CORRESPONDENCE

GLI activated epithelioid cell tumour: report of a case and proposed new terminology

Sir,

In 2018, Antonescu *et al.* reported a series of six cases of an unusual tumour characterised by round to ovoid cells with a nested, cord-like and cribriform architecture, infiltrative growth, strong S100 expression, and *GLII* gene rearrangements, which usually arose in soft tissues and often showed clinically aggressive behaviour.¹ They noted that the tumours appeared distinct compared with previously described actin positive perivascular myoid tumours displaying *ACTB-GLII* gene fusions known as ‘pericytoma with t(7;12) translocation’ and two recently reported gastric tumours, plexiform fibromyxoma and gastroblastoma, that both harboured *MALAT1-GLII* fusions. In view of the distinctive clinical, morphological, and immunohistochemical profile of their cases, Antonescu provisionally proposed the descriptive terminology ‘malignant epithelioid tumour with *GLII* rearrangement’. Recently, a case series was published describing a related group of tumours that showed morphological overlap with the earlier examples, but lacked the defining *GLII* translocation. Rather, these harboured *GLII* amplification as an alternative pathway of *GLII* activation.² Here, we report a case of *GLII* amplified tumour, expanding the clinicopathological spectrum of described features, and propose the term ‘*GLI* activated epithelioid cell tumour’ to more aptly describe it. We also highlight the utility of FISH for *DDIT3*, which lies in close proximity to *GLII* on chromosome 7, as a surrogate marker for *GLII* amplification.

A 9-year-old female presented with a 5 year history of a slowly growing lesion on the left great toe. It came to medical attention as a painless mass causing functional restriction, and local excision was performed. The overlying skin had a nodular outline with focal ulceration (Fig. 1A,B). The cut surface had a uniform tan appearance. Microscopy revealed a dermally-based tumour with a multinodular growth pattern (Fig. 1C,D). The tumour nodules had an organoid arrangement with tight nests separated by thin fibrovascular septa reminiscent of paraganglioma (Fig. 1E). Some cribriform gland-like structures were present (Fig. 1F). The cells had uniform round to ovoid nuclei with granular chromatin and inconspicuous nucleoli (Fig. 1G). The cytoplasm was scant eosinophilic to clear. Necrosis was absent, but mitoses were readily identified (up to 8/mm²). There was prominent perivascular tumour growth, and vascular invasion with multiple intravascular tumour deposits (Fig. 1C,D) was noted. Immunohistochemically (Fig. 2A–E), the lesional cells showed strong diffuse positivity for BCL2, Glut A, and CD56. S100 was positive in isolated cells, probably representing associated dendritic cells. There was patchy staining for EMA and focal p63. SMA showed staining of perivascular cells at the periphery of the nests of tumour cells. The tumour was negative for desmin, calponin, CEA, CD21, Melan A, synaptophysin, chromogranin, myogenin, and a broad range of cytokeratins. As Ewing sarcoma was considered in the differential diagnosis, FISH testing for

EWSR1 rearrangement was performed, which was negative. The tumour was found to be negative for *GLII* rearrangement on FISH testing but there was amplification of the *GLII* locus. Since *GLII* lies in close proximity to *DDIT3* on chromosome 12, FISH for *DDIT3* was also performed (Fig. 2F). As expected, co-amplification of this gene was observed. Further investigations revealed no sites of metastatic disease. The patient was well at last follow-up, 10 months after her surgery.

GLII is a transcription factor that functions as the terminal effector of the Sonic Hedgehog (Shh) signalling pathway. This pathway is critical for normal tissue growth, differentiation, and polarity, but is also implicated in the pathogenesis of a number of human cancers. Indeed, *GLII* was first identified in glioma,³ where a 50-fold amplification of the gene was reported. It was subsequently found to be amplified and/or overexpressed in a number of other established tumour types.⁴ However, there has been inconsistency regarding the classification of mesenchymal neoplasms harbouring *GLII* associated chromosomal abnormalities reported in the literature to date (Table 1). *GLII* rearranged soft tissue tumours were first described in a series of five cases that showed the t(7;12) translocation by cytogenetic analysis.⁵ This abnormality resulted in *ACTB-GLII* gene fusion in all cases, leading the authors to conclude that the *ACTB* promoter caused overexpression of *GLII* transcripts with subsequent activation of downstream genes. The cases reported in this initial series showed spindle cell morphology with a perivascular growth pattern and variable expression of SMA, and were therefore considered to have a pericytic phenotype. Further case reports of tumours with similar histological features and an identical molecular abnormality were then added to the literature, occurring in bone,⁶ stomach,⁷ and ovary.⁸ Interestingly, the last of these cases was negative for SMA and positive for S100, despite its designation as pericytoma with t(7;12). Subsequently, *GLII* translocations were shown to occur in two distinct rare entities in the stomach, namely gastroblastoma⁹ and plexiform fibromyxoma.¹⁰ Up to this point, all of the reported cases had pursued a benign clinical course. The spectrum of tumours with *GLII* gene abnormalities was further expanded in 2018 when Antonescu *et al.* published their aforementioned series of six tumours with *GLII* fusions, epithelioid morphology, and negativity for SMA.¹ Unlike the t(7;12) pericytomas, these tumours preferentially occurred in the soft tissues and bone, and three of the cases metastasised. Recently, a further three cases of *ACTB-GLII* fusion associated tumour were reported,¹¹ and served as a possible link between the t(7;12) pericytomas and Antonescu’s cases.¹ Similar to our case, these tumours showed morphological overlap with the latter cohort, with packeted growth of round to oval cells and a prominent vascular component. In contrast, however, there was immunohistochemical evidence of at least partial myogenic differentiation. Follow-up revealed malignant behaviour in two of the tumours. The authors speculated that tumours with *ACTB-GLII* fusions may represent related entities that lie on a morphological spectrum and display variable pericytic phenotype and biologic potential.

