Targeting Acquired Hemophilia A with Rheumatoid Arthritis by a Rituximab Shot: A Case Report and Review of the Literature

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Patient: Male, 66
Final Diagnosis: Acquired hemophilia A
Symptoms: Polyarticular flare
Medication: —
Clinical Procedure: —
Specialty: Rheumatology

Objective: Challenging differential diagnosis
Background: Acquired hemophilia A (AH) is a rare hemorrhagic diathesis, characterized by the presence of autoantibodies directed against the pro-coagulant activity of factor VIII. It is associated with rheumatoid arthritis (RA) in 4% to 8% of cases and its prognosis remains severe.

Case Report: A 66-year-old patient has been followed up for 20 years for deforming and severe RA, which was in low-disease activity. However, the patient presented a polyarticular flare involving the metacarpophalangeal and the proximal interphalangeal joints, the left elbow, and the right knee, which was warm and swollen. Articular puncture of this knee yielded a hematic fluid that did not coagulate. Its cytological analysis showed significant presence of red blood cells, which were also abundantly present in the other cell lines. Activated partial thromboplastin time was lengthened and not corrected by the addition of control plasma. Prothrombin time (Quick’s test), fibrinogen level, and vitamin K-dependent factors were without abnormalities. In contrast, factor VIII was collapsed at 7% and the anti-factor VIII antibody was positive. The diagnosis of AH with anti-factor VIII inhibitor was thus retained. With regard to RA, the Disease Activity Score was 6.32 and exhibited a very active RA. Rituximab with methotrexate was begun and the evolution was favorable. After 6 months, the reappearance of the anti-factor VIII inhibitor was found, thus justifying a second cycle of rituximab.

Conclusions: AH is not exceptional in RA. Rituximab remains a relevant alternative for managing simultaneous AH with inhibitor and RA.

MeSH Keywords: Arthritis, Rheumatoid • Biological Therapy • Hemophilia A

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**Background**

Acquired hemophilia A (AH) is a rare hemorrhagic diathesis characterized by the presence of autoantibodies directed against the pro-coagulant activity of factor VIII [1]. Moroccan epidemiological data on acquired hemophilia are not currently available, but its overall annual incidence is about 1–4 per million inhabitants, with an average age of 75 years and without any sex predominance [2]. Its pathogenesis is poorly understood and its prognosis remains severe [3,4]. Indeed, AH always surprises, and kills in 5–15% of cases [2]. It is considered idiopathic in 60% of cases, is associated with autoimmune disease in 20% of cases, and with rheumatoid arthritis (RA) in 4–8% of cases [5]. It may be associated with neoplasia, lymphoproliferative syndrome, pregnancy, or multiple transfusions [6]. It usually occurs in older forms of RA, with no association with cause, activity, or severity [7]. The hemorrhagic syndrome is abrupt, sometimes confusing, and can occur without a history of coagulopathy [8]. Acquired hemophilia constitutes a therapeutic emergency that can be rapidly evoked in the presence of any hemorrhagic syndrome in a context of autoimmunity [9]. Here, we report the case of a patient treated for rheumatoid arthritis who presented with hemorrhagic syndrome in the context of acquired hemophilia with an anti-factor VIII inhibitor.

