealed a malignant neoplasm with a nodular growth pattern. The tumor cells were arranged in anastomosing cords and strands. The neoplastic cells revealed mild to moderate pleomorphism, hyperchromatic nuclei, prominent nucleoli, and moderate to scant eosinophilic cytoplasm and were present in lobules embedded in an abundant myxoid, basophilic matrix. A cord-like arrangement of the neoplastic cells was evident.

Figure 2. Morphology of primary extraskeletal myxoid chondrosarcoma of the breast (hematoxylin and eosin): (A). malignant neoplasm with a nodular growth pattern and the tumor cells were arranged in anastomosing cords and strands (4x); (B). Nodular architecture of the tumor with collagenized septae and clear cell features (10x); (C). The neoplastic cells with mild to moderate pleomorphism, hyperchromatic nuclei, prominent nucleoli, and moderate to scant eosinophilic cytoplasm and were present in lobules embedded in an abundant myxoid, basophilic matrix (20x); (D). A cord-like arrangement of the neoplastic cells was evident (40x).
li, and moderate to scant eosinophilic cytoplasm and were embedded in an abundant myxoid, basophilic matrix. Areas reminiscent of chondrosarcoma were present. Necrosis, hemorrhage, and brisk mitotic activity were noted. No malignant epithelial element was seen. The benign breast acini and ductules were present in between the above-mentioned nodules. No organoid (ducto-lobular) arrangement was observed. No periacinar/ductular condensation of stroma was observed; there was lack of a cambium layer (Fig. 2). Lymphovascular invasion was not identified. Eighteen axillary lymph nodes examined were negative for tumor. A battery of immunohistochemical stains, including mesenchymal, epithelial, and mammary lineage-associated markers were performed to subtype the tumor and ascertain its histogenesis. The tumor cells were immunoreactive for vimentin, S-100 protein, neuron specific enolase (NSE), CD99, synaptophysin (SYN), and osteopontin in variable degrees (multifocal to diffuse) and intensity (moderate to strong), while the epithelial markers (pancytokeratin [panCK], epithelial membrane antigen, high molecular weight CK, CK7, CK19, and CK5/6, CD34, CD117, CD10, myoepithelial markers (smooth muscle actin and p63) and mammary lineage-associated markers (GATA3, mammaglobin, and gross cystic disease fluid protein-15 [GCDFP-15]) were negative in the tumor (Figs. 3 and 4). The Ki-67 labeling index was 40%. Epidermal growth factor receptor (EGFR) was uniformly expressed in the tumor and p16 was negative. A fluorescence in situ hybridization (FISH) was performed to detect a rearrangement of the EWSR1 locus, using the LSI EWSR1dual-color, break-apart probe. The average percent positive tumor cells with split signal were 35%, confirming a rearrangement involving the EWSR1 locus (Fig. 5).

Figure 3. Immunohistochemical characteristics of primary extraskeletal myxoid chondrosarcoma of the breast. The tumor cells showed positivity for S100 (10x), neuron specific enolase (10x), CD99 (10x), and synaptophysin (20x).
A diagnosis of extraskeletal myxoid chondrosarcoma was offered. Prognostic markers, including estrogen and progesterone receptors, HER2/neu, isocitrate dehydrogenase, and ERG were negative. A whole body imaging by PET-CT scan was within normal limits. The patient received six cycles of 5-Fluorouracil, Cyclophosphamide, and Adriamycin. The patient was in clinical and radiologic remission on the last follow-up (18 months post surgery).

**Discussion**

Our findings are consistent with diagnosis of pEMC of the breast. While EMC is a rare entity in itself and makes up only 1% of all chondrosarcomas\(^1,2\), the occurrence of primary EMC of the breast is equally unusual with only 20 cases reported in the literature\(^5-23\). Clinical, imaging, pathologic, treatment, and follow-up data were available in 20 previously published patients and the present case. The patients’ age ranged from 24 years to 80 years, with a mean of 52.3 years. There were 19 females and 2 males. All the tumors were unifocal; the right breast was involved in 12 patients and left in 8 patients. Laterality was unknown in one patient. The tumor size ranged from 1.5 cm to 25 cm, with mean of 10.1 cm. Imaging information was available in 13 patients. Heterogeneous hypoechoic and lobulated mass with irregular margins was present in all these patients. Either core needle biopsy (7/21), fine needle biopsy (5/21), or incisional biopsy (5/21) was performed for the primary diagnosis. Microscopy showed a multinodular tumor with interspersed fibrous septae dividing the tumor into nodules rich in hyovascular chondromyxoid matrix. The tumor cells within the nodules were ar-

