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Case Report

Papillary Intralymphatic Angioendothelioma of the Spleen: A Rare Lymphatic Tumour in the Context of a *PIK3CA* Mutation

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Abstract

Papillary intralymphatic angioendothelioma (PILA) is a locally aggressive, rarely metastasising lymphatic tumour that typically arises within the skin and soft tissues. We report a case of PILA arising within the spleen of a 6-year-old boy with megacephaly-capillary malformation (MCAP/MC-M) syndrome. MCAP/MC-M represents part of the phosphatidylinositol-4,5-biphosphate 3 kinase catalytic subunit alpha (*PIK3CA)* related overgrowth spectrum (PROS). This is the 6th reported case in the literature of a splenic PILA and the 2nd known to have occurred in the context of a confirmed *PIK3CA* mutation. In reporting this case we review prior reports of PILA occurring within the spleen and discuss the potential role of the *PIK3CA* mutation in the aetiology of the lesion, and note a theoretical application of mammalian target of rapamycin (mTOR) inhibitors as a possible therapeutic strategy.

Keywords

Spleen, Lymphatic Malformation, Papillary Intralymphatic Angioendothelioma, PIK3CA Mutation, PROS

1. Introduction

Papillary intralymphatic angioendothelioma (PILA) and retiform haemangioma are described together within the WHO tumour classification series 5th edition Bone and Soft tissue book as locally aggressive, rarely metastasising lymphatic tumours with hobnail endothelia [1], typically occurring within the skin and soft tissues. This case represents the sixth [2-6] described incidence of a PILA occurring within the spleen, and the second known to have occurred in the context of a somatic phosphatidylinositol-4,5-biphosphate 3 kinase catalytic subunit alpha (*PIK3CA)* mutation [6].

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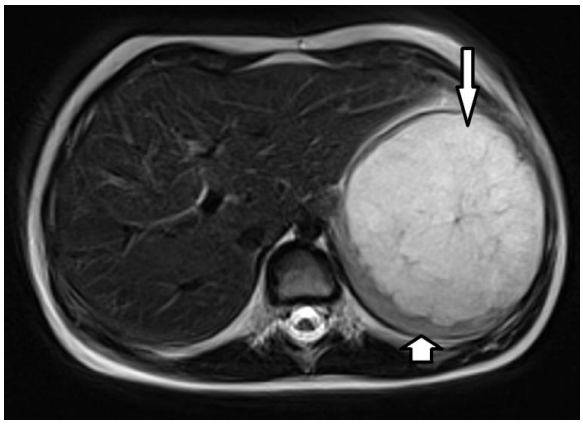

Figure 1. *Axial T2W sequence of the abdomen demonstrated a large rounded splenic lesion (long arrow). Normal splenic tissue is seen stretched around the mass posteriorly (short arrow).*

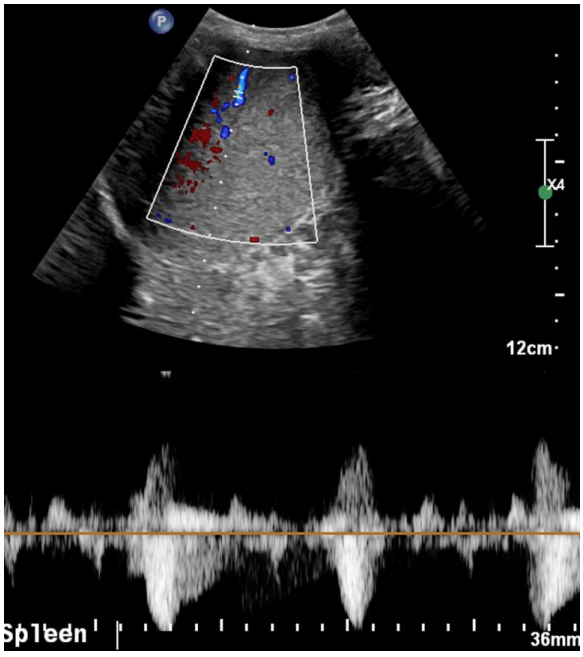

Figure 2. *Arterial spectral Doppler waveforms were obtained from intralesional vessels throughout the homogeneous splenic mass in keeping with a vascular lesion.*

