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## Breast Metastasis of Extraskeletal Myxoid Chondrosarcoma: A Case Report

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Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
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**Patient:** Female, 58  
**Final Diagnosis:** Extraskeletal myxoid chondrosarcoma with widespread metastases  
**Symptoms:** —  
**Medication:** —  
**Clinical Procedure:** Left below knee amputation  
**Specialty:** Oncology

**Objective:** Rare disease

**Background:** Extraskeletal myxoid chondrosarcoma is a unique and distinct clinicopathological entity in terms of its origin, morphology, and biologic behavior. Despite being a slow-growing tumor, it has a high rate of local recurrences and history of metastases to uncommon sites like the mandible, liver, retroperitoneum, right ventricle, pancreas, and central nervous system. Here, we report a very unique case of extraskeletal myxoid chondrosarcoma that metastasized to the breast, which itself is a very rare site for metastases.

**Case Report:** A 58-year-old woman presented with a large, firm, and tender soft-tissue mass (6.0×7.0 cm) underneath the sole of the left foot. A computerized tomography (CT) scan showed a heterogeneous lobulated mass in the plantar aspect of the forefoot, measuring 8.6×8.0×7.1 cm. Punch biopsies revealed histology consistent with extraskeletal myxoid chondrosarcoma. Metastatic work-up was negative. The mass was fully resected with left below-knee amputation. The histology of the resected mass was consistent with extraskeletal myxoid chondrosarcoma. A follow-up CT showed a new right breast nodule along with metastases to lung and bones. The results of the core needle biopsies of the right breast masses seen on mammogram were morphologically identical to extraskeletal myxoid chondrosarcoma.

**Conclusions:** Although rare, metastases to the breast should be considered in the differential diagnosis of a breast mass. A close long-term follow-up is needed due to the unpredictable behavior of extraskeletal myxoid chondrosarcoma and the high frequency of local recurrences, metastases, and death due to disease.

**MeSH Keywords:** Breast • Chondrosarcoma • Neoplasm Metastasis

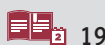
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## Background

Extraskeletal myxoid chondrosarcoma (EMC) is a soft-tissue chondrosarcoma, initially described by Stout and Verner in 1953 as an extrasosseous chondrosarcoma that develops in soft tissues, but with histology similar to that of chondrosarcoma of the bones [1]. Enzinger and Shiraki (1972) delineated EMC as a distinct sarcoma of chondroblastic origin that arises from extraskeletal soft tissues [2]. EMC is currently classified as a tumor of uncertain differentiation in the revised version (2002) of the World Health Organization classification of tumors of soft tissue and bone [3]. EMC accounts for 2.5% of all soft-tissue sarcomas. The median age at diagnosis is around 50 years and the median tumor size ranges from 1 to 25 cm in diameter. It occurs more commonly in men than in women (2:1). Despite the prolonged clinical course, it is locally aggressive and has metastasizing potential. Metastasis is an adverse prognostic factor in EMC and about 50% of the cases will develop metastases [4]. Here, we report the case of a 58-year-old woman with metastases from EMC to the breast – a rare tumor with metastases to a rare site.

## Case Report

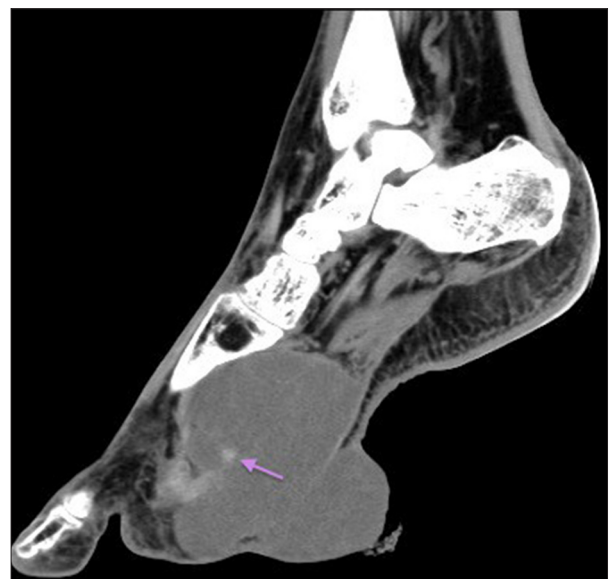
A 58-year-old Jamaican woman presented at our hospital with complaints of a growth underneath the sole of her left foot for 1 year, with worsening pain. Physical examination showed a large 6.0×7.0 cm soft-tissue mass with areas of maceration (Figure 1). The mass was firm and tender on palpation. There was no active bleeding or discharge. A computerized



