



Case report: An acquired hemophilia A revealing a rheumatoid arthritis.

Abstract:

Acquired hemophilia A (AH) is a rare autoimmune haemorrhagic disorder. It occurs secondary to the appearance of anti-factor VIII autoantibodies. The hemorrhagic manifestations are sometimes very serious, noisy and brutal in a patient with no personal or family history of hemorrhagic disease.

A regular monitoring should be provided to detect the occurrence of associated neoplasia (leukemia, lymphoma, solid carcinoma, ...). Its association with RA remains a rare entity but should be kept in mind.

We report here the case of a patient in whom acquired hemophilia revealed RA.

Introduction :

Acquired hemophilia A (AH) is a rare autoimmune haemorrhagic disorder. It occurs secondary to the appearance of anti-factor VIII autoantibodies (inhibitors). The disease remains exceptional since its annual incidence does not exceed 1 to 2 cases per million inhabitants. [1]

Its incidence increases with age and exceptionally occurs in children. In adults, there are two frequency peaks: one in young women where acquired hemophilia occurs in the postpartum and the other in patients over 60 years old, the sex ratio is 1/1. [2]

In the most recent literature, the hemorrhagic mortality is estimated to 3% in the EACH2 register and 3.3% in the French study SACHA, but the total mortality is more than 30% due to the comorbidities or infectious complications [3].

The hemorrhagic manifestations are sometimes very serious but very different from the hemorrhagic manifestations found in constitutional hemophilia. It is most often a noisy and brutal haemorrhage in a patient with no personal or family history of hemorrhagic disease. The most common clinical manifestation is the appearance of diffuse bruises all over the body, but there may also be mucous bleeding like epistaxis, deep hematomas or even hemorrhages of the central nervous system, sometimes hemarthroses or even digestive hemorrhages. In 28–50% of cases there is multiple bleeding in these patients, recurrent in the third of these cases. [4-5]

The diagnosis of acquired hemophilia A should be evoked in front of any isolated prolongation of the activated partial thromboplastin time (APTT). On the other hand, the diagnosis is confirmed by the drop in Factor VIII activity of less than 30% associated to the presence of anti Factor VIII antibodies according to the Bethesda method. In addition, the

occurrence of this disease requires a search for associated diseases including autoimmune diseases, neoplasia, postpartum, infections, iatrogenic causes. In 50% of cases, the etiological investigation is negative. Only few cases of the association of acquired hemophilia with rheumatoid arthritis (RA) are published.

We report here the case of a patient in whom acquired hemophilia revealed RA.

Case report:

We report the case of a 58-years-old male, with 6 years history of controlled type 2 diabetes mellitus treated with gliclazide 30mg/day, a 5 years history of hypertension, treated with a combination of Irbesartan and amlodipine, and a coronary angioplasty was performed one year ago at clopidogrel currently.

The patient also reports a chronic inflammatory arthralgia in the small joints (proximal interphalangeal and metacarpophalangeal joints) for 8 months subsided with paracetamol.

The patient was admitted in the emergency department for digestive hemorrhage made of important rectorrhagia and melaenas. The clinical examination has found diffuse abdominal and thigh bruises and a macroscopic hematuria.

The biological assessment revealed a low hemoglobin level at 3.8 g / dl, platelets at 262000 / mm³, normal pro thrombin time, elongated Activated partial thromboplastin time (APTT) at 102 seconds. After stabilization, the patient underwent an oeso-gastroduodenal fibroscopy with a colonoscopy and a video capsule showing no active bleeding.

The blood level of coagulation factors showed a collapse of the activity of factor VIII (1%) with the presence of circulating antibodies (inhibitors) at 22 Bethesda units (BU)/ml. The patient had benefited from a 7-days cure of bypassing treatment (recombinant activated factor VII), with partial clinical improvement, regression of digestive haemorrhage and persistence of the macroscopic hematuria.

Then a corticosteroid treatment at a dose of 1 mg / kg / day of prednisone was initiated with good outcome, regression of the symptomatology and improvement of the general condition.

Throughout the follow-up, the patient had a stable hemoglobin levels with a correct hemostasis balance, and the corticotherapy was withdrawn gradually.

One year later, the patient was admitted again in the emergency department for a hemorrhagic syndrome revealed by a sudden onset intracranial hypertension syndrome associated with memory impairment, disturbance of consciousness with right hemiparesis.

The brain MRI revealed a left temporal subacute hematoma associated with intraventricular hemorrhage, small left lenticular hematoma and some sequential ischemic vacancies.



The patient received 1g/day pulses of methylprednisolone for 3 days, followed by a corticosteroid therapy (1mg/kg/day) with good clinical response.