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**Figure 4.** Immunohistochemical characteristics of primary extraskeletal myxoid chondrosarcoma of the breast. The tumor cells were negative for GATA3 (20x), calponin (10x), p63 (10x), and gross cystic fluid protein-15 (20x).
ranged in anastomosing cords, trabeculae, and small clusters. These cells were round to oval to spindle with mild to moderate nuclear atypia, hyperchromatic nuclei, small to prominent nucleoli, and scant to moderate granular eosinophilic to vacuolated cytoplasm. Mitotic activity was variable within the tumor. Necrosis and hemorrhage were seen. Well-formed hyaline cartilage was virtually never seen. Absence of any epithelial component and presence of chondromyxoid areas with cellular atypia and pleomorphism are cardinal morphologic attributes in the diagnosis of an EMC. The tumor cells exhibited a vimentin+/S100+/synaptophysin+/NSE+/CD99+ immunoprofile, with negativity for epithelial markers (except for 2 patients), smooth muscle actin, myoepithelial markers, ER, PgR, and HER2/neu. Ki-67 data was available in two patients (40% and 80%). Details of FISH studies in the index case revealed a rearrangement involving the EWSR1 locus. A surgical resection with microscopically negative margins remained the primary treatment modality. All the reported patients were treated with a surgical resection of the breast mass (mastectomy, n = 20; quadrantectomy, n = 1). Complete axillary dissection was performed in 8 patients and sentinel lymph node sampling in 3 patients. Only one patient had axillary nodal metastatic disease. One patient each developed pulmonary (2 months) and cutaneous and hepatic (1 month) metastasis during the course of the disease. Neoadjuvant chemotherapy was administered in one patient and adjuvant postoperative chemotherapy in 5 patients. Post-operative radiation was given in 6 patients including two patients who underwent both chemotherapy and radiation therapy. Follow-up information was
available in 13 patients, and the follow-up duration ranged from 3 months to 9.5 years. Three patients died 9 months (the patient with lung and skin metastasis later developed congestive heart disease), 10 months (the patient with hepatic metastasis), and 9.5 years (cerebral hemorrhage but no tumor recurrence) following the primary diagnosis (Tab. I) 5-23. The differential diagnoses included secondary EMC to the breast, metaplastic carcinoma, and malignant phyllodes tumor with predominant chondrosarcomatous component, myxoid liposarcoma, malignant mixed tumor, and malignant myoepithelioma. Although breast is a rare site for metastasis of EMC with only a single case reported in literature till date 2,4, the negative PET-CT examination excluded out the possibility of a metastatic EMC in the present case. The tumor was entirely submitted for histopathologic evaluation. The conspicuous absence of the epithelial elements in all the sections examined and the negative immunoreactivity of chondrosarcomatous cells to all the epithelial, myoepithelial, and mammary lineage-associated markers argue against the diagnosis of a metaplastic carcinoma of the breast 2,25. Of note, metaplastic breast cancer may completely lack CK expression 26. Rakha et al. 26 suggested that sarcomatoid breast neoplasms without CK expression and epithelial/ carcinomatous histology may represent an extreme end of dedifferentiation that can be considered as carcinomas rather than sarcomas for management purposes, after an extensive morphologic and IHC work-up. The differentiation from malignant phyllodes tumor with heterologous chondrosarcomatous component was made based on the absence of typical foci of malignant phyllodes tumor and negativity for CD34, CD10, and CD117 27. A myxoid liposarcoma can be differentiated by the absence of plexiform vascular pattern and lipoblasts 2. Malignant mixed tumor and malignant myoepithelioma often display an intricate admixture of epithelial-looking and spindled areas and express epithelial and myoepithelial markers, including CK, S100, calponin, and sometimes p63 and GFAP 27.

