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Factor VIII Eradication in Acquired Hemophilia A

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Introduction

Acquired Hemophilia A (AHA) is a rare autoimmune condition characterized by spontaneous synthesis of IgG against Factor VIII (FVIII) occurring with an incidence of approximately 1.5 per million per year, with an approximate 9-22% rate of mortality. Unlike congenital hemophilia, AHA occurs in males and females with incidence increasing with age. Disease phenotype may range from asymptomatic, presenting with abnormal lab values, to severe, with significant life-threatening or fatal bleeding. Patients often present with widespread subcutaneous bleeds, muscle hematomas, urogenital tract bleeding and mucosal bleeding. Unlike Congenital Hemophilia A, hemarthroses are uncommon. Patients remain at risk of life-threatening bleeding until the inhibitor has been eradicated. The factor VIII level and the inhibitor titer are not predictive of bleeding occurrences or the severity of bleeding events. The diagnosis of AHA is confirmed by the presence of an isolated prolongation of aPTT, non correcting mixing study, reduced FVIII levels and evidence of FVIII inhibitor. The following patient provides an example of a case of Acquired Hemophilia A.

Case Description

The patient is 78 year-old-male with a recent hospitalization for ESBL UTI and small bowel obstruction that was complicated by a right femoral DVT. He returned to the hospital with chief complaint of weakness, fatigue, exertional dyspnea and diffuse ecchymosis while on Xarelto. Admission labs revealed a Hgb of 8.0 with a significantly elevated PTT of 199 without prior personal or family history of coagulopathy. Subsequent evaluation demonstrated non corrective mixing studies, preliminary FVIII activity of 0.26% (normal 50-150%) and FVIII inhibitor level of 112.0 Bethesda units (BU). The patient's hospital course was complicated by development of significant right lower extremity hematoma and recurrent drops in hemoglobin. During admission the patient required multiple transfusions of blood products, including multiple transfusions of FEIBA (factor eight inhibitor bypassing activity) for continued spontaneous bleeding.

The patient was initially treated with prednisone 1mg/kg and Cyclophosphamide 2mg/kg daily. There was minimal change of FVIII activity/inhibitor levels after seven days. The cyclophosphamide dose was subsequently increased to 3mg/kg daily and 800mg Rituximab weekly for four weeks and adjuvant IVIG 1g/kg for two days were added. Cyclophosphamide was discontinued after 19 days of therapy due to neutropenia. While the FVIII inhibitor levels decreased promptly after giving Rituximab, FVIII activity remained relatively stagnant throughout the treatment course until the inhibitor level breached 10 BU. Over the 35 day admission, The FVIII inhibitor decreased from 112 to 1.6BU, FVIII activity increased from 0.26% to 17%, and PTT decreased from 199s to 38s. Three days after discharge, repeat labs demonstrated Factor VIII activity of 59% and FVIII inhibitor level of 0.00BU. The patient was discharged home on a steroid taper.

Relevant Medications and Laboratory Values

Prednisone		Date	Factor VIII activity (norm. 50-150%)	Factor VIII inhibitor (BU)	PTT (norm. 22-36 seconds)
10/10 -11/5	80 mg/day				
11/6	Begin Taper	10/6	0.26	112.00	122
Cyclophosphamide					
10/12 – 10/21	150 mg	10/11	-	200.00	
10/22 – 10/27	250 mg	10/15	0.47	320.00	88
10/28 – 10/31	200 mg	10/16	0.51	288.00	85
11/1 – 11/2	175 mg	10/19	0.53	160.00	87
		10/22	0.32	112.00	108
Rituximab					
10/17	800 mg	10/23	0.59	-	97
10/24	800 mg	10/25	0.64	40.00	92
10/31	800 mg	10/29	0.47	20.00	117
11/7	800 mg	11/1	0.64	15.00	98
		11/5	1.99	6.00	107
IVIG					
10/26	75 g	11/8	17	1.60	114
10/27	75 g	11/12	59	0.00	55
		12/3	112	0.00	34

Table 1. Treatment regimen utilized in the eradication of FVIII Inhibitor. Patient weight approximately 80 kilograms.

Table 2. Trend of Factor VIII inhibitor activity, Factor VIII inhibitor levels and PTT. BU = Bethesda units.

Coagulation Studies	
INR	1.12
PT (12.1 – 14.5)	21.8
PTT (22 – 36 sec)	199
Mixing Study*	Non Corrective

Table 3. Initial Coagulation studies on day of hospital admission. *Mixing study results initially reported as correcting with addition of plasma. Final result of mixing study were available on day 4 of hospital admission.

