

Pseudomyogenic haemangioendothelioma: a case report and overview of a potential diagnostic pitfall

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Abstract

Pseudomyogenic haemangioendothelioma (PHE) is a rare vascular tumour which can arise in skin, soft tissue and bone, posing a diagnostic challenge due to its similar histological appearances to several soft tissue and skin neoplasms. We report an unusual case of PHE with aggressive behaviour and provide an overview of this unique entity, discussing important differential diagnoses and highlighting key histological, immunohistochemical and genetic features which aid in its accurate diagnosis.

Keywords differential diagnosis; *FOSB*; sarcoma; vascular tumour

Case report

A 30 year old female presented of multiple lesions on her thigh which had been increasing in size. Physical examination revealed multiple superficial nodules ranging from 10 to 15 mm on her left thigh. An excision biopsy was performed which revealed a multifocal dermal tumour with infiltrative growth into the subcutaneous tissue that involved the resection margin. The tumour was formed of spindled to epithelioid cells with eosinophilic cytoplasm and distinct nucleoli arranged in sheets and fascicles (Figure 1). Focal necrosis was present, and occasional mitoses (3–4 per 10 high powered fields) were seen. On immunohistochemical analysis the tumour cells were diffusely positive for AE1/AE3 with weak expression of CD31 (Figures 1e and 1f), and were negative for SMA, desmin and S100. INI1 expression was retained. Taken together these features pointed to a diagnosis of pseudomyogenic haemangioendothelioma.

Despite wide excision of the original positive margin, multiple areas of relapse around surgical scar were noted after 3 months. Re-excision was performed but again failed to achieve clear margins. Several years later the patient experienced another local relapse, which on histology showed more aggressive features including increased cellularity, geographic tumour necrosis and increased mitotic activity. Immunohistochemistry showed diffuse

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FOSB positivity. The patient soon after experienced widespread disease with bone and lung metastases and was managed with palliative radiotherapy, but ultimately succumbed to disease.

Discussion

Vascular tumours can often pose a diagnostic challenge, particularly when failing to show prominent vasoformative architecture. Pseudomyogenic haemangioendothelioma (PHE) is a rare vascular tumour of intermediate malignancy, most commonly arising on the lower extremities of young to middle-aged males. These tumours often present as multiple cutaneous nodules,¹ but typically invade multiple tissue planes (skin, subcutaneous tissue, muscle) in as many as 50% of cases.² A subset of PHE also show bony involvement, and primary PHE of bone has been reported in the literature.

PHEs have variable histological appearances, inviting a wide range of differential diagnoses. Originally referred to as epithelioid sarcoma-like haemangioendothelioma³ for its often extensive epithelioid component, these tumours characteristically comprise spindled to epithelioid cells arranged in fascicles and solid sheets in a fibrous to myxoid stroma.^{1,4} Tumour cells may also demonstrate a myoid appearance due to the presence of bright eosinophilic cytoplasm. Significant nuclear pleomorphism is only seen in a minority of cases, and mitotic activity is rare. These tumours are also often accompanied by a prominent neutrophilic infiltrate, which is helpful in identifying this tumour type.

The immunoprofile of these tumour cells includes positivity for endothelial markers ERG, FL1 as well as CD31 in approximately 50% of cases.⁴ PHEs are also diffusely positive for AE1/AE3 with variable EMA and p63. MNF116 is consistently negative. INI-1 expression is retained, distinguishing from epithelioid sarcoma. Tumour cells do not express CD34, SMA, desmin, MYOD1, S100 or HMB45. Recently, *FOSB* expression has emerged as a fairly specific marker of PHE⁴ which is not expressed by the majority of its mimics, with the notable exception of epithelioid haemangioma.

Translocations involving the *FOSB* gene on chromosome 19 have been increasingly recognised in this tumour, with t(7;19) translocations resulting in a *SERPINE1-FOSB* fusions first reported in 2014.⁵ Since this first study, several additional fusion partners including *ACTB*, *WWTR1*, *EGFL1* and *CTLC* have subsequently been detected.

Diagnosis of these tumours may be challenging with the differential varying based on anatomic location and

