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Acquired hemophilia A treated with rituximab in a 62-year-old female with rheumatoid arthritis: a case-based review

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SUMMARY

Acquired hemophilia A (AHA) is a rare autoimmune disorder with unpredictable hemostasis that is caused by autoantibody formation against coagulation factor VIII. AHA can occur in the context of autoimmune inflammatory rheumatic disorders. Here we report the case of a 62-year-old female with an 11-year history of rheumatoid arthritis (RA) who presented with cutaneous and mucosal bleeding. Activated partial thromboplastin time was prolonged and not corrected by the mixing test. Factor VIII activity was decreased, and the anti-factor VIII antibody was positive. AHA associated with RA was diagnosed. The patient was treated with rituximab 500 mg weekly for 4 doses and prednisolone 10 mg/daily. The patient did not experience bleeding events after treatment, and factor VIII activity and inhibitor normalized. At the end of the article, we discuss similar cases of RA-associated AHA.

Key words: *Acquired hemophilia A, rheumatoid arthritis, rituximab.*

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease with an unknown etiology that is characterized by symmetrical inflammation of the joints. It affects about 0.5-1% of the population, and it is more frequent in women than in men (female-to-male ratio: 3/1). Extra-articular organ involvement, including the heart, lungs, pericardium, pleura, eyes, skin, and hematologic system, also occurs. Previous studies have shown that a hypercoagulation state is prevalent in RA. Pro-inflammatory cytokines disturb the coagulation-fibrinolytic system, and the levels of D-dimer, fibrinogen, and platelet count increase (1). While bleeding disorders are not commonly associated with RA, antibody formation against coagulation factor VIII (FVIII) leads to a disorder with unpredictable hemostasis named acquired hemophilia A (AHA) (2). AHA in the context of RA has been rarely reported, and there is yet no guideline for its management. Through this manuscript, we aim to discuss the reported cases of RA-related AHA to raise awareness of the clinical features and appropriate management of this rare association.

CASE REPORT

The patient is a 62-year-old female who had been diagnosed with seropositive [for both IgM rheumatoid factor and anti-cyclic-citrullinated peptides (118 U/mL normal values <12 U/mL)] RA since 11 years with the symmetrical involvement of the small joints of the hands and feet. She did not have extra-articular organ involvement. The patient presented to the Kermanshah University of Medical Sciences associated rheumatology clinic complaining of a 2-week history of spontaneous cutaneous ecchymosis and gingival bleeding. She denied gastrointestinal bleeding, hematuria, pain or swelling of the joints, and hemoptysis. She did not report a previous personal or familial history of bleeding events. No symptoms of infection were reported. Her past medical history

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included hypertension (HTN) and diabetes mellitus (DM) for about five years. Her drug history included methotrexate (MTX) tablets 10 mg weekly, folic acid 1 mg daily (except the day of MTX), valsartan 160 mg daily, amlodipine 5 mg daily, hydrochlorothiazide 12.5 mg daily, metformin 1000 mg twice daily, sitagliptin 50 mg twice daily, vitamin D 50000 monthly, and meloxicam 7.5 mg as needed. She had never received anti-rheumatic treatments other than MTX, and she had not started any new medication within the last month. No antiplatelet or anticoagulant medications were ever taken. She has not experienced a flare-up of RA in recent years. On the general examination, vital signs were stable. Multiple large ecchymotic patches were observed on the trunk and limbs. Gingivorrhagia was detected in the oral cavity. The rest of the physical examination, including the respiratory, cardiovascular, and musculoskeletal systems, was within normal limits. Initial differential diagnoses included thrombocytopenia, acquired hemostatic abnormality, MTX-induced hepatocellular insufficiency causing coagulation factor deficiency, and vitamin K deficiency.

