A PURPLE PLAQUE IN A PATIENT WITH SYSTEMIC SCLEROSIS

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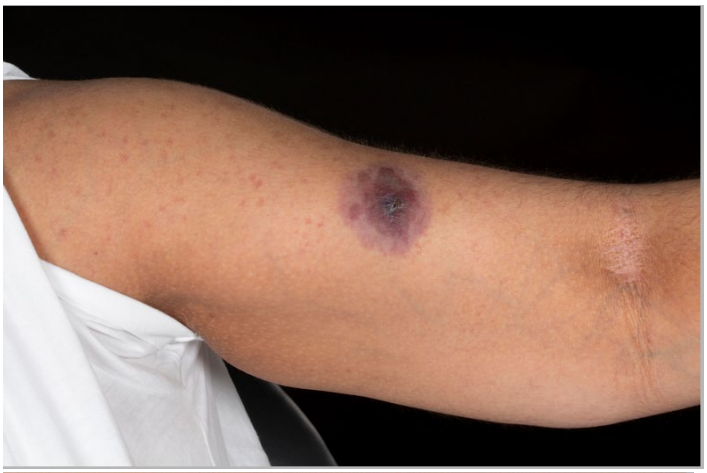
We present the case of a 43-year-old lady with anti-U3 ribonucleoprotein antibody-positive (anti-fibrillarin; AFA) limited cutaneous systemic sclerosis (SSc). Her clinical manifestations of disease included Raynaud's, sclerodactyly, digital calcinosis and striking extensive telangiectases over her limbs, face and torso. She had never been on immunosuppressive therapy.

She presented to our Dermatology department with a 5cm purple plaque on her left upper arm that arose from a pre-existing cluster of telangiectases, however the skin at that site was not sclerotic (figure.1).

a)



b)

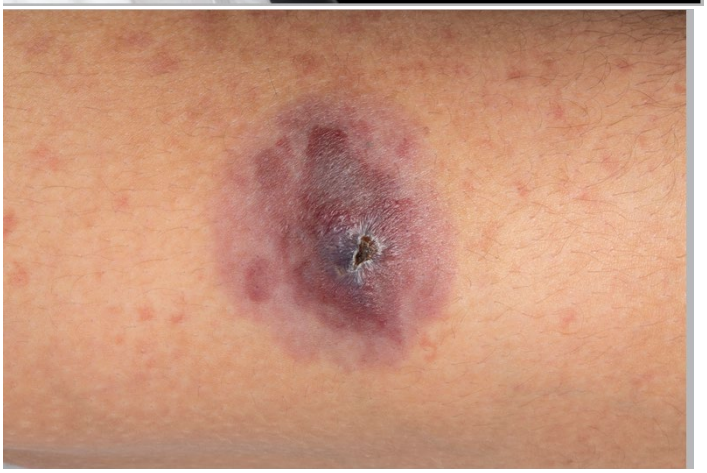
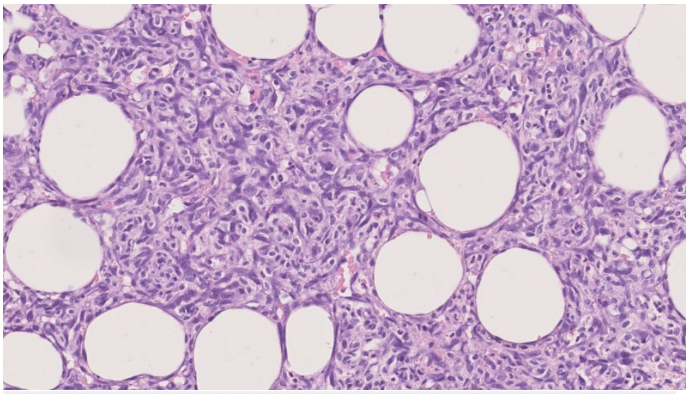


Figure 1: A large purple plaque on the left upper arm with surrounding telangiectasia (a). A closer view of the plaque with a central nodule (b).

