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Acquired Hemophilia A: A Single-Center Case Series Highlighting Clinical Presentation, Management, and Outcomes

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Abstract | **Original Research Article**

***Objective*:** To describe the clinical, biological, therapeutic, and outcome characteristics of patients with acquired hemophilia A (AHA) managed in a Department of Internal Medicine and Onco-Hematology, and to highlight the challenges associated with severe and refractory cases. ***Methods*:** We conducted a retrospective descriptive study of patients diagnosed with AHA and managed in the Department of Internal Medicine and Onco-Hematology between January 2017 and December 2025. Clinical, biological, therapeutic, and outcome data were collected from medical records and analyzed descriptively. ***Results*:** Five patients were included, comprising four women and one man, with a median age of 34 years (range: 27–58 years). Two cases occurred in the postpartum period. Deep soft-tissue and intramuscular hematomas were the most common presenting manifestations, including iliopsoas hematomas in two patients. All patients exhibited isolated prolongation of activated partial thromboplastin time, reduced factor VIII (FVIII) activity, and detectable FVIII inhibitors. FVIII activity was below 1% in four patients. High-dose corticosteroids were administered as first-line therapy in all cases. Additional immunosuppressive treatments included azathioprine, cyclophosphamide, and rituximab. Hemostatic agents, including recombinant activated factor VII and activated prothrombin complex concentrate, were used in severe bleeding episodes. During follow-up, three patients achieved sustained remission. One patient experienced relapse associated with a high inhibitor titer (768 Bethesda Units), while another developed persistent neurological sequelae secondary to a compressive hematoma. ***Conclusion*:** Acquired hemophilia A remains a rare but serious hemorrhagic disorder with heterogeneous clinical presentations. Early recognition, prompt hemostatic management, and timely immunosuppressive therapy are essential to improve outcomes. Our findings highlight the clinical diversity of AHA and emphasize the importance of multidisciplinary management, particularly in postpartum-associated and refractory cases.

Keywords: Acquired Hemophilia A, factor VIII Inhibitor, Autoimmune Bleeding Disorder, Postpartum, Hematoma, Immunosuppressive Therapy, Rituximab.

INTRODUCTION

Acquired hemophilia A (AHA) is a rare but potentially life-threatening autoimmune bleeding disorder characterized by the development of autoantibodies directed against coagulation factor VIII (FVIII), resulting in its functional inhibition and impaired hemostasis [1]. Unlike congenital hemophilia A, AHA occurs in individuals without a personal or family history of bleeding disorders and is frequently associated with severe and sometimes spontaneous hemorrhagic manifestations [1, 2].

The estimated annual incidence of AHA ranges from 1 to 1.5 cases per million population, with a bimodal age distribution characterized by a major peak among older adults and a smaller peak in women during pregnancy and the postpartum period [2, 3]. Although approximately half of all cases are classified as idiopathic, several underlying conditions have been implicated, including autoimmune diseases, solid and hematological malignancies, pregnancy, and drug exposure [3, 4].

The pathogenesis of AHA involves a loss of immune tolerance to endogenous FVIII, leading to the production of neutralizing autoantibodies that interfere with coagulation activity [4]. Clinically, patients typically present with extensive ecchymoses,

subcutaneous and intramuscular hematomas, mucosal bleeding, or, less frequently, life-threatening hemorrhage. In contrast to congenital hemophilia, hemarthrosis is uncommon in AHA and therefore should not be considered a predominant clinical feature [1-5].

The diagnosis of AHA should be suspected in patients presenting with unexplained bleeding associated with an isolated prolongation of activated partial thromboplastin time (aPTT). Confirmation relies on a mixing study demonstrating the absence of correction of the prolonged aPTT, together with reduced FVIII activity and the detection of a FVIII inhibitor quantified using the Bethesda assay [1-6].

