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Anaemia, thrombocytopenia and coagulopathy due to occult diffuse infantile haemangiomatosis of spleen and pancreas

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Abstract Diffuse infantile haemangiomatosis of the spleen is a very rare lesion. Large haemangiomas may cause trapping of platelets and coagulation disorders known as Kasabach-Merrit syndrome. We here report the case of an infant with splenic and pancreatic haemangiomatosis presenting with life-threatening thrombocytopenia, anaemia and intravascular coagulation. Diagnosis was hampered by reactive erythroblastosis and non-conclusive radiological findings. While treatment with corticosteroids was ineffective, administration of antithrombin III improved coagulation parameters. After splenectomy the child recovered promptly and has remained free of disease for 3 years to date.

Conclusion Occult visceral haemangiomatosis without visible cutaneous haemangiomas should be included in the differential diagnosis of thrombocytopenia, anaemia and consumption coagulopathy. Antithrombin III treatment may be considered to overcome bleeding problems in patients with Kasabach-Merrit syndrome.

Key words Antithrombin III · Coagulation · Haemangiomatosis · Kasabach-Merrit syndrome

Abbreviation *ATIII* antithrombin III

Introduction

Diffuse infantile haemangiomatosis frequently involves multiple organ systems [2, 4, 8, 27]. Small cutaneous haemangiomas may be present at birth or develop rapidly in the first weeks of life. Visceral haemangiomas may involve any organ [3, 6, 12, 15, 27, 30, 31]. Only rarely do infants with visceral haemangiomatosis exhibit no cutaneous haemangiomas. Zervos et al. [34] first reported a solitary splenic haemangioma associated with thrombocytopenia. In 1987, Sencer et al. [23] reviewed 14 paediatric patients with splenic haemangiomas. Out of these 14 children, 5 had isolated spleen involvement, and 9 a combination of liver, skin, kidney and/or bone haemangiomas. Since then, other cases of splenic haemangiomas have occasionally been reported [4, 11, 14, 17, 24], but no pancreatic haemangioma has been published to date.

Diffuse haemangiomatosis or large solitary tumours can lead to trapping of platelets and disorders of coagulation known as Kasabach-Merrit syndrome [13]. Because more extensive stages of Kasabach-Merrit syndrome are refractory to treatment, the disease is still a potentially life-threatening condition. In this paper, we report on a child with diffuse haemangiomatosis of the spleen and pancreas causing thrombocytopenia, anaemia and coagulopathy with excessive reactive erythroblastosis cured by splenectomy and partial pancreatectomy.

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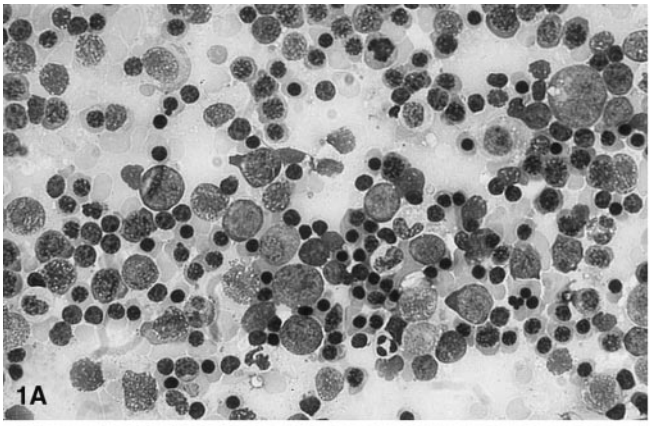
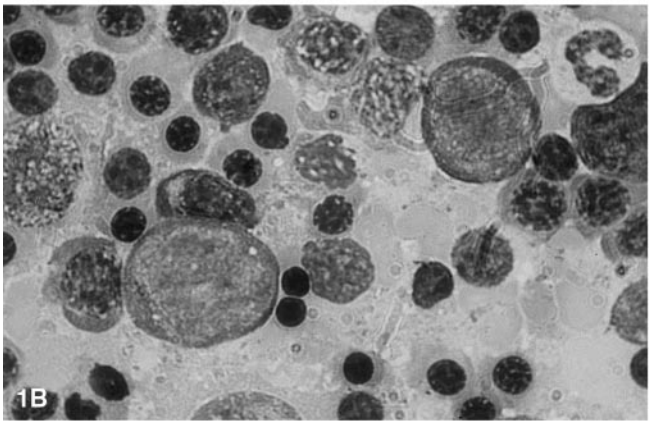
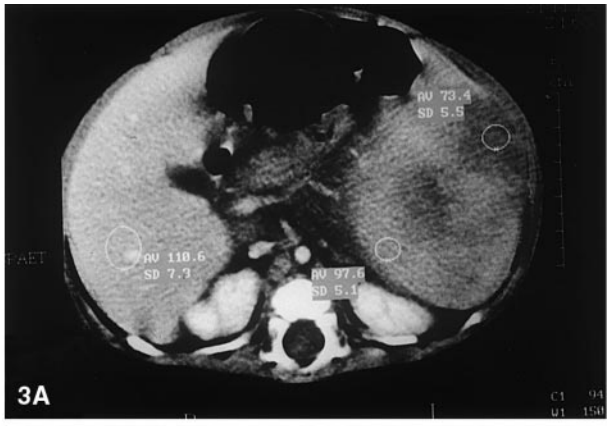
Case report

