KMT2G has not been previously implicated in mesenchymal neoplasms, gene fusions involving another member of the *KMT2* family (*KMT2A/MLL*) have been recently described in aggressive sarcomas in young adults, suggesting a broader role for *KMT2* family of histone methyltransferases in the pathogenesis of mesenchymal tumour.¹²

In summary, we have identified a novel *SETD1B-FOSB* gene fusion in a case of intravascular EH of deep soft tissue with uncommon histological features. This supports the association of certain unusual morphological features of EH with recurrent genetic rearrangements in the *FOS* gene family, hinting at a distinct subgroup defined by *FOS* gene family alterations within this heterogeneous entity.

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Glomeruloid haemangioma pattern in reactive angioendotheliomatosis leading to the diagnosis of POEMS syndrome

Sir,

Reactive angioendotheliomatosis (RAE) is a rare, self limited, reactive cutaneous vascular proliferation with a wide spectrum of histological patterns including intravascular and/or extravascular proliferation of endothelial cells and pericytes.^{1,2} Despite its benign behaviour, it is an important diagnosis that should not be overlooked due to its association with underlying systemic diseases in about 75% of cases.¹ These include autoimmune diseases, chronic infections, cryoglobulinaemia, lymphoproliferative disease and post-organ transplantation.¹ However, to our knowledge, the association of RAE with polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes (POEMS) syndrome has yet to be reported. Here, we describe a case of RAE which subsequently led to the discovery of underlying POEMS syndrome, preventing future systemic morbidities which may lead to end stage organ failure.

An 81-year-old woman was referred to a dermatologist for multiple skin nodules of 2 years duration. Physical examination revealed approximately 50 scattered erythematous nodules and papules of varying sizes ranging from 0.5 cm to 1.0 cm in maximum dimension over the anterior trunk, posterior trunk, scalp, and pubic region (Fig. 1A). The clinical impression was that of cherry angiomas. Biopsies were taken from the chest and vulvar skin nodules. Microscopic examination featured vascular proliferation composed of multiple lobules of closely packed capillaries lined by flat to plump, monotonous endothelial cells accompanied by thin layers of pericytes around capillaries. There were many plump stromal cells, some of which were vacuolated, separating the capillaries. Most of the endothelial proliferation were observed within dilated vascular spaces, forming conglomerates of capillaries resembling glomeruloid haemangioma (GH) (Fig. 1B). In areas, the endothelial proliferation showed tufted morphology with crescent shaped vascular spaces at the periphery, exhibiting those of a tufted angioma-like pattern (Fig. 1C). Extravascular proliferation of endothelial cells with pericytes was also observed (Fig. 1D). Fibrin thrombi and erythrocytes were evident in the vascular lumina. Moreover, there were conspicuous eosinophilic hyaline globules which were periodic acid-Schiff (PAS) positive and diastase resistant, present in the endothelial and stromal cells (Fig. 2A,B). Hyaline globules were not seen in the endothelial cells lining the dilated vascular spaces (native dilated vessels). CD31 (Fig. 2C) and ETS related gene (ERG) immunomarkers highlighted the endothelial cells. Smooth muscle actin (SMA) stained pericytes around the capillaries (Fig. 2D). Human herpesvirus-8 (HHV-8) immunostain was negative. There were no atypical features to suggest a malignant process.

Prior to this, there was a skin biopsy from the same patient which was diagnosed as benign capillary haemangioma. Subsequent review of the aforementioned biopsy showed a similar appearance to the current biopsies, including intravascular and extravascular capillary proliferation with glomeruloid and focal tufted patterns as well as presence of

Fig. 1 Reactive angioendotheliomatosis. (A) Erythematous nodules and papules on the trunk. (B) Conglomerates of capillaries within dilated vascular spaces which resembled glomeruli. (C) Tufted angioma-like pattern with peripheral clefts. (D) Extravascular proliferation of endothelial cells and pericytes.

intracytoplasmic eosinophilic globules. These features, in conjunction with the clinical history of multiple skin nodules, were consistent with RAE. Given the presence of GH-like component, the suggestion of underlying POEMS syndrome was raised in the report. This prompted further clinical investigations. Nerve conduction studies performed showed a predominantly symmetrical, axonal, sensorimotor polyneuropathy affecting the lower limbs more than the upper

limbs and presence of bilateral median neuropathies. Bone marrow flow cytometry yielded a 1.2% clonal population of plasma cells that were kappa light chain restricted with aberrant CD117 expression, suggestive of an underlying plasma cell dyscrasia. Vascular endothelial growth factor (VEGF) was elevated at 269 pg/mL. In addition, she has a history of primary hypothyroidism and was also previously admitted for bilateral pleural effusion. All these findings

Fig. 2 Reactive angioendotheliomatosis. (A) Intracytoplasmic hyaline globules (arrow) were seen in the endothelial and stromal cells. (B) Hyaline globules in the endothelial and stromal cells were positive for PAS stain. (C) Endothelial proliferation highlighted by CD31. (D) Pericytes around the capillaries were positive for SMA while the stromal cells were negative.

fulfilled the criteria and hence she was diagnosed with POEMS syndrome.

