Kasabach-Merritt-like syndrome in a dog secondary to isolated splenic haemangiomatosis

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SUMMARY

A 13-year-old intact male miniature schnauzer presented with lethargy, distended abdomen and pallor. Pancytopenia was identified on complete blood count with a severe thrombocytopenia. Cavitatory severe splenomegaly was identified on abdominal ultrasound. Two weeks of immunosuppressive therapy had no effect on the thrombocytopenia and a splenectomy was performed. The platelet count returned to normal within 24 hours of splenectomy. Isolated splenic haemangiomatosis was confirmed on histopathology and immunohistochemistry. The anaemia and severe thrombocytopenia in conjunction with the ultrasound findings and histopathology are characteristic of Kasabach-Merritt syndrome in people. This is the first case of Kasabach-Merritt-like syndrome described in the dog.

BACKGROUND

Haemangiomatosis is characterised by vascular endothelial proliferations permeating within and widely replacing the affected organ parenchyma. The aetiology of haemangiomatosis is controversial and is considered either a vascular malformation or a neoplasm.(1-3) Splenic haemangiomatosis may occur together with haemangiomatosis of the liver,(4, 5) or may be part of a more widespread angiomatosis in different organs.(6, 7) Isolated splenic haemangiomatosis is a very rare lesion in humans, with only a few previous reports.(1, 2, 8)

Haemangiomatosis associated with haematological changes consistent with a consumptive coagulopathy, characterised by severe thrombocytopenia and mild anaemia, is known in humans as Kasabach-Merritt syndrome.(2, 9) Blood stasis within the vascular spaces results in excessive intravascular blood-clotting due to sequestration of platelets in fibrin thrombi. This results in mild anaemia and severe thrombocytopenia.(10) A rapid resolution of thrombocytopenia has been shown in people after splenectomy.(1, 2)

Recently one case of isolated diffuse haemangiomatosis in a dog was recorded. In that case however, no remarkable haematological changes were detected.(11) Mandibular haemangiomatosis was suspected in one dog and associated with mandibular bone lysis.(12) To the authors' knowledge, Kasabach-Merritt-like syndrome associated with isolated splenic haemangiomatosis has not been previously described in dogs.

CASE PRESENTATION

A 13-year-old intact male miniature schnauzer presented with a two week history of lethargy and one episode of suspected syncope. Physical examination revealed a 3/9 body condition score,(13)

pallor and severely enlarged abdomen with palpable splenomegaly. No further clinical abnormalities were detected.

Pancytopenia was detected on a complete blood count, characterised by a normocytic normochromic non-regenerative mild anaemia, mild leukopenia and severe thrombocytopenia (Table 1). Faecal floatation was negative. Complete blood count and serum biochemistry results are summarised in Table 1.

Table 1. Complete blood count results at presentation, 10 & 17 days after starting immunosuppressive (IS) therapy and 1 & 6 days after splenectomy.

Test	Unit	Day 1	10 Days after starting IS therapy	17 Days after starting IS therapy	1 Day after splenectomy	6 Days after splenectomy	Reference range
Haemoglobin	g/L	99	130	138	131	131	120-180
Red cell count	$X10^{12}$/L	4.1	5.3	5.5	5.2	5.3	5.5-8.5
Haematocrit	L/L	0.31	0.40	0.43	0.40	0.40	0.37-0.55
Mean corpuscular volume	fL	75.6	74.8	78.3	76.7	76.1	60-77
Mean corpuscular haemoglobin concentration	g/dL	32.4	32.6	31.9	32.9	32.6	32-36
White cell count	$X10^{9}$/L	3.17	15.3	26.6	30.9	8.4	6-15
Segmented neutrophils	$X10^{9}$/L	2.16	13.8	24.5	27.2	7.4	3-11.5
Band neutrophils	$X10^{9}$/L	0.06	0	0.5	0.31	0	0-0.5
Lymphocytes	$X10^{9}$/L	0.32	0.31	0.53	0.31	0.08	1.4.8
Monocytes	$X10^{9}$/L	0.38	1.23	1.06	2.78	0.59	0.15-1.35
Eosinophil	$X10^{9}$/L	0.25	0	0	0.31	0.33	0.1-1.25
Basophil	$X10^{9}$/L	0.00	0	0	0	0	0-0.1
Platelet count	$X10^{9}$/L	4	12	11	343	1879	200-500
Reticulocyte percentage		1.1					
Absolute reticulocyte count	$X10^{9}$/L	45.2					
Albumin	g/L	31.3		36.5			28-41
Globulin	g/L	34.6		27.5			20-41
Alkaline phosphatase	U/L	229		6889			20-165
Alanine aminotransferase	U/L			747			9-73
Creatinine	µmol/L	52		39			59-109
Urea	mmol/L			7.2			2.3-8.9
Sodium	mmol/L			145			142-151
Potassium	mmol/L			4.28			3.6-5.1

