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Brief Report

Gastrointestinal haemorrhage due to lymphangiectasia caused by protein-losing enteropathy in the Fontan circulation

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Abstract We report the case of a 14-year-old boy with severe protein-losing enteropathy after Fontan surgery that led to lymphangiectasia, which caused gastrointestinal haemorrhage and required invasive treatment to stop the bleeding. Through this case and a review of the literature on protein-losing enteropathy after Fontan surgery, we highlight a rare and serious presentation of the disease and the difficulties of diagnosis and management.

Keywords: Tricuspid atresia; protein-losing enteropathy; lymphangiectasis, intestinal; gastrointestinal haemorrhage

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Case report

A white infant, born with tricuspid atresia, normally related great vessels, and without pulmonary stenosis, underwent pulmonary artery banding at birth, a bidirectional Glenn procedure at the age of 2 years, and a total cavopulmonary connection with an extracardiac conduit 2 years later. Pre-Fontan haemodynamics indicated normal pulmonary pressure and pulmonary arteries of suitable size. The conduit was not fenestrated. He received anticoagulation treatment with aspirin. At the age of 7 years, hypoalbuminaemia (albumin level 24 g/L, normal range 31–48 g/L) revealed protein-losing enteropathy (α-1-antitrypsin clearance 167 ml/24 hours, normal range 5–10 ml/24 hours). Cardiac catheterisation demonstrated normal mean pressure (14 mmHg) in the Fontan circulation, with no evidence of stenosis. The patient received a strict medium-chain triglyceride-enriched diet. At the age of 12 years, he developed thrombosis of the left innominate vein, revealed by worsening of the enteropathy, and required repeated albumin infusions (Fig 1). Cardiac catheterisation showed normal pulmonary artery dimensions, normal connection to the vena cava, and normal mean pressure measurements (10–13 mmHg) but a stenosed left innominate vein. Curative anticoagulation with antivitamin K (fluindinone) was introduced. The left innominate vein was dilated with a 10-mm-diameter balloon catheter. The procedure, however, failed to relieve obstruction and was complicated by venous thrombosis of the left arm, despite continuous anticoagulation therapy. His albumin levels decreased, and generalised oedema developed. Further control angiography confirmed failure of the dilatation and complete occlusion of the left innominate vein, with no possibility of recanalisation. He continued to require albumin infusions every 3 months. At the age of 14 years, he experienced rapid clinical deterioration, with severe anaemia (4.8 g/dl, normal range 11.5–15.1 g/dl) and hypoalbuminaemia (18 g/dl). At admission, he had gained ~2 kg of weight in the past 2 months. He had moderate generalised oedema, and his stool frequency had increased over the past 2 weeks (watery, twice a day). Albuminaemia decreased further to 15 g/L. He required blood transfusions every other day. A Meckel diverticulum was ruled out. Complete gastroscopy and colonoscopy showed only minimal gastroduodenitis.

Video capsule endoscopy revealed non-specific signs of duodenitis, with a diffuse snowflake pattern.

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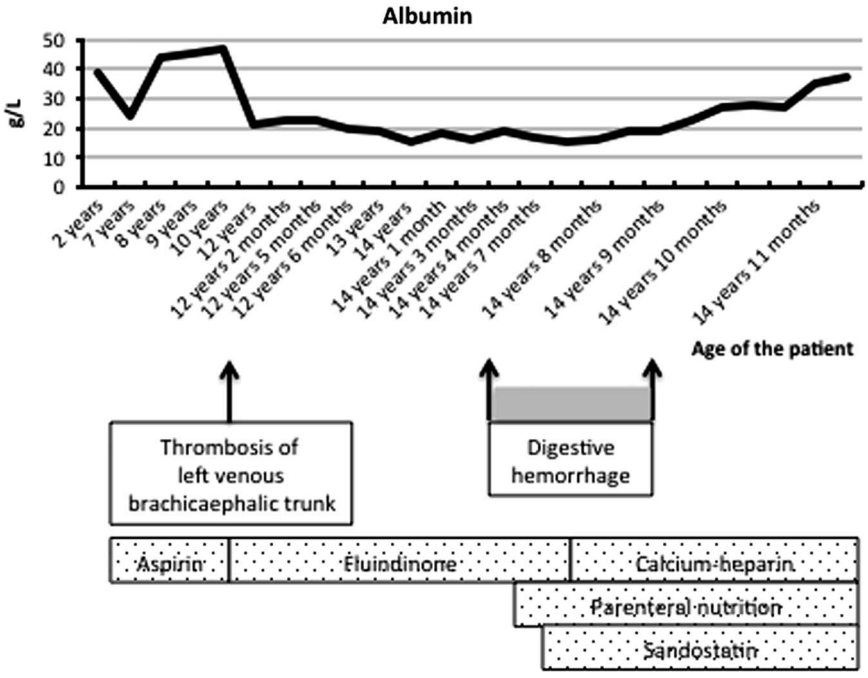

Figure 1.
Patient's albumin values.