This 2,750 g female infant was delivered at an estimated gestational age of 37 weeks without any complications or symptoms. After discharge, the mother noted increasing paleness of the child accompanied by scleral icterus. At 3.5 months of age, the infant presented to hospital with extreme paleness and hepatosplenomegaly in the absence of infection. At 4 months of age, the child was referred to our hospital. The skin colour was pale-icteric and some petechiae were noted. The liver was enlarged by 2 cm; the spleen by 4 cm. Blood cell counts revealed leucocytosis (25,000/μl) with lymphocytosis (76%), anaemia (Hb 8.9 g/dl, MCV, MCH and MCHC in the normal range), thrombocytopenia (12,000/μl) and reticulocytosis (176%). Bone marrow aspiration showed excessive haematopoiesis. Dysplastic precursor cells of erythroid and myeloid origin with signs of accelerated maturation were noted (Fig. 1). Total bilirubin (138 μmol/l), direct bilirubin (17 μmol/l), and lactate dehydrogenase (382 U/l) were elevated, and haptoglobin (<5 mg/dl) decreased. At this time, coagulation parameters were normal. Various laboratory tests were performed with normal results. Sonographic evaluation revealed marked splenomegaly







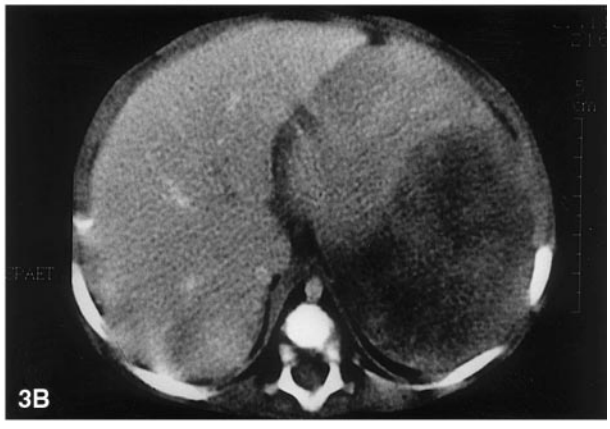
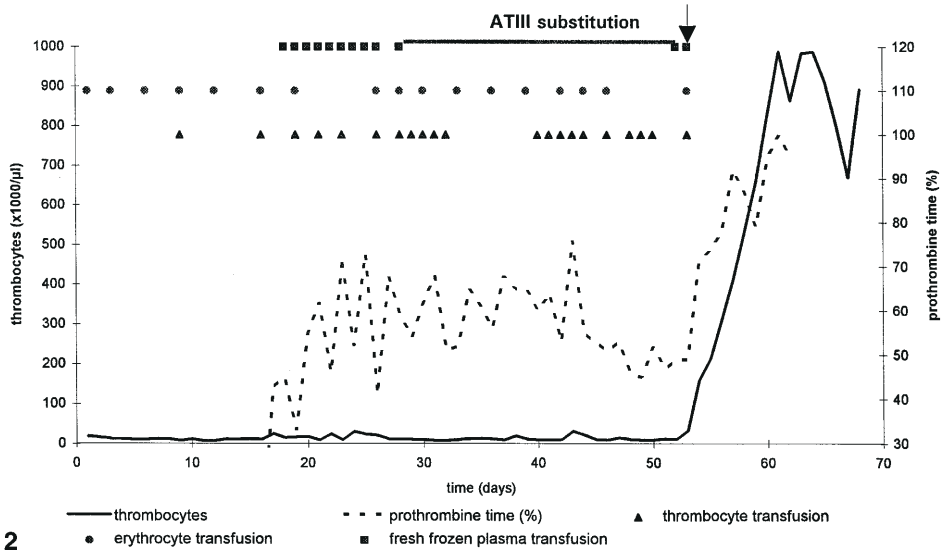


Fig. 1 Bone marrow aspirate showing excessive erythropoiesis: **A** magnification ×40, **B** magnification ×200

Fig. 2 Follow up of laboratory findings and treatment. The *vertical arrow* indicates the time of splenectomy and partial pancreatectomy

Fig. 3 CT scan of the abdomen, showing **A** liver, spleen, and pancreas, and **B** the massively enlarged spleen



(total length 11 cm) and an enlarged pancreas with increased echogenicity. Furthermore, erythrocyte and thrombocyte transfusions were needed within short intervals (Fig. 2).

