ISSN: 2476 - 2415

Research Article

International Journal of Clinical & Experimental Dermatology

Pseudomyogenic Hemangioendothelioma: A Distinctive, Often Multicentric Tumor With Indolent Behavior

Kenza Barbri[1*], Fouzia Hali[2], Soumia Chiheb[3], Anas Meftah[4] and Mounia Diouri[5]

[1,2,3]Resident Dermatology and Venerology department Ibn Rochd University Hospital Morocco

[4,5]The national center for burns and reconstructive surgery Ibn Rochd University Hospital Morocco

[*]Corresponding Author
Kenza Barbri, Resident Dermatology and Venerology Department Ibn Rochd University Hospital Morocco.

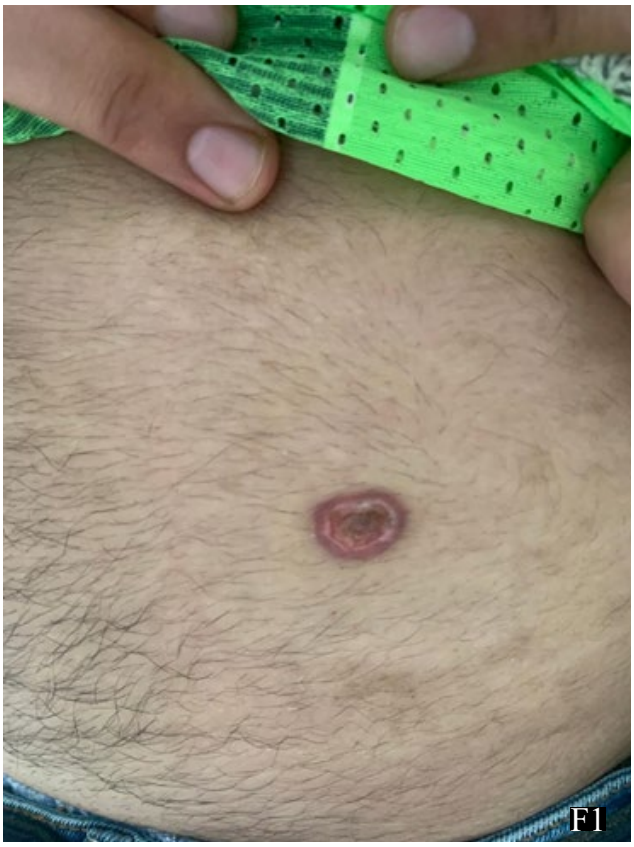
Submitted: 2023, Oct 20; **Accepted:** 2023, Dec 15; **Published:** 2024, Feb 16

Citation: Barbri, K., Hali, F., Chiheb, S., Meftah, A., Diouri. M. (2024). Fractional CO2 laser Combined with TCA for the Treatment of Keloid Scars. *Int J Clin Expl Dermatol,* 9(1), 01-04.

Dear editor,

Pseudomyogenic hemangioendothelioma (PHE) is a rare vascular tumor of intermediate malignancy that commonly occurs in soft tissue of distal extremities of young adults[1,2]. PHE typically has a multifocal presentation and can involve several tissue planes, including the dermis, subcutis, muscle and bone [3]. We report a case of young patient with PHE.

