Repeated bleeding caused by acquired hemophilia A after endoscopic submucosal dissection: A case report and literature review

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Abstract. Endoscopic submucosal dissection (ESD) has been widely used in the treatment of gastrointestinal tract lesions, and hemorrhage is one of the most common complications. The aim of the present study was to investigate the clinical characteristics of hemorrhage after ESD in patients with acquired hemophilia A (AHA). Firstly, a case of AHA with multiple bleeding events after ESD is reported. Colonoscopy was used to perform ESD treatment of the submucosal tumor, and immunohistochemical analysis was used to analyze the tumor properties. Secondly, literature relevant to postoperative hemorrhage caused by AHA was researched and analyzed, with the changes in activated partial thromboplastin time (APTT) before and after operation, coagulation factor VIII (FVIII) activity, FVIII inhibitor value and treatment plan noted. The majority of patients with AHA had no history of coagulation disorder or genetic disease and showed a normal APTT. However, it was found that the APTT value gradually increased after bleeding. In addition, the APTT correction test did not correct for prolonged APTT and FVIII antibody positivity in AHA. There was no bleeding or bleeding tendency prior to surgery in patients with AHA. The study concludes that when repeated bleeding and a poor hemostatic effect occurs, it is necessary to be alerted to the possibility of AHA, as an early diagnosis is essential for effective hemostasis.

Introduction

Endoscopic submucosal dissection (ESD) is a widely recognized interventional therapy for en bloc resection of gastrointestinal lesions (1). ESD is a minimally invasive treatment method. Regardless of the size and location of the lesion, superficial gastrointestinal tumors can be completely removed. ESD has higher technical requirements, especially for larger and more invasive injuries. However, it carries a high risk of complications, including perforation, bleeding and post-ESD coagulation syndrome (2,3), among which hemorrhage is the most serious and common. Yang *et al* (4) reported that there has been no agreement on the definition of bleeding after ESD, resulting in the reported rates of bleeding after ESD ranging from 1.3 to 13.0%. Post-ESD bleeding can be controlled through endoscopic intervention or blood transfusion (5), but it cannot be completely prevented and may lead to life-threatening conditions such as hemorrhagic shock (6). Acquired hemophilia A (AHA) is a severe bleeding disorder characterized by an autoantibody directed against coagulation factor VIII, and these antibodies arise in individuals with no prior history of AHA; it is characterized by bleeding in 90% of patients, of which 70% have severe bleeding (7,8). In total, 50% of AHA cases are idiopathic, while the remaining 50% are related to pregnancy, autoimmune diseases, malignant tumors and drugs (9). In clinical practice, multiple postoperative bleeds combined with AHA is rare. By reviewing both domestic and foreign literature and combining this with a case report from Wuhan No. 1 Hospital (Wuhan, China), the clinical characteristics of rare concurrent AHA after ESD are discussed and analyzed in the present study. The aim of the present study was to aid the analysis and diagnosis of clinical ESD postoperative hemorrhage.

Case report

The patient in the present case report (age, 48 years; sex, male) was admitted to Wuhan No. 1 Hospital (Wuhan, China) in November 2019 due to irregular stools accompanied by increased stool frequency for half a year. A colonoscopy was performed in another hospital due to a change of stool shape, which suggested rectal polyps. No medical treatment was administered during this period. The patient had no history of any chronic disease, such as hypertension, diabetes or heart disease, and reported no family history of inherited diseases, spontaneous bleeding or non-continuous bleeding after trauma. After admission, no obvious abnormalities were found in the blood analysis, liver function, renal function, carcinoembryonic antigen or coagulation function [prothrombin time

