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Case Report

Successful treatment with low-dose rituximab and cyclosporine in acquired hemophilia A: a case report and review of the literature

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Abstract: Acquired hemophilia A (AHA) is a bleeding disorder caused by auto-antibodies to coagulation factor (F) VIII (Factor VIII inhibitor). Eradication of factor VIII inhibitor is vital therapy of AHA. Here, an AHA case is presented that was successfully treated with unconventional combination of low-dose rituximab and cyclosporine. Additionally, the literature about treatment of AHA with rituximab and/or cyclosporine AHA is also reviewed.

Keywords: Acquired hemophilia, factor VIII inhibitor, low-dose rituximab, cyclosporine, immuno-suppression

Introduction

Acquired hemophilia A (AHA) is a rare bleeding disorder with a high potential for severe bleeding and an inhibitor-related mortality rate of 7.9-22% [1], which is caused by an auto-antibody to factor VIII and might be associated with pregnancy, autoimmune diseases, malignancy, infections, or medication. Effective treatment of actual bleeding episodes and eradication of factor VIII inhibitor are the two important aspects in treatment. Rituximab has been shown to be a safe and effective therapy when used alone or in combination with other immunosuppressive agents as second-line therapy for AHA. In most studies, rituximab was conventionally prescribed as 375 mg/m^2 intravenously per week for 4-6 doses [2], while the effect of low-dose rituximab has seldom been reported. Here, an idiopathic AHA case is presented that was successfully treated with an unconventional combination of low-dose rituximab and cyclosporine.

Case report

A 27-year-old woman was admitted to our hospital in May 2011 due to multiple ecchymosis in left lower and right upper limbs. Two weeks previously, she had a sudden left lower limb pain without obvious incentive prior to ecchymosis in left lower limb. Ten days later, she presented right upper limb pain and ecchymosis. She didn't have bleeding symptoms of other organs or any symptoms of connective diseases. Laboratory study revealed activated partial thromboplastin time (APTT) of 90.5 seconds with normal PT and platelet count. Her medical history was notable for acute tonsillitis one month ago and she accepted antibiotics. Her past history was negative for constitutional or connective tissue disease symptoms or family history of bleeding complications.

Physical examination revealed ecchymosis and swell in left ankle and right forearm, which was exquisitely tender on palpation. Her bilateral amygdala was swollen (II). The rest of her examination results were unremarkable. There was no hepatomegaly, splenomegaly, or enlarged lymph node.

Laboratory studies revealed the following (reference ranges provided parenthetically): hemoglobin, 13.2 g/dL (11.5-15.0 g/dL); platelet count, 175 × 10^9/L (125-350 × 10^9/L); A coagulation screen produced the following results, indicating an isolated prolonged APTT: PT, 11.5

Table 1. Laboratory test results during treatment

	Treatment protocol	APTT (20 S-40 S)	FVIII:C (80%-150%)	Inhibitor titer
D0		77.9	31.7	15 BU/ml
D1	Cryoprecipitate 10 U/d*2 d	80	26.6	
D3	Plasmapheresis + melthylprednisone			
D7	+cyclosporine			
D21	+rituximab 100 mg/w*3 w	37.1	48.5	
D42		21.5	93.8	Negative

s (9.5-15.0 seconds); APTT, 77.9 s (20-40 s); fibrinogen, 4.0 g/L (1.8-4.0 g/L). A mixing test did not correct the observed prolonged APTT. FVIII activity was 31.7% (80%-150%) and an inhibitor titer of 15.00 BU/mL was obtained in the Bethesda assay. The blood smear did not detect any abnormal cells or fragmented red cells. Examination for the presence of auto-antibodies was done, but neither lupus anti-coagulant nor anti-cardiolipin antibodies were detected and there was no evidence of tumor, lymphoproliferative, or autoimmune disease upon further investigation. So this patient was diagnosed with idiopathic AHA.

She was administered cryoprecipitate 10 U/d for 2 days, but it had no efficiency on this patient, FVIII: C was 26.6%, APTT was still long (80 s) and the ecchymosis didn't fade away. On the 3rd day, plasmapheresis was administered combined with methylprednisolone at a dose of 40 mg/day. On the 7th day, she received oral cyclosporine 150 mg/d furthermore. FVIII activity increased from a pre-therapy value of 31.7% to 48.5%, and APTT dropped from 77.9 to 37.1 seconds after 2-week therapy. Given the appearance of the sodium-water retention symptom and still lower FVIII activity, low-dose rituximab 100 mg/w was administered for 3 weeks and glucocorticosteroid doses were reduced. She responded well to rituximab, and after 3 infusions, her APTT normalized to 21.5 seconds and her factor VIII inhibitor disappeared. Her factor VIII levels normalized at 93.8%. The ecchymosis and swell in left ankle and right forearm all fade away. The patient was discharged in July 2011. She continued to be administered with cyclosporine and decreased the dose gradually. She was followed up every 6-8 months with measurements of factor VIII level and APTT. Her APTT remained normal with no further bleeding events. She had no recurrence of her acquired hemophilia since then (see **Table 1**).

Discussion

AHA is a potentially life-threatening bleeding disorder caused by the development of auto-antibodies against FVIII [3]. In around half of patients, underlying disorders associated with AHA included pregnancy, autoimmune disease, and malignancy [4]; the remaining cases are idiopathic. Diagnosis involves an isolated prolongation of the APTT, without correction in mixing studies, low FVIII activity levels and evidence of a FVIII inhibitor [3]. Management of acquired hemophilia A involves controlling and preventing bleeds and using immunesuppression to eradicate the inhibitor [5]. First-line hemostatic treatment should be with bypassing agents such as recombinant activated FVII or activated prothrombin complex concentrate [2]. The guidelines recommend initial treatment with corticosteroids or combination therapy with corticosteroids and cyclophosphamide and suggest second-line therapy with rituximab if first-line therapy fails or is contraindicated [6, 7]. But the optimal strategy for inhibitor eradication is unknown [7].

