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Primary Alveolar Soft Part Sarcoma (ASPS) of the Breast

Report of a Deceptive Case with Xanthomatous Features Confirmed by TFE3 Immunohistochemistry and Electron Microscopy

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Alveolar soft part sarcoma (ASPS) is a rare neoplasm that most commonly presents in the lower extremities. Although ASPS has distinctive histologic features, it may cause diagnostic problems when it arises in unusual locations. To our knowledge, only 1 case of ASPS arising within the breast has previously been reported. Here, we report a second case of primary mammary ASPS. The patient was a 44-year-old woman who presented with a breast mass. Needle biopsy was performed, yielding a polygonal cell lesion with abundant, predominantly xanthomatous cytoplasm. The cells labeled strongly for the histiocytic marker CD68, suggesting a benign macrophage-rich lesion. However, the unusual nature of the lesion as well as the prominence of nucleoli prompted suggestion for an excision. The excision more clearly revealed the lesion's alveolar architecture and demonstrated cells with more eosinophilic cytoplasm, along with the xanthomatous cells. The diagnosis of ASPS was confirmed by electron microscopy, which revealed characteristic membrane-bound rhomboidal crystals, as well as by nuclear labeling for TFE3 protein by immunohistochemistry. With this report, we confirm the utility of a novel immunohistochmical technique for the identification of an ASPS presenting in an unusual locale.
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Alveolar soft part sarcoma (ASPS) is a rare malignancy that constitutes 0.5% to 0.9% of all soft tissue sarcomas in adults [1,2] and 0.8% to 1.8% of those in children [3]. Whereas ASPS most commonly presents in the lower extremities in adults [4], cases have also been reported in the retroperitoneum, lung, pulmonary vein, sacrum, stomach, mediastinum, and female genital tract [5]. ASPS has distinct histologic features that are usually diagnostic on routine H&E sections. The tumor cells are arranged in nests separated by thin, sinusoidal vessels, and their prominent discohesion gives rise to an alveolar architecture. Cytologically, the tumor cells of ASPS are polygonal with vesicular chromatin, prominent nucleoli, and abundant granular eosinophilic cytoplasm. Characteristic intracyto-

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plasmic crystals may be identified on a PAS-diastase stain, which correspond ultrastructurally to membrane-bound, rhomboidal crystals. However, crystals can range from numerous to sparse [4].

When ASPS presents in unusual locations and/or the biopsy sample is small, the diagnosis may become quite difficult. This is in part because a large number of more common neoplasms also typically feature eosinophilic, polygonal cells in an alveolar architecture, including malignant melanoma, renal cell carcinoma, granular cell tumor, paraganglioma, and alveolar rhabdomyosarcoma. Furthermore, ASPS that present in the head and neck of children commonly have a more compact architecture easily confused with that of benign granular cell tumor. Since ASPS has traditionally lacked a specific immunohistochemical marker, such cases were often difficult to resolve with certainty without ultrastructural examination.

Recently, ASPS has been shown to harbor a specific der(17) t(X;17)(p11.2;q25) chromosome translocation, which results in a *ASPL-TFE3* gene fusion [6]. Because the ASPL-TFE3 fusion protein is overexpressed relative to native TFE3, we previously postulated that the ASPL-TFE3 fusion protein might be detectable by immunohistochemistry, whereas native TFE3 is not. Indeed, we have recently shown that nuclear labeling for the TFE3 protein in formalin-fixed, paraffin-embedded material is a sensitive and specific immunohistochemical marker for ASPS and a subset of pediatric renal carcinomas that also bear *TFE3* gene fusions [7]. The immunohistochemical assay for TFE3 should be particularly useful for establishing the diagnosis of ASPS in unusual clinical settings.

We now report an unusual case of an ASPS arising in the breast. Because of this tumor's unusual xanthomatous, histiocyte-like morphology, and immunoreactivity for CD68, along with the unusual location, the diagnosis was par[illegible]

magnetic resonance imaging (MRI) showed a 5 mm lesion in the left cerebral hemisphere thought to represent a venous angioma. Concurrent with the initial brain MRI, she underwent mammography and breast ultrasonography; the latter revealed a 1.5 cm nodule in the left breast. A follow-up mammogram 1 month later again showed a 1.6 cm nodule in the left breast. An ultrasound-guided core needle biopsy was taken, the results of which are discussed in the following section. Because of the unusual nature of the lesion encountered in the needle biopsy, an open biopsy was recommended and performed 1 month later. Following the excision, a repeat mammogram showed another lesion near the chest wall. Computed tomography (CT) of the chest confirmed the presence of this lesion, but also showed multiple bilateral pulmonary masses consistent with metastasis. The patient was started on single-agent chemotherapy (Gemcitabine) 4 months after diagnosis. The therapy was discontinued 25 months after diagnosis secondary to Gemcitabine-associated hemolytic uremic syndrome (HUS) and renal failure.

