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Acquired Hemophilia A Revealing Occult Splenic Marginal Zone Lymphoma

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Study Design A
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Statistical Analysis C
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Patient: Male, 77-year-old
Final Diagnosis: Acquired hemophilia A secondary to splenic marginal zone lymphoma
Symptoms: Spontaneous bruising
Clinical Procedure: —
Specialty: Hematology • Oncology

Objective: Rare disease

Background: Acquired hemophilia A is a rare autoimmune bleeding disorder caused by inhibitory autoantibodies against coagulation factor VIII and is associated with significant morbidity and mortality. Although malignancy-associated acquired hemophilia A is well recognized, its presentation as the initial manifestation of an otherwise clinically subtle indolent B-cell lymphoma, such as splenic marginal zone lymphoma, remains exceedingly uncommon. We report a case highlighting the importance of recognizing acquired factor VIII inhibitors, evaluating for underlying lymphoproliferative disorders, and the potential role of rituximab monotherapy in achieving control of both the inhibitor and the underlying lymphoma.

Case Report: A 77-year-old man presented with spontaneous bruising and an isolated prolonged activated partial thromboplastin time that failed to correct on mixing studies. Further evaluation demonstrated markedly reduced factor VIII activity, a factor VIII inhibitor, diffuse splenomegaly, and flow cytometry and bone marrow biopsy findings most consistent with splenic marginal zone lymphoma. Treatment with activated prothrombin complex concentrate, corticosteroids, and rituximab resulted in normalization of coagulation parameters, recovery of factor VIII activity, decline in inhibitor titers, resolution of bleeding manifestations, and sustained clinical stability without recurrent bleeding or evidence of lymphoma progression.

Conclusions: This case highlights acquired hemophilia A as a rare paraneoplastic manifestation of splenic marginal zone lymphoma and emphasizes the importance of evaluating for an underlying lymphoproliferative disorder in older adults presenting with newly identified factor VIII inhibitors, particularly in the setting of cytopenias or splenomegaly. It also demonstrates that rituximab-based therapy can effectively achieve sustained remission of both the inhibitor and the underlying indolent lymphoma.

Keywords: Hemophilia A • Factor VIII • Lymphoproliferative Disorders • Partial Thromboplastin Time • Rituximab

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/953683

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Introduction

Acquired hemophilia A (AHA) is a rare autoimmune bleeding disorder caused by inhibitory autoantibodies against coagulation factor VIII and is associated with significant morbidity and mortality [1-3]. Although approximately 40% to 50% of cases are idiopathic, acquired hemophilia A has been associated with a variety of underlying conditions, particularly solid tumors and lymphoproliferative disorders [2,3]. Prompt recognition is essential, as patients can present with spontaneous bleeding and isolated prolongation of the activated partial thromboplastin time that fails to correct on mixing studies [1,3,4].

Splenic marginal zone lymphoma (SMZL) is a rare indolent mature B-cell lymphoproliferative disorder accounting for approximately 1% to 2% of all non-Hodgkin lymphomas and primarily affecting older adults [5-8]. The disease commonly presents with splenomegaly, cytopenias, bone marrow involvement, and occasionally peripheral lymphocytosis or autoimmune manifestations [5-8]. Diagnosis is typically established by integrating clinical findings, bone marrow morphology, and immunophenotypic analysis, often without requiring splenic histology [6-8]. Management strategies range from observation in asymptomatic patients to rituximab-based therapy or splenectomy, while chemoimmunotherapy is generally reserved for selected patients with refractory or advanced disease [6,9,10].

Although malignancy-associated acquired hemophilia A is well recognized, its association with indolent B-cell lymphomas, such as splenic marginal zone lymphoma, remains rare, particularly as the initial presenting manifestation. Prompt recognition of isolated prolonged activated partial thromboplastin time with failure to correct on mixing studies is critical for identifying an acquired factor VIII inhibitor and initiating appropriate diagnostic evaluation. We report a case of acquired hemophilia A revealing previously unsuspected splenic marginal zone lymphoma, highlighting the importance of considering underlying lymphoproliferative disorders, including indolent lymphomas, in older adults presenting with unexplained bleeding manifestations and factor VIII inhibitors, as well as the potential role of rituximab monotherapy in achieving control of both the inhibitor and the underlying lymphoma.

