

Peer Review File

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Reviewer A

Overall, the management of a voluminous enterocutaneous fistula in a patient with EDS can be complex and challenging. A multidisciplinary approach, including input from surgeons, nutritionists, wound care specialists, and medical management experts, is essential for optimizing outcomes.

Nutritional support is critical in patients with enterocutaneous fistulas, particularly those with high-volume output. Enteral feeding via a feeding tube may provide the necessary nutrition while allowing the bowel to rest. Do you have any ideas on this through your experience?

Response: The patient underwent extensive intestinal resection (two segmental resections of the small intestine and colon) and had a significantly reduced intestinal absorption surface, making enteral feeding impossible. The patient relied exclusively on parenteral nutrition. Before undergoing surgical management, the patient had a nasogastric tube on suction. On postoperative day 3 of the second surgical procedure, the nasogastric tube was removed after the return of bowel function. On day 9, due to a recurrence of enterocutaneous fistula, it was decided to reinsert the nasogastric tube on suction. One month after the second surgical procedure, oral feeding was resumed after improving the patient's nutritional status.

We have modified our text as advised (see page 7, lines 109-115).: “One stoma was placed in the right hypochondrium, and the other in the left flank. The postoperative course of this procedure was marked by an evisceration complicated by a complex enterocutaneous fistula (Figure 1) with multiple open intestinal loops in the middle of the abdominal wall. Evisceration is a frequent and typical complication in patients with Ehlers-Danlos syndrome. The patient underwent extensive intestinal resection (two segmental resections of the small intestine and colon) and had a significantly reduced intestinal absorption surface, making enteral feeding impossible. The patient relied exclusively on parenteral nutrition.”

Wound care is also essential, as the skin around the fistula can become macerated and prone to infection. Dressings should be changed frequently, and skin protectants may be used to prevent breakdown. Do you have any ideas on this through your experience?

R: To absorb secretions around the edges of the fistula orifice, we used alginate-based dressings that were changed daily. We performed a cleansing of all scars using soap and water. No antiseptic products or skin creams were used. To prevent pressure ulcers, the patient was provided with a dynamic air-fluidized mattress, and we changed the patient's position every 3 hours.

Have you used medical management that may involve using medications such as somatostatin

analogs, which can reduce the volume of output from the fistula?

R: We have modified our text as advised (see page 8, line 134-138) : “We initiated treatment with somatostatin, antibiotics, negative pressure therapy and nasogastric tube aspiration. The dosage of somatostatin was 6 mg per day. After one week of treatment, the output from the enterocutaneous fistula decreased by one-third. Six weeks later, the fistula had completely healed.”

Reviewer B

This is a case report of the management for large full-thickness abdominal defect in the patient with Vascular Ehlers-Danlos (vEDS). vEDS is a rare form of the Ehlers-Danlos Syndrome (EDS) where arterial fragility results from germline variants in the COL3A1 that encodes type III collagen. We past encountered similar patient, who couldn't have been closed abdomen after colon perforation, and had great difficulty managing and treating it. So, I found it very interesting and informative to read. This is a well-written and well-discussed article. However, I have some questions and some revisions are necessary for publishing:

The comments are as follows:

1. Generally, it is better not to write a specific year or date when publishing, but to write the following, for example, “2 years ago” and “30 months ago”.

R: Thank you for your comment. We have modified the text accordingly to line 104 and line 108 (pages 6 and 7).

2. When and how was the patient suspected and diagnosed with vEDS?

R: We modified the text between line 97 and line 102 (page 6) : “During childhood, the patient exhibited a certain degree of cutaneous fragility, with thin, transparent skin and particularly visible veins. He also experienced hematomas after minimal trauma. After several digestive complications, including peritonitis, intestinal perforation, hemoperitoneum, and years of diagnostic uncertainty, the patient was referred to the French reference center for rare vascular diseases. Genetic analysis of the COL3A1 gene confirmed the diagnosis. There were no other affected relatives in the patient's family..”

3. Because patients with vEDS usually have very fragile tissues, it is recommended to avoid as much as possible any operative procedures. Minimal life-saving procedures are considered to prevent secondary injuries. If the patient has been diagnosed with vEDS, performing a one-stage anastomosis for the sigmoid colon perforation is associated with appreciable risk. Furthermore, is there any reason to perform a two-stage subtotal colorectal resection afterward?

I think that the question may be somewhat off the subject of this paper. I'd like to hear your opinion.

R: We edited the text between line 147 and line 155 (page 8 and 9): "in patients with vascular Ehlers-Danlos Syndrome, it is recommended to avoid as much as possible any operative procedure. However, this patient was dependent on parenteral nutrition. The enterocutaneous fistula was highly productive, leading to significant weight loss, as parenteral feeding was insufficient. Restoring gastrointestinal continuity through surgery was therefore essential. It was a life-saving procedure. A one-stage procedure was considered too risky. Ensuring the viability of the flap was a critical requirement for covering the enterocutaneous fistula. Necrosis of the flap after restoring gastrointestinal continuity would have resulted in the patient's death, as evisceration would occur without the possibility of subsequent coverage."

4. In case report, authors state " Digestive surgeons (ER, MK) first proceeded to full abdominal viscerolysis, fistula removal, and intestinal continuity restoration with an end-to-end jejunioileal anastomosis."(line 156-158). Resection of the fistula must be very difficult, how was it done?

R: The visceral surgeons performed the procedure as follows:

- peristomal incision on the right and left flanks
- a cutaneous incision around the enterocutaneous fistula
- entry into the abdominal cavity
- complete upstream and downstream adhesiolysis
- resection of the fistula and the two previous ileostomies as a single unit
- creation of an end-to-end ileo-ileal anastomosis using Vicryl 3-0 sutures.

This was a standard procedure with no difficulties.

5. How did such a large abdominal wall defect make from? In our cases, we couldn't close abdomen after colon perforation, and the defect was made.

R: We have modified our text as advised (see page 7, lines 109-115): "One stoma was placed in the right hypochondrium, and the other in the left flank. The postoperative course of this procedure was marked by an evisceration complicated by a complex enterocutaneous fistula (Figure 1) with multiple open intestinal loops in the middle of the abdominal wall. Evisceration is a frequent and typical complication in patients with Ehlers-Danlos syndrome. The patient underwent extensive intestinal resection (two segmental resections of the small intestine and colon) and had a significantly reduced intestinal absorption surface, making enteral feeding impossible. The patient relied exclusively on parenteral nutrition."