

A case of acquired hemophilia A after pancreaticoduodenectomy for distal cholangiocarcinoma

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Abstract. Acquired hemophilia A (AHA) is a rare disease that results from factor VIII inhibitors causing abnormal coagulation, and certain cases may develop after highly invasive surgery. The present case study reports on a 68-year-old male patient who developed AHA after undergoing a subtotal stomach-preserving pancreaticoduodenectomy for distal cholangiocarcinoma. The patient experienced complications after surgery, requiring reoperation on postoperative day (PD) 5 due to rupture of the Braun's enterostomy. On PD 6, angiography was performed after bleeding was detected in the jejunal limb, but hemostasis occurred spontaneously during the examination. Bleeding was observed again on PD 8 and direct surgical ligation was performed. On PD 14, bleeding recurred in the jejunal limb and angiography was performed to embolize the periphery of the second jejunal artery. During the procedure, the prothrombin time was normal, but only the activated partial thromboplastin time was prolonged. A close examination of the coagulation system revealed a decrease in factor

VIII levels and the presence of factor VIII inhibitors, resulting in the diagnosis of AHA. Administration of steroids was initiated on PD 15 and, in addition to daily blood transfusions, activated prothrombin complex concentrate was administered to achieve hemostasis. The patient was discharged from the intensive care unit on PD 36 but later developed an intractable labial fistula due to suture failure at the gastrojejunostomy site. As the use of factor VIII inhibitors continued despite the administration of steroids, cyclophosphamide (CPA) pulse therapy was added at PD 58. However, CPA was ineffective and the administration of rituximab was initiated on PD 98. After 12 courses of rituximab, the patient tested negative for factor VIII inhibitors on PD 219. On PD 289, labial fistula closure was performed with continuous replacement of factor VIII and the patient was discharged on PD 342.

Introduction

Acquired hemophilia A (AHA) is a rare disease, that may result from factor VIII inhibitors causing abnormal coagulation. Patients with AHA are characterized by a prolonged activated partial thromboplastin time (APTT) despite a normal prothrombin time (PT) (1). In Japan, the incidence of AHA has been reported to be 0.8-1.83 per million individuals per year (2,3). Recently, the number of reported cases of AHA has increased (4). There is no gender difference in the incidence of AHA, but it tends to be more common in the elderly (5). AHA presents suddenly with subcutaneous or intramuscular hemorrhage in patients without a history or family history of bleeding tendencies (6). The bleeding phenotype of AHA is variable, ranging from life-threatening bleeds to mild or no bleeding (5). Patients with AHA also have a high early-onset mortality rate, most of which are caused by severe hemorrhage and severe infections (7). AHA has been reported to be associated with autoimmune diseases, malignant tumors, pregnancy, delivery and drugs (8-10). According to certain reports, AHA may develop after surgery (11,12). The present study reported a case of AHA that developed after subtotal

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Abbreviations: AHA, acquired hemophilia A; APCC, activated prothrombin complex concentrate; APTT, activated partial thromboplastin time; CPA, cyclophosphamide; GFO, glutamine, fiber and oligosaccharide; ICU, intensive care unit; PD, postoperative day; PSL, prednisolone; PT, prothrombin time; SSPPD, subtotal stomach-preserving pancreaticoduodenectomy

Key words: acquired hemophilia A, distal cholangiocarcinoma, subtotal stomach-preserving pancreaticoduodenectomy, surgery, activated prothrombin complex concentrate, factor VIII inhibitor, rituximab, recombinant factor VIII preparation

stomach-preserving pancreaticoduodenectomy (SSPPD) for distal cholangiocarcinoma.

Case report

A 68-year-old male presented to the emergency department of Tokyo Metropolitan Tama Medical Center (Tokyo, Japan) with upper abdominal pain in September 2019. The patient was a sedentary worker on active duty and had no apparent history of carcinogen exposure. He had no history of dementia, hepatitis B or C, or diabetes. The patient was diagnosed with gallstone pancreatitis at the first visit and underwent endoscopic retrograde cholangiography the next day, during which a plastic stent was placed at the department of gastroenterology. However, endoscopic removal of a common bile duct stone revealed stenosis due to a neoplastic lesion in the distal bile duct, and a biopsy confirmed distal cholangiocarcinoma, so the patient was referred to our department in November 2019. Preoperative blood tests indicated that no blasts were present.