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(PT), 10.6 sec (reference value, 9-13 sec); activated partial thromboplastin time (APTT), 28.8 sec (reference value, 20-40 sec)] tests. Gastroscopy indicated reflux esophagitis, erosive gastritis and duodenitis. Colonoscopy performed in Wuhan No. 1 Hospital (Wuhan, China) revealed a submucosal tumor of the rectum 15 cm from the anus. Ultrasound colonoscopy (Fig. 1) suggested a submucosal hypoechoic eminence (considering the possibility of neuroendocrine neoplasm). Consequently, ESD therapy was performed on day 4 after admission. ESD involved marking around the lesion ~5 mm from the edge using an Erbe electric knife system (Erbe Elektromedizin GmbH), submucosal injection to lift the lesion from the muscularis propria, circumferential incision into the submucosa outside the marked points and submucosal dissection until the lesion was removed. The electric cutting mode was ENDO CUT® Q and FORCED COAG, with effect 3 and power 50. There was ~20 ml of blood loss during the ESD operation, and the operation went smoothly. Multiple titanium clips completely closed the wound surface (Fig. 2). The pathological results indicated a spindle cell tumor in the rectum, with a diameter of 0.6-0.8 cm. Immunohistochemical results (Fig. 3) were as follows: caldesmon(+) (data not shown), CD117(-), CD34 [tumor cell(-); vascular(+); data not shown], desmin(+), dog-1(-), GFAP(-), Ki-67 (<1%), S-100(-), SMA(+) and Sox10(-). A diagnosis of leiomyoma was eventually considered (Fig. 3).

The first bleed occurred on day 4 after the operation, indicated by a small amount of bloody stool. A colonoscopy was performed and found a little bleeding of the wound, which a titanium clip was used to stop. On day 7 after the operation, fresh bloody stool was released again, to an amount of ~800 ml. Under colonoscopy, it was found that part of the titanium clip closing the ESD wound surface had fallen off, and three small blood vessels were actively bleeding on the exposed wound surface. Erbe electric coagulation hemostatic forceps were used to stop the bleeding using the electric knife system. After the operation, the patient temporarily fasted and was treated with octreotide (48 ml physiological saline + 0.3 mg octreotide via micro pump, 4 ml/h) for hemostasis, and a blood transfusion was performed. On day 10 after the operation, the stool turned yellow and the patient began a liquid diet. On day 14 after the operation, fresh bloody stool was discharged again, with a volume of ~1,000 ml, accompanied by fatigue. Colonoscopy showed that there was blood spurting from the exposed ESD wound surface. Consequently, the wound was sealed with electrocoagulation hemostatic forceps and a nylon rope titanium clip. On day 18 after the operation, fresh bloody stools appeared again, and active vascular bleeding was seen under colonoscopy. Electrocoagulation was applied again to stop the bleeding, and a nylon rope titanium clip was used to suture the wound. On day 24 after the operation, another bleeding spot was found on the ESD wound by colonoscopy, and the bleeding was stopped by electrocoagulation once again. On the same day, a routine blood examination showed that the white blood cell count was 10.89×10^9 cells/l (reference range, $3.5\text{-}9.5 \times 10^9$ cells/l), the red blood cell count was 3.41×10^{12} cells/l (reference range, $3.8\text{-}5.1 \times 10^9$ cells/l) and the hemoglobin level was 102 g/l (normal range, 130-175 g/l), while coagulation function tests showed that PT and APTT

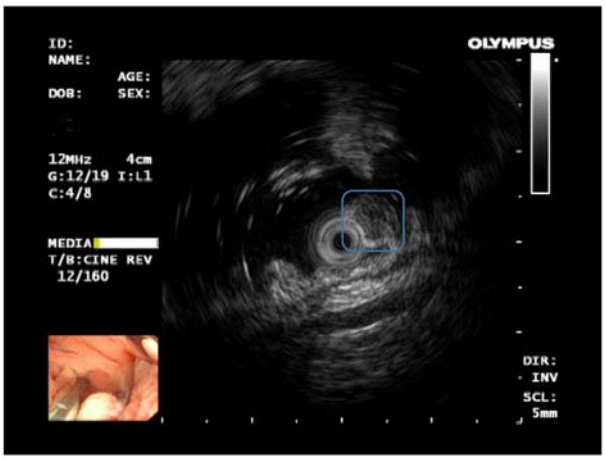

Figure 1. Endoscopic ultrasonography showed that the rectal submucosa had a low echo convex lesion, 0.6-0.8 cm in size. The blue box indicates the location of the convex lesion.

were normal and the D-dimer level was in the normal range. On day 27 after the operation, a small amount of dark red bloody stool was discharged. Endoscopy showed no active bleeding, and no special treatment was given. Once again, routine blood examination showed a white blood cell count of 8.81×10^9 cells/l, a red blood cell count of 2.85×10^{12} cells/l and a hemoglobin level of 96 g/l. Coagulation function tests indicated that PT and APTT were still within the normal range, the fibrinogen level (1.72 g/l; normal range, 2-4 g/l) was slightly decreased and the level of fibrinogen degradation products (50.7 mg/l; normal 0.0-5.0 mg/l) was increased. The activity of plasma antithrombin III was normal. Fresh bloody stools were once again discharged on day 28 after operation. One of the ESD wounds was found to be bleeding near the titanium clip, which was again stopped by electrocoagulation. The number of bleeding incidents was as high as seven in the month after the ESD operation, as shown in Fig. 4.