Since diagnosis, the patient has been followed up with serial chest CT scans, which were unchanged until 30 months after diagnosis. At this time, increased sizes of the pulmonary nodules were noted. The patient has also undergone serial brain MRIs, which were unchanged again until 30 months after diagnosis, when a new 2–3-mm enhancing lesion suspicious for metastasis was identified. At this writing, the patient is alive with metastatic disease 32 months after diagnosis.

Pathologic Findings

Although it was designated "breast biopsy," the needle core biopsy lacked breast epithelium, but instead was composed almost entirely of a sheet of [illegible]

thought to be unusual for histiocytes. The diagnosis of alveolar soft part sarcoma (ASPS) was considered, and PAS-diastase stain was performed, yielding abundant particulate material within the cytoplasm but no definitive crystals. Because of the diagnostic uncertainty, a complete excision was suggested.

The excision revealed a 1.1 cm mass with cytologic features identical to those described above. In this larger sample, the nested architecture of the lesion was more evident, as was its intramammary location adjacent to benign ductal epithelium (Fig. 1). The tumor cells were again immunoreactive for CD68. A PAS-diastase stain showed abundant granular material with a suggestion of incipient crystal formation. With use of previously published methods [7], the tumor cells showed strong nuclear labeling for TFE3 protein by immunohistochemistry, while surrounding stromal cells were completely negative.

