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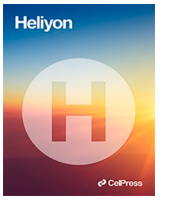

Case report

A rare case of postoperative hemorrhage following laparoscopic cholecystectomy - A case report

Mei-Ling Chen [a], Ruo-Tong Cai [a], Haitham Salameen [a], Xiu-Lin Wang [b], Peng Chen [a], Xiong Ding [a,**,1], Yun-Bing Wang [a,*,1]

[a] *Department of Hepatobiliary Surgery, The Second Affiliated Hospital of Chongqing Medical University, No. 288, Tianxing Avenue, Chayuan, Nan'an District, Chongqing, 400010, China*

[b] *The Second Clinical College, Chongqing Medical University, Chongqing, 400010, China*

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ABSTRACT

Laparoscopic cholecystectomy (LC) is widely accepted as the gold standard procedure for gallbladder removal. While LC is generally acknowledged for its safety and efficacy, this surgical intervention still carries the risk of complications, including postoperative hemorrhage, alongside other rare causes of bleeding. Postoperative recurrent bleeding often arises from complex underlying causes and demands swift identification and intervention for effective management. Here, we present a rare case of a patient diagnosed with an overlapping syndrome comprising primary biliary cholangitis (PBC) and autoimmune hepatitis (AIH), along with Sjögren's syndrome (SS). This patient experienced recurrent massive hemorrhage following cholecystectomy and was ultimately diagnosed with acquired hemophilia A (AHA). We provide a detailed account of the diagnostic and management processes involved.

1. Introduction

Laparoscopic cholecystectomy (LC), as the main procedure and gold standard for benign gallbladder diseases, has emerged as the preferred clinical procedure in surgical operations [1]. Nowadays, the high clinical value of LC becomes increasingly apparent. However, despite its benefits, postoperative complications persist, among which intra-abdominal hemorrhage stands out as one of the more severe complications [2]. Relevant studies have reported the incidence of intra-abdominal bleeding after LC is 0.77 % [3]. The associated risk factors include vascular anatomical abnormalities, patient factors (obesity, history of previous surgeries, underlying liver disease), gallbladder pathology (acute and chronic cholecystitis, gallbladder malformation), and insufficient surgical experience, among others [4]. Nevertheless, rare causes of bleeding following cholecystectomy persist in clinical practice, posing diagnostic and therapeutic challenges. Here, we present a case of a patient who underwent elective LC was found to have an overlapping syndrome of PBC-AIH, along with SS. The patient experienced severe bleeding attributed to acquired Factor VIII (FVIII) deficiency, ultimately leading to a diagnosis of AHA.

AHA represents a severe, life-threatening autoimmune bleeding disorder characterized by the presence of circulating inhibitors to FVIII, often resulting in high rates of disability and mortality [5]. The incidence of AHA is low, estimated at approximately 1.5 cases per

* Corresponding author.
** Corresponding author.
E-mail address: wangyunbing@cqmu.edu.cn (Y.-B. Wang).
[1] Yun-Bing Wang and Xiong Ding contributed equally to this work.

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million people, it exhibits two peaks in occurrence: one during the peripartum period in women of childbearing age and another among individuals over the age of 60, with rare cases reported in children [6,7]. Patients with AHA typically present with acute bleeding symptoms in the absence of a prior history of bleeding. Laboratory tests typically show an isolated prolonged Activated Partial Thromboplastin Time (APTT) and reduced FVIII activity, with levels below 1 % in approximately 50 % of cases, below 5 % in 75 % of cases, and below 40 % in all cases. The Bethesda assay or enzyme-linked immunosorbent assay (ELISA) is utilized to detect the presence of autoantibodies [8,9]. While there are a few isolated case reports of patients without a prior history of bleeding who were diagnosed with AHA following surgery [10], the role of surgery as a trigger for AHA remains uncertain [11,12]. Furthermore, AHA is primarily a diagnosis of exclusion, and distinguishing it from other postoperative coagulopathies, such as disseminated intravascular coagulation (DIC) and thrombocytopenia, can pose significant challenges. Therefore, accurate identification, diagnosis, and treatment of post-operative AHA are imperative in clinical practice.