The poor prognostic factors of EMC in general include older age, large tumor size (> 10 cm), proximal location, high cellularity, high Ki-67 proliferation index (10%), high mitotic activity (> 2 mitotic figures/10 HPF), rhabdoid phenotype, and anaplasia 15. The gold standard of treatment for EMC is wide local resection with or without radiation therapy and the median survival ranges from a few months to 18 years 2. Due to the limited number of published primary mammary EMC cases, the definite therapeutic role of chemotherapy and radiotherapy has not been well established. A combination regime with cyclophosphamide, vincristine sulfate, doxorubicin, 5-FU, Adriamycin, ifosfamide, and epirubicin demonstrated partial to complete response with a disease free survival ranging between 2 months to 30 months 5-23. Stacchiotti et al. have reported variable responses in EMC patients to sunitinib, particularly those harboring a EWSR1-NR4A3 fusion, while no response in patients with an alternative TAF15-NR4A3 fusion 28,29.

Conclusion

In conclusion, pEMC of the breast is an extremely rare entity and surgical pathologists should include EMC in differential diagnosis when dealing with myxoid lesions of the breast, particularly in the core needle biopsies. Additionally, IHC studies should be performed to render a definitive diagnosis. An expeditious diagnosis of EMC of the breast would allow the surgeon to carry out conservative breast surgery instead of more radical to more radical approaches taken in cases of other primary malignant mammary neoplasms. Furthermore, the therapeutic benefit of intraoperative sentinel lymph node sampling would avoid unnecessary complete axillary dissection.

Conflict of interest

The authors declare no conflict of interest. All authors have read and approved the manuscript and have contributed sufficiently to the project to be included as authors.

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Ethical consideration

The patient’s consent was taken before submission of the manuscript. This case report does not include anything that would hamper the management and follow-up of this patient.

Authors’ contributions

Conception and Design: SS, AL, AS, and SKM. Development of Methodology: SS, AL, AS, and SKM. Acquisition of Data: SS, AL, AS, NYS, MK, RK, SSM, and SKM. Analysis and interpretation of Data: SS, AL, AS, and SKM. Writing and review/revision of the manuscript: SS, AL, AS, NYS, MK, RK, SSM, and SKM. Technical Support: MK.

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Table I a and I b. demographics, clinical, pathologic, immunohistochemical, fluorescence in situ hybridization, therapy, and follow-up details of the published cases of primary extraskeletal myxoid chondrosarcomas of the breast with or without EWSR1 rearrangement.

Table I a.