**Case Report**

Our patient was a 66-year-old man who was a 30-pack-year long-time tobacco-smoker who quit smoking 10 years ago, and with a 25-year history of Leo Buerger disease, currently in remission. He had been followed up for 20 years for deforming (Figure 1) and severe RA (Figure 2), with positive rheumatoid factor and anti-cyclic citrullinated peptide [Anti-CCP]. He had a destructive rheumatoid arthritis, with no systemic impairment, but with an important functional deterioration (difficulty eating, holding a glass, and walking). RA was in low-disease activity at 20 mg daily of leflunomide and 5 mg of prednisone per day. However, the patient presented a polyarticular flare involving the metacarpal-phalangeal (MCP) and the proximal inter-phalangeal (PIP) joints, the left elbow and the right knee were warm and swollen on clinical examination, and with spontaneous ecchymotic patches. There were no other extra-articular signs. The general condition was maintained and there were no symptoms of an infection. The articular puncture of this knee yielded a moderate amount of hematic fluid that did not coagulate (Figure 3). Cytological analysis did not show any abnormalities except for a significant presence of red blood cells, which was also found abundantly in the other cell lines. There were no microorganisms or microcrystals. This hemarthrosis suggested a synovial local disease (e.g., villonodular synovitis or synovial angioma). However, in the presence of spontaneous bruising, a general disorder was suspected, especially an acquired abnormality of hemostasis including thrombocytopenia, thrombopathy, capillary fragility secondary to long-term corticosteroid use, a deficit in factor II, V, VII, IX, and X in the context of hepatocellular insufficiency caused by leflunomide, or hypo-avitaminosis K, and finally, acquired hemophilia through the presence of a circulating anticoagulant; while noting the absence of trauma or taking an anticoagulant. The imaging of the knee did not

![Figure 1. Rheumatoid arthritis with ulnar deviation of the metacarpal-phalangeal joints, button hole deformity, and swan neck deformity.](image-url)
detect synovial anomalies. Platelet and leukocyte levels were normal in the blood count, which nevertheless revealed hypochromic and microcytic anemia at 10.6 g/dL of hemoglobin, originating from an iron deficiency. Activated partial thromboplastin time (APTT) was lengthened to 49 s (normal range 25–35 s) and not corrected by the addition of control plasma. However, prothrombin time (Quick’s test), fibrinogen level, vitamin K-dependent factors, and hepatic function tests were without abnormalities. In contrast, factor VIII was collapsed at 7% and the anti-factor VIII antibody was positive at 19 Bethesda Units (BU)/mL. The diagnosis of acquired hemophilia A with anti-factor VIII inhibitor was thus retained. However, the patient had never presented extensive mucosal cutaneous hemorrhages such as epistaxis, gingivorrhagia, or hematuria, nor was there a history of melena or another digestive bleeding. The anti-nuclear ac was negative and the pelvic thoraco-abdominal computerized tomography scan for other sites of

Figure 2. X-ray of the hands showing erosive rheumatoid arthritis with carpal bones involvement and metacarpal-phalangeal joints space narrowing.

Figure 3. Spontaneous ecchymotic patches with a hematic articular fluid at the articular puncture.
bleeding or lymphoma was normal. Tumor markers suggestive of para-neoplastic origin were negative. With regard to RA, the C-reactive protein (CRP) was 26 mg/L and the erythrocyte sedimentation rate was 45 mm/1st hour. The Disease Activity Score (DAS28,RF) was 6.32 and exhibited a very active RA. The patient was given 240 mg of methylprednisolone in bolus IV infusion for 3 days combined with a recombinant active factor VII infusion (initial dose of 90 µg/kg body weight every 3 h by an electrically operated syringe pump). The dose of 90 µg/kg was given every 12 h for 12 days until factor VIII was normalized. Rituximab was introduced according to the therapeutic modalities of RA at a dose of 1 g by giving 2 infusions at 2-week intervals to better control both the severely progressive RA and acquired hemophilia. Simultaneous with in eradicating the inhibitor, the patient was given methotrexate at 20 mg per week combined with 7.5 mg of prednisone, which could be gradually lowered to 4 mg/day after 6 months. A regular follow-up was recommended to assure optimal therapeutic compliance. The patient was seen at the consultation every 2 weeks for 3 months, then once every month. Our patient was warned about the severity of his hematological pathology and that he had to immediately go to the hospital if he experienced any abnormal symptoms and he was given the phone numbers of the attending physicians. The evolution was favorable. After 6 months of treatment with rituximab, factor VIII was 75% and the RA was in remission (DAS28,RF=2.3). However, the reappearance of the anti-factor VIII inhibitor was 8–11 BU/mL, thus justifying a second cycle of rituximab.

**Discussion**

Acquired hemophilia A is a rare non-hereditary hemorrhagic disease and a therapeutic emergency that usually occurs in older RAs [10]. It is diagnosed in 90% of cases before a hemorrhagic syndrome and in 10% of cases on an isolated prolongation of the APTT [11].