An urgent incisional biopsy was performed. Histological examination revealed an endothelial tumour that stained positive with CD31, CD34 and ERG in keeping with an angiosarcoma (figure 2). An MRI showed no evidence of muscle invasion and this patient underwent a wide local excision with a flap reconstruction. Although adjuvant radiotherapy would usually be offered following surgery for local disease, it was thought that radiotherapy might complicate this patient's systemic sclerosis and so she underwent surgery only but remains under close follow-up.

a)



b)

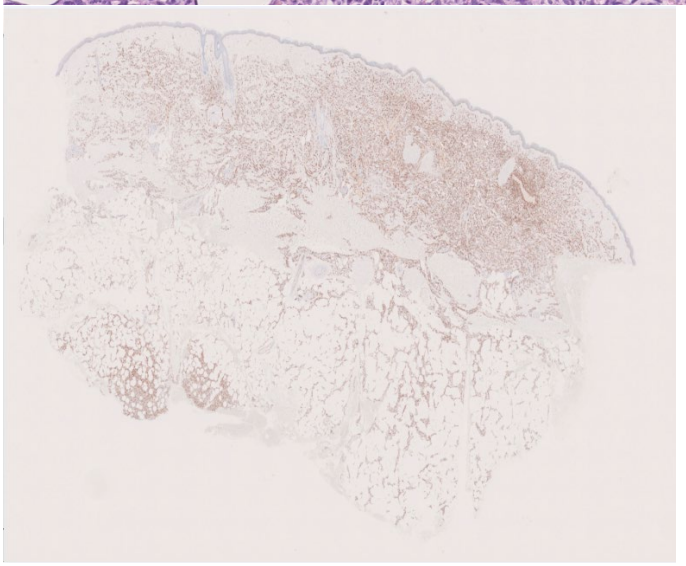


Figure 2: The tumour consists of vascular channels lined by atypical endothelial cells, with nuclear pleomorphism and increased mitotic activity (a). The atypical endothelial cells show strong diffuse expression with CD31 (immunoperoxidase) (b).

Angiosarcoma is a rare malignant tumour of endothelial origin, most frequently occurring on the skin. They most commonly develop on the head and neck and affect older people. Other risk factors are chronic lymphoedema and radiotherapy. They are associated with a high rate of local recurrence and metastasis at presentation is estimated to be between 16 – 40%.[1]

SSc is characterised by vascular damage and widespread fibrosis of the skin and internal organs. About 7% of patients develop a malignancy, the higher incidences being in autoantibody subgroups RNA polymerase III (11%) and PM/Scl (20%).[2] Angiosarcoma arising from a benign vascular malformation/haemangioma is extremely rare and to our knowledge, telangiectases undergoing malignant transformation has not been described in the literature. Furthermore, angiosarcoma occurring in the setting of systemic sclerosis is rare with only five previous case reports.[3-4] Of those five, all occurred on sclerotic skin and four on the head and neck. Our case differed, occurring on non-sclerotic skin and on a limb.

The pathways involved in the pathogenesis of angiosarcoma are complex. However, two key components are transforming growth factor beta (TGF-β) and vascular endothelial growth factor (VEGF). Vasculopathy is a hallmark of SSc pathogenesis and accounts for early manifestations of her disease such as Raynaud's phenomenon but also severe complications such as pulmonary hypertension (PAH) and cardiopulmonary involvement.[5] It involves endothelial cell dysfunction and overexpression of proangiogenic factors – two of the most important being also VEGF and TGF beta, highlighting overlapping mechanisms between angiosarcoma and SSc. These microvascular changes happen in the context of intricate inflammation involving both innate and adaptative immunity, with specific autoantibody production. Later on, it leads to endothelial to mesenchymal transition and fibrosis.

The anti-U3RNP antibody is a highly specific antibody for systemic sclerosis. It is associated with significant vascular dysfunction. A study looking at over 1300 patients with systemic sclerosis and aiming to classify their disease outcomes according to their antibody profile showed that although anti-U3 RNP is associated with a low incidence of pulmonary fibrosis, it related to the highest incidence of vascular complications, namely PAH and cardiovascular disease.[6] It would not be unusual for these patients to have extensive telangiectases, very abnormal nail fold capillaries and pulmonary hypertension.

This case was memorable as the angiosarcoma arose from telangiectases on non-sclerotic skin of a patient with a U3RNP+ SSc presenting with a striking vasculopathic phenotype. We would urge clinicians to adopt a high index of suspicion when patients with systemic sclerosis present with atypical vascular tumours.

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Which antibody subgroup of patients with systemic sclerosis frequently associate with a concurrent cancer diagnosis?

a) anti – RNA polymerase III (RNAP III)
b) anti-topoisomerase I (Scl70)
c) ACA
d) anti-U1RNP
e) anti-U3 RNP

What SSc autoantibody subgroup has the highest incidence of PH and cardiac involvement?

a) ACA
b) anti- U3 RNP
c) RNAP III
d) anti-PM/SCL
e) anti- Scl70