the same group, contributed eight new cases (and three previously reported cases) from the head and neck region. Two of the new cases showed *GLI1* amplification, the rest being characterised by *GLI1* fusions. Again, a consistent immunophenotype failed to emerge: positivity for S100, SMA, and cytokeratin was seen in 6/10 (60%), 4/10 (40%), and 2/9 (22%) cases, respectively. Of the two patients with *GLI1* amplified tumours, one had follow-up and was free of disease at 3 months.

A number of differential diagnoses should be considered during work up of this neoplasm. Morphologically, the pattern most resembles a neuroendocrine neoplasm such as carcinoid or paraganglioma; however, the lack of synaptophysin or chromogranin excludes these possibilities. Myoepithelial tumours and epithelioid schwannoma may arise as possibilities in SMA positive and S100 positive cases, respectively. However, *GLI1* activated tumours lack other markers of myoepithelial differentiation such as calponin and p63, while its infiltrative growth pattern is incompatible with a diagnosis of schwannoma. Given the acral location in our case, we also considered digital papillary adenocarcinoma and mucin producing sweat gland carcinoma. However, the morphological features and immunoprofile were not consistent with these alternatives.

Our case expands the growing body of knowledge about the novel group of tumours associated with *GLI1* abnormalities. Whilst a disease spectrum is emerging, the precise pathogenetic relationship between the reported cases is difficult to elucidate. Nevertheless, it is clear that a subset of tumours with either *GLI1* gene fusions or amplifications can show similar epithelioid cytomorphology that can aid their recognition and prompt consideration of *GLI1* molecular studies. For these reasons, we propose the term '*GLI1* activated epithelioid cell tumour' to aptly and succinctly describe them. Awareness and recognition of this entity may aid in a refined understanding of its pathogenesis.

Acknowledgements: We thank Dr Diane Payton for the opportunity to review the case and Dr Cristina Antonescu and Dr Andrew Folpe for their input and performing *GLI1* FISH studies. Support from colleagues at the Royal Prince Alfred Hospital, New South Wales Health Pathology, and Melanoma Institute Australia is also gratefully acknowledged.

Conflicts of interest and sources of funding: Karina Aivazian is supported by a Deborah and John McMurtrie Melanoma Pathology Fellowship through Melanoma Institute Australia. Richard A. Scolyer is supported by an Australian National Health and Medical Research Council Fellowship. The authors state that there are no conflicts of interest to disclose.

Karina Aivazian^{1,2}, Annabelle Mahar¹, Louise A. Jakkett^{1,2,3}, Roy M. Kimble⁴, Richard A. Scolyer^{1,2,3}

¹Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital, and NSW Health Pathology, Sydney, NSW, Australia; ²Melanoma Institute Australia, North Sydney, NSW, Australia; ³Sydney Medical School, The University of Sydney, Sydney, NSW, Australia; ⁴Department of Paediatric Surgery and Urology, Queensland Children's Hospital, Brisbane, NSW, Australia

Contact Prof Richard A. Scolyer.