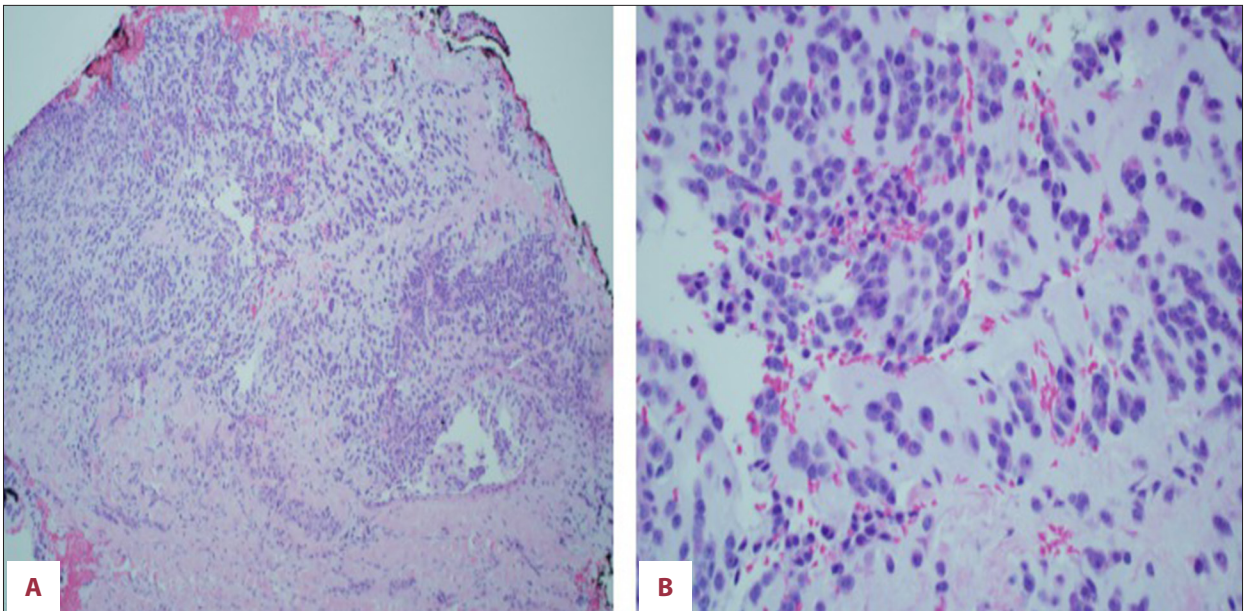
**Figure 1.** Extraskeletal myxoid chondrosarcoma presenting as a large soft-tissue tan-gray lobulated mass underneath the sole of the left foot.

tomography (CT) scan of the left lower extremity showed a lobulated low-attenuation soft-tissue mass on the plantar aspect of the forefoot, measuring 8.6×8.0×7.1 cm (Figure 2). Multiple punch biopsies of the mass revealed monomorphic round tumor cells with minimal cytoplasm in the loose myxoid background, consistent with extraskeletal myxoid chondrosarcoma (EMC) (Figure 3 [A – 100×, B – 400×]). The immunohistochemical stain was positive for synaptophysin (Figure 4A) and weakly positive for S 100 (Figure 4B). To confirm the diagnosis, a specimen was sent to the Mayo Clinic Medical Laboratories for molecular testing.

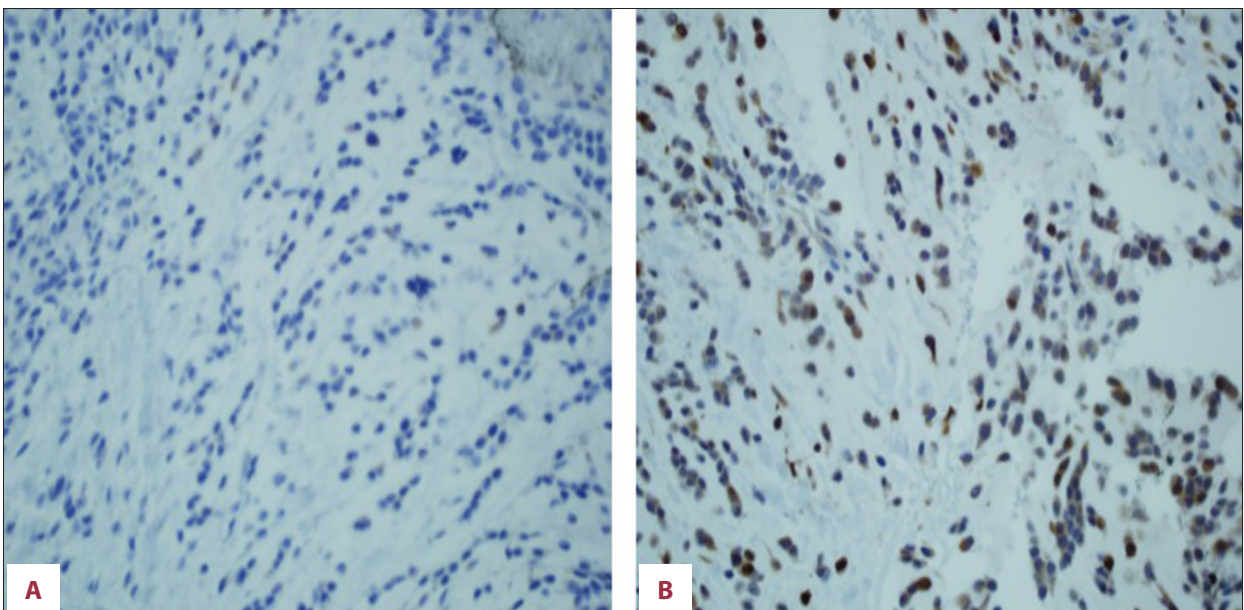
Metastatic work-up was negative and the patient underwent left below knee amputation while awaiting the results of molecular testing. The amputation was planned because the location of the mass would have precluded skin closure. The mass was fully resected with negative margins. The resected tumor was tan-gray and bulging, measuring 9.0×7.0×5.5 cm. The cut surface of the tumor was tan-red and mucinous in appearance, with areas of hemorrhages. The tumor extended to the interdigital area of the second and third toe and involved the articular surfaces of the distal metatarsal heads of the second and third toes. The skin, bone, and soft-tissue margins were grossly viable. The resected margins were negative. As per World Health Organization classification of the soft-tissue tumors, the tumor was identified as EMC (Figure 5). Mitotic rate was 5/10 high-power fields (HPF) and necrosis was present (extent 50%). Histologic grade as per French Federation of Cancer Centers Sarcoma Group (FNCLCC) was Grade 2. Pathologic staging was pT2bNX. The results of molecular testing were positive