Case Report

A 77-year-old man presented to the emergency department on August 14, 2025, with a 1-week history of left upper-extremity pain and progressive gross hematuria. On the day of presentation, he was noted to have new-onset extensive bruising over the left chest wall and flank. He denied any history of trauma or urinary symptoms. His medical history was notable for coronary artery bypass grafting, and he was taking aspirin.

On presentation, vital signs were stable, including blood pressure 161/77 mm Hg, heart rate 62 beats per minute, temperature 36.4 °C, respiratory rate 16 breaths per minute, and oxygen saturation 100% on room air. Physical examination revealed a large, confluent ecchymosis over the left flank with superior extension, with progressively fainter involvement of the lateral chest wall, axillary region, and upper anterior chest (**Figure 1A, 1B**). He denied direct trauma to the bruised area.

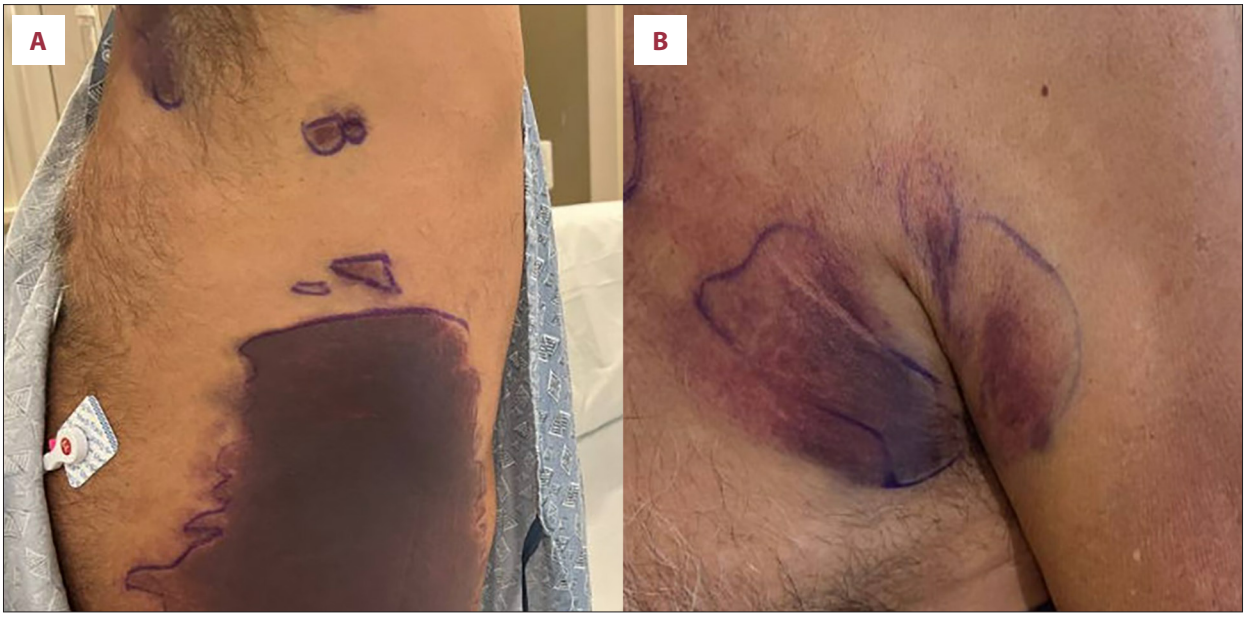

Figure 1. (**A, B**) Extensive spontaneous ecchymosis involving the left flank, lateral chest wall, axillary region, and upper anterior chest at presentation.