E-mail: richard.scolyer@health.nsw.gov.au

1. Antonescu CR, Agaram NP, Sung YS, *et al.* A distinct malignant epithelioid neoplasm with *GLI1* gene rearrangements, frequent S100 protein expression, and metastatic potential: expanding the spectrum of pathologic entities with *ACTB/MALAT1/PTCH1-GLI1* fusions. *Am J Surg Pathol* 2018; 42: 553–60.
2. Agaram NP, Zhang L, Sung Y, *et al.* *GLI1*-amplifications expand the spectrum of soft tissue neoplasms defined by *GLI1* gene fusions. *Mod Pathol* 2019; 32: 1617–26.
3. Kinzler K, Bigner S, Bigner D, *et al.* Identification of an amplified highly expressed gene in human glioma. *Science* 1987; 236: 70–3.
4. Stein U, Eder C, Karsten U, *et al.* *GLI* gene expression in bone and soft tissue sarcomas of adult patients correlates with tumor grade. *Cancer Res* 1999; 59: 1890–5.
5. Dahlen A, Fletcher CD, Mertens F, *et al.* Activation of the *GLI* oncogene through fusion with the beta-actin gene (*ACTB*) in a group of distinctive pericytic neoplasms: pericytoma with t(7;12). *Am J Pathol* 2004; 164: 1645–53.
6. Bridge JA, Sanders K, Huang D, *et al.* Pericytoma with t(7;12) and *ACTB-GLI1* fusion arising in bone. *Hum Pathol* 2012; 43: 1524–9.
7. Castro E, Cortes-Santiago N, Ferguson LM, *et al.* Translocation t(7;12) as the sole chromosomal abnormality resulting in *ACTB-GLI1* fusion in pediatric gastric pericytoma. *Hum Pathol* 2016; 53: 137–41.
8. Koh NWC, Seow WY, Lee YT, *et al.* Pericytoma with t(7;12): the first ovarian case reported and a review of the literature. *Int J Gyn Pathol* 2018; 38: 479–84.
9. Graham RP, Nair AA, Davila JJ, *et al.* Gastroblastoma harbors a recurrent somatic *MALAT1-GLI1* fusion gene. *Mod Pathol* 2017; 30: 1443–52.
10. Spans L, Fletcher CD, Antonescu CR, *et al.* Recurrent *MALAT1-GLI1* oncogenic fusion and *GLI1* up-regulation define a subset of plexiform fibromyxoma. *J Pathol* 2016; 239: 335–43.
11. Kerr DA, Pinto A, Subhawong TK, *et al.* Pericytoma with t(7;12) and *ACTB-GLI1* Fusion. Reevaluation of an unusual entity and its relationship to the spectrum of *GLI1* fusion-related neoplasms. *Am J Surg Pathol* 2019; 43: 1682–92.
12. Xu B, Chang K, Folpe AL, *et al.* Head and neck mesenchymal neoplasms with *GLI1* gene alterations. *Am J Surg Pathol* 2020; 44: 729–37.

DOI: <https://doi.org/10.1016/j.pathol.2020.07.013>

Intravascular epithelioid haemangioma of deep soft tissue with novel *SETD1B-FOSB* gene rearrangement

Sir,

Epithelioid vascular neoplasms encompass a spectrum of benign to malignant entities that can show overlapping morphological features, belying significant differences in biological behaviour.¹ In recent years, the molecular underpinnings of several epithelioid vascular neoplasms have been delineated, and molecular testing serves as a useful adjunct diagnostic tool in cases with unusual morphology and/or clinical presentation. We herein present a case of an epithelioid haemangioma of deep soft tissue with an unusual intravascular growth pattern, harbouring a novel *SETD1B-FOSB* gene fusion.

A 33-year-old female presented with a painful deep soft tissue mass on the left posterior chest wall of 3 years duration. The initial clinical impression was a possible vascular malformation. Computed tomography (CT) angiogram showed a solitary, non-enhancing, 1.7 cm nodular lesion between the left 8th and 9th ribs underlying the posterior latissimus dorsi. No feeding vessel was identified. As the patient experienced

persistent, severe pain that did not respond to conventional analgesia and radiofrequency ablation, hookwire-guided excision of the nodule was performed.

Histological evaluation of the excised specimen showed skeletal muscle and fibroadipose tissue involved by an epithelioid tumour with a predominantly intravascular growth pattern, filling the lumina of medium sized blood vessels (Fig. 1A–C). The tumour comprised solid aggregates of relatively uniform epithelioid cells with round, centrally placed nuclei and ample eosinophilic cytoplasm (Fig. 1D). Vascular lumina were inconspicuous. No accompanying inflammatory infiltrate or myxohyaline stroma was seen. There was no high grade nuclear atypia, mitotic activity or necrosis. On immunohistochemistry, the epithelioid tumour cells showed positive expression of endothelial markers ERG and CD31 (Fig. 1E,F), and were negative for SMA, Cam5.2,

AE1/3, desmin, TFE3 and CAMTA1. The overall findings were most in keeping with an epithelioid haemangioma with a predominant intravascular growth pattern. Anchored multiplex polymerase chain reaction (PCR) analysis (FusionPlex custom assay; Archer, USA) detected a novel *SETD1B* (exon 4)-*FOSB* (exon 2) gene fusion (Fig. 2), which was subsequently confirmed by reverse transcription polymerase chain reaction (RT-PCR) and Sanger sequencing. There was no clinical or radiological evidence of recurrent disease at one year follow-up.