To address this issue, a hematologist was invited for consultation in order to explore the cause of bleeding. Based on the consultation, further examinations were performed. The results were as follows: von Willebrand factor antigen, 54.5% (reference range, 50-150%); coagulation factor VIII activity (FVIII:C), 22.5% (decreased significantly; reference value, 50-150%); coagulation factor IX, XI and XII activities, 132.3% (reference range, 50-150%), 85.2% (reference range, 50-150%) and 45.3% (reference range, 50-150%), respectively; PT, 12.7 sec (reference value range, 9-13 sec); APTT, 43.2 sec (reference range, 23.9-31.9 sec); and international normalized ratio 1.17 (reference range, 0.7-1.3). It was concluded that the repeated bleeding after ESD was related to the decrease in FVIII:C, and the treatment plan was adjusted accordingly. The diet provided to the patient was mainly liquid, and the patient was given multiple fresh plasma (containing FVIII, 400 ml, once), cryoprecipitate (containing FVIII, 400 ml, once) and enteral nutrition (containing amino acids, fat emulsion, glucose, vitamins, etc.; 1,500 ml, daily for 5 days in total). There was no re-bleeding. Colonoscopy showed that the rectal ESD wound had healed well on the 51st day after the operation (Fig. 5), showing a favorable prognosis.

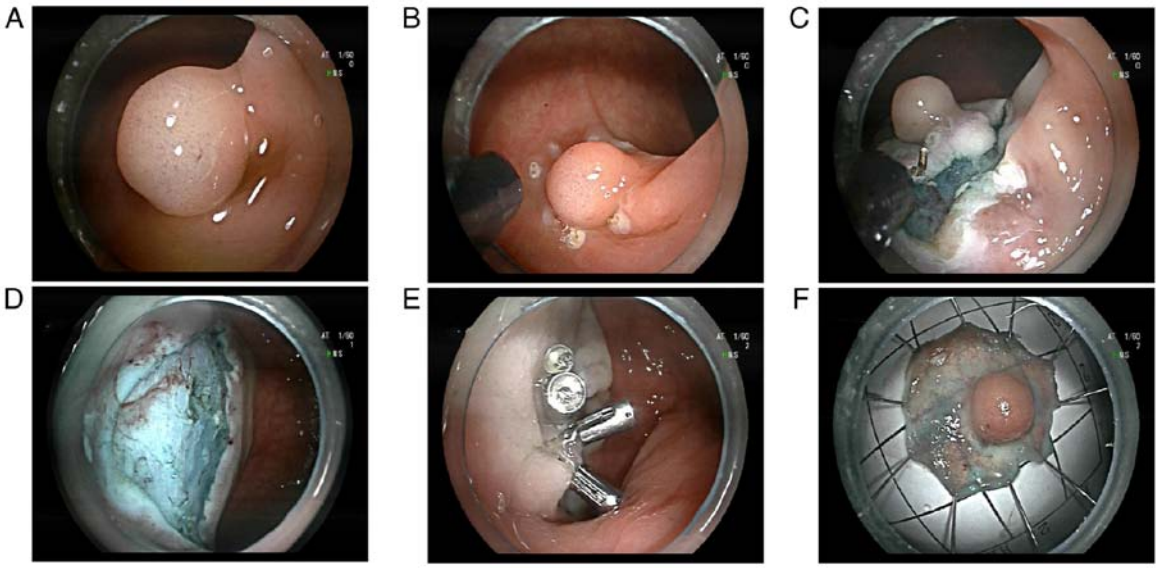

Figure 2. (A) Rectal submucosal tumor. (B) Submucosal tumor of the rectum marked with a hook knife. (C) Submucosal tumor of the rectum cut and peeled with the hook knife edge. (D) Wound surface after ESD resection. (E) Multiple titanium clips closed the wound. (F) The excised specimen area was ~1.8x1.8 cm and the tumor size was 0.6x0.8 cm.

