

Pleomorphic Hyalinizing Angiectatic Tumor [PHAT]: A Case Report Focusing on the Differential Diagnosis

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1. Abstract

Pleomorphic hyalinizing angiectatic tumor [PHAT] is a very rare entity of soft tissue non- metastatic tumor, of unknown etiology and uncertain behavior, considered a “neoplasm of uncertain behaviour of connective or other soft tissue” by the World Health Organization [2020] which may recur locally. It develops in subcutaneous tissue of the lower extremities, more frequently in the region of the ankle and foot, and rarely as a deep-seated soft tissue mass in locations such as the perineum, arms, head and neck, and viscera. Although inconsistent cytogenetic data have been reported on PHAT so far, there are potential morphological and genetic overlaps with hemosiderotic fibrolipomatous tumor [HFLT] and myxoinflammatory fibroblastic sarcoma [MIFS]. Here, we report a case of an 87-year-old man presented with an edema in left mama, present for 6 months. On examination, a 48x35x21 mm heterogeneous nodule with abundant vascularization was observed.

2. Introduction

The pleomorphic hyalinizing angiectatic tumor [PHAT] is a rare tumor of uncertain lineage described by Smith et al in 1996 in a series of 14 cases [1]. In “Soft Tissue and Bone Tumours” by the World Health Organization 2020, PHAT is considered a “neoplasm of uncertain behavior of connective or other soft tissue”[2] and is defined as “very rare” with, to our knowledge, about 100 cases reported in international literature [3]. It affects patients with a mean age of 50 years, ranging from the first to the eighth decade of life, with slight female predilection [4,5]. It occurs as a painless, slow-growing mass and is often found in the subcutaneous tissue of the lower extremities, especially in the ankle and foot, and rare-

ly presents as a deep soft tissue mass in locations as perineum, buttock, arms, head and neck, and viscera [6]. In the current World Health Organization classification, PHAT, Hemosiderotic Fibrolipomatous Tumor [HFLT], and Myxoinflammatory Fibroblastic Sarcoma [MIFS] are considered 3 different entities. However, because of their similar clinical presentation, overlapping morphologic features, and shared cytogenetic change of t[1;10] [p22;q24] translocation, their relationship has been debated, with controversial opinions being held among different experts [7]. We report a case of PHAT at the level of breast in an 84-year-old patient. We also focus on the differential diagnoses of these entity and review the literature.

3. Case Report

An 87-year-old patient with a personal history of hypertension, hypercholesterolemia, chronic bronchitis, and prostate cancer. He came to the consultation due to a tumor in the left breast, which during the examination revealed a soft and mobile submammary tumor associated with edema and skin redness. No axillary or supraclavicular lymphadenopathy was detected. A mammography and ultrasound scan were performed. The mammography described a nodule with clear edges and the ultrasound scan an ovoid hypoechoic nodule with clear edges, heterogeneous with abundant vascularization and a dimension of 48 x 35 x 21 mm.

Microscopically, this tumor was well circumscribed, with numerous ectatic blood vessels of various sizes, close to each other with perivascular hyalinization and subendothelial fibrin deposit. Between vessels atypical cells can be observed, arranged in groups or dispersed, with hyperchromatic and spindle pleomorphic charac-

teristics, some with intranuclear inclusions and multinucleate cells as well. The stroma showed a dense and diffuse infiltrate of mixed inflammatory cells composed of lymphocytes, plasma cells, mast cells and few hemosiderin-laden macrophages. Mitotic figures were scarce. It did not show clearly thrombotic blood vessels or calcification, but it showed areas of hemorrhage.

4. Discussion

PHAT was first reported by Smith et al in 1996. They described 14 cases of a low-grade tumor with features of both neurilemmoma and malignant fibrous histiocytoma [MFH], because of several common features, such as unusual vasculature, intranuclear cytoplasmic inclusions, absence of mitosis, and mast cell abundance [1,7]. To date, about 100 cases have been reported, the largest series included 41 cases [1,8-14]. PHATs mainly occur in adults of both sexes during their fifth or sixth decade of life [range, 10–86 years]. The average dimensions are around 5.3 cm, with an exceptional case of 26.3 cm in male breast reported by Lee et al. in 2005[13]. The tumors frequently involve the subcutis of lower extremities, such as feet, ankles, and legs.