INVESTIGATIONS

Abdominal ultrasound revealed severe splenomegaly with multiple heterogeneous hypo to almost anechoic areas in the cranial margin and splenic body (Fig.1, 2 & 3). Several hypoechoic up to 3 mm round nodules were seen throughout the parenchyma, as well as some intensely hyperechoic shadowing nodules up to 5 mm wide. Colour flow Doppler revealed all structures to be avascular. A

small amount of free hypoechoic peritoneal effusion was noted. There was no evidence of other organ involvement on abdominal ultrasound.

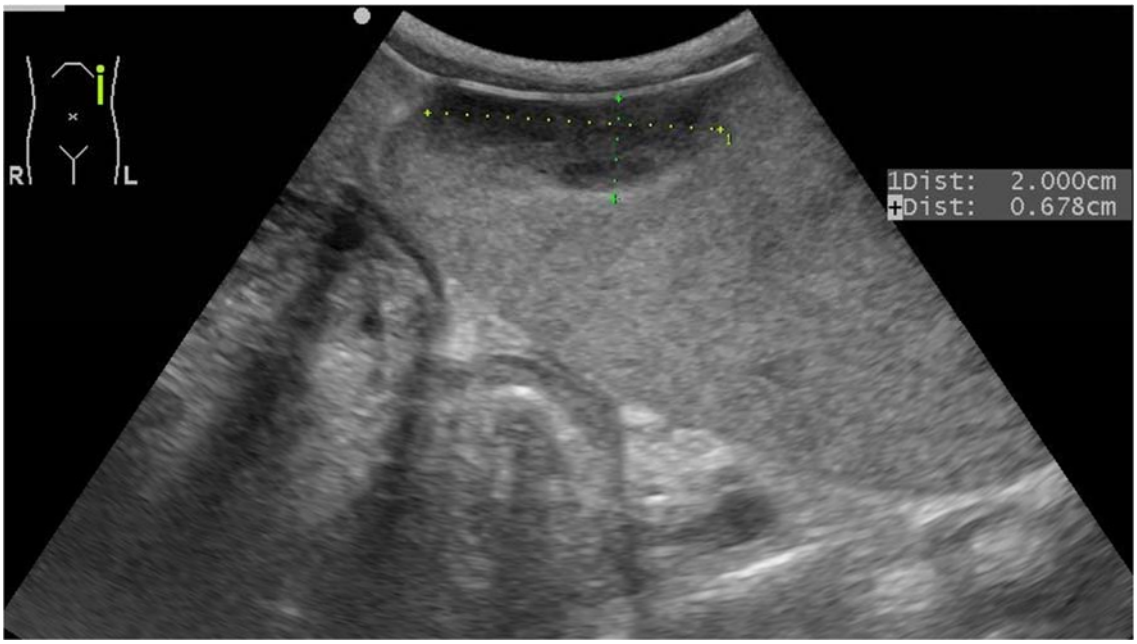

Fig 1. A 20 x 6 mm heterogenous hypo to almost anechoic zone subcapsularly along the splenic cranial margin.

