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Teaching cases

Pleomorphic hyalinizing angiectatic tumor of soft parts: Case Report with unusual ganglion-like cells and review of the literature

Yi-Che Changchien*, Pál Bocskai, Ilona Kovács, Zoltán Hargitai, Sándor Kollár, Miklós Török

Department of Pathology, Kenézy Gyula County Hospital, Debrecen, Hungary

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ABSTRACT

Pleomorphic hyalinizing angiectatic tumor (PHAT) is a recently described, non-metastasizing tumor of uncertain lineage. This tumor distributes equally between the genders and has a predilection for the subcutaneous soft tissue, particularly in lower extremity, other locations are rare. Based on the recent literature, PHAT is suspected to encompass the morphological spectrum with other tumors such as myxoinflammatory fibroblastic sarcoma (MIFS) and hemosiderotic fibrolipomatous tumor (HFLT), although cytogenetic data remain inconsistent. We report a case of PHAT that arose in the upper arm with unusual morphology which showed ganglion-like cells similar to Reed-Sternberg-like cells found in MIFS. The tumor had strong immunohistochemical expression of CD34, CD99, and was negative for S-100. The ganglion-like cells were positive for both CD34 and CD68 but negative for CD30. The translocation between chromosome 1 and 10, a frequent finding of MIFS and HFLT, was not identified by FISH excluding the possibility of hybrid PHAT and MIFS. We conclude FISH can be a potential useful tool to separate PHAT with atypical morphology from hybrid tumor in doubted cases. Due to the rarity of PHAT and lack of consistent pathogenetic signatures, more cases and further studies will be needed to elucidate the pathogenesis and nature of this tumor.

Introduction

Pleomorphic hyalinizing angiectatic tumor (PHAT) of soft part is a rare soft tissue tumor. PHAT is generally considered a locally aggressive low-grade tumor with possible primitive undifferentiated mesenchyme origin. Since ultrastructural analysis of the tumor cell reveals no recognized feature specific differentiation [4], it is categorized as "tumor of uncertain differentiation" based on the latest World Health Organization classification [19]. PHAT often develops in the lower extremity of middle-aged adults. Involvement of the upper extremity, head and neck region, groin/genital area, and viscera is relatively rare [5,8,10,11,14,18]. Although inconsistent cytogenetic data have been reported in PHAT so far, there are potential morphological and genetic overlaps with hemosiderotic fibrolipomatous tumor (HFLT) and myxoinflammatory fibroblastic sarcoma (MIFS) [1,6,9,17,21].

We report a case of PHAT located at the upper extremity showing atypical morphology with the presence of ganglion-like cells mimicking MIFS based on morphological and immunohistochemical examinations. We ruled out the latter possibility by performing fluorescence in situ hybridization (FISH) which showed negative for t(1;10) in both classical tumor and ganglion-like cell components. Differential diagnosis, current pathogenetic controversies and literature search will also be discussed.

Materials and methods

Clinical data

The patient, a 76-year-old Hungarian man, with medical history of hypertension and autoimmune myositis, was referred to our surgery department due a slow-growing subcutaneous mass on the dorsomedial aspect of his left upper arm over the previous 5 months. No particular complain was given. The skin surface

Abbreviations: BAC, bacterial artificial chromosome; DAPI, 4',6-diamidino-2-phenylindole; FISH, fluorescence in situ hybridization; HFLT, hemosiderotic fibrolipomatous tumor; MIFS, myxoinflammatory fibroblastic sarcoma; PHAT, pleomorphic hyalinizing angiectatic tumor.

* Corresponding author at: Department of Pathology, Kenézy Gyula County Hospital, H-4043 Debrecen, Bartók Béla út 2-26, Hungary. Tel.: +36 302235273.
E-mail addresses: ccwilly@hotmail.com (Y.-C. Changchien), pal.bocskai@freemail.hu (P. Bocskai), csupai@gmail.com (I. Kovács), z.hargy@gmail.hu (Z. Hargitai), dr.kollar.sandor@gmail.com (S. Kollár), torok-miklos@freemail.hu (M. Török).

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was grossly unremarkable. Neither motion restriction nor lymph node swelling was noticed during preoperative physical examination. Surgical exploration found the tumor situated in front of the bicep muscle and excision was performed for pathology diagnosis.

Informed consent was given to the patient for the research purpose to use of his tissue, and the research was conducted in concordance with the Institutional Ethical Guidelines.

Immunohistochemistry

After sectioning of 4 μm slides from the formalin-fixed, paraffin-embedded blocks, deparaffinization in xylene and rehydration in a series of decreasing concentration of ethanol were done. Antigen retrieval using either the Bond Epitope Retrieval Solution 1 (pH ~6) or the Bond Epitope Retrieval Solution 2 (pH ~9) (Leica Microsystems, Wetzlar, Germany) at 99–100 °C for 20–30 min was performed. The slides were treated with vimentin (prediluted, clone V91, Dako, USA), CD34 (1:300, clone QBEnd 10, DAKO), CD99 (1:50, clone: MIC-2, DAKO), S-100 (1:300, clone S-100, DAKO), CD30 (1:50, clone MEM-268, Life Technologies, USA), CD31 (1:30, clone JC70A, DAKO), epithelial membrane antigen (EMA) (1:20, clone sc-9121, Santa Cruz Biochemicals, USA), smooth muscle actin (SMA) (1:50, clone α-SMA, DAKO), desmin (prediluted, clone DE-R-11, Leica Bond, UK), Ki-67 (1:50, clone MIB-1, Dako), chromogranin A (1:200, clone 5H7, Novocastra, Germany), synaptophysin (1:50, clone M7315, DAKO) and CD68 (1:100, clone EBM11, DAKO) separately. Immunostaining was performed on Leica BOND-MAX™ autostainer (Leica Microsystems) and we used peroxidase/DAB Bond™ Polymer Refine Detection System (Leica Microsystems) for visualization.

