

# Acquired Hemophilia in a Patient With Rheumatoid Arthritis: Case Report and Literature Review

Case Report

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## Abstract

Acquired hemophilia (AH) is a rare bleeding disorder caused by the spontaneous development of autoantibodies against coagulation factors, most commonly factor (F) VIII (acquired hemophilia A, AHA). The clinical manifestation of AHA includes mostly spontaneous hemorrhages into skin, mucous membranes, muscles, soft tissues, or joints. AHA should be suspected when a patient with no history of hemorrhages presents with bleeding and an unexplained prolonged activated partial thromboplastin time. The diagnosis is based on the clinical picture, the presence of low FVIII activity and evidence of FVIII inhibitor. In around half of patients, an underlying disorder (rheumatic diseases, malignancy, infections) or taking some drugs are associated with AHA; the remaining cases are idiopathic. Rheumatoid arthritis is a chronic inflammatory condition, marked by swelling and tenderness of small joints; it is usually treated with steroid and immunosuppressive drugs such as methotrexate, TNF-alpha inhibitors, and other biologic therapies (abatacept, tocilizumab, rituximab).

We presented a patient with rheumatoid arthritis who developed acquired hemophilia A with hemarthroses; starting from this case, we focused on the literature about AHA in rheumatic diseases. We found 35 cases, 15 in systemic lupus erythematosus and 12 in rheumatoid arthritis, while the remaining cases were reported in Sjögren's syndrome, polymyalgia rheumatica, systemic sclerosis, and psoriatic arthritis. Ecchymosis and cutaneous hematomas were the main clinical features while hemarthroses was quite a rare condition, shown in just three patients.

**Keywords:** Acquired Hemophilia; Arthritis, Rheumatoid; Rheumatic Diseases  
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## INTRODUCTION

Acquired hemophilia (AH) is an autoimmune disease caused by the formation of inhibitory autoantibodies against coagulation factors.

These inhibitory autoantibodies (immunoglobulin IgG) neutralize the activation or function or accelerate the clearance of a specific clotting factor [1], mainly FVIII (acquired hemophilia A—AHA), although all the coagulation factors can be involved.

### Why Do we Describe This Case

AH is an underdiagnosed and misdiagnosed disease in the daily clinical practice. It is important to suspect AH in a rheumatic patient with spontaneous hemorrhages with no apparent cause. Due to its potential fatal outcome, AH should promptly be recognized in order to control the hemorrhagic events and eradicate the clotting inhibitor with a strong immunosuppressive treatment

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AHA is a rare but challenging picture due to the frequent delayed diagnosis or inadequate treatment, which contribute to a high mortality rate.

Data from three large cohorts from Australia, South Wales, and UK described an incidence between 1.20 and 1.48 cases per million/year [2-5]. AHA predominantly affects the elderly, but can also be found in younger patients in pregnancy and rheumatic/autoimmune diseases. About half of cases are idiopathic, while the other half is secondary to other conditions: malignancy, autoimmune diseases, pregnancy, medications, infections [6].

The etiology is probably multifactorial: genetic and environmental factors interact in order to cause a loss of the immune tolerance and the formation of the inhibitory antibodies [2].

These ones cause a rapid inactivation of FVIII followed by a slow phase and usually they do not completely inactivate it, in contrast with the congenital form of hemophilia, in which alloantibodies inhibit FVIII in linear proportion to their concentration and in a complete manner. Consequently, the antibody and measurable levels of FVIII in AHA may be found simultaneously in circulation. Moreover, there is just a slight correlation between FVIII level and bleeding severity [2], thus FVIII level cannot be used to identify patients at higher risk.

The diagnosis of AHA is hard and should be made by a Hematological Division with experience in the setting of coagulation disorders. Main features supporting its formulation are spontaneous bleeding events and laboratory investigations pointing to a coagulation disorder.

AHA should be suspected in every patient with abnormal or spontaneous bleeding and coagulation abnormalities, such as prolongation of activated partial thromboplastin time (APTT) with normal prothrombin time (PT) and normal platelet count. AHA can also present just with an isolated prolonged APTT without bleeding events.

