Acquired Haemophilia Complicated with Gastrointestinal Bleeding and Spontaneous Iliopsoas Muscle Haematoma in a Woman with Chronic C Hepatitis under Treatment with Pegylated IFN alpha 2a and Ribavirin

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Abstract

Acquired haemophilia A is a very rare condition due to the production in adult life of antibodies which inactivate factor VIII. Unlike congenital haemophilia A, both sexes can be affected in the acquired forms. Diagnosis is based on the finding of a low factor VIII associated with the presence of a time dependent inhibitor in the plasma. The isolated prolongation of activated partial thromboplastin time (APTT) does not normalize after the addition of normal plasma. The condition is underestimated, diagnosis being difficult or mistaken for other acquired bleeding disorders such as disseminated intravascular coagulation. More than 50% of cases are idiopathic but underlying conditions include: autoimmune diseases, malignancy, pregnancy, infections and drugs (in particular, antibiotics, psychiatric, immunomodulating drugs, etc). The development of these inhibitors in association with antiviral therapy or chronic hepatitis C is poorly understood and extremely rare [1, 2]. To our knowledge, so far, few cases have been reported in the literature, starting with 2005 [3-7].

Case presentation

A 55 years old woman, working as a medical nurse, was diagnosed with active chronic viral C hepatitis in 2007. She had no personal or family history of haemorrhagic disorders. Before initiating the antiviral treatment, liver enzymes, complete blood count, coagulation tests (INR, APTT, Howell time) and immunoglobulin levels were all normal; the viral load was of 76,926 IU/ml, and liver biopsy showed a Metavir score of A2 F2.

The antiviral treatment - Pegylated α2a interferon (IFN) 180 micrograms/week, ribavirin 1g/day - was started in December 2008. In March 2009, the viral load was not detectable, the patient had no hemorrhagic syndrome and laboratory tests were normal. In May 2009 she presented mild gingivorrhagia, followed by extensive ecchymosis and mucosal purpura. In June-July 2009, the APTT values progressively increased. At the end of June 2009, the antiviral treatment was stopped. In July 2009, the patient was admitted to our service presenting a severe haemorrhagic
syndrome consisting of heavy bleeding at the insertion site of venous catheters (one central and multiple peripheral venous catheters), gingivorrhagia, haematuria, conjunctival purpura. The patient did not present articular haemorrhage. Due to the prolonged APTT, an acquired coagulation factor deficiency was suspected and blood tests were supplemented. Coagulation tests showed an APTT of 80.9 sec (significantly prolonged and not correcting with addition of normal plasma), normal INR, fibrinogen, platelets count and negative D-dimer test; factor VIII level -1%, factor VIII antibodies in titre of 30 Bethesda Units, von Willebrand factor - 73%.

Intensive treatment was started with high dose haemostatic agents: rFVII (Novoseven), FEIBA (factor VIII Inhibitor Bypassing Activity), factor VIII, adrenostazin, cryoprecipitate, fresh frozen plasma, vitamin C. Immunosuppressive therapy was also started: corticotherapy, cyclophosphamide, high dose intravenous immunoglobulins. Prophylactic antibiotics and gastric protection with proton pump inhibitors was also started.

The patient presented limited episodes of melena and rectorrhagia. Gastrointestinal endoscopy was not repeated because of the poor general status and the high risk of bleeding at any invasive procedure. Pretreatment upper endoscopy had been normal and the patient was known to have haemorrhoids. On 7th August, the patient presented moderate pain at the right inguinal region. Emergency computed tomography was performed showing the presence of a right iliopsoas muscle haematoma (Fig. 1). Hemoglobin values oscillated during the hospital stay, with a drop to 10.22 g/dl when the iliopsoas haematoma was diagnosed.

Under intensive treatment, the evolution was slowly favourable. The patient was discharged in September 2009. Her state was improved with no haemorrhagic episodes. Cutaneous purpura was still present but in progressive regression. Laboratory tests were normal except a prolonged APTT (62.2sec). The patient was discharged, corticotherapy, cyclophosphamide, high dose intravenous immunoglobulins. Immunosuppressive therapy was continued at home. 

After discontinuing progressively the corticotherapy in November 2009, a spontaneous oral haematoma (palate and right tonsil) occurred. Immunosuppressive treatment (methylprednisolone and cyclophosphamide) and rFVII substitution (14 days) were restarted. Immunosuppressive treatment was stopped in July 2010, when the clinical evolution was favourable and the APTT normalized. Antiviral therapy was not restarted.

Based on clinical and laboratory data, the established diagnosis was of acquired haemophilia type A in a patient with chronic viral C hepatitis and antiviral treatment.

**Discussion**

Acquired haemophilia is idiopathic in more than 50% of cases [1]. The first case of acquired haemophilia in a patient with chronic viral C hepatitis under IFN therapy was reported in 2005 [4]. Few cases have been reported afterwards, but increased evidence for the rare but possible association between acquired haemophilia A and IFN therapy administered as treatment for hepatitis C virus infection has been gathered [5-7]. There have also been reported cases of acquired haemophilia following IFN therapy for Hodgkin disease [8], multiple sclerosis treated with autologous haematopoietic stem cell transplantation [9] and chronic myeloid leukaemia [10]. The causal relationship is debatable: it is possible that chronic HCV infection itself, which has been associated with immunological disorders, is responsible for the phenomenon, but also the immunomodulating effects of IFN alpha may also contribute to this rare disorder [1-3, 11]. This case, as well as those reported in the literature, suggest that the APTT should be regularly checked in patients treated with IFN therapy, especially in cases of unexplained bleeding, even in the presence of other possible causes (thrombocytopenia, etc). If the bleeding is prolonged, coagulation factor levels as well as antibodies testing are mandatory.

Treatment of acquired haemophilia involves two directions: haemostatic agents and immunosuppressive therapy. Immunosuppressive therapy is mandatory in order to suppress production of the underlying inhibitory antibody. The usual immunosuppressive therapy involves prednisone associated with cyclophosphamide. Azathioprine is an option in women of child bearing age [11-13]. In recent years, anti CD20 monoclonal antibodies such as rituximab have been used with good results, but the condition is considered an off label indication [12, 13]. In patients with active viral C infection, immunosuppressive therapy remains a problem. Currently, due to the rarity of this diagnosis, therapeutic indications are based on expert opinions and the clinical aspect. In our patient, the viral load was not detectable before initiating immunosuppressive therapy. Immunosuppression was mandatory due to the lack of clinical improvement with haemostatic therapy alone as well as the high lethal risk caused by diffuse bleeding. In a recently reported case, immunosuppressive therapy was initiated with good results after obtaining a sustained viral response at the antiviral therapy [5].

**Conclusion**

Though rare, acquired haemophilia should be considered...
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in the differential diagnosis of any coagulopathy, especially in the presence of an isolated prolongation of APTT. The development of coagulation factors inhibitors in association with antiviral therapy for chronic hepatitis C is extremely rare and poorly understood, but particular attention should be given to HCV infected patients under treatment in the presence of a worsening coagulation disorder, even if other possible causes coexist.

References