Management is based on two complementary objectives: prompt control of bleeding and eradication of the inhibitor. Hemostatic treatment primarily relies on bypassing agents, including recombinant activated factor VII (rFVIIa) and activated prothrombin complex concentrate (aPCC), which remain the cornerstone of therapy in patients with significant bleeding [1, 2]. Immunosuppressive treatment is aimed at inhibitor eradication and commonly includes corticosteroids alone or in combination with cyclophosphamide, rituximab, or other immunosuppressive agents [2-6]. More recently, emicizumab has emerged as a promising therapeutic option in selected refractory cases, although evidence remains limited [2].

Given the rarity of AHA and the challenges associated with its diagnosis and management, the accumulation of clinical experience remains essential to improve patient care. In this study, we report a series of five patients diagnosed with acquired hemophilia A and managed in our department. We describe their clinical presentations, laboratory findings, therapeutic approaches, and outcomes, and discuss our observations in the context of the current literature.

PATIENTS AND METHODS

Study Design and Patients

We conducted a retrospective descriptive study of patients diagnosed with acquired hemophilia A (AHA) and managed in the Department of Internal Medicine and Onco-Hematology between January 2017 and December 2025.

All patients meeting the diagnostic criteria for AHA were included. The diagnosis was established based on the association of acquired bleeding manifestations, isolated prolongation of activated partial thromboplastin time (aPTT), reduced factor VIII (FVIII) activity, and the presence of a FVIII inhibitor quantified using the Bethesda assay. Patients with congenital hemophilia or any other inherited bleeding disorder were excluded from the study.

Data Collection

Clinical and laboratory data were retrospectively collected from medical records and laboratory reports. The following variables were analyzed: demographic characteristics, medical history, circumstances leading to diagnosis, clinical manifestations, laboratory findings, associated underlying conditions, therapeutic management, and outcomes.

Laboratory parameters included complete blood count, coagulation profile, FVIII activity level, and inhibitor titer expressed in Bethesda Units (BU). Associated conditions potentially related to AHA, including autoimmune diseases, malignancies, pregnancy, and other comorbidities, were systematically recorded when present.

Treatment and Outcome Assessment

Therapeutic management was aimed at controlling bleeding episodes and eradicating the FVIII inhibitor. Hemostatic treatment was administered according to the severity and location of bleeding, using appropriate hemostatic agents when required. Immunosuppressive therapy was initiated with the objective of inhibitor eradication.

Outcome measures included clinical response, changes in FVIII activity, inhibitor disappearance, occurrence of relapse, and treatment- or disease-related complications. Complete remission was defined by normalization of FVIII activity and the absence of detectable inhibitor during follow-up.

Statistical Analysis

Data were analyzed descriptively. Results are presented as numbers and percentages for categorical variables and as medians with ranges for continuous variables, as appropriate.

Ethical Considerations

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Patient data were collected and analyzed anonymously, and confidentiality of medical information was strictly maintained throughout the study.

RESULTS

Five patients diagnosed with acquired hemophilia A (AHA) were identified during the study period. The median age at diagnosis was 34 years (range: 27–58 years). The cohort included four women (80%) and one man (20%). In two female patients (40%), AHA occurred during the postpartum period.

Clinical Characteristics

The initial clinical presentation was predominantly characterized by deep soft-tissue and intramuscular hematomas, which were observed in four

patients (80%). Iliopsoas hematomas were documented in two cases. One patient presented with diffuse ecchymoses associated with gross hematuria, whereas another was diagnosed following prolonged bleeding after invasive procedures. None of the patients had a personal or family history of hemophilia or other inherited bleeding disorders (table 1).

Laboratory Findings

All patients exhibited an isolated prolongation of activated partial thromboplastin time (aPTT) associated with reduced FVIII activity. FVIII levels were below 1% in four patients (80%) and measured 29% in one patient (20%). A FVIII inhibitor was detected in all cases. The highest inhibitor titer was observed in a patient who subsequently experienced relapse, reaching 768 Bethesda Units (BU).