The patient, at the time of diagnosis, was a 6 year old boy with a history of megacephaly-capillary malformation (MCAP/MC-M) syndrome with a confirmed somatic *PIK3CA* mutation (PIK3CA c.2176G>A p.(Glu726Lys) (mosaic) 10%). MCAP/MC-M represents part of the *PIK3CA* related overgrowth spectrum (PROS). One feature of PROS is a pre-disposition to the development of vascular malformations, involving capillary, venous, arteriovenous or lymphatic channels [7]. Previously this young boy had been diagnosed with a facial capillary haemangioma with an associated left facial nerve palsy. His other medical issues include non-progressive ventriculomegaly with an associated cord syrinx, and it was during imaging of this multi-loculated syrinx of the cervical and thoracic spine that an incidental splenic lesion was discovered. In regard to the splenic lesion the patient was asymptomatic.

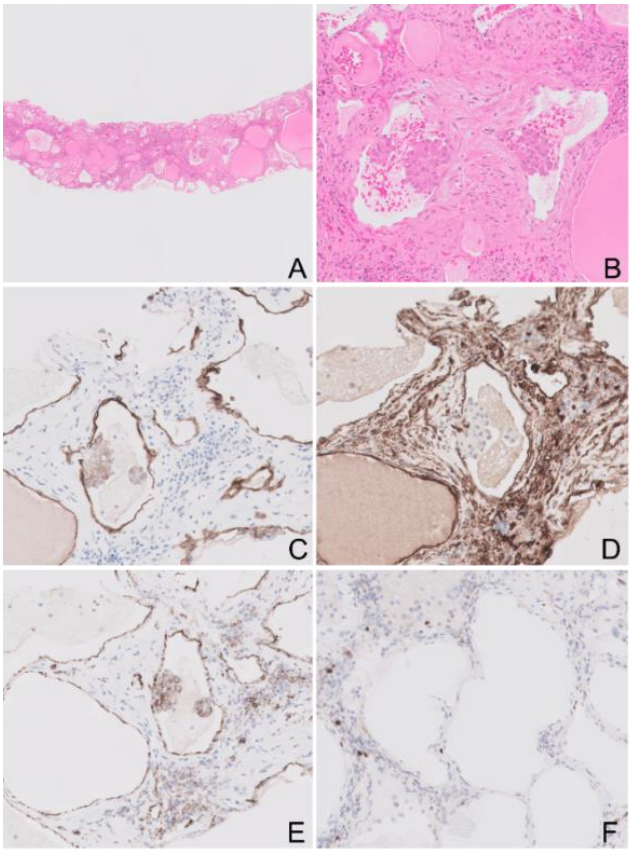

Figure 3. *A: Low power (20x) view of the core biopsy comprising variably sized vascular channels with intraluminal proteinaceous debris. B: Vascular channels containing intraluminal pseudoglomerular projections lined by hobnailed epithelium. (200x). C: Immunohistochemistry showing positivity with the vascular channels and pseudo-glomeruli for CD31 (200x). D: Immunohistochemistry showing positivity within the vascular channels, but only focal staining at the base of the the pseudo-glomerular structures, for CD34 (200x). E: Immunohistochemistry showing positivity with the vascular channels and pseudo-glomeruli for D240 (200x). F: Immunohistochemistry demonstrating the low rate of Ki67 within the lesion (200x).*

Magnetic resonance imaging (MRI) demonstrated an 8.7cm well-defined rounded splenic lesion which was isointense to splenic tissue on T1W and hyperintense on T2W sequences (figure 1). Contrast sequences demonstrated gradual centripetal enhancement. Ultrasound was also performed to further assess blood flow within the lesion. This demonstrated a homogeneous lesion with internal arterial spectral doppler waveforms (figure 2). The differential diagnoses based on imaging were splenic haemangioma or splenic hamartoma. A multidisciplinary team meeting decision was taken to proceed with an ultrasound

guided biopsy of the lesion for further characterisation.

