Acquired Hemophilia A as Early Manifestation of Multiple Myeloma: A Case Report

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Abstract

Acquired Hemophilia A is a relatively rare bleeding disorder with an incidence of 0.2–1.9 per million population per year [1-3]. The disease is commonly associated with other underlying medical conditions such as pregnancy and postpartum status, autoimmune disorders, malignancies, dermatological conditions, infections or drug interactions [4-10]. However, up to 50% of cases have no identifiable underlying disorders. The main principles of treatment for AH are to control bleeding, eradicate the inhibitor and treat underlying disorders [11,12].

AHA treatment management will depend on the site and severity of the bleed and patient characteristics. Immunosuppressive agents administered for eradication of inhibitor include corticosteroids and cytotoxic drugs such as cyclophosphamide, azathioprine, 6-mercaptopurine and vincristine [13-17]. We here report the case of a patient referred to our institution for AHA, diagnosed with overt multiple myeloma (MM) five year after AHA onset, with a long-lasting response to factor FVIII autoantibodies after specific treatment for the underlying Multiple Myeloma.

Case Presentation

In October 2008, a 59 year old woman was admitted to our hospital because of a large spontaneous hematoma in her right arm. Blood testing revealed significant prolongation of the aPTT. AHA was than suspected and confirmed by reduced coagulation factor VIII activity (FVIII: c=12%) and presence of inhibitor (70 BU). Patient history was negative for any known bleeding disorder or previous surgical procedures. Complete blood cells count showed a mild microcytic anemia (hemoglobin= 97 g/L, MCV=76fL, ferritin=3 mcg/L). Total body CT scan and laboratory tests, including serum electrophoresis, kidney and liver function, oncological serum markers, HBV, HCV, HIV, autoimmune parameters, were all unremarkable.

The patient was treated with activated prothrombin complex concentrate (APCC) to control the bleeding symptom and received therapy with steroids (prednisone at the dosage of 1 mg/kg/day), to eradicate inhibitor. She was discharged after 15 days with normal aPTT and FVIII: c levels were observed. Steroids treatment was administered up to six weeks after diagnosis. In August 2012, the patient was again admitted to our Unit for a hematoma in her right arm. Coagulation profile showed a prolonged a-PTT (68 sec), reduced coagulation Factor VIII (FVIII: c= 8%) and high titer inhibitor (31 BU). She was started on APCC and Rituximab (375 mg/m2) with 4 doses weekly, followed by a restoration of normal FVIII: c levels and persistently not detectable inhibitor. In August 2013, she had a new AHA relapse with hemarthrosis on right knee and FVIII () and inhibitor (). At that time, serum protein electrophoresis showed a monoclonal band in the gamma region. Serum albumin level was 3.36 g/dL, IgG was 1550 g/dL, IgA 96 g/dL, IgM 20 g/dL. In addition an IgG lambda chain paraprotein was identified by immunofixation of serum. Liver and kidney function parameters, serum calcium and lactate dehydrogenase levels were within normal ranges.
The serum beta2 microglobulin level was……. X-ray films of the bones did not reveal lytic areas. Bone marrow aspiration showed normal cellularity, with 20% plasma cell infiltration. The patient was than diagnosed with IgG-lambda multiple myeloma (Durie-Salmon stage II A) associated with acquired FVIII inhibitor. Chemotherapy treatment of MM was promptly administered with VMP (bortezomib, melphalan and prednisone). During the first cycle of chemotherapy, the patient experienced hemoperitoneum with severe anemia requiring blood transfusion and a combined antihemorrhagic treatment with bypassing agents (recombinant activated Factor VII and APCC).After four cycles, VMP treatment was discontinued for gastrointestinal toxicity (WHO grade 3). The patient achieved a very good partial response. Coagulation parameters returned normal by the end of the first chemotherapy (a-PTT=32s, FVIII: C=110%, not detectable inhibitor). At the last available follow-up, 24 months after chemotherapy, the patient had undetectable M component and normal coagulation parameters.

**Discussion**

Underlying malignancy is diagnosed in approximately 10% of cases of acquired hemophilia [9–11]. In the majority of cases, malignancy is predated, or diagnosed concurrently with AHA.

The association between the occurrence of neutralizing antibodies to factor VIII and hematological malignancies is well known [11,12]. Among the hematological malignancies, lymphoproliferative disorders are most frequently associated with AHA but the occurrence of acquired FVIII inhibitor associated with plasma cell disorders is quite rare. Up to date, only five cases of AHA associated with MM or monoclonal gammapathy of undetermined significance have been reported [7,8], the first in 1965 [13]. The patient developed factor VIII inhibitor one year and half after the diagnosis of MM without serious bleeding. Sallah et al. [14] reported the first patient with MM who presented with acquired FVIII inhibitor and manifested gastrointestinal hemorrhage and soft tissue ecchymosis. Muzaffar et al. [9] described a life-threatening hemorrhage secondary to AHA in a patient with MM in complete remission. Recently, Holme et al. [15] described, in a case series, the history of a patient with MGUS concurrently diagnosed with AHA because of postoperative bleeding.

In the reported case, the presence of FVIII inhibitor occurred early before over TMM diagnosis, as a paraneoplastic phenomenon reminding the well known association between autoimmune hemolytic anemia (AIHA) and lymphoproliferative disorders. The main principles of treatment for AHA are to control bleeding and to eradicate the inhibitor. To cure AHA is, however, mandatory to rule out any underlying disorder and treat it [11,12,16,17]. In the current case, we documented a long-lasting response of AHA by treating MM, without the need for any additional eradication therapy. In conclusion, in patients presenting with severe bleeding secondary to AHA, clinicians should be alert for underlying rare neoplastic diseases such as MM. Chemotherapy might be applicable for the eradication of FVIII inhibitor in patients with MM who have no active bleeding.

**References**