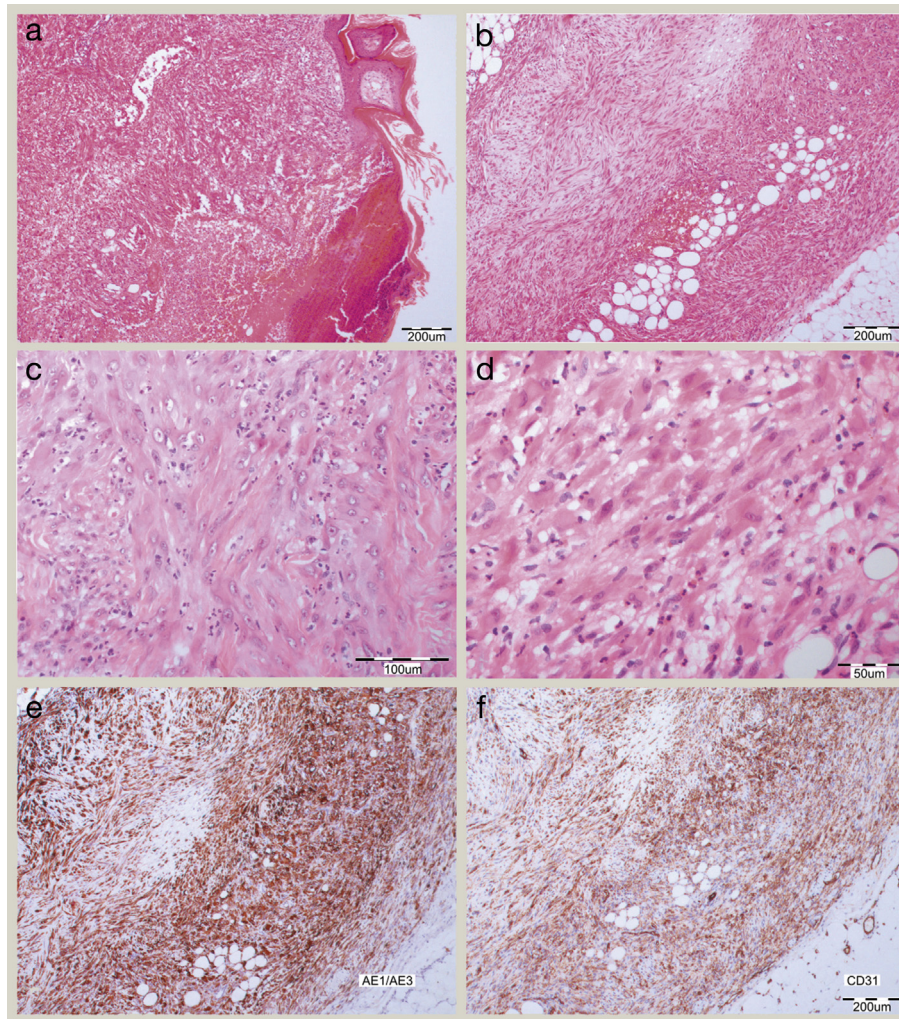


Figure 1 **a)** Low power view of primary dermal lesion with overlying ulceration and adjacent epidermal hyperplasia. **(b)** Tumour infiltrating the subcutaneous fat, comprising spindled cells in a fibromyxoid stroma. In areas the tumour showed fascicles of plump spindled cells **(c)** and bright pink cytoplasm with prominent nucleoli **(d)** giving the impression of a smooth muscle neoplasm. A brisk infiltrate of neutrophils is also present. Tumour cells were positive for both **(e)** AE1/AE3 and **(f)** CD31.

histopathological features. Cutaneous presenting tumours with multifocal involvement raise the differential of various vascular neoplasms. Superficial PHE can also elicit epidermal hyperplasia,¹ thus predominantly spindled appearances are easily mistaken for cellular benign fibrous histiocytomas. For tumours with prominent epithelioid cells several epithelioid tumours may be considered including epithelioid sarcoma, epithelioid haemangioendothelioma and epithelioid angiosarcoma. In these instances FOSB immunohistochemistry or FISH studies can help establish the diagnosis. Finally, diffuse cytokeratin expression (AE1/AE3 but not MNF116) may also prompt the differential of a sarcomatoid carcinoma in a dermal/cutaneous setting.

Current management of patients with PHE is largely surgical, aiming for complete resection where possible. Patients may be offered adjuvant chemotherapy and/or radiotherapy in cases of widespread or progressive disease.¹ In addition, recent reports have demonstrated the responsiveness of PHE harbouring *FOSB* rearrangements to tyrosine kinase inhibitor telatinib⁶ as well as mTOR inhibitors,⁷ providing new therapeutic options for patients

with advanced disease. PHE is associated with significant morbidity due to its locally aggressive behaviour and high rate of relapses. Prior to our case, only a handful of cases have been reported with distant metastases.^{1,8}

Conclusion

Our case brings awareness to PHE, an unusual vascular tumour that mimics many other spindled and epithelioid cutaneous tumours and can also pose diagnostic challenges when arising in deeper soft tissue. Furthermore, we highlight the importance of careful interpretation of immunohistochemical and molecular results in conjunction with clinical and pathological features to avoid pitfalls in the diagnosis of soft tissue neoplasms. ◆

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Practice points

- PHE is an uncommon vascular tumour which due to its predominantly spindled and epithelioid appearances can mimic several skin and soft tissue tumours
- A significant proportion of PHEs harbour *FOSB* fusions, and *FOSB* expression on immunohistochemistry is a fairly specific marker for PHE.
- PHE is locally aggressive with a high propensity for multifocal disease and local relapses, and patients require long term follow up.

Self-assessment questions

1. Which histological feature is NOT typical of a pseudomyogenic haemangioendothelioma?

- a) Nodules of epithelioid cells
- b) Neutrophilic infiltrate
- c) Vasoformative appearances
- d) Overlying epithelial hyperplasia

Correct answer: c) Vasoformative appearances (not usually seen in PHE)

2. Which immunoprofile BEST represents a pseudomyogenic haemangioendothelioma?

- a) AE1/AE3 (+), MNF116 (+), CD31 (+), SMA (-), Desmin (-)
- b) AE1/AE3 (+), INI1 (+), ERG (+), FOSB (-), SMA (-)
- c) AE1/AE3 (-), CD31 (+), FOSB (+), SMA (+), Desmin (-)
- d) AE1/AE3 (+), ERG (+), FOSB (+), SMA (-), Desmin (-)

Correct answer: d) AE1/AE3 (+), ERG (+), FOSB (+), SMA (-), Desmin (-)

3. Which of the following raises the differential of a pseudomyogenic haemangioendothelioma?

- a) Multiple skin nodules in a 30 year-old male
- b) Spindled to epithelioid tumour cells which retain INI1 expression
- c) Translocation involving *FOSB* on FISH studies
- d) All of the above

Correct answer: d) all of the above