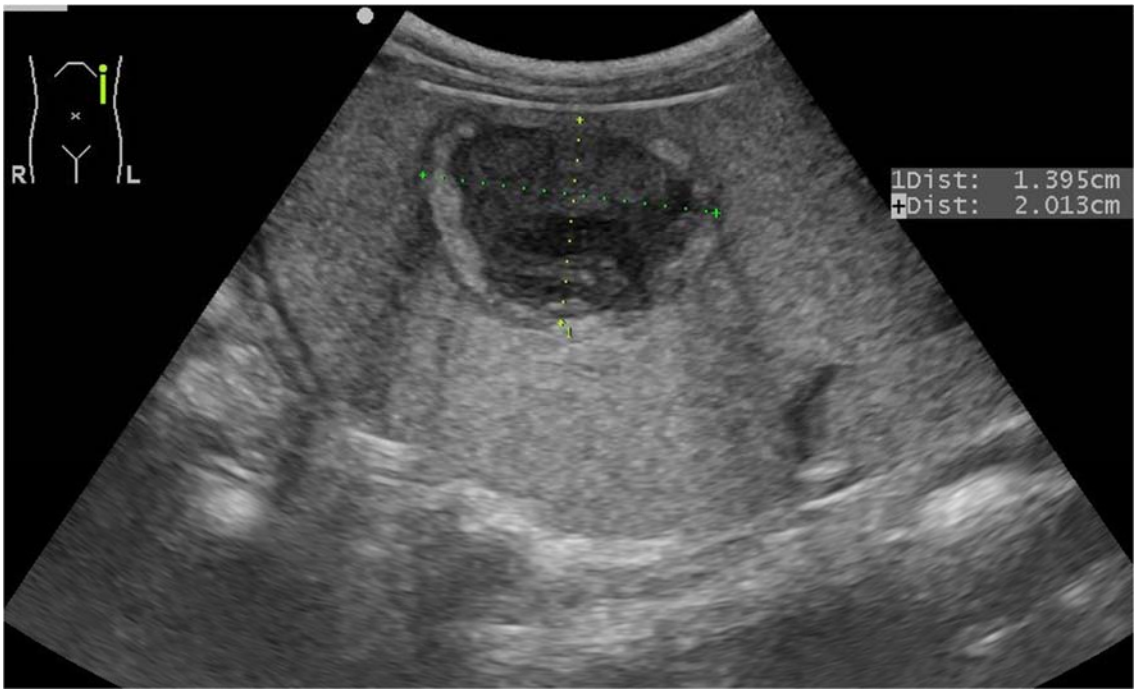

Fig 2. Within the splenic body, there were two large up to 20 x 14 mm irregular heterogeneous hypoechoic foci, with a more central and loculated almost anechoic appearance. Along the periphery of the two large foci were hyperechoic 2 mm wide margins, which did not encircle the structures completely.

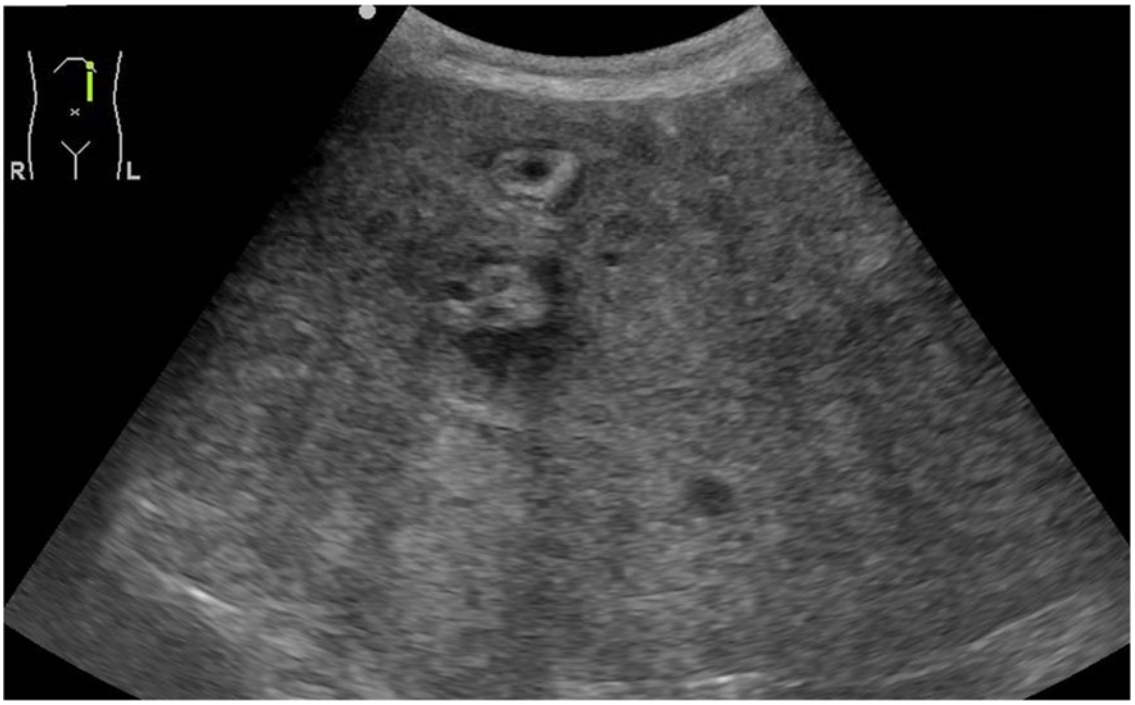

Fig 3. Two lobulated-to-ring-like hyperechoic up to 5 mm wide structures with a central anechoic region were also noted within the mid body of the spleen.

Thoracic radiographs (right lateral, left lateral and ventrodorsal views) showed a mild diffuse bronchial pattern with no radiological evidence of thoracic neoplasia or pulmonary haemorrhage. *Ehrlichia canis* immunoglobulin M and G immunoflourescent antibody titres were negative at a screening dilution of 1:40. Bone marrow aspiration and cytology, although low in numbers, showed unremarkable erythroid, myeloid and megakaryocyte morphology, with orderly maturation and all stages of maturation were present. No erythrophagocytosis was identified. The percentage of plasma cells and small lymphocytes was unremarkable. Core bone marrow histopathology showed normal bone-marrow cell lines in both quantity and quality.

