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Case report

Pseudomyogenic hemangioendothelioma: A misleading vascular tumor

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ABSTRACT

Introduction: Pseudomyogenic hemangioendothelioma (PHE) is a rare vascular soft tissue tumor of intermediate malignancy. The aim of this study was to present a rare case of PHE in the back and to review its clinicopathological features, therapeutic modalities, evolutionary aspects and prognosis.

Case presentation: We report the case of a 21-year-old man who consulted for a multinodular mass at the scapula level, that increased in size within 2 months. An excisional surgery was performed. Macroscopic examination showed ulcerated centimetric nodules with a crusty surface. Microscopic examination showed a multinodular proliferation arranged in clusters, made of spindle cells or epithelioid cells with variable atypia. Immunohistochemical study showed the expression ofAE1-AE3, ERG and INI-1. There was no staining for EMA, CD34, and CD-31. The diagnosis of PHE was retained.

Discussion: PHE affects young adult males and usually develops in the extremities. Clinically, more than half of the patients present with local recurrence. Distant metastases have also been reported. Microscopically, PHE resembles a myoid tumor or epithelioid sarcoma because of the abundant eosinophilic cytoplasm and cell shape. Tumor cells express cytokeratin and inconsistently CD34 and CD31. Hence the need to complete the study of ERG and INI1 expression in all soft tissue epithelioid tumors. The translocation t(7;19)(q22; q13) as well as the expression of FOSB in immunohistochemistry allow to differentiate with epithelioid sarcoma. Surgery is the treatment option.

Conclusion: PHE is a confusing entity with several mesenchymal neoplasms that must be carefully differentiated. Data regarding age, sex, location, course, and recurrence are important for proper diagnosis.

1. Introduction

Pseudomyogenic hemangioendothelioma (PHE), a rare and recently discovered endothelial tumor, was formerly known as a fibroma-like variant of epithelioid sarcoma due to its physical resemblance to that tumor. PHE is an infrequently metastasizing intermediate-grade tumor, according to the World Health Organization (WHO) 2020 [1]. Young adults, particularly males, are often found to have PHE [2]. Although it can occur anywhere, this tumor often affects the extremities, mainly the lower limbs. The case of a young man diagnosed with PHE in the back reported here emphasizes the importance of a proper differential diagnosis in order to protect individuals whose PHE can be confused for more aggressive sarcomas. The aim of this study was to review clinicopathological features, emphasize on differential diagnosis and discuss therapeutic modalities and prognosis of this rare entity.

2. Case presentation

A 21-year-old man with no past medical or trauma history consulted for a back, at the scapula level, multinodular mass that increased rapidly in size within 2 months. A wide excision surgery was performed. Macroscopic examination of the skin specimen showed multiple ulcerated centimetric nodules with a crusty surface. Microscopic examination showed a multinodular proliferation arranged in clusters sometimes delimiting slits. It was made of spindle cells or epithelioid cells with brightly eosinophilic cytoplasm sometimes mimicking rhabdomyoblasts (Fig. 1). Tumor cells contained a nucleated nuclei with variable atypia. Mitotic figures were rarely observed without any atypical mitotic figure. No necrosis was noticed. The tumor ulcerated the epidermis, proliferated throughout the dermis, subcutaneous fat tissue and infiltrated the skeletal muscle in depth. The immunohistochemical study showed the

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expression of Cytokeratin (AE1-AE3) (Fig. 2), and INI-1. No staining for EMA, CD34 (Fig. 3), CD-31, PS-100 and Desmin was observed. ERG was positive in tumor cells (Fig. 4). The tumor was completely resected with safe margin status. Based on these findings, the diagnosis of PHE was retained. A thoraco-abdominal pelvic scan was performed and showed no distant localization. No recurrence was observed six months after the resection. The patient will be followed every 6 months for 4 years with complete clinical examination.

The work has been reported in line with the SCARE 2020 criteria [3].