The patient underwent SSPPD as the first surgery. Intraoperative rapid diagnosis was performed according to standard procedures, and the result was positive for a bile duct stump, so additional resection was performed. The bile duct stump was negative for cancer, and had two holes: The posterior segment branch of the low confluence and the common hepatic duct (Fig. 1), which formed a hole for the hepatocholejojejunostomy. The operative time was 608 min, the amount of bleeding was 1,055 ml and no blood transfusion was required.

Pathological examination was performed by standard procedures and revealed a well-to-moderately differentiated tubular adenocarcinoma (pT1, pN1, pM0, pStage IIA) (Fig. 2A and B). On postoperative day (PD) 3, the patient developed a surgical site infection, and on PD 5, intestinal juice leaked from the wound, requiring a second surgery to resuture the Braun's anastomotic rupture. On PD 6, there was significant bleeding from the gastric tube and dynamic computed tomography showed bleeding into the jejunal limb. Angiography was performed, but hemostasis occurred spontaneously during the examination (first angiography). On PD 8, bleeding in the jejunal limb reoccurred and direct surgical ligation was performed (third operation) (Fig. 3). There was a small hole in the Braun's enterostomy and gastrojejunostomy sutures. The afferent leg was transected, bypassing to the anal side, and the hole was closed on the efferent leg side. The gastrostomy tube was inserted through the suture failure of the gastrojejunostomy. On PD 14, bleeding recurred in the jejunal limb and angiography was performed to embolize the periphery of the second jejunal artery (second angiography) (Fig. 4).

As the patient continued to exhibit hemorrhagic tendencies, a prolonged activated partial thromboplastin time (APTT) (44.5 sec) was observed from PD 2, despite the preoperative APTT (22.9 sec) being within the almost normal range (24.3-36.0 sec). Although the prothrombin time (PT) was within the normal range postoperatively, the APTT reached 91.5 sec on PD 12. On PD 14, acquired hemophilia A (AHA) was suspected and activated prothrombin complex concentrate (APCC; FEIBA®; 100 U/kg, q12h, four times) was administered while performing a coagulation factor activity test. Prednisolone (PSL) was also started on PD 15

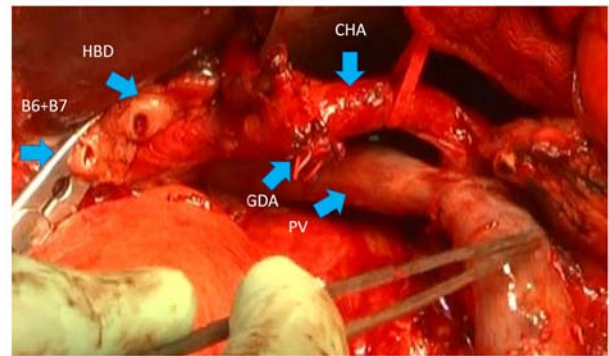


Figure 1. Intraoperative image indicating that the bile duct had two holes: The posterior segment branch of the low confluence and the common hepatic duct. CHA, common hepatic artery; GDA, gastroduodenal artery; PV, portal vein; HBD, hepatic bile duct; B6, posterior inferior subsegmental branch of bile duct; B7, posterior superior subsegmental branch of bile duct.

at 1 mg/kg/day. However, the gastrojejunostomy site was perforated, resulting in a labial fistula. On PD 18, the diagnosis of AHA was confirmed by a decrease in factor VIII activity (<1%; normal range, 60-150%), the appearance of a factor VIII inhibitor (18 BU/ml; normal value, undetectable) and the absence of a lupus anticoagulant. Other results of coagulation factor activity tests were as follows: Factor IX activity, 73% (normal range, 70-130%), factor IX inhibitor, 0 BU/ml (normal value, undetectable); factor XIII activity, 37% (normal range, 70-140%), von Willebrand factor, 294% (normal range, 60-170%); anticardiolipin antibody-anti- β 2-glycoprotein I, <1.2 U/ml (upper limit of normal, 3.5 U/ml). Loss due to hemorrhage was thought to be the reason for the decreased factor XIII clotting activity.