Twenty two years old patient with no particular pathological history presenting a painful ulcerated lesion on the abdomen which had been evolving for one month. Dermatological examination revealed a violaceous ulcerated lesion with a raised inflamed border with a subcutaneous component measuring approximately 5 cm located on the abdomen (figure 1), a small painful violaceous nodule located on the umbilicus(figure2). The patient underwent an initial skin biopsy, which was inconclusive, followed by excision of the entire ulcerated lesion with histological result in favor of an Pseudomyogenic Hemangioendothelioma with immunohistochemical study of tumor cells expressing beta-catenin, cytokeratin AE1/AE3 and CD31 with preservation of IN1 expression. The ki 67 profiling index is estimated at 10%.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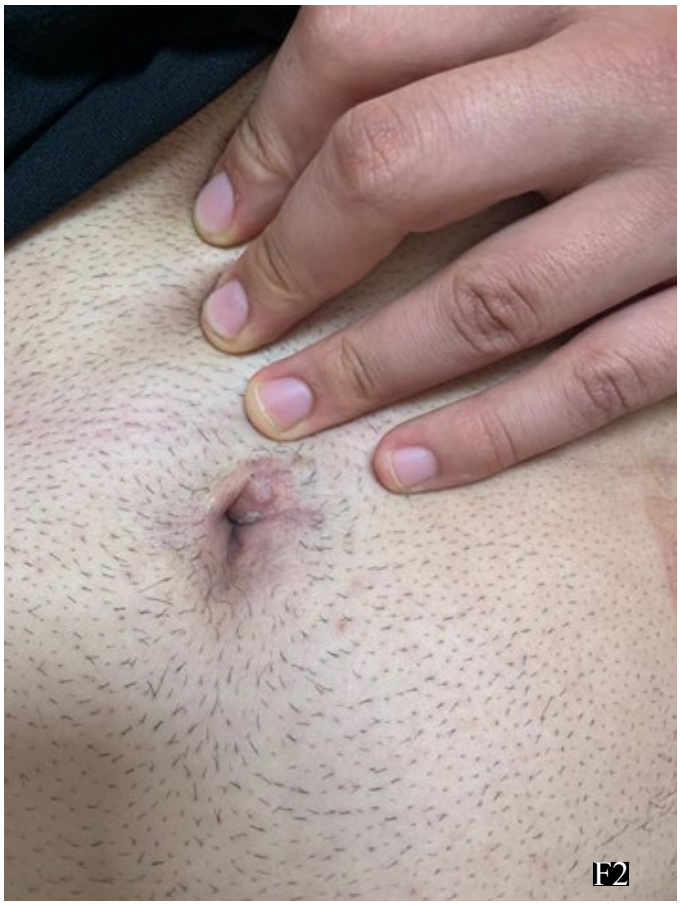

In 1992, Mirra et al. firstly described five cases of an unusual multifocal soft tissue tumor and called the unique lesions as "the Fibroma-like variant of epithelioid sarcoma", describing it as a "fibrohistiocytic/myoid cell lesion often confused with benign and malignant spindle cell tumors". In 2003, Billings et al. described seven distinct cases of a low-grade vascular tumor and proposed renaming this tumor "epithelioid sarcoma-like hemangioendothelioma", which was based on the presence of large cells with abundant eosinophilic cytoplasm upon microscopy with keratin positivity. Based on a series of 50 patients and the advent of newer immunohistochemical markers, Hornick and Fletcher subsequently proposed changing the terminology to PHE, confirming its vascular origin and indolent behavior. In 2013, the current World Health Organization classification of soft tissue and bone listed PHE as an intermediate, rarely metastasizing, vascular tumor with peculiar clinical and pathological features [2-8].

In general, this neoplasm appears to be more common in males than in females (4.6:1) and typically occurs in men between 20 and 50 years . Clinically, PHE most commonly presents as multiple nodules in one anatomic region involving the soft tissues of the upper and lower extremities, but lesions may also arise in the trunk, spine, head, neck, bone and oral cavity [9-13]. Our patient is the first reported case of PHE presenting in the abdomen. Histopathologically, PHE/ESH resembles a neoplasm with ill-defined nodules of plump spindle-shaped and epithelioid cells with abundant densely eosinophilic cytoplasm that grow in sheets and fascicles, sometimes mimicking rhabdomyoblasts. This infiltrative tumor often has a stromal neutrophilic infiltrate and sometimes also has a focal myxoid change in the matrix. Unlike other vascular tumors, PHE/ESH lacks multicellular vascular channels or intralesional hemorrhage. Cytologic atypia is typically mild to moderate, though rare cases have exhibited severe atypia. Mitotic activity is low, with most tumors having fewer than 5 mitoses per 50 HPFs or a mean mitotic rate of 2/10 HPFs [13].

Our case had a mean mitotic rate of 1/10 HPFs. The neoplastic cells usually express cytokeratin AE1/AE3, FLI-1, ERG and are negative for Desmin and S100. Furthermore, CD34 negativity is observed, which differentiates it from other vascular tumors such as epithelioid hemangioendothelioma or epithelioid angiosarcoma. Most notably, the tumor cells in our case were also positive for CD31, with linear membranous staining, which may facilitate diagnosis. Recently, the specific balanced translocation t (7; 19) (q22; q13) resulting in the fusion of the SERPINE1 and FOSB genes was reported. This SERPINE1- FOSB gene fusion might lead to strong expression of FOSB, and identification of this genetic derangement is useful for diagnostic purposes [14, 15]. In our case, the tumor cells expressed CD31, AE1/AE3, FLi-1, and ERG and were negative for CD34. More importantly, FOSB overexpression was observed, which is consistent with the literature.

