Diagnostic Challenges in a Patient with Acquired Hemophilia A: a Case Report from Rural Hospital

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ABSTRACT

Acquired Hemophilia A (AHA) is a rare autoimmune bleeding disorder caused by autoantibodies against factor VIII, typically affecting older adults without prior bleeding history. Its nonspecific presentation often leads to underdiagnosis, particularly in resource-limited settings. We report a 62-year-old woman presenting with spontaneous extensive bruising without trauma or anticoagulant use. Examination revealed multiple hematomas. Laboratory findings showed anemia (Hb 9.1 g/dL), normal platelet count and prothrombin time, and isolated prolonged APTT that failed to correct on mixing study, indicating an inhibitor. Factor VIII activity was markedly reduced (5%). Due to limited facilities, inhibitor titration could not be performed. A diagnosis of AHA was established, and the patient was treated with corticosteroids and azathioprine, resulting in clinical improvement. Diagnosis of AHA relies on recognizing isolated prolonged APTT uncorrected by mixing studies. In rural hospitals, limited access to specialized assays poses challenges, making early clinical suspicion essential. Management includes bleeding control and inhibitor eradication using immunosuppressive therapy. AHA should be suspected in patients with unexplained bleeding and isolated prolonged APTT. This report highlights a pragmatic diagnostic approach to AHA in resource-limited settings where confirmatory assays are unavailable.

Keywords: Acquired Hemophilia A; factor VIII; prolonged APTT

Introduction

Acquired Hemophilia A (AHA) is a rare autoimmune bleeding disorder caused by the development of neutralizing autoantibodies (inhibitors) against coagulation factor VIII (FVIII), resulting in sudden-onset hemorrhage in individuals with previously normal hemostatic function. Its estimated annual incidence is 1–1.5 cases per million population, with a bimodal age distribution predominantly affecting older adults (median age 70–80 years) and, to a lesser extent, postpartum women[1]. Despite its rarity, AHA carries a substantial mortality risk of 8%–22%, largely attributable to delayed diagnosis and suboptimal hemostatic management[2].

Clinically, AHA presents distinctly from congenital hemophilia A. While inherited hemophilia classically manifests with recurrent hemarthrosis, patients with AHA more commonly experience spontaneous bleeding into the skin (ecchymoses), soft tissues (muscle hematomas), and mucous membranes (epistaxis, gastrointestinal, or genitourinary bleeding), with hemarthrosis occurring in fewer than 10% of cases[3]. This atypical presentation, coupled with the sudden onset in elderly or postpartum patients, frequently leads to initial misdiagnosis as anticoagulant-related bleeding, liver disease, or disseminated intravascular coagulation. The bleeding can be severe and life-threatening, with intracranial and retroperitoneal hemorrhages representing the most feared complications[4].

The diagnostic hallmark of AHA is an isolated prolonged activated partial thromboplastin time (aPTT) with a normal prothrombin time and platelet count, where the prolonged aPTT fails to correct upon 1:1 mixing with normal plasma indicating the presence of a circulating inhibitor[5]. Definitive confirmation relies on the Bethesda assay to quantify inhibitor titers, with values >0.6 Bethesda units/mL considered positive[6]. However, this specialized testing requires sophisticated laboratory infrastructure, quality-controlled reagents, and trained personnel, which are typically unavailable in primary or secondary-level healthcare facilities, particularly in developing countries.

The diagnostic challenge is profoundly amplified in rural and resource-limited settings, where access to coagulation laboratories is severely constrained and frontline clinicians often have limited awareness of AHA due to its extreme rarity. In such environments, patients frequently experience diagnostic delays of several weeks, during which time they remain at risk of catastrophic bleeding[7]. This case report describes a patient with AHA who presented with spontaneous bleeding in a rural Indonesian healthcare facility, highlighting the diagnostic obstacles encountered and the therapeutic strategies implemented within the constraints of limited laboratory resources. Through this report, we aim to raise clinical awareness of AHA

among practitioners in similar settings and propose a practical diagnostic algorithm applicable when specialized Bethesda testing is not immediately accessible.