Fluorescence in situ hybridization

In order to detect the potential t(1;10), FISH was performed on the tumor cells from formalin-fixed, paraffin-embedded blocks described by Antonescu et al. [1] and Mohajeri et al. [17] using mixture of bacterial artificial chromosome (BAC) probes to target *TGFBR3* gene located at chromosome 1. Briefly, three probes target the 5′ side of the *TGFBR3* gene (RP11-1011D5, RP11-135F24, and RP11-43G5) were labeled with Alexa 488 (green), and two probes target the 3' side of the gene (RP11-77A10 and RP11-28O2) were labeled with Cy3 (red). Probe mixtures were denatured and hybridized to the pretreated slides, which were counterstained by 4′,6-diamidino-2-phenylindole (DAPI).

The fluorescence microscope (Axioskop 2 Mot Plus, Carl Zeiss MicroImaging GmbH Heidelberg, Germany) equipped with a Hamamatsu C 4800 CCD camera and PSI Cytovision 3.6 (Scientific Systems, UK) computer analysis systems were used for the evaluation of the results. At least 100 consecutive nuclei were investigated, and positive for rearrangement was considered if more than 20% of the examined nuclei showed a break-apart signal.

Results

Gross findings

During the pathology examination; the tumor grossly measured 4.6 × 4.5 × 3.0 cm in size. The outer surface was yellowish-brown in color and elastic. On sectioning, it was uncapsulated, the border was partially circumscribed with focal peritumoral soft tissue infiltration. Serial sections revealed grayish-white with focal hemorrhagic cutsurface, and focal myxoid areas were also observed. The surgical specimen was fixed in 10%-buffered formalin and embedded in paraffin for hematoxylin-eosin and immunohistochemical stains.

Histopathological finding

Microscopically, the tumor showed hyper- and hypo-cellular areas composed of spidle to ovoid cells possessed mild to moderate pleomorphic nuclei and nuclear hyperchromasia within a fibromyxoid background. The tumor cells had scanty, eosinophilic cytoplasms with indistinct cellular borders. Some of them contained hemosiderin pigments and arranged in either fascicular or storiform patterns, surrounding clusters of variable-sized, congested, ectatic, thin-walled blood vessels with focal hemangiopericytoma-like patterns. Prominent intraluminal fibrin deposition and perivascular hyalinization with stromal extension were noted (Fig. 1A). Intranuclear cytomplasmic pseudoinclusions could also be observed (Fig. 1B). Inflammatory cell (including eosinophil and multinucleated giant cell) infiltration, red blood cell extravasation and siderophages were found. The diagnosis of PHAT was established. At the peripheral areas of the tumor showed tumor cells infiltration within adipose tissue without obvious clusters of ectatic vessels and nuclear atypia implying so-called "early pleomorphic hyalinizing angiectatic tumor (early PHAT)" region (Fig. 1C). Within the tumor mass, multifocal areas also showed nodular myxoid changes containing tumor cells with vacuolar cytoplasm, and also fairly large, epithelioid cells containing large, eosinophilic, viral inclusion-like nucleoli resembling ganglion or Reed-Sternberg cells (Fig. 1D). Such morphology shows high similarity with the ones found in MIFS. Low mitotic activities (2 to 3 mitosis per 10 high power fields) are detected, and atypical mitotic figures are not found. Tumor necrosis was absent.

The results of immunohistochemical stain are summarized in Table 1. The tumor cells showed strong, diffuse vimentin, CD34 and CD99 positivity (Fig. 2A and B). Whereas S-100, CD30 (Fig. 2C and D), CD31, EMA, SMA and desmin were negative. The peripheral "early PHAT" region revealed similar results. Ki-67 proliferative index was approximately 2%. The ganglion-like cells displayed CD34 and variable CD68 positivity (Fig. 2E and F). They were negative for Chromogranin A, Synaptophysin and S-100.

Under FISH examination; less than 3% of the split signal in *TGFBR3* gene was detected in both typical PHAT areas or ganglion-like cells indicating absence of t(1;10) (Fig. 3).

The surgical margin was free of tumor, and there was no tumor recurrence up to 2 months follow-up period since the operation.

Table 1
Summary of the immunohistochemical stains.

Marker	Result
Vimentin (prediluted, clone V91, Dako cytomation, USA)	Positive
CD34 (1:300, clone QBEnd 10, DAKO)	Positive[a]
CD99 (1:50, clone MIC-2, DAKO)	Positive
S-100 (1:300, clone S-100, DAKO)	Negative
CD30 (1:50, clone MEM-268, life technologies, USA)	Negative
CD31 (1:30, clone JC70A, DAKO)	Negative
EMA (1:20, clone sc-9121, Santa Cruz Biochemicals, USA)	Negative
SMA (1:50, clone α-SMA, DAKO)	Negative
Desmin (prediluted, clone DE-R-11, Leica Bond, UK)	Negative
Chromogranin A (1:200, clone 5H7, Novocastra, Germany),	Negative
Synaptophysin (1:50, clone M7315, DAKO)	Negative
Ki-67 (1:50, clone: MIB-1, Dako)	Low (2% proliferative index)
CD68 (1:100, clone EBM11, DAKO)	Variable Positive (ganglion-like cells)

[a] In typical/early PHAT tumor cells and also ganglion-like cells (SMA: smooth muscle actin; EMA: epithelial membrane antigen).