Our patient, followed up for an RA evolving over 20 years, had been a 30-pack-year smoker, which undoubtedly triggered the Leo Buerger disease currently in remission. The involvement of tobacco in RA pathogenesis is well established [12,13]. However, a causal relationship between tobacco and the occurrence of acquired hemophilia has not been found in the literature. Some drugs may induce AH (e.g., penicillin, methyldopa, and phenytoin) [14,15]. Our patient was on leflunomide, which has immunomodulatory properties and remains an effective and tolerated conventional disease-modifying anti-rheumatic drug (DMARD) for RA [16–18]. However, there is insufficient data on the involvement of leflunomide in the production of anticoagulant inhibitors. The patient’s disimmune profile due to the RA was probably the main cause of the development of AH, regardless of the drugs administered [9].

In our patient, the ecchymotic patches facing the knee led us to suspect hemorrhagic arthritis, which prompted us to perform an articular puncture. However, in the case of any RA flare, a puncture of the articular fluid, especially of a large joint, is always recommended, so as not to neglect an infectious etiology or a hematological abnormality [19].

A problem encountered in acquired hemophilia is the anticipation of a massive fatal hemorrhage [2,6]. For this reason, our patient received recombinant activated factor VII (rFVIIa), a pro-hemostatic agent originally developed for the treatment of alloimmune hemophiliacs [20], as well as a bolus of methylprednisolone to better contain the inflammatory reactivation of RA [21]. Indeed, rFVIIa induces hemostasis independent of the presence of factor VIII and IX by forming either complexes with tissue factor (TF) whose expression is stimulated by tissue aggression or by directly activating the factor X at the surface of the activated platelets located at the site of the lesion, independent of the TF [22]. Thus, rFVIIa allows generation of thrombin and hemostasis targeted at the hemorrhagic site [23]. The efficacy and safety of rFVIIa in hemophilia with inhibitors have been demonstrated in several clinical studies [24–27]. Studies show that rFVIIa is effective in 80–90% of cases at a dose of 90 µg/kg body weight in a bolus IV infusion, repeated at 60 to 120 µg/kg 2–3 h later. The interval between doses can be gradually increased (from 4 to 12 h) as long as necessary [20,24,26].

It is also imperative to introduce an appropriate immunosuppressive treatment to eliminate the inhibitor in order to achieve complete remission, which is defined by normal factor VIII activity with an undetectable inhibitor [28–30]. The sustained response is considered to be maintained if the inhibitor is less than 0.6 BU/mL and the activity of factor VIII is greater than 50%, whereas partial remission is established by an inhibitor titer of less than 5 BU/mL and a factor VIII activity of 30% [31].

Freire et al. [32] suggested a 3-cycle treatment at 21-day intervals, with 700 mg/day of methylprednisolone, 2 cycles of 25 g immunoglobulin, and 500 mg of cyclophosphamide. Factor VIII (FVIII) was introduced from the start at 1250 IU every 12 h for 15 days. However, human FVIII replacement is not effective in the presence of high titer inhibitors [33]. If used in patients with lower titers (<5 BU/mL), the dose must be increased sufficiently to overcome the inhibitor. Especially for patients in geographic locations where other hemostatic alternatives are not readily available, human FVIII replacement could be a sufficient first-line therapy and has proven effective in some patients [34]. Other treatment regimens, including corticosteroid therapy, immunosuppressants, immunoglobulin, and coagulation factors having a factor VIII inhibitor short-circuiting activity, have been reported [10,31,35–37]. The results were often favorable, but a few deaths were reported, which were mainly
due to the comorbidities associated with AH rather than the hemorrhagic syndrome.

Our patient presented active and severely progressive RA despite the correct intake of leflunomide, which justified switching to biologic DMARDs [38,39]. Anti-tumor necrosis factor (TNF) α antibody therapies, if effective for RA, can cause fatal hemophilia in some cases [40,41]. The first-choice treatment in our case was rituximab (anti-B cells therapy), as its efficacy and safety in acquired hemophilia and RA are widely demonstrated [42–47]. Indeed, the aim of the treatment was to target the B lymphocyte secreting the anti-FVIII inhibitor, the rheumatoid factor, and the anti-CCP [48].