**Figure 2.** An approximately 8-cm heterogeneously enhancing, hypodense, mass in the plantar aspect of the forefoot. Flexor digitorum tendon (purple arrow) is encased in the mass.



**Figure 3.** (A – 100×, B – 400×): Histopathology of multiple punch biopsy of mass revealing monomorphic round tumor cells with minimal cytoplasm in loose myxoid background, consistent with extraskeletal myxoid chondrosarcoma.



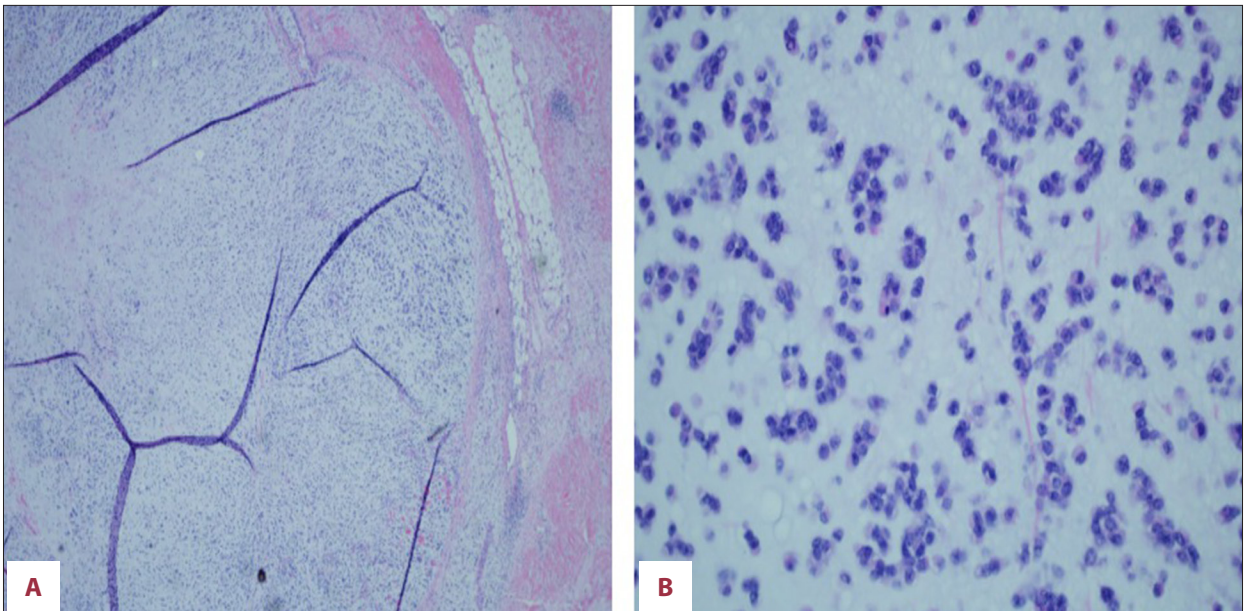
**Figure 4.** (A) Immunohistochemical staining was positive for synaptophysin. (B) Weakly positive for S 100.

for rearrangement of EWSR1 gene at 22q12, thus confirming the diagnosis of EMC.

