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CASE REPORT

Acquired Factor VIII Inhibitor in Sjögren's Syndrome

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Introduction

Patients with factor VIII (FVIII) inhibitors, defined by the presence of autoantibodies to the FVIII molecule, present clinically with mucosal, soft tissue, and systemic bleeding episodes. Most cases are idiopathic, but up to 50% may be associated with autoimmune diseases or malignancies or may occur in the postpartum period (1,2). Associated autoimmune diseases include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and, rarely, primary Sjögren's syndrome (SS) (3,4). We describe here a case of FVIII inhibitor in a patient with primary SS and its successful treatment with rituximab, a chimeric, monoclonal anti-CD20 antibody.

Case Report

A 58-year-old white woman with SS presented to the rheumatology clinic with new-onset spontaneous ecchymoses on the neck and upper extremities. There was no history of trauma and no symptoms of mucosal bleeding or of blood in the stool or urine. Approximately one year ago, a diagnosis of SS had been made based on sicca symptoms, Raynaud's phenomenon, a positive antinuclear antibody (ANA) at >1:640 in a speckled pattern, and positive SSA/SSB antibodies. At that time she had been treated with artificial tears but declined medications to stimulate salivary flow. At the present time, she did not report worsening of sicca symptoms, arthralgias, abdominal pain, nausea, diarrhea, cough, dyspnea, weight changes, or a new rash. Her medications included citalopram, levothyroxine, lisinopril, verapamil, and artificial tears, with no new or over-the-counter medications. Physical examination revealed normal vital signs and was only remarkable for the presence of extensive ecchymoses over the neck and both upper extremities (Figures 1 and 2). Laboratory data showed a normochromic, normocytic anemia with a hemoglobin level of 10 gm/dl (patient's baseline hemoglobin 12 gm/dl, normal range 12–16 gm/dl) and a serum creatinine level of 1.5 mg/dl (baseline; normal range 0.7–1.4 mg/dl); the remainder of the blood count and the metabolic profile were normal. Coagulation tests showed an activated partial thromboplastin time (APTT) of 108 seconds (normal range 19.5–38.5 seconds), a prothrombin time (PT) of 13.3 seconds (normal range 12.2–15 seconds), and an international normalized ratio of 0.9 (normal range 0.9–1.1). Examination of the urine was negative for red or white blood cells, casts, blood, or protein.

Serologic testing revealed an ANA of 1:640 in a speckled pattern, positive anti-SSA/SSB antibodies, and negative anti-Sm, double-stranded DNA and RNP antibodies. Assays for anticardiolipin antibodies and lupus anticoagulant were negative. A computed tomography scan of the brain showed no evidence of intracranial bleeding. Evaluation of the prolonged APTT was undertaken in a stepwise manner. In our patient, the APTT did not correct with mixing studies or the addition of phospholipids to the plasma, suggesting the presence of a clotting factor inhibitor, which was then confirmed by the Bethesda assay. The Bethesda assay both establishes the diagnosis of an FVIII inhibitor (the most common clotting factor inhibitor) and quantifies the antibody titer (5). The Bethesda assay showed a FVIII inhibitor level of 287 Bethesda units (BU; normal range 0–0.7 BU), and a factor IX activity of 62% (normal range 60–160%). Our patient was thus diagnosed with the presence of an acquired FVIII inhibitor.

The patient was started on oral prednisone at a dosage of 2 mg/kg/day (100 mg/day). After 3 days of therapy, the APTT was 58.7 seconds (108 second APTT before treatment); however, the FVIII inhibitor titer was 512 BU (287 BU prior to treatment). The ecchymosis in the left upper extremity had increased in size, although the patient did not develop new ecchymosis. Rituximab was initiated in 4 weekly infusions of 375 mg/m^2. Prednisone was decreased to 60 mg/day, tapered, and discontinued after a total of 2 months of treatment. Within a few days of the first infusion of rituximab, the patient's ecchymoses improved. She also felt that her sicca symptoms improved. Following the second infusion, the APTT was 41.9 seconds and the FVIII inhibitor titer was 44 BU. After the fourth infusion of

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1. **the APTT did not correct with mixing studies or the addition of phospholipids to the plasma, sugges...**
Anchor Name: diagnosis of AH *[AOJE (Anthony Ojeil)]*

2. **Bethesda units (BU; normal range 0 – 0 .7 BU), and**
Anchor Name: normal range for Bethesda units
[AOJE (Anthony Ojeil)]

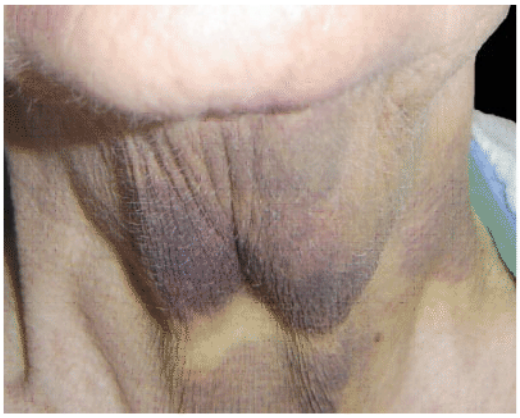

Figure 1. Neck ecchymosis.

rituximab, the FVIII inhibitor titer was 0.64 BU (normal range 0–0.7 BU), and the APTT was 29.1 seconds (normal range 18.5–38.5 seconds). The patient's ecchymoses continued to resolve.