She was admitted to the rheumatology unit for further evaluation. The laboratory test results were as follows: hemoglobin of 11.7 mg/dL, white blood cell count $7.2\times10^3/mm^3$ (differential count: neutrophils 59%, lymphocytes 34%), platelet count $262\times10^3/mm^3$, creatinine 0.8 mg/dL, fasting blood sugar 180 mg/dL, aspartate transaminase 21 IU/L (normal: 5-40 IU/L), alanine transaminase (ALT) 18 IU/L (normal: 5-40 IU/L), alkaline phosphatase 241 U/L (normal: 64-306 U/L), bleeding time (IVY method) 3 minutes (normal: 3-7 minutes), prothrombin time (PT) 10.2 seconds (normal: 10-13 seconds), activated partial thromboplastin time (APTT) 87 seconds (normal: 28-38 seconds), thrombin time 19 seconds (normal: 17-27 seconds), international normalized ratio 1.1, fibrinogen (Clauss method) 3.32 g/L (normal: 1.5-4.5 g/L), erythrocyte sedimentation rate 37 mm/1st hr and normal C-reactive protein. Serologic tests for hepatitis B and C viruses, human immunodeficiency virus, and tumor markers were negative. An abdominopelvic sonography was performed, and no pathological findings were reported. APTT was prolonged, and it was not corrected by the mixing test (addition of the normal plasma to the patient's plasma). Therefore, the presence of a coagulation factor inhibitor was suspected. The activity of FVIII was decreased (FVIII activity=2%, normal: 50-150). Anti-FVIII antibody was positive at 4 Bethesda units (BU)/mL. Immunological blood tests revealed negative results for antinuclear antibodies, anti-double stranded DNA antibodies, and antiphospholipid antibodies. AHA was diagnosed. Rituximab was administered at a dose of 500 mg weekly for four doses, along with prednisolone 10 mg/daily. High-dose corticosteroids were not administered due to HTN history, uncontrolled DM, and the patient's refusal to receive them. Due to the absence of massive and serious bleeding, there was no need for FVIII concentrates or recombinant activated FVII (rFVIIa). The patient was followed up monthly until 6 months. No major bleeding events happened during the follow-up period. FVIII activity increased gradually to 75% after 6 months. The factor inhibitor level was 1 BU/mL 4 months after treatment and became undetectable after 6 months.

DISCUSSION AND CONCLUSIONS

AHA is a rare autoimmune disorder with unpredictable hemostasis that could be potentially life-threatening due to severe bleeding. Autoantibody formation against coagulation FVIII is its cause. The incidence rate is about 1-1.5 cases per million people each year, which increases with age; the mortality rate is about 20%. There is no gender preference. There are major differences between congenital hemophilia A and AHA, including:

1) the presence of autoantibodies in AHA, and
2) the tendency for cutaneous, mucous membrane, soft tissue, and intramuscular bleeding in AHA instead of intra-articular bleeding.

The diagnosis is mostly delayed due to the absence of a personal or familial history of bleeding events. APTT is prolonged in AHA, while PT is normal. In AHA, the prolongation of APTT is not corrected by the mixing test due to the presence of an FVIII inhibitor. The possible causes are pregnancy, medications, autoimmune disorders, multiple transfusions, lymphoproliferative disorders, and other neoplasms. In the majority of cases, the exact cause remains unknown, and AHA is considered idiopathic. The autoimmune disorders associated with AHA include systemic lupus erythematosus, RA, multiple sclerosis, temporal arteritis, Sjögren syndrome, autoimmune hemolytic anemia, Goodpasture syndrome, adult-onset Still's disease, diabetes mellitus, and autoimmune thyroid diseases. The treatment is focused on the control of acute bleeding and long-term treatment to decrease the concentration of the autoantibody against FVIII. Preferable treatments for the bleeding episode depend on the titer of the FVIII inhibitor. Treatment for patients with a low titer of inhibitor (<5 BU/mL) includes human FVIII concentrates and desmopressin. Treatment for patients with a high titer of inhibitor (>5 BU/mL) includes porcine FVIII concentrates, activated prothrombin complex concentration (aPCC), and rFVIIa. Therapeutic plasmapheresis and intravenous immunoglobulin induce a temporary reduction of the FVIII inhibitor. Immunosuppressive agents include corticosteroids, cyclophosphamide, rituximab, azathioprine, *etc*., leading to a long-term reduction of the FVIII inhibitor (2-6). While high-dose corticosteroids are a good first-line treatment option with acceptable efficacy and safety, they were not prescribed to our patient due to uncontrolled DM and the patient's refusal.