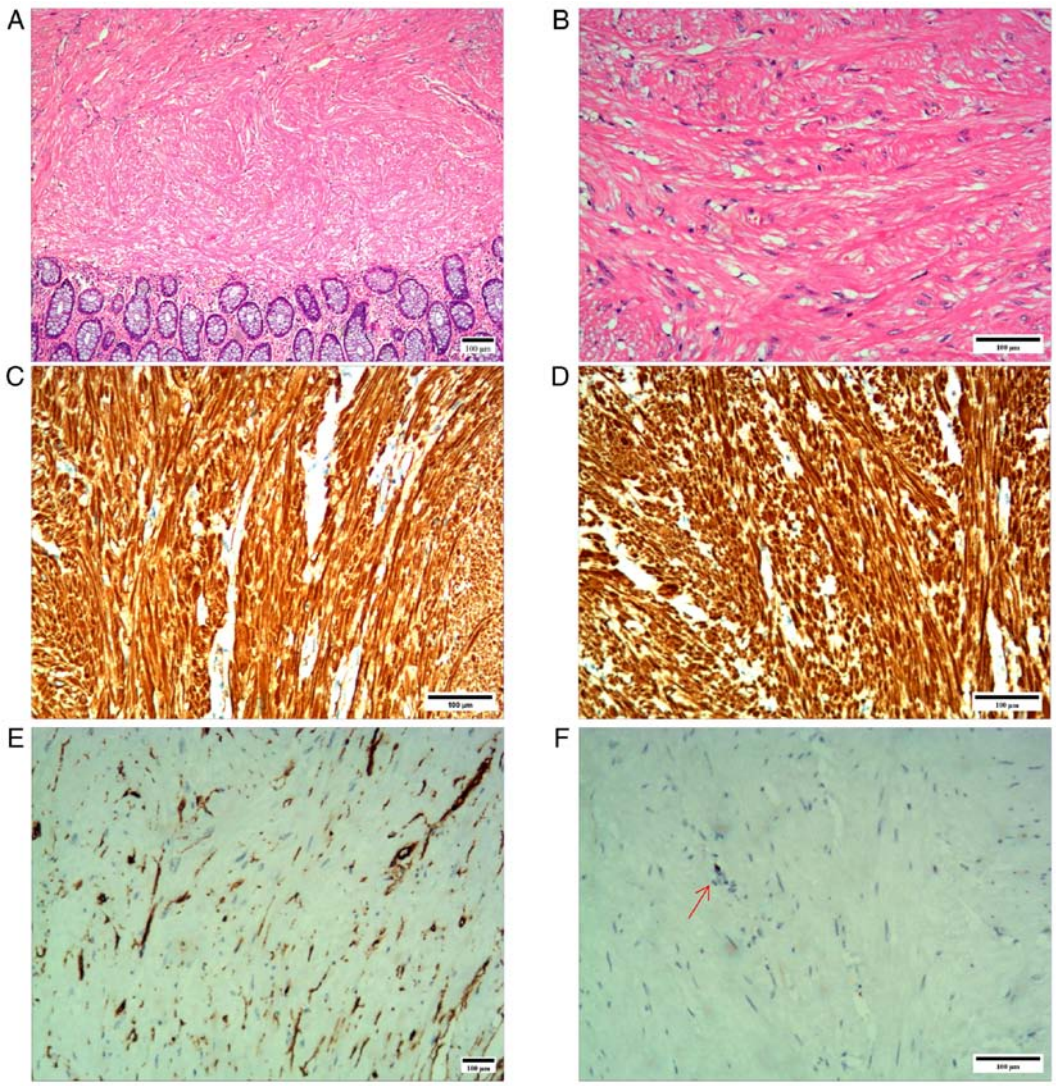

Figure 3. (A and B) H&E staining (x100 and x200 magnification, respectively). Under a light microscope, the cells appeared to be arranged in parallel, clustered into bundles, fusiform in shape and have their cytoplasm stained red. Cells were (C) SMA-positive (diffuse; x200), (D) desmin-positive (diffuse; x200), (E) CD34-negative (x100 magnification) and (F) Ki-67-positive (red arrow; x200 magnification).