Associated Conditions

Etiological investigations identified a postpartum setting in two patients and evidence of an underlying autoimmune condition in one patient. No malignancy or systemic disease was detected in the remaining cases.

Treatment

All patients received high-dose corticosteroid therapy as first-line treatment. Additional immunosuppressive therapy was required in four patients, consisting of azathioprine in three cases and cyclophosphamide in one case. One patient received rituximab because of an inadequate response to conventional immunosuppressive therapy.

Hemostatic agents were administered in patients with severe bleeding manifestations. Recombinant activated factor VII (rFVIIa) was used in one patient, while activated prothrombin complex concentrate (aPCC; FEIBA®) was administered in another.

Outcomes

After prolonged follow-up, three patients achieved sustained clinical and biological remission. One patient experienced a hemorrhagic relapse associated with a markedly elevated FVIII inhibitor titer. Another patient developed persistent functional neurological sequelae secondary to a compressive upper-limb hematoma.

Table 1: Clinical, laboratory, treatment, and outcome characteristics of the five patients with acquired hemophilia A

Variable	Case 1	Case 2	Case 3	Case 4	Case 5
Sex	Female	Female	Female	Female	Male
Age (years)	34	31	49	27	58
Associated context	Postpartum	Postpartum	None	None	None
Initial presentation	Iliopsoas hematoma	Ecchymoses and gross hematuria	Iliopsoas hematoma	Extensive muscular hematomas	Postoperative bleeding
Initial aPTT (s)	>120	75	92.5	>100	39
FVIII activity (%)	<0.5	<1	<1	<0.5	29
FVIII inhibitor	Positive	39 BU	768 BU (at relapse)	Positive	Positive
Associated condition	None	Autoimmune background (ANA+, anti-Sm/RNP+)	None	None	None
Immuno suppressive therapy	Corticosteroids + azathioprine	Corticosteroids + cyclophosphamide	Corticosteroids + azathioprine	Corticosteroids + azathioprine	Corticosteroids + azathioprine + rituximab
Hemostatic treatment	Fresh frozen plasma	None	rFVIIa	FEIBA® (aPCC)	None
Outcome	Remission	Remission	Relapse	Persistent neurological sequelae	Response after rituximab

DISCUSSION

Acquired hemophilia A (AHA) is a rare autoimmune bleeding disorder caused by the development of neutralizing autoantibodies against factor VIII (FVIII). Despite its low incidence, estimated at 1–1.5 cases per million population per year, AHA remains associated with substantial morbidity and mortality due to severe hemorrhagic complications and adverse events related to immunosuppressive therapy [1, 2].

The median age of our patients was 34 years, which is markedly younger than that reported in large international registries. In the European Acquired Haemophilia Registry (EACH2), the median age at diagnosis was 74 years, while the German GTH registry reported a median age of approximately 78 years [7, 8].

This discrepancy is likely explained by the high proportion of young female patients and the significant contribution of postpartum-associated cases in our cohort.

Female predominance was observed in our series (80%), contrasting with the nearly equal sex distribution generally reported in the literature outside pregnancy-related cases [3-7]. Two patients developed AHA during the postpartum period. Postpartum AHA accounts for approximately 7–15% of reported cases and typically occurs within the first months following delivery [3-9]. The relatively high proportion observed in our cohort is most likely attributable to the limited sample size. Consistent with previous reports, both patients experienced favorable outcomes following immunosuppressive therapy, supporting the generally better prognosis described in postpartum-associated AHA compared with idiopathic disease occurring in older adults [9].

Deep soft-tissue and intramuscular hematomas represented the predominant clinical presentation in our patients. Two cases involved iliopsoas hematomas, and one patient developed extensive bleeding complicated by severe compressive neurological impairment. These findings are consistent with data from the EACH2 registry, in which subcutaneous and muscular bleeding were among the most common clinical manifestations [7]. In contrast to congenital hemophilia, hemarthrosis remains uncommon in AHA and was observed in only one patient in our series during disease relapse associated with a very high inhibitor titer [1-5].