In contrast to the cases characterised by chromosomal translocations involving *GLII*, amplification of the *GLII* gene

Fig. 1 Clinical and histological findings. (A,B) Dorsal and medial views of the lesion. (C,D) The tumour is multinodular with prominent subendothelial growth. (E) Nested growth with intervening fibrovascular septa. (F) A less compact area showing admixed nests and tubules. (G) High power reveals nests of epithelioid cells with oval nuclei and clear to pale eosinophilic cytoplasm. Mitoses are readily identified.

Fig. 2 Immunohistochemistry and FISH findings. (A) The tumour cells are negative for cytokeratin AE1/AE3. (B) SMA highlights a subset of cells at the periphery of the tumour nodules, while the central cells are negative. (C) Patchy weak staining for EMA. (D) Strong diffuse staining for CD56. (E) S100 stains the occasional dendritic cells only. (F) Break-apart FISH for *DDIT3* shows amplification, and is a useful surrogate marker for *GLI1* amplification due to the proximity of the two loci.

as the defining molecular event has been previously described in only two case series, in a total of 12 patients.^{2,12} The first included 10 cases that showed histological similarities to our case and the malignant epithelioid tumours previously reported by Antonescu and colleagues, but lacked *GLI1* rearrangements.² These cases did not show any consistent morphological features or immunophenotypes, occurred at a variety of anatomical sites, and showed variable clinical behaviour. The morphological spectrum was wider than previously reported. Whilst all cases showed the characteristic nested epithelioid

growth, some tumours also included biphasic epithelioid and spindled areas, cells growing in single file in a fibrous stroma, or significant cytological atypia. Intriguingly, one of the cases was from an acral location in a child and showed striking morphological similarities to our case. In addition to *GLI1* gene amplification, this tumour had an unbalanced translocation involving the *GLI1* locus. It is possible that the chromosomal instability inherent to unbalanced translocations resulted in amplification, the latter being responsible for some of the morphological features seen. The second series,¹² from

Table 1 Clinicopathological features of mesenchymal neoplasms with chromosomal abnormalities involving the *GLI1* gene reported to date