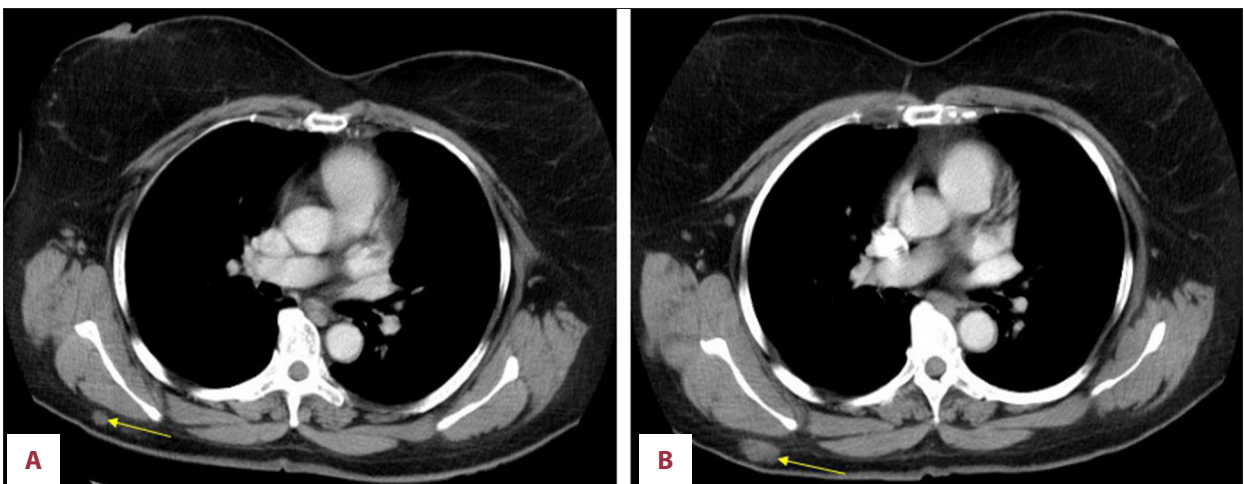
A CT scan of the chest 2 months after the surgery showed a 0.8-cm nodule in the subcutaneous tissues posterior to the right scapula suspicious for metastases (Figure 6A). The patient went back to Jamaica and returned after 6 months. A follow-up CT scan showed a new pulmonary nodule in the right lower lobe measuring 0.4 cm and new lucencies involving T7 and T12 vertebral bodies suspicious for metastases (Figure 7A, 7B).

A new nodule in the right breast measuring 1.3×1.4 cm was also reported (Figure 8A, 8B). There was an interval increase in the size of the soft-tissue nodule in the subcutaneous fat posterior to the right scapula, measuring 1.6×1.1 cm (Figure 6B).

A mammogram showed an irregular nodular mass in the upper outer quadrant of the right breast and a smaller well-defined round mass in the lower aspect of the right breast (Figure 9A, 9B). There were no suspicious microcalcifications, skin thickening, or nipple retraction in either breast. Bilateral



**Figure 5.** Histopathology of surgical specimen revealing. (A) A multinodular architecture and well circumscribed masses with internal fibrous septa. (B) An abundant myxoid matrix containing round or slightly elongated cells with small hyperchromatic nuclei.



**Figure 6.** Chest CT (A) demonstrates a small subcutaneous nodule overlying the right scapula that on follow up (B) has increased in size.

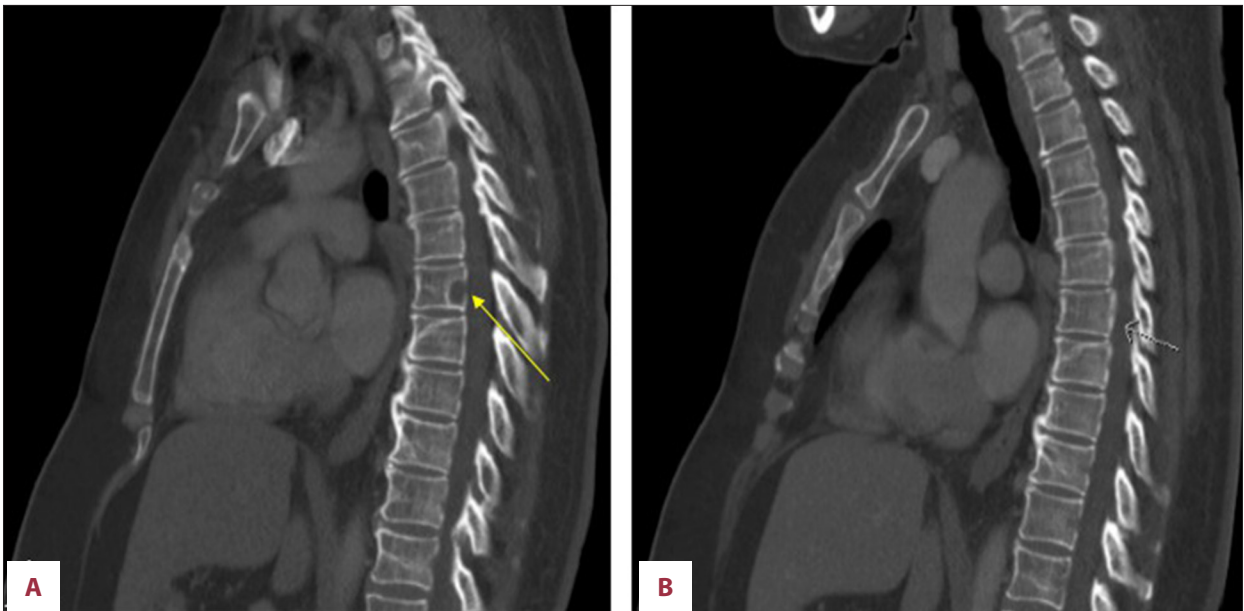
breast ultrasound findings corresponded to that of the mammography (Figure 10A, 10B). A bone scan showed skeletal metastatic disease in the shoulder, thoracolumbar spine vertebra, and single mid-thoracic left rib (Figure 11A, 11B).