On PD 21, blood transfusion was no longer required and hemostasis was observed, allowing us to initiate the administration of glutamine, fiber and oligosaccharide (GFO) through the intestinal fistula. However, on PD 22, the patient experienced melena and anemia progressed, prompting us to halt the administration of GFO and administer APCC for two days.

However, on PD 26, melena resumed and APCC was administered again for two days. The administration of GFO was resumed on PD 29 through an intestinal fistula, but it was required to stop again on PD 31 due to the recurrence of melena, leading to the administration of APCC for three days. The patient also exhibited decreased factor XIII activity, and hence, freeze-dried blood-coagulation factor XIII derived from human plasma (Fibrogammin P®; CSL Behring; 1,440 U/day) was administered for three days. By PD 36, the patient was stable and was discharged from the intensive care unit (ICU) (Fig. 5A), after receiving APCC for 10 days and 102 units of red blood cells. Hemostasis was achieved by PD 41 and enteral nutrition was resumed.

On PD 58, the factor VIII inhibitor levels increased (54 BU/ml), prompting the initiation of combination therapy with cyclophosphamide (CPA; 15 mg/kg, every three weeks) and PSL. On PD 79, negative pressure wound therapy was started at a different wound location from the labial fistula of the wound (Fig. 6A and B). On PD 98, the factor VIII inhibitor levels increased (35 BU/ml), prompting the initiation of