3. Discussion

Several publications have reported on the clinical and pathological features of PHE. Males are more likely than females to develop the tumor [2] and young adults in the third or early fourth decade have the highest incidence rates [2,4]. In 60 % of the cases, it affects the lower body; the upper body and trunk are less frequently affected [5]. In our case, the lesion involved the back.

Patients with PHE may present with pain in half of the cases or may be asymptomatic [5]. Our patient consulted for a back mass that increased in size rapidly.

PHE can be multifocal, affecting several tissue planes in about two thirds of patients. Most patient's lesions are in the dermis or subcutaneous tissue. Tumor size ranges from a few millimeters to a few centimeters for PHE. Superficial lesions can manifest as ulcerated nodules mimicking an epithelioid sarcoma [6] or a dermatofibroma [7]. In our case, the lesion was centimetric and presented as nodules with a crusty surface.

Microscopically, the tumor's histological architecture is vaguely nodular, and it occasionally exhibits a desmoplastic reaction as it infiltrates the adipose or skeletal muscle tissue around it. The tumor cells are organized in sheets or short fascicles within a background of inflammatory infiltrates that vary in prominence and are typically made up of neutrophils, or less frequently, lymphocytes, plasma cells, or eosinophils. In exceptional cases, a myxoid background is observed. Tumor cells range from spindle to round and epithelioid. Transitional forms have been described [2]. Rhabdomyoblast-like cells with abundant eosinophilic cytoplasm and eccentric nuclei can be found in some areas. Regardless of the morphology, the cells usually feature a highly eosinophilic cytoplasm, bland nuclei with fine chromatin, and variably discernible nucleoli. Most cases of nuclear pleomorphism are mild to moderate; a few cases exhibit significant nuclear atypia. Typically, there are fewer than 5 mitoses per 10 high-power fields, although there have been certain cases where there have been more mitoses. Intratumoral hemorrhage or the development of vascular channels are often absent in the tumor. Geographic necrosis, a hallmark of epithelioid sarcoma, is uncommon. A few intracytoplasmic vacuoles suggestive of epithelioid hemangioendothelioma may occasionally be seen in rare situations [8].

Although PHE expresses vascular immunohistochemistry antibodies, conventional hematoxylin-eosin examinations may not often show morphologic signs of vascular differentiation, and more researches are required to validate endothelial differentiation.

PHE stains for Cytokeratin (AE1/AE3), ERG, FLI1, and FOSB [2,9,10]. Hornick et al. [2] reported that 22/47 cases expressed CD31. In some cases, it is possible to see focal staining for epithelial membrane antigen and smooth muscle actin (SMA). Importantly, integrase interactor 1 (INI-1) exhibits complete nuclear expression within every case. In this study, tumor cells expressed Cytokeratin (AE1-AE3), ERG and INI-1 and were negative for EMA, CD34, and CD-31 which is in accordance to literature.

On a molecular level, a balanced t(7;19)(q22;q13) translocation resulting in the fusion of the SERPINE1 and FOSB genes was discovered by Walther et al. [11] who employed cytogenetics, fluorescence in situ hybridization, messenger RNA sequencing, and real-time polymerase chain reaction. The Fos family, which also includes the smaller splice variants Fra-1 and Fra-2, dimerizes with Jun proteins to form the AP-1 transcriptional factor complex, which includes FOSB. This family is associated with the occurrence of several malignancies, including colorectal, endometrial, and breast tumors [12]. Since SERPINE1 is thought to be a FOSB promoter and this translocation is exclusive to soft tissue tumors, it is thought to be pathognomonic for PHE [13].