Epithelioid haemangioma (EH) is an uncommon, benign vascular neoplasm that mainly affects adults aged 20–50 years with no gender predominance.¹ Initially described as having a predilection for the skin and subcutis of the head and neck, later studies have reported various anatomical locations including the deep soft tissue, bone, lymph nodes, viscera,

Fig. 1 (A–C) Histological and immunohistochemical features of intravascular epithelioid haemangioma occurring in deep soft tissue. Multiple discontinuous foci of tumour within intravascular spaces, occurring as solid proliferations of epithelioid cells with minimal vasoformative features (H&E). (D) High power examination shows relatively uniform tumour cells with round to ovoid central nuclei, granular chromatin and moderately abundant eosinophilic cytoplasm. Immunohistochemistry shows expression of (E) ERG and (F) CD31 by tumour cells.

Fig. 2 A gene fusion between *SETD1B* (exon 4) and *FOSB* (exon 2) was detected by anchored multiplex PCR analysis (Archer FusionPlex Solid Tumour Assay, top panel). RT-PCR and Sanger sequencing shows the junction sequence between *SETD1B* exon 4 and *FOSB* exon 2 (bottom panel).

eyes and penis.² Typically, it has a lobulated growth pattern, well-circumscribed or pushing borders, and well-formed vascular channels lined by prominent epithelioid endothelial cells. There is usually abundant accompanying stromal chronic inflammation, with a brisk eosinophilic infiltrate characteristic of most lesions.¹ However, EH also displays a diverse range of histological appearances, which if under-recognised may pose diagnostic pitfalls.

We report this unusual case of EH arising in the deep soft tissue of the chest wall, as it shows several features not typically seen in its cutaneous counterpart in the head and neck region. In particular, the intravascular growth pattern, solid architecture, minimal vasoformative features and absence of accompanying inflammatory infiltrate are emphasised. Although EH with focal solid growth is not uncommon, a predominantly solid growth pattern with minimal peripheral maturation, as seen in our case, is rare.² In addition to the lack of overt vasoformation, the locally confined intravascular growth pattern is also uncommonly described, particularly in non-cutaneous EH.³ An eosinophilic stromal infiltrate is a classic feature of EH, as reflected in the original description of this entity, angiolymphoid hyperplasia with eosinophilia (ALHE). However, it has since been recognised that the eosinophilic stromal infiltrate is only occasionally seen in deep seated soft tissue or bone EH,⁴ as illustrated in this case.

For cases of EH with unusual histological features, ancillary molecular tests may be helpful in providing a higher degree of diagnostic confidence and excluding more aggressive epithelioid vascular neoplasms such as epithelioid haemangioendothelioma and epithelioid angiosarcoma. In recent years, several gene rearrangements involving *FOSB* and *FOS* genes have been described in EH, and are summarised in a recent review.⁵ *ZFP36-FOSB* fusion has been described in a subset of EH with atypical features,⁶ whilst *FOS-LMNA* fusion has been observed in a third of EHs across different anatomical locations and histological variants and *VIM-FOS* fusion was identified in two cases of intraosseous cellular EH.⁷ Cases of EH showing *FOSB* or *FOS* gene rearrangements have been reported to be enriched

in morphological variants displaying solid growth, atypical features and less conspicuous eosinophilic infiltrate.^{6,7} Interestingly, our case which similarly displayed some of these unusual histological traits also harboured a genetic rearrangement in the *FOSB* gene, with a novel fusion partner *SETD1B*. Of note, *FOSB* gene rearrangements were not detected in a recent case series of cutaneous intravascular EH, suggesting different genetic underpinnings of cutaneous versus non-cutaneous intravascular EHs.³

The *FOS* gene family consists of four members: *FOS* (chromosome 14q24.3), *FOSB* (chromosome 19q13.32), *FOSL1*, and *FOSL2*. These genes encode leucine zipper proteins that can dimerise with proteins of the JUN family, constituting the major components of the transcription factor complex AP-1 (Activating Protein-1). The AP-1 transcription factor binds to TPA-responsive elements (TREs; 5'-TGAC/GTCA-3') of the promoter and enhancer regions of target genes, and is critical for accurate regulation of numerous genes implicated in cell proliferation, differentiation, apoptosis, angiogenesis, oncogenic transformation and tumour progression.⁸ Although the functional roles of the *FOSB* and *FOS* gene rearrangements in EH have not been well-characterised, there is evidence of increased expression of *FOSB* and *FOS* mRNA expression in cases of *FOSB*- and *FOS*-fusion positive EH, respectively, compared to the other types of vascular neoplasms.^{6,7} In the *FOSB*-fusion EH index cases, there was also an increase in the mRNA expression of *IL8*,⁷ a gene that encodes a FOSB regulated protein which plays a role in stress induced tumour growth and microvessel density.⁹ Of note, recurrent *FOSB* fusions (*SERPINE1-FOSB*, *WWTR-FOSB* and *ACTB-FOSB* fusions) have also been described in pseudomyogenic haemangioendothelioma,¹⁰ another uncommon vascular neoplasm with borderline malignant potential.

