Pleomorphic hyalinizing angiectatic tumor (PHAT) of soft parts was first reported by Smith et al in 1996.1 It is characterized by clusters of ectatic, fibrin-lined, thin-walled vessels which are surrounded by a spindled or pleomorphic neoplastic stroma that contains a variable inflammatory component. The tumor cells are similar to those of malignant fibrous histiocytoma but differ from them by having a low mitotic figure, intranuclear cytoplasmic inclusion and CD34 expression. The peculiar vascular pattern, low mitotic figure, intranuclear cytoplasmic inclusion and mast cell infiltration are also reminiscent of neurilemmoma. However, PHAT usually shows an infiltrative border and no S-100 protein expression.1–4 Here, we report a case of PHAT and review the literature.
Pleomorphic hyalinizing angiectatic tumor

Case Report

A 49-year-old man had a soft, progressively enlarged, non-painful mass over the right buttock for several years. He came to our hospital because the mass increased in size. There was no personal or family history of major medical problems. Hemography and serum chemistry data were within the normal range. Physical examination showed a mass that measured about 10 × 7 cm; it was deep-seated and immovable in the right buttock. No skin change or other associated symptom was found. Under the suspicion of right gluteal lipoma, he underwent surgical excision in December 2005. During the operation, a well-circumscribed, fusiform, yellowish tumor was noted deep in the muscle layer. The excised lesion measured 14 × 6 × 3.5 cm in size (Figure 1A). It had a variegated appearance with a white-tan to yellowish color on the cut surface. Some punctate hemorrhage and vessel thrombosis were observed.

Microscopically, there were obvious clusters of thin-walled ectatic blood vessels of various sizes scattered in the adipose tissue. Luminal thrombus formation, subendothelial fibrin deposition, and perivascular hyalinization were clearly seen in these vessels (Figure 1B). In addition to the impressive vascular structure, plump pleomorphic cells or slender, wavy spindle cells were randomly arranged in sheets between the angiectatic vessels (Figure 1C). Mitotic figures were scarce. The extent of vascular clustering and tumor cell pleomorphism was more prominent at the center of the lesion. The slender, wavy spindle cells were mainly distributed around the periphery of the lesion (Figure 1D). Intranuclear inclusions were seen within the pleomorphic cells (Figure 1C). Hemosiderin deposition, myxoid area and moderate inflammatory cell infiltration were also noted. The above

Figure 1. (A) Gross appearance of specimen of pleomorphic hyalinizing angiectatic tumor of soft parts excised at first operation. (B) Characteristic clusters of ectatic, fibrin-lined, thin-walled vessels [hematoxylin and eosin staining (HE); original magnification, 100×]. (C) Pleomorphic neoplastic cells in between the angiectatic vessels (arrow; HE; original magnification, 200×) and tumor cell with intranuclear inclusion (inset; HE; original magnification, 400×). (D) Area of low cellularity, with bland, slender neoplastic cells (HE; original magnification, 100×).
characteristics were typical for PHAT. An infiltrative border was observed under the microscope. Meanwhile, immunohistochemical study showed that the tumor cells were positive for CD34, and negative for S-100 (Figures 2A and 2B), HMB45 and actin.

The patient experienced local recurrence 6 months later. Computed tomography showed an ill-defined mass that measured 2 cm in diameter in the right gluteus muscle. There was relative pre-contrast high density, about 100 HU, but no post-contrast enhancement. Positron emission tomography showed mildly increased uptake activity of the tumor (the standardized uptake value of the lesion was 1.4). The recurrent tumor was widely excised. No evidence of metastasis from the recurrent lesion was found in the 18 months following the second operation. The recurrent lesion showed some plump pleomorphic cells and hyalinized vessels within the adipose tissue, which was microscopically similar to the initial lesion.

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), yet distinctive from both entities in several aspects. PHAT is a tumor of adults, which is mainly located in the subcutaneous tissue of the lower extremities. We reviewed studies published in the years following the paper by Smith et al, and found 74 cases of PHAT in patients aged 10–89 years (median = 56 years), without sex predilection (41 female and 33 male). Tumor diameter ranged from 0.3 to 26.0 cm. Three tumors were located in the intramuscular area, and the others were in the subfascial subcutaneous area. The legs (n = 24) and feet/ankles (n = 20) were the most frequently involved site. Other locations such as the upper extremities, buttocks, inguinal region, knee/patella, chest wall, shoulder, axilla, back, hands, waist, breasts and perineum were also reported.