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Laboratory studies revealed leukopenia (WBC 3 × 10^9/L), anemia (Hb 11.5 g/dL), and thrombocytopenia (83 × 10^9/L). Coagulation studies demonstrated a markedly prolonged activated partial thromboplastin time (aPTT) of 72 seconds with a normal prothrombin time (PT) of 11 seconds. Urinalysis confirmed hematuria.

Computed tomography (CT) of the chest, abdomen, and pelvis demonstrated diffuse splenomegaly measuring approximately 21.2 cm in craniocaudal length, with mass effect on adjacent structures (**Figure 2**), as well as asymmetric enlargement of the left subscapularis muscle with surrounding fat stranding, consistent with intramuscular hematoma. CT of the head and renal ultrasound showed no acute abnormalities. Given the isolated prolongation of aPTT, hematology was consulted. Mixing studies failed to correct the aPTT, raising suspicion for a circulating inhibitor. Further evaluation demonstrated severely reduced factor VIII activity (2%) and an elevated factor VIII inhibitor titer of 7.1 Bethesda Units, confirming acquired hemophilia A (AHA).

Evaluation for secondary causes, including autoimmune disease, infection (including hepatitis C), medication exposure, and JAK2-associated myeloproliferative neoplasm, was unrevealing. However, the presence of pancytopenia and diffuse splenomegaly without significant lymphadenopathy raised concern for an underlying hematologic malignancy. Flow cytometry was performed, and a bone marrow biopsy was conducted during hospitalization. While the diagnostic workup was ongoing, the patient was started on factor VIII inhibitor bypassing activity (FEIBA), an activated prothrombin complex concentrate, at a dose of 5000 units every 12 hours along with prednisone 1 mg/kg daily. Notably, aPTT transiently worsened during early hospitalization, peaking above 90 seconds, before demonstrating progressive improvement with therapy.

Flow cytometry identified a small (~ 2-5%) monoclonal mature B-cell population (CD19+, CD20+) consistent with a low-level B-cell lymphoproliferative disorder. The immunophenotype was negative for CD5, CD10, and CD103, making chronic lymphocytic leukemia/small lymphocytic lymphoma, mantle cell lymphoma, follicular lymphoma, and hairy cell leukemia unlikely, narrowing the differential diagnosis to lymphoplasmacytic lymphoma and marginal zone lymphoma. Serum IgM was low (33 mg/dL), suggesting a less likely diagnosis of lymphoplasmacytic lymphoma. The significance of these findings was discussed with the patient during hospitalization.

The patient had progressive clinical improvement during hospitalization. Hematuria resolved with conservative urologic management by hospital day 3. Hemoglobin stabilized at 9.6 to 10.6 g/dL, with improvement in aPTT to 56 seconds. After receiving 7 doses of FEIBA (50 units/kg every 12 hours), he

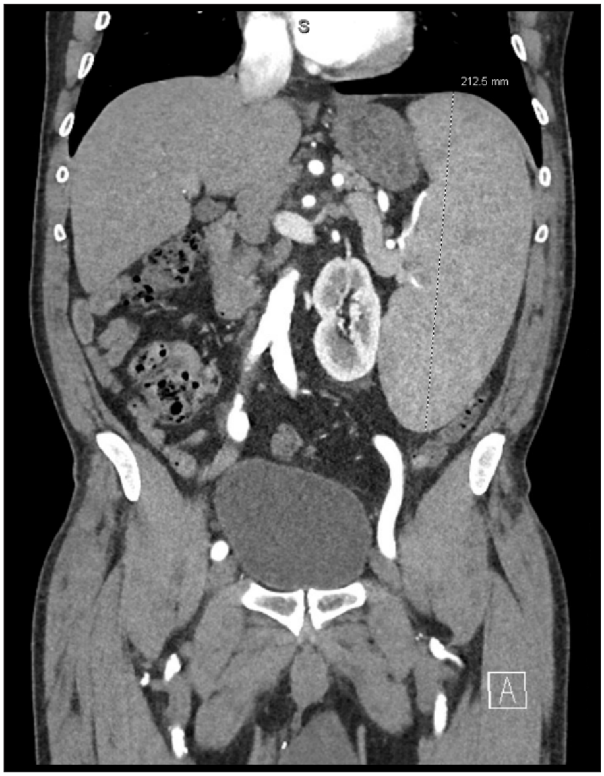

Figure 2. Computed tomography (CT) of the abdomen and pelvis demonstrating marked splenomegaly measuring approximately 21.2 cm in craniocaudal length with associated mass effect on adjacent structures.

was discharged on August 21, 2025, following a 7-day hospitalization, on prednisone 1 mg/kg daily with close outpatient hematology-oncology follow-up.

