Unveiling a 25-Year Journey: The Story of an Acquired Hemophilia Patient

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KEYWORDS: Acquired hemophilia A; Rituximab; Cyclophosphamide; Case report

CASE PRESENTATION

A 27-year-old Hispanic male with no past medical or family history presented to the hospital with progressively worsening skin bruising of six-week duration that started after a trivial leg injury (Year 1998). On physical examination, he was noted to have diffuse skin ecchymosis involving his bilateral lower extremities. Laboratory investigations revealed severe anemia with a hematocrit of 20% [Reference range (RR): 40–52%], prolonged activated partial thromboplastin time (APTT) of 112 s [RR: 25–37 s], and normal prothrombin time (PT). APTT did not correct on mixing studies. Factor VIII activity (FVIII) was undetectable [RR: 50–150%] with a FVIII inhibitor titer of 180 Bethesda Unit (BU) [RR: 0–0.5 BU]. Factor IX (FIX) activity was 198% [RR: 50–150%] and Factor XI (FXI) activity was 149% [RR: 50–150%]. Lupus anticoagulant (LA) was not detected. Ristocetin cofactor activity was 141% [RR: 40–163 %]. He was diagnosed with Acquired hemophilia A (AHA). Antinuclear antibody (ANA), Human immunodeficiency virus (HIV), and Hepatitis B and C serologies were negative. Chest X-ray was unremarkable. Along with supportive blood transfusions, he was started on a prednisone taper and oral cyclophosphamide after appropriate fertility counseling. Six months later, FVIII activity increased to 67% and the inhibitor titer became undetectable.

Over the last 25 years, his clinical course was largely unremarkable apart from intermittent episodes of bleeding. Bleeding manifestations included significant ones, such as a traumatic right calf hematoma in 2016, which was treated with two doses of desmopressin (DDAVP), resulting in a rise of FVIII levels from 1% to 32%, rituximab and steroids. Despite adequate treatment, he developed a calf pseudotumor, likely due to re-bleeding over time. Additionally, his only severe/life-threatening bleed occurred when he had a retropharyngeal hematoma in 2021 requiring recombinant activated factor VIIa (rFVIIa) and recombinant porcine FVIII (rpFVIII) after having been lost to follow-up during the coronavirus disease 2019 (COVID-19) pandemic. He also had knee hemarthrosis and minor bleeding instances like oromucosal bleeding.

For immunosuppressive therapy, he received intermittent cyclophosphamide and steroids for the initial five years. Azathioprine was briefly attempted but discontinued due to inefficacy. Due to concerns about stem-cell damage and secondary neoplasms associated with long-term cyclophosphamide use, he was treated with intermittent rituximab starting in 2003 based on reports of its successful use in treating AHA. Over the next 19 years, his FVIII levels were measured every one to two months and he had a relapsing-remitting clinical course with remission lasting for an average of eight to 12 months. He was treated with rituximab when his disease became active, as evidenced by decreased FVIII levels, and responded well to treatment (**Figure 1**). His FVIII inhibitor titers were also measured intermittently, and their values fluctuated over time (**Table 1**). Early in his disease course, rituximab was dosed similarly to that utilized in lymphoma treatment (four weekly doses of 375mg/m2). The dose was subsequently reduced to one or two doses per disease exacerbation, both to minimize exposure to rituximab and due to the lower dose's efficacy in increasing his FVIII levels as described in other autoimmune diseases. He has received 40 doses of rituximab so far, mostly dosed at 375mg/m2, with few doses of 700mg (324 mg/m2). To date, he has not developed any infectious complications from rituximab. He had transient, intermittent lymphopenia with rituximab and did not require prophylactic antibiotics. Immunoglobulin levels were not measured. Due to concerns about rituximab-induced immunosuppression amidst the COVID-19

Figure 1. Fluctuating FVIII levels between 2008–2023 and response to Rituximab. X-axis represents time in years. Y-axis represents FVIII levels. Red arrow head represents Rituximab.

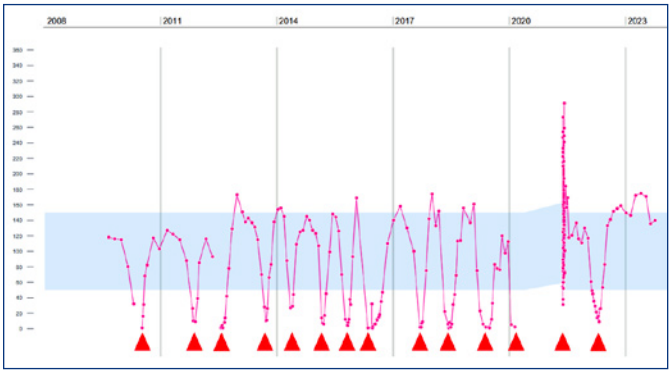

Table 1. Fluctuating FVIII inhibitor titers over time.

Date	Inhibitor titer(BU)
8/6/1998	180
8/10/1998	260
10/29/1998	46
2/15/1999	Undetectable
2/4/2003	22
2/12/2003	24
2/19/2003	31
2/26/2003	14
3/11/2003	4
5/13/2021	105
5/24/2021	52
6/1/2021	13
6/9/2021	<0.05

pandemic, his treatment regimen was changed from rituximab to oral cyclophosphamide in early 2022. He has been tolerating cyclophosphamide well apart from mild anemia. Steroid course and tapering regimen varied depending on the clinical situation, patient response, and side effects, particularly hyperglycemia. Steroids were used alongside rituximab only in some relapses due to long term side effect concerns given patient's young age. Typically, prednisone was started at 40 mg daily (around 0.4 mg/kg) and tapered by 10 mg every 2 to 3 weeks.

