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Pleomorphic Hyalinizing AngiectaticTumor: A Case Report and Literature Review

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1. Abstract

Pleomorphic hyalinizing angiectatictumor (PHAT), a rare low-grade non-metastasizing tumor, was first reported in 1996[1]. It affects patients with a mean age of 54.5 years and no predilection for gender[2], and has a preference for the subcutaneous soft tissue in the lower extremity. The main histology features are clusters of hyalinized ectatic blood vessels and scattered pleomorphic cells or spindle cells with nuclear pseudoinclusions. The clinical behavior is characterized by local recurrence in 30-50%, and no cases have been known to metastasize. A wide intralesional excision and long-term postoperative follow-up become the main therapeutic approach. So far, about 130 cases have been reported in the literature, and its manifestation on electron microscope and imaging has not yet been fully described. Here, we report a case of PHAT and describe its morphological and imaging performance.

2. Case Report

A 35-year-old man had been aware of a protruding mass in his left ankle for one year. The patient didn't complain of any other symptoms except the enlargement of the mass. The patient underwent pathological puncture before admission, and its diagnosis supported PHAT. Physical examination showed it that measured about 4.0cm × 5.0cm at the lateral malleolus was solitary, firm, non-tender and non-pulsatile. The skin surface was grossly unremarkable (Figure 1(A)). There was no motion restriction or lymph node swelling. The result of initial laboratory examination was normal. Magnetic resonance imaging (MRI) demonstrated a T1 isointense or low intense and T2 hyperintense mass (maximum diameter: 3.2cm × 1.7cm × 3.8cm) with a clear boundary (Figure 2(A-C)). The rest of adjacent structures around the lesion was also unremarkable to be seen. The patient received surgery under general anesthesia without additional treatment, and postoperative follow-up. A yellowish-brown, oval lesion, which grossly measured 2.0cm × 5.0cm × 4.0cm in size, was noted intra-operatively. The tumor was soft, completely encapsulated and light adhesion to the surrounding tissue, which could be excised with ease (Figure 1(B)). On sectioning, the cut surface revealed a variegated appearance with a white-tan color. Microscopically, scattered pleomorphic and spindle cells were mostly arranged in fascicles and sheets (Figure 3(A, B)). The nuclei were hyperchromatic and heteromorphic sometimes containing intranuclear pseudoinclusions (Figure 3(B)) and nucleoli. Dilated blood vessels are obvious. Lymphocyte infiltration and hemosiderin pigments were observed in part of neoplastic cells adjacent to small vessels (Figure 3(C)). Some areas showed slit-shaped structure (Figure 3(D)). There was low mitotic activity and no necrosis. Immunohistochemical study (Figure 4(A-C)) revealed diffusely positive staining for CD34, CD31, CD99 and Ki67 (5%).Ultrastructural examination showed that tumor cells were arranged randomly and widely in the lesion, with various sizes and shapes, and they were oval to spindle-shaped. The nuclei were large and irregular in shape, with many nuclear envelope folds with intranuclear pseudoinclusions (Figure 5(A, B)). The proportion of nucleus to cytoplasm increased (Figure 5(C)). Low incidence of mitotic activity was difficult to identify. There were abundant rough endoplasmic reticulum dilatations, a large number of lysosomes and Intermediate-sized cytoplasmic filaments, and occasionally mitochondria and Golgi apparatus in cytoplasm. Major microfilaments could be seen in cytoplasm arranged in either bundle-like or spiral-like patterns (Figure 5(D)). A few lipid droplets were observed. There were no other special structures in tumor cells. No junctions between cells were found. An extracellular matrix rich in collagen surrounded each cell. In addition to the presence of blood vessels, lymphocyte infiltration could also be noted in the lesion area.MRI imaging follow-up at 6 months (Figure 2(D-F)) and 18 months (Figure 2(G-I)) after surgery revealed no recurrence of the tumor. The patient was well with no evidence of relapsed disease.

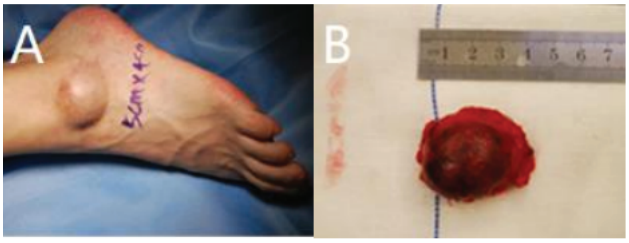

Figure 1: There was no obvious change in the skin surface of the tumor (A). Excised tumor was completely encapsulated and light adhesion to the surrounding tissue (B).

