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Case Report

Post Splenectomy Fatal Pulmonary Embolism in a Patient with Moderate Hemophilia A

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Abstract

Hemophilia A is a bleeding disorder caused by defective production of factor VIII. The main concern associated with the disease is bleeding, especially after trauma and surgeries. Factor VIII replacement therapy is associated with substantial decrease of bleeding events during surgery. However, there have been a number of reports of thromboemblic events in this situation. The present report describes a case of moderate hemophilia A in which splenectomy did lead to pulmonary embolism and subsequent death.

The patient was a 25-year-old man with hemophilia A admitted after a car accident and trauma to left lower chest and abdomen. He received factor VIII concentrates for replacement therapy. He was hemodynamically stable on the first day, but on the second day his hemoglobin declined and he showed signs of abdominal tenderness. He, therefore, was subjected to laparatomy and splenectomy. After the operation, he suddenly developed dyspnea and decline in blood pressure, and death afterwards. Autopsy of the patient revealed massive pulmonary thromboembolism. The symptoms and outcome of the present case indicate that although pulmonary thromboembolism in the early postoperative period in patients with hemophilia A undergoing splenectomy and receiving factor VIII concentrate for replacement is rare, it should not be assumed a far-fetched event, and prophylactic measures to prevent thromboemboly must be considered.

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Keywords ● Hemophilia A ● pulmonary thromboembolism ● splenecetomy ● factor VIII

Introduction

Hemophilia A is a congenital X chromosome–linked hemorrhagic disorder caused by a deficit or defective functioning of clotting factor VIII. The incidence of haemophilia is around one in every 5000 males.[1]

Hemophilia is classified clinically into three categories on the basis of severity of factor VIII deficiency including severe, moderate and mild. Severe hemophilia (factor VIII level <1 Iu/dl or <1% factor VIII activity) is manifested by repeated and severe hemarthrosis or hemorrhage with or without trauma. Moderate hemophilia (factor VIII level 1 to 5 Iu/dl) is associated with less frequent and less severe hemorrhage, and affected patients have occasional hematoma and hemarthrosis, which usually but not always, are associated with known trauma. Mild hemophilia is defined by factor VIII levels between 5 to 40 IU Iu/dl. Spontaneous bleeding is rare in mild hemophilia, and

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bleeding associated with mild haemophilia most frequently occurs during surgery or following trauma.[2,3]

Currently, treatment of serious bleeding in all subtypes of hemophilia A is facilitated by the introduction of various factor VIII concentrates for replacement therapy. The amount of factor VIII must be enough to ensure that its blood level does not fall to <30 to 50 IU/dl for any length of time. Maintenance doses are usually given every 8 to 12 hours.[2] An important considerations in the treatment of bleeding due to hemophilia is to begin the treatment as soon as possible, especially in car accidents injuries, which require prompt replacement and subsequent further laboratory investigations.[4]

Pulmonary embolism (PE) is a major cause of morbidity and mortality in high risk surgeries, and might be one of the worst nightmares for most surgeons, therefore, thromboprophylaxis should be considered in some cases. However, patients with hemophilia, due to nature of the bleeding disorder, are extremely at low risk for PE. In such patients, despite the normalization of homeostasis with replacement therapy, which inevitably takes place to allow the surgery to be performed, prophylactic anticoagulation is not always considered necessary.[5]

However, thromboemboli is an area of significant debate, especially after splenectomy. Herein, a case with moderate haemophilia A, who underwent splenectomy and expired from massive pulmonary embolism, is presented.

Case Presentation

A 25-year-old man with moderate degree of hemophilia (factor VIII activity 1 to 5 percent) was admitted to the Shahid Beheshti General Hospital, Kashan, Iran for trauma in left lower chest and abdomen due to car accident. On the admission, the level of consciousness was normal (Glascow coma score was equal to 15). In physical examination vital signs was normal (blood pressure; 120/80 mmHg, pulse; 90 beats/min and respiratory rate; 16/min). He had tenderness in the lower chest and left flank. Examination of other organs did not show any abnormality.