TREATMENT

Immune-mediated thrombocytopenia was suspected at this point and the patient placed on immunosuppressive dosages of prednisolone (Adcock Ingram, Midrand, South Africa) at 1.5mg/kg orally q12 hours for 2 weeks. Re-evaluation ten days after initiation of therapy revealed resolution of anaemia and leukopenia, while the severe thrombocytopenia remained (Table 1). Azathioprine (Roxane Laboratories, Columbus, United States of America) at 2mg/kg, orally q24 hours was added to the treatment. Seven days later the severe thrombocytopenia was still present with the erythrogram similar to previously and a leucocytosis believed secondary to steroids. An elevation in alkaline phosphatase (ALP) and alanine aminotransferase (ALT) was noted. The cause was suspected secondary to corticosteroids. Splenic neoplasia was suspected as the cause of the severe thrombocytopenia given the ultrasonographic appearance of the spleen and ineffective immunosuppressive therapy. Both prednisolone and azathioprine were stopped just prior to splenectomy. Although clinically rare, abrupt cessation of the glucocorticoid therapy should prompt monitoring for iatrogenic hypoadrenocorticism.(14)

Splenectomy was performed using a 10 mm vessel sealing device (Atlas, LigaSureTM ValleylabTM Covidien, France). Macroscopically the spleen was extremely blood-rich with a spongy consistency. The splenic capsule had an irregular surface with multiple variably-sized nodular protrusions (Fig. 4). On cut section the nodular protrusions were blood-filled. There was no evidence of additional organ involvement seen during the splenectomy. The patient made an uneventful recovery and by the next day the thrombocytes had returned to within the reference interval (Table 1).

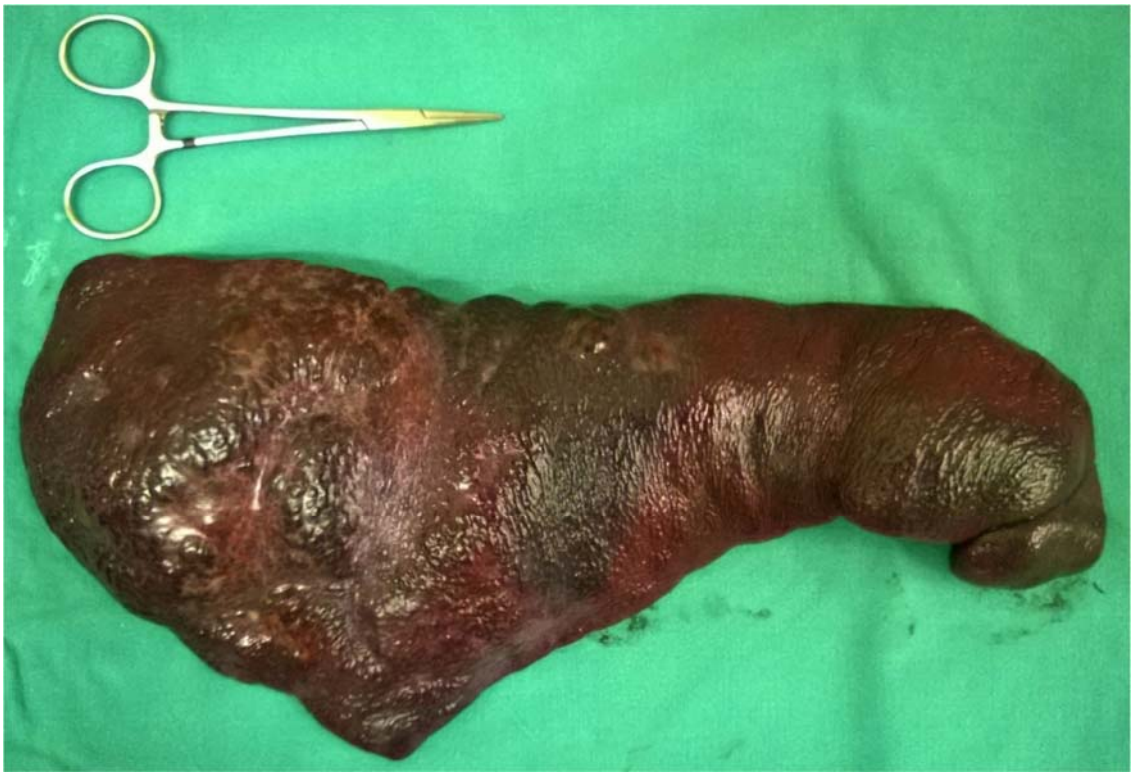

Fig 4. The irregular splenic capsule directly after splenectomy is clearly visible.

