**TITLE**

**Atypical spindle cell/pleomorphic lipomatous tumor with pleomorphic hyalinizing angiectatic tumor-like growth pattern: a search for diagnostical clues**

**Authors**

Fleur Cordier, MD (1)\*, Ann-Sophie Candaele, MD (1)\*, Jo Van Dorpe, MD, PhD (1,2), David Creytens, MD, PhD (1,2)

**Institution/affiliations**

1. Department of Pathology, Ghent University Hospital, Ghent University, Ghent, Belgium
2. CRIG, Cancer Research Institute Ghent, Ghent University Hospital, Ghent University, Ghent, Belgium

\*joined first authors

**Orcid numbers:**Fleur Cordier: [https://orcid.org/0000-0003-0876-3398](%20https://orcid.org/0000-0003-0876-3398%20)Ann-Sophie Candaele: <https://orcid.org/0000-0002-7176-2542>   
Jo Van Dorpe: <https://orcid.org/0000-0001-8175-2930>   
David Creytens: <https://orcid.org/0000-0002-6064-1673>

**Address for correspondence**Prof. Dr. David CreytensDepartment of PathologyGhent University Hospital

Corneel Heymanslaan 10B-9000 GhentBelgium

Tel: +32-9-3323676, Fax: +32-9-3324965 Email: [david.creytens@uzgent.be](mailto:david.creytens@uzgent.be)

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**Abstract:**

Atypical spindle cell/pleomorphic lipomatous tumor (ASPLT) is a newly described adipocytic tumor type, recently included as a separate tumor entity in the 5th edition of the World Health Organization (WHO) classification of soft tissue and bone tumors. Here, we describe a case of an ASPLT with a striking pleomorphic hyalinizing angiectatic tumor (PHAT)-like growth pattern and discuss the diagnostical clues, which led to the diagnosis of ASPLT. To our knowledge, a PHAT-like growth pattern has not yet been reported in the setting of ASPLT.

**Atypical spindle cell/pleomorphic lipomatous tumor with pleomorphic hyalinizing angiectatic tumor-like growth pattern: a search for the diagnostical clues**

Atypical spindle cell/pleomorphic lipomatous tumor (ASPLT) is a relatively new adipocytic tumor entity, recently included in the World Health Organization (WHO) classification of soft tissue and bone tumors (5th edition, 2020). [1] ASPLT is regarded as a benign adipocytic tumor, with low risk of recurrence (10-15% for incomplety removed lesions) and without risk for dedifferentiation or metastases. Loss of 13q14, including the *RB1* gene, has been identified in a significant subset of ASPLT cases. [1-5]

The present case concerns a 59-year-old man presenting with a deep soft tissue mass surrounding the right fibula. Microscopic evaluation of the lesion showed an unencapsulated, ill-defined mesenchymal tumoral proliferation of atypical spindle cells, vaguely arranged in fascicles. The spindle cells contained enlarged, irregular, and hyperchromatic nuclei and were mixed with ‘bizarre’ pleomorphic cells showing multinucleated and pleomorphic nuclei (Figure 1A, 1B). Scattered ‘floret-like’ giant cells were also seen (Figure 1B). In the background, there was a fibromyxoid stroma with a diffuse chronic inflammatory infiltrate, mainly consisting of lymphocytes and histiocytes. Scattered mast cells and ropey type collagen were focally present. There was no necrosis, nor abundant mitotic activity. Heterologous (metaplastic) differentiation was not observed. Notably, there was increased vascularity in the lesion with individual or focally clustered, highly congested and dilatated blood vessels. The blood vessels were remarkably hyalinized with fibrin-like deposition in the wall, as well in the lumen of the vessels (Figure 1C).