A relevant feature of AHA is the difference in the bleeding pattern compared with the congenital form. Bleeding frequently start spontaneously but some episodes can even occur after trauma or surgery. Many potential sites may be involved: subcutaneous or mucosal bleeding [4] are the most common manifestations, followed by muscle bleeding and bleeding in other sites (genitourinary, gastrointestinal tract, retroperitone-

al, intracranial) [7]. Hemarthroses are quite rare, in contrast to the congenital form [4].

Diagnosis should be confirmed by laboratory investigation: the initial step is based on the demonstration of an elevated APTT, not corrected by a mixing study (i.e. incubation of patient plasma with pooled normal plasma (1:1) for 1-2 h at 37°C) [8]. The second step is the demonstration of reduced FVIII activity and evidence of a FVIII inhibitor, estimated with the Bethesda assay [1]. In AHA, FIX and FXI levels can be normal. As underlined by the most recent guidelines presented by the United Kingdom Haemophilia Centre Doctors' Organization (UKHCDO), it is also important to exclude heparin treatment measuring thrombin time (TT) [9].

Data from a large European registry including 501 patients (European Acquired Haemophilia Registry, EACH2) [10] showed an inverse correlation between the inhibitor titer and the residual FVIII activity. Patients who had a bleeding event had a significant lower FVIII activity and higher inhibitor titers at presentation than patient who were diagnosed by abnormal APTT on routine blood test [2,10]. The inhibitor titer or residual FVIII activity are not directly related to the severity of bleeding symptoms or mortality; consequently, the clinician cannot use them as predicting factor, but the titers are common measure to monitor the eradication therapy efficacy [2,10].

Treatment consists on bleeding control on the one hand and on the antibody eradication on the other hand.

It is recommended to immediately start antihemorrhagic treatment in patients with active bleeding symptoms, although small bleeding do not require intervention.

The most common treatment are recombinant factor VII (rFVII) and activated prothrombin complex concentrate (aPCC) [2], which demonstrate an efficacy rate of about 90% [11-13].

The eradication of the inhibitory antibodies is mandatory, independently by the clinical picture severity and is achieved with the use of a strong immunosuppressive treatment.

Corticosteroids (prednisone 1 mg/kg daily), in association with cyclophosphamide or rituximab are the main therapeutic option [6]. Data from the EACH2 registry showed better results in the steroid-cyclophosphamide group than in the steroid-rituximab or in the steroid groups [14]. Therapy should anyway be individualized considering con-

	06/26/2017 (diagnosis)	07/05/2017	08/18/2017	09/01/2017
Hb (g/dl)	9.5	10.9	13.8	13.5
PT (ratio)	1.05	0.98	0.90	0.95
APTT (ratio)	2.49	2.35	1.01	0.89
FVIII (%)	1	6	63	113
FVIII Ab (BU/ml)	22	NA	1	Absent

**Table 1.** Laboratory parameters during therapy.

APTT = activated partial thromboplastin time; BU = Bethesda unit; FVIII = factor VIII activity; FVIII Ab = factor VIII inhibitory antibodies; Hb = hemoglobin level; NA = not available; PT = prothrombin time

comitant disease, general condition and prognostic factors (high inhibitor title).

The FVIII activity usually restores in 5 weeks or more but patients with FVIII activity < 1% at baseline require longer time compared with other patients [6].

Prognosis can be severe due to the fatal bleeding rate, especially those with intracranial or gastrointestinal manifestations. Overall mortality has been estimated in a range between 7.9% and 33% [5,15-17]: age, malignancy and lower hemoglobin levels are poor risk factors [2].

## CASE REPORT

A 76-year-old woman affected by long-standing seropositive rheumatoid arthritis (RA) experienced persistent clinical remission for many years with a combination therapy made by hydroxychloroquine (HCQ, 200 mg/day) and low dose steroid (methylprednisolone, 4 mg/day).

