Annals of Diagnostic Pathology 20 (2016) 40–43

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

Pleomorphic hyalinizing angiectatic tumor revisited: all tumors manifest typical morphologic features of myxoinflammatory fibroblastic sarcoma, further suggesting 2 morphologic variants of a single entity☆,☆☆

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ARTICLE INFO

Keywords:
Pleomorphic hyalinizing angiectatic tumor
Myxoinflammatory fibroblastic sarcoma
Soft tissues

ABSTRACT

We describe 9 cases of pleomorphic hyalinizing angiectatic tumor (PHAT). Recently described TGFBR3 and MGEA5 gene rearrangements in these tumors have confirmed the long-hypothesized link between PHAT and another soft tissue entity, the myxoinflammatory fibroblastic sarcoma (MIFS). Myxoinflammatory fibroblastic sarcoma and PHAT share the same translocation and in addition have a very similar clinical presentation. However, to our best knowledge, no study has ever addressed the striking morphologic similarities between MIFS and PHAT. Our findings based on histological criteria suggest that most, if not all, tumors diagnosed as PHAT might, in fact, represent examples of MIFS that, in addition to a conventional MIFS morphology, manifest aberrant angiectatic hyalinized vessels.

1. Introduction

Pleomorphic hyalinizing angiectatic tumor (PHAT), first described in 1996 by Smith et al [1], is currently considered a low-grade, locally aggressive neoplasm of uncertain lineage with a high predilection for the lower extremity. Although as much as 50% of lesions recur locally, no metastases have so far been documented. Nonetheless, the progression to a myxofibrosarcomalike sarcoma has been described in several cases [2–4]. While working on another project on a high-grade variant of myxoinflammatory fibroblastic sarcoma (MIFS) [5], we came across a recurrent PHAT initially diagnosed as myxofibrosarcoma. Thanks to our current better knowledge of the wide spectrum of MIFS's morphology, when we re-reviewed both biopsies again, it became obvious that both the original and the recurrent lesions show typical cytological features of MIFS, albeit the recurrent tumor harbored prominent cytological atypia. This surprising finding compelled us to review all 13 cases filed as PHATs from our files, which resulted in further noteworthy observations. With the exception of 4 cases, all the remaining 9 lesions contained cells morphologically indistinguishable from MIFS on the background of predominant features of PHAT characterized by thin-walled angular ectatic vessels surrounded by perivascular hyaline material.

In this study, we report a series of 9 lesions originally diagnosed as PHAT, which, based on our histological criteria for MIFS, all most likely represent examples of the latter tumor, merely having an additional component of aberrant angiectatic hyalinized vessels.

2. Materials and methods

The 9 cases of PHAT constituting the subject of this study were retrieved from the authors' files; they came from the period between the years 1993 and 2015. The clinical information was extracted from the registry records, and follow-up data were obtained from attending clinicians. To retrieve the cases, we searched our consultation registry files using keywords, including *pleomorphic hyalinizing angiectatic tumor*, *PHAT*, *myxoid malignant fibrous histiocytoma*, and *myxofibrosarcoma*. This search yielded altogether 13 specimens which were reviewed to confirm the diagnosis. Upon revision, 2 cases were excluded for their incompatible morphology, of which one was reminiscent of low-grade fibromyxoid sarcoma with prominent vessels rather than a PHAT and the second one was reclassified as myxofibrosarcoma, not otherwise specified. In another case, we were not able to render any final diagnosis, and the

☆ This study was supported by the National Sustainability Program I (NPU I) No. LO1503 provided by the Ministry of Education Youth and Sports of the Czech Republic.
☆☆ The authors have no funding or conflicts of interest to disclose.
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http://dx.doi.org/10.1016/j.anndiagpath.2015.10.006
1092-9134/

remaining excluded tumor lacked any clinical information. In all but 2 cases, paraffin blocks or unstained reserve slides were available for the study.

For conventional microscopy, tissues were fixed in formalin, routinely processed, embedded in paraffin, cut into 4-μm–thick sections, and stained with hematoxylin-eosin (H&E).

For immunohistochemical studies, 4-μm–thick sections were cut from paraffin blocks, mounted on slides coated with 3-aminopropyltriethoxy-silane (Sigma, St Louis, MO), deparaffinized in xylene, and rehydrated in descending grades (100% to 70%) of ethanol. Sections were then subjected to heat-induced epitope retrieval by immersion in a CC1 solution at pH 8.0 at 95°C. Endogenous peroxidase was blocked by a 5-minute treatment with 3% hydrogen peroxide in absolute methanol. The slides were then stained by immunostainer BenchMark ULTRA (Roche, Switzerland). The immunohistochemical analysis was performed using a Ventana BenchMark ULTRA (Ventana Medical System, Inc, Tucson, AZ).

The following primary antibodies were used: Cyclin D-1 (polyclonal, Thermo Fisher Scientific, Fremont, CA; monoclonal) and Cyclin D-1 (monoclonal, SP4, Dako, Glostrup, Denmark). The primary antibodies were visualized using the enzymes alkaline phosphatase or peroxidase as detecting systems (both purchased from Ventana Medical System, Inc, Tucson, AZ).