Histologically multiple sections of spleen were examined and all sections revealed similar changes. Innumerable, variably sized, blood-filled vascular channels lined by flattened endothelial cells replaced most of the splenic red pulp (Fig 5). The endothelial cells were well differentiated and showed no features of malignancy. Some vascular channels contained variably sized fibrin thrombi. The more cellular areas in-between the vascular channels consisted primarily of extra-medullary haematopoiesis (EMH) with particularly numerous megakaryocytes.

Immunohistochemistry was performed with CD31, CD34 and von Willebrand factor to confirm the endothelial origin of the cells lining the cavernous spaces in the spleen (Fig 6, 7 & 8).(15-17).

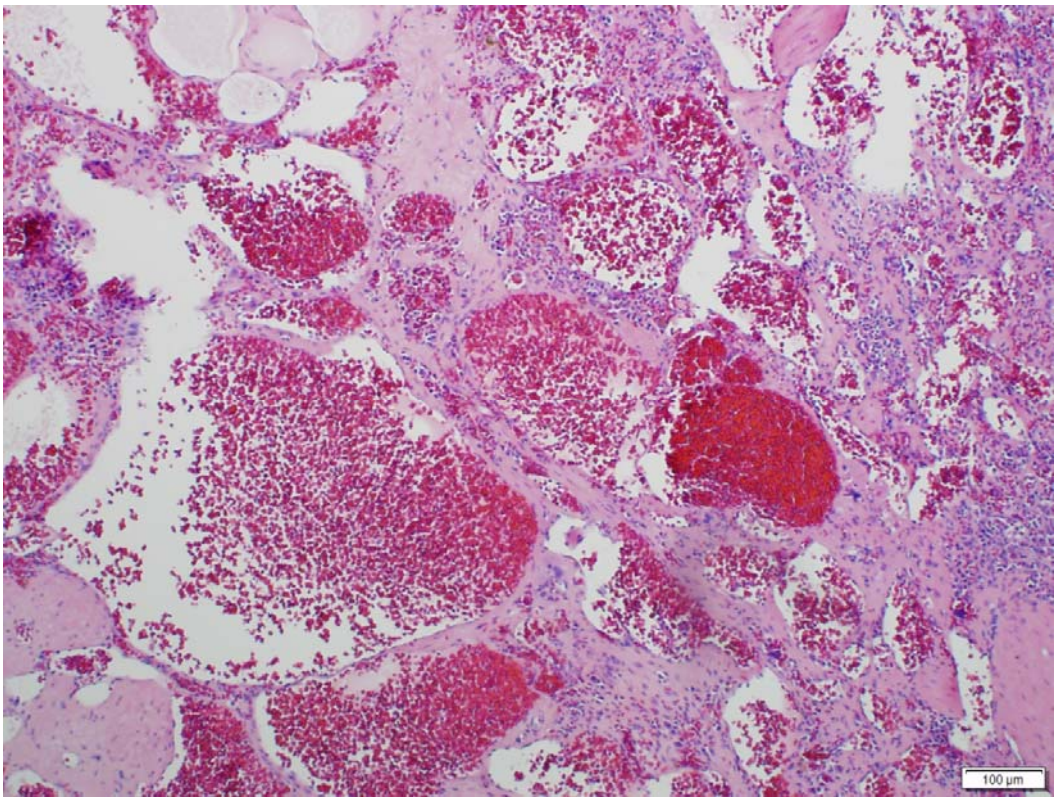

Fig 5. Variably sized blood-filled vascular channels lined by flattened endothelial cells could be observed diffusely throughout the splenic red pulp examined (HE stain, 100x magnification).