On June 2017, the patient consulted the emergency department (ED) for the development of acute left knee swelling; the arthrocentesis made by a rheumatologist revealed a clear hematic synovial fluid and the X-ray examination excluded any fracture. No history of trauma were reported and no antiplatelet or anticoagulant medications were ever taken.

The patient came back to the ED just few days later, showing large and multiple ecchymosis on both arms and legs, on the abdomen and on both breasts. A Doppler ultrasound revealed a muscular hematoma on the left thigh and preliminary blood tests showed an abnormal APTT (2.03 ratio, normal values 0.80-1.20), thus she was hospitalized into the Hematological Unit for further investigations.

Laboratory tests were as follows: white blood cell count  $10.3 \times 10^9/l$ , hemoglobin level 9.5 g/dl, platelets  $241 \times 10^9/l$ , C-reactive protein 73 mg/l. Renal function was

normal: creatinine 0.8 mg/dl. The blood coagulation study confirmed the elevated APTT (2.49 ratio) with normal PT (1.05 ratio), while further laboratory studies highlighted a low FVIII activity (1%, normal values 50-150) and the presence of an FVIII inhibitor (22 Bethesda units/ml, normal values < 0.5). These data suggested the diagnosis of acquired hemophilia A.

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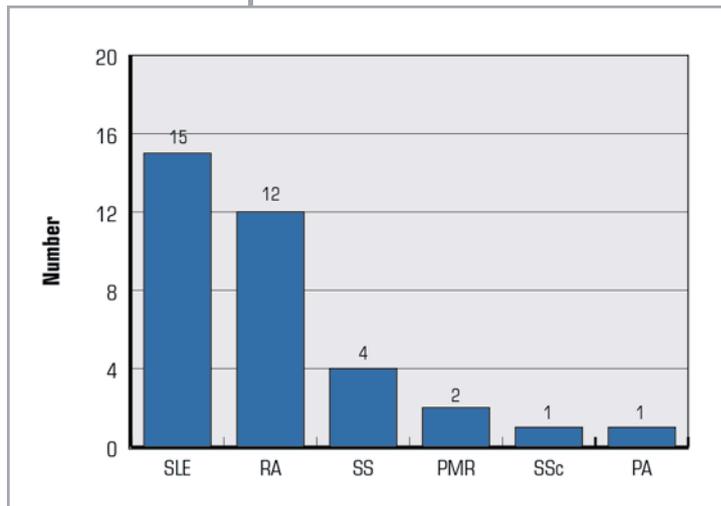
CT total body excluded malignant forms.

The patient immediately started oral prednisone (1 mg/kg, 75 mg/day) and then rituximab few days later ( $375 \text{ mg/m}^2$ , 4 weekly infusions). During the next weeks the ecchymosis and the muscular hematoma slowly regressed and blood tests gradually improved: after one month of steroid and rituximab therapy, hemoglobin level rose to 11.5 g/dl, while APTT was still abnormal (2.11 ratio), turning back to a normal value after another month of steroids. At that time FVIII activity was 63% and FVIII inhibitor antibody title was 1 BU/ml, becoming undetectable few weeks later (Table I).

Prednisone was slowly reduced during the following months while rituximab was not repeated considering the clinical and laboratory improving picture. At the time of the writing (May 2018) the patient is taking just 5 mg prednisone for the chronic treatment of rheumatoid arthritis and no new hemorrhagic events are reported; hemoglobin level and blood coagulation tests are normal.

## DISCUSSION

As mentioned above, acquired hemophilia can occur in a patient with an underlying rheumatic disorder. Other potential causes are: malignancy, pregnancy, infections or



**Figure 1.** Reported acquired hemophilia cases in rheumatic diseases.

PA = Psoriatic Arthritis;  
PMR = Polymyalgia  
Rheumatica;  
RA = Rheumatoid  
Arthritis; SLE = Systemic  
Lupus Erythematosus;  
SS = Sjogren's Syndrome;  
SSc = Systemic Sclerosis

idiopathic forms, which accounts for about half of cases. Using PubMed database, we searched for acquired hemophilia case reports in rheumatic diseases.

