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## Breast Imaging

# Synchronous breast cancer and alveolar rhabdomyosarcoma bone marrow metastases

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## ABSTRACT

Alveolar rhabdomyosarcoma (RMS) is primarily a malignancy of childhood and adolescence. While RMS is rare in adults, the breast and the bone marrow are known but uncommon sites for metastatic disease. Bone marrow is also a known sanctuary site for metastatic breast cancer. We present the case of a woman with a remote history of breast cancer and RMS who developed anemia and thrombocytopenia of unknown etiology. Additional laboratory tests were negative for a cause; therefore, the decision was made to proceed with a bone marrow biopsy. The initial biopsy results were consistent with breast cancer metastasis. Subsequent diagnostic imaging of the breast led to biopsy of an enlarging morphologically benign breast mass, unexpectedly yielding alveolar RMS. This unanticipated diagnosis led to re-evaluation of the bone marrow, this time showing synchronous metastases from breast carcinoma and alveolar RMS. Imaging findings of this patient, along with literature review of RMS imaging characteristics, will be reviewed.

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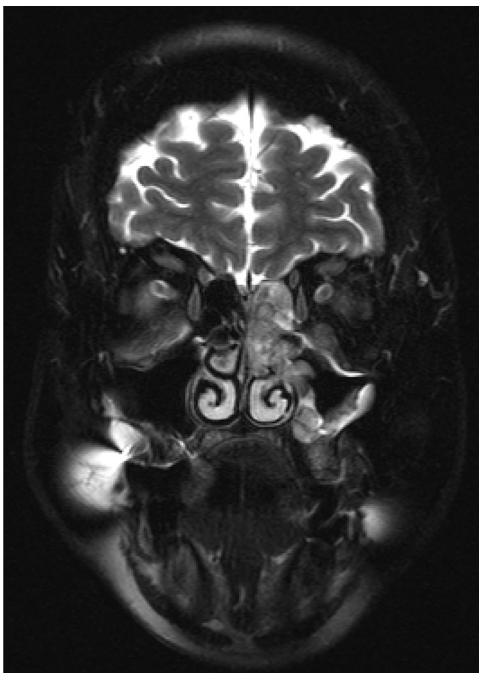
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## Introduction

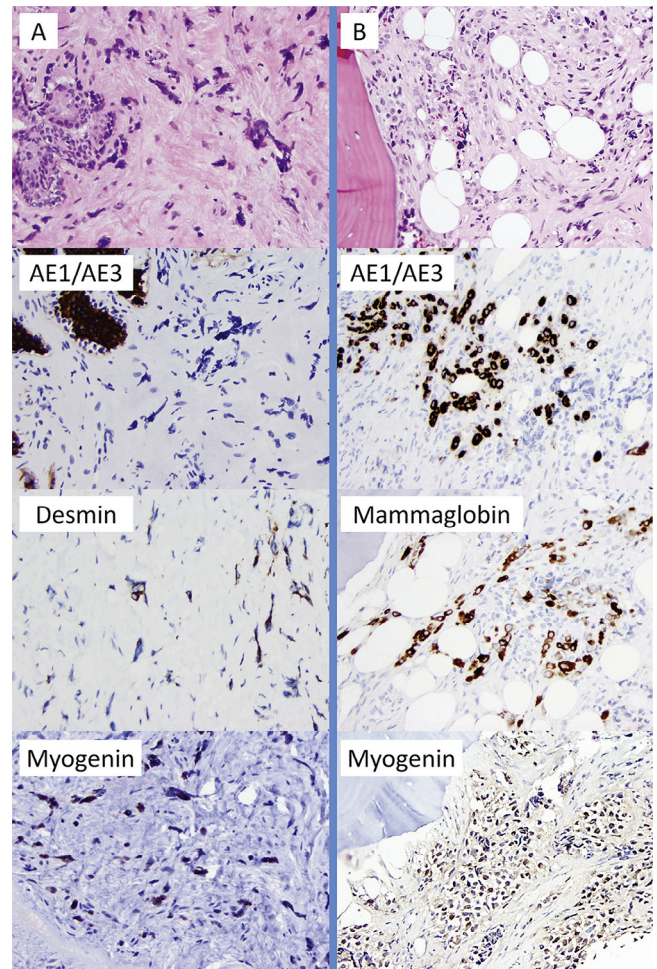
Alveolar rhabdomyosarcoma (RMS) is primarily a malignancy of childhood and adolescence [1]. While RMS is rare in adults, the breast and the bone marrow are known but uncommon sites for metastatic disease [2]. Bone marrow is also a known sanctuary site for metastatic breast cancer [3]. We report a case of a woman with a history of stage III estrogen receptor± breast cancer and stage IV alveolar RMS, who presented with anemia and thrombocytopenia. She was found to have bone marrow involvement of both malignancies along with RMS metastatic to the breast. Although there are certain imaging features that may be associated with metastatic lesions within the breast, the characteristics are not specific [4]. Therefore, a high level of suspicion must be employed by the interpreting radiologist in such cases. Imaging findings of this patient, along with literature review of RMS imaging characteristics, will be reviewed.