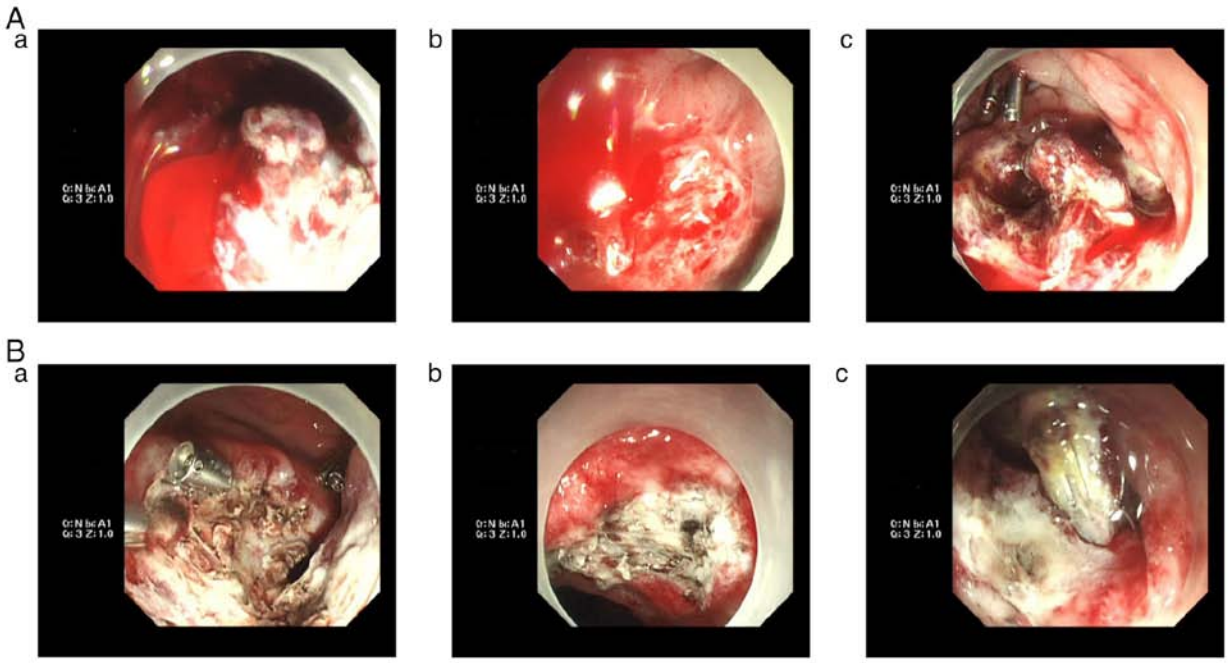

Figure 4. Endoscopic hemostasis process. (A-a) The third postoperative hemorrhage. (B-a) The third electrocoagulation hemostasis and titanium clip hemostasis. (A-b) The fifth postoperative hemorrhage. (B-b) The fifth electrocoagulation hemostasis. (A-c) The seventh postoperative hemorrhage. (B-c) The seventh electrocoagulation hemostasis.

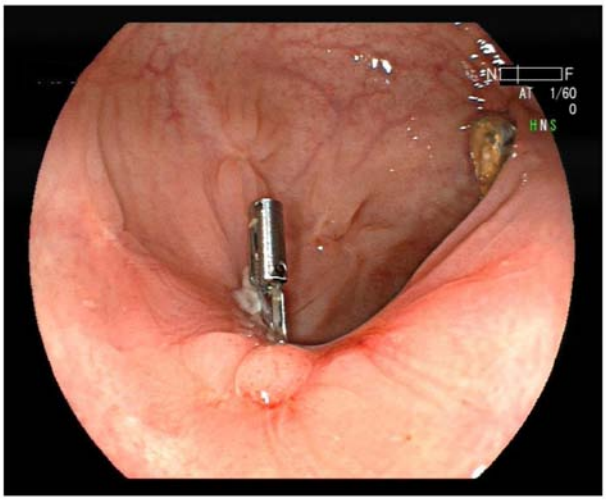

Figure 5. Final colonoscopy result. Re-examination result of the colonoscopy on day 51 after the operation showed that the wound had healed well, and 1 titanium clip remained.