We found 35 cases (Figure 1): 15 in systemic lupus erythematosus (SLE) [18-32], 12 in rheumatoid arthritis [28,33-43], 4 in Sjögren's syndrome (SS) [44-47], 2 in polymyalgia rheumatica (PMR) [48,49], 1 in systemic sclerosis (SSc) [50], and 1 in psoriatic arthritis (PA) [51].

Among the 34 publications found (1 publication presented 2 case reports, one in RA and one in SLE):

- 19 were full text available;
- 3 were not full text but abstract available and with sufficient laboratory and clinical data about the case;
- 12 were not full text or abstract available or the abstract was without sufficient laboratory and clinical data about the case.

Among the 23 patients' records available, 18 were women and 5 were men. Mean age was 52.9 years. A higher mean age was evident in RA group than the SLE one, a detection quite predictable considering the natural course of the two diseases.

Factor VIII inhibitor antibodies were present in all cases while factor IX antibodies just in three cases [21,23,44].

The main clinical presentation was ecchymosis/cutaneous hematomas, (19 of 23, 82%) [19-22,24,25,28,29,35-38,40,44,45,48,50,51] followed by muscular hematomas (10 of 23, 43%) [22,23,28,36,37,39,40,44,49,51], the latter mainly in the RA group (Table II). As expected, hemarthroses were quite rare in the literature, described in just two cases, one in RA and

another one in SLE [23,40]. These clinical results reflect other data reported in the literature, first those showed by Knoebel et al. in the EACH2 registry, except for a higher rate of cutaneous involvement (82% versus 53%) [10].

All the hemorrhagic events were spontaneous, with no history of relevant trauma. One patient with SLE experienced intraperitoneal massive hemorrhage due to gallbladder rupture with consequent multiple organ failure and death [30]. Another woman died for massive abdominal wall hemorrhage [37].

RA patients showed disease remission at the time of the hematological diagnosis except for one [39]; two patients were on biological therapy with TNF-alpha inhibitors at the time of the AHA discovery [36,37].

In the SLE group, the connectivity diagnosis was concomitant with the AH one in 5 patients [19-22,29], suggesting a potential role of the disease activity on the inhibitory FVIII antibodies formation. The only systemic sclerosis patient developed AH after autologous hematopoietic stem cell transplantation [50]. A case of AH in SLE during pregnancy was reported [2].

Treatment of AH consists of two essential ways: control of bleeding and elimination of the inhibitor.

In our literature review, 11 patients required antihemorrhagic treatment, which consisted in: factor VIII concentrates, recombinant factor VIIa, FIX plasma concentrate, factor eight inhibitor bypassing activity (FEIBA), or activated prothrombin complex concentrates (aPCC) [20,21,23,25,29,30,35,37,38,40,50].

To eliminate or suppress the activity of the FVIII inhibitor, steroid therapy was the first and essential step, since all patients took it. Oral route was the preferred one.

A variety of immunosuppressive drugs were used in association, proving that many cases don't respond to steroid as monotherapy, especially when inhibitory titers are high. Only one patient reached disease regression with just steroids [20].

Cyclophosphamide was the main immunosuppressant reported, since its administration was observed in 15 patients [20,22-25,28,35-38,40,48,49,51] as first-line treatment or after failure of other immunosuppressive drugs, showing to be effective in 11 of them. Rituximab was another choice, mainly as weekly infusion, as in our case. Six cases reported its use, 3 of them as

Reference	Age/sex	Hemorrhagic feature	APTT (s)	FVIII (%)	FVIII in. (BU/ml)	Hemorrhagic treatment	CS	IS	
1	34	48/F	1	112	5.4	29.9	Yes	Yes	CyC > RTX
2	35	47/F	1,3	84	1	45	No	Yes	CyC > AZA
3	36	78/F	1,3	56	3	22	Yes	Yes	CyC
4	37	78/M	1	115	1	839	Yes	Yes	CyC
5	38	61/F	3	61	NA	2	No	NA	RTX
6	39	71/F	1,2,3	86	1	28	Yes	Yes	IVIG + CyC
7	27	54/F	1,3	91	1	145.6	No	Yes	CyC
8	Current case	76/F	1,2,3	83	1	22	No	Yes	RTX

second choice therapy [20,35,39,45,48,50]; in all those reports, treatment ended with eradication of the inhibitory antibodies and disease control.