| Reference                           | Age (Years) | Gender | Anatomic location and laterality of the tumor | Maximum dimension of the tumor (cm) | Duration of presenting symptoms (months) | Imaging features                                                                 | Diagnostic procedures                                                                 | Immunohistochemical profile                                                                 |
|-------------------------------------|-------------|--------|-----------------------------------------------|-------------------------------------|-----------------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| 1 Our case                          | 45          | Female | Left breast                                   | 6                                   | 1                                       | Mammography; fairly circumscribed mass with spicules of calcifications             | Core needle biopsy                                                                      | Vimentin+/S100+/NSE+/CD99+/SYN+/Osteopontin+456-7 (40%); PanCK+/EMA-/HMWCK-/CK5/6-/CD10-/CD34-/ SMA+/p53-/Calponin-/COLFP-15-/Mammaglobin+/GATA3-/ER-/PgR-/HER2/neu+/IDH1-/ERG-/CD31- |
| 2 Cong et al., 2018                 | 50          | Female | Right breast                                  | 3.3                                 | NA                                      | Chest X-ray: Right Breast Calcification; USG of Bilateral Breasts: multiple masses in the bilateral breasts in lower outer quadrant of right breast (BIRADIS 4A); Mammography: multiple nodules in the bilateral breasts, largest in the lower outer quadrant of the right breast, with popcorn calcification noted in one nodule (BIRADIS 4B). There was no axillary lymphadenopathy | NA                                                                                        | Vimentin+/S100+/p53(50%)/CD68(40%)/EMA+/OCT4+/PanCK+/ER+/PgR+/HER2/neu+/                  |
| 3 Mittelloa et al., 2017            | 41          | Female | Right breast                                  | 3                                   | NA                                      | USG/MRI: Hypoechoic lump with polylobulated shape and bilateral axillary lymphadenopathy | Vacuum assisted core needle biopsy                                                     | Vimentin+/PanCK+/EMA-/CD99+/S100+/CD10+/CD34+/SMA+/p53+/Calponin-/COLFP-15-/Mammaglobin+/GATA3-/ER-/PgR-/HER2/neu+/ |
| 4 Pasta et al., 2015                | 63          | Female | Right breast                                  | 6.5                                 | NA                                      | USG/Mammography: hypoechoic and solid mass with irregular margins                  | Core needle biopsy                                                                      | NA                                                                                        |                           |
| 5 Kumar Boppi P et al., 2015        | 66          | Male   | Right breast                                  | 10.4                                | 5                                       | MRI: multiloculated cystic-solid mass, with central areas of necrosis; no axillary lymphadenopathy | NA                                                                                        | S100+/Vimentin+, PanCK+/ER+/PgR-/                                                             |
| 6 Farhat et al., 2014               | 36          | Female | Right breast                                  | 19                                  | NA                                      | USG: a large well-defined heterogeneous hypoechoic lobulated mass; no axillary lymphadenopathy | Core needle biopsy                                                                      | S100+, Casein kinase-/Calponin+/SMA-                                                     |
| 7 Sinhasan et al., 2014             | 55          | Female | Left breast                                   | 10                                  | 4                                       | USG: Heterogeneous echogenic mass with an anterior halo and posterior shadowing with enhancement, no areas of calcification or lymphadenopathy | FNAC                                                                                     | Vimentin+, PanCK+/ER/-                                                                      |
| 8 Ernath et al., 2013               | 24          | Female | Right breast                                  | 15                                  | 5                                       | USG: a well-defined lobulated lesion; Mammography: a round and well-delimited opaque mass in the lower outer quadrant of the right breast | Incisional biopsy                                                                      | Vimentin+, PanCK+/ER/CD99+/S100+/CD10+/CD34+/SMA+/p53+/Calponin-/COLFP-15-/Mammaglobin+/GATA3-/ER-/PgR-/HER2/neu+/ |
| 9 Mutabaa et al., 2013              | 40          | Female | Right breast                                  | 21                                  | 10                                      | Mammography                                                                       | NA                                                                                        | Vimentin+/S100+, PanCK+/EMA/Ck7-                                                          |
| 10 Badal et al., 2012               | 80          | Male   | Right breast                                  | 20                                  | 9                                       | NA                                                                               | FNAC                                                                                     | NA                                                                                        |
| 11 Patterson et al., 2011           | 52          | Female | Left breast                                   | 5.6                                 | 12                                      | Mammography                                                                       | FNAC and Core needle biopsy                                                                 | NA                                                                                        |
| 12 Lakshman et al., 2010            | 42          | Female | Left breast                                   | 13                                  | 6                                       | Core needle biopsy                                                                  | NA                                                                                        | NA                                                                                        |
| 13 Bhosale et al., 2010             | 45          | Female | Right breast                                  | 7                                   | 6                                       | Incisional biopsy of the mass and FNAC of the axillary lymph node                   | S100+/ER+/PgR+/HER2/neu-                                                                  |                                                                                        |
