Pleomorphic Hyalinizing Angiectatic Tumor: Immunohistochemical Study with Review of Literature

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INTRODUCTION

Pleomorphic hyalinizing angiectatic tumor (PHAT) is a relatively recently recognized neoplasm. The term was coined by Smith et al.¹ to name a soft tissue tumor that they had identified as a new entity as it exhibited histological features distinctive enough to deserve separate nomenclature. In their series of 14 cases, the tumor was described as a low grade neoplasm with close resemblance to neurilemmoma. In addition to neurilemmoma, it bears a striking resemblance to low grade malignant fibrous histiocytoma (MFH). WHO has categorized this tumor as a benign neoplasm of uncertain differentiation in its 2002 iteration of classification of tumors.²⁻³ Since its recognition, less than 100 cases of this rare tumor have been documented.⁴⁻⁷ From India, only one case has been reported.⁸ In this article, we have analyzed a case of PHAT immunohistochemically and reviewed the literature.

CLINICAL PRESENTATION

A 22-year-old young woman presented with a progressively enlarging mass in her right buttock. She first noticed it as a painless swelling about 2 months prior to seeking medical attention. On examination, her general condition was within normal limits. There was no significant past or family history. The laboratory investigations did not reveal anything unusual. The swelling in the right gluteal region was painless, non-tender and firm. It appeared well demarcated and mobile. It was not adherent to overlying skin or underlying structures. The mass was diagnosed clinically as fibrolipoma and was surgically excised.

RESULTS

The specimen we received in pathology laboratory consisted of an unencapsulated, firm, well-circumscribed mass measuring 6 cm × 3 cm × 2 cm. It was partly nodular. The cut surface was tan yellow with small foci of brownish discoloration due to hemorrhage (Figure 1a). The specimen was adequately sampled and processed for paraffin embedding. A minimum of six 3 µ thick section were cut from each block. Apart from routine hematoxylin and eosin stain, immunohistochemistry was done using novocastra (Leica) mouse monoclonal antibodies and diaminobenzidine substrate to demonstrate the following marker; CD 34. Demonstration of CD 68, CD 99, S100 and desmin was outsourced and was done at Sri Ramachandra University using BioGenex reagents.

Microscopically, the lesion was well demarcated but without a capsule. It was highly vascular with a variable cellularity. There were many large ectatic thin-walled
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The characteristic histology and distinctive immunological profile were diagnostic of PHAT. Following surgical excision, the patient has remained symptom-free for last 4 months.

**DISCUSSION**

PHAT was first recognized as a distinctive morphological entity in 1996 by Smith et al.[1] Majority of their cases arose in the subcutaneous plane of lower extremities. Apart from the presence characteristic thin walled ectatic blood vessels, the authors noted a close resemblance to MFH and neurilemmoma. Occasional expression of CD 34 by PHAT helped it to be distinguished from MFH, while the absence of S100 expression separated it from neurilemmoma. The authors suggested that PHAT is a “low grade sarcoma of uncertain lineage.” But, PHAT was included in 2002 WHO classification of soft tissue tumors under “benign tumors of uncertain differentiation.”[2]

Since its recognition, only about 100 cases of PHAT have been documented. Folpe and Weiss[9] have published the largest series so far in which they analyzed 41 reported cases. The clinical presentation of PHAT has been summarized in several articles.[9-11] The tumor affects broad age-range. Youngest patient recorded to be affected by the tumor so far was 10 years old, while oldest patient was 89 years of age. Average age of incidence is 55 years. Women are more frequently affected by the tumor than men (F:M = 4:3). In the present study, the patient was 24-year-old female. The lesion presented as slowly enlarging, painless, non-tender, unencapsulated mass in the gluteal region. Almost all the cases reported in the literature have been unencapsulated, slowly growing, painless masses affecting lower extremities in nearly two-thirds of cases. Sites of predilection include foot and ankle (~28%) and legs. Less frequently affected sites include upper extremities, chest, gluteal region, groin and back. The tumor has also been reported in oral cavity,[12] mesorectal soft tissue[4] and

The tumor cells showed a strong membranous positivity for CD 34 (Figure 3a). CD 68 stained only a few scattered background leucocytes, but tumor cells remained unstained (Figure 3b). The tumor cell nuclei failed to show any staining with S100 (Figure 3c). They were completely negative for desmin (Figure 3d) and CD 99 (Figure 3e).