Assuming an immunological disorder, prednisolone (2 mg/kg per day) was administered for about 4 weeks but failed to prolong the transfusion intervals. However, 1 and 4 weeks after the start of steroid therapy, bone marrow aspirates no longer revealed abnormal bone marrow cells. Peripheral blood smears now showed Howell-Jolly bodies suggesting a non-functional spleen. At this time, disseminated intravasal coagulation developed. Accordingly, prothrombin time was decreased, fibrinogen was decreased to about 0.3 g/l (normal range 1.0–4.5 g/l), fibrinogen degradation products were elevated to about 40 μg/ml (2–8 μg/ml), D-dimers were elevated to about 5 μg/ml (0.0–0.4 μg/ml), thrombin-antithrombin complex was elevated to about 100 μmol/l (1.0–4.1 μmol/l), and prothrombin fragments 1 and 2 were elevated to about 50 μmol/l (0.44–1.11 μmol/l) (Fig. 2). The patient was insufficiently treated with fresh frozen plasma and vitamin K. Subsequently, antithrombin III (ATIII) was administered elevating the serum levels from 100% to about 200%. This resulted in normal prothrombin time and normal fibrinogen levels, eliminated the need of further plasma transfusions and stopped bleeding. During this period, splenic enlargement increased and diagnostic imaging was performed. CT of the upper abdomen showed marked splenomegaly and cloudy, inhomogenous, hypodense regions were found in about 50% of the organ (Fig. 3). Haemangiomas or blood vessel malformations could not be detected. The pancreas showed blurred boundaries and an increased density. MRI was not available at this time due to logistic reasons.

One week thereafter ultrasonographic and Doppler sonographic studies showed rarification of splenic veins, an increased venous flow within the spleen (greater than 50 cm/s), and infarction of parts of the spleen. Immunosuppressive therapy was stopped, and splenectomy was performed. Due to the enormous size of the spleen, splenectomy was complicated and parts of the pancreas adherent to the spleen were resected as well.

Post-operatively, erythrocyte and thrombocyte counts as well as plasma coagulation parameters normalised within a few hours. About 3 years later the child is still doing well without any signs of relapse and/or pancreatic dysfunction.

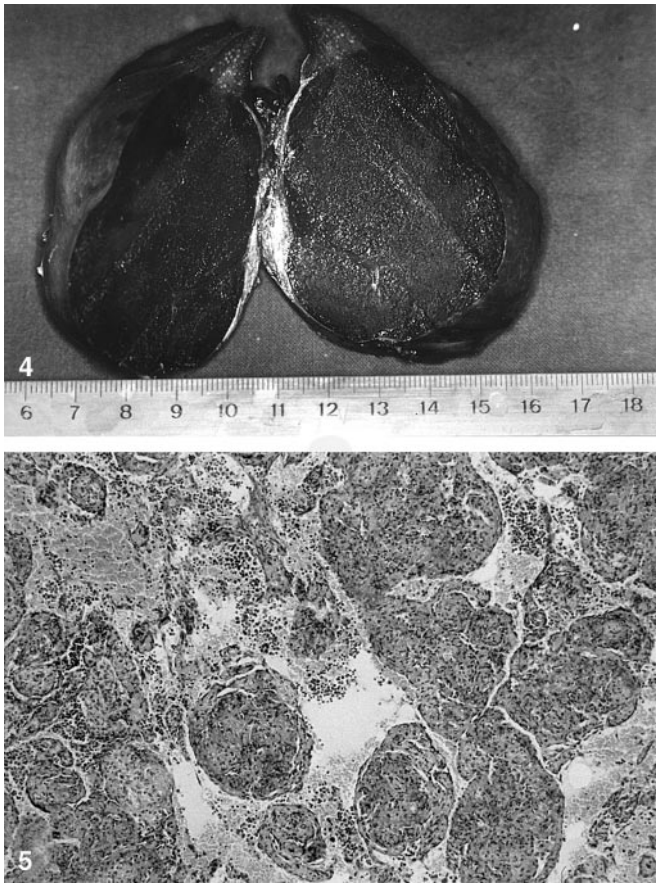


Fig. 4 Gross appearance of haemangiomatosis of the spleen (fixed in formalin). Cut surface with small regular tissue tip at the upper edge of the picture