Subsequently, bone marrow biopsy demonstrated low-level (~ 5%) clonal B-cell involvement consistent with an indolent B-cell lymphoproliferative disorder. In the setting of splenomegaly, pancytopenia, absence of significant lymphadenopathy, and the flow cytometry findings, the diagnosis was most consistent with splenic marginal zone lymphoma (SMZL), presenting with acquired hemophilia A. Next-generation sequencing did not identify any pathogenic mutations.

At his first outpatient follow-up in late August, 1 week after discharge, findings were discussed with the patient. Given the likely paraneoplastic etiology of acquired hemophilia A in the setting of splenic marginal zone lymphoma, rituximab monotherapy (375 mg/m^2 weekly × 4) was planned to target both the inhibitor and the underlying B-cell clone, with continuation of prednisone followed by a gradual taper. By early September 2025, he had marked clinical improvement with resolution of bruising and hematuria; aPTT normalized with rising factor VIII activity, and inhibitor levels declined (to 0.8 BU), supporting effective inhibitor suppression. Rituximab was subsequently

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Table 1. Patient's clinical course, treatment timeline, and laboratory response.

Parameter	Admission*	Discharge**	First follow-up***	Sep 25	Oct 25	Nov 2025 admission	Dec 25	Feb 26
Hemoglobin (g/dL)	11.5 (nadir 8.1)	10	11.6	13.2	14.4	11-12	13.7	14.8
Platelets (× 10⁹/L)	83 (nadir 52)	~ 50-70	71	~ 70	~ 99	~ 100	131	98
aPTT (sec)	72-98 (peak > 90)	57	Improved	31	Normal	Normal	Normal	~ 35
Factor VIII (%)	2	2	5	53	118	Normal	215	59
Inhibitor (BU)	7.1	7.1	—	0.8	—	—	—	—
LDH (U/L)	317	—	314	246	223	—	170	225
Key treatment	FEIBA + steroids	Prednisone	Prednisone continued, rituximab initiated	Steroid taper	Rituximab completed, steroid taper	Hospitalization for neutropenic diverticulitis, steroid taper	Off steroids	Surveillance

Footnotes: * 8/14/2025; ** 8/21/2025; *** 8/27/2025. Reference ranges: Hemoglobin 13.5-17.5 g/dL; platelets 150-450 × 10⁹/L; aPTT 25-35 seconds; factor VIII activity 50-150%; factor VIII inhibitor < 0.6 BU. aPTT, activated partial thromboplastin time; FVIII, factor VIII; BU, Bethesda Units; FEIBA, factor VIII inhibitor bypassing activity.

initiated and completed as 4 weekly doses between September and October, with 1 dose briefly delayed due to leukopenia.

In early November 2025, he was hospitalized for neutropenic diverticulitis, which was treated with antibiotics and filgrastim, with recovery of counts. Prednisone taper was completed and discontinued thereafter. On subsequent follow-ups in December 2025 and February 2026, he remained clinically stable without recurrent bleeding; hemoglobin and leukocyte counts normalized, with persistent mild thrombocytopenia attributed to splenomegaly. Factor VIII activity remained in or near the normal range. Inhibitor titers were not consistently measurable at higher factor VIII levels, as institutional assay protocols precluded testing after factor VIII activity exceeded a predefined threshold.