All patients presented with the characteristic biological profile of AHA, including isolated prolongation of activated partial thromboplastin time, reduced FVIII activity, and detectable FVIII inhibitors. Four patients exhibited FVIII levels below 1%, indicating severe coagulation impairment. However, previous studies have demonstrated that bleeding severity does not always correlate with residual FVIII activity or inhibitor titer, highlighting the heterogeneous clinical spectrum of the disease [2-6].

With regard to associated conditions, one patient had evidence of an autoimmune background characterized by positive antinuclear and anti-Sm/RNP antibodies. The remaining cases were either postpartum-related or considered idiopathic. This distribution is in line with previous studies showing that nearly half of AHA cases remain without an identifiable underlying cause despite extensive investigation [3, 4].

All patients received high-dose corticosteroids as first-line therapy. Additional immunosuppressive treatment was required in most cases and included azathioprine, cyclophosphamide, or rituximab. This therapeutic strategy is consistent with current international recommendations advocating early immunosuppression to achieve inhibitor eradication and restoration of normal FVIII activity [2-10]. Bypassing agents, including recombinant activated factor VII and activated prothrombin complex concentrate, were successfully used in patients with severe bleeding manifestations.

Two cases illustrate the heterogeneous clinical course of AHA. One patient experienced relapse associated with an exceptionally high inhibitor titer of 768 Bethesda Units, emphasizing the challenges posed by refractory disease. Another developed persistent neurological sequelae secondary to a large compressive hematoma. Although such complications are uncommon, they underscore the importance of prompt diagnosis and rapid initiation of hemostatic therapy to prevent irreversible functional impairment [11].

Recently, emicizumab has emerged as a promising therapeutic option in AHA. Originally developed for congenital hemophilia A with inhibitors, this bispecific monoclonal antibody mimics FVIII cofactor activity by bridging activated factor IX and factor X. Several recent observational studies have reported reduced bleeding rates, decreased reliance on bypassing agents, and shorter hospital stays in patients with severe or refractory AHA [2]. Nevertheless, current evidence remains limited, and further prospective studies are required to better define its role within the therapeutic algorithm of AHA.

Overall, outcomes in our cohort were favorable, with sustained remission achieved in the majority of patients and no disease-related mortality. These findings highlight the effectiveness of a multidisciplinary approach combining appropriate hemostatic therapy, early immunosuppression, and close follow-up. However, the occurrence of relapse and persistent neurological sequelae in two patients confirms that AHA remains a potentially severe disorder whose prognosis largely depends on timely diagnosis and treatment.

STRENGTHS AND LIMITATIONS

The main strengths of this study include the detailed description of five patients with acquired hemophilia A managed in a tertiary referral center and the prolonged clinical follow-up. The study also highlights postpartum-associated AHA and a refractory case requiring rituximab.

However, this study has several limitations, including its retrospective design, small sample size, and single-center setting. Nevertheless, because acquired hemophilia A is an exceptionally rare disease, small case series remain valuable to improve current knowledge regarding diagnosis and management.

CONCLUSION

Acquired hemophilia A is a rare but potentially life-threatening hemorrhagic disorder that constitutes both a diagnostic and therapeutic emergency. Through this series of five patients, we highlight the heterogeneity of clinical presentations, the predominance of deep soft-tissue hematomas, and the occurrence of postpartum-associated forms. Our findings support the effectiveness of prompt hemostatic management combined with early immunosuppressive therapy aimed at inhibitor eradication.

Clinicians should maintain a high index of suspicion for AHA in any patient presenting with unexplained bleeding and isolated prolongation of activated partial thromboplastin time in the absence of a personal or family history of bleeding disorders. Early recognition and treatment are essential to improve outcomes and prevent irreversible complications. Larger multicenter studies are warranted to further clarify prognostic factors and to define the optimal role of emerging therapies, particularly emicizumab, in the management of AHA.

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