Rituximab, a chimeric human/murine monoclonal antibody targeting the CD20 antigen on B-cell surface, is used to treat CD20-positive hematological cancers [8] and is now being increasingly employed to treat several autoimmune disorders including AHA [9]. Karwal et al. first reported rituximab was effective in eradicating the inhibitors in AHA in 2001 [10]. Large randomized clinical trials are considered unfeasible due to the rarity of AHA and the heterogeneity of patients and clinical manifestations of the condition. Thus, data from registries (including SACHA, HTRS, EACH2 and GTH-AH), single-center studies and many case reports only provide practical advice on the therapeutic management of AHA [3]. The cases of most studies about AHA treated with rituximab are less than 5 due to the uncommon of AHA, only a small number of studies are more than 5. Stasi et al. published an open label trial reporting 10 AHA cases treated with rituximab. All patients achieved complete remission (CR).

Among them, 2 patients with inhibitor titers higher than 100 BU/ml obtained a complete and sustained response following a combination therapy with rituximab plus pulsed intravenous cyclophosphamide [11]. Onitilo et al. also observed a rapid reduction of inhibitor titers in all 6 AHA patients treated with rituximab, with very little requirement for costly bypassing therapy (rFVIIa) and no need for long-term immunosuppressive maintenance [12]. Boles et al. and Wilson B et al. reported 14/15 and 7/8 AHA patients treated with rituximab alone or with the addition of immunosuppressive agents obtained CR respectively [13, 14]. In 2007, Franchini et al. summarized the effect of 65 AHA patients treated with rituximab alone or in combination with other immunosuppressive agents through a careful literature search, the results indicated that more than 90% (57/65) of cases achieved complete or partial response and the presence of high inhibitor titers (> 100 BU/ml) being a negative prognostic factor for response to rituximab [15]. In these studies, combination immunosuppressive agents included prednisone, cyclophosphamide, CVP (cyclophosphamide, vincristine and prednisone) and azathioprine but without cyclosporine. In 2015, D'Arena G et al. reviewed the literature on rituximab and AHA including all single-case-reports. Overall, 123 patients (77%) achieved complete response [9]. However, most data derived from small case reports, the limited follow-up of these cases and the concomitance of many immunosuppressive therapies interfere with the evaluation of the role of rituximab in inhibitor eradication. Consequently, the outcome data should be evaluated with caution [9, 15, 16]. The most authoritative results are the findings of EACH2 Registry: there were 51 analyzable patients who received rituximab as part of their regimen, 61% achieved remission; patients who received rituximab and another agent had a 67% CR, similar to the 70% rate observed for patients treated with corticosteroids and cyclophosphamide. Relapse was uncommon after a rituximab-based regimen (3%) whereas the adverse event rate for rituximab was 37%, similar to that for treatment with corticosteroids and cyclophosphamide. On the basis of these results, the authors concluded that there is actually no evidence to support the use of this agent as first-line therapy in AHA patients [17].

The dose of rituximab infused in all cases was 375 mg/m^2. Given the relative high relapse rate and adverse event rate of standard-dose rituximab, several cases had been reported a lower dose (100 mg) rituximab or with other immunesuppressive agents treating AHA [18-21]. Wermke M et al. first reported that 100 mg rituximab could achieve complete B-cell depletion and suggested that low-dose regimen rather than the classical lymphoma-dose (e.g. 375 mg/m^2) in the treatment of AHA [18]. Qingmin Yao et al. reported an 88-year-old man diagnosed with acquired coagulation factor deficiency received low-dose rituximab only, no sequential steroids or other immunosuppressive therapy, and it also got a similar effect to the conventional dose, and the sustained response is significantly. Nevertheless, the overall effects of this regimen need further evaluation in controlled trials [20].

Cyclosporin A, by diminishing synthesis and release of interleukin-2, inhibits T helper cell function and also has a sparing effect on T suppressor cell regulatory mechanisms [22]. Pardos-Gea J et al. enrolled a total of 11 AHA patients to assess prospectively a first-line calcineurin inhibitor based immunosuppressive therapy. A total of 8 patients received cyclosporine and 3 patients received tacrolimus. Sustained response (SR) was achieved in 10/11 patients (90.9%), whereas none of them relapsed during a median follow-up time of 14 months. Combination therapy of calcineurin inhibitors and pulse steroids was clinically effective as a first-line treatment of AH [23]. G. KAM et al. reported a 62-year-old lady diagnosed with surgery-associated acquired hemophilia A received standard-dose rituximab and Cyclosporin A and achieved faster inhibitor elimination [24]. Furthermore, a 58-years-old AHA patient didn't response to prednisone plus cyclophosphamide, but low-dose rituximab combined with cyclosporine induced durable remissions and was of particular benefit [19]. In the presenting case, at a low dose of rituximab with cyclosporine administration rapidly was found to eradicate the inhibitor, with the time to achieve a CR being 35 days, which was similar to first-line therapy (32 days) [17], but shorter than standard-dose rituximab-based regimens (65 days) [17]. No side effects were observed.

In conclusion, the combination of low-dose rituximab with cyclosporine was unconvention-

al but successfully eradicated inhibitors with rapid response time and acceptable side effects. Clinicians encountering this rare situation may wish to consider our strategy in their management decisions.

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Disclosure of conflict of interest

None.

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