POEMS syndrome is a rare syndrome associated with underlying plasma cell disorder and overproduction of VEGF. This condition is potentially fatal; mostly contributed by congestive heart failure, respiratory or renal failure.^{3,4} Other associated morbidities include extravascular volume overload, endocrinopathy, organomegaly, calciphylaxis, thrombocytosis and sclerotic bone lesions.^{3,4} In this case, the patient had developed bilateral pleural effusion and hypothyroidism prior to the diagnosis. After she was started on lenalidomide and dexamethasone, her condition improved. She remains clinically stable (at approximately 2 years) and is on regular outpatient follow-up.

RAE is a benign, cutaneous vascular lesion with various histological patterns. At low power, RAE can show diffuse, lobular or mixed diffuse and lobular growth patterns.¹ Diffuse growth pattern is frequently observed in diffuse dermal angiomatosis which is considered to be a variant of RAE.⁵ Lobular growth pattern is usually observed in RAE with tufted angioma-like or GH-like patterns. A case series of RAE reported by McMenamin *et al.* mentioned these features including proliferation of capillaries in the dermis, presence of fibrin microthrombi, fasciitis-like dermal alterations, and foci of epithelioid endothelium were frequently seen.¹

In view of the varying histological patterns, features of RAE commonly overlap with other vascular lesions. The important differential diagnoses include papillary haemangioma, GH, tufted angioma, lobular capillary haemangioma, Kaposi sarcoma and angiosarcoma. Papillary haemangioma is a benign, solitary, cutaneous lesion located in the head and neck region. Histologically, it comprises distinct papillary architecture in the ectatic dermal vessels with the papillae covered by plump endothelial cells. There are many SMA positive pericytes and conspicuous collagenous material in the papillary cores.^{6,7} Hyaline globules are usually discerned, mostly limited to the endothelial cells lining the papillae and not seen within the cores. In contrast, the GH-like component of RAE in our case showed thin layers of pericytes around the capillaries and there were predominantly plump stromal cells in between capillaries that were negative for SMA. Also, hyaline globules were seen in both endothelial and stromal cells, compared to mainly in endothelial cells in papillary haemangioma. GH was an important differential diagnosis in this case given the prominent glomeruloid component. However, there were other different patterns of endothelial proliferation within the same lesion, which were more in keeping with RAE. In the case series that initially described GH, the authors mentioned that GH could represent a form of RAE.⁸ Our case further supports this notion by showing a spectrum of features including GH-like component within the same lesion, which are in line with the reactive nature of this entity. The mixed histological patterns of RAE were also observed in a recent case report of drug induced RAE.⁹

Tufted angioma is commonly seen in children. It demonstrates tightly packed capillaries with surrounding pericytes in the dermis, imparting a cannonball appearance. Frequently, crescent shaped thin walled vessels are present around the periphery of the lobules. Whilst tufted endothelial proliferation was observed in this case, the overall features and clinical history were not corroborative. Furthermore, fibrin thrombi and hyaline globules are not the features of tufted angioma. Lobules of benign capillary proliferation is a

classical feature described in lobular capillary haemangioma. There are often interlobular septa containing small feeding arteries and veins. Although lobules of capillaries were seen in this case, the presence of other histological patterns and hyaline globules were against the diagnosis of lobular capillary haemangioma. Kaposi sarcoma was a consideration because of the presence of hyaline globules. It is associated with HHV-8 infection. Histologically, the nodular stage often shows fascicles of spindled endothelial proliferation with slit-like vascular spaces. Lymphoplasmacytic infiltrate is typically present. In this case, the clinical history together with negative HHV-8 immunostaining ruled out Kaposi sarcoma. Angiosarcoma is a malignant vascular tumour that should always be considered and ruled out in a vasoproliferative lesion. It usually shows endothelial multilayering, hobnail endothelial cells, cytological atypia and increased mitosis. These features were not observed in this case.

Various inciting agents have been proposed in the pathogenesis of RAE including deposition of immunoglobulins, immunocomplexes or cryoproteins, bacterial antigens and changes in systemic haemodynamic.^{1,10} A recent case report showed that drug induced anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis also plays a role in RAE.⁹ Most of the stimuli result in vascular injury or local hypoxia which eventually lead to angiogenesis.^{1,10} In POEMS syndrome, studies showed that expression of VEGF has a role in endothelial proliferation of haemangioma.¹¹

Despite RAE being recognised to be associated with various systemic diseases, RAE occurring in patients with POEMS has not yet been reported. In this case, the observation of different components including GH-like, and tufted angioma-like areas as well as extravascular endothelial proliferation within the same lesion, were likely parts of the spectrum or represent different stages of development of RAE. Most are aware that in patients with POEMS syndrome, GH is the frequent associated haemangioma. However, some of the reported GH cases in patients with POEMS actually showed a mixture of different components within the same lesion.^{8,12} These cases were probably RAE that exhibited a wide spectrum of features.