Fig. 5 Histological appearance of haemangiomatosis of the spleen. Placenta-like picture of lesion

Pathological findings

Macroscopic evaluation of the spleen (Fig. 4) revealed an enormous increase in size ($12 \times 7 \times 4.5$ cm) and weight (260 g, normal splenic weight 11 g). The cut surface of the organ, after fixation in formalin, displayed a homogeneous dark brown colour. At the hilus of the spleen, a $2.5 \times 2 \times 1$ cm part of the pancreatic tail was adherent. Microscopically, the spleen was completely occupied by capillary and cavernous proliferations disclosing a placentoid appearance (Fig. 5). The cellular constituents of the pathological blood vessels were not pleomorphic; mitosises could only rarely be found. Within the endothelial cells as well as within the interstitium there were extensive deposits of iron pigment. Originating from the splenic hilus, the tail of the pancreas was infiltrated by the angiomatous malformations. Frequently, microthrombi and foci of extramedullary haematopoiesis were present within pathological blood vessels.

Immunhistologically, the endothelial cells forming the lesions in spleen and pancreas contained von Willebrand factor (factor VIII related antigen). In addition, single cells expressed CD31 antigen. However, CD8 antigen was not detectable.

Discussion

This case report demonstrates some puzzling diagnostic and therapeutic aspects of a visceral haemangiomatosis, disclosing the peculiar histomorphological features described by Enjolras et al. [6]. The patient showed anaemia and thrombocytopenia in conjunction with a markedly enlarged spleen. Although CT and MRI examinations in general are helpful in diagnosis [9, 19, 20], in this case CT examinations did not identify the vascular lesions in spleen and pancreas. MRI, which was not available, might have solved the diagnostic puzzle [28].

Extensive enhanced but ineffective erythropoiesis suggested a malignant haematological disorder in this infant. Anaemia and reactive erythropoiesis however may be explained as secondary to local erythrocyte trapping. Significant hypofibrinogenaemia is a constant feature of paediatric patients with splenic haemangiomas and Kasabach-Merrit syndrome [11, 23]. Histologically, microthrombosis was evident within pathological blood vessels of the spleen (Fig. 5). Vascular malformation in conjunction with a pathological endothelium may

permit coagulopathy. Accelerated fibrinogen turnover, pooling of blood constituents and thrombocytopenia, potentiating each other, may well trigger a fatal clinical course. Similar to other cases described in the literature [18, 22, 23, 29, 34], the disease in our patient became refractory to substitution of blood products. Erythrocytes, thrombocytes, and fresh frozen plasma had to be substituted within short time intervals (Fig. 2), resulting in a rapid increase in splenic size. Some patients have been treated with ε-aminocaproic acid in order to stabilise fibrinogen turnover prior to splenectomy [1, 11, 25]. We decided to start an ATIII substitution therapy that appeared to be more favourable and easier to handle in this situation. ATIII substitution yielding a serum level of about 200% resulted in the increase in serum fibrinogen and thromboplastin time, stopped bleeding and was able to replace transfusion of fresh frozen plasma. Thus, we could demonstrate for the first time the effect of ATIII treatment in a patient with Kasabach-Merrit syndrome.

Therapy was a major challenge in this infant, who was critically ill for several weeks. Some infantile haemangiomas have been successfully treated with prednisone. Sadan et al. [21] found satisfactory results in 93% of 60 cases treated with high doses of prednisolone (up to 5 mg/kg/day). However, corticosteroids are of limited value in the treatment of vascular lesions associated with thrombocytopenia [5]. In particular patients with splenic haemangiomas and Kasabach-Merrit syndrome seem to be refractory to steroid treatment [18, 22, 29, 34]. In the present case, prednisolone at a dose of 2 mg/kg per day for about 4 weeks was not effective. It could not be excluded that the steroid doses chosen were to low and/or the period of application was too short [21]. Interferon-alpha which is known to inhibit smooth muscle cell, fibroblast, and endothelial cell proliferation has been successfully used in diffuse neonatal haemangiomatosis [26], progressive invasive angiomatous disease [26, 32, 33], in an infant with a giant haemangioma of the retroperitoneum [10], in two infants with haemangio-endotheliomas [16] and a large series of infant haemangiomatoses [7]. In the present case, splenectomy and partial pancreatectomy had to be performed due to infarction of the spleen prior to the start of high dose steroid or interferon therapy. Splenectomy led to a rapid clinical improvement and the child has remained free of disease for more than 3 years to date.

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This paper is dedicated to Prof. E. Kleihauer on his retirement.

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ANNOUNCEMENTS

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