Seven cores were received and macroscopically described as haemorrhagic soft tissue. On histology, all of the cores comprised lesional tissue composed of numerous variably sized lymphovascular channels lined by endothelial cells with scattered intraluminal glomeruloid projections. (Figure 3). The endothelial cells lining the glomeruloid projections had a hobnailed appearance. The lumina were expanded by a mixture of proteinaceous and haemorrhagic debris. There were no mitotic figures. Immunohistochemistry revealed dual staining within the vascular channels for lymphoid (D240) and vascular (CD31) markers. Focal staining with CD34 was noted at the base of the intraluminal pseudoglomerular structures. The combined morphological and immunophenotypic impression was that of a papillary intralymphatic haemangioendothelioma.

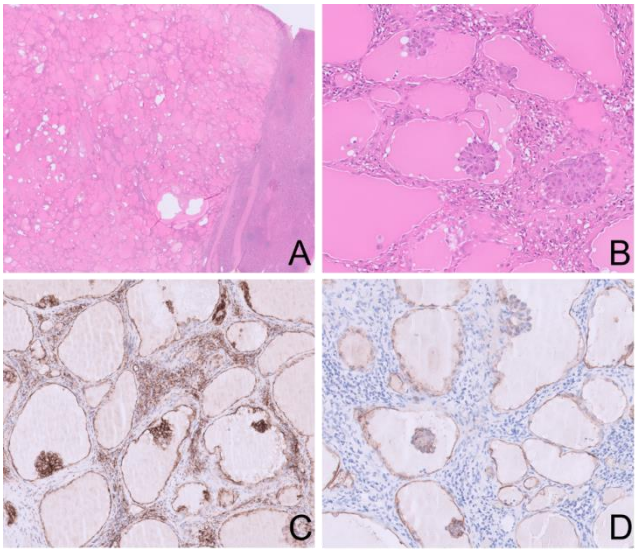

Figure 4. *A: Low power (50x) view of the mass within the spleen showing the well defined lesional to uninvolved splenic interface to the right of the image. B: Vascular channels with intraluminal pseudo-glomerular projections (100x). C: Immunohistochemistry showing positivity with the vascular channels and pseudo-glomeruli for CD31 (100x). D: Immunohistochemistry showing positivity with the vascular channels and pseudo-glomeruli for D240 (100x).*

Splenectomy was recommended and performed 2 months following the biopsy. A spleen measuring 16x10x8.5cm was received and on sectioning found to contain a solid, dark red, well-circumscribed mass measuring 9x9x10cm with occasional pale areas, the largest of which measured 4.2cm in diameter. The lesion abutted normal spleen. Histological examination revealed an unencapsulated, but well-defined lesion composed of vascular spaces lined by flattened endothelial cells with focal intra-luminal pseudo-glomerular projections lined by hobnail endothelium. The interstitium between the vascular channels had an appearance reminiscent of the background splenic tissue, containing a mixed population of inflammatory cells including lymphocytes, eosinophils and plasma cells. The vascular spaces were expanded by a mixture of proteinaceous fluid and red blood cells. Within the lesion there was an area of central fibrosis. The background spleen was unremarkable. Immunohistochemistry once again confirmed the dual positivity with lymphatic (D240) and vascular (CD31 markers within the lesional vascular channels, weaker staining was noted with D240 within the luminal pseudo-glomerular projections. CD34 highlighted the cores of the pseudo-glomerular projections only, possibly highlighting feeder vessels. Glut1 showed focal weak positivity. There was no evidence of the lesion at any surgical resection margin. Overall, the appearances in the resection specimen confirm the biopsy diagnosis of a papillary intralymphatic angioendothelioma (PILA).