Overall, the sustained clinical and laboratory response was consistent with ongoing remission of acquired hemophilia A and stable underlying splenic marginal zone lymphoma without evidence of disease progression. He continues routine surveillance with periodic laboratory monitoring and planned repeat CT abdomen imaging in 3 months to reassess splenic size and disease status. Repeat bone marrow biopsy will be considered if recurrent cytopenias, worsening splenomegaly, or other signs of disease progression develop. The patient's clinical course, treatment timeline, and laboratory response are summarized in **Table 1**.

Discussion

Acquired hemophilia A (AHA) is a rare autoimmune bleeding disorder caused by IgG autoantibodies against coagulation factor VIII (FVIII) in the setting of immune dysregulation [1-3]. After tissue injury, the extrinsic pathway generates a small amount of thrombin that activates factor VIII, enabling the formation of the intrinsic tenase complex and further amplification of thrombin generation that is critical for stable fibrin clot formation [1,3,11]. In AHA, inhibitory IgG antibodies prevent FVIII from participating in the intrinsic tenase complex, resulting in impaired fibrin clot formation and placing patients at risk of potentially life-threatening bleeding [1-3].

Laboratory evaluation typically demonstrates normal PT and prolonged aPTT, reflecting preservation of the extrinsic pathway and disruption of the intrinsic pathway. Because the abnormality results from a circulating inhibitor rather than a simple factor deficiency, the prolonged aPTT typically fails to correct on mixing study [1,4].

Effective management of AHA requires both control of active bleeding and suppression of the inhibitor. Even low inhibitor titers rapidly inactivate FVIII, rendering replacement therapy ineffective [1-3]. Hemostasis is typically achieved using bypassing agents such as recombinant activated factor VII (rFVIIa) or activated prothrombin complex concentrate (FEIBA), both of which promote thrombin generation independent of factor VIII activity [1,12]. In practice, rFVIIa is commonly administered at approximately 90 mcg/kg at 2 to 3-hour intervals

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until bleeding is controlled, whereas FEIBA is typically given at doses of 50 to 100 units/kg every 8 to 12 hours, with a recommended maximum daily dose of 200 units/kg [1,12]. In selected cases, particularly when inhibitor levels allow for reliable monitoring, recombinant porcine factor VIII may also be considered as an alternative therapeutic option [1,3].

Immunosuppressive therapy is used to eradicate the inhibitor, most commonly with prednisone at approximately 1 mg/kg/day, either alone or in combination with agents such as rituximab or cyclophosphamide, depending on disease severity and inhibitor burden [1-3]. Despite advances in treatment, AHA remains a potentially life-threatening condition, with reported mortality rates ranging from 8% to 22%, largely driven by severe bleeding and treatment-related infectious complications [1-3].

While 40% to 50% of AHA cases are idiopathic [2], underlying conditions such as autoimmune disorders, pregnancy, medications, infections (eg, hepatitis C), and malignancy are identified in many patients. Malignancy accounts for 10% to 15% of these cases [2,3,13,14], particularly B-cell lymphoproliferative disorders, in which lymphoma-associated immune dysregulation or direct antibody production by malignant B cells can result in loss of immune tolerance to FVIII and the development of inhibitory antibodies [1,3].

Splenic marginal zone lymphoma (SMZL) is a rare indolent mature B-cell neoplasm arising from memory B lymphocytes in the splenic marginal zone of secondary lymphoid follicles. It accounts for approximately 1% to 2% of all non-Hodgkin lymphomas and about 20% to 30% of marginal zone lymphoma subtypes. The disease predominantly affects older adults, with a median age at diagnosis of approximately 65 to 70 years, and has been associated with chronic hepatitis C infection in certain geographic regions, particularly southern Europe. SMZL most commonly involves the spleen and bone marrow and may also be detectable in the peripheral blood [5-8].

Clinically, SMZL often follows a prolonged indolent course and may be incidentally detected through splenomegaly on imaging, cytopenias, or peripheral lymphocytosis identified on routine laboratory evaluation. In more advanced disease, patients can present with left upper-quadrant discomfort or pain related to splenomegaly, along with symptomatic cytopenias. Approximately 20% of patients develop autoimmune manifestations, including autoimmune hemolytic anemia, immune thrombocytopenia, cold agglutinin disease, circulating anticoagulants, and acquired von Willebrand disease [5,6,8]. The development of coagulation inhibitors such as acquired hemophilia A, however, remains exceedingly rare.