The microscopic characteristics of PHAT are clusters of different-sized, ectatic vessels that show subendothelial and intraluminal fibrin deposits due to vascular injury and leakage. The organization of the fibrin creates prominent perivascular collagen cuffs, which, in some tumors, give rise to large areas of stromal hyalinization. In between these scattered vessels, there are plump, spindle, and round pleomorphic cells that are arranged randomly in sheets, which simulates neurilemmoma, or in long fascicles that simulate fibrosarcoma. 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. Mast cells can be seen in the tumor stroma. Flope et al identified a distinctive, low-grade, partially myxoid lesion that appeared to represent a precursor lesion of PHAT. 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. The background is variably myxoid. Ultrastructural analysis of the tumor cell shows no recognized feature that implies specific mesenchymal differentiation. A primitive fibroblast or fibrohistiocytic origin is favored to date. Immunohistochemically, CD34 and S-100 protein are useful markers. PHAT expresses CD34 and vimentin but does not stain for S-100 protein. This is different from neurilemmoma. PHAT also has expressed CD99 in some studies. Epithelial membrane antigen, actin,
desmin, CD31 and von Willebrand factor are not expressed by PHAT. The pronounced pleomorphism of the tumor, together with our inability to identify features of a specific mesenchymal lineage (despite the application of both immunohistochemical and ultrastructural techniques), could make MFH a convenient broad group into which this tumor can be placed. However the peculiar low level of mitosis, odd pleomorphic cells with intranuclear inclusions, and ectatic damaged vessels are rarely seen in MFH. Moreover, flow cytometry has shown diploidy and there have been no reports of metastasis.7,10,12 All of these features make PHAT worthy of being separated from MFH.

Local excision is the best therapeutic approach, but PHAT has to be closely followed up. PHAT has a local recurrence rate of about 33%.2 Some patients have experienced multiple recurrences or high-grade malignant changes.1,2,6

The clinical impression of PHAT is usually a slow-growing benign tumor. However, its microscopic features must be differentiated from those of several other tumors.7 By combining the clinical picture and microscopic details, we can make the appropriate diagnosis. Our patient presented with an infiltrative border and positivity for CD34, which meant that a diagnosis of neurilemmoma could be excluded. Scarce mitosis, pleomorphic and/or spindle stromal cells and characteristic vascular structure fitted with a diagnosis of PHAT rather than MFH. Computed tomography and positron emission tomography both indicated a tumor with low malignant activity.

The most notable feature of PHAT is the hyalinizing angiectatic vascular structure. However, its significance and pathogenesis are not yet fully understood. Smith et al proposed that the vessels arise from encroachment of normal vessels by tumor cells.1 The slow growth of the tumor results in clustering, angiectasia, and subtle endothelial injury rather than massive vascular destruction and tumor necrosis that are characteristic of high-grade malignancy. Another cause of the vascular leakage could be the presence of mast cells, which might release vasoactive substances during tissue injury induced by tumor infiltration.1 In contrast, Flope et al suggested that the vascular change is an early pivotal event by itself, after observing damaged vessels in the early lesion in which the number of tumor cells was low.2

Groisman et al suggested that angiogenesis and the angiogenic factor vascular endothelial growth factor (VEGF) play a role in the development of PHAT.12 They found VEGF expression in tumor cells and endothelial cells of the non-hyalinized vessels but not the hyalinized ones. Thus they concluded that the progressive perivascular hyalinization induces hypoxia and therefore stimulates angiogenesis via increased VEGF production. Our case showed more engorged, damaged vessels and more pleomorphic tumor cells centrally of the tumor. Lesser vascular changes and wavy spindle tumor cells were located peripherally of the tumor. This phenomenon, so-called “classic PHAT” centrally and “early PHAT” peripherally, is similar to Flope’s observation.2 The recurrent lesion in the present case showed some pleomorphic tumor and inflammatory cell infiltration around some ectatic vessels. Although there were no marked clusters or vessel engorgement, the fibrinoid degenerative change in the vessel walls was obvious. From the timing of these events and our observations of the tumor specimen, we agree with Flope’s opinion that vascular leakage and damage were the key features of this tumor, rather than the result of tumor cell engulfment.2 The peculiar pleomorphism of tumor cells is a late, time-dependent, degenerative phenomenon.

In summary, we describe a typical case of PHAT in terms of both early stages and of recurrence. However, the histogenesis of PHAT is still unclear, even with the recent immunohistochemical and ultrastructural analyses, therefore, the pathogenesis can only be inferred from microscopic observation. More cases will need to be reported to understand the pathogenesis of PHAT.

References