Study	Age/ sex	Site	Mitoses (per 10 HPF)	GLI1 abnormality	Architecture	Cytology	S100/ SMA/CK	Clinical behaviour	FU (months)
Dahlen <i>et al.</i> ⁵	61/M	Calf	<1	ACTB-GLI1 fusion	Nested, arranged around thin-walled vessels	Spindle to ovoid, clear cytoplasm	−/+−	NED	60
	27/F	Tongue	<1	ACTB-GLI1 fusion			−/+−	NED	60
	11/M	Tongue	<1	ACTB-GLI1 fusion			−/−	NED	22
	65/F	Stomach	<1	ACTB-GLI1 fusion			−/−	NED	24
	12/F	Tongue	<1	ACTB-GLI1 fusion			−/−	NED	120
Bridge <i>et al.</i> ⁶	67/M	Talus	Low	ACTB-GLI1 fusion	Solid with prominent thin-walled vessels	Spindle to ovoid	−/−	NED	168
Castro <i>et al.</i> ⁷	9/F	Stomach		ACTB-GLI1 fusion	Solid and cystic, plexiform vasculature	Ovoid, eosinophilic to clear cytoplasm	−/−	NED	6
Antonescu <i>et al.</i> ¹	20/M	Thigh	<5	ACTB-GLI1 fusion	Solid-cystic, large malformed vessels	Round to oval to epithelioid nuclei, cytoplasm varies from scant to abundant and clear to eosinophilic	+/−	No FU data	—
	16/M	C2 spine	<5	MALAT-GLI1 fusion	Nests and cords, rich capillary network		+/−	No FU data	—
	30/F	Foot	<5	ACTB-GLI1 fusion	Nested, rich capillary network		+/−	Inguinal LN met	21
	34/F	Neck	<5	PTCH1-GLI1 fusion	Nests and cords, rich capillary network, myxoid stroma		+/−	LN and lung mets	80
	79/F	RP	<5	ACTB-GLI1 fusion	Cribriform/sieve-like, myxoid stroma		−/−	LN mets	—
	38/F	Chest wall	<5	ACTB-GLI1 fusion	Solid sheets with scattered tubular structures		−/−	No FU data	—
Koh <i>et al.</i> ⁸	11/F	Ovary	Low	ACTB-GLI1 fusion	Fascicles, sheets, nests; hypo- and hypercellular areas; arborizing capillaries and larger thick vessels	Round to spindled nuclei, eosinophilic cytoplasm	+/−	No FU data	—
Agaram <i>et al.</i> ²	4/F	Shoulder	5	Amplification	Cord-like growth, rich capillary network	Monomorphic ovoid cells	F/−	No FU data	—
	10/M	Finger	15	Amplification, fusion	Nested, rich capillary network, dilated vascular spaces	Round and uniform, clear cytoplasm	−/−	No FU data	—
	17/M	Thigh	5	Amplification	Nested, rich capillary network	Round and uniform, eosinophilic to clear cytoplasm	−/−	No FU data	—
	23/F	Thigh	2	Amplification	Cribriform/rosette-like growth, trabecular areas	Round and uniform, eosinophilic to clear cytoplasm	−/−	NED	36
	26/F	Lung	4	Amplification	Trabecular and sinusoidal patterns	Round and uniform, eosinophilic to clear cytoplasm	F/−	No FU data	—
	39/M	Neck	>25	Amplification	Nests alternating with short fascicles	Biphasic, epithelioid and spindle cell component	−/+−	Lung met	26
	51/F	Back	>25	Amplification	Single files to sheets in collagenous stroma	Epithelioid, focally increased atypia	F/−	Local recurrence	16
	54/F	Elbow	15	Amplification	Multinodular, nested, rich capillary network	Round and uniform, eosinophilic to clear cytoplasm	F/F	No FU data	—
	60/M	Forearm	10	Amplification	Nested, rich capillary network	Round and uniform, eosinophilic to clear cytoplasm	−/−	No FU data	—
	65/M	Tongue	5	Amplification	Compact nested growth in fibrotic stroma	Epithelioid uniform, clear cytoplasm	−/−	No FU data	—
Kerr <i>et al.</i> ¹¹	57/F	Tibia	5	ACTB-GLI1 fusion	Multinodular and trabecular growth, HPC-like and fine vessels	Round to oval, clear to eosinophilic cytoplasm	−/−	Met to 8th rib	27
	62/M	Scapula	<1	ACTB-GLI1 fusion	Tight nests; delicate vasculature; areas of myxoid change	Round to oval, clear to eosinophilic cytoplasm	−/−	Lung, thigh met	168
	41/F	Ovary	<1	ACTB-GLI1 fusion	Hypo and hypercellular areas; sheet-like growth; delicate vasculature	Oval	F/F+	NED	14
Xu <i>et al.</i> ¹²	46/F	Tongue	0	Amplification	Multinodular or plexiform growth, with nested architecture and rich arborizing vascular network. Frequent protrusion of tumour into vascular spaces.	Monomorphic round to oval nuclei, clear cytoplasm	F/+−	NED	3
	60/M	Tongue	11	Amplification			F/−/ND	No FU data	—
	38/M	Tongue	1	PTCH1-GLI1 fusion			+/−	NED	2
	37/M	Neck	0	ACTB-GLI1 fusion			−/−	NED	30
	1/M	Tongue	4	ACTB-GLI1 fusion			ND/−/ND	NED	2
	28/M	Tongue	0	ACTB-GLI1 fusion			+/−	No FU data	—
	14/M	Tongue	0	ACTB-GLI1 fusion			−/ND	No FU data	—
	56/F	Tongue	8	MALAT-GLI1 fusion			−/−	No FU data	—
Aivazian <i>et al.</i> (our case)	9/F	Great toe	20	Amplification	Nested, rich capillary network	Round to epithelioid	−/−	NED	10

−, negative; +, positive; CK, cytokeratin; F, focally positive; FU, follow-up; met, metastasis; mo, months; ND, not done; NED, no evidence of disease; SMA, smooth muscle actin.

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.

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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