Diagnosis relies on integrating clinical features with hematologic and immunophenotypic findings. Although splenic histology remains the diagnostic gold standard, splenectomy is not required in most cases. In patients with characteristic splenomegaly, a diagnosis can be established based on bone marrow morphology and immunophenotype demonstrating a mature B-cell population (typically $CD19^+/CD20^+$ and negative for CD5, CD10, and CD103), along with compatible peripheral blood findings. In the present case, the combination of marked splenomegaly, pancytopenia, and a low-level clonal B-cell population on flow cytometry and bone marrow biopsy supported the diagnosis of SMZL in the absence of splenic histology [6-8].

Although SMZL is generally considered an indolent lymphoma, with a median overall survival often over 10 years, clinical behavior can be heterogeneous, and approximately 20% to 30% of patients develop more aggressive disease associated with significantly worse survival outcomes [6,8]. Given its rarity and indolent nature, there have been few prospective studies and there is no universally accepted standard treatment approach. Asymptomatic patients may be observed, while treatment is indicated for symptomatic splenomegaly, progressive cytopenias, or autoimmune complications [6,8].

Historically, splenectomy was commonly used for rapid control of hypersplenism, but current practice has increasingly shifted toward rituximab-based therapy [9]. Rituximab monotherapy, often administered weekly for 4 weeks with or without maintenance, has demonstrated high response rates and durable remissions in retrospective studies, offering a less invasive alternative to splenectomy [9,10]. Chemoimmunotherapy is generally reserved for patients with more advanced or refractory disease, particularly in the presence of disseminated involvement, suspected histologic transformation, or other features suggestive of more aggressive disease biology [6]. In the present case, rituximab monotherapy was selected, given the indolent nature of the lymphoma and its potential to simultaneously address both the malignant B-cell clone and the acquired factor VIII inhibitor.

Few reports of SMZL-associated acquired hemophilia A have been published, making this presentation particularly unusual. Compared with previously reported malignancy-associated AHA cases, our patient had a favorable clinical course, with rapid resolution of bleeding manifestations, normalization of aPTT, recovery of factor VIII activity, and early decline in inhibitor titers after corticosteroid therapy and rituximab monotherapy. The marked clinical and biochemical response observed after lymphoma-directed therapy strongly supports a paraneoplastic association between acquired hemophilia A and the underlying splenic marginal zone lymphoma [1,3,10,13].

These findings underscore the importance of evaluating for an underlying lymphoproliferative disorder in patients presenting

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with acquired hemophilia A, particularly in the presence of cytopenias or splenomegaly, as effective treatment of the underlying malignancy can result in parallel resolution of both the factor VIII inhibitor and the underlying malignant B-cell clone, leading to sustained clinical remission [3,10].

Conclusions

This case highlights acquired hemophilia A as the initial manifestation of an otherwise clinically subtle splenic marginal zone lymphoma. While malignancy-associated AHA is well recognized, it has been more commonly reported in association with solid tumors and other hematologic malignancies, whereas reports involving indolent B-cell lymphomas such as SMZL remain limited [2,3,5-8,13,14].

The development of severe factor VIII inhibitor-mediated bleeding despite minimal marrow involvement suggests that immune dysregulation in indolent lymphomas can be disproportionate to overall tumor burden. Clinicians should maintain a high index of suspicion for an underlying lymphoproliferative disorder in older adults presenting with newly diagnosed AHA, particularly in the presence of unexplained cytopenias or splenomegaly [5-8]. Importantly, this case also illustrates that rituximab-based monotherapy can effectively address both the underlying lymphoma and the associated inhibitor, leading to sustained clinical and biochemical remission [10].

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Institution Where Work Was Done

Orlando Health Cancer Institute, Orlando, FL, USA.

Informed Consent

Written informed consent was obtained from the patient for publication of this case report.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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