This remarkable vascularization raised the diagnosis of a pleomorphic hyalinizing angiectatic tumor (PHAT), which is characterized by clusters of ectatic blood vessels surrounded by fibrin‑rich hyaline material. PHAT also contains spindle‑shaped, plump, and round pleomorphic cells, commonly arranged in sheets. [6-12] There is a mixed chronic inflammatory infiltrate that is notable for the presence of mast cells, but also includes lymphocytes, plasma cells and eosinophils. However, the performed immunohistochemical staining in this case did not add up for the diagnosis of PHAT (see also Table 1). There was strong, diffuse expression for CD34 (which is also seen in PHAT [12]), but there was also a strong, focal expression of smooth muscle actin (SMA) and desmin, which is not compatible with PHAT. [6]

Furthermore, if we looked closely at the lesion, an adipocytic component was recognizable focally, existing of immature-looking adipocytes, varying in size and form (Figure 1D). In addition, lipoblasts and some ‘pleomorphic’ lipoblasts could be seen. The presence of this atypical adipocytic component with lipoblasts was suggestive for the diagnosis of an ASPLT. This was further supported by immunohistochemistry demonstrating diffuse nuclear and cytoplasmatic staining for p16 and, especially, by the loss of expression for retinoblastoma (Rb) in the atypical spindle and pleomorphic cells (Figure 1E). No nuclear overexpression of MDM2 was seen. S100 stained the fat component and ERG the endothelium of the vessels. Next, fluorescence in situ hybridization (FISH) confirmed the diagnosis showing a deletion of the *RB1* gene and absence of *MDM2* gene amplification.

Based on the morphology (showing a heterogenic adipocytic lesion with pleomorphic/atypical spindle cells, an atypical fat component with (pleomorphic) lipoblasts in a background of scattered mast cells, ropey collagen and floret-like giant cells, lying in a fibromyxoid stroma), the immunohistochemistry (demonstrating strong and diffuse expression of p16 and CD34, loss of Rb expression, and focal expression of SMA and desmin) and the molecular profile (deletion of the *RB1* gene and no *MDM2* gene amplification) the diagnosis of ASPLT was made. [1-5] The differential diagnosis of ASPLT includes pleomorphic liposarcoma and atypical lipomatous tumor (ALT)/well-differentiated liposarcoma (WDL). [2,3] Despite some overlapping morphologic, immunohistochemical and genetic features between ASPLT and pleomorphic liposarcoma (e.g., infiltration, pleomorphism including ‘pleomorphic’ lipoblasts, and loss of *RB1*), pleomorphic liposarcoma is characterized by a much higher degree of pleomorphism, presence of tumor necrosis and high mitotic activity, all of which were missing in the current case. Moreover, the presence of a pleomorphic lipoma-like component demonstrating floret-like multinucleated cells and ropy collagen in this case is a defining feature of ASPLT, not present in pleomorphic liposarcoma. ALT/WDL was ruled out by MDM2 immunohistochemistry (negative nuclear staining) and absence of *MDM2* amplification by FISH.

It’s well known that ASPLTs can show a wide range of microscopic appearances. [1-5] However, the striking PHAT-like growth pattern as described in this case has, as far as we know, not yet been described in ASPLT. Pathologists should be aware of this morphologic mimic in ASPLT and search thoroughly for diagnostic clues, in particular an atypical adipocytic component. Confirmation by immunohistochemistry and FISH (with loss of *RB1)* is recommended in such cases.

**Figures legends**

Fig1.

1. Overview of the lesion (HE, Original magnification 50x).
2. Atypical spindle cells, ‘bizarre’ multinucleated pleomorphic cells and ‘floret-like’ giant cells (HE, Original magnification 200x).
3. Remarkable vascularity of the lesion with highly congested and dilatated blood vessels. The blood vessels are hyalinized with fibrin deposition in the wall, as well in the lumen of the vessels. (HE, Original magnification 200x).
4. Scattered atypical adipocytes with pleomorphic lipoblasts. Also note the ‘floret-like’ giant cell in the right upper corner (HE, Original magnification 200x).
5. Rb1 immunohistochemistry with loss of expression in atypical spindle and pleomorphic cells. There is a positive control in endothelial cells and inflammatory cells (original magnification 400x).