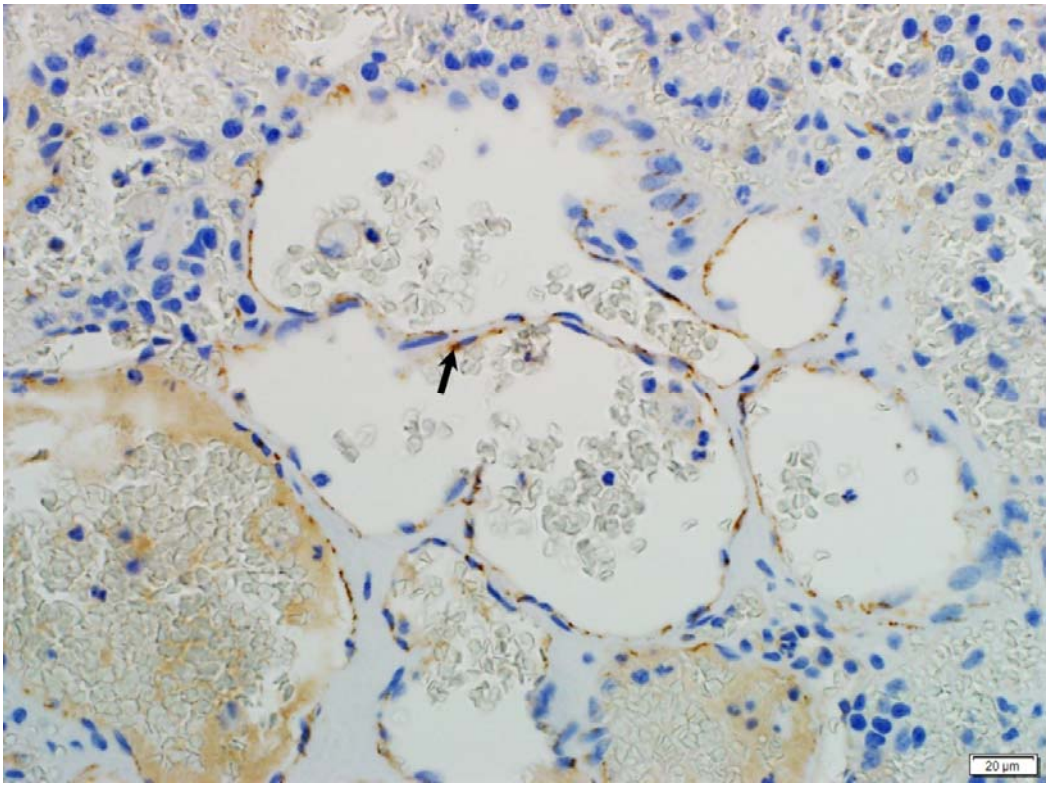

Fig 6. CD31-specific positive labelling of the cells lining the cavernous spaces (arrow), 400x magnification.

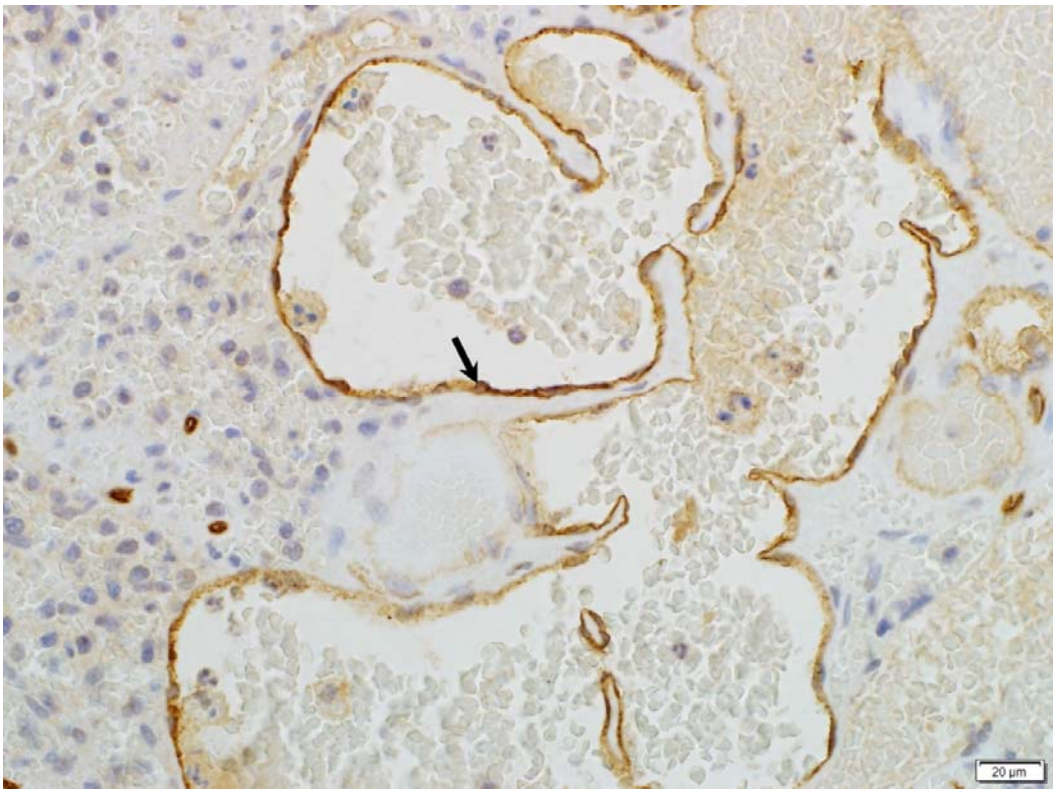

Fig 7. CD34-specific positive labelling of the cells lining the cavernous spaces (arrow), 400x magnification).