Epithelioid sarcoma is the most crucial differential diagnosis to rule out. Both epithelioid sarcoma and PHE share several clinical characteristics in common, including the tendency to affect young patients,

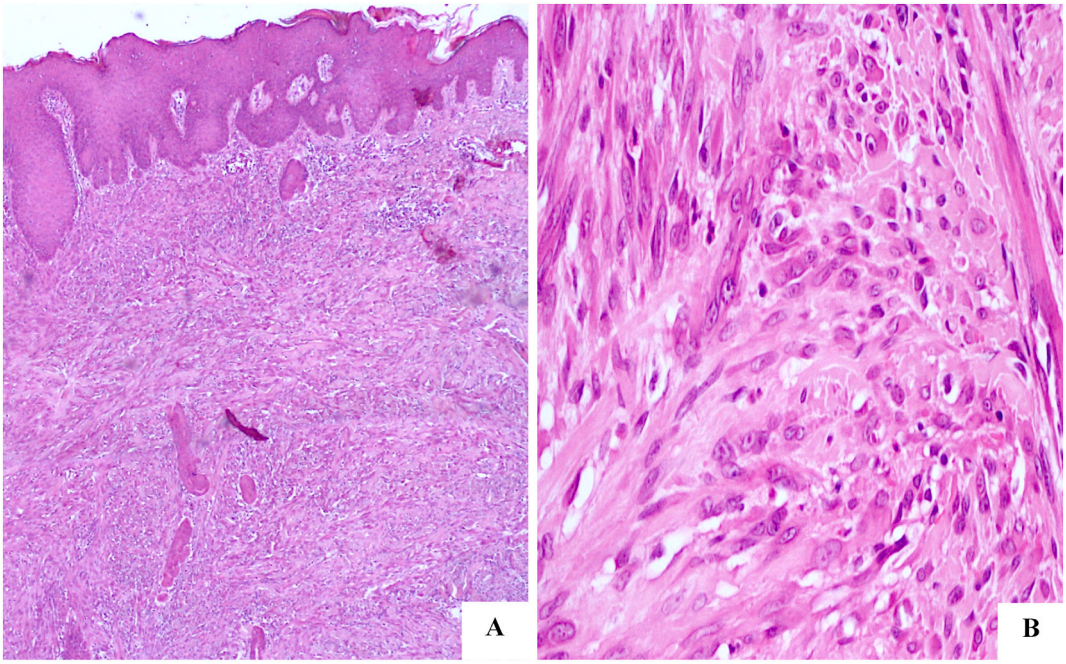

Fig. 1. Hematoxylin and Eosin staining of a pseudomyogenic hemangioendothelioma.
A: Tumor arranged in clusters composed of a mix of spindle and epithelioid cells (×100).
B: Epithelioid and tumor cells showing mild nuclear atypia and rare mitosis (×400).