The results of the core needle biopsies of masses in the right breast showed an infiltrating, poorly differentiated, mammary carcinoma with mucinous and myxochondroid features, which were morphologically identical to EMC (Figure 12A, 12B). CA 27.29 was normal at 24.4 Units/ml (0.0–37.7 Units/ml). The case was presented to the tumor board. Due to the poor prognosis, treatment options were to seek a second opinion for clinical trial at Memorial Sloan Kettering Cancer Center versus

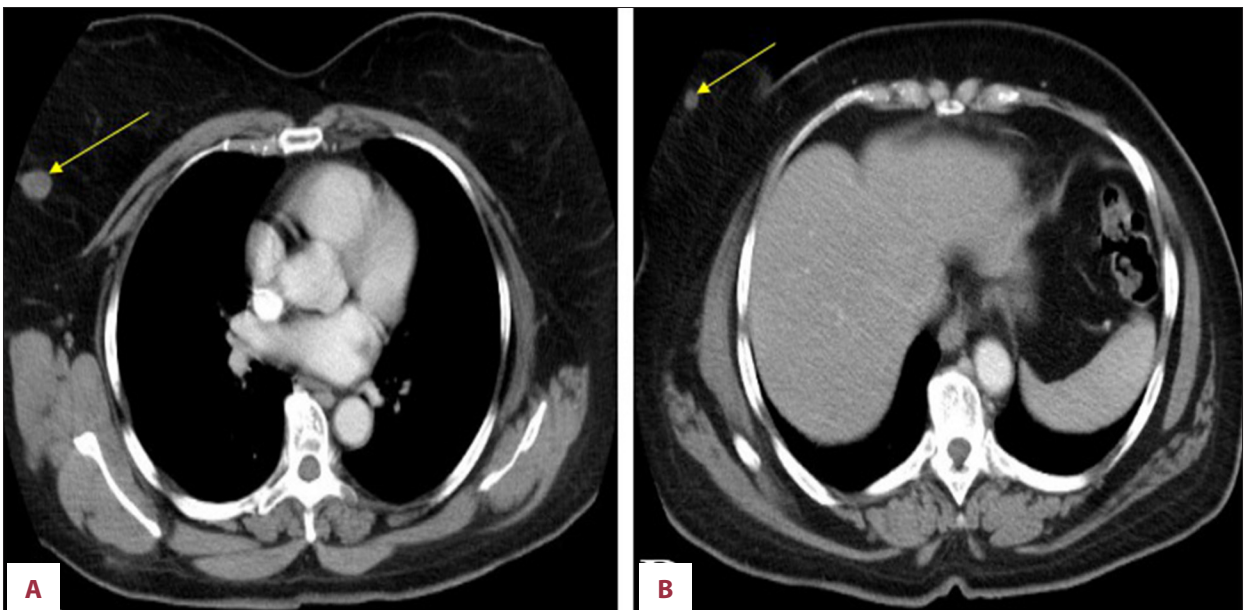
palliative chemotherapy with Ifosfamide/Adriamycin. The patient refused chemotherapy and is currently awaiting a second opinion.

## Discussion

Extraskeletal myxoid chondrosarcoma (EMC) is a rare, low-grade, soft-tissue sarcoma characterized by chondroid and neurogenic differentiation. Tumor cells typically resemble the developing chondroblasts; thus, it is suggested that EMC originates from the primitive cartilage-forming mesenchymal cells [5]. EMC typically presents as a slow-growing mass in the deep



**Figure 7.** Follow-up surveillance CT (A) demonstrates a new lytic lesion in the thoracic spine, not seen on initial study (B).