## Case report

A 66-year-old woman presented with left-sided epistaxis, excessive lacrimation, and a palpable left cervical mass. Magnetic resonance imaging showed a mass centered within the left ethmoid complex with extension to local structures, mediastinal and cervical lymphadenopathy, and a thoracic spine lesion (Fig. 1). Biopsy of the dominant mass revealed a high-grade RMS with morphologic features of alveolar subtype (Fig. 2). She com-

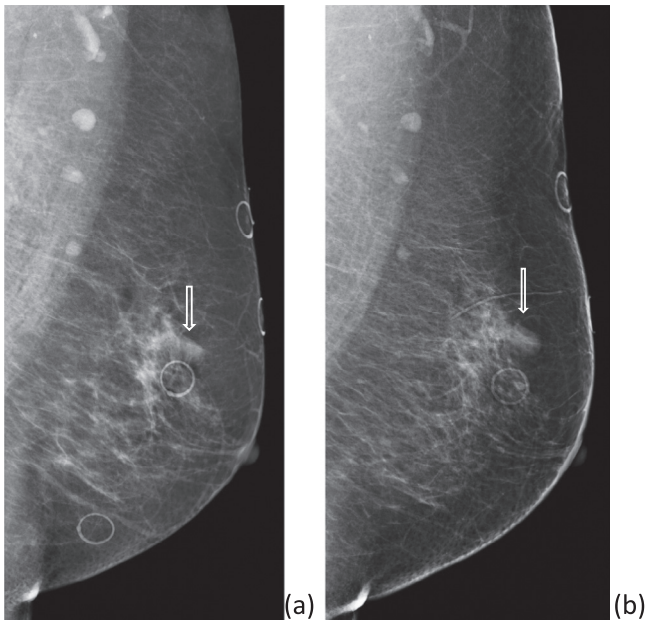


**Fig. 1 – Contrast-enhanced T2-weighted magnetic resonance imaging image demonstrates a heterogeneously enhancing mass centered in the left nasal cavity with extension into the maxillary and ethmoid sinuses, biopsy-proven to be rhabdomyosarcoma.**



**Fig. 2 – Pathology. Representative microscopic sections of the patient's left breast biopsy (column A) including a hematoxylin and eosin (H&E) stained section showing a benign breast duct on the left as well as an infiltrate of large atypical cells that are negative for epithelial marker AE1/AE3 and positive for muscle markers desmin and myogenin, consistent with metastatic rhabdomyosarcoma. The patient's H&E stained bone marrow biopsy (column B) shows a mixed infiltrate consisting of epithelioid cells with round nuclei that are positive for AE1/AE3 and breast marker mammaglobin, consistent with metastatic breast carcinoma, as well as a more atypical population that is morphologically similar to the tumor in the breast biopsy that is positive for myogenin, consistent with metastatic rhabdomyosarcoma.**

pleted 10 of 14 cycles of chemotherapy (stopped due to patient's preference) resulting in resolution of chest lymphadenopathy and a partial response of nasopharyngeal tumor. She additionally received radiation to the residual tumor in left neck lymph nodes. Interestingly, the patient also had a remote history of stage III breast cancer 16 years prior, which had been treated with a right mastectomy and axillary lymph node dissection, followed by chemotherapy, radiation therapy, 1 year of tamoxifen, and 4 years of anastrozole.



