Case Presentation

Acquired Hemophilia A Associated with Venous Thrombosis and Very High Inhibitor Titer: A Challenging Scenario

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Abstract

Acquired Hemophilia (AH) poses several challenges to clinicians due to potential delays in diagnosis, based on a high index of suspicion, and a high risk of limb and life-threatening bleeding. We here report a case of AH with extremely high inhibitor titer (up to 1200 BU) in a patient who also developed venous thrombosis requiring anticoagulant treatment after prolonged immobilization for femur fracture. Multiple lines of immunosuppressive treatment were needed to achieve inhibitor eradication, probably due to the extremely high inhibitor titer, bleeding management also required several lines of treatment with bypassing agents. Bleeding treatment was here monitored by global hemostatic assays. Management of AH in a reference center allowed to achieve complete remission even in a very intricate condition.

Case Report

Acquired Hemophilia (AH) A is characterized by hemorrhagic manifestations due to the formation of antibodies against human FVIII [1]. The incidence of AH is 1.4/million people/year, idiopathic cases most commonly occur in elderly patients of both sexes [2,3]. Bleeding in AH is severe and unexpected; it occurs spontaneously or after trauma [2]. The treatment of AH is currently based on results from registries, derived from the experience of single centers. The treatment goals are both controlling and preventing bleeding using bypassing agents and inhibitor eradication with immunosuppressive therapy [3-8]. We here report the unusual case of a patient with AH and extremely high inhibitor titer who developed venous thrombosis during treatment.

A 69-year-old 54-kg man with diabetes mellitus and rheumatic polymyalgia was transferred to our unit for transfusion-dependent anemia and persistently prolonged Activated Partial Thromboplastin Time (APTT). The patient was first admitted to a psychiatric unit for a reduction in his mood and attempted suicide; a fracture of the left femur secondary to an accidental fall at home was diagnosed. In consideration of the time since the fall, the patient was managed with conservative therapy with complete immobilization and prophylaxis of venous thromboembolism with Low Molecular Weight Heparin (LMWH). During rehabilitative therapy, painful chest wall and right lower limb muscle hematomas occurred associated with progressive anemia requiring transfusion. The patient was then transferred to an internal medical unit after a CT scan detected active bleeding in the thoracic muscle associated with prolonged APTT for which LMWH was discontinued and fresh frozen plasma administered. He was admitted to our unit 12 days after the first detection of prolonged APTT. The patient presented poor general clinical conditions with a high thrombotic risk due to immobilization for the fracture. A clinical exam revealed a large hematoma of the lower and upper limbs:

and back. His blood count showed severe anemia. Isolated prolonged APTT (106 seconds) was confirmed. AH was suspected, clotting FVIII activity (FVIII:c) and inhibitor to FVIII were tested, and a diagnostic work-up was started including total body CT and PET scans to rule out any underlying diseases. AH was diagnosed with undetectable FVIII:c and an extremely high inhibitor titer to FVIII (825 BU/ml). Prothrombin time, fibrinogen levels, antithrombin, von Willebrand Factor, coagulation Factor IX, coagulation Factor XIII were all normal. A CT scan with contrast showed a hematoma of the left lateral chest wall (12 x 7 x 5 cm) and an increased bone density area of the left fifth rib. The results of a PET scan were unremarkable.

The treatment schedules for bleeding control and inhibitor eradication are summarized in (Table 1).