Alternative immunosuppressive drugs were cyclosporine [29,30] and azathioprine [19,36,44], while intravenous immunoglobulin were used in association with cyclophosphamide or azathioprine in two patients and as monotherapy in just one, showing however no efficacy [23,40,44].

Table II shows the main characteristics of available papers concerning acquired hemophilia cases with rheumatoid arthritis.

Rituximab is a humanized chimeric anti-CD20 monoclonal antibody initially used for the treatment of some hematological malignancies, mainly lymphomas. Thanks to its specific anti-B cells activity, it is also used in a variety of autoimmune disorders, even rheumatic ones, such as rheumatoid arthritis, granulomatosis polyangiitis, and microscopic polyangiitis.

We chose rituximab in order to use a drug that could be helpful to tackle both AH and

RA, since it is indicated in the treatment of RA [52]. Although both rituximab and cyclophosphamide can induce an immunosuppression condition with a higher infection risk, the rituximab choice was also supported by the patient's fear about bladder complications with cyclophosphamide. In the rheumatological setting, rituximab is usually administered on two different infusions 2 weeks apart (1000 mg × 2), repeated after 6 months. A monthly scheme was preferred in our patient, since the hematological condition imposed a more aggressive treatment than those used in RA. Rituximab therapy is also reported in other cases of AH not related to autoimmune diseases [53-63].

## CONCLUSION

We described a case of acquired hemophilia A in a patient with long-standing rheumatoid arthritis, treated with steroids and rituximab with excellent response. The use of immunosuppressive drugs in associa-

**Table II.** A review of reported acquired hemophilia cases with rheumatoid arthritis.

Hemorrhagic features:

- 1 = cutaneous hematoma/ecchymosis;
- 2 = hemarthroses;
- 3 = muscular hematoma

Hemorrhagic treatments were: factor VIII concentrates, recombinant factor VIIa, FIX plasma concentrate, factor eight inhibitor bypassing activity (FEIBA), and activated prothrombin complex concentrates (aPCC).

- > = switch;
- APTT = activated partial thromboplastin time;
- AZA = azathioprine;
- BU = Bethesda unit;
- CS = corticosteroid therapy;
- CyC = cyclophosphamide,
- F = female; FVIII = factor VIII activity; FVIII in. = FVIII inhibitor;
- IS = immunosuppressive drug; IVIG = intravenous immunoglobulin; M = male;
- NA = not available;
- RTX = rituximab

### Key points

- AH is a potentially fatal condition marked by spontaneous bleeding, mainly ecchymosis, mucosal bleeding, and muscular hematomas
- AH can be idiopathic or associated to an underlying condition such as malignancy, autoimmune disease or pregnancy
- AH develops after the formation of inhibitory antibodies against one or more clotting factor, mainly factor VIII
- Laboratory investigations are mandatory to confirm the diagnosis: rise in APTT, reduced FVIII activity, presence of a FVIII inhibitor
- The therapeutic approach relies on immunosuppressive drugs, mostly high dose steroids associated with cyclophosphamide or rituximab. Use of antihemorrhagic treatment relies on the clinical condition and on the bleeding's severity
- Many rheumatic patients developing AH are described in the literature database, especially SLE and RA patients. We described a case of AHA in a woman with long-standing RA, treated with steroid and rituximab followed by an excellent outcome.

tion with steroids is largely diffuse. Thanks to our clinical case description, we supported the use of rituximab, even as first approach, although its real efficacy is still a matter of debate mainly due to the short literature material available.

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#### Conflicts of Interest

Authors declare they have no competing financial interests concerning the topic of this article.

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