However, it is still easily misdiagnosed. In fact, approximately half of the patients in the largest published series were clinically diagnosed with various other pathologies, such as epithelioid

sarcoma, leiomyosarcoma, and EHE. These three tumors are particularly aggressive, and it is thus important to distinguish PHE. In general, ES, EHE and PHE share certain features: they all affect the young, show epithelioid and spindle cell morphology, and express FLI1 and ERG to varying degrees [6]. PHE/ESH always has a neutrophil background, whereas the other two tumors are negative. Except for the immunophenotypic overlap, ES typically lacks reactivity for CD31 and lacks SMARCB1 (INI-1) expression, unlike PHE/ESH. The WWTR1-CAMTA1 mutation is found in EHE, which is absent in PHE/ESH. Additionally, leiomyosarcoma shows reactivity to Desmin, Actin and Myogenin, but vascular markers are not expressed.

Moreover, PHE/ESH has no unique radiological, the exact diagnosis can only be made on histopathologic examination. Neither fine-needle aspiration cytology nor core needle biopsy easily diagnoses PHE/ESH because it is difficult to obtain representative cells for a correct diagnosis by these techniques [16]. Histologically, both tumors share the same features, such as many spindle cells, mild to moderate nuclear atypia, and mitoses, with diffuse expression of keratins and lacking expression of ER, PR, and c-erb-B2. Metaplastic carcinoma, especially spindle cell carcinoma is characterized by atypical spindle cells, arranged in a multitude of architectural patterns raging from long fascicles in herringbone or interwoven patterns to short fascicles in a storiform pattern [17]. Infammatory infiltrate is often found in a proportion of cases, but usually with lymphocytes and dendritic cells not neutrophils. Clearly, vascular markers are not expressed in metaplastic carcinoma. Nonetheless, the diagnosis is not difficult if we are aware of this rare clinical entity .

PHE/ESH is a locally recurrent, rarely metastasizing tumor. A total of 82 patients with PHE/ESH have been reported, with follow-up available for 61 (74%); only 3 patients (5%) developed distant metastasis at 4, 8.5 and 16 years after the initial diagnosis. Almost half of patients had local recurrence or new lesions in the same region as the initial tumor, especially in the first year after diagnosis [18]. The efficacy of treatment is only partially known and still the object of study. Surgical excision is the first therapeutic choice for PHE/ESH, followed by chemotherapy or radiation. Most cases can be treated with wide local excision; however, amputation may be recommended for patients with extensive multifocal disease. Moreover, over one-third of patients exhibit relapse after surgery [19]. Based on this, systemic treatment is most likely necessary. Regardless, there are no guidelines because PHE/ESH is so rare. Different systemic therapies (Table 1) have been described in case reports in the literature. Among them, inhibitors of mammalian target of rapamycin (mTOR) show major efficiency in cases of progressive metastatic and relapsing multifocal PHE/ESH resistant to multiagent chemotherapy. mTOR, a serine/threonine kinase regulated by phosphoinositide-3-kinase (PI3K), acts as a master switch for numerous cellular processes, such as cellular catabolism and anabolism, motility, angiogenesis and growth. Several members of the PI3K/mTOR pathway have been implicated in the generation and propagation of vascular anomalies. As inhibitors of mTOR target protein synthesis downstream of the Akt pathway, they are predicted to be effective in disorders in which mTOR pathway-mediated growth control is affected. PHE/ESH is associated with the specific translocation t (7; 19) involving the SERPINE1-FOSB fusion gene. SERPINE1 encodes a serine protease inhibitor family protein, known as plasminogen activator inhibitor-1 (PAI-1), which is reported to inhibit apoptosis by activating the Akt pathway [1,11,12,13,20,21]. Akt functions just upstream of mTOR and is overexpressed in endothelial cells of murine models of cutaneous vascular malformations. Therefore, inhibition of mTOR might constitute a target for therapy in the future. In our case, after total mastectomy, the patient did not show recurrence in the half year of follow-up.In summary, we present a unique case of PHE/ESH in the abdomen. Although extremely rare, PHE/ESH can present in the breast mimicking breast carcinoma. A high degree of suspicion is required to arrive at an accurate diagnosis. In view of the high incidence of local recurrences, continued close follow-up of the patient is mandatory.

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