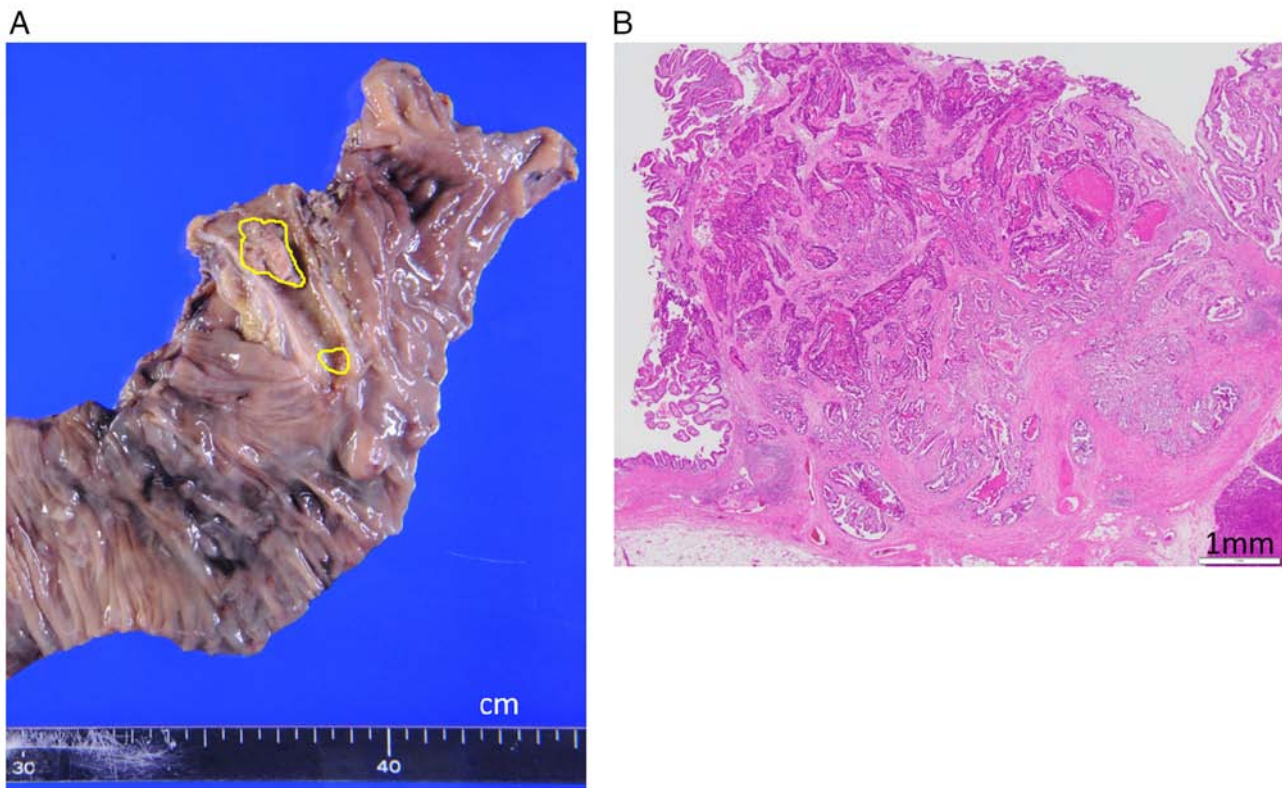


Figure 2. (A) Specimen before additional resection of bile duct, which had two tumors, highlighted by yellow circles (26x18 and 17x14 mm in size, nodular-expanding type). (B) Hematoxylin-eosin stain (scale bar, 1 mm). Histopathologically, both were well-to-moderately differentiated tubular adenocarcinomas.

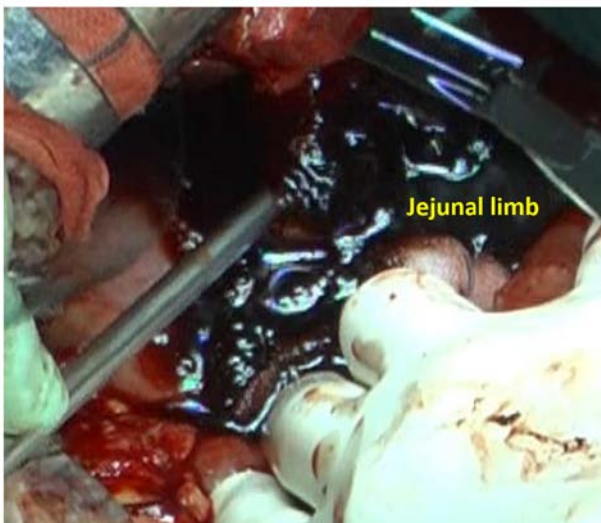


Figure 3. On postoperative day 8, bleeding reoccurred in the jejunal limb and direct surgical ligation was performed.

combination therapy with rituximab (375 mg/m², weekly) and PSL. With treatment, the factor VIII inhibitor levels gradually decreased, factor VIII coagulation activity increased and APTT prolongation improved. The PSL dose was subsequently reduced gradually.

After 12 courses of rituximab, the factor VIII inhibitors became negative on PD 219, but factor VIII activity remained low at 20-30% (Fig. 5B). The patient was temporarily discharged on PD 245, with a labial fistula and enteral



Figure 4. On postoperative day 14, bleeding (yellow arrows) reoccurred in the jejunal limb and an angiography was performed to embolize the periphery of the second jejunal artery.

nutrition management (Fig. 6C). Surgery under general anesthesia was planned to close the labial fistula and it was decided to perform the surgery while supplementing factor VIII. On PD 268, a pharmacokinetic test was conducted by intravenous injection of a recombinant factor