In summary, we report a case of RAE that was associated with POEMS syndrome which further expands the list of related systemic diseases in RAE. RAE should be included in the list of differential diagnosis when one encounters a dermal vascular lesion with a wide spectrum of histological features, as it may act as a trigger for the clinician to further investigate the possible underlying systemic illness. Furthermore, an effort should be made to subclassify the different histological patterns within a RAE case as it would help to narrow down the possible list of related systemic disease.

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Malignant gastrointestinal neuroectodermal tumour in soft tissue

Sir,

Malignant gastrointestinal neuroectodermal tumour (GNET) is an uncommon and aggressive primitive mesenchymal neoplasm of the digestive tract, predominantly occurring in young to middle aged adults (median age 35 years), with no obvious gender predominance. Malignant GNET is also known as clear cell sarcoma-like tumour of the gastrointestinal tract, because it shares with clear cell sarcoma of soft tissues (CCS-STs) a similar morphological appearance and a common genetic characteristic of *EWSR1-ATF1/CREB1* fusion genes resulting from t (12; 22) (q13; q12) or t (2; 22) (q34; q12).¹ The recent reports have presented several novel confirmed or suspected cases, respectively located in palate,² tongue³ and bronchus,⁴ but malignant GNET with extra-gastrointestinal origin is actually extremely rare. Herein, we present an unusual case of malignant GNET arising in the deep soft tissue of the thigh, a hitherto unreported occurrence site for the tumour. We briefly discuss the clinicopathological features of malignant GNET.

A 47-year-old female presented with a subcutaneous mass in her right thigh for 10 years without local swelling, tenderness, skin ulceration, stiffness or difficult movement. The mass had increased slightly in size over several months. Imaging included ultrasound scan, magnetic resonance

imaging and digital radiography and showed a 6 cm well defined soft tissue mass, located in the intermuscular space between the adductor magnus and sartorius muscle on the right. However, antero-posterior and lateral radiograph of the right femur indicated no skeletal abnormality. Additionally, there was no evidence of regional lymph node metastasis and distant metastasis. Her physical examination and laboratory findings were unremarkable except for serology analysis which showed that the patient was positive for the hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb). Abdominal ultrasound and computed tomography (CT) scan of the abdomen and pelvis revealed no mass in the gastrointestinal tract.

Surgical excision of the mass was performed. Macroscopic examination revealed a greyish-red lobulated mass measuring 6×5×4.5 cm; the mass was slightly firm, smooth surfaced, and not obviously adherent to surrounding tissue. No haemorrhage or necrosis was observed on multiple cut sections. Microscopically, the tumour was well circumscribed with a multinodular appearance separated by fibrous connective tissue (Fig. 1A). The tumour nodule was composed of a proliferation of uniform spindle cells arranged in short fascicles (Fig. 1B). The tumour cells displayed abundant predominantly clear cytoplasm, fine nuclear chromatin, and indistinct nucleoli (Fig. 1C). Mitoses were very rare. There was focal cystic change (Fig. 1D). Characteristic osteoclast-like giant cell was not identified. Immunohistochemistry staining showed that the tumour cells were strongly and diffusely positive for S-100 protein (Fig. 1E) and SOX10 (Fig. 1F), weakly positive for CD99, focally and weakly positive for CD56 and EMA, while negative for HMB45, Melan A, synaptophysin, Chromogranin A, CD117, CD34, DOG-1, CK, SMA, desmin, myogenin, and myoD1. Ki-67 proliferation index was about 5%. Fluorescence *in situ* hybridisation (FISH) analysis demonstrated the presence of *EWSR1* rearrangement and *EWSR1-ATF1* fusion (Fig. 2), while the other common gene fusions involving *EWSR1*, including *EWSR1-FLI1*, *EWSR1-CREB1* and *EWSR1-WT1*, were all absent.

Given that the case occurred in soft tissue of a lower extremity and was characterised by spindle cell appearance, our differential diagnoses mainly included CCS-STs, monophasic synovial sarcoma and malignant peripheral nerve sheath tumour (MPNST). Malignant GNET shares overlap with CCS-STs in morphological appearance and genetic abnormalities. Nevertheless, CCS-STs harbours melanocytic differentiation and is variably positive for HMB45, Melan-A or MiTF,⁵ while all reported cases of malignant GNET, including our case, are unexceptionally lacking expression of melanocytic markers. Monophasic SS histologically exhibits fascicles of monomorphic spindled cells without an epithelial component, which should be differentiated from our case. Although S-100 protein has been observed in 10–40% of SS cases, its expression is often focal^{6–8} instead of the diffuse and strong staining pattern in malignant GNET.¹ The detection of *SYT* gene rearrangement resulting from specific chromosomal translocation t (X; 18) (p11.2; q11.2) can aid in confirming the diagnosis of a synovial sarcoma. MPNST is characterised by a proliferation of spindle cells with alternating hypercellular and hypocellular areas, and is ordinarily positive for the neural markers including S-100 protein, Leu-7, PGP9.5 and myelin