Here we reported a case of AHA in a 62-year-old female with RA who was treated with rituximab. As we mentioned, common etiologies of AHA are autoimmune diseases, infections, medications, and neoplasms. Our patient had no symptoms or signs of infection or malignancy. Abdominopelvic sonography and the results of tumor markers were unremarkable. Her drug history included MTX, and, as far as we know, there has been no report of MTX-associated AHA. In contrast, MTX is a useful treatment option for AHA in many cases. Therefore, we concluded that antibody formation against FVIII was associated with RA. FVIII activity and inhibitor normalized after treatment with RTX.

We also reviewed reported cases of AHA associated with RA. Table I includes detailed information about 20 previous cases and the present one (7-23). Of these, 76.19% were female. It is known that there is no gender predilection for AHA. But as we are discussing AHA cases in the context of RA, the gender ratio was similar to that of RA (female/male: 3/1). The mean age was 64.66 years with a standard deviation of 8.81 (the youngest patient was 47 and the oldest was 78). The mean RA duration was 17.07 years with a standard deviation of 9.96 (the shortest was 6 years and the longest was 40 years). Almost all 21 cases reported some form of mucocutaneous or intramuscular bleeding as the most common clinical manifestation. 23.81% of the patients (5 cases) presented with gastrointestinal bleeding, which led to death in two cases. Also, 23.81% of the cases presented hemarthrosis. 10 patients required some type of blood product to control the acute bleeding episode. In five patients, rFVIIa was used, and aPCC was used in two patients. Except for a 57-year-old male in 1965, the rest of the patients received immunosuppressive treatment. Corticosteroids were used in 16 patients (including methylprednisolone pulses in 5 patients), cyclophosphamide in 11 patients, rituximab in 6 patients, azathioprine in 3 patients, tocilizumab in one, and mycophenolate mofetil in one. A total of 18 patients improved after treatment (mortality rate was 14.28%).

In conclusion, AHA can be associated with RA, and it can occur at any time during the course of RA. The most common clinical manifestation is cutaneous and intramuscular bleeding. Corticosteroids, along with cyclophosphamide or rituximab, are effective treatment options.

Table I - Reported cases of acquired hemophilia A associated with rheumatoid arthritis.

Article/year/country	Sex/age	Duration of RA (years)	Clinical presentation	Treatment	Outcome
Soriano et al./ 1987/UK (7)	57/M	9	Skin ecchymosis, muscle hematoma, shoulder bleeding	Blood and plasma transfusion	Death
Soriano et al./1987/UK (7)	61/F	18	Hematemesis, melena	PDN, AZA 200 mg/d	Improved
Soriano et al./ 1987/UK (7)	59/F	_	Anemia, purpura, occult blood in stool, infected hematoma, massive GIB	AZA 100 mg/d, porcine factor VIII	Died due to massive GIB and ATN
Soriano et al./1987/UK (7)	71/M	_	Bruising	CYC 100 mg/d	Improved
Struillou et al./ 1993/France (8)	78/F	10	Hematoma, GIB	IVIG 400 mg/kg/d for 5 days, CYC 100mg/d	Improved
Ruiz Calderon et al./ 1993/Spain (9)	66/F	_		Corticosteroids, IVIG	Improved
Jones et al./ 1994/UK (10)	62/M	13	Hemarthrosis, epistaxis, sub-conjunctival hemorrhage, intramuscular hematoma	PDN40 mg/d, factor VIII infusion	Improved
Nishino et al./ 2001/Japan (11)	54/F	6	Purpura, subcutaneous bleeding, muscular hematoma	PDN50 mg/d, CYC 100mg/d	Improved
Sato et al./ 2004/Japan (12)	71/F	31	Hemarthrosis, ecchymosis, intramuscular hematoma	PDN1 mg/kg/d, IVIG 10 g/d for 3 days, CYC 500 mg, rFVIIa	Improved
Patel et al./2006/UK (13)	78/M	_	Oral mucosal bleeding, skin ecchymosis	Corticosteroids, CYC 100 mg/d, rFVIIa	Improved
Oliveira et al./ 2007/USA (14)	61/F	40	Hematoma at the insertion site of a peripheral catheter	RTX 375 mg/m^2 in 4 weekly doses, methylprednisolone pulses, MM	Improved
Freire et al./ 2009/Brazil (15)	64/F	23	Ecchymosis, hematoma	Methylprednisolone 700 mg/d for 3 days, IVIG 25 g/d for 2 days, CYC 500 mg	Improved
Arthanari et al./ 2012/UK (16)	78/F	10	Petechial rash, skin ecchymosis, anemia, abdominal wall hematoma, GIB	CYC 100mg/d, aPCC	Died due to massive GIB and multi-organ failure
Drobiecki et al./2013/ Poland (17)	48/F	_	Vaginal bleeding, anemia, massive subcutaneous and intramuscular bleeding	rFVIIa, CYC 200 mg/d, methylprednisolone, RTX	Improved after several relapses
Banse et al./ 2015/France (18)	47/F	_	Ecchymosis, hematoma	PDN1 mg/kg/d, RTX 1 gr every 2 weeks for 2 doses, AZA 2 mg/kg/d	Improved
Barbosa et al./ 2016/Brazil (19)	69/F	6	Ecchymosis, multiple hematoma, hematuria, melena, anemia and massive hematochezia,	Methylprednisolone 1 g/d for 3 days, aPCC, CYC	Improved
Hashimoto et al./ 2017/Japan (20)	61/F		Extensive subcutaneous bleeding	Corticosteroids, CYC, tocilizumab	Improved
Jaber et al./2018/Italy (21)	76/F	_	Hemarthrosis, ecchymosis, muscular hematoma	PDN1 mg/kg/d, RTX 375 mg/ m2 in 4 weekly doses	Improved