Occasionally the tumor cells may extend to nearby skeletal muscle or superficial dermis with entrapment of skin adnexa. There are case reports of PHAT occurring at other body sites, such as the back, chest wall, buccal mucosa, breast, forearm, buttock, hilum of kidney, renal parenchyma, palpebra, and pelvic retroperitoneum [15-18]. The best therapeutic strategy is represented by large surgery with free margins [19,20]. The recurrence rate is around 30–40% of cases [2,19,20] when it is not possible to be surgically radical, although distant metastases have never been reported [2].

Local radiotherapy has also been shown to reduce the rate of local recurrence [19,20]. Grossly, tumors may be encapsulated, and they have partially infiltrative margins, which may contribute to frequent local recurrences [more than 30%] [10]. The cut surface is usually lobulated and usually tan-yellow to brown, depending on the degree and duration of hemorrhage. Most tumors are solid, marked cystic degeneration has also been reported [10]. The microscopic characteristics of PHAT are ectatic hyalinizing blood vessels; pleomorphic stromal cells; no necrosis and rare or no mitotic (Figures 1-3) [1 of 50 high-power fields]; variable inflammatory infiltrate, mainly mast cells [eosinophils, lymphocytes, plasma cells, or a mixture can be present]; and infiltrative border. The blood vessels are thin-walled and ectatic, and frequently arise in clusters with intravascular thrombi. The vessel walls and surroundings are lined with different amounts of amorphous material, consistent with fibrin or collagen. Mitotic figures are very scarce. The pleomorphic cells contain easily identifiable intranuclear inclusions. The cells adjacent to the vessels contain fine dusty hemosiderin pigment within their cytoplasm. Flope et al identified a distinctive, low-grade, partially myxoid lesion that appeared to represent a precursor lesion of PHAT [10,21] So-called “early PHAT” is defined by hypocellular proliferation of generally bland, hemosiderin-stippled spindle cells that infiltrate fat and surrounded congeries of small damaged vessels. PHAT expresses both spindle and pleomorphic vimentin, with varied expression of CD34, factor XIIIa, VEGF, and CD99, but are negative for S100 protein, cytokeratin, desmin, epithelial membrane antigen, smooth muscle actin, HMB-45, MyoD1, p63, and CD31 [determined by immunohistochemistry] [4,7,11,15,16].

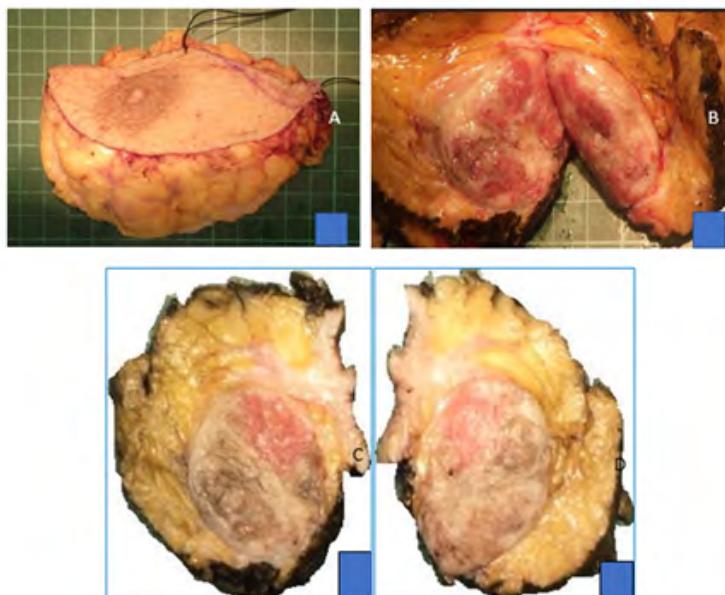


Figure 1A: Appearance of the mastectomy specimen and gross appearance of PHAT tumor. The lesion measured 14 × 6 × 3.5 cm in size.