Discussion

AHA is an autoimmune disease caused by inhibitors of FVIII, which is rare but life threatening (10). The rarity of AHA means that clinicians have insufficient treatment experience, which often leads to delayed diagnosis and treatment. The incidence of AHA ranges from 0.2 to 1.48 cases per 1 million individuals per year (11). In the present case report, the patient had no history of bleeding and no family history of AHA/bleeding. AHA is usually discovered incidentally when patients experience bleeding during surgery, trauma or other invasive examinations, or when APTT is found to be prolonged slightly in a routine coagulation function test. However, a timely diagnosis allows for effective hemostasis to be achieved. In clinical practice, gastrointestinal bleeding is one of the predictable complications of ESD. According to the literature, the causes of bleeding after ESD may be related to the following factors: i) Basic diseases, such as hypertension, liver cirrhosis, coronary heart disease, old cerebral infarction, renal insufficiency and atrial fibrillation; ii) drugs used prior to operation, such as anticoagulant or antiplatelet drugs, antihypertensive drugs (for example, nifedipine) and heparin replacement therapy; and iii) lesion factors, including submucosal vascular proliferation, submucosal fibrosis formation, intraoperative massive bleeding, arterial bleeding location and quantity, lesion location (for example, proximal stomach, ileocecal or low rectum), multiple lesions, larger lesions and longer operation time (12-14).

To further understand the association between postoperative bleeding and AHA, 'acquired hemophilia A', 'postoperative' and 'bleeding' were used as key words and searched in PubMed (http://www.ncbi.nlm.nih.gov/pubmed/). A total of six studies reporting 7 cases were assessed by descriptive analysis (15-20) (Table I).

The patients included in the literature had no history of chronic disease, hemorrhagic disease or genetic disease. The age distribution of the patients ranged from 12 to 80 years old, among which 4 cases were in patients ≥60 years old. The results of the preoperative examination showed that APTT was normal in 3 cases and slightly elevated in 2 cases, while in 2 cases, no relevant data were provided. However, all cases showed postoperative bleeding with APTT increasing significantly. Furthermore, FVIII activities were markedly low and patients were positive for the FVIII inhibitor. After active treatment of AHA, bleeding stopped in all the reported cases.

Table I. Characteristics of included literature studies.

First author, year	Age	Sex	Origin	Primary disease	Means of intervention	Preoperative APTT, sec	Days of bleeding after operation	Postoperative APTT, sec[a]	Factor VIII activity, %[a]	FVIII inhibitor, BU/ml	Treatment for bleeding	(Refs.)
Hosoya *et al*, 2013	80	Female	Japan	Superficial esophageal squamous cell carcinoma	Thoracic esophagectomy with radical lymph node dissection	34.9 (normal)	39	140 increased	1 decreased	36	rFVIIa, PSL, endoscopically with clipping, cyclophosphamide, methylprednisolone sodium succinate and red cell concentrates	(15)
Okamura *et al*, 2015	65	Male	Japan	Ruptured aneurysmal subarachnoid hemorrhage, hydrocephalus and neurogenic dysphagia	Aneurysmal clipping, external ventricular drainage and percutaneous endoscopic gastrostomy	27.2 (normal)	6	79.2 increased	4 decreased	10	PSL	(16)
Onishi *et al*, 2013	71	Male	Japan	Bile duct obstruction, cholangitis and bile duct cancer	Endoscopic retrograde biliary drainage, endoscopic nasal biliary drainage tube and radical pancreaticoduodenectomy	ND	8	83.1 increased	1 decreased	8	Activated prothrombin complex concentrate, PSL and rituximab	(17)
Saito *et al*, 2018	63	Male	Japan	Gastric cancer	Gastrectomy	ND	5	74.2 increased	3.18 decreased	7.59	Red blood cell transfusions, PSL and tranexamic acid	(18)
Khan *et al*, 2020 (Case 1)	12	Female	China	Congenital choledochal cyst	Resection of common bile duct cyst and gallbladder, Roux-en-Y anastomosis of hepatic duct to jejunum	45 (normal)	7	150.9 increased	5 decreased	ND	Blood transfusion and surgery	(19)

Table I. Continued.