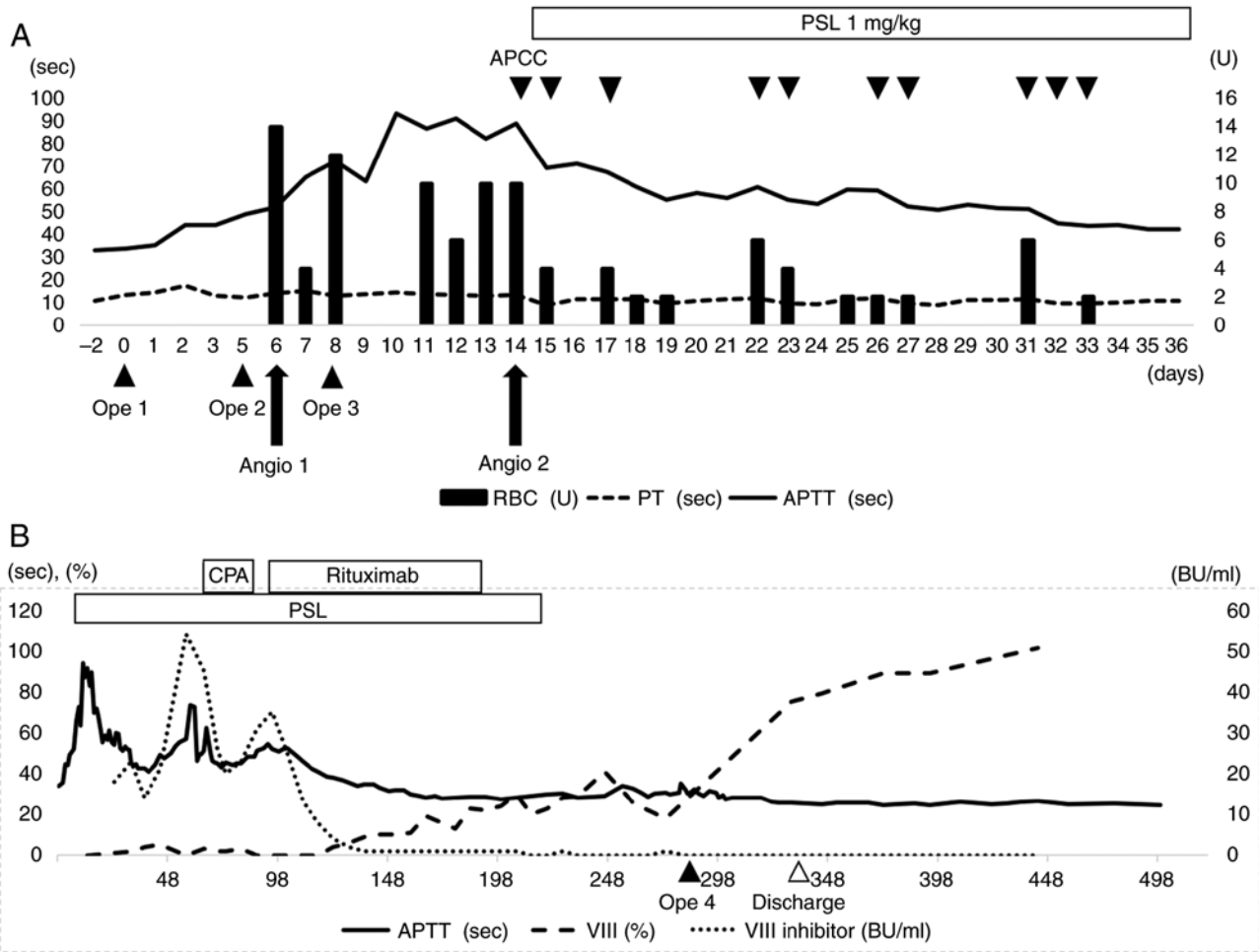


Figure 5. (A) Course of treatment at the ICU. PT was consistently within the normal range before and after surgery and reached 91.5 secs on PD 12. Acquired hemophilia A was suspected on PD 14 and APCC was administered. The administration of steroids started on PD 15. While at the ICU, APCC was administered for 10 days and a total of 102 units of red blood cells were administered. (B) The long-term therapeutic course is indicated. On PD 58, CPA was administered in addition to steroids, but since factor VIII inhibitors increased, administration of rituximab was started on PD 98. After 12 courses of rituximab, the factor VIII inhibitor finally became negative on PD 219. ICU, intensive care unit; PT, prothrombin time; APTT, activated partial thromboplastin time; APCC, activated prothrombin complex concentrate; CPA, cyclophosphamide; PD, postoperative day; PSL, prednisolone; OPE, operation; RBC, red blood cells; Angio, angiography.

