—Case Reports—

Mild Hemophilia A Diagnosed in a 55-year-old Patient after Pancreatoduodenectomy for Carcinoma of the Papilla of Vater

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Abstract

Hemophilia A is a sex-linked hereditary disease, and the total number of patients with this condition is small. It is quite rare for general surgeons to encounter a patient with hemophilia A. Moreover, it is extremely rare for surgeons to encounter adult patients with undiagnosed hemophilia. We describe a patient in whom intra-abdominal bleeding persisted after open abdominal surgery, leading to a diagnosis of hemophilia A. The patient was a 55-year-old man with carcinoma of the papilla of Vater who underwent pancreatoduodenectomy, during and after which hemostatic difficulties were encountered. Our initial diagnosis was complex coagulopathy; however, transfusion of a large volume of fresh frozen plasma did not improve the activated partial thromboplastin time, which led us to suspect hemophilia. Thorough personal and family histories and determination of coagulation factor VIII showed that the patient belonged to a family with hemophilia A, which had not been recognized by his parents, leading to a diagnosis of mild hemophilia A based on decreased coagulation factor VIII levels. After diagnosis, intermittent administration of a coagulation factor VIII product controlled the bleeding. The patient is currently being treated on an outpatient basis and remains free of cancer recurrence.


Key words: hemophilia A, surgery, carcinoma of the papilla of Vater

Introduction

Hemophilia is a rare congenital bleeding disorder with an incidence of 5 to 10 per 100,000 live male births¹. The total number of patients with this condition is so small that general surgeons rarely encounter it. Moreover, it is extremely rare for surgeons to encounter adult patients with undiagnosed hemophilia. We describe a patient, in whom intra-abdominal bleeding persisted after open abdominal surgery, leading to a diagnosis of hemophilia A.

Case Report

A 55-year-old man with a chief complaint of melena, a history of chronic hepatitis C virus (HCV)
infection, and no significant family history consulted a local clinic and was referred and admitted to our hospital for further evaluation. On physical examination at admission, the palpebral conjunctivae were slightly pale. The abdomen was flat and soft with no palpable masses or superficial lymph nodes. On admission, laboratory studies showed moderate anemia with a hemoglobin level of 8.6 g/dL, mild diabetes with a fasting blood glucose of 112 mg/dL, and moderate liver dysfunction with an aspartate aminotransferase level of 111 IU/L and an alanine aminotransferase level of 182 IU/L. Blood coagulation studies demonstrated a normal clotting time of 12.3 minutes (normal range, 5–15 minutes) and a mildly prolonged activated partial thromboplastin time (APTT) of 41.8 minutes (normal range, 26–38 minutes).

Abdominal computed tomography showed a mass lesion in the descending duodenum corresponding to the head of the pancreas, but there were no other abnormalities (Fig. 1). Upper gastrointestinal endoscopy demonstrated a tumor with a bleeding ulcer on the top at the papilla of Vater (Fig. 2). A biopsy of the tumor led to a diagnosis of well-differentiated adenocarcinoma. There were no other lesions that could have caused bleeding. Angiography did not show deep tumor staining or an active source of bleeding. After angiography, hemostasis of the catheter puncture site was performed as usual, and no difficulty was encountered. Lower gastrointestinal endoscopy did not demonstrate any lesions that were possible sources of bleeding.
Pancreatoduodenectomy (modified Child’s method) was performed. There were no apparent lymph node metastases. Although hemorrhage per diapedesis gradually increased over time during surgery, transfusion of blood and fresh frozen plasma (FFP) decreased the bleeding; therefore, a drainage tube was inserted to complete the surgery, which had lasted 7 hours and 40 minutes. The resected specimen showed an elevated tumor with an ulcer at the papilla of Vater (Fig. 3). The histopathological diagnosis was carcinoma of the papilla of Vater (well-differentiated adenocarcinoma), pT4pN0M0 stage IB (the Criteria of the Japanese Society of Biliary Surgery) (Fig. 4).

On the second postoperative day, the disseminated intravascular coagulation (DIC) score was 1 point (normal range <7 points; criteria of the Ministry of Health, Labor and Welfare). Intraoperative bleeding was attributed to complex coagulopathy, and the transfusion of blood and FFP was continued after surgery because bleeding from the peritoneal drainage tube and the gastric tube persisted. On the third postoperative day, abdominal distention and a decrease in blood pressure led to the diagnosis of massive intraabdominal hemorrhage, for which emergency surgery was performed. The DIC score was 2 points. The abdominal cavity was filled with large number of blood clots, which were removed. Although the peritoneal cavity was washed with physiological saline, no definite source of bleeding was identified. An additional drainage tube was inserted to complete the surgery. However, bleeding continued, requiring transfusions of large volumes of blood and FFP.

On the eighth day following the surgery, the continued bleeding led to consummational coagulopathy and DIC (the DIC score was 9 points). There was no improvement in the APTT despite transfusions of large volumes of FFP, and the continued deep tissue bleeding, as well as the initial prolongation of APTT, led to a suspicion of hemophilia. A detailed personal and family history was taken again and showed that the firstborn son of the patient’s oldest sister’s oldest daughter had hemophilia A, indicating that the present patient belonged to a family with hemophilia A (Fig. 5). In addition, a mild decrease in the level of coagulation factor VIII to 10.5% indicated mild hemophilia A (anticoagulation factor VIII-negative; von Willebrand factor, 171%). On the basis of these findings, a coagulation factor VIII product was administered and led to gradual control of the intraperitoneal bleeding and an improvement in the patient’s condition. The DIC score returned to the normal range. Thereafter, the patient had no bleeding episodes, followed a favorable course, and was discharged from the hospital. He is being treated on an outpatient basis and remains free of recurrence or metastasis.

