PHACES Syndrome with Intestinal Hemangiomatosis

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ABSTRACT We present a rare case of a neonate with PHACES syndrome (***p***osterior fossa malformations, large facial ***h***emangiomas, cerebral ***a***rterial anomalies, ***c***ardiovascular anomalies, ***e***ye anomalies and ***s***ternal clefting or ***s***upraumbilical raphe) and diffuse hemangiomatosis of the ileum, presenting with multiple intestinal perforations and peritonitis. The infant was successfully treated with propranolol and methylprednisolone as well as octreotide, tranexamic acid, and supportive therapy for massive intestinal bleeding.

KEY WORDS: PHACES syndrome, neonate, intestinal hemangiomatosis

INTRODUCTION

PHACES syndrome (***p***osterior fossa malformations, large facial ***h***emangiomas, cerebral ***a***rterial anomalies, ***c***ardiovascular anomalies, ***e***ye anomalies and ***s***ternal clefting or ***s***upraumbilical raphe) is a neurocutaneous disorder with more than 300 reported cases (1). Although the first association of facial hemangiomas and vascular and nonvascular malformations was described by Pascual-Castroviejo in 1978, in 1996 Frieden and colleagues summarized the clinical features of patients with large facial hemangiomas and brain, arterial, heart, and eye abnormalities, and coined the term PHACE syndrome (2,3). The acronym PHACES is used when ventral developmental defects, such as sternal clefting or supraumbilical raphe, also occur (3).

Vascular malformations of the small intestine are rare, causing 5% of gastrointestinal bleeding with angiodysplasia as the most common type (4). They may present at any age with bleeding, anemia, or intussusception (5). Gastrointestinal hemangiomas are uncommon benign vascular tumors most frequently situated in the jejunum. Endoscopic therapy is recommended for bleeding lesions. Other treatment options are: hormonal therapy, octreotide, aminocaproic acid, danazol, and surgery (4). The greatest risk is associated with diffuse infiltrating cavernous hemangiomas (5).

CASE REPORT

A five-day-old girl was hospitalized due to acute omphalitis. The pregnancy was uncomplicated, and she was born by spontaneous vaginal delivery at term, with a birth weight of 4000 g. Examination upon admission to hospital revealed a hemangioma on the lower lip, a hemangioma on the left ear and on the left retroauricular area, as well as a concave area of hypopigmentation (1×1 cm) in the lower part of the sternum (Figure 1).

A cardiac echocardiography found a patent foramen ovale and coarctation of the descending aorta in

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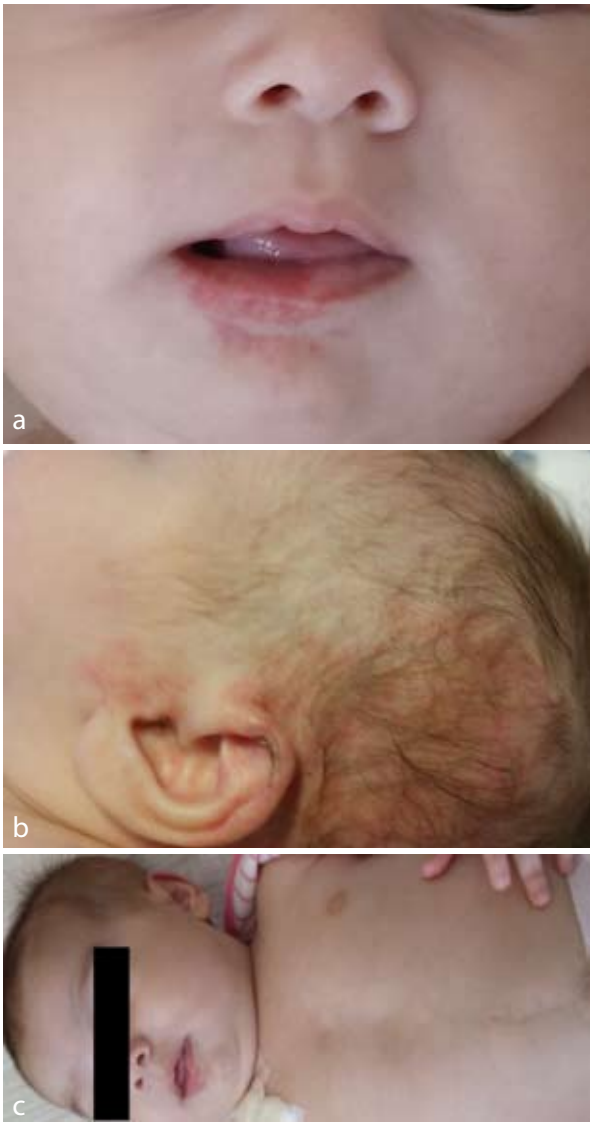