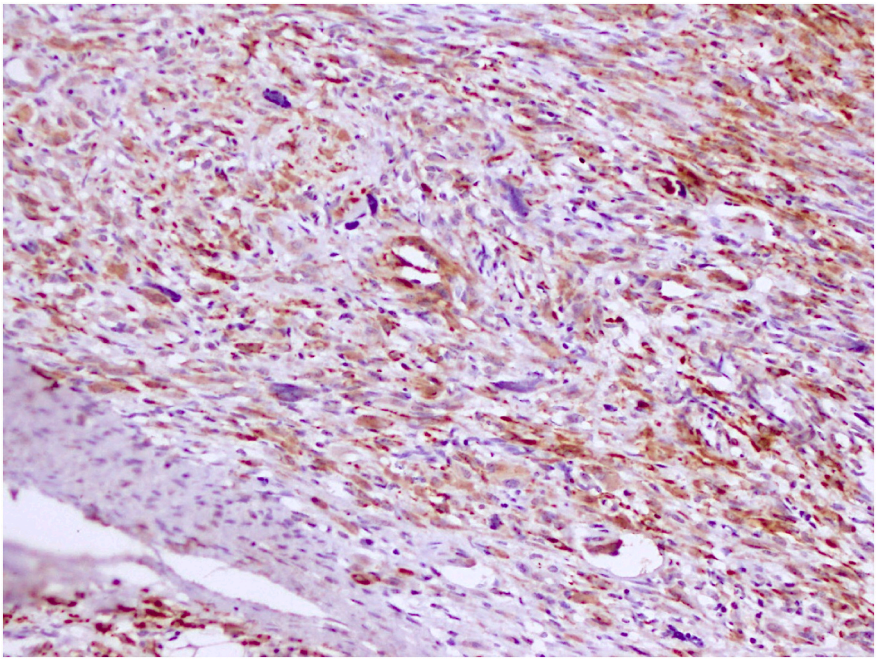

Fig. 2. Tumor cells showing an intense and diffuse positivity for keratin AE1/AE3 (×400).

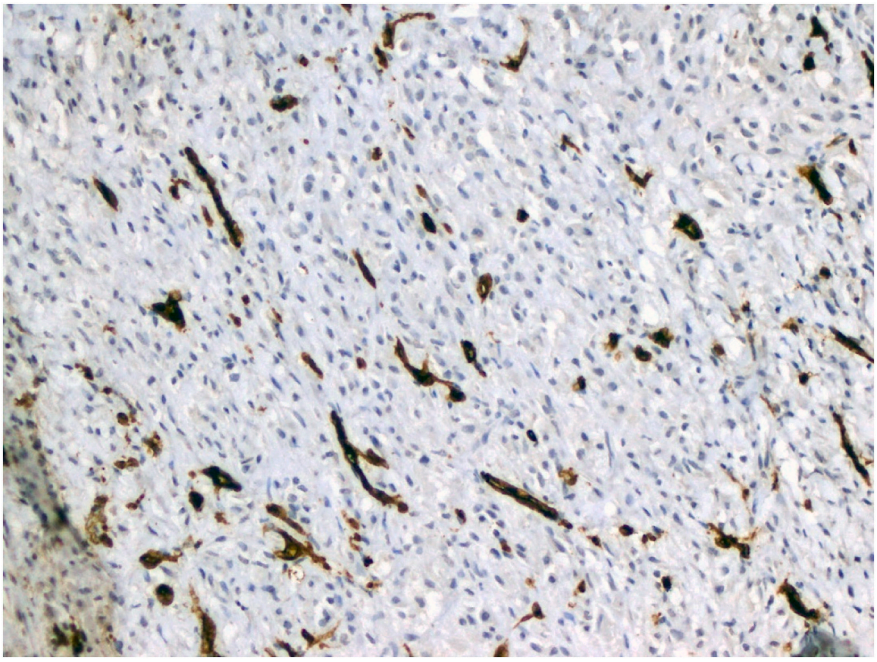

Fig. 3. Tumor cells negative for CD34 with positive internal control (×400).

preference for soft tissue in the distal extremities, epithelioid and spindle cell shape, and diffuse keratin expression. Additionally, FLI1 and ERG are positive in some epithelioid sarcoma patients. Epitheloid sarcoma is a more aggressive tumor than PHE with a higher propensity for local metastasis and recurrence [14]. Thus, it is crucial to distinguish between epithelioid sarcoma and PHE due to these differences. In addition to geographic necrosis, epithelioid sarcoma exhibits increased nuclear atypia. It generally lacks reactivity to CD31, FLI1, and INI-1. The absence or mild immunoreactivity for ERG can be beneficial, while epithelioid sarcomas are commonly ERG+ when antibodies against the N-terminus are used [15]. In addition, a study showed that 51/97 cases (52.6 %) of epithelioid sarcoma positive for CD34; while CD34 is consistently negative in PHE [8].

In some PHE cases, focal nuclear atypia and enhanced mitotic activity may prompt the diagnosis of epithelioid angiosarcoma. Most epithelioid angiosarcoma cases, unlike PHE, have vascular channels or cysts lined by malignant endothelial cells. Furthermore, as CD34 is often positive in angiosarcoma and negative in PHE, it will help in resolving that differential diagnosis.