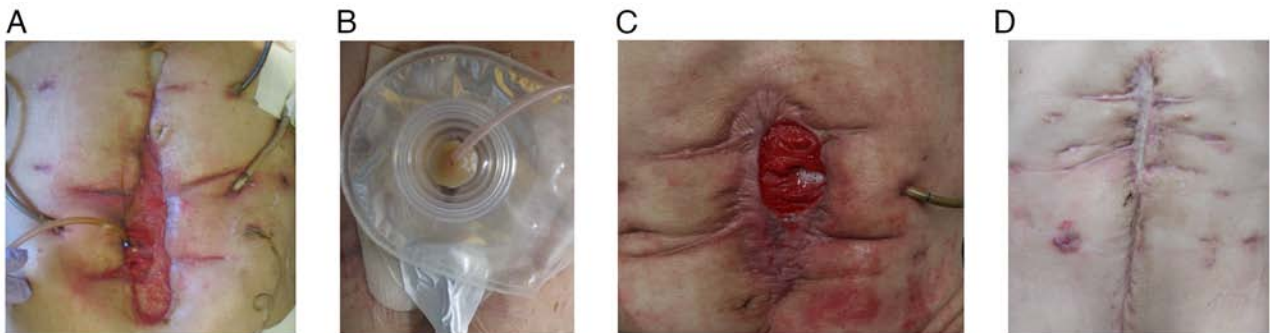


Figure 6. (A) The ruptured gastrojejunostomy suture appeared as a labial fistula (PD 79). (B) Negative pressure wound therapy in a place other than the labial fistula of the wound (PD 79). (C) The incision improved, leaving only a labial fistula (PD 245). (D) The incision was completely closed (PD 342). PD, postoperative day.

VIII preparation (rFVIII) (ADVATE®). As a result, *in vivo* recovery, half-life time and clearance using rFVIII was 1.79 (IU/dl)/(IU/kg), 17.6 h and 2.5 ml/kg/h, respectively. Suzuki *et al* (13) analyzed 34 patients and determined that the *in vivo* recovery, half-life time and clearance using rFVIII

was 1.42 ± 0.36 (IU/dl)/(IU/kg), 12 h and 4.25 ± 2.25 ml/kg/h, respectively.

On PD 289, the fourth surgery was performed, trimming and closing the perforated site of the gastrojejunostomy with an Albert-Lembert suture. Before the surgery, a bolus

dose of 58 IU/kg rFVIII was administered, and during the surgery, rFVIII was continuously infused at 2.35 IU/kg/h. Factor VIII coagulation activity was monitored during and after surgery, and the rFVIII dose was gradually reduced while maintaining $\geq 100\%$. On the third day after the fourth surgery (PD 292), continuous intravenous infusion of rFVIII was discontinued.

The patient was able to resume oral intake on PD 322 and was discharged from the hospital on PD 342 (Fig. 6D). However, on PD 765, the patient passed away due to the recurrence of liver metastasis from distal cholangiocarcinoma.

Discussion

AHA is a rare bleeding disorder caused by neutralizing autoantibodies known as inhibitors of coagulation factor VIII. It is associated with underlying conditions such as pregnancy, delivery, autoimmune diseases, malignant diseases and drug reactions (5). Napolitano *et al* (14) conducted a study involving 105 patients with AHA with underlying malignant tumors, including 60 solid tumors and 45 hematological malignancies. Prostate (25.3%) and lung (15.8%) cancers had the highest frequency, followed by colon cancer (9.5%). Of the 105 cases, only two (1.9%) had distal bile duct cancer. It is worth noting that the patient of the present study and the two aforementioned patients had no coagulation abnormalities prior to pancreaticoduodenectomy and they developed AHA after tumor resection.

In certain cases, AHA may develop following major surgery, including pancreaticoduodenectomy (11,12,15). APCC (16) and recombinant activated factor VII (NovoSeven[®]) (17) preparations are typically used in the acute phase of AHA for hemostasis (5). Clinical trial data have indicated that recombinant porcine factor VII is also effective in treating AHA (18).