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Article/year/country	Sex/age	Duration of RA (years)	Clinical presentation	Treatment	Outcome
Ghozlani et al./ 2018/Morocco (22)	66/M	20	Skin ecchymosis, hemarthrosis	Methylprednisolone 450 mg/d for 3 days, rFVIIa, RTX 1 gr every 2 weeks for 2 doses	Improved
Majeranowski et al./ 2022/Poland (23)	69/F	25	Epistaxis, skin ecchymosis, muscle hematoma	rFVIIa, CYC 1000 mg, prednisone 1 mg/kg/d	Improved
The present case/ 2023/Iran	62/F	11	Skin ecchymosis, gingivorrhagia	RTX 500 mg weekly for 4 doses, PDN10 mg/d	Improved

F, female; M, male; RA, rheumatoid arthritis; rFVIIa, bypass-concentrate-recombinant activated factor VII; GIB, gastrointestinal bleeding; ATN, acute tubular necrosis; aPCC, activated prothrombin complex concentrate; PDN, prednisolone; AZA, azathioprine; CYC, cyclophosphamide; RTX, rituximab; IVIG, intravenous immunoglobulin; MM, mycophenolate mofetil.

Contributions
SA, conceived the idea to report the case and was responsible for data collection; DM, SA, drafted the manuscript; FF, commented on the manuscript. All authors read and approved the final manuscript.

Conflict of interest
The authors declare that they have no competing interests, and all authors confirm accuracy.

Ethics approval and consent to participate
Approval was not needed by the local Clinical Research Ethics Committee.

Patient consent for publication
Written informed consent for publication was obtained from the patient.

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Availability of data and materials
Data is available if requested.

