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CASE REPORT

Saleem Islam · Erika A. Newman · Peter J. Strouse
James D. Geiger

Antiangiogenic therapy for a large splenic hemangioma

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Abstract Hemangiomas involving the spleen are rare and seldom symptomatic. Treatment options for large lesions usually consist of splenectomy, embolization, or both. Antiangiogenic treatment has not been reported previously as an effective alternative for this type of lesion. We report our experience of successfully using glucocorticoids in an infant with a large hemangioma of the spleen.

Keywords Glucocorticoids · Angiogenesis · Vascular malformation · Hemangioma · Spleen

Introduction

Despite the fact that hemangiomas, or vascular tumors, represent the most common primary neoplasm of the spleen, less than 100 cases have been reported [1]. This lesion is even less common in infants and young children [2]. The patients are often asymptomatic, with many diagnoses made at autopsy. The indications for surgical intervention and other therapy remain unclear. There is an increased risk of splenic injury and rupture, as well as the possibility of developing hypersplenism or Kasabach–Merritt syndrome, especially in larger lesions [3]. In addition there is the concern for malignancy, which prompts splenectomy in most cases [4].

S. Islam (✉)
Department of Surgery, Division of Pediatric Surgery, University of Mississippi Medical Center, 2500 North State Street, Jackson, MS, 39216 USA
E-mail: sislam@surgery.umsmed.edu
Tel.: +1-601-9845050
Fax: +1-601-8153734

E. A. Newman · P. J. Strouse · J. D. Geiger · S. Islam
Section of Pediatric Surgery, CS Mott Children's Hospital, University of Michigan, Ann Arbor, MI, USA

P. J. Strouse
Department of Radiology, CS Mott Children's Hospital, University of Michigan, Ann Arbor, MI, USA

Antiangiogenic treatment has been primarily directed at cutaneous or other lesions with a proliferative component, also known as a "capillary" pattern [5]. The majority of solid visceral hemangiomas are thought to be resistant to antiangiogenic or steroid treatment, therefore either expectant observation or surgery has been recommended [2]. We present a case in which a large splenic hemangioma regressed with antiangiogenic therapy using glucocorticoids, avoiding a splenectomy. This is the first such case reported to our knowledge.

Case

A 3-month-old boy presented with an asymptomatic left abdominal mass that was discovered by his pediatrician during a routine physical exam. The patient was otherwise healthy and was the product of a full term, uneventful pregnancy with no prenatal ultrasound diagnosis of abdominal mass. Physical examination revealed a firm, non-tender mass in the left side of the abdomen without any bruit auscultated. There were no cutaneous hemangiomas or vascular malformations noted. A CT scan revealed a large, well-circumscribed mass within the left upper quadrant that appeared to be arising from the spleen. The mass was heterogeneous with focal areas of high attenuation closely resembling blood. A splenic ultrasound was performed which confirmed a large hypervascular mass within the lower pole of the spleen. Doppler studies were indicative of active blood flow within the mass. The lesion measured 5.7×4.8×5.3 cm^3 in dimensions (Fig. 1 a, b). The splenic vein was found to be enlarged. There were both hyper and hypoechoic components to the lesion. The remainder of the spleen was separate from the mass and had normal sonographic appearance. This was consistent with the diagnosis of a splenic hemangioma (SH). The infant had a mild anemia but was without any signs of immunosuppression or thrombocytopenia. In order to avoid splenectomy, we decided to treat him with oral Prednisone (2 mg/kg/day) for antiangiogenic effect. No