First author, year	Age	Sex	Origin	Primary disease	Means of intervention	Preoperative APTT, sec	Days of bleeding after operation	Postoperative APTT, sec[a]	Factor VIII activity, %[a]	FVIII inhibitor, BU/ml	Treatment for bleeding	(Refs.)
Khan *et al*, 2020 (Case 2)	18	Male	China	Large common bile duct cyst involving left and right hepatic bile ducts	Resection of choledochal cyst and gallbladder followed by Roux-en-Y anastomosis	45 (normal)	1	105.1 increased	11.2 decreased	16	Activated prothrombin complex concentrates, fresh frozen plasma, blood plasma cryoprecipitate, intravenous immunoglobulin, methylprednisolone, plasmapheresis and rFVIIa	(19)
Oba *et al*, 2020	46	Male	Japan	Buccal mucosal squamous cell carcinoma	Preoperative chemotherapy and radical oral tumor resection	31.2 (normal)	1	110.8 increased	4 decreased	2	Red blood cells and fresh frozen plasma, rFVIIa and prednisolone	(20)

[a]Compared with reference range. APTT, activated partial thromboplastin time; ND, no relevant data; rFVIIa, recombinant activated factor VII; PSL, prednisolone.

According to the literature, the diagnosis of AHA mainly depends on the laboratory examination, as well as determining the related causes and symptoms of bleeding (10,21,22). When APTT prolongation occurs, the APTT temperature correction test cannot be performed, which indicates that an endogenous coagulation factor antibody is present in the plasma. This suggests that FVIII activity is reduced and an FVIII antibody is present. When the activity of multiple coagulation factors decreases, it is necessary to clarify whether to use lupus anticoagulant drugs, so as to provide a basis for differential diagnosis (10). The key goal of AHA treatment is to control acute bleeding and eliminate inhibitors (23). Treatment options include the following: i) Hemostasis treatment, including application of deaminase-8-d arginine vasopressin, FVIII concentrate, bypass activation pathway (activated prothrombin complex or recombinant activated coagulation FVIII), immunoglobulin, plasma exchange and immunoadsorption; and ii) eradication of inhibitors via the application of immunosuppressive agents, including glucocorticoids, cytotoxic drugs (such as, cyclophosphamide and azathioprine), CD20 monoclonal antibody preparation, cetuximab, cyclosporine and tacrolimus (22,24).

The characteristics and summary of the patient in the present case report were as follows: i) Middle-aged and male; ii) no history of hereditary disease or hemorrhagic disease; iii) diagnosis of rectal submucosal tumor (benign leiomyoma confirmed by postoperative pathology); iv) ESD treatment was performed; v) APTT and platelet count were normal before operation; vi) intermittent and repeated bleeding after ESD; and vii) APTT began to prolong and FVIII activity decreased after ESD (FVIII inhibitors were not tested). Hemophilia was not initially considered in this patient with postoperative bleeding. However, repeated endoscopic hemostasis was ineffective and APTT began to prolong on day 28 after the operation. Thus, potential AHA should be considered when repeated bleeding occurs after invasive procedures.

Autoimmune disease refers to the disease caused by the immune response to autoantibodies, which leads to the damage of an individual's own tissues. The existence of autoantibodies is not the same as the presence of autoimmune diseases; autoantibodies may exist in normal people without autoimmune diseases. A stress state can lead to the production of autoantibodies, but such antibodies have no pathogenic effect and belong to a secondary immune response (25,26). The present patient suffered from rectal leiomyoma before admission, which was a benign tumor and had no significant association with AHA. By contrast, the trauma caused by resection of the rectal leiomyoma may have led to the production of related antibodies, thus inducing AHA.

In conclusion, when repeated gastrointestinal bleeding occurs and endoscopic hemostasis is ineffective, even if there is no history of coagulation disorders or genetic hemorrhage, the possibility of secondary AHA should not be ignored. The risk of bleeding caused by a delayed diagnosis of AHA may be one of the reasons for its high mortality. A timely and accurate diagnosis can quickly control the bleeding from AHA, which is key to preventing serious complications.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

SL and NW contributed to study conception and design, data collection, the literature search and manuscript writing. SL and NW contributed equally to this work. ZM and XG obtained the medical images in the patient treatment and searched the literature. ZS designed the study and reviewed the manuscript. All authors have read and approved the final manuscript. SL and ZS confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent to publish this case report was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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