SETD1B (SET domain containing 1B), also known as *KMT2G*, is a member of the KMT2 family of histone H3K4 methyltransferases that mediates genome accessibility and transcription. The KMT2 family dependent epigenetic regulation is implicated in several biological processes, including tumour development and progression.¹¹ Whilst *SETD1B*/

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.

Acknowledgements: We thank Professor Brian Rubin for his assistance with this case.

Conflicts of interest and sources of funding: This study was supported by the VIVA-KKH Paediatric Brain and Solid Tumour Programme. The authors state that there are no conflicts of interest to disclose.

Li Yin Ooi¹, Jian Yuan Goh², Chik Hong Kuick², Kenneth Tou-En Chang^{2,3}, Yingting Mok¹

¹Department of Pathology, National University Health System, Singapore; ²Department of Pathology and Laboratory Medicine, KK Women's and Children's Hospital, Singapore; ³Duke-NUS Medical School, Singapore

Contact Dr Yingting Mok.

E-mail: yingting_mok@nuhs.edu.sg

1. Fletcher CDM, Bridge JA, Hogendoorn PCW, *et al.* *World Health Organization Classification of Tumours of Soft Tissue and Bone*. 4th ed. Lyon: IARC Press, 2013.
2. Fetsch JF, Sesterhenn IA, Miettinen M, *et al.* Epithelioid hemangioma of the penis: a clinicopathologic and immunohistochemical analysis of 19 cases, with special reference to exuberant examples often confused with epithelioid hemangioendothelioma and epithelioid angiosarcoma. *Am J Surg Pathol* 2004; 28: 523–33.
3. Luzar B, Jeremia E, Antonescu CR, *et al.* Cutaneous intravascular epithelioid hemangioma. A clinicopathological and molecular study of 21 cases. *Mod Pathol* 2020; 33: 1527–36.
4. Errani C, Zhang L, Panicek DM, *et al.* Epithelioid hemangioma of bone and soft tissue: a reappraisal of a controversial entity. *Clin Orthop Relat Res* 2012; 470: 1498–506.
5. Papke Jr DJ, Hornick JL. What is new in endothelial neoplasia? *Virchows Arch* 2020; 476: 17–28.
6. Antonescu CR, Chen H-W, Zhang L, *et al.* ZFP36-FOSB fusion defines a subset of epithelioid hemangioma with atypical features. *Genes Chromosomes Cancer* 2014; 53: 951–9.
7. Huang S-C, Zhang L, Sung Y-S, *et al.* Frequent *FOS* gene rearrangements in epithelioid hemangioma: a molecular study of 58 cases with morphologic reappraisal. *Am J Surg Pathol* 2015; 39: 1313–21.
8. Durchwald M, Angel P, Hess J. The transcription factor Fos: a Janus-type regulator in health and disease. *Histol Histopathol* 2009; 24: 1451–61.
9. Shahzad MMK, Arevalo JM, Armaiz-Pena GN, *et al.* Stress effects on FosB- and interleukin-8 (IL8)-driven ovarian cancer growth and metastasis. *J Biol Chem* 2010; 285: 35462–70.
10. Panagopoulos I, Lobmaier I, Gorunova L, *et al.* Fusion of the genes *WWTR1* and *FOSB* in pseudomyogenic hemangioendothelioma. *Cancer Genomics Proteomics* 2019; 16: 293–8.
11. Rao RC, Dou Y. Hijacked in cancer: the *KMT2* (*MLL*) family of methyltransferases. *Nat Rev Cancer* 2015; 15: 334–46.
12. Yoshida A, Arai Y, Tanzawa Y, *et al.* *KMT2A* (*MLL*) fusions in aggressive sarcomas in young adults. *Histopathology* 2019; 75: 508–16.

DOI: <https://doi.org/10.1016/j.pathol.2020.06.020>

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