Materials and Methods

This study is a case report of a single patient managed in a rural hospital. Clinical data were obtained from medical records, including history, physical examination, and laboratory findings. Basic coagulation tests including prothrombin time (PT), APTT, and mixing study were performed. Factor VIII activity assay was conducted, while inhibitor titration (Bethesda assay) was unavailable due to limited laboratory resources. The patient received standard clinical management for AHA, including immunosuppressive therapy. Ethical considerations were maintained with patient confidentiality preserved.

Case Presentation

A 62-year-old female with no prior personal or family history of bleeding disorders presented to the emergency department of a rural hospital with spontaneous, extensive bruising over both lower limbs and upper limbs for one week as seen in Figure 1. The patient denied any history of trauma, recent surgery, or anticoagulant use. She also reported mild fatigue but no joint swelling or hematuria. She had type 2 diabetes mellitus managed with oral medication.

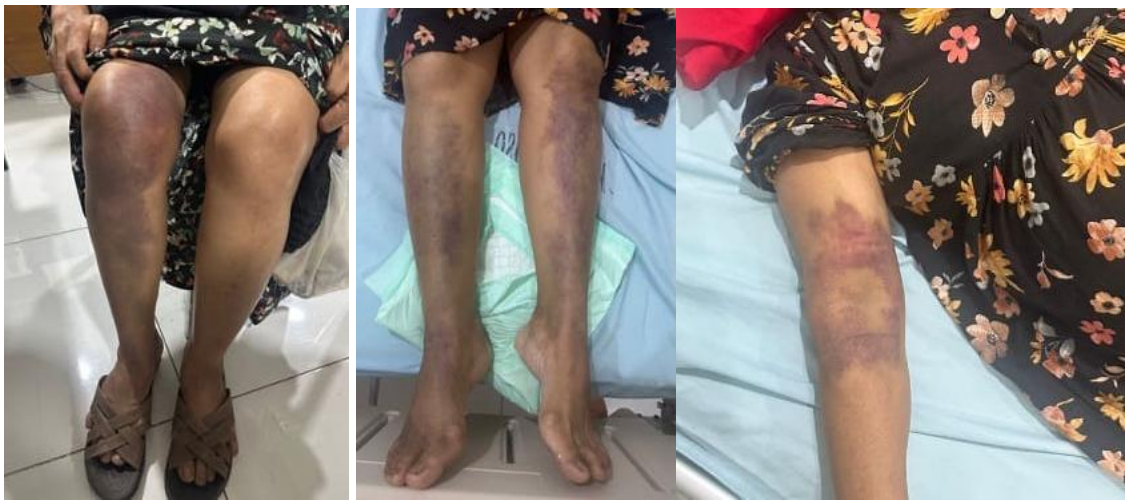

Figure 1. Extensive bruising over both lower limbs and upper limbs in patient.

On physical examination, the patient appeared with multiple hematomas of varying sizes over the extremities. There was no evidence of active external bleeding, hepatosplenomegaly, or lymphadenopathy. Vital signs were stable.

Initial laboratory investigations revealed a hemoglobin level of 9.1 g/dL, WBC 8700 cell/mm^3, platelet count of 244.000 cell/mm^3, glucose 362, normal prothrombin time (PT) at 14 seconds (reference range 11-14 seconds). However, the activated partial thromboplastin

time (APTT) was markedly prolonged at 54 seconds (reference range 28–38 seconds). A mixing test performed by combining patient plasma with normal plasma failed to correct the APTT, suggesting the presence of an inhibitor. Further evaluation demonstrated a significantly reduced factor VIII activity level of 5%.

Based on the clinical presentation and laboratory findings, a diagnosis of Acquired Hemophilia A was established. The patient was managed with bypassing agents for bleeding control and immunosuppressive therapy consisting of corticosteroids and azathioprine. During hospitalization, her bleeding episodes gradually subsided.