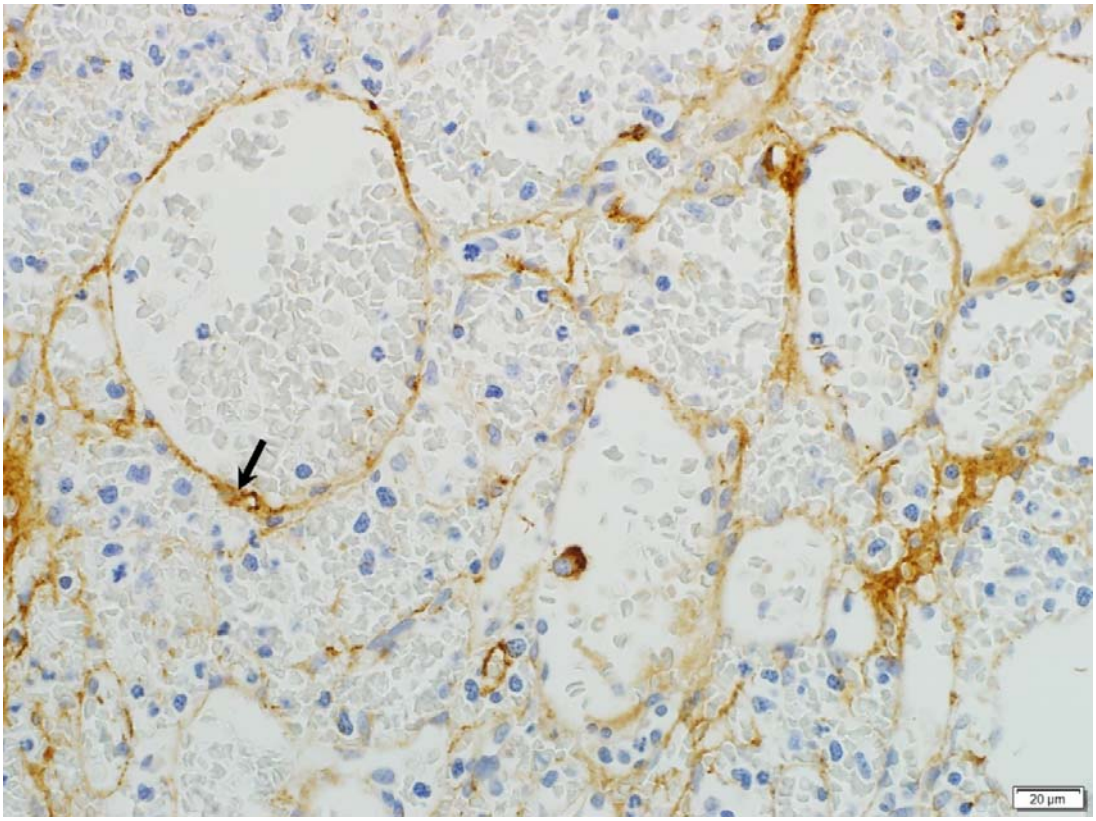

Fig 8. Von Willebrand factor (vWF)-specific positive labelling of the cells lining the cavernous spaces (arrow), 400x magnification.

OUTCOME AND FOLLOW-UP

Six days post splenectomy, a severe rebound thrombocytosis was present (Table 1). A thromboelastogram, consistent with a hypercoagulable state, prompted aspirin (Disprin, Reckitt Benckiser Pharmaceuticals, Elandsfontein, South Africa) therapy at 0.5mg/kg orally q24 hours. Post-splenectomy thrombocytosis resolved by day 72 (days 14, 42 and 72; platelet count: 1260, 1067 and $442x10^9$/L, respectively). The elevation in ALP activity declined at each follow-up examination post-splenectomy (days 14, 42, 72 and 6 months; 2792, 1584, 1038 and 360U/L respectively). The patient's habitus and body condition returned to normal after splenectomy. Ten months after splenectomy, the patient developed diabetes mellitus, believed to be unrelated to the previously diagnosed condition.

