High-Output Stoma Leading to the Diagnosis of Antiphospholipid Syndrome

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Abstract
Diverting stoma (DS) is widely created in colorectal surgery. High-output stoma (HOS) is a major complication of DS, which can lead to dehydration and thrombosis. Additionally, antiphospholipid syndrome (APS) is a risk factor for thrombosis, and it rarely occurs in men. Herein, we describe a case of multiple thromboses caused by chronic dehydration after HOS. A 48-year-old man visited our hospital with fever and lower abdominal pain; he was diagnosed with sigmoid diverticulitis. He underwent laparoscopic high anterior resection for relapsing diverticulitis and diverting ileostomy during the same operation. On postoperative day 1, an output of 3,000 mL/day was observed from the ileostomy. The stoma output exceeded 2,000 mL/day, which was diagnosed as HOS, and chronic dehydration persisted despite supplementation and restriction of oral water intake. Three months postoperatively, a computed tomography scan before ileostomy closure showed multiple thrombi in the inferior vena cava, right common iliac vein, and pulmonary artery. After antithrombotic therapy, ileostomy closure was performed. As lupus anticoagulant was positive twice and APS was diagnosed, antithrombotic therapy was changed from warfarin to direct oral anticoagulants. Thrombosis did not recur 6 months postoperatively. This is the first report of a case wherein APS was present in the background of thrombosis caused by HOS or chronic dehydration. It is important to be cautious about APS when there is thrombosis after HOS to select appropriate therapeutic agents.
Introduction

In colorectal surgery, anastomotic leakage (AL) is one of the major complications and the most important condition to avoid for surgeons. There have been many studies about AL, and many risk factors have been reported, including preoperative patient factors such as male, obesity, and undernutrition, as well as factors from perioperative management such as infusions and mechanical bowel preparation [1]. One of the postoperative factors of AL is increased intestinal pressure due to diarrhea and other fecal infections, and a temporary colostomy may be performed to prevent AL, which is called diverting stoma (DS) [2].

One of the complications of DS is high-output stoma (HOS), which requires therapeutic intervention; persistent loss of large amounts of small bowel fluid can cause dehydration, electrolyte disorders, and related problems, including peristomal dermatitis. Thus far, there is no clear definition of HOS. Previous reports defined HOS as the excretion of >2,000 mL/day from the stoma or excretion of >1,500 mL for more than 2 days [3, 4]. Early intervention to prevent thrombosis is necessary because persistent HOS can cause intravascular dehydration and lead to the occurrence of thrombosis.

In contrast, antiphospholipid antibody syndrome (APS) is an autoimmune disease characterized by thrombotic tendencies and can be an isolated risk factor for thrombosis [5]. There are several theories on the mechanism of thrombogenesis in APS, one of which is the 2-hit theory. The 2-hit theory proposes that thrombus formation is accelerated by direct damage to the vascular endothelium caused by infection or inflammation, in addition to antiphospholipid antibody stimulatory effect on the coagulation cascade [6]. Herein, we report a case of multiple thromboses that supposedly resulted from chronic dehydration due to HOS, which led to a confirmed APS diagnosis.

Case Presentation

A 48-year-old man visited his previous hospital with fever and lower abdominal pain; he had six episodes of sigmoid colon diverticulitis in 4 years, each time treated conservatively by his previous physician. One month after the last treatment, fever and lower abdominal pain worsened, and after a week of taking antipyretic and analgesic medications with no improvement, he was seen by the same hospital. He was treated conservatively under fasting conditions, together with antibiotics. Consequently, his symptoms improved, but the diverticulitis recurred repeatedly; he was referred to our hospital for further treatment. He had a history (no family history) of cholelithiasis and sigmoid diverticulitis. During his first visit to our hospital, no abnormalities in vital signs were observed. The abdomen was flat and soft on physical examination, but there was tenderness mainly in the left lower quadrant. His blood test findings at the first visit were as follows: white blood cell count, 15.6 × 10^3/µL; red blood cell count, 449 × 10^6/µL; hemoglobin, 12.2 g/dL; hematocrit, 38.6%; platelet, 277 × 10^3/µL; total protein, 5.2 g/dL; albumin, 3.1 g/dL; alanine aminotransferase, 17 U/L; aspartate aminotransferase, 22 U/L; total bilirubin, 2.1 mg/dL; direct bilirubin, 0.7 mg/dL; indirect bilirubin, 1.4 mg/dL; C-reactive protein, 23.83 mg/dL; blood urea nitrogen, 11 mg/dL; creatinine, 0.90 mg/dL; serum sodium, 137 mmol/L; serum potassium, 4.7 mmol/L; prothrombin percentage activity, 13.1%; and the international normalized ratio of prothrombin time, 1.16. Results of laboratory blood tests showed an elevated inflammatory response and no abnormalities in renal function or blood coagulation ability.