In initial paraclinic examination, chest radiograph was normal. Ultrasonography of abdomen showed 200-300 ml fluid in abdominal cavity, and Computerized Tomography Scan (CT Scan) of abdomen showed evidence of mild splenic injury. The results of initial laboratory blood tests were as follows: hemoglobin level; 13.3 g/dl, platelet count; 196000/µl, partial thromboplastine time (PTT); 47 sec, and international normalized ratio (INR); 2.2

He was observed closely in ICU for replacement therapy, and was given an initial bolus dose 50 IU/kg of high purity factor VIII concentrate, and then 25 IU/kg every 8 hours (three times a day). After this, PT and PTT returned to normal. On the day of admission the vital signs were stable, but on the second day hemoglobin level, PTT and INR declined to 11.3 gr/dl, 46 sec, and 1.6, respectively. Platelet count increased to 219000/ µl, and PT was 15 sec.

Due to the presence of signs suggestive of continuing bleeding such as abdominal tenderness and rebound, he underwent laparatomy. The operation revealed that there was 800-1000 ml blood in the abdominal cavity, and there was injury in the hillar region of the spleen. Therefore, he underwent splenectomy. Six hours after the surgery, hemoglobin was 13.5 g/dl and platelet count was 245000/µl.

The patient's postoperative recovery was going well, but approximately 12 hours after the surgery, the patient's condition was suddenly deteriorated, and he developed dyspnea, hemoptysis and a decline in blood pressure. In spite of tracheal intubation and initial medical management, the patient arrested, and cardiopulmonary resuscitation was not successful The autopsy of the patient showed a massive pulmonary thromboembolism, but there was not blood in the abdominal cavity or problem in other organs.

Discussion

In a resting state it is clear that in the presence of hemophilia the risk of hemorrhage is greater than the risk of thrombosis,[6] thus the main goal of treatment in hemophilia is to control bleeding. The most significant complication of treatment in hemophilia is the development of alloantibodies that inhibit factor VIII activity.[7] When an inhibitor is suspected, Bethesda inhibitor assay (BIA) should be performed.[7] Such patients should be managed in a well-equipped medical center, and Fv111 titration is recommended.[8]

For life threatening bleeding or prophylaxis of bleeding in major surgical procedures, a target of 100% factor VIII activity in plasma is required. For replacement therapy, each unit of factor VIII per kilogram of body weight is assumed to raise its plasma level by 2%. Since factor VIII has a half life of 8 to 12 hours, after an initial bolus dose, repeating one half of the initial dose at least two or three times a day is required to maintain the desired factor VIII level.[9] Note that the treatment of postsurgical or major traumatic hemorrhage in patients with mild hemophilia A requires nearly as much the-

rapeutic product as needed for the severely affected patients.[2] Many authors recommend treatment for 10 to 14 days or longer, depend on the severity of the bleeding or surgical intervention.[10]

Treatment can be started a few hours before surgery and continued intraoperatively. Postoperatively, factor VIII levels should be monitored at least once or twice a day to ensure that adequate levels are maintained, and since factor VIII may be consumed during surgery higher than normal doses of factor VIII may be required.[3] Continuous infusion regimens, consisting of one to two unit factor VIII concentrate per kilogram per hour after a bolus dose maintains a plateau level without the necessity for frequent laboratory testing, and reduces total concentrate consumption by 30 to 75% in surgical setting.[11]

For the present case, high purity factor VIII concentrate for replacement therapy with an initial bolus dose of 50 IU/kg and a maintenance dose of 25 IU/kg every 8 hours was prescribed. Unfortunately, the Hospital did not have the set up to measure plasma levels of factor VIII, therefore, we could not do anything but hope that the prescribed dose and regimen of factor VIII concentrate would prepare adequate homeostasis, and prevent further bleeding before and during the surgery. The values of routine coagulation assays such as PT and PTT returned to normal in the present patient after replacement therapy. However, such a return to normal doesn't mean that normal level of factor VIII was achieved. The findings of a number of studies do not recommend the use of PTT or PT as a guide for appropriate factor VIII replacement, since the values of these tests may be within normal range at hazardously low plasma levels of factor VIII.[2] Therefore, it might be legitimate to suggest that hemophilia A patients should be managed in a hospital with facilities to measure plasma levels of factor VIII.