3. Discussion

PHAT is a rare, mesenchymal tumor arising in subcutaneous and intramuscular soft tissues with a low-grade malignancy. It was first described by Smith et al. in 1996 in a series of 14 cases of unusual mesenchymal tumors[1]. The 2020 WHO classification classified PHAT as " tumor of uncertain differentiation"[2]. The most common site to be involved is the lower extremity (65.8%)[3]. Additional regions have also been reported, such as the upper limbs, buttocks, inguinal region, knees/patellas, axilla, buccal mucosa, breasts, oral cavity, renal hilum and perineum[4-7]. PHAT distributes equally between males and females. Of the patients, 61% were female. A statistical analysis of studies published following Smith's paper showed PHAT in patients aged 10–89 years with a median age of 54.5 years[8]. There are no obvious features in the early state of PHAT. Most patients usually come to hospital for a slowly growing painless mass. Rush et al[9].Found the lesions had a mean size of 6.02 cm ± 4.6. Local recurrence occurs in about 30%-50% of PHAT ranging from 3 months to 25 years[10, 11]. There have been reports of 3 cases progressing to myxofibrosarcoma[7]. To the best of our knowledge, metastases have not yet been documented.We have been aware of about 10 articles on imaging-related descriptions up to now[6, 10, 12-15]. Kuang

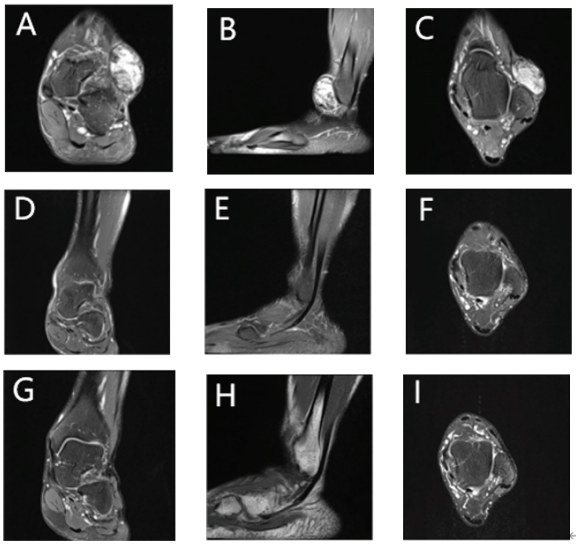

Figure 2: MRI respectively showed imaging characteristics of the preoperative soft-tissue mass on the coronal (A), sagittal (B), and transverse (C) planes. It was completely wrapped by capsule, and there was an enlarging solid component in it, showing uneven hyperintense signals. MRI showed imaging features of the patient's ankle at 6 months (D-F) and 18 months (G-I) postoperatively.

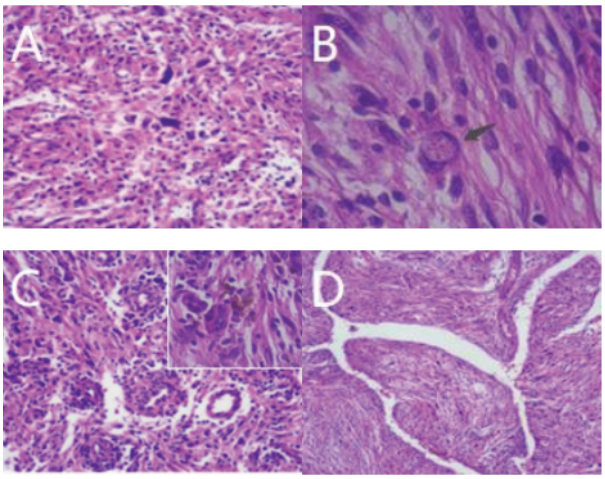

Figure 3: Spindle and pleomorphic cells were arranged in fascicles and sheets(A, original magnification 100×). Occasional intranuclear pseudoinclusion (arrow) could be present (B, original magnification 400×). Lymphocyte infiltration and hemosiderin deposits (inset C; original magnification 200×) were found around small vessels (C, original magnification 100×).Some areas displayed slit-shaped structure(D, original magnification 40×).

et al, [16].Discovered that CT findings of typical PHAT showed a shallow and lobulated mass with part of incomplete borders. MRI appearance of an enhancing, subcutaneous tumor with ill-defined margins and various imaging features may raise suspicions for PHAT, according to Subhawong et al, [12]. Chu et al, [14].Found it was a well-defined mass with uneven signal on plain MRI and CT scan, showing isointense and slight hypointense on T1-weighted images, and isointense and hyperintense on T2-weighted images.The most notable cellular feature of typical PHAT is the composed of clusters of thin-walled ectatic vessels with thrombosis and fibrin deposition[6, 11]. The vascular leakage could result from tumor cells encroaching into normal vessels and causing endothelial injury and angiectasia, and mast cells being present[1, 4]. The simultaneous presence of pleomorphic cells, intranuclear pseudoinclusions and intracytoplasmic hemosiderin pigments may also appear on behalf of PHAT. Other characteristic features include the presence of inflammatory cells and the absence of mitotic activity and ischemic necrosis. The pigments in coarse granules in PHAT were hemosiderin, rather than melanin, as determined by fine-needle aspiration cytology[17, 18]. However, it is important to

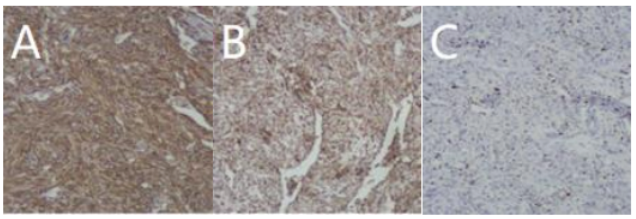

Figure 4: Tumor cells showed diffuse positive immunoreactivity in the cell membrane for CD34, CD31 and Ki67 (A-C, original magnification 40×).