2. Case presentation

The patient is a 59-year-old Chinese male who presented with recurrent and persistent postoperative bleeding, accompanied by abdominal distension and pain 12 days after LC. Nine years prior, the patient was diagnosed with autoimmune hepatitis (AIH) based on elevated levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and positive antinuclear antibody (ANA) test results. Viral serology was negative. During the course of the disease, the patient repeatedly experienced jaundice in the eyes, skin, and urine, and regular follow-ups indicated abnormal liver function. After liver-protecting treatment, the condition improved. Five years ago, a liver biopsy confirmed the diagnosis of PBC. Additionally, six months prior, the patient was diagnosed with SS and initiated treatment with prednisone (10 mg/day, 08/2023-02/2024) and hydroxychloroquine (400 mg/day, 08/2023-02/2024). One months ago, due to jaundice, a liver puncture biopsy was performed again, which further clarified the pathological diagnosis as PBC (Stage III), with Chronic Hepatitis Scheuer grading staging: G2, S3.

The patient is 165cm tall and weighs 60kg, with a BMI of 22.04. Twelve days ago, they underwent a LC for gallstones with acute cholecystitis at another hospital. The medical history reveals that the surgery lasted approximately 3 hours, with an estimated blood loss of about 700 mL. According to the introduction from the doctors from that hospital, due to profuse bleeding and severe adhesions leading to difficult dissection, a complete cholecystectomy was not feasible. Therefore, after partially resecting the gallbladder and removing all calculi, a drainage catheter was left in place. And the reason why they keep the drain for an extended period was due to ongoing concerns about potential bleeding, infection, and other complications. If these complications were found early, immediate treatment could be conducted. On the first postoperative day, the drain yielded about 300ml of bloody fluid. After symptomatic treatment including the transfusion of hemostatic drugs, no significant fluid has been drained since then. Upon admission, a CT scan revealed post-cholecystectomy changes, a hematoma in the gallbladder fossa, a right upper abdominal drainage tube, and evidence of active extravasation in the abdominal cavity. Blood tests indicated moderate anemia (hemoglobin 73 g/L), and coagulation abnormalities (prothrombin time (PT): 15.5 seconds, APTT: 78.7 seconds), while white blood cells, platelets, and infection markers were normal. Reviewing the patient's follow-up examination results 20 days prior to the LC, only mild anemia was indicated (hemoglobin 126 g/L), with normal coagulation profile. Considering that the cause of postoperative abdominal bleeding was initially unknown, no active bleeding was observed in the patient's abdominal drainage tube at present, and no sustained decline in hemoglobin was observed during follow-up, conservative treatment was initiated.

On the fifth day following admission, the patient exhibited a decline in hemoglobin levels, dropping from 67 g/L to 53 g/L, concomitant with a significant decrease in blood pressure to 70/40 mmHg. Given the presence of active abdominal bleeding, emergent laparoscopy was promptly undertaken. During the surgical procedure, significant pooling of dark red blood accumulation, estimated at approximately 3000 ml, was observed within the abdominal cavity. Additionally, the wound site of the gallbladder exhibited extensive active bleeding. Given the extensive nature of the bleeding wound, achieving hemostasis proved challenging during laparoscopy. Consequently, the surgical approach was transitioned to laparotomy. By applying pressure to the bleeding wound with saline-soaked gauze and coagulating the oozing with bipolar electrocoagulation, followed by suturing some of the bleeding points with 3-0 vascular sutures, a hemostatic gauze was then applied. Following meticulous hemostasis, the wound at the base of the gallbladder was sutured, and a cholecystostomy tube was repositioned to replace the original one. Upon re-inspection of the abdominal cavity and the wound, no active bleeding was observed.