Figure 1. (a) Hemangioma of the lower lip; **(b)** Hemangioma in the left retroauricular and temporal region; **(c)** A concave area of hypopigmentation in the lower part of the sternum.

the isthmus area (just after the origin of the left subclavian artery). On the fourth day of hospitalization (at 9 days of age), melena was noticed. The results of the microbiological and coagulation tests, abdominal ultrasound, and abdominal X-ray imaging were normal. The source of bleeding was not identified on a technetium-99m-pertechnetate (Meckel) scan, technetium-99m tagged red blood cells, and MR of the abdomen. Hemoglobin levels had fallen to levels of 59 g/L, so intensive treatment with red blood cell transfusions, plasma transfusions, and vitamin K was started. Despite the therapy, severe gastrointestinal bleeding continued and the infant's general condition progressively deteriorated, so an explorative laparotomy was performed. The surgical procedure found two intestinal perforations, and resection of 20 cm of the small intestine with a termino-terminal anastomosis was done. The pathohistological exami-

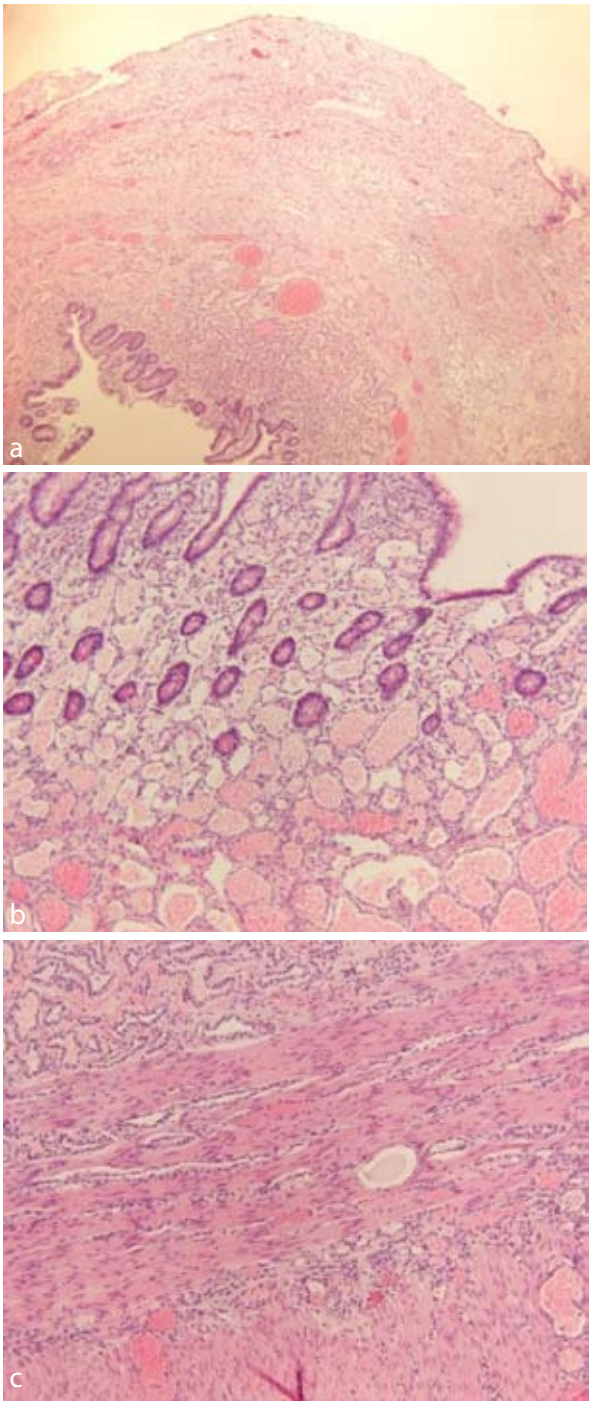

Figure 2. Diffuse neonatal hemangiomatosis of the resected small intestine: a large number of cavernous blood-filled spaces lined with regular and thin endothelium, shown in: **(a)** a segment of resected small intestine, magnification ×40; **(b)** submucosa, magnification ×100; **(c)** muscles, magnification ×100.