**Fig. 3 – Successive mammography.** Mammograms performed 5 years apart (A) 2011 and (B) 2016 demonstrate a stable oval, circumscribed mass without suspicious features concerning for malignancy.

Six months after completion of radiation therapy for her RMS, she complained of light-headedness and was found to have anemia and thrombocytopenia. Workup for infectious causes, hemolysis, and microangiopathic hemolytic anemia was unrevealing. Given the history of 2 primary carcinomas, the decision was made for nontargeted marrow biopsy of the right iliac crest for further evaluation. Biopsy results showed findings compatible with metastatic breast cancer.

Due to the metastatic breast cancer diagnosis, the patient was referred to our breast imaging center for diagnostic evaluation. Bilateral mammogram and ultrasound were performed. An oval, circumscribed mass was identified in the upper outer left breast. The mass was stable mammographically dating back to 2011 and had been followed sonographically in the past as a probably benign mass. After documenting 2-year stability on sonographic follow-up, the mass had been deemed benign. Because no additional findings were identified on diagnostic

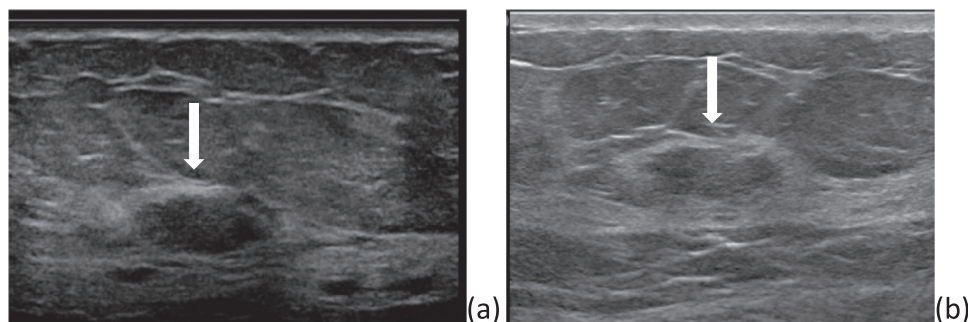
mammogram, targeted ultrasound evaluation was obtained of the mass. At the 1:00 location in the left breast, corresponding to the mass on mammography, an oval, circumscribed, parallel oriented mass was identified (Figs. 3 and 4). Although no significant change could be appreciated mammographically, the mass showed 28% interval growth compared to an ultrasound performed 6 months prior. Therefore, ultrasound-guided biopsy was recommended per Breast Imaging Reporting and Data System (BI-RADS) recommendations. Tissue sampling revealed a minute focus of atypical cell consistent with RMS (Fig. 2). This prompted a repeat bone marrow biopsy that showed cells morphologically similar to those in the initial bone marrow biopsy but with AE1/AE3 negative, desmin rare positive, and myogenin positive cells consistent with metastatic RMS (Fig. 2). Findings were compatible with 2 different solid primary cancers (breast and RMS) with synchronous bone marrow metastases. She is currently undergoing chemotherapy for both cancers.

## Discussion

### *Patterns of bone marrow metastasis*

RMS is the most common pediatric soft-tissue sarcoma but only accounts for about 3% of adult sarcomas and is associated with a worse prognosis in adults [1–3]. The alveolar subtype is characterized by typical morphologic findings and FOXO1-PAX3 translocation. Typical presentation is with a mass of the head and neck, extremities, or urogenital organs [4]. Bone marrow infiltration has been described in about one-third of patients with metastatic disease [5].