**Tables**Table 1: overview of PHAT vs. ASPLT

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|  | **PHAT** | **ASPLT** |
| **Localization** | Subcutaneous tissue of the lower extremities | Subcutis, predominant in the limbs |
| **Diagnostical clue** | - Ectatic, blood vessels showing fibrin-like hyalinization, surrounded by a cellular proliferation of pleomorphic, hemosiderin-laden cells with very few mitotic figures  - mixed inflammatory infiltrate | - variable proportions of mild to moderately atypical spindle cells, adipocytes, lipoblasts, pleomorphic cells and multinucleated and floret-like giant cells.  - myxoid or collagenous extracellular matrix. |
| **Immunohistochemistry** | - CD34 positive  - S100, desmin, SMA negative | - variable expression of CD34, S100, SMA, and desmin  - Loss of nuclear Rb expression |
| **Molecular level** | - *TGFBR3* and/or *OGA* (*MGEA5*) rearrangements (some cases) | - Loss of *13q14*, including the *RB1* gene  - lack of *MDM2* or *CDK4* amplification |
| **Prognosis** | 50% local recurrence | Low rate of local recurrence with incomplete resection |

PHAT: pleomorphic hyalinizing angiectatic tumor; ASPLT: atypical spindle cell/pleomorphic lipomatous tumor

**References**

1. Creytens D, Marino-Enriquez A. Atypical spindle cell/pleomorphic lipomatous tumour. In WHO Classification of Soft Tissue and Bone Tumours; IARC Press: Lyon, France, 2020.
2. Creytens D, Mentzel T, Ferdinande L, Lecoutere E, van Gorp J, Atanesyan L, de Groot K, Savola S, Van Roy N, Van Dorpe J, Flucke U. ["Atypical" Pleomorphic Lipomatous Tumor: A Clinicopathologic, Immunohistochemical and Molecular Study of 21 Cases, Emphasizing its Relationship to Atypical Spindle Cell Lipomatous Tumor and Suggesting a Morphologic Spectrum (Atypical Spindle Cell/Pleomorphic Lipomatous Tumor).](https://pubmed.ncbi.nlm.nih.gov/28877053/) Am J Surg Pathol. 2017 Nov;41(11):1443-1455.
3. Lecoutere E, Creytens D. [Atypical spindle cell/pleomorphic lipomatous tumor.](https://pubmed.ncbi.nlm.nih.gov/32068239/) Histol Histopathol. 2020 Aug;35(8):769-778.
4. Anderson WJ, Fletcher CDM, Jo VY. [Atypical Pleomorphic Lipomatous Tumor: Expanding Our Current Understanding in a Clinicopathologic Analysis of 64 Cases.](https://pubmed.ncbi.nlm.nih.gov/33782225/) Am J Surg Pathol. 2021 Sep 1;45(9):1282-1292.
5. Creytens D. [What's new in adipocytic neoplasia?](https://pubmed.ncbi.nlm.nih.gov/31501988/) Virchows Arch. 2020 Jan;476(1):29-39. doi: 10.1007/s00428-019-02652-3.
6. Jaramillo CJ, Wojcik J, Weber K, Sebro R. Imaging and histological appearance of pleomorphic hyalinizing angiectatic tumors: A case series and literature review. *Oncol Lett.* 2018 Apr;15(4):4720-4730.
7. Cazzato G, Colagrande A, Cimmino A, Lettini T, Savino MT, Martella C, Ingravallo G, Resta L. Pleomorphic Hyalinizing Angiectatic Tumor (PHAT): Review of the Literature with Case Presentation. *Dermatopathology* (Basel). 2021 Apr 4;8(2):97-102.
8. Peng HC, Huang MT, Chen DJ, Leung TK, Chu JS. Pleomorphic hyalinizing angiectatic tumor of soft parts. *J Formos Med Assoc*. 2010 Aug;109(8):616-20.
9. Smith ME, Fisher C, Weiss SW. Pleomorphic hyalinizing angiectatic tumor of soft parts. A low-grade neoplasm resembling neurilemoma. *Am J Surg Pathol* 1996; 20:21–9.
10. Folpe AL, Weiss SW. Pleomorphic hyalinizing angiectatic tumor: Analysis of 41 cases supporting evolution from a distinctive precursor lesion. *Am J Surg Pathol* 2004;28: 1417–25.
11. Matsumoto K, Yamamoto T. Pleomorphic hyalinizing angiectatic tumor of soft parts: a case report and literature review. *Pathol Int* 2002; 52:664–8.
12. Silverman JS, Dana MM. Pleomorphic hyalinizing angiectatic tumor of soft parts: immunohistochemical case study shows cellular composition by CD34 + fibroblasts and factor XIIIa + dendrophages. *J Cutan Pathol* 1997; 24:377–83.