Although cyclophosphamide is undeniably recommended in acquired hemophilia immunosuppressive therapy [29,34], it is not a standard treatment for severe, active, and progressive forms of rheumatoid arthritis [38,49,50], and its toxicity is more severe than with conventional DMARDs in RA [51]. It is nevertheless used in uncommon cases of rheumatoid vasculitis, with disparate results [52–54]. Therefore, from the outset we opted for rituximab to hit 2 targets (AH and RA) with 1 shot. Indeed, this anti-CD20 monoclonal antibody is increasingly used as first-line and second-line treatments for the elimination of inhibitors in HA [34].

There is no evidence to support the claim that rituximab alone or in combination with other immunosuppressants results in higher or faster remission rates [55]. However, patients with high levels of inhibitor (>100 BU/mL) should be given a combination of cyclophosphamide and rituximab, whereas patients with a low inhibitor (<100 BU/mL) may respond favorably to rituximab monotherapy [56]. According to the European Register of Acquired Hemophilia (EACH2), stable clinical remission was achieved in 59% of patients (30 out of 51) treated with rituximab. This is a success rate halfway between that obtained with steroids alone (48%) and steroids associated with cyclophosphamide (70%). Nevertheless, some patients resistant to the primary standard immunosuppressant have responded favorably to rituximab [57]. In our patient, we chose a combination of rituximab and methotrexate with immunosuppressive properties and considered it as part of the relevant rheumatoid arthritis treatment [38,39,58]. A low dose of prednisone is maintained but stopping cortisone administration is expected.

Recently, the Hemostasis and Thrombosis Research Society of North America formed a consensus to guide the management of AH-related bleeding [59]. It focuses mainly on the control and prevention of bleeding, eradication of the inhibitor, and treatment of an underlying disease if applicable. Indeed, recombinant porcine FVIII (50–100 U/kg initially) can achieve measurable FVIII levels and hemostasis in AH, even if the human inhibitor is high. Similarly, rFVIIa (70–90 μg/kg every 2–3 h until hemostasis achieved) and activated prothrombin complex concentrate (50–100 U/kg every 8–12 h) are both appropriate first-line bypassing treatments [59].

Although the inhibitor may disappear after a few months, inhibitor eradication by immunosuppressive therapy (IST) is strongly recommended according to this consensus, which is based on corticosteroid alone as the first-line treatment (prednisone 1 mg/kg orally daily ×4–7 days). For a faster response rate than that achieved with steroids alone, but higher adverse event profile, corticosteroid as above can be used in association with cyclophosphamide (1–2 mg/kg orally daily or 5 mg/kg intravenous every 3–4 weeks). Finally, rituximab is not recommended as monotherapy unless another IST is contraindicated. It is administered in combination with corticosteroids at the dose of 375 mg/m² intravenous weekly ×4. It should be noted that both hemostatic and immune therapy impose considerable risks and require close monitoring to ensure safety [59].

Our patient, given rituximab, is in clinical remission that can last 6 months as reported in the literature [60–62]. Indeed, the activity of the B cells after treatment with rituximab was recovered after 6 months of the last cycle of the anti-CD20, even if lymphocyte depletion can spread over 2 years [63]. Thus, the inhibitor may reappear and another cycle of rituximab may be justified [64]. Our patient lived near the hospital and was hospitalized after the first clinical signs. He had a health insurance that allowed him easy access to care and very expensive treatment, but this is not the case for most people in Morocco, which could jeopardize their prognosis in a similar context.

**Conclusions**

Acquired hemophilia A is not exceptional in rheumatoid arthritis. Its evolution is unpredictable and its prognosis can be very serious. Even if its treatment is based on conventional immunosuppressants and hemostatic factors, rituximab remains a relevant alternative for simultaneously managing AH with inhibitor and RA.

**Acknowledgements**

We thank the nurses Abderrazak Adraoui and Rida Nazihi for their precious help in the care of this patient.

**Conflicts of interest**

None.
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