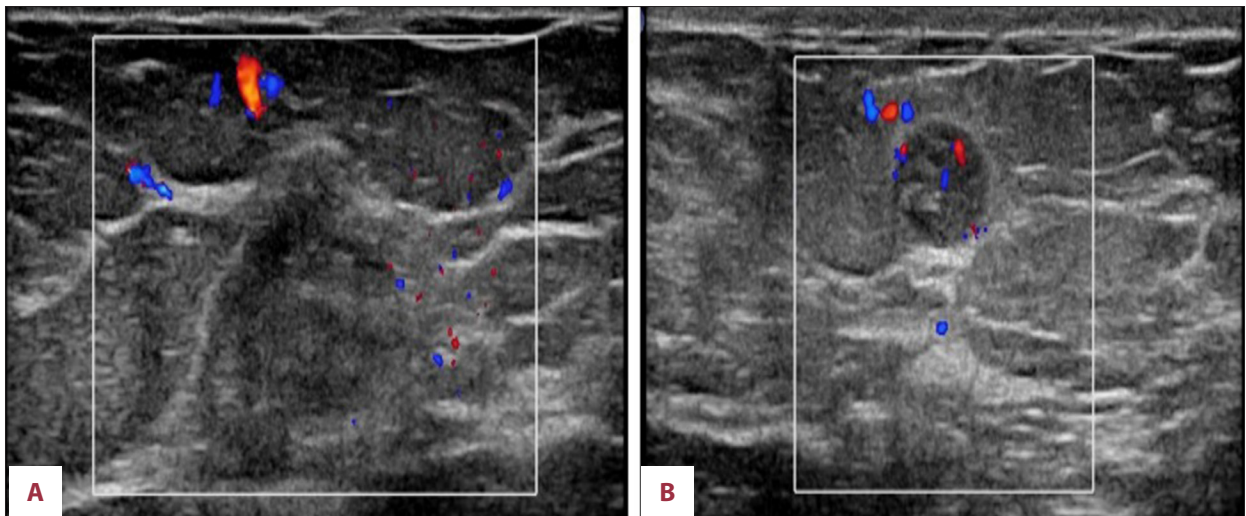
**Figure 8.** New right breast nodules on follow-up surveillance CT.

soft tissues of the lower extremities. It usually involves proximal extremities and limb girdle (60%), distal extremities (20%), and trunk (20%), but can have several unusual sites of origin like the scrotum, finger [6], nasal cavity, central nervous system, and vulva [7]. Recent studies have found that EMC has high propensity for metastases along with a high rate of local recurrences. Metastases have been reported to occur anywhere between 6 to 15 years after the initial diagnosis [8] and were discovered in 1 case after 20 years [4].

The most frequent site for metastasis is the lung, followed by soft tissues, lymph nodes, and bones. In Miess-Kindblom's study of 76 patients, the lung was the most common metastatic site (32%), followed by soft tissue (18%) and bones (5%) [8]. Saleh et al. found that all 10 patients in his study developed lung metastases [9]. Other rare sites of metastases are the mandible, liver, retroperitoneum, right ventricle, pancreases [4], and intracranium [10]. Here, we report the first case of extraskeletal myxoid chondrosarcoma metastatic to the breast.



**Figure 9.** Craniocaudal (A) and mediolateral (B) views of right breast demonstrates two nodular masses. The larger is in the upper outer quadrant and the smaller is in the lower outer quadrant.