Following on from surgery, at 4 months, the patient is recovering well with no significant surgical complications. He will remain on long-term antibiotics as per standard care following splenectomy for prevention of infection. The plan is for a follow up abdominal ultrasound 1 year following surgery as routine surveillance.

3. Discussion

PILA is a rare lesion, with less than 50 reported cases, that is deemed to be locally aggressive and normally seen within the superficial soft tissue of the lower limb [1]. It was previously known as a 'Dabska tumour', named eponymously by Dr Maria Dabska who first described the lesion in 1969 [8]. Debate exists regarding the malignant potential of the lesion with the WHO paediatric tumours describing them as '*not reported to metastasis or cause death*' [9], whereas in contrast, the WHO bone and soft tissue book describes the lesion as known to '*very rarely cause lymph node metastases and death'* [1]. Within a 30 year review of 30 cases of the lesion published in 2000 by Dr Maria Dabska and colleagues, two instances of lymph node metastases were described and one instance of death [10]. At this point PILA was regarded as a low-grade angiosarcoma [10]. Colmenero et al (2013) discuss the difficulty of assessing the long-term behaviour and the development a standardised approach to treatment given the rarity of PILA; overall they surmise that an extended wide local excision (in skin/soft tissue cases) with a clear margin and follow up to monitor regional lymph nodes, as the recommended course of treatment [11]. In our case the lesion was confined to the spleen with clear margins, thereby excision is felt likely to be curative.

Six cases of PILA have previously been described in the spleen. The first reported case, in 1988, occurred in a 5 year old boy, with no significant past medical history, who underwent investigation for palpable splenomegaly [2]. Computerised tomography (CT) imaging revealed multiple low-density nodules throughout the splenic parenchyma. The entire spleen measured 14.5cm and, on sectioning, contained multiple nodules ranging in size from 0.5cm to 3cm. The adjacent splenic tissue was normal. No information regarding

follow up is available. The second case, published in 2007, occurred in a 6 year old girl who presented with a palpable left upper quadrant mass and early satiety over a 6 month period [3]. CT revealed a heterogenous and irregularly enhancing splenic mass. In this instance on pathological examination an isolated lesion accounting for 70% of the splenic parenchymal mass and measuring 7 cm was found. At 1 year post surgery the child remained well with no evidence of recurrence or metastasis. A third case, published in 2022, reports an incidentally detected multinodular splenic lesion detected on a routine ultrasound of an 18-year-old male [4]. MRI showed multiple masses with internal stellate scars and a hypointense signal on T2W sequences. Pathological examination revealed a PILA with a central scarred area noted within the lesion, the dimensions of the lesions are not described and there is no available information regarding follow up. The fifth reported case, in 2023, occurred in a 33-year-old woman who presented with a left upper quadrant mass, who on CT scan was found to have a markedly enlarged spleen with multifocal space-occupying lesions. No specific imaging appearances are described. A splenectomy was performed, and PILA diagnosed. Post operatively the patient developed a portal vein thrombosis, treated with enoxaparin. The patient is reported to be well at 6 months post operatively [5].

In 2023, Debelenko et al published the first reported case of a PILA occurring in the spleen in the context of a *PIK3CA*-related overgrowth spectrum (PROS) disorder [6] in a 3-year-old girl. The PROS disorder in this instance had features of CLOVES at birth, with an underlying somatic mutation in *PIK3CA* c1357G>A p.(Glu453Lys) in 10.6% of alleles. A similar clinical course to our case is described, with an incidental lesion initially found on screening imaging, followed by needle biopsy and splenectomy. Pathological examination of the splenectomy revealed a well defined 4cm mass, once again with a central scar, that was unencapsulated. Morphologically it had the classical features of a PILA with numerous glomeruloid intra-lymphatic projections. Vascular markers were positive (including CD31. Unlike our case D240 (mouse monoclonal antibody Biolegend, San Diego, CA) was negative, the antibody used is noted to be different from that used within our case. Sadly the patient in this case died at 4.5 years of age from streptococcal pneumonia sepsis.