REFERENCES

1. Zhang P, Liu J, Tan B, Zhu F, Fang L. Hypercoagulable state is associated with NF-kappa B activation and increased inflammatory factors in patients with rheumatoid arthritis. Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi. 2016; 32: 364-8. [Article in Chinese].
2. Franchini M, Gandini G, Di Paolantonio T, Mariani G. Acquired hemophilia A: a concise review. Am J Hematol. 2005; 80: 55-63.
3. Kruse-Jarres R, Kempton CL, Baudo F, Collins PW, Knoebl P, Leissinger CA, et al. Acquired hemophilia A: updated review of evidence and treatment guidance. Am J Hematol. 2017; 92: 695-705.
4. Tiede A, Collins P, Knoebl P, Teitel J, Kessler C, Shima M, et al. International recommendations on the diagnosis and treatment of acquired hemophilia A. Haematologica. 2020; 105: 1791-801.
5. Shetty S, Bhave M, Ghosh K. Acquired hemophilia a: diagnosis, aetiology, clinical spectrum and treatment options. Autoimmun Rev. 2011; 10: 311-6.
6. Tang Q, Liao J, Xie X. Acquired hemophilia associated with rheumatic diseases: a case-based systematic review. J Inflamm Res. 2022; 15: 4385-93.
7. Soriano RM, Matthews JM, Guerado-Parra E. Acquired haemophilia and rheumatoid arthritis. Br J Rheumatol. 1987; 26: 381-3.
8. Struillou L, Fiks-Sigaud M, Barrier JH, Blat E, Magadur-Joly G. Acquired hemophilia and rheumatoid arthritis. Value of intravenous immunoglobulins. Rev Rhum Ed Fr. 1993; 60: 524-6. [Article in French].
9. Ruiz-Calderón AJ, Carrasco F, Duro R, Constantino M. Acquired factor VIII inhibitor in a patient with rheumatoid arthritis. Sangre. 1993; 38: 403-5. [Article in Spanish].
10. Jones SM, Dippy JE, Gaywood IC. Acquired haemophilia presenting with a haemarthrosis in a patient with rheumatoid arthritis and carcinoma of the lung. Br J Rheumatol. 1994; 33: 992.
11. Nishino Y, Ueki K, Suto M, Uchiumi H, Ota F, Tamura S, et al. Successful treatment of patients with rheumatic disorders and acquired factor VIII inhibitors with cyclophosphamide and prednisolone combination therapy: two case reports. J Int Med Res. 2001; 29: 432-6.
12. Sato T, Hagiwara K, Chikazoe J, Nakagawa Y, Akiyama O. A case of acquired hemophilia caused by factor VIII inhibitor with rheumatoid arthritis, successfully treated with immunosuppressive treatment and recombinant acti-

vated factor VII. Mod Rheumatol. 2004; 14: 320-2.
13. Patel RS, Harman KE, Nichols C, Burd RM, Pavord S. Acquired haemophilia heralded by bleeding into the oral mucosa in a patient with bullous pemphigoid, rheumatoid arthritis, and vitiligo. Postgrad Med J. 2006; 82: e3.
14. Oliveira B, Arkfeld DG, Weitz IC, Shinada S, Ehresmann G. Successful rituximab therapy of acquired factor VIII inhibitor in a patient with rheumatoid arthritis. J Clin Rheumatol. 2007; 13: 89-91.
15. Freire M, Teodoro RB, Nogueira DA, Rita DP, Ribeiro Filho E, Sousa LV. Acquired hemophilia associated with rheumatoid arthritis. Bras J Rheumatol. 2009; 49: 302-7.
16. Arthanari S, Ahmad H, Nisar M. Fatal acquired hemophilia A in a patient with rheumatoid arthritis treated with adalimumab. J Clin Rheumatol. 2012; 18: 50-1.
17. Drobiecki A, Pasiarski M, Hus I, Sokolowska B, Watek M. Acquired hemophilia in the patient suffering from rheumatoid arthritis: case report. Blood Coagul Fibrinolysis. 2013; 24: 874-80.
18. Banse C, Benhamou Y, Lequerré T, Le Cam-Duchez V, Lévesque H, Vittecoq O. Acquired hemophilia possibly induced by etanercept in a patient with rheumatoid arthritis. Joint Bone Spine. 2015; 82: 200-2.
19. Barbosa OA, Evangelista PD, Paiva JG, de Lima TG, Brasileiro RB, Neto RR, et al. Acquired hemophilia secondary to rheumatoid arthritis: case report and literature review. J Hematol. 2016; 5: 34-7.
20. Hashimoto A, Takafuta T, Kido M, Okikawa Y, Ito T. Successful management of recurrent bleeding with tocilizumab in an acquired hemophilia A patient with rheumatoid arthritis. Rinsho Ketsueki. 2017; 58: 738-42. [Article in Japanese].
21. Jaber MA, Bortolotti R, Martinelli S, Felicetti M, Aloisi T, Paolazzi G. Acquired hemophilia in a patient with rheumatoid arthritis: case report and literature review. Clin Manag Issues. 2018; 12.
22. Ghozlani I, Mounach A, Ghazi M, Kherrab A, Niamane R. Targeting acquired hemophilia a with rheumatoid arthritis by a rituximab shot: a case report and review of the literature. Am J Case Rep. 2018; 19: 582-8.
23. Majeranowski A, Lebiedziński F, Topolewska I, Cegła A, Palus D, Osowski J, et al. Acquired hemophilia A secondary to rheumatoid arthritis. J Transf Med. 2022; 15: 57-9.