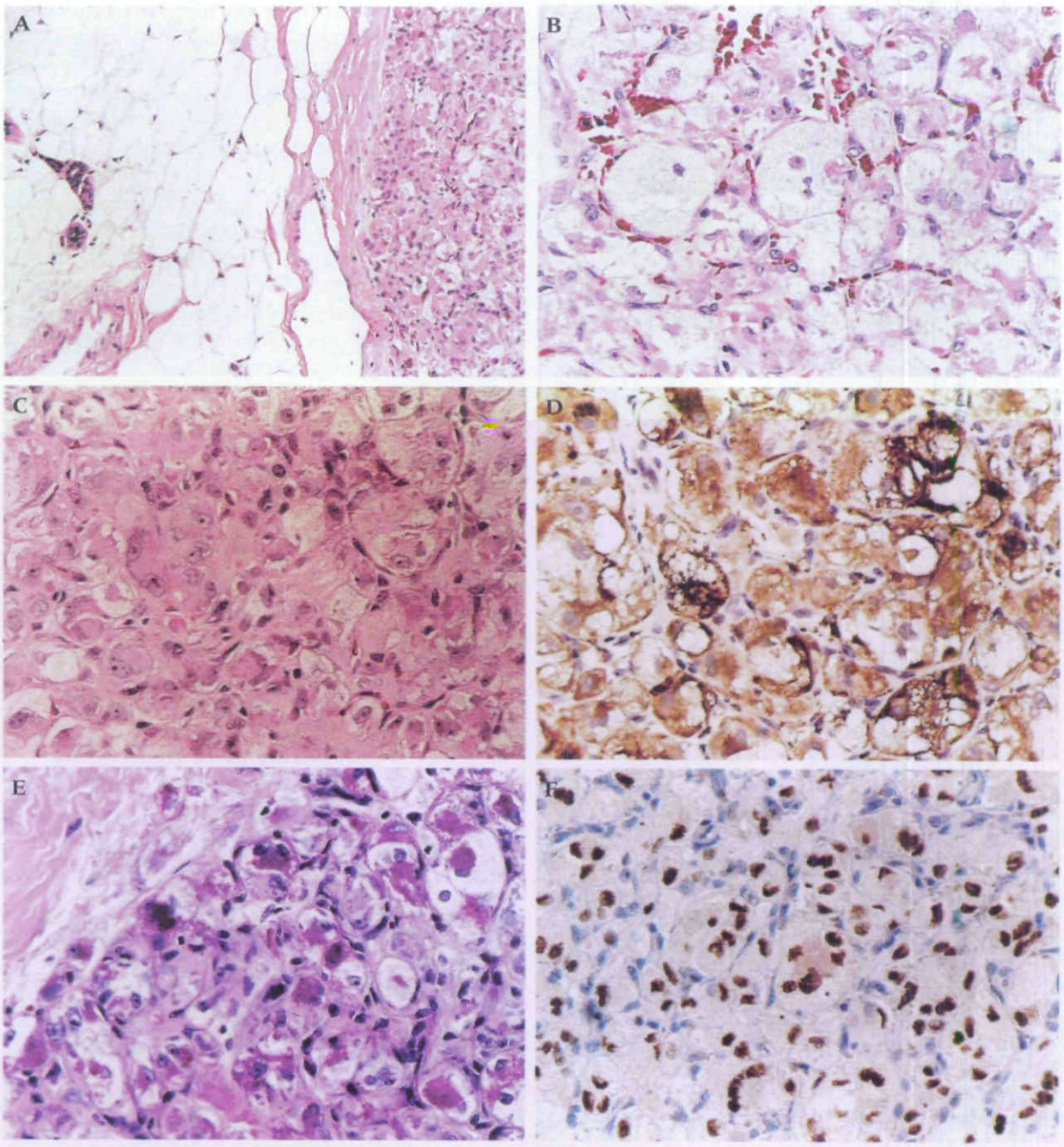


Fig. 1. Breast excision specimen. **A.** Low-power view shows the polygonal cell lesion adjacent to benign breast epithelium. **B.** High-power view highlighting the xanthomatous appearance of the tumor cells. **C.** Other foci show the usual abundant eosinophilic cytoplasm typically seen in ASPS. **D.** CD68 (KP-1) labels the tumor cells diffusely. **E.** Abundant PAS-positive, diastase-resistant material is present in the tumor cells' cytoplasm. **F.** Immunohistochemical staining for TFE3 labels tumor cell nuclei intensely but does not label surrounding stromal cells.

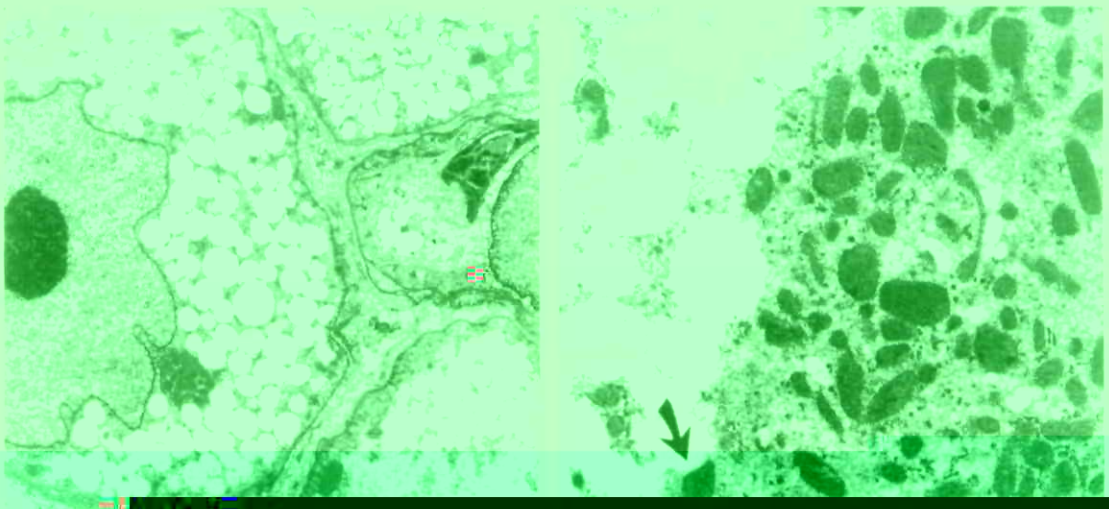
Ultrastructural Analysis

Electron microscopy (EM) was performed on a sample of the lesion that was removed from the paraffin block and deparaffinized. By EM, the cells contained numerous membrane-bound, electron-dense granules of varying size and shape, with occasional granules having a rhomboid shape (Fig. 2). The largest granules measured 600–700 nm in greatest dimension, although the majority were between 200 and 400 nm. Periodicity within the granules was not observed, although this could be related to the tissue having been reprocessed from paraffin. Many of the cells contained abundant lipid vacuoles, corresponding to the appearance of the cytoplasm by light microscopy.