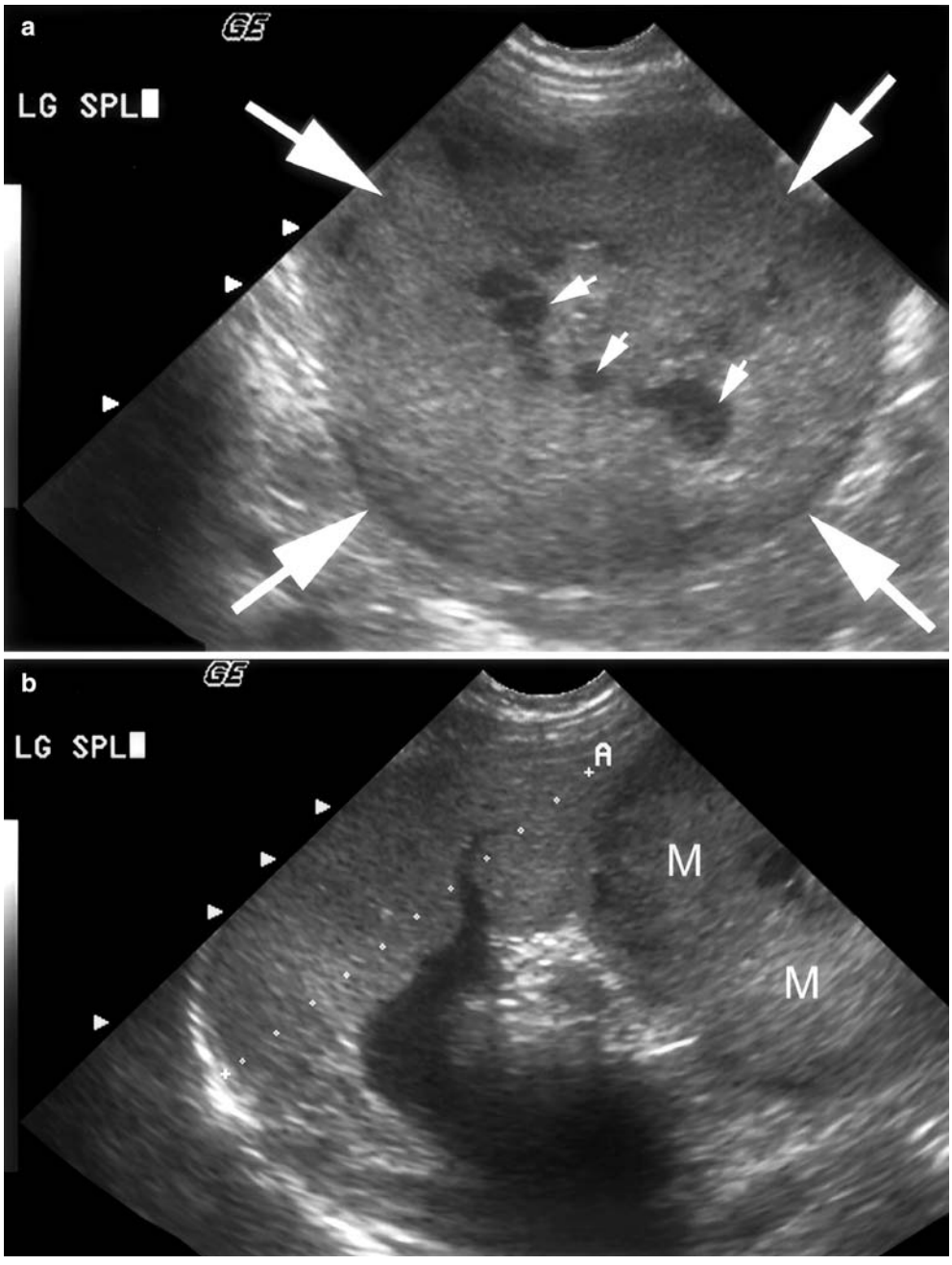

Fig. 1 (**a**) Transverse ultrasound image of the left upper quadrant shows a 5–5.5 cm diameter solid mass (*large arrows*). Focal hypo echoic areas (*small arrows*) did not completely show flow, and may represent necrosis, hemorrhage or stagnant flow (**b**) Longitudinal image showing that the mass (*M*) arises exophytically off the inferior tip of the spleen

additional therapy was required for gastrointestinal prophylaxis. He was monitored closely with serial ultrasound and physical examination. Two weeks after starting treatment, a repeat ultrasound showed the mass to measure 4.0×4.3×4.2 cm, with decreased vascularity of the splenic mass. Six weeks after steroid therapy the mass was 3.0×3.5×3.2 cm^3. The mass was also more homogeneous and the hypoechoic areas were no longer well visualized. Ten weeks after presentation the mass measured 2.6×2.1×2.6 cm^3 (Fig. 2) with much less vascularity and virtually no hypoechoic areas. At 14 weeks, the mass was barely detectable by ultrasonography. The steroids were discontinued at this point.

The patient has done well clinically and had no ill effects from the treatment. He is now over 3.5 years old, with no evidence of recurrence of the lesion on repeat ultrasound evaluation.

Discussion

Pediatric cases of SH are rare, with fewer than 20 cases previously reported [2, 6]. This vascular lesion is detected in adults more frequently, usually during the third to fifth decade of life, or at autopsy [3, 7]. SH may be isolated or associated with other skin, skeletal, or visceral vascular