Computed tomography (CT) findings revealed diverticulitis of the sigmoid colon and an abscess in the rectovesical pouch (shown in Fig. 1). Colonoscopy showed a stricture of the sigmoid...
colon resulting from inflammation and pus drainage into the intestinal tract (shown in Fig. 2). We continued to treat the patient with antibiotics, but there was little improvement; therefore, we performed surgery for diverticulitis.

We performed a laparoscopy-assisted high anterior resection; anastomosis was performed using the double-stapling technique. The intestinal edema was severe, owing to inflammation; a diverting ileostomy was constructed to prevent AL. The operation time was 378 min, and the volume of blood loss was 400 mL. From the first postoperative day (POD), the drained stoma output was >3,000 mL/day. After the second POD, the drainage output exceeded 2,000 mL/day, and we diagnosed the patient with HOS. When he was treated with rehydration and oral water intake was restricted, the stoma drainage output decreased, and the urine volume increased on the sixth POD. The patient was discharged on the 27th POD because the DI drainage decreased to <1,000 mL/day, but the drainage continued even after discharge; therefore, the patient was readmitted because of dehydration. A CT scan performed before ileostomy closure revealed thrombosis in the inferior vena cava, right common iliac vein, and pulmonary artery (shown in Fig. 3). The patient was diagnosed with multiple thromboses and was admitted to the hospital’s emergency department; he was administered anticoagulation agents. Continuous intravenous heparin infusion was started immediately after admission; the heparin dose was adjusted to maintain activated partial thromboplastin time at 6,080 s. Simultaneously, rivaroxaban was orally administered at 30 mg/day. A follow-up CT scan indicated the resolution of all thrombi (shown in Fig. 4).

When the thrombus was confirmed, various antibody tests were performed because of multiple thrombi, and the lupus anticoagulant (LAC) level was 1.5. Three months later, the
LAC level was still positive at 1.4; hence, the patient was diagnosed with APS based on the thrombus image on CT. He underwent ileostomy closure on the 30th POD after thrombi resolution. The postoperative course was uneventful; he was discharged on the 17th POD. After surgery, he continued to take rivaroxaban. After the APS diagnosis, he stopped taking rivaroxaban, which was changed to warfarin 5 mg/day. Three years have passed since the surgery, and there has not been any recurrence of thrombosis.

**Fig. 3.** CT performed before ileostomy closure. CT performed before ileostomy closure showing thrombus in the inferior vena cava (a, white arrows) and pulmonary artery (b, white arrow). The thrombus in the inferior vena cava is large, measuring about 10 cm.

**Fig. 4.** CT after anticoagulation therapy. CT after anticoagulation therapy shows that the thrombi in the inferior vena cava (a, white arrows) and pulmonary artery (b, white arrow) have resolved.
Discussion/Conclusion

This is the first report of a case wherein HOS after ileostomy caused thrombosis, which led to APS diagnosis. HOS and APS are two different clinical conditions, but both cause thrombosis.