| 14 De Padua et al., 2009            | 56          | Female | Right breast                                  | 18                                  | 12                                      | NA                                                                               | FNAC                                                                                     | Vimentin+/S100+, PanCK+/EMA/Ck7-                                                          |
| 15 Gurleyik et al., 2009             | 52          | Female | Right breast                                  | 5                                   | 3                                       | USG: A hypoechoic solid mass with ill-defined corners; Mammography: a large hypodense and relatively regular mass (? Benign) | FNAC and incisional breast biopsy                                                       | ER-/PgR+/HER2/neu-                                                                         |
| 16 Verfalle et al., 2005             | 77          | Female | Right breast                                  | 3                                   | NA                                      | USG and mammography                                                                | Core needle biopsy                                                                      | NA                                                                                        |
| 17 Gupta et al., 2003                | 46          | Female | Left breast                                   | 12                                  | 8                                       | NA                                                                               | FNAC                                                                                     | ER-/PgR/-                                                                                 |
| 18 Rao L et al., 2002                | 30          | Female | Left breast                                   | NA                                  | NA                                      | NA                                                                               | FNAC                                                                                     | NA                                                                                        |
| 19 Bellos et al., 1979               | 51          | Female | Left breast                                   | 5                                   | 4                                       | Core needle biopsy                                                                  | NA                                                                                        | NA                                                                                        |
| 20 Bellos et al., 1979               | 73          | Female | Left breast                                   | 15                                  | 96                                      | Mammography                                                                       | Incisional biopsy                                                                      | NA                                                                                        |
| 21 Kennedy et al., 1967              | 77          | Female | NA                                            | 12.5                                | 9                                       | NA                                                                               | NA                                                                                        | NA                                                                                        |
| Case Number | Reference | Therapeutic Surgical Procedure | Lymph Node Status | Chemotherapy | Radiation Therapy | Follow-up |
|-------------|-----------|---------------------------------|------------------|--------------|------------------|-----------|
| 1           | Our case  | Modified radical mastectomy     | 18 lymph nodes pathologically negative for tumor | Six cycles of 5-Fluorouracil, Cyclophosphamide, and Adriamycin | No | DFS for 18 months |
| 2           | Cong et al., 2018 | Mastectomy with sentinel lymph node sampling | Negative sentinel lymph node | No | No | DFS for 18 months |
| 3           | Millitelloa et al., 2017 | Skin nipple sparing mastectomy | Pathologically negative | NA | 5 cycles | DFS for 24 months |
| 4           | Pasta V et al., 2015 | Quadrantectomy | Clinically negative | 6 cycles of Epirubicin and Ifosfamide | 5 cycles | DFS for 30 months |
| 5           | Bagri et al., 2015 | Radical mastectomy with grafting | Pathologically negative | No | No | DFS for 3 months |
| 6           | Farahat et al., 2014 | Breast conservation surgery | Clinically negative | No | No | DFS for 15 months |
| 7           | Sinhasan et al., 2014 | Mastectomy | Clinically negative | NA | NA | NA |
| 8           | Errahay et al., 2013 | Mastectomy | Clinically negative | NA | NA | NA |
| 9           | Mujtaba et al., 2013 | Mastectomy | Clinically negative | NA | Yes | NA |
| 10          | Badyal et al., 2012 | Mastectomy with axillary sampling | Pathologically negative | NA | NA | NA |
| 11          | Patterson et al., 2011 | Mastectomy with sentinel lymph node sampling | Pathologically negative | No | Yes | DFS for 12 months |
| 12          | Lakshmikant et al., 2010 | Mastectomy | Pathologically negative | NA | NA | NA |
| 13          | Bhosale et al., 2010 | Modified radical mastectomy | Pathologically positive | Yes | Yes | NA |
| 14          | De Padua et al., 2009 | Mastectomy with axillary sampling and excision of the superficial aspect of the pectoralis major | Pathologically negative | No | Yes | NA |
| 15          | Gurleyik et al., 2009 | Modified radical mastectomy with level I axillary dissection | Pathologically negative | No | No | NA |
| 16          | Verfaille et al., 2005 | Mastectomy with sentinel lymph node sampling | Pathologically negative | No | No | DFS for 12 months |
| 17          | Gupta et al., 2003 | Neoadjuvant chemotherapy and modified radical mastectomy | Pathologically negative | Cyclophosphamide, Adriamycin, and 5-FU for 3 cycles with partial response | No | DFS for 12 months |
| 18          | Beltaos et al., 1979 | Radical mastectomy | Pathologically negative | Doxorubicin Hydrochloride, high doses of Cyclophosphamide, Actinomycin, and Vincristine Sulfate | No | lungs metastasis in 2 months; later developed cutaneous metastasis, survived for 9 months and died due to congestive heart failure |
| 19          | Beltaos et al., 1979 | Mastectomy | Clinically negative | NA | NA | Survived for 10 months, reason for death is unknown - possibly hepatic metastasis developed within 1 month postoperative |
| 20          | Kennedy et al., 1967 | Mastectomy | Clinically negative | NA | NA | Died from cerebral hemorrhage 9.5 years later, no tumor recurrence |
| 21          | Rao L et al., 2002 | Mastectomy | NA | NA | NA | NA |
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