Venous thromboembolism occurs more in the elderly, patients with inherited thrombophilia diseases, and those undergoing high risk surgeries such as splenectomy, or pelvic or orthopedic surgery.[12] Although the occurrence of spontaneous or post surgery thromboembolism in patients with hemophilia A has been reported in literatures [6,13-15], the risk of hemorrhage in such patients is usually greater than the risk of thrombosis.[7]

Hemophilia A cases undergoing major surgeries are rare, and have been rarely encountered by us. The case in the present study was a young male without any risk factor for hospital acquired venous thromboembolism. He had been treated occasionally with factor VIII concentrates at the time of bleedings. Although thrombophilia screening had never been performed, he didn't have any significant risk factor for thromboembolism. The fact that the patient had hemophilia made us fear more from a catastrophic hemorrhagic event rather than thromboemboli, therefore we cautiously prepared adequate factor VIII concentrate for the patient, and double-ligated all of the vessels and injured tissues in the operation field. With this hemostatic treatment strategy, we never thought an unexpected thromboembolic event might occur. However, during treatment with factor VIII concentrate for replacement therapy, the balance of risk turned in favor of thrombosis and pulmonary emboli. It has been proposed that individuals with hemophilia A, who receive factor VIII for replacement to achieve near normal levels, have a risk of thromboembolism approximating that of the general population.[16] Moreover, it has been suggested that patients with hemophilia A have an equal chance of having an inherited thrombophilia as the general population. This is thought to explain the fact that some patients with severe hemophilia (factor VIII activity < 1%) have a milder clinical picture of the disease.

The risk of thromboembolism in hemophilia A patients is particularly important if they were to be placed in a situation with high risk for thromboembolic disease, while being fully replaced with factor VIII to achieve normal levels of the factor. Deep vein thrombosis and subsequent pulmonary embolism has been documented in hemophilia A patients undergoing high risk orthopedic surgeries.[17] Also, it is well documented that children with hemophilia and long term portocaths are at risk of upper limb thrombosis.[18-20] Post splenectomy thromboemboli occurs in approximately 5% of patients, and possible risk factors are thrombocytosis, splenomegaly and congenital thrombophilia disorders.[21] However, we were unable to find a previous report regarding thromboembolic events after splenectomy in patients with hemophilia A.

Compared to other surgical interventions, the postoperative thrombotic risk in patients after splenectomy has specific features. The spleen obviously has an important function in the clearing of prothrombotic factors, although yet undefined well. Therefore, the removal of spleen is associated with an elevated long-lasting thrombotic risk, even in patients without an underlying disease such as splenectomy after splenic traumatic injuries.[22,23] Post operative thrombocytosis is much more pronounced

after splenectomy, and may increase the thrombotic risk per se, however, this has not been proven yet. Thrombosis of the portal venous system is a unique and potentially life-threatening complication after splenectomy. Since, post-operative thrombocytosis can occur low dose aspirin should be considered when the platelet counts is more than 1,500,000/µl to minimize the risks of thrombosis or embolism.[24]

It has been well documented that in normal subject chronic elevation of plasma factor VIII levels to more than 150 IU/dl is associated with an increased risk of thrombosis.

However, in the present case and other hemophilic patients the elevations to more than 150 IU/dl after replacement therapy are usually transient, and it is unlikely that levels more than 150 IU/dl are sustained for periods greater than a few hours in every 24-hour period. This is in contrast with the situation in a nonhemophilic patient where the elevated levels, if raised to more than 150 IU/dl as an acute phase response, would be persistent.[25-27] Although these high factor VIII levels are unlikely to be the major risk factor, inevitably these high factor VIII levels may well have contributed to the risk of thromboembolism in the present patient. Therefore, to prevent under or over treatment in hemophilic patients, we suggest the regular measurement of factor VIII levels after replacement therapy for surgeries, especially after splenectomy. In addition, since splenectomy is associated with an insult to hemostasis systems in the body, it may be associated with a hypercoagulable state leading to thromboembolic accidents even in hemophilic patients undergoing replacement therapy.

Conclusion

The findings surrounding the present case indicate that in patients with hemophilia A receiving factor VIII for replacement therapy who are candidate for splenectomy, formal risk assessment for thromboembolism, pharmacological thromboprophylaxis, intermittent pneumatic compression or inferior vena cava filter should be seriously considered.

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Conflict of Interest: None declared

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