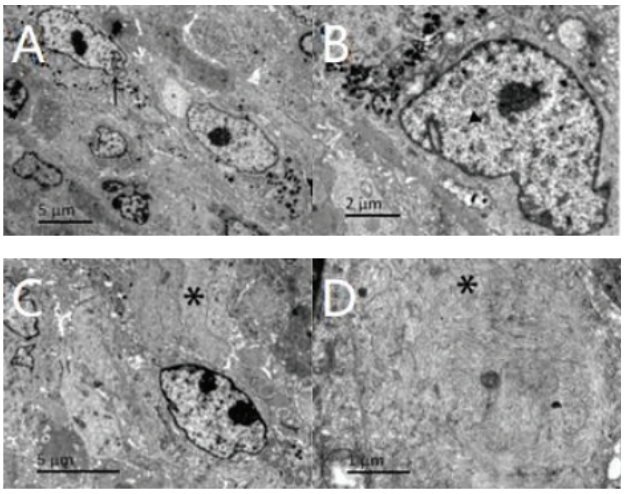

Figure 5: Oval to spindle-shaped cells contained bizarre nuclei with many nuclear envelope folds (arrow) and abundant lysosomes (A, bar = 5 μm). The nucleus membranes were mostly of irregular shapes, and the existence of intranuclear pseudoinclusions could be seen inside it (B, bar = 2 μm). The ratio of nucleus to cytoplasm increased, most of these nuclei were large and irregular, with abundant chromatin (C, bar = 5 μm). Intermediate cytoplasmic filaments (star) were distributed in the cytoplasm in bundle-like or spiral-like patterns (D, bar = 1 μm).

emphasize that intracytoplasmic hemosiderin pigments are not unique to PHAT, as they might also be detected in schwannoma, angiosarcoma, and Kaposi sarcoma[17]. Aside from the above-mentioned diseases, PHAT should also be differentiated from hemosideroticfibrolipomatoustumor (HFLT)myxoinflammatory fibroblastic sarcoma、malignant fibrous histiocytoma、vascular malformation、nodular fasciitis and leiomyosarcoma[3, 5, 13]. When encountering low mitotic activity, it is also possible to diagnose ancient schwannoma[19]. Boland and Folpe[20] found that both HFLT and PHAT demonstrated the presence of scattered pleomorphic tumor cells and intranuclear pseudoinclusions.PHAT shows strong expression of CD34, which may account for up to 70% of lesions[21]. Vimentin, CD99, CD31, VEGF and factor XIIIa are also expressed on it[17, 22]. Whereas it is negative for muscle markers, S-100, desmin, α-1-AT, bcl-2, HMB45, p53, CD30, CD117, NSE, EMA and PG-M1[4, 20]. The lipid-laden macrophages in hyalinized vessels walls displayed CD68 positivity. Compared with PHAT, neurofibroma may be positive of CD34, S-100, EMA but the absence of cluster ectatic vessels. Lack expression of CD34 is of benefit to eliminate undifferentiated pleomorphic sarcoma[19]. Negativity for S-100 and HMB45 could be used as an auxiliary signal to help exclude schwannoma and melanin-producing tumors. Immunohistochemical study appears to be superior in helping in the differential diagnosis in relation to other diseases.The most common image under electron microscope shows that tumor cells are large in size and different in shape. Within tumor cells one can observe abnormal nuclei with multiple folds in the nuclear envelope as well as an abundance of lysosomes. Intranuclear pseudoinclusions appear in some nuclei. There are cytoplasmic intermediate filaments arranged in bundles or spirals in the cytoplasm. Lack of specific elements suggests that PHAT appears to be of primitive fibroblastic differentiation due to a small amount of mitochondria and Golgi apparatus, along with abundant rough endoplasmic reticulum[23]. Mitotic activity is absent or very low (<1/50HPF). The

microscope shows that almost tumor cells invade the surrounding normal tissues, resulting in unclear boundaries, which determines wide local excision as the best therapeutic strategist. On the basis of a statistical analysis concerning on PHAT, Rush et al, [9].Concluded that tumor size, location, and histological type had no bearing on the recurrence rate, but there was a significant relationship between surgery type and recurrence. Local excision has the characteristics of high recurrence rate and low growth potential. Compared with local excision, extensive local resection is more effective in reducing its recurrence rate. Local radiotherapy also could reduce the rate of local recurrence.We report a case of PHAT involved in the ankle and conduct a review. Its performance on imaging and electron microscopy haven't been sufficiently described with scarce published reports. The pathogenesis could be difficult to be inferred, therefore, more studies with large case series to be reported are needed to clarify the pathogenesis of PHAT..

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