Following surgery, the patient continued to experience worsening hemodynamic instability, accompanied by coagulation dysfunction and drainage of bloody fluid from the abdomen. Consequently, the patient underwent repeated component transfusions, totaling 1000 ml of cryoprecipitate coagulation factor, 1550 ml of plasma, and 1700 ml of packed red blood cells. Despite aggressive attempts to correct his coagulopathy, the patient's bleeding remained refractory to control. Meanwhile, his coagulation tests revealed a markedly prolonged APTT and a mildly prolonged PT. FVIII levels were significantly lower compared to other coagulation factors and was lower than that observed in typical liver dysfunction. Therefore, the possibility of AHA was considered. Further testing revealed persistent failure to correct in the APTT correction test. Subsequently, a Bethesda titer was conducted to quantify FVIII levels, yielding a result of 6.00 BU/ml, thus confirming the diagnosis of AHA. Considering the patient's concurrent severe abdominal infection, inhibitor clearance therapy posed notable risks. Accordingly, in consideration of the patient's condition, temporary administration of piperacillin sodium and tazobactam sodium was initiated for infection prophylaxis, while acetylcysteine and ademetionine 1,4-butanedisulfonate combined with glutathione were used for primary disease management. During the hospitalization period, the patient received symptomatic treatment aimed at maintaining a stable internal environment and providing nutritional support. Hemostasis was initially managed with recombinant human coagulation factor VIIa. Subsequently, the patient's coagulation function was regularly monitored to guide the administration of recombinant human coagulation factor VIIa. After three days of continuous treatment,

the patient's hemostatic therapy was transitioned to prothrombin complex concentrate (PCC) due to cost considerations. However, after seven days of treatment, the patient's condition recurred. Plasma FVIII inhibitor quantification rose to 40.00BU/ml. Ascitic fluid culture from the patient revealed an infection caused by enterococcus faecalis. Serological examinations exhibited positivity for antinuclear antibodies and antimitochondrial antibodies at a titer of 1:100, along with a significantly elevated level of anti-M2 mitochondrial antibody at 893.4 RU/ml. Given the patient's autoimmune disease and the suboptimal control of infection, linezolid was added to enhanced antimicrobial treatment, alongside an intensified approach to managing the primary condition. After nine days of continuous prothrombin complex treatment, the patient's plasma FVIII inhibitor quantification decreased to 1.5 BU/ml. Meanwhile, in response to the postoperative intra-abdominal hematoma observed in the patient, continuous close monitoring was conducted based on the drainage from the indwelling abdominal drain, CT imaging, and the dynamic changes in various laboratory test results. After correcting the coagulation function targeting the underlying cause, a follow-up abdominal CT scan indicated a reduction in the hematoma in the gallbladder fossa compared to previous images, while the surrounding hematoma showed no significant change. Therefore, it was considered that the patient's hematoma was essentially stable, with no further enlargement of the hematoma, no blood-tinged fluid drained from the drain, and no significant blood loss.

After treatment, there was a significant reduction in the patient's plasma FVIII inhibitor titer (from 6.0 BU/ml to 1.5 BU/ml). This reduction occurred despite the presence of multiple autoimmune diseases and incomplete control of the abdominal infection. Following thorough consideration, no additional medications were administered to eliminate the inhibitor. Consequently, after receiving active treatment for the underlying condition, along with anti-infective and adjunctive therapies, the patient's condition improved, leading to discharge. The patient's total hospital stay was 34 days. As of six months post-discharge, there have been no recurrences or new hemorrhagic manifestations observed (Figs. 1 and 2).

3. Discussion

Postoperative bleeding is one of the most severe complications following cholecystectomy, and rapid identification of the cause of bleeding and subsequent treatment is crucial in clinical practice. In the diagnostic and therapeutic approach for this case, we employed a strategy of initially excluding common etiologies before considering and addressing rarer causes. Initially, we empirically considered vascular injury as the likely cause of postoperative bleeding. Moreover, the patient had a history of PBC. The patient underwent a liver biopsy one month prior to admission, with the pathological diagnosis confirmed as PBC (Stage III) with chronic hepatitis scheuer grading staging: G2, S3. Therefore, a diagnosis of cirrhosis is not considered; however, due to the limitations of the biopsy tissue and the potential for disease progression, the possibility of the patient having concurrent cirrhosis cannot be absolutely excluded. Cirrhosis associated with PBC can induce portal hypertension, leading to the opening of collateral circulation and increased pressure in the portal vein branches. This heightened pressure predisposes to vascular injury and subsequent bleeding at the surgical or puncture site [13,14]. During the emergency laparotomy, it was conclusively excluded as the cause. Intraoperative examination revealed widespread oozing at the surgical site, which did not correspond to the characteristic bleeding pattern associated with vascular injury or rupture. We ensured effective hemostasis during the surgery by ligating and suturing the surrounding collateral vessels. Additionally, a cholecystostomy tube was inserted following the application of a purse-string suture to the residual gallbladder. However, the patient continued to experience recurrent hemodynamic instability postoperatively. Second, taking into account the patient's medical history, we considered that the bleeding was caused by coagulopathy resulting from long-term Chronic Hepatitis, which led to postoperative coagulation dysfunction. However coagulopathy attributed to Chronic Hepatitis and Liver Cirrhosis typically involves diminished synthesis of hepatic coagulation factors II, V, VII, IX, X, and XI, alongside elevated levels of von Willebrand factor (vWF) and FVIII. In