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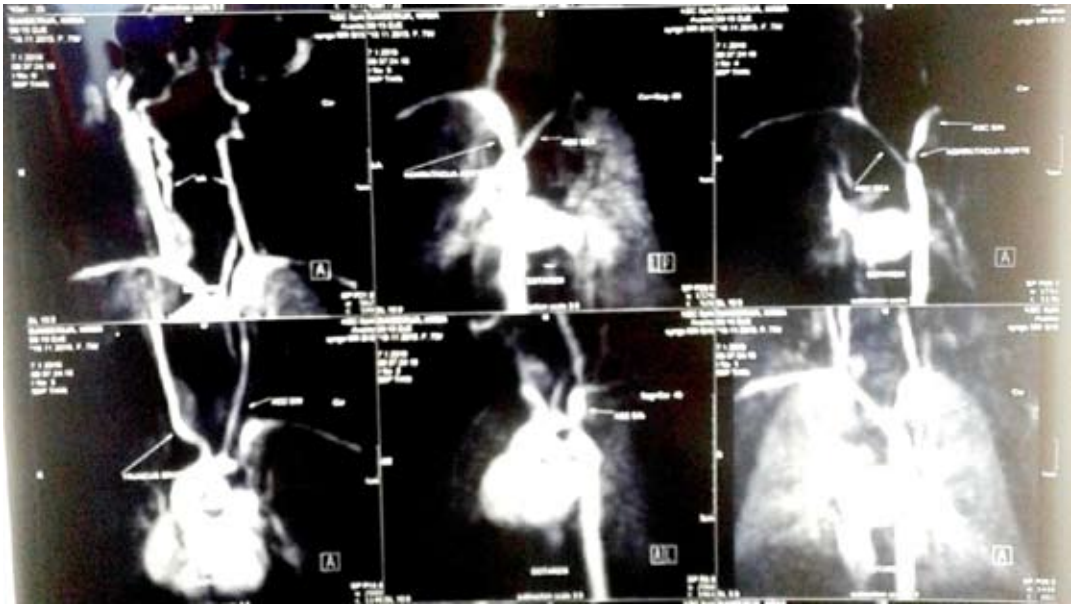

Figure 3. The tortuosity of the left ACI in the upper cervical segment and slightly reduced lumen of the upper part of the artery (left upper picture) and coarctaction of the aorta (right upper picture).

nation of the resected small intestine showed a large number of cavernous spaces lined with thin endothelium, most evident in the submucosis but present in all layers of the intestinal wall as well as the areas of necrosis (Figure 2).

A diagnostic procedure to evaluate other possible anomalies associated with PHACES syndrome was also performed. The ophthalmological evaluation found no evidence of eye malformations and there were no structural brain anomalies. The MRA of the head and neck showed tortuosity of the left ACI in the upper cervical segment and slightly reduced lumen of the upper part of the artery (Figure 3).

As PHACES syndrome was diagnosed, propranolol (3 mg/kg/day in three daily doses) and methylprednisolone (2 mg/kg/day in two daily doses) treatment was started.

Despite propranolol and corticosteroid therapy, bloody stool was present again 9 days after surgical procedure. Therapy with octreotide (somatostatin analog) infusions (50 µg/kg/day), plasma and red blood cells transfusions, tranexamic acid therapy (20 mg/kg/day), and total parenteral nutrition were started. Four days later the intestinal bleeding had stopped, but reappeared twice over the next 45 days. Therapy was gradually titrated. Tranexamic acid was administered for one week when gastrointestinal bleeding was present. Corticosteroid therapy was interrupted after two months of treatment, and octreotide after two and a half months after beginning of the therapy. Treatment was continued with only propranolol. The infant was also treated with antibiotics due to the clinical and laboratory signs of sepsis and osteomyelitis of the right hip. Coarctation of the aorta was successfully surgically treated at the age of six months. The patient is now a healthy three-year-old girl without intestinal bleeding, and hemangiomas of the face and head have been visibly reduced.