The initial treatment of the bleeding was based on Activated Prothrombin Complex Concentrate (APCC), and prednisone was chosen as a single agent immunosuppressant. On day 4 of therapy, APTT was 106 seconds, FVIII:c was <0.1%, inhibitor was 880 BU/ml, and hemoglobin was persistently low, requiring daily Red Blood Cell (RBC) transfusions. After ruling out concomitant hemolysis and complement activation as a potential contributing cause of anemia, alternate treatment with recombinant activated FVII (rFVIIa) every 6 hours and Prothrombin Complex Concentrate (PCC) was then started. On day 9, due to pain and edema of the right arm at the site of the central line insertion, a color Doppler ultrasound was performed with evidence of partial brachial Vein Thrombosis (VT). Treatment with LMWH at an intermediate dose due to bleeding risk was then contemporary administered. On day 13, due to persistently high inhibitor titer and daily RBC transfusion requirements, treatment with APCC (FEIBA) for bleeding control was administered again with poor results. On day 15, second-line immunosuppressive therapy with anti-CD20 (Rituximab, 375 mg/m2 weekly for 4 weeks) was started. On day 21, a CT scan was repeated for abdominal and
lower limb pain, and muscle hematomas in the rectus abdominis, in the left and right gluteus, and in the left femoral rectus were detected. On day 26, due to the lack of clinical and laboratory response, recombinant porcine FVIII, rpFVIII (Obizur) was administered at an initial dosage of 100 U/Kg (Table 1). At the post-therapy control, FVIIIc was undetectable and the administration of Obizur 100 U/kg was required 6 hours after the first infusion. The next day, a third administration of Obizur at an increased dose of 200 U/kg was attempted without any response. High titer antibody (35 BU/ml) against rpFVIII was detected and treatment discontinued. Taking into account the partial response to the previous rFVIIa treatment, rFVIIa therapy was restarted at a standard dose of 90 mcg/Kg every 3 hours. On day 35, cyclophosphamide as an immunosuppressive agent was added as a persistent high titer inhibitor. On day 57, the agent was added as a persistent high titer inhibitor. The response to immunosuppressive therapy was very late and several combined treatments were required for persistent high titer inhibitor with active bleeding. APCc administration was not immediately effective, while rFVIIa was partially effective as a single agent, probably because it was sufficient to compensate for the lack of FVIII activity by generating an amount of activated FX able to guarantee hemostasis via thrombin formation. Femur fracture could have acted in this specific case as a trigger to the immune system for the constant and high inhibitor synthesis from one side and the development of VT on the other side. The management of AH in highly specialized settings with frequent clinical and laboratory monitoring has contributed to a successful outcome, even in this extremely risky condition.

Table 1: Treatment and timing schedules.

| Treatment of bleeding | Dose      | Timing                  | APTT (seconds) | Mean Hb level, g/dl | FVIII level (inhibitor) | Days after admission |
|-----------------------|-----------|-------------------------|----------------|---------------------|------------------------|---------------------|
| APCc                  | 60 U/Kg/day | Every 8 hours for 3 days | 106            | 7                   | <0.1% (880 BU)         | 1                   |
| rFVIIa                | 60 mcg/kg   | Every 6 hours for 10 days | >120           | 8.5                 | NP                     | 4                   |
| PCC                   | 1000 IU     | Every 12 hours for 10 days | >120           | 8.5                 | NP                     | 4                   |
| APCc                  | 92 U/Kg/day  | Every 8 hours for 12 days | >120           | 7.2                 | NP                     | 13                  |
| PCC                   | 500 IU       | Every 12 hours for 12 days | >120           | 7.2                 | NP                     | 13                  |
| rpFVIII               | 100 U/kg     | Twice a day for 1 day     | >120           | 7                   | < 0.1% (1246 BU)       | 26                  |
| rpFVIII               | 200 U/kg     | Once a day for 1 day      | >120           | 7                   | 0%                     | 27                  |
| rFVIIa                | 90 mcg/kg    | Every 3 hours until discharge | >120         | 8.4                 | NP                     | 28                  |

Immunosuppressive therapy

| Prednisone            | 1 mg/kg/day | Twice a day for 15 days | 106            | 7                   | <0.1% (880 BU)         | 1                   |
| Rituximab             | 375 mg/mq   | Weekly for 4 weeks      | >120           | 7.2                 | NP                     | 15                  |
| Cyclophosphamide      | 2 mg/kg     | Every day               | 82             | 10.4                | 0.1%                   | 35                  |

Anticoagulant therapy

| LMWH                  | 5700 IU     | Every 24 hours          | >120           | 8                   | NP                     | 9                   |

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