Discussion

Acquired Hemophilia A (AHA) is a rare but potentially fatal autoimmune bleeding disorder caused by the development of neutralizing autoantibodies against coagulation factor VIII (FVIII). This case illustrates the characteristic clinical presentation and diagnostic challenges of AHA in a resource-limited setting, where access to specialized coagulation testing is severely constrained. In this discussion, we contextualize our findings within the existing literature, examine the diagnostic and therapeutic dilemmas encountered, and propose practical strategies for managing AHA in rural healthcare environments[8].

The diagnosis of AHA often poses a significant challenge, especially in rural or resource-limited settings. The key laboratory hallmark of AHA is an isolated prolongation of activated partial thromboplastin time (APTT) with normal prothrombin time and platelet count. The failure of APTT correction in a mixing study strongly suggests the presence of an inhibitor rather than a simple factor deficiency. Confirmation is made by demonstrating low factor VIII activity and detecting an inhibitor using the Bethesda assay. Diagnosis pathway for AHA can be seen in **Figure 2**.[1] In this case, the diagnosis was based on markedly prolonged APTT that did not correct with mixing, combined with reduced FVIII activity, although inhibitor testing could not be performed due to limited diagnostic resources [9, 10].

Definitive diagnosis of AHA requires demonstration of reduced FVIII activity (<50%) and detection of FVIII inhibitors using the Bethesda assay, with titers >0.6 Bethesda units/mL considered positive[11]. In our case, however, confirmatory inhibitor testing could not be performed due to the unavailability of the Bethesda assay at our facility a limitation commonly encountered in rural Indonesian hospitals. Despite this constraint, the combination of typical clinical presentation, isolated prolonged aPTT, non-correcting mixing study, and low FVIII activity provided sufficient evidence to establish the diagnosis with reasonable certainty. This aligns with recommendations from the European Acquired Haemophilia Registry (EACH2),

which acknowledge that a presumptive diagnosis may be made in resource-limited settings based on clinical and laboratory features, even in the absence of formal Bethesda quantification[4]

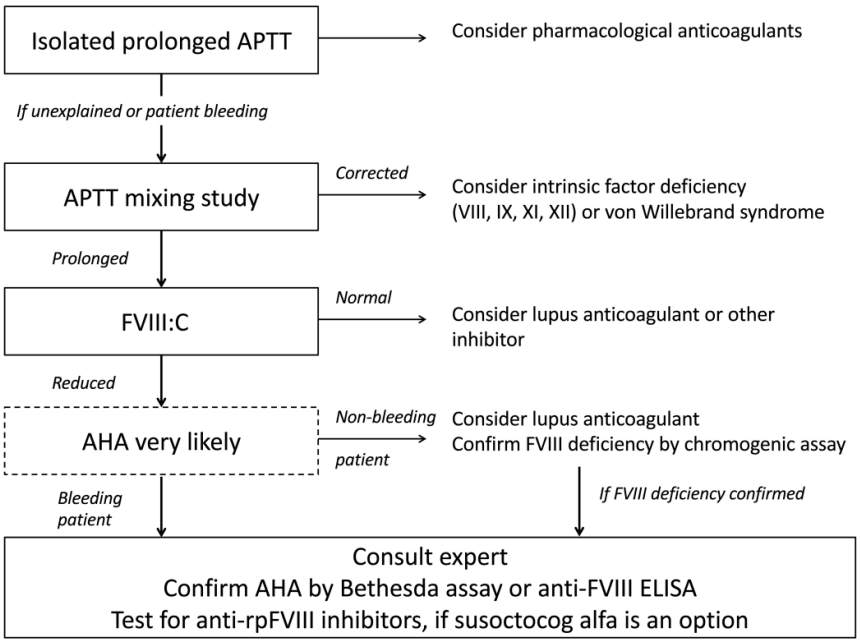

Figure 1. Diagnostic pathway for acquired hemophilia A. The activated partial thromboplastin time (APTT) mixing study will not be needed in an environment in which factor VIII (FVIII) activity is immediately available. Note that the presence of lupus anticoagulant does not exclude acquired hemophilia A. See the 'Diagnosis' section for more details. FVIII:C: factor VIII activity; AHA: acquired hemophilia A; ELISA: enzyme-linked immunosorbent assay; rpFVIII: recombinant porcine factor VIII.