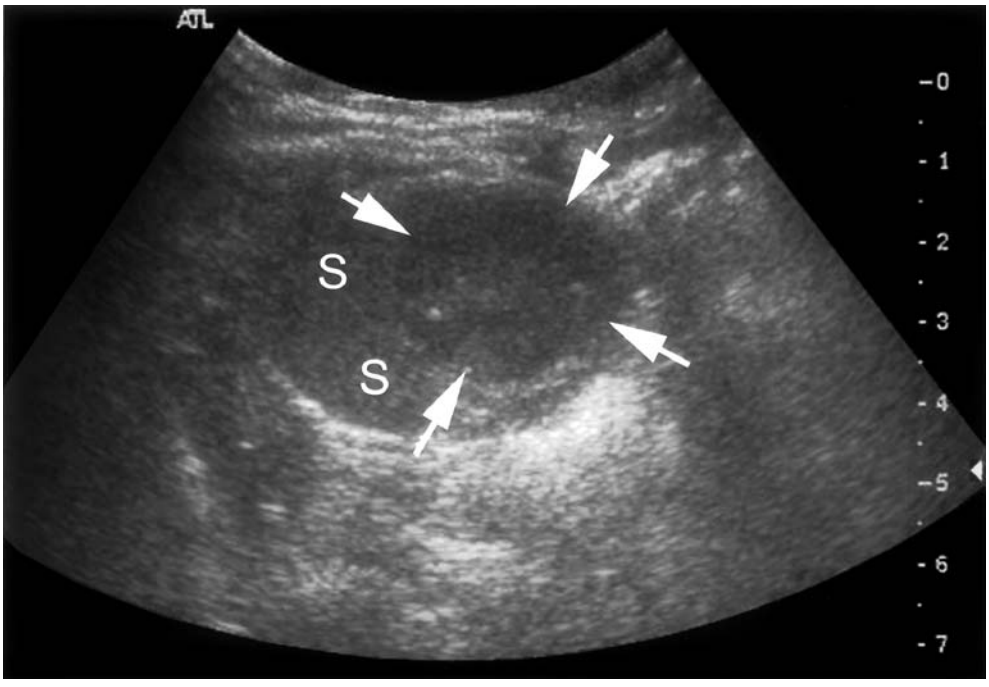

Fig. 2 Longitudinal image of the spleen after 10 weeks of therapy shows substantial decrease in the size, now 2–2.5 cm in diameter. (*S* spleen)

anomalies and may occur in patients with Klippel–Trenaunay–Weber syndrome [8]. These lesions have been reported in both Beckwith-Wiedemann and Turner syndromes, as well as one of the various manifestations of Proteus syndrome [9, 10]. The incidence of splenic vascular malformations ranges from 0.03% to as high as 14% in autopsy series [1, 3, 7].

It is important to differentiate the vascular malformations from hemangiomas, as it is the latter which have a proliferative component that may respond to anti angiogenic treatments [11]. Vascular malformations usually do not have a growth phase and, unless very large, mostly remain asymptomatic. Hemangiomas are the most common primary neoplasm of the spleen and are composed of rapidly proliferating endothelium-lined vascular channels filled with red blood cells [12]. The lesions may be solitary or multiple. On gross examination it can be identified from the surface as a more intensely blue/purple area, darker than the normal splenic pulp [12]. The natural course of these lesions is usually enlargement, possible slow involution, or rupture [3, 7]. The exact course for a given hemangioma is difficult to predict. Larger tumors (>4 cm) are likely more prone to rupture, either spontaneously or from minor trauma than smaller ones, and may result in fatal hemorrhage [3]. There has also been a reported rare association with possible malignant transformation to angiosarcoma with large SH, which leads most surgeons to favor a splenectomy [4, 7].

The majority of patients are asymptomatic. Clinical signs of pediatric cases of SH include an incidentally discovered left upper quadrant mass, as was in our case. Some patients may have early satiety or malaise from the mass effect on the stomach. There have also been reports of congestive heart failure, portal hypertension, and gastrointestinal bleeding [2, 3, 7]. Thrombocytopenia, anemia, and consumptive coagulopathy (Kasabach–Merritt syndrome) have been associated with larger SH [2, 6].

SH are usually diagnosed by ultrasonography, computed tomography, or magnetic resonance studies, although reported features are variable [13, 14]. The lesions may be calcified, cystic, solid, or mixed [13]. Sonographically, hemangiomas are frequently hyper echoic with hypoechoic areas, may be well-marginated with occasional calcifications or cysts depending on the size [13, 15]. Our case demonstrated hypo echoic areas with well defined margins. Doppler ultrasound may be helpful and demonstrate blood flow within the mass, which was noted in our case as well [13].

Previously, it was suggested that SH may present with severe hematologic symptoms or rupture, and splenectomy was recommended for all [3]. Recent reviews in adult patients report that asymptomatic patients with small SH (<4 cm) have been managed conservatively with observation, without rupture or other complications [7]. All pediatric cases, to our knowledge, have been treated with partial or total splenectomy, both approaches which have been successful [2, 6]. Partial splenectomy maintains functional splenic tissue and possibly mitigates the deleterious immunologic effects of total splenectomy [12]. Our case would have been ideal for a partial resection, as it was off the pole of the spleen. There are also reports of using hand assisted laparoscopy to treat these lesions with success [16].

The treatment for symptomatic or potentially disfiguring cutaneous hemangiomas during the proliferative phase is antiangiogenic with corticosteroids or interferon, although the exact mechanism remains unclear [5]. Folkman demonstrated that hemangiomas secrete

angiogenic agents such as B-FGF which can be detected in the urine, and these are reduced with anti angiogenic therapy. Other drugs successfully used have been the COX-2 inhibitors and Thalidomide [5, 11].

Review of the literature did not reveal any cases of SH showing progressive regression with antiangiogenic therapy. In our case, we decided to attempt therapy with corticosteroids to avoid a splenectomy with its potential for long term immunosuppression and possible overwhelming sepsis. We had planned for a partial splenectomy, in case our therapy failed. We used an initial regimen of Prednisone 2 mg/kg/day. The lesion showed regression after 2 weeks of treatment, which persisted during and after the therapy. The steroids were weaned during the 14 week period. This duration of therapy was chosen after the mass had reduced in size and then the steroids were tapered. Long term follow up is needed to determine the efficacy of this treatment.

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