The gastric and duodenal mucosa was petechial and friable, suggestive of lymphangiectasia responsible for blood loss. The duodenal biopsies did not prove lymphangiectasia, but demonstrated inflammation with an increased number of intraepithelial lymphocytes. An abdominal CT scan showed thickening of the small bowel wall.

Management consisted of exclusive parenteral nutrition, iterative transfusions, and albumin infusions. Subcutaneous calcium heparin replaced fluindinone for anticoagulation treatment. Persistent bleeding and refractory hypoalbuminaemia over a one-month period led to the initiation of oral corticotherapy (budesonide 9 mg/day). When it was determined to be inadequate, 20 days later, intravenous somatostatin (25 mcg/h) was added. After a month, his clinical and laboratory statuses began to improve progressively: melenas disappeared, haemoglobin levels stabilised, and albumin levels increased to 28 g/L. A second video capsule endoscopy showed complete recovery of the small-bowel mucosa.

Corticoids were tapered because of side-effects. Somatostatin was switched to a subcutaneous route (50 mcg twice a day) on discharge. Low-fat oral feeding was progressively re-introduced 8 weeks later, but it resulted in expanded oedema. Exclusive parenteral nutrition was then restored. Gastrointestinal symptoms, albuminaemia, and haemoglobin levels remained stable. Parenteral nutrition, somatostatin, and anticoagulation were continued at home.

The patient finally underwent heart transplantation 1 year later, while he was still receiving parenteral nutrition, somatostatin, and anticoagulation, mainly because of the refractory protein-losing enteropathy. The immediate 1-month postoperative period was free of complications. The protein-losing enteropathy remained stable, but 3 months later the patient developed invasive Epstein–Barr virus infection, probably related to immunosuppressors and prolonged corticotherapy. It progressed into aggressive B lymphoblastic lymphoma. He died 6 months after the transplantation at the age of 15 years.

Discussion

Protein-losing enteropathy is seen in 1–15% of Fontan patients,[1–3] with 50% survival at 5 years after diagnosis.[1,2]

Intestinal lymphangiectasia is a disorder of the lymphatic system[4] that can be seen in patients with Fontan circulation. It presents with non-specific gastrointestinal symptoms such as diarrhoea, nausea, vomiting, weight loss, or oedema caused by protein-losing enteropathy. Bleeding intestinal lymphangiectasia have previously been described in abdominal lymphangioma associated with protein-losing enteropathy.[5] In this case, bleeding from intestinal lymphangiectasia in protein-losing enteropathy after Fontan surgery was confirmed after investigations, including video capsule endoscopy, ruling out any other causes of haemorrhage. Vyas et al in 2006 described this phenomenon in a three-case series

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and concluded that gastrointestinal bleeding, although rare, could be part of the clinical spectrum of protein-losing enteropathy.[6]

The case reported here illustrates the complex mechanisms of the disease, including low cardiac output, elevated pressures in the venous circulation, impaired mesenteric flow, dilation of the gut lymphatics, and inflammation.[3,7]

Our patient's cardiac parameters did not suggest low cardiac output. Systemic venous pressure was within normal ranges, contrary to the elevated right atrial mean pressure of 15–20 mmHg in the case series by Vyas et al[6]; however, thrombosis of the left innominate vein aggravated the disease. Elevated pressures upstream of the lymphatic drainage and the systemic venous return may have affected mesenteric flow. Somatostatin might have acted on that mechanism. It has previously been reported to be a successful therapeutic option for refractory intestinal lymphangiectasia,[8] reducing acetylcholine release in the intestinal plexus and improving gastrointestinal motility, triglyceride flow in the thoracic duct lymph, and intestinal absorption of fats. This appeared particularly useful for our patient with obstruction of the thoracic duct involving thrombosis of the left innominate vein.

In this scenario, the low-flow state induced by Fontan surgery appears to have stimulated the inflammatory system.[9] This induced vasoconstriction, increasing mesenteric vascular resistance and impairing mesenteric flow. Corticosteroids have been reported to successfully treat this disease in the literature,[3] but they were not effective in our patient. Careful administration of heparin has also been reported to be effective in some patients as a potent anti-inflammatory and vasoactive agent.[10] Heparin is a negatively charged molecule that may form a barrier to passage of the negatively charged albumin molecules.[3]

We cannot determine which of these treatments was most helpful. Their synergistic actions likely increased mesenteric flow, decreased lymphatic pressure, and helped resolve the lymphangiectasia. Recovery, however, was only partial and transient. Of note, heparin therapy did not worsen the gastrointestinal haemorrhage. Refractory protein-losing enteropathy after Fontan surgery remains one of the more controversial indications for heart transplantation.[11] It is thought to increase cardiac output, but not to modify the mesenteric inflammation and other unknown mechanisms that continue to contribute to disease after heart transplantation. In view of the risks illustrated by the lethal outcome for this patient, this issue must be discussed with patients.

Conclusion

This report presents a case of haemorrhagic intestinal lymphangiectasia induced by protein-losing enteropathy after Fontan operation. Symptomatic treatment of protein-losing enteropathy eventually stabilised symptoms but did not cure the illness. Further studies are needed to discover the pathophysiological mechanisms that can be targeted by therapy.

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Conflicts of Interest

None.

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