Figure 2. Diagnostic pathway for Acquired Hemophilia A (Adapted from Tiede *et al.*, 2020)[1]

Differential diagnoses in patients presenting with prolonged APTT include lupus anticoagulant, heparin contamination, and congenital hemophilia. Lupus anticoagulant is typically associated with thrombotic events rather than bleeding manifestations, helping to distinguish it clinically from AHA[3] Careful interpretation of clinical presentation alongside laboratory findings is therefore essential to avoid misdiagnosis.

Management of AHA consists of two main goals: (1) control of active bleeding and (2) eradication of the inhibitor. Bleeding control may require bypassing agents such as activated prothrombin complex concentrate (aPCC) or recombinant activated factor VII (rFVIIa), both of which bypass the FVIII-dependent pathway. Eradication of the inhibitor is typically achieved using immunosuppressive therapy most commonly corticosteroids alone or in combination with cytotoxic agents such as cyclophosphamide. In refractory cases, rituximab or other immunomodulatory therapies may be considered.[2,4]

In rural hospitals, the diagnosis and management of AHA are particularly challenging due to limited access to specialized coagulation assays and bypassing agents. Many facilities lack the capability to perform factor assays or Bethesda titration, leading to delays in diagnosis

and treatment. Early recognition of the clinical pattern spontaneous soft tissue bleeding with isolated APTT prolongation should prompt clinicians to suspect AHA and initiate appropriate management or referral.[1]

This case underscores the importance of maintaining a high index of suspicion for acquired hemophilia in patients presenting with unexplained bleeding and abnormal coagulation profiles, even in settings with limited diagnostic resources. Prompt recognition and early initiation of immunosuppressive therapy are critical for achieving remission and reducing mortality.

Comparison with published cases. Our case shares several features with previously reported AHA cases from developing countries. A case series from Indonesia reported by Setiawan et al. (2021) documented similar diagnostic delays and reliance on clinical diagnosis due to the unavailability of Bethesda testing in six patients across three referral centers[12]. The clinical presentation of extensive ecchymoses, muscle hematomas, and mucosal bleeding was consistent with our observations, highlighting the reproducibility of the AHA phenotype across settings. A multinational registry study from Asia by Suzuki et al. (2020) found that idiopathic AHA represented approximately 55% of cases in the Asian population, consistent with the 50% figure reported in Western registries[11]. This suggests that despite geographic and ethnic differences, the underlying etiology and clinical manifestations of AHA remain largely uniform. However, the mortality rate in Asian cohorts was slightly higher (18% vs. 14% in European cohorts), possibly reflecting delayed diagnosis and reduced access to bypassing agents in resource-limited healthcare systems[12]. Our case also reinforces the observation from the EACH2 registry that the presence of underlying malignancy should be systematically investigated in older patients with AHA, as up to 10–15% of cases are associated with solid tumors or hematological malignancies[8]. In our patient, consistent with current recommendations for age-appropriate cancer screening in AHA patients.

Conclusion

Acquired Hemophilia A is a rare but serious bleeding disorder that requires a high level of clinical suspicion for timely diagnosis and management. This case highlights the diagnostic difficulties encountered in a rural hospital setting, where limited laboratory resources can delay confirmation. The presence of spontaneous bleeding with isolated prolongation of APTT that fails to correct in a mixing test should alert clinicians to the possibility of an acquired inhibitor. Early recognition, appropriate laboratory evaluation, and prompt initiation of immunosuppressive therapy are essential to reduce morbidity and mortality. Strengthening

awareness and diagnostic capacity in peripheral healthcare centers can significantly improve outcomes for patients with this uncommon condition.

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