DISCUSSION

Only a few studies have reported gastrointestinal hemangiomas associated with PHACE syndrome (6-8). Soukolis *et al.* reported 16 children with visceral hemangiomas and 1 met the diagnostic criteria for PHACE syndrome. Most of them were girls, and the most common localizations were the jejunum and ileum. Melena and hematochezia in the first 4 months of life were the presenting symptoms, and in half the patients they were diagnosed by laparotomy or laparoscopy. Propranolol and corticosteroids were the most commonly used drugs, and two patients required bowel resection because of perforation (7). Drolet *et al.* reported 10 patients with gastrointestinal IHs, 9 of which with PHACE syndrome. Gastrointestinal bleeding occurred at the age of 8 days to 6 months, also most commonly in the area supplied by the superior mesenteric artery. In these patients, as in the study by Soukolis *et al.* and in our patient, the source of the gastrointestinal bleeding was very difficult to identify, so 4 patients underwent exploratory laparotomy and the diagnosis was confirmed histologically. All patients required more than one

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drug to control the bleeding; all received intravenous steroids and three patients received vincristine and one received interferon. Five patients received propranolol therapy but with second agents, and two underwent a resection of the small intestine. Vascular dysplasia of the abdomen was found in 5 patients on computed tomographic angiography/MRA (8). As can be seen from these studies, the therapy for gastrointestinal hemangiomas is diverse. Corticosteroids have been most frequently used, followed by propranolol, vincristine, and interferon. One study reported successful treatment of extensive infantile hemangiomatosis (two thirds of the small bowel) in a 3-month-old infant with thalidomide and somatostatin analog (9). Due to the severity of the gastrointestinal bleeding despite therapy with propranolol and corticosteroids, our patient was also treated with octreotide and tranexamic acid, therapy options that are not commonly reported in infants; however, there were no side-effects.

The incidence of PHACE syndrome in children with hemangiomas is 2.3%, but is as much as 20% to 31% in patients with large segmental facial hemangiomas (6,10). The risk increases with the size of facial hemangiomas, especially segmental (10). They are more often left-sided (11). Metry et al reported that 71% of patients had combined structural cerebral and arterial anomalies, with 90% of them developing neurological sequelae such as severe neurodevelopmental delay, unexplained seizures, or headaches ipsilateral to facial hemangiomas (11). Intracranial hemangiomas are also commonly seen in these patients and deserve special attention (12).

PHACE syndrome is more common in girls (female-to-male ratio: 5.6:1 to 9:1) (6,10,11,13). The aberrant origin of the subclavian artery and coarctation of the aorta are the most common cardiac malformations (1,11,14). The arch obstruction is most often long-segment, with regions of arch narrowing or interruption and segments of aneurysmal dilatation. Both subclavian arteries commonly arise distal to the obstruction (15). Our patient had a coarctation of the descending aorta just after the origin of the left subclavian artery, surgically treated with success.

Treatment of patients with PHACE syndrome with systemic beta blockers, especially in children with vascular anomalies and thus a higher risk for stroke, should be administered with extreme caution. Use of the lowest possible dosage, slow titration, and dividing the daily dose into three intakes are suggested to minimize abrupt changes in blood pressure. Neurological and cardiological follow-up is also recommended (16). The initial dose is suggested to be 0.5-1.0 mg/kg/day in the first week progressively increasing to 2.0-3.0 mg/kg/ day b.i.d. or t.i.d. (17). New studies have shown the efficacy of nadolol, a synthetic, nonselective β-blocker which does not cross the blood-brain barrier and has minimal negative cardiac inotropic activity and longer half-life than propranolol, thereby requiring less frequent dosing with fewer side-effects. Captopril, an ACE inhibitor, has also shown benefits in treatment of problematic proliferating IHs (1).

The term "diffuse neonatal hemangiomatosis" describes the association of cutaneous with visceral vascular lesions, with a mortality between 60% and 95% in the first months of life due to high-output cardiac failure and hemorrhage from the upper respiratory or gastrointestinal tract (18). There are only a few studies describing the association of large skin hemangiomas or multifocal vascular skin lesions with visceral hemangiomas (6,19-21). The most common sites for visceral hemangiomas among patients with PHACES syndrome are the brain and the mediastinum (19).

CONCLUSION

The possibility of intestinal hemangiomatosis should be considered in patients with large facial hemangiomas and gastrointestinal bleeding in early infancy. We report a rare case of neonatal intestinal hemangiomatosis presenting with multifocal intestinal perforations in a patient with PHACES syndrome. The patient was treated with regular doses of propranolol therapy for infantile hemangiomas, corticosteroids, octreotide, and tranexamic acid with success and no side-effects.

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