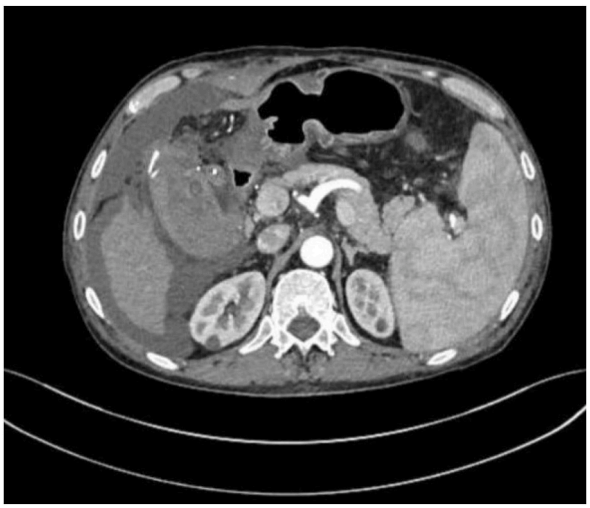

Fig. 1. The pre-treatment axial CT image demonstrates a large gallbladder fossa hematoma.

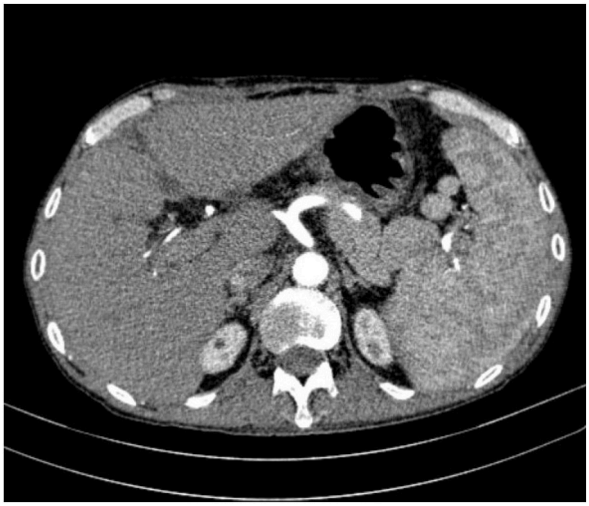

Fig. 2. The post-treatment axial CT image shows that the hemorrhage has been controlled.

most cases, bleeding occurs as a result of the imbalance between pro-coagulant and anti-coagulant systems, stemming from decreased levels of coagulation factors synthesized by the liver [15]. However, in this particular case, subsequent tests unveiled a notable decrease in factor VIII activity (FVIII:C) (11 %) in contrast to the activities of factors VII, XI, and XII (34 %, 49 %, and 22 %, respectively). This pattern differs from the typical reduction in coagulation factor activity observed in liver cirrhosis, indicating coagulopathy stemming from other etiologies. Therefore, under the guidance of a hematologist, we performed an APTT correction test and a coagulation factor VIII inhibitor assay. The results indicated that the APTT was not corrected, and the concentration of FVIII inhibitor was elevated (6.00 BU/ml). Given these factors, including the patient's medical history encompassing AIH, PBC, and SS, absence of prior bleeding episodes or positive family history, lack of heparin use or thromboembolic incidents, clinical presentation of recurrent postoperative abdominal bleeding, ineffective surgical hemostasis, coagulation function tests indicating significantly prolonged APTT (82.1s) and slightly prolonged PT (15.7s), markedly reduced FVIII:C, negative lupus anticoagulant, inability to correct the APTT correction test, and elevated concentration of FVIII inhibitor, a definitive diagnosis of AHA can be established.