Discussion

We report herein the second documented case of primary mammary ASPS. We are aware of 1 other reported case, included within a review of 25 primary mammary sarcomas [8]. Details of the clinical presentation and outcome for that case were not provided. We know of 1 other case of ASPS of the pectoralis major muscle presenting as a breast mass [9]. Additionally, there have been 2 reports of ASPS metastatic to the breast [10,11], 1 of which presented with bilateral tumors [11]. Hence, ASPS involvement of the breast is not common.

The differential diagnosis for this unusual lesion was broad, and included rhabdomyosarcoma, granular cell tumor, histiocytoid mammary carcinoma, and a macrophage-rich benign process. Rhabdomyosarcoma was suggested by the abundant eosinophilic cytoplasm of the tumor cells, as well as the focal immunohistochemical labeling for desmin. While primary rhabdomyosarcoma of the breast is exceedingly rare, it is known that alveolar rhabdomyosarcoma has a strong predilection to metastasize to the breast. The absence of actin labeling diminished this possibility, as did the ultrastructural findings. Granular cell tumor is a relatively common mimic of breast cancer, given its infiltrative border and tendency to cause skin retraction. The negativity for S100 protein essentially eliminated this possibility. Lipid-rich or histiocytoid breast carcinomas would label for cytokeratin, and the absence of any reactivity for epithelial markers eliminated this consideration.



Most problematic in this case was the distinction from a benign macrophage-rich lesion such as xanthogranuloma, a fibrohistiocytic lesion with xanthoma cells, or a xanthoma. These possibilities were suggested by the vacuolated cytoplasm of the tumor cells, the lack of mitotic activity or necrosis that would suggest malignancy, and the strong immunoreactivity for CD68. However, all of these features are compatible with the diagnosis of ASPS. While it is uncommon, ASPS tumor cells may bear intracytoplasmic lipid droplets within their cytoplasm that contribute to a clear cell appearance [1,5]. ASPS is a notoriously slow-growing neoplasm, so mitoses and other "aggressive" histologic features are typically absent. Finally, immunohistochemical labeling for CD68 is essentially a nonspecific sign that a cell contains a significant number of lysosomes. While macrophages characteristically have abundant lysosomes and hence label intensely for CD68, any tumor cell with prominent macrophages will label for this marker. Indeed, both of the 2 ASPS reported in the literature to have been stained for CD68 were positive [5].

Given the unusual nature of this lesion, and the distinct clinical consequences of the diagnosis of ASPS versus a benign histiocyte-rich lesion, we felt that additional confirmatory studies were needed. Electron microscopy has until recently been the most definitive way to establish a diagnosis of alveolar soft part sarcoma. However, as mentioned previously, not all tumors will demonstrate the characteristic membrane bound rhomboidal crystals in the sampled material, and ultrastructural morphology may be suboptimal in formalin-fixed, paraffin-embedded tissue blocks, as was the case here. Additionally, electron microscopy is relatively expensive and time-consuming. Immunohistochemistry for TFE3 has recently emerged as a specific marker of ASPS and a subset of pediatric renal cell carcinomas that bear *TFE3* gene fusions. While TFE3 is ubiquitously expressed, gene fusions involving *TFE3* result in overexpression of the fusion protein relative to native TFE3, such that it becomes detectable by immunohistochemistry. Nuclear labeling for TFE3 by immunohistochemistry has proven to be more than 97% sensitive and more than 99% specific for these neoplasms [7]. TFE3 thus joins a group of immunohistochemical assays that reflect gene fusions in a highly sensitive and specific fashion; other examples include ALK (for anaplastic large cell lymphoma and inflammatory myofibroblastic tumors), EWS (for Ewing sarcoma/PNET), WT-1 (for desmoplastic round cell tumor), and PPARγ (for PAX8-PPARγ positive thyroid follicular tumors). Since it is a routine immunohistochemical assay, TFE3 labeling has the considerable advantage of being less expensive and less time consuming than electron microscopy.

In summary, we report the second known case of alveolar soft part sarcoma arising in the breast. In making this diagnosis, we confirm the utility of a novel immunohistochemical technique in the identification of ASPS.

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