The etiological investigation in search of associated diseases had revealed:

- o chest x-ray: Normal
- o tumor markers suggestive of paraneoplastic origins: Negative.
- o thoraco-abdominopelvic tomography scan: Normal.
- o Immunological assessment: Negative anti-nuclear antibodies with Anti CCP strongly positive (300UI/l).
- o X-ray of the hands: pinching of the proximal inter phalangeal joints with respect of the distal inter phalangeal joints and bilateral carpalitis.



Thus, the diagnosis of hemophilia A acquired on rheumatoid arthritis was retained, and the therapeutic management consisted in establishing a basic treatment for RA based on methotrexate at 10mg/week and the prevision of initiation biotherapy based on Rituximab.

The last biological control revealed a hemoglobin level at 14.4 g/dl with a APTT at 30 sec/ 30 sec of the witness.



Discussion:

We report the case of a patient with acquired hemophilia A. Our case is in agreement with the data of the literature on several points: the sudden revelation, the collapse of the activity of factor VIII to 1%, the presence of auto antibodies anti factor VIII, and the good response to corticotherapy. [5-6]

However, there were some points where our observation differs significantly from the results of the literature: the age of our patient is 58 years, while in the literature the age is over 70 years old (post-partum AH excluded). [6]

Acquired hemophilia A remains a fatal disease. To date, only age (> 65 years) and the presence of an underlying disease (excluding postpartum) seem to be factors of poor survival prognosis. It has already been shown that FVIII and the anti-FVIII levels are correlated neither with the severity of the clinical picture nor with mortality.

Acquired hemophilia is considered idiopathic in about 50% of cases, and associated with another disease (neoplasia, autoimmune disease) or pregnancy in other cases. However, the association of AH with old RA is rare.

In the European register carried out in 11 countries representing the largest world cohort (register EACH2: European Acquired Hemophilia 2), between 2003 and 2009, including 235 women and 266 men with an average age of 74 years; Fifty-two percent of cases were considered as idiopathic, 13% associated with autoimmune pathologies (rheumatoid arthritis in a third of cases), 12% with cancer and 8% in the postpartum period. [8-9-10]

The first-choice treatment:

The choice of background therapy is not standardized. In the French EACH2 study, until 2006–2007, patients were treated (unless contraindicated or postpartum) by corticosteroid – cyclophosphamide combination. The initial treatment decision appeared to be related only to the habits of the prescribers and the prescription period. The frequency of infectious complications in these elderly patients had led to a reduction in management, reserving cyclophosphamide for failures of corticosteroids alone. [11-12-13]

However, the prescription of bypass agents is reserved exclusively for situations of severe active hemorrhagic syndrome.

Second line treatment: rituximab

Most reviews and recommendations indicate that rituximab is the alternative of choice if first-line treatment fails. [14-15-16-17]

Rituximab is a hybrid murine / human monoclonal antibody specifically directed against the surface antigen CD20 of B lymphocytes. Its immunosuppressive effect aims to block the synthesis of immunoglobulins and, therefore, of **autoantibodies directed against FVIII**.

The usual regimen involves administering weekly doses of 375 mg / m² / week for 4 weeks.

Rituximab requires several weeks or months to achieve eradication of the inhibitor. In an analysis of 42 previously published cases, 78% of cases had a positive response regardless of whether other immunosuppressive agents have already been used.

A response rate of 60% has been described, higher in patients treated with rituximab and other immunosuppressive drugs in combination compared to monotherapy. [18]

In the EACH2 register, rituximab was not more effective than steroids (77% versus 61%), and the time to remission was higher (median 32 days versus 64 days). [19]

According to EACH2, the relapse rate in subjects treated with rituximab seems to be lower than with steroids plus cyclophosphamide or steroids alone (4%, 14% and 19% respectively). Rituximab 100 mg / m² allows to get a satisfying experience.

briefly, large prospective randomized trials would be necessary to determine the actual performance of rituximab in terms of efficiency and safety in order to define its use as a first-line treatment.

Other therapeutic alternatives:

Other drugs have been used occasionally, mainly immunosuppressors and cytotoxics, such as azathioprine, cyclosporine, mycophenolate, tacrolimus, cladribine, vincristine or polychemotherapy according to the CVP scheme (cyclophosphamide, vincristine, prednisone) or tocilizumab [20-21]

The Medical literature is scarce. Its use would be limited to the failure of the first 2 lines.

Conclusion

HA is a fatal disease for which rapid diagnosis and initiation of the treatment is essential. A brutal cutaneous or mucous bleeding associated with a prolongation of activated partial thromboplastin time (APTT), must call up the diagnosis.

Its association with RA remains a rare entity but should be kept in mind.

A regular monitoring should be provided to detect the occurrence of associated neoplasia (leukemia, lymphoma, solid carcinoma, ...).

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