DISCUSSION

Isolated splenic haemangiomatosis was diagnosed in this case based on clinical presentation, severe cavitatory splenomegaly, histopathology and immunohistochemistry. Splenic haemangiomatosis in humans may be asymptomatic or may present, as in this case, with symptoms of hypersplenism, thrombocytopenia and anaemia, as well as by disturbances of blood coagulation. The latter is known as Kasabach-Merritt syndrome.(1, 9, 18-21) The presence of anaemia and thrombocytopenia is a common finding in human haemangiomatosis and is suspected to be a result of sequestration and destruction within the cavernous vessels. Consumption of fibrinogen and other coagulation factors occurs secondary to activation of fibrinolysis.(22-24) Additionally, blood pooled within the vascular spaces is biochemically characterised by low glucose, cholesterol and pH resulting in premature erythrocyte aging and excessive intravascular clotting.(10) The anaemia in this case resolved with corticosteroid therapy before splenectomy. The corticosteroids may have caused increased erythropoiesis and a reduced inflammatory response, resulting in reduced erythrocyte destruction.(25)

After splenectomy in human cases, as in this case, the thrombocyte count increased to within reference interval.(1, 2) The rebound thrombosis seen may be considered normal as the cause of platelet sequestration was removed.

An unusual finding in this case was the presence of mild leukopaenia at presentation, not previously reported in Kasabach-Merritt syndrome in people. The leukopaenia resolved before splenectomy with corticosteroid administration, possibly secondary to inhibition of cell migration into tissues (26). A number of vascular lesions affecting the spleen had to be differentiated as only one case of haemangiomatosis of the spleen has been described in dogs.(11) Haemorrhage as the cause of the splenic lesions was excluded by flat endothelial cells lining the lesions, a finding inconsistent with haemorrhage. A simple haemangioma was excluded based on the absence of a single distinct mass, with concurrent extensive changes in the spleen. The vascular lesions excluded by histopathology and immunohistochemistry included splenic hamartoma, haemangiosarcoma, lymphangioma, littoral cell angioma and peliosis.

Splenic hamartomas, or benign overgrowths of normal splenic tissues, consist of normal red pulp elements in an abnormal quantity that usually present as well-circumscribed masses.(1, 3, 11, 27-29) In this case the red pulp elements were abnormal or absent and were replaced by vascular spaces and EMH.

Splenic haemangiosarcomas are single or multifocal masses with smaller slit-like irregular vascular spaces lined by plump endothelial cells displaying marked cellular atypia and an increased mitotic count, which was not present in this case.(10, 28-31)

Lymphangiomas, which usually occur in a subcapsular location, consist of large irregular vascular spaces lined by flattened endothelial cells; the spaces are filled with homogenous eosinophilic proteinaceous material.(1, 29, 30) Increased lymphocytes and plasma cells are often present in the surrounding connective tissue.(30) In this case, the cavernous spaces contained blood.
Littoral cell angioma is a primary benign tumour of the splenic red pulp sinus lining cells. These tumours are characterised by a well-circumscribed nodular growth pattern of anastomosing vascular channels lined by enlarged tombstone-like endothelial, which display phagocytic properties.(1, 28, 29, 31, 32) In this case, the lesion was diffuse and the cells lining the vascular spaces were small and flattened and did not show signs of phagocytosis.

Peliosis of the spleen is characterised by multiple cavernous spaces, that lack an endothelial lining or are only partially lined by flattened endothelial cells.(1, 29, 32, 33) In this case, all the distended vascular spaces were lined by endothelial cells as evidence by positive immunohistochemistry staining.

The origin of splenic haemangiomatosis in humans is unclear although one proposed aetiology includes derivation from splenic sinus lining cells as evidenced by expression of CD8 by some endothelial cells.(34) Not all endothelial cells lining the pathological vessels express CD8, thus others consider a splenic sinusoidal origin unlikely.(1-3) Whether haemangiomatosis in humans is a vascular malformation or a neoplasm still requires clarification. In fifteen human cases of splenic haemangiomatosis, all age groups were represented (from 1 to 74 years of age), with middle to advanced ages predominating.(1) If haemangiomatosis represents a vascular malformation, it is unclear why it manifests so late. A slow-growing neoplasm arising from splenic sinus lining cells is another possibility, which gradually lose CD8 expression with lesion progression to large cavernous vessels.

To the authors' knowledge, this is the first case report of Kasabach-Merritt-like syndrome with isolated splenic haemangiomatosis in the dog. Kasabach-Merrit-like syndrome should be considered as a differential for any dog presenting with thrombocytopenia, anaemia and cavitatory splenomegaly.

LEARNING POINTS

- Kasabach-Merritt syndrome in humans is defined as parenchymal haemangiomatosis associated with haematological changes consistent with a consumptive coagulopathy, characterised by severe thrombocytopenia and mild anaemia.
- This is the first report of Kasabach-Merrit-like syndrome in a dog consistent with the findings in humans and should be considered as a differential for any dog presenting with thrombocytopenia, anaemia and cavitatory splenomegaly.
- Removal of the parenchymal haemangiomatosis results in resolution of clinical and haematological signs.

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