Surgery, including wide excision, chemotherapy, and radiotherapy are used as treatment options. Distant metastasis only occurred in 3 patients (5 %) and was discovered 4, 8.5, and 16 years after the initial diagnosis. A second patient's concomitant squamous cell carcinoma caused their death [16]. Twenty-six patients (43 %) had new lesions or

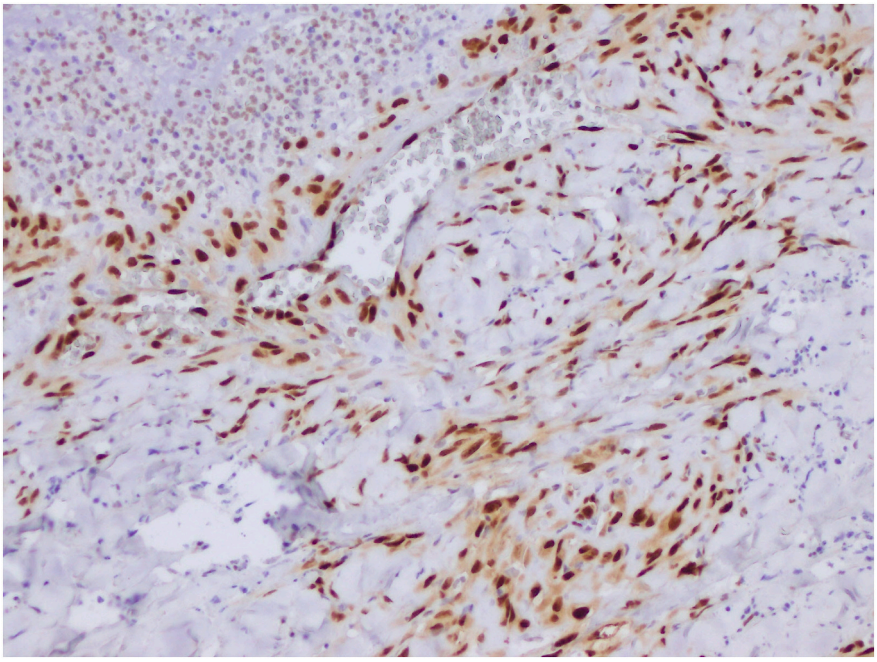

Fig. 4. Tumor cells positive for ERG (×400).

signs of a local recurrence in the same area as the original tumor; these recurrences were primarily noticed in the first year following diagnosis. Interesting though, a lot of the lesions remained unchanged throughout time [2,7]. In this report, the patient is doing well, and no recurrence was observed six months after the resection.

4. Conclusion

PHE is a rare vascular tumor of intermediate malignancy that has been documented in several body sites. It exhibits a clinical presentation resembling epithelioid sarcoma. It can be difficult to diagnose this tumor without morphologic evidence of a vascular pattern, thus an immunohistochemistry panel is needed. The clinical course of PHE appears to be variable, with frequent local recurrence but a low rate of distant metastases. Prolonged intervals of follow-up are advised due to the real, although slight, potential of distant metastasis developing several years after the initial diagnosis.

Ethical approval

No ethical approval.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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All the authors read and approved the final version of the manuscript.

Farah Sassi (MD): conception, acquisition of data, literature research and preparing the manuscript.

Ghada Sahraoui (MD): acquisition of clinical data, preparing and revising the manuscript.

Lamia Charfi (MD): conception, literature research supervision and revising the manuscript.

Olfa Jaidane (MD): clinical data and revising the manuscript critically.

Karima Mrad (MD): manuscript editing and revising the manuscript critically.

Raoudha Doghri (MD): final approval of the version to be published.

Guarantor

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Registration of research studies

None.

Declaration of competing interest

The authors report no declarations of interest.

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