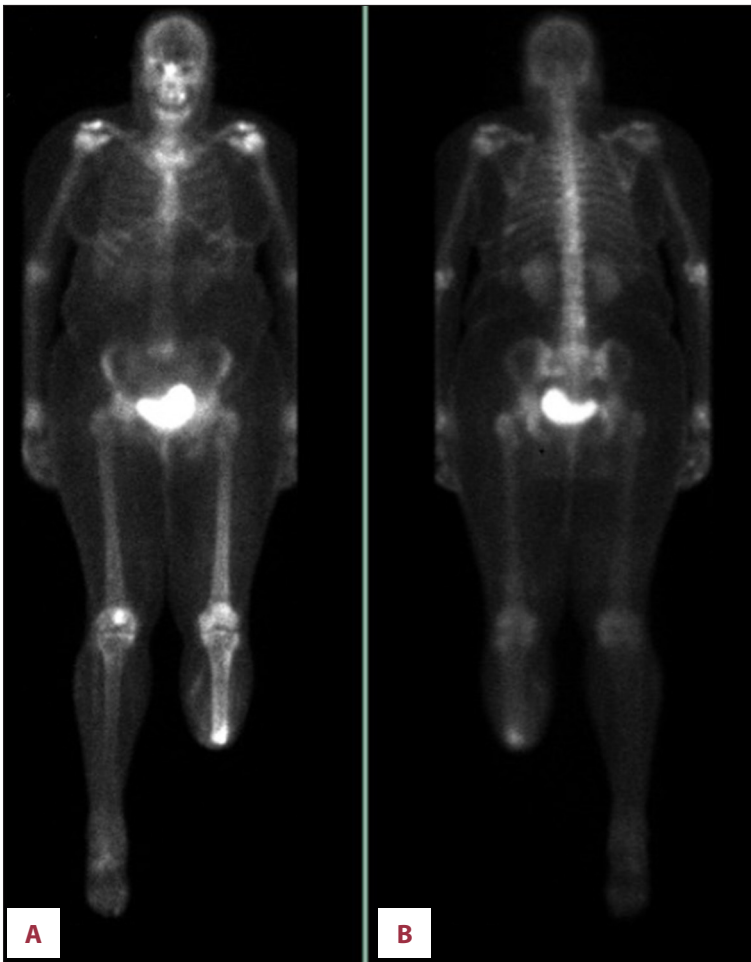


**Figure 10.** Ultrasound images of the right breast reveal the 2 corresponding heterogeneous masses with internal vascular flow that were subsequently biopsied.

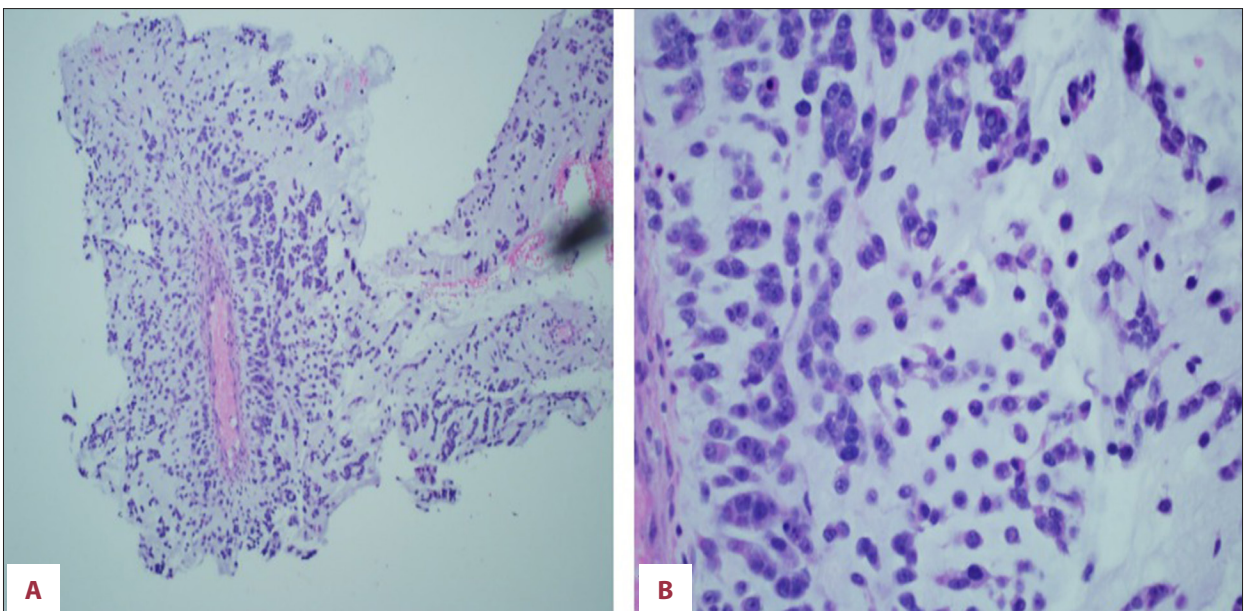
Breast cancer is the most common malignancy in females. However, secondary malignancy metastatic to the breast is rare, accounting for only 0.5–2% of all breast malignancies [11]. Metastases to the breast (in order of decreasing frequency) are: contralateral breast, malignant melanoma, lymphoma,

lung cancer, ovarian cancer, soft-tissue sarcoma, and gastrointestinal and genitourinary tumors [12].

Metastases to breast occur via hematogenous route. Since the upper outer quadrant has the highest blood supply, metastatic



**Figure 11.** A bone scan showed skeletal metastatic disease in the shoulder, thoracolumbar spine vertebra, and single mid-thoracic left rib. (A) Anterior, (B) Posterior.



**Figure 12.** (A – 100 $\times$ , B – 400 $\times$ ): Histology of the breast metastatic lesion showing an infiltrating poorly differentiated mammary carcinoma with mucinous and myxochondroid features.

lesions are frequently found in this area. Mammography may be helpful in distinguishing between primary and metastatic breast malignancy [12]. It is important to differentiate between metastases to the breast and primary breast carcinoma, due to the marked difference in the prognosis. Metastases to the breast are predictive of poor prognosis. In a study of metastatic neoplasms in the breast by Sneig et al., 11 out of 20 patients died soon after the breast metastases were diagnosed [13].