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**Figure 1:** (a) Gross appearance of the tumor, (b) Low power view of the tumor showing ectatic blood vessels with mural fibrin and luminal thrombi (H and E, ×40)

**Figure 2:** Characteristic histologic features, (a) Hemosiderin pigment, (b) perivascular hyaline, (c) intranuclear pseudo-inclusion (arrow), and cellular pleomorphism, (d) inflammation and focal myxoid background (H and E, ×100 [B and D], ×400 [A and D])

**Figure 3:** Immunohistochemistry, (a) CD 34, strong membranous positivity, (b) CD 68, tumor cells negative, (c) S100, negative, (d) desmin, negative, (e) CD 99, negative (H-diaminobenzidine, ×100)
The morphological features of PHAT are now well established. The major features include ectatic thin-walled vessels with subendothelial fibrin deposition and luminal thrombi, perivascular hyalinization, pleomorphic cells, intranuclear inclusions, inflammatory cells and myxoid areas. All these features were present in our case (Figures 1 and 2). The most characteristic histological feature is the presence of ectatic thin-walled vessels in clusters (Figure 1b). Smith et al. speculated that the vascular changes are probably secondary to release of vasoactive amines by the large number of mast cells found in the tumor. It may be also be due to slow encroachment of the vessels by the tumor cells. According to Folpe and Weiss, these vascular changes are seen even in early PHAT and might lead to leakage and progression of the lesion. Groisman et al. found increased expression of vascular endothelial growth factor (VEGF) in perivascular tumor cells and endothelial cells of normal vessels but not in the endothelial cells of hyalinized vessels. They hypothesized that the progressive hypoxia induced by hyalinized vessels might trigger enhanced VEGF production and neovascularization.

Despite the sinister looking histology, low or nearly absent mitotic activity has been recorded in most reports. Cell proliferation marker MIB-1 (Ki67) expression was found to be very low by Ke et al. Flow cytometric analysis has resulted in a diploid DNA histogram and an absence of aneuploidy. These findings suggest that the cytological pleomorphism is not related to tumor growth but is a reflection of progressive degenerative change.

Additional morphological changes that are seen sometimes include areas resembling “hemodidteric fibrohisticytic lipomatous lesion” (HFLL), which Folpe and Weiss considered to be an early form of PHAT and not as a reactive lesion it was once thought to be. Similar view was also expressed by Luzar et al. in their report on an ankle swelling in a 47-year-old woman. That lesion had the histological features of both HFLL and PHAT. They too thought that HFLL is an early form of PHAT. In a more recent report, Suzuki et al. documented a case of PHAT in a 68-year-old woman that was completely surrounded by HFLL. In our case, areas resembling HFLL were not found.

A variety of immunohistochemical stains have been used to characterize the tumor immunologically. Only CD 34 has been found to be fairly consistently but variably expressed by the tumor. Some reports have claimed positive immunohistochemical reaction for CD 99, VEGF and factor XIIIa, but in most of the studies, the tumor is negative for CD 99. The tumor is also consistently negative for CD 68, desmin and S100. This is particularly relevant as lack of expression of CD 68 is useful in distinguishing it from MFH with which it is most often confused. Similarly, S100 helps to differentiate it from neurilemmoma, which is usually strongly positive for S100. In our study, only CD 34 showed a strong membranous positivity. All other markers used (CD 68, CD 99, S100 and desmin) were negative.

Other conditions with which PHAT might be confused include solitary fibrous tumor, giant cell angiofibroma and cutaneous myxofibrosarcoma.

Biological behavior of these tumors is predominantly indolent. About one-third of these tumors is known to recur after surgical removal. Although no cases of overt metastasis have been reported, Kazakov et al. recorded an instance of recurrence as a malignant neoplasm. In their report, a 76-year-old woman initially presented with a solitary axillary mass that was diagnosed as PHAT. Seven months after its excision, the patient came back with a rapidly growing tumor that had all the features of myxofibrosarcoma.

Immunohistochemical analysis and ultrastructural studies have so far failed to establish the histogenesis of this tumor. While one electron microscopic study of the tumor cells revealed features of primitive fibroblast with no specific differentiation, another study has shown the presence of ganglion like cells. For the present, this tumor is to be considered a low grade, locally aggressive mesenchymal neoplasm of uncertain histogenesis.

**CONCLUSION**

A case of PHAT in a 22-year-old woman has been analyzed immunohistochemically using CD 34, CD 68, CD 99, S100 and desmin. It was found that it was positive only for CD 34, thus helping to differentiate it from neurilemmoma and MFH, the two tumors with which it is often confused. At present, its histogenesis remains uncertain.

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