Discussion and Treatments

The goal of treatment in AHA is to reduce the duration of time at which the patient is at risk of life threatening bleeding events, this is achieved through inhibitor eradication. Although spontaneous remission may occur, the standard is to initiate treatment as soon as AHA has been identified. Treatment regimens largely consist of glucocorticoids alone, glucocorticoids and cyclophosphamide, and glucocorticoids and rituximab. Glucocorticoids alone may achieve eradication in approximately 30% of cases. The addition of cyclophosphamide may improve response to therapy to 60-100%. Although use of cyclophosphamide has been shown to improve inhibitor eradication a substantial proportion of patients die as a result of neutropenia-related infections. Combination therapy of prednisone and cyclophosphamide is largely regarded as the most effective standard first-line immune suppressive therapy to achieve inhibitor eradication. Despite this, up to one third of patients may not respond to initial treatment of steroids and cyclophosphamide. Rituximab has been implicated as an effective treatment option for patients resistant to initial therapy. The efficacy of IVIG remains unclear. A prospective study of 19 patients treated with IVIG demonstrated a $\geq 25\%$ decline of inhibitor titer in 8 of 16 assessable patients. Of note, patients achieving complete remission were noted to have low baseline inhibitor levels, one of which additionally received glucocorticoids.

Our patient presented with high titers of FVIII inhibitor. Initiation of prednisone therapy, with the addition of cyclophosphamide on day 3 of treatment, resulted in paradoxical increase inhibitor titers. A fall in titer levels correlates with the addition of weekly rituximab to the treatment regimen. Of note, cyclophosphamide was discontinued prior to inhibitor eradication. Final eradication of the inhibitor was achieved with continued prednisone and rituximab. Our patient also received 2 doses of IVIG between the second and third doses of rituximab. Examining the inhibitor titers during the treatment course suggests that rituximab was an important element of our treatment regimen. However, it is difficult to come to a conclusion on the true efficacy of components in our treatment regimen.

An important consideration of immunosuppressive therapy is risk of infection., particularly in an elderly patient. A two year observational study by Collins et al., included 172 patients with a median age of 78 years. Sepsis resulting from immunosuppression was the most commonly reported adverse event and contributed to the death in 12 patients. Following eradication our patient experienced multiple hospital readmission

Conclusion

AHA is a rare disease that is challenging to treat. A review of current literature shows numerous documented cases of successful inhibitor eradication. The large heterogeneity of reported cases poses significant challenges in the development of a standardized treatment protocol. Associated preexisting conditions such as malignancy, autoimmune disorders, pregnancy and previous treatment exposures make conclusions difficult. Another significant limitation is reporting bias, whereas successfully treated cases are more likely to be reported. When considering effectiveness of treatment regimens an additional factor to consider is the spontaneous resolution of inhibitors in approximately 30% of patients.

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Imaging

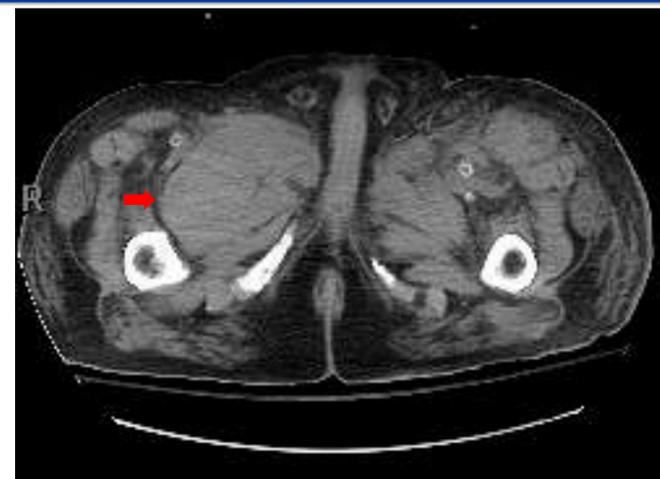


Image 1. CT abdomen and pelvis demonstrating the formation of spontaneous hematoma of the right medial compartment of the thigh

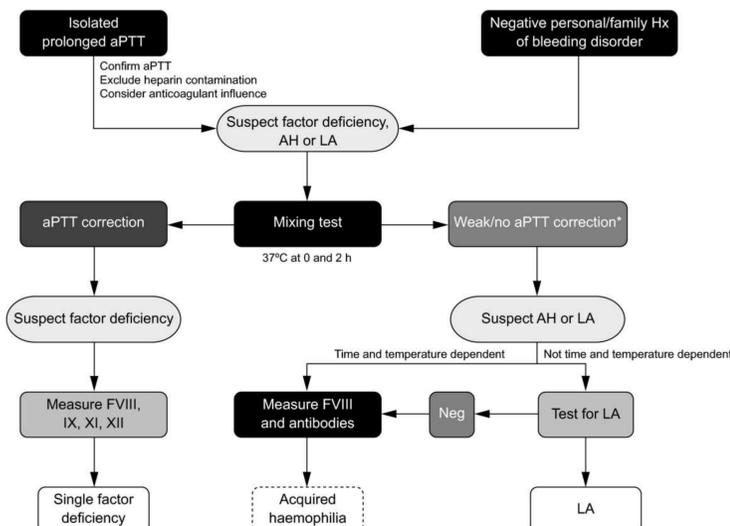


Figure 1. Flowchart in evaluation of acquired hemophilia. AH = acquired hemophilia. LA = lupus anticoagulant.