AHA is characterized by spontaneous bleeding or abnormal bleeding after surgery, trauma, or invasive procedures in patients without a prior history of bleeding or positive family history [16]. Approximately seventy to ninety percent of patients suffer from severe bleeding episodes in the abdomen, gastrointestinal tract, or intracranial regions, posing life-threatening risks, with mortality rates ranging from 9 % to 22 % [17,18]. Due to the challenging nature of diagnosis, delayed diagnosis can lead to severe consequences. Therefore, recognizing underlying diseases that can lead to AHA is beneficial for rapid identification of the condition. Fifty percent of AHA cases are idiopathic, while the remaining fifty percent are typically associated with autoimmune diseases, malignancies, pregnancy, medications, infections, and surgical trauma [19]. The intrinsic pathophysiological and mechanistic links between AHA and these underlying related diseases are still poorly understood [20]. Among autoimmune diseases, potential underlying conditions associated with AHA include rheumatoid arthritis (7.9 %), systemic lupus erythematosus (5.7 %), temporal arteritis, dermatomyositis/polymyositis, and Sjögren's syndrome [21]. There is limited research available on the co-occurrence of AIH and PBC with AHA. The precise mechanisms through which autoimmune diseases precipitate AHA remain elusive. It is hypothesized that immune dysregulation may trigger the production of IgG4 autoantibodies targeting FVIII. These antibodies typically disrupt the normal function of FVIII by enzymatically cleaving it, consequently obstructing the coagulation cascade reliant on FVIII [22]. Furthermore, these autoantibodies have the potential to impede the interaction between FVIII and von Willebrand factor or phospholipids, thereby hindering the binding of FVIII to factor IXa. They may also obstruct the binding of factor Xa to FVIII or interfere with the assembly of the factor VIIIa-factor IXa-phospholipid (tenase) complex [23].

Medications are also potential triggers for AHA. Known drugs that can cause drug-related AHA (D-AHA) include penicillin, sulfonamides, phenytoin sodium, and interferons, among other immunomodulators [24]. A retrospective study recently published revised the list of suspected drugs associated with D-AHA, to include piperacillin/tazobactam [25]. It is worth noting that piperacillin/tazobactam was continuously administered during the hospitalization period to manage infections, yet the patient ultimately attained clinical management of acquired hemophilia A (AHA). Hence, deliberation is warranted regarding the potential direct association between piperacillin/tazobactam and AHA in this instance. Additionally, surgery-associated AHA (SAHA) may also be a potential trigger in this case. There are few reports related to SAHA, and some studies have pointed out that certain surgeries, such as gastrointestinal surgery, may carry a higher risk of inhibitor formation. It is also noted that although the specific mechanism is not clear, it may be related to tissue damage, where surgery leads to immune dysregulation, exposing autoantigens [26]. In conclusion, AHA in this case may have been precipitated by a combination of the aforementioned factors.

For patients diagnosed with AHA following cholecystectomy and presenting with recurrent bleeding, the treatment goals primarily encompass two aspects: one is to control bleeding, and the other is to eliminate inhibitors [27–29]. To manage bleeding, alongside

surgical procedures and drainage, active medical treatment for AHA was pursued in this case. The initial step in AHA medical treatment involves hemostatic therapy. Guidelines advocate for the use of bypassing agents such as recombinant activated factor VII (rFVIIa) and activated prothrombin complex concentrate (aPCC) for achieving hemostasis. In instances where bypass therapy is unavailable, human FVIII concentrates, recombinant porcine FVIII, or desmopressin are suggested as alternative treatments. Subsequently, immediate initiation of immunosuppressive therapy is recommended upon confirmation of the diagnosis to eradicate inhibitors. Given the high risk of bleeding and significant bleeding-related complications, studies propose immunosuppressive therapy (IST) for all AHA patients, irrespective of their bleeding phenotype [20]. The preferred treatment regime typically involves single or combined therapy with corticosteroids, cyclophosphamide, and rituximab, along with other immunosuppressants [6]. However, unlike the treatment strategy recommended by the guidelines, this patient only underwent hemostatic therapy. This decision was made considering the patient's persistent infection and the significant decrease in inhibitor concentration (from 6.0 BU/ml to 1.5 BU/ml) after a period of using PCC (Fig. 3), which effectively controlled the bleeding. Additionally, studies have shown that there is no strong correlation between factor VIII activity or inhibitor titers and the risk of bleeding [6,23,29]. Further application of immunosuppressive therapy might have led to exacerbation of the infection and the development of related complications; hence we did not proceed with inhibitor eradication treatment.