The bone marrow is known to be a sanctuary site for breast cancer. A pooled analysis of 4703 patients with stage I-III breast cancer demonstrated that 30.6% had micrometastases to the bone marrow. Increasing prevalence was seen with increasing stage [6]. The rates of bone marrow micrometastases increase with tumor grade (22.5%, 29.9%, and 34.5% for grade 1, 2, 3 tumors, respectively,  $P < .001$ ) and high 21-gene recurrence score (7% vs 21% for  $RS < 18$  vs  $RS \geq 18$ ,  $P = .03$ ) [6,7]. After multivariate analysis adjusting for tumor size, grade, lymph node metastasis, and hormone-receptor expression, the presence of micrometastases to the bone marrow is associated with increased risk of disease recurrence (hazard ratio 1.85, 95%



**Fig. 4 – Successive sonography.** Ultrasounds performed 5 years apart. (A) In 2011, the ultrasound demonstrates a circumscribed  $1.1 \times 0.4 \times 1.0$  cm oval, circumscribed, parallel oriented hypoechoic mass. (B) In 2016, the mass enlarged, measuring  $1.2 \times 0.5 \times 1.5$  cm, while maintaining similar benign features.

confidence interval 1.59-2.14) and breast cancer mortality (hazard ratio 1.93, 95% confidence interval 1.58-2.36 [6]. While the continued presence of bone marrow micrometastases is associated with worse prognosis, it has been known to persist despite adjuvant chemotherapy [8,9]. Although their presence or absence is prognostic, evaluation for bone marrow micrometastases by bone marrow biopsy is not a routine part of breast cancer evaluation because it may never be clinically significant, and there is no data suggesting additional therapy would provide benefit. Nevertheless, a small portion of breast cancer patients can develop symptomatic bone marrow carcinomatosis which is associated with a poor prognosis and the resultant cytopenias make treatment with cytotoxic chemotherapy a challenge [10].

Based on our review, 2 simultaneous solid malignancies in the bone marrow have not been described. Case reports have described hematologic and solid malignancies concurrently infiltrating the bone marrow [11–13].

### Breast metastasis and radiographic presentation

Breast masses are characterized by a standardized system called BI-RADS, and a number is assigned for its classification based on suspicion of malignancy [14]. BI-RADS 3 masses are considered “probably benign” and are felt to have a less than a 2% chance of malignancy. It is recommended that these masses are followed up at 6-, 12-, and 24-month intervals after initial imaging and ultimately need to demonstrate 2 years of stability to be considered benign. Probably benign features include a circumscribed margin, oval shape, and parallel orientation [15].

Although less common, pediatric RMS series have reported breast cancer metastases, especially in patients with the alveolar subtype [16,17]. Adult patients with RMS and a metastasis to the breast have only been described in 2 recent case reports [18,19]. Metastatic disease to the breast account for 0.4%-3% of breast masses with melanoma, lymphoma, gastric cancer, and lung cancer being more common as primary sites [20–22]. RMS in the breast has been shown to have variable imaging characteristics, including oval or nodular masses on mammography that may be large. Sonographic examination has been shown to demonstrate an inhomogeneous, hypoechoic mass with defined margins and an oval shape, characteristics that are typically considered probably benign [23]. RMS masses have also been shown to have posterior acoustic enhancement, a finding that has also been described with simple cysts [15,24]. Importantly, however, even when a mass retains benign features, radiology literature recommends tissue sampling any mass with a greater than 20% increase in volume in 6 months [15]. In addition, the clinical context should be considered, and biopsy should be performed if clinically warranted.

In this case report, the breast mass appeared stable mammographically for over 5 years with overall benign imaging characteristics. Although the mass retained benign features, it did increase in size by 28% over a course of 6 months. The decision to ultimately biopsy was guided by the increase in size and the findings of metastatic breast cancer in the bone marrow.

### Conclusion

Cytopenias in patients with solid tumors have a broad differential including toxic effects of chemotherapy or radiation, secondary malignancies, and marrow infiltration from the primary tumor. While RMS and breast cancer metastases to the bone marrow are not uncommon, this is the first case, to our knowledge, in which the presence of 2 solid tumors in the bone marrow have been reported. When evaluating a patient with breast cancer, clinical context must be considered and bone marrow biopsy may be required to arrive at an accurate diagnosis. Likewise, imaging characteristics should also be viewed with clinical context in mind. Biopsy may be necessary in a certain subset of patients even with classically “benign” or “probably benign” features, particularly when there is a documented significant change in size or high clinical suspicion.

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