Typically, a metastatic lesion appears as a round, dense mass on mammogram and is generally not associated with microcalcifications or spiculations. The metastatic mass does not cause breast distortion or involve the skin. Moreover, metastatic lesions are likely to be multiple and bilateral. However, sometimes it is difficult to differentiate metastatic lesion from benign lesions like fibroadenoma and certain malignant neoplasms. Fine-needle aspiration cytology (FNAC) plays an important role in differentiating metastases from the primary breast malignancy. Accurate diagnosis of breast metastasis is crucial to avoid unnecessary mastectomy and to implement an appropriate systemic therapy [12].

EMC is characterized by multinodular architecture and well-circumscribed masses with internal fibrous septa. They are composed of round or elongated cells of uniform shape and size separated by variable amounts of mucoid material, and are interconnected to form cords, strands, or clusters. Neoplastic cells have uniform round-to-oval hyperchromatic nuclei with a modest amount of eosinophilic (occasionally vacuolated) cytoplasm. EMC, unlike chondrosarcoma of the bone, rarely have differentiated cartilage cells with distinct lacunae and ossification [14].

A unique feature of EMC is nonrandom reciprocal chromosomal translocation [14]. The most common reciprocal translocation in 75% of the cases of EMC is t(9; 22) (q22; q12), which leads to juxtaposition of the gene EWSR1 (also termed as EWS) on chromosome 22 and NR4A3 (also known as TEC, NOR1 or CHN) on chromosome 9 [4]. It is reported that TAF2N can replace the EWS gene, forming TAF2N-TEC gene fusion, which may account for other cases of EMC [4]. The translocation t(9; 22) (q22; q12) has never been reported in other mesenchymal tumors [14], other translocations being t(9; 17) (q22; q11) and t(9; 15) (q22; q21) [3]. A recently discovered translocation, t(9; 22) (q22; q11), is associated with EMC-producing neuroendocrine secretions [15].

Currently the only curative option for EMC is aggressive control of the localized disease, with early wide local resection with or without radiation therapy. In the published data no chemotherapeutic agent or combination agents have demonstrated efficacy in the treatment of EMC [16]. Only a partial response has been observed with the use of interferon alpha

2b [17]. Complete response in 1 patient and partial response in 1 out of 6 patients was seen with the use of multi-agent chemotherapy by McGory et al. [18]; however, data regarding the agents used was unavailable. Due to the ineffectiveness of chemotherapy, few alternative agents have been studied. In a study by Stacchiotti et al., Sunitinib has been confirmed to have anti-tumor activity in EMC. A correlation was observed between response and EWSR1-NR4A3 fusion. Pazopanib, another antitumor agent, is under clinical trial for use in patients with EMC [19].

EMC is a resilient tumor with an unpredictable behavior. It can behave aggressively with a high rate of metastases and local recurrences, leading to early mortality. McGrory et al. suggested that EMC should be graded as an intermediate- and not a low-grade tumor [18]. It is important to know and recognize the adverse prognostic factors in EMC for early management. Cellularity is one of the most important prognostic factors. High cellularity, Ki-67 activity ( $\geq 10\%$ ) and high mitotic activity ( $> 2$  mitotic figures/10 HPF) are poor prognostic factors. Studies have also shown that tumor size ( $\geq 10$  cm) is also an important prognostic factor in terms of survival rate as well as metastases [2]. However, a study by Kapoor et al. showed no correlation between the tumor size and metastases-free interval [6]. Rhabdoid phenotype and anaplasia may be associated with poor prognosis [2]. Kapoor et al. proposed the hypothesis that higher tumor density on contrast-enhanced CT may be associated with poor prognosis. However, contrary to the above hypothesis, the tumor density in our patient was not high (32 Hounsfield units).

Local recurrences occur in about 45–50% of the cases but do not affect the overall survival, in contrast to metastases, which is an adverse prognostic factor [4]. Female sex and higher mitotic rate are adverse prognostic factors for local recurrences [8]. Survival has been reported to range from few months up to 18 years from the time of initial diagnosis [4]. Meis-Kindblom et al. estimated that the survival rate at 5-, 10-, and 15-years was 90%, 70%, and 60%, respectively [8].

## Conclusions

This case demonstrates that even low-grade tumors can metastasize to rare sites – in our case, the breast. Although rare, metastases to the breast should be considered in the differential diagnosis of a breast mass to avoid unnecessary mastectomy and to implement appropriate systemic therapy. EMC, despite being a slow-growing tumor, has a very poor long-term prognosis due to the high propensity for metastases resulting in tumor-associated death. Thus, in accordance with previously published data, we recommend that EMC should be classified as intermediate as opposed to low grade. Wide excision



helps control the local recurrences, but does not necessarily prevent distant metastases, as in our case. Close long-term follow-up is needed due to the unpredictable behavior of EMC. Since the lung is the most frequent site for metastases, imaging of the chest at regular intervals is crucial.

### Statement

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