Discussion

Hemophilia is a typical congenital hematological disorder and is classified into hemophilia A, B, and C, due to deficiency of coagulation factors VIII, IX, and V, respectively, of which hemophilia A is reportedly the most common. All forms of hemophilia present with the same clinical symptoms and appear to follow the same mode of inheritance, that is, sex-linked recessive inheritance of gene mutations at the distal end of the long arm of chromosome X. Studies have shown that approximately one-third of cases of hemophilia are not associated with a family history of the disorder and thus represent new mutations. Hemophilia is characterized by such features as infrequent body-surface bleeding, frequent deep-tissue bleeding, normal platelet count and bleeding time, clotting time prolongation, normal prothrombin
time, and APTT prolongation. The severity of the bleeding tendency in hemophilia is considered to be proportional to the activity levels of coagulation factors in the blood. Most patients with severe or moderate hemophilia (with coagulation factor activities of less than 1% and 1%–5% of normal, respectively) demonstrate some abnormal bleeding during childhood. In contrast, those with mild hemophilia (with a coagulation factor activity of more than 5% of normal) do not demonstrate abnormal bleeding in daily life, and hemophilia frequently goes undiagnosed until abnormal bleeding occurs after trauma, tooth extraction, or surgery.

Our patient had no history of abnormal bleeding and showed only mild prolongation of APTT, with a clotting time falling within the normal range. Because he was engaged in physical labor, he had often sustained body surface injuries but had not been exposed to a hemostatic challenge. Furthermore, hemostasis of the catheter puncture site after preoperative angiography was successfully performed as usual, leading to the judgment that the mild prolongation of APTT was due to HCV-associated coagulopathy.

Because pancreatoduodenectomy is a type of major surgery and because the DIC score was within the normal range, the difficulty in achieving hemostasis during and after surgery was initially ascribed to complex coagulopathy. It is generally thought that treatment of hemostatic difficulties associated with complex coagulopathy requires a minimum of 30% coagulation factors, corresponding to 400 to 600 mL/day of FFP for adults. Therefore, this dose of FFP was administered, resulting in decreased bleeding. However, administration of a large volume of FFP did not improve the mildly prolonged APTT, and bleeding continued, leading to a suspicion of hemophilia. We did not suspect hemophilia until a more detailed family history revealed that the patient’s niece’s eldest son had hemophilia, suggesting that the taking of a family history of bleeding/clotting disorders should involve at least third-degree relatives. In addition, physicians should be aware that, when there is a suspicion of hemophilia, a sex-linked recessive hereditary disease, males are affected, whereas females carry the gene for hemophilia but are not otherwise affected by the disorder.

When hemophilia A is determined to be the cause of poor hemostasis, coagulation factor VIII replacement is the therapeutic mainstay. In our patient, we used human plasma-derived coagulation factor VIII products. Although these products have almost never transmitted blood-borne viruses, such as human immunodeficiency virus, hepatitis B virus, and HCV, because of the introduction of a heat inactivation step into the production process, a few studies have reported the transmission of heat-resistant viruses, protein contamination-induced immunological hypofunction, and hemolysis. One study has shown that it is appropriate to choose recombinant coagulation factor VIII products, especially for surgery, which frequently involves their use in large amounts.

In the field of abdominal surgery, a literature search of the Japana Centra Revuo Medicina database identified 4 published cases of hemophilia diagnosed after surgery and 4 cases presented at medical conferences. However, to our knowledge, there have been no previous reports of hemophilia A diagnosed after pancreatoduodenectomy, a type of major surgery, as in our patient.

In our patient, the target level of coagulation factor VIII replacement was set at 80% according to the criteria of the Ministry of Health, Labor, and Welfare. According to the formula –target level (%) = prereplacement factor activity (%) + 2 × (factor to be administered) (U)/weight (kg)^2 – 2,000 U/day (expected value 88.5% = calculated value 78% + patient’s coagulation factor activity level 10.5%) of coagulation factor VIII was administered intermittently (100 U/min/day). There was no bleeding requiring blood transfusion on the day after administration, complete hemostasis was achieved 4 days following administration, and the DIC score returned to the normal range. One study has reported that because the half-life of coagulation factor VIII is approximately 15 hours, its continuous administration maintains a more stable level of factor VIII activity than does intermittent administration. The issue of factor VIII inhibitor development remains unresolved, and the dose and

J Nippon Med Sch 2007; 74 (5)
method of administration of coagulation factor VIII require further investigation. We judged that the underlying cause of hemorrhage in our patient was hemophilia.

We have described a patient in whom the persistence of intra-abdominal bleeding after pancreatoduodenectomy led to the diagnosis of hemophilia A. The failure to diagnose hemophilia A before surgery led to the development of a dangerous situation. Advances in coagulation factor VIII replacement therapy have allowed surgical treatment in patients with hemophilia to be similar to that in patients without hemophilia if an accurate diagnosis is made. In mild hemophilia, which is reportedly often detected after surgery, as in this patient, adequate replacement therapy can achieve hemostasis even after major surgery. Regrettably, if we had re-examined and re-evaluated the patient when the prolonged APTT was detected and had taken a detailed family history, the patient might not have been in such a dangerous situation. The present case emphasizes the importance of an accurate diagnosis, including the taking of a detailed personal and family history, in patients with an abnormal coagulation profile recognized before surgery.

References


(Received, May 28, 2007)
(Accepted, June 27, 2007)