Figure 1B: Fresh section of the tumor.

Figure 1C and D: Formalin-fixed tumor section. A heterogeneous appearance was seen with areas of white color and other reddish spots with hemorrhagic appearance.

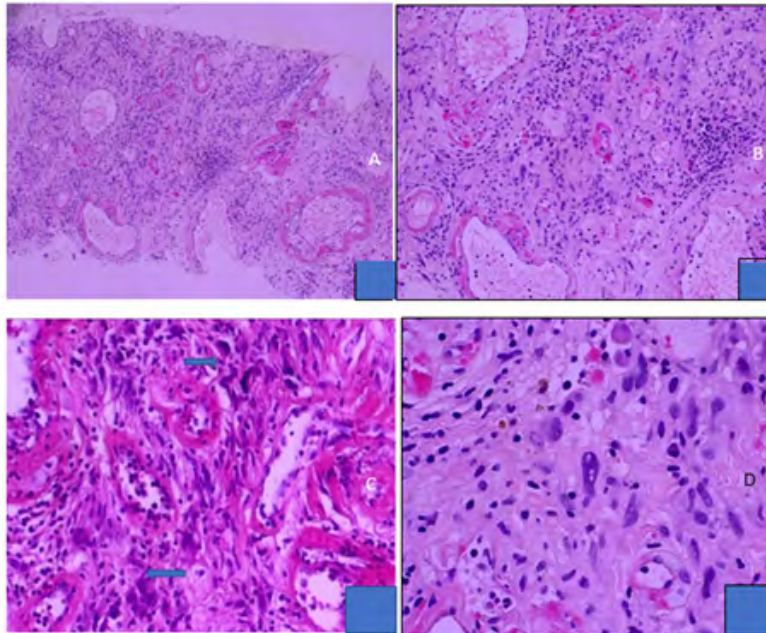


Figure 2: (A–C): The tumor was composed of clusters of variably sized, thin walled, ectatic blood vessels scattered and surrounded by a thick rim of amorphous eosinophilic material, with fibrosis phenomena (A: HE 10x and B: HE20x). Hyperchromatic and pleomorphic spindle cells between blood vessels (up arrow) and multinucleate cells and neoplastic cell with intranuclear cytoplasmic inclusion, mitotic figures are absent. An infiltrate of mixed chronic inflammatory cells is usually present, with a predominance of lymphocytes and plasmatic cells(C: HE 40x and D: HE60x).