In the case of the present study, the bleeding was finally stopped after repeated use of APCC. For the chronic phase of AHA, international recommendations from 2020 (5) suggest first-line treatment with PSL alone for three to four weeks for patients with factor VIII ≥ 1 IU/dl and inhibitor titer ≤ 20 BU at baseline (19), while those with factor VIII < 1 IU/dl or inhibitor titer > 20 BU receive a combination of PSL with rituximab or a cytotoxic agent (CPA or mycophenolate mofetil) as first-line treatment (20). As a second-line treatment, rituximab or a cytotoxic agent that was not used during first-line treatment has been suggested (19).

In the present case, factor VIII activity was $< 1\%$ and factor VIII inhibitor was 18 BU. As the present case was encountered before the 2020 guidelines were published, PSL was first administered, followed by combination therapy of CPA and PSL as the second-line treatment and a combination of rituximab and PSL as the third-line treatment (1,21).

In the case of the present study, factor VIII inhibitor disappeared after 31 weeks of treatment. Reports of surgery in patients with AHA are scarce. As in the second and third surgeries in the present case, emergency surgery has been reported in the presence of a bleeding tendency (22-24), and while a small number of studies reported that surgery was performed after confirming negative factor VIII

inhibitor status, as in the fourth surgery in the present case. Ichikawa *et al* (25) reported that a patient with AHA was treated with rituximab and underwent surgery for sigmoid colon cancer after the disappearance of factor VIII inhibitors with no adverse events. Jena *et al* (26) performed a pancreaticoduodenectomy on a patient with periampullary carcinoma and AHA after treating AHA.

Upon scheduling intestinal fistula closure, it was observed that while factor VIII inhibitor had resolved, factor VIII activity remained low. In such cases, it becomes challenging to assess both hemostatic and thrombotic tendencies while using bypass preparations due to the incomplete resolution of AHA. Kruse-Jarres *et al* (27) reported that rFVIII replacement therapy is also a treatment option when the factor VIII inhibitor level is < 5 BU/ml. There have been certain reported cases where hemostatic management and surgery were performed while administering rFVIII (28-31), and in the present case, hemostatic management with rFVIII under adequate monitoring was chosen. As a result, there were no perioperative bleeding or thrombotic complications and AHA did not recur.

The pathogenesis of AHA remains to be fully elucidated. Although in the present study, it was considered to measure autoantibodies and complement, they were not examined because the effects of surgical invasion and early initiation of immunosuppressive therapy with steroids may make the interpretation of the results difficult. In addition to malignant tumors and autoimmune diseases that have been reported so far, there have been an increasing number of reports of onset triggered by infectious diseases, such as reports related to COVID-19 (32-34). Furthermore, Alzheimer's dementia, hepatitis B and diabetes may also be important risk factors for AHA (35). In the case of the present study, AHA developed just after surgery for a malignant tumor, so it was difficult to collect information that may be related to the pathogenesis, but at least there was no background of Alzheimer's dementia, hepatitis B or diabetes. Further cases need to be accumulated to study the pathogenesis and establish a suitable management strategy.

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Availability of data and materials

The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Authors' contributions

MT drafted the manuscript. YM contributed to the preoperative checks and diagnoses. MT, THa, YM and ZD performed the initial surgery. MT, THa and ZD performed the second surgery. YM and MT performed the third surgery. YM, NI and

MT performed the fourth surgery. KS directed the management of perioperative care for the patient in the care unit. YK and YC supervised hemostatic therapy and immunotherapy for the patient. NI and NS managed the patient's labial fistulas. FH contributed to the nutritional management of the patient. YM followed up the patient. THi, KK, SSat, SY, SSas, KF, TS, AI, HOH and YI provided postoperative management for the patient. HOk made the pathological diagnosis. MT and YK checked and approved the authenticity of the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this case report.

Competing interests

The authors declare that they have no competing interests.

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