DS is commonly performed to prevent AL after colorectal surgery, especially in the lower rectum. However, one of the complications of DS is HOS, which is clinically problematic because persistent HOS causes dehydration, renal dysfunction, and electrolyte abnormalities. Particularly, if intravascular dehydration persists, thrombosis may occur consequently [7]. Therefore, an adequate infusion solution is necessary to prevent dehydration and thrombosis [3, 4, 7]. Although there is no clear definition of HOS, it refers to a disease state wherein a large amount of excretion from the stoma is observed. In past reports, HOS is defined as an output of ≥2,000 mL/day or ≥1,500 mL/day for 2 days or more [3, 4].

In contrast, APS is defined as an autoimmune disease wherein patients have antiphospholipid antibodies (aPL) such as LAC or anticardiolipin antibodies and present clinically with perinatal complications, including arteriovenous thrombosis, thrombocytopenia, and habitual stillbirth [5, 8]. The detailed mechanism of APS onset is unclear [8]. The ratio of men to women for the APS prevalence rate was reported to be 1:3.5; therefore, APS occurrence in men, as in our case, is very rare [8, 9]. APS is diagnosed based on the presence of aPL and imaging evidence of thrombus, but the detailed mechanism of aPL production is unknown [5, 10].

HOS promotes thrombosis via intravascular dehydration, but no reports state that intravascular dehydration enhances aPL production. Herein, a patient originally predisposed to APS developed HOS due to DS. We believe intravascular dehydration triggered the high thrombogenicity of APS, causing multiple thromboses. The present case is the primary APS discovered in the background of HOS. APS commonly causes thrombosis and should always be considered when a patient is diagnosed with multiple thromboses [5, 6].

Currently, we can only differentiate between HOS and APS based on early thrombosis detection. If HOS persists, especially after DI, the patient is prone to chronic dehydration; hence, strict fluid management and thrombosis prevention are important [4, 11]. In most cases, HOS tends to subside after approximately 1.5 months, but chronic dehydration can persist even when the output from the ileostomy is reduced [12, 13]. Routine imaging studies should be performed, if necessary, and if thrombi are found, various antibody tests should be performed to differentiate HOS and APS.

The treatment for thrombosis is different when the cause is dehydration and APS [6, 8, 14]. Treatment of venous thromboembolism (VTE) includes anticoagulation and thrombolysis, either alone or in combination [15]. Fast-acting direct oral anticoagulants were approved for VTE treatment in Japan in 2014; their use has since become more common. However, using direct oral anticoagulants in patients with APS is contraindicated because of the reported increased risk of thrombosis recurrence and bleeding events [16]. This makes warfarin the first choice in maintenance therapy for APS thrombosis relapse prevention in patients with multiple thromboses.

We presented a case of thrombosis caused by HOS, which led to an APS diagnosis. The occurrence of APS in men is very rare, and this is an extremely rare condition wherein thrombosis due to APS developed in the background of chronic dehydration caused by HOS. Patients with HOS are more likely to develop thrombosis, but we believe that APS should be actively ruled out when multiple thromboses are observed. Unless there are special factors, DS closure is usually performed about 3 months after the initial surgery; therefore, imaging evaluation is also performed about 3 months later. Considering HOS, it is preferable to perform imaging evaluation at an earlier stage to investigate the presence of thrombosis. If thrombus formation is found, a closer examination, considering the presence of APS, will allow earlier diagnosis...
and treatment. If a patient with HOS develops VTE, it is essential to exclude APS because the choice of therapeutic agent may be different.

This is a single case report; thus, the present patient's clinical course cannot be generalized to all HOS patients. However, the presence of APS should always be considered for thrombosis in HOS patients as it can be fatal if not managed properly. We would like to accumulate more reports of similar cases in the future to identify conditions and risk factors that should be considered as contributing factors to APS in HOS patients.

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Statement of Ethics

This study was reviewed and approved by the Institutional Review Board of Kure City Medical Association Hospital on February 1, 2022 (approval number: R4-1-220201). Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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Data Availability Statement

The data that support the findings of this study are openly available from the corresponding author, Shoichiro Mukai, upon reasonable request. The data are not publicly available due to restrictions; they are containing information that could compromise the privacy of research participants.
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