Though our lesion was isolated, multifocally is noted as a common feature of splenic PILA in half of the reported lesions [2, 4, 5]. The presence of an area of scarring/fibrosis was a common feature within several of the reported lesions [4, 6] and the lesion described within our case report and may represent a feature of splenic PILA. Where information is available regarding follow-up [3, 5, 6]), as discussed, one patient has died from sepsis and the remaining patients remain well at 6 months and 1 year. Long term information regarding metastasis and survival is not available.

PROS disorders arise as a result of mutations in *PIK3CA*, a protein coding gene which regulates cell survival and growth via activation of the mTOR1-AKT pathway [12]. In the context of congenital lymphatic malformations, mutations in *PIK3CA* have been localised to the lymphatic endothelium [13], and there is a recognised strong association with the development of vascular and lymphatic malformations [12]. It is not unreasonable in this instance thereby to extrapolate that the development of this rarely described tumour, PILA, occurring in an unusual location, the spleen, may have been contributed to by the known somatic mutation in *PIK3CA* underlying the previous diagnosis of MCAP/MC-M, a PROS disorder. This is in keeping with the previously reported case in a similar context. Debelenko et al [6] suggest that D240 in their case is lost due to the development of PILA from the lymphatic system prior to lymphoepithelial differentiation and podoplanin acquisition. This hypothesis is not supported by our case, however; it is noted that the specific *PIK3CA* mutations and immunohistochemical antibodies used are different. Each of these factors may have contributed to differences in expression.

4. Conclusion

In summary; this case report adds to the existing literature by outlining a further instance of a PILA arising within the spleen of a child and reports the second recognised splenic PILA to have occurred in the context of a somatic *PIK3CA* mutation. Further work involving the sequencing of mutations in this rare vascular tumour may aid recognition of this lesion, molecular characterisation and the potential theoretical application of mTOR inhibitors as a treatment strategy in lesions that may not be amenable to excision.

Table 1. *Details of immunohistochemical methods used.*

Antibody	Clone	Retrieval	Dilution	Product code	Detection system
CD31	JC70A	ER2(20)	1:50	PA0250 (Leica)	BOND polmer refine detection system (product code: DS9800)
CD34	QBEN10	ER1(20)	1:50	NCL-L-END (Leica)	BOND polmer refine detection system (product code: DS9800)
D2-40	D2-40	ER1(20)	1:50	M3619 (Dako)	BOND polmer refine detection system (product code:

Antibody	Clone	Retrieval	Dilution	Product code	Detection system
					DS9800)
Glut1	SPN498	ER2(20)	1:500	Ab40084 (Abcam)	BOND polmer refine detection system (product code: DS9800)
Ki67	MIB-1	ER2(30)	1:200	M7240 (Dako)	BOND polmer refine detection system (product code: DS9800)

Abbreviations

PILA	Papillary Intralymphatic Angioendothelioma
MCAP-MC-M	Megacephaly-Capillary Malformation
PIK3CA	Phosphatidylinositol-4,5-biphosphate 3 Kinase Catalytic Subunit Alpha
PROS	(*PIK3CA)* Related Overgrowth Spectrum
mTOR	Mammalian Target of Rapamycin
MRI	Magnetic Resonance Imaging
CT	Computerised Tomography

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Author Contributions

Jacinta Murray: Data curation, Writing – original draft

Sadia Zafreen: Formal Analysis, Investigation, Supervision, Validation, Writing – review & editing

Susie Goodwin: Investigation, Writing – review & editing

Christopher Driver: Investigation, Supervision

Clair Evans: Formal Analysis, Investigation, Supervision, Validation, Writing – review & editing

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Conflicts of Interest

The authors declare no conflicts of interest.

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