Although we did not perform inhibitor eradication therapy for the patient, subsequent serological testing still indicated a significant reduction in the patient's inhibitor concentration, and the bleeding was effectively controlled. In regard to the factors contributing to the decrease in inhibitor concentration, several considerations arise. Firstly, the control of bleeding resulted in an augmentation of circulating blood volume, consequently leading to a reduction in inhibitor concentration. Secondly, by mitigating hepatic compromise and alleviating jaundice to manage the underlying primary condition, PBC, the production of autoantibodies may have been curtailed. Thirdly, certain studies propose that approximately 36 % of patients who do not receive immunosuppressive therapy will undergo spontaneous disappearance of autoantibodies. However, the predictive factors for spontaneous remission remain elusive [30].

4. Conclusion

This report describes a rare case of a patient with recurrent postoperative bleeding following LC, alongside the coexistence of multiple autoimmune diseases and AHA. This highlights the importance for clinicians to be highly alert to the possibility of AHA when managing patients with recurrent postoperative bleeding. It is essential to promptly conduct a comprehensive screening of hemostasis and coagulation functions, as well as to test for coagulation factors and the titers of coagulation factor inhibitors to assist in making a diagnosis. Once the condition is confirmed, there should be an active approach to manage the underlying primary disease, rapidly control the bleeding, and eliminate autoantibodies from the body to achieve a favorable prognosis.

CRediT authorship contribution statement

Mei-Ling Chen: Writing – review & editing, Writing – original draft, Software, Investigation, Formal analysis. **Ruo-Tong Cai:** Writing – review & editing, Writing – original draft. **Haitham Salameen:** Writing – review & editing, Conceptualization. **Xiu-Lin Wang:** Writing – review & editing, Investigation. **Peng Chen:** Writing – review & editing, Investigation. **Xiong Ding:** Writing – review & editing, Validation, Supervision, Investigation, Conceptualization. **Yun-Bing Wang:** Writing – review & editing, Validation, Supervision, Funding acquisition, Conceptualization.

Informed consent statement

Informed consent from patients has been obtained and their anonymous information will be published in this article.

Ethical declaration

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

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Xiong Ding AND Yun-Bing Wang reports financial support was provided by oint project of Chongqing Health Commission and Science and Technology Bureau. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

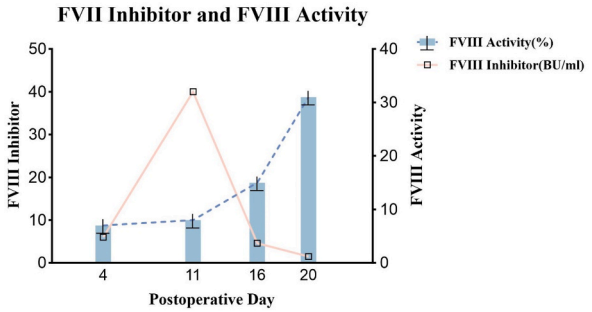

Fig. 3. Temporal Changes in Factor VIII (FVIII) Inhibitor Levels and FVIII Activity Post-Surgery. The graph shows postoperative FVIII activity (%) and FVIII inhibitor levels (BU/ml) over 20 days. Initially, FVIII inhibitor levels was 6BU/ml. On day 11, inhibitor levels peaked at 40 BU/ml while FVIII activity slightly increased. By day 20, inhibitor levels dropped to 1.5BU/ml, and FVIII activity rose to 31 %. This highlights the inverse relationship between FVIII inhibitors and activity, demonstrating the impact of inhibitor development on FVIII efficacy post-surgery.

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