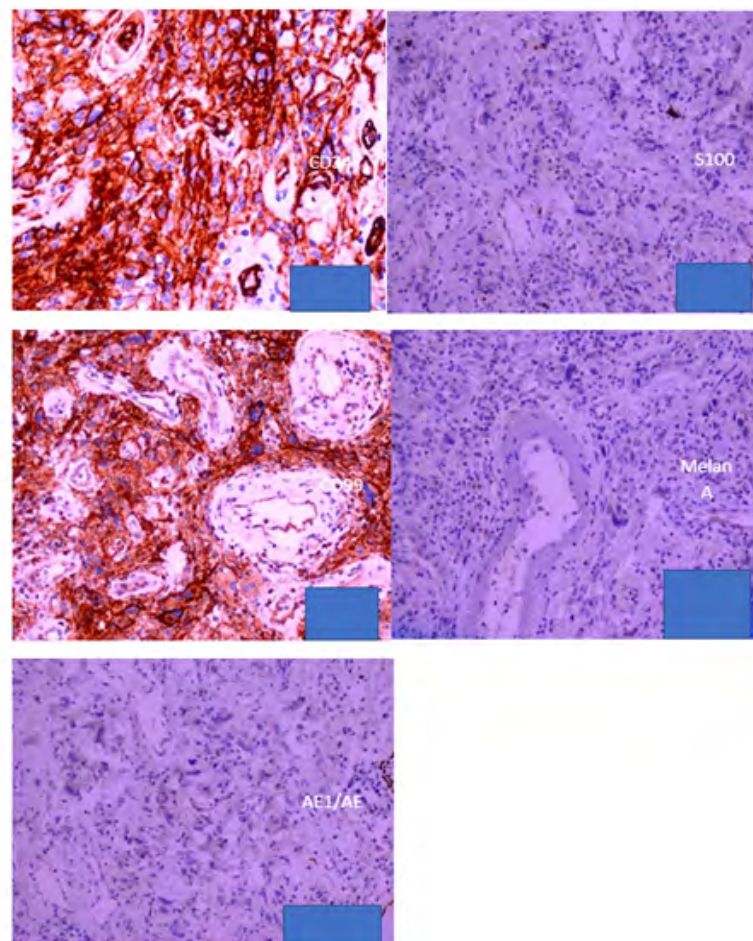


Figure 3: The immunohistochemical showed that the tumor cells were positive for CD34 and CD99, and negative for S-100, Melan A and pankeratin.

5. Differential Diagnosis

The main differential diagnoses found are schwannoma, pleomorphic sarcomas [formerly called malignant fibrous histiocytoma], solitary fibrous tumor [SFT] and giant cell angiofibroma [1,9,22]. Tumor cells resemble those of pleomorphic sarcomas, but differ from them by the presence of prominent intranuclear cytoplasmic pseudoinclusions, the scarcity of mitotic figures, and the frequent presence of CD34 expression [1]. These tumors also share several characteristics with schwannomas, such as their hyalinized vessel wall, intranuclear cytoplasmic inclusions, very low mitotic activity, and the presence of mast cells; however, they are differentiated by the frequent presence of infiltrating margins and the absence of S-100 protein labeling [1,22].

PHAT shares morphological characteristics with SFT and giant cell angiofibroma [1,9]. Nuclear atypia found in PHAT are more prominent than those seen in SFT, and the presence of multinucleated giant cells is seen only in PHAT [1,9,23]. Prominent clusters of thin-walled ectatic vessels surrounded by perivascular hyaline material are characteristic in PHAT, but may also be present in SFT and giant cell angiofibromas, and may correspond to secondary changes due to circulation disorders often seen in tumors of slow growth [1,9,23]. Two other entities mentioned in the literature are relevant for discussion about the morphological diagnosis of PHAT: hemosiderotic fibrolipomatous tumor [HFLT] and myxoinflammatory fibroblastic sarcoma [MIFS].

In the current World Health Organization classification, PHAT, HFLT, and MIFS are considered 3 different entities. However, because of their similar clinical presentation, overlapping morphologic features, and shared cytogenetic change of t[1;10] translocation, their relationship has been debated [2, 8]. Boland and Folpe proposed that HFLT is the early stage of PHAT, whereas MIFS is not related to either HFLT or PHAT [24]. Based on their overlapping clinical, morphological, and genetic characteristics, PHAT, HFLT, and MIFS may represent a family of closely related lesions with different morphological manifestations of a single entity, characterized by a predilection for the distal extremity, locally aggressive behavior, and very low metastatic potential [2,10,19,25,26]. More studies are needed to elucidate the pathogenesis and biological potential of these entities.

6. Conclusion

In summary, PHAT is a soft tissue tumor with low-to-intermediate malignancy potential, sharing histological similarities with benign and low-grade malignant tumors. Therefore, recognizing this entity and placing it among the differential diagnoses facing a mesenchymal lesion is essential, given the wide variety of entities that comprise this group of lesions. In this context, the histopathological aspects are essential for the diagnosis of this lesion, as well as the appropriate therapeutic management. The histogenesis of PHAT is still unclear, so more cases will need to be reported to understand the pathogenesis of PHAT.

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