3. Results

The clinical features are summarized in Table 1. The patients were 5 women and 3 men, and in the remaining case, the sex was unknown. The age of the patients at the time of diagnosis ranged from 53 to 76 years (mean, 62.9 years). Follow-up was available for 4 patients, of whom 1 suffered multiple recurrences. No metastases occurred. The average duration of follow-up was 5.9 years (range, 0.4-14 years). Locations were available for 8 tumors and included soft tissues of the lower extremity [4] and 1 each of the axilla, forearm, inguinal area, and the abdomen. The patient with the inguinal lesion had a history of inguinal hernia, and the tumor was initially suspected to represent recurrent hernia. The patient with abdominal lesion had been operated on for a colorectal carcinoma 13 years ago; the PHAT developed 4 cm away from the colostoma scar. The tumor size ranged from 2 to 7. 5 cm in the largest dimension, with a mean size of 5.0 cm.

All PHATs in this series matched our cytological and histological criteria for MIFS used in our previous publication concerning this tumor [5], merely adding the hyalinized, ectatic vessel to the morphologic picture (Fig. 1). The inclusion morphologic criteria were as follows: (1) Presence of mats of neoplastic cells with eosinophilic cytoplasm having accentuated cell membranes, with thin collagen fibers

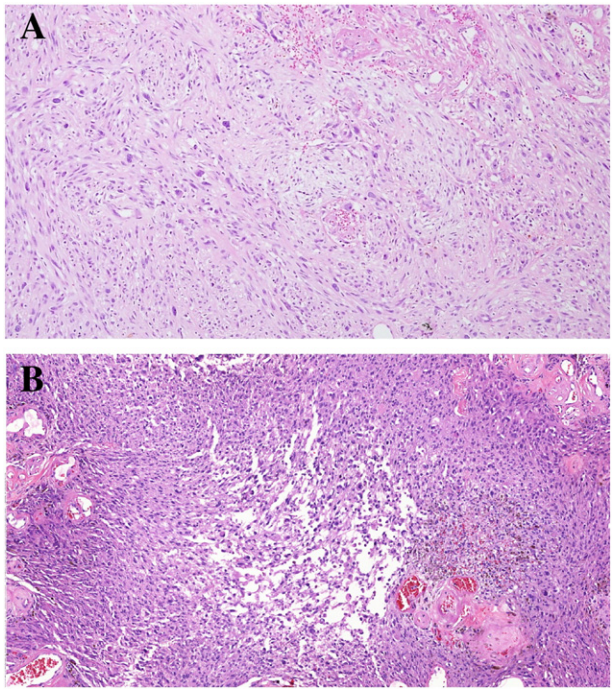

Fig. 1. Cell composition of tumor in between the ectatic vessels is identical to the myxoinflammatory fibroblastic sarcoma (A and B) (H&E, 100×).

permeating between the neoplastic cells often creating mosaiclike appearances (Fig. 1A). These areas had gradual transitions to less cohesive foci, in which the extracellular mucous substance began to percolate between cells, with appearances reminiscent of "dilapidated brick wall" in areas where larger amounts of extracellular mucin have produced pools containing scattered individual neoplastic cells (Fig. 1B). However, the above-described stroma so typical for MIFS differed slightly in 3 of our cases of PHAT where it was more hypocellular and edematous (Fig. 2.), usually with prominent hemosiderin deposition. In addition, in some cases, there were groups of foam cells present in the stroma. (2) Presence of lipoblastlike cells with an ample, distended, mucin-filled cytoplasm, compartmentalized by a variable number of intracytoplasmic bridges or septa, thus remotely resembling soccer balls (Fig. 3). (3) Occurrence of large, polygonal, bizarre ganglionlike cells similar to those seen in Hodgkin disease, also called *RS-like cells*. These cells possessed an oval nucleus with vesicular chromatin and a large, inclusionlike

Table 1
Main clinicopathologic features and follow-up.

	Age/sex	Size (cm)	Location	Therapy	Recurrence and therapy	Metastasis	Follow-up
1	57/F	5 cm	Scar on the abdomen	E	N	N	NED in 8-y follow-up after the extirpation
2	66/F	6 × 5.5 × 3.5 cm	Thigh	E	N	N	NED in 13-y follow-up after the extirpation
3	76/F	Ø 3.5 cm	Axilla	E	2× in 31 mo (as myxoinflammatory fibroblastic sarcoma), E	N	NED in 7-y follow-up after the last re-extirpation
4	62/F	4.5 × 4 × 2 cm	Ankle	E	N	N	NED in 3-y follow-up after the extirpation
5	63/M	4 × 3.5 × 2.5	Forearm	E	NA	NA	NA
6	64/F	3 × 3 × 2.2 cm	Instep	NA	NA	NA	NA
7	53/M	7.7 × 5.5 × 4.5 cm	Thigh	E	N	N	DONR (colorectal adenocarcinoma) 4 y after the extirpation
8	62/M	Ø 5.9 cm	Inguinal area, history of inguinal hernia	E	N	N	NED in 3 mo after the extirpation
9	NA	NA	Soft tissue, not specified	NA	NA	NA	NA

Abbreviations: DONR: died of nonrelated causes, NA: not available, NED: no evidence of disease, E: extirpation.