Etiology of AHA in our patient has remained unidentifiable despite over two decades of follow-up. Computerized tomography of chest, abdomen and pelvis have been unrevealing without any evidence of lymphadenopathy.

DISCUSSION

AHA is a rare, acquired bleeding diathesis usually seen in individuals over 65 years old. In our patient, AHA was initially diagnosed at a young age of 27, which is uncommon. It is caused by production of autoantibodies directed against epitopes present on FVIII molecule. Underlying etiologies like post-partum state, rheumatologic diseases and less commonly malignancies and exposure to drugs are identified in only half the cases.

Management of AHA involves inhibitor eradication and management of bleeding. Hemostatic management can be done using bypassing agents (BPA). BPA can either be rFVIIa, rpFVIII or activated prothrombin complex concentrates (aPCC) with paucity of data suggesting superiority of one over the other.[1,2] In our patient, rFVIIa, rpFVIII and DDAVP were used for hemostatic support at different times throughout his clinical course.

Inhibitor eradication is another major component of treating AHA. Per recent guidelines, combination treatment of glucocorticoids with either rituximab or cyclophosphamide is recommended initially if FVIII activity is less than one percent or inhibitor titer is over 20BU. If FVIII activity is over one percent and inhibitor titer is less than 20BU, starting with glucocorticoid monotherapy is a reasonable approach.[3] Consistent with these recommendations, our patient was started on prednisone and cyclophosphamide at the time of diagnosis given his undetectable FVIII activity and high titer inhibitor of 180BU. Rituximab was added intermittently for disease control as described above. There is a lack of data establishing the superiority of one immunosuppressive regimen over another.[4]

There is no clear consensus regarding optimal treatment dose and duration with rituximab. Most clinicians follow the regimen used for the treatment of lymphoma, which is four doses of 375mg/m2 one week apart. In our patient, single dose of 375mg/m2 of rituximab was generally effective in treating AHA relapse. One of the complications of rituximab therapy is increased risk of infections. About 30–50% patients with chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL) treated with rituximab had infectious complications.[5] However, our patient has not developed any infections. This could be because patients with CLL and NHL are at heightened risk of infection at baseline due to B-cell dysfunction and the ensuing secondary immunodeficiency intrinsic to these diseases. Lack of underlying disorder in our patient puts him at a relatively lower risk of infection with rituximab.

Rituximab is an effective treatment for autoimmune diseases in addition to hematological diseases. A retrospective, observational, single-center study analyzed 70 patients who received rituximab for a median of 10 cycles for various autoimmune and systemic inflammatory diseases. 1000mg Rituximab was given on weeks zero and two, then subsequently every six months for a median treatment duration of 54 months. One-third patients needed hospitalization for infectious complications.[6] However, only three patients were on rituximab monotherapy, so the results cannot be extrapolated to our patient.

Up to 23% of cases of AHA have reported instances of relapse.[7] In a retrospective analysis aiming to understand the natural history of AHA, 14 patients were studied over a median duration of 29.9 months (Range: 0.4–142.3 months). 13.4 months was the median time within which the 14 studied patients experienced one or more relapses.[7] This study concluded that the only risk factor with statistically significant risk of relapse was the presence of lymphoproliferative disorder. The levels of FVIII and FVIII inhibitors did not serve as predictive factors for a higher risk of relapse. Relapse was not associated with poor overall survival.[7] The reason for frequent relapses of AHA in our patient is unknown. It is a well-known fact that pregnancy-associated AHA has a much lower relapse rate compared to non-pregnancy associated AHA since pregnancy is a self-limited physiologic

condition.[8] There are also reports of resolution of cancer associated AHA after curative colon cancer surgery.[9] In our patient, etiological evaluation for AHA has been unrevealing. Perhaps, a lingering, unrecognized driving factor may be responsible for frequent relapses in our patient. Our case underscores the need for better pathophysiological understanding of AHA to guide treatment decisions.

Our case also highlights the chronic nature of an idiopathic autoimmune disorder, which is often underappreciated due to the typically shortened natural history owing to the advanced age of most patients. Younger individuals with acquired hemophilia usually have transient risk factors such as pregnancy, infections, or medication use, with AHA often resolving once these factors are eliminated. If thoroughly investigated, cases like ours could offer valuable insights into the immunopathology of acquired hemophilia. This would include comprehensive analysis of the patient's humoral and cellular immune responses, characterization of FVIII inhibitor(such as epitope specificity, inhibitor kinetics), and patient's FVIII variant. However, gathering such detailed information is not feasible in a community setting like ours. Nevertheless, our case remains an interesting anecdote and serves as a reminder of our incomplete understanding of this rare disease. Over two decades since its approval, rituximab has shown no new safety concerns. Our case reaffirms rituximab's safety and efficacy in treating AHA, highlights the relapsing-remitting nature of AHA, and serves as a reference for long-term management.

List of abbreviations

AHA: Acquired hemophilia A
RR: Reference range
APTT: Activated partial thromboplastin time
PT: Prothrombin time
LA: Lupus anticoagulant
ANA: Antinuclear antibody
DDAVP: Desmopressin
rFVIIa: Recombinant activated factor VIIa
rpFVIII: Recombinant porcine FVIII
COVID-19: Coronavirus disease 2019
aPCC: Activated prothrombin complex concentrates

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Disclosures

Funding: none

Acknowledgment: none

Conflicts of interest: none

Patient consent statement: Patient consent obtained

Ethics approval and consent to participate: Not applicable

Author contributions: ZK: involved in conception and design, collected data, drafted the manuscript, and finally approved the version to be published. MS and RS: supervised, revised the manuscript, and finally approved the version to be published.

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