Approximately 5 months after treatment with rituximab, the patient presented with right hip pain, and avascular necrosis was diagnosed based on magnetic resonance imaging findings. She was experiencing easy bruising without spontaneous ecchymoses, mucosal bleeding, or blood in the stool or urine. The APTT was 45.6 seconds (increased from 29.1 seconds after the fourth rituximab infusion). Work-up of the prolonged APTT was consistent again with the presence of an acquired FVIII inhibitor; the Bethesda assay was not performed to quantify the antibody titer and CD19 counts were not performed. The patient was retreated with rituximab and received 4 weekly infusions of 375 mg/m^2. Due to her recent diagnosis of avascular necrosis of the hip, she was not treated with prednisone. After completing the second course of rituximab, the APTT was 41.1 seconds (normal range 18.5–38.5 seconds) and the FVIII inhibitor titer was 0.90 BU (normal range 0–0.7 BU). The patient remained in remission. The most recent APTT value, measured 9 months after the last treatment, was 40.1 seconds (normal range 18.5–38.5 seconds) and the FVIII inhibitor titer was 0.90 BU (normal range 0–0.7 BU).

Discussion

The sudden presence of extensive ecchymoses in an older individual without significant trauma or a known bleeding disorder, with prolongation of the APTT, raises the clinical suspicion for an acquired clotting factor inhibitor. A prolonged APTT is also seen in antiphospholipid syndrome (APS), but these patients present with thrombotic rather than bleeding episodes. Prolongation of the APTT is also a hallmark of disseminated intravascular coagulation (DIC), but this diagnosis was unlikely in our patient who had a normal PT and normal platelet counts; also, our patient did not have conditions commonly associated with DIC such as sepsis, trauma, neoplasm, or obstetric complications (6,7). Normal liver function tests and a normal PT excluded liver disease as a possible explanation for her clinical picture.

The most common autoantibodies that affect clotting factor activity and lead to a bleeding disorder are directed against and interfere with the activity of FVIII. Most are IgG antibodies that do not bind complement, in contrast to the alloantibodies against FVIII that develop in patients with hemophilia that do bind complement (8). One population-based study from Wales suggested a prevalence of acquired FVIII inhibitor of 1.34 cases per million per year. Major associated conditions (each group is responsible for 5–10% of the total cases) were pregnancy and the postpartum period, rheumatic diseases such as RA, SLE, and less commonly, SS, and malignancies, especially adenocarcinomas of the lung and prostate and chronic lymphocytic leukemia. No underlying disorder was found in almost one-half of the patients with the acquired inhibitor. Most patients were older than age 50 years, except those in whom the condition was related to pregnancy or the postpartum period (9).

Bleeding is the clinical hallmark of acquired FVIII deficiency, sometimes noted postoperatively. Symptomatic patients often present with large hematomas, extensive ecchymoses, or severe mucosal bleeding that manifests as epistaxis, gastrointestinal bleeding, or gross hematuria. Spontaneous hemarthroses, which are common in hered-

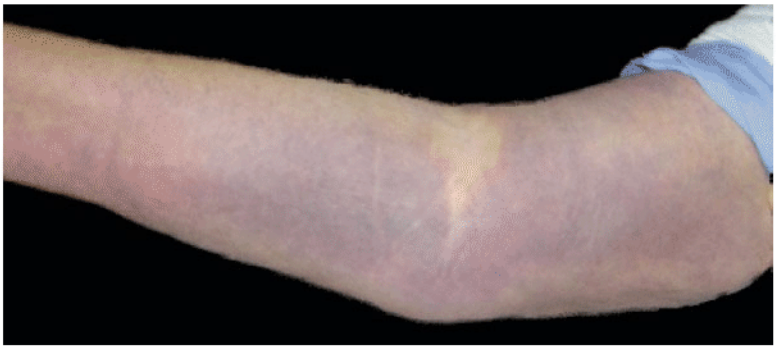

Figure 2. Forearm ecchymosis.

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Table 1. Summary of patients with factor VIII (FVIII) inhibitors and Sjögren's syndrome*

Author, ref.	Clinical presentation	Inhibitor titer, APTT	Treatment	Response to treatment
Dannhauser et al, 3	Spontaneous ecchymosis, hematuria	26 BU, 65 seconds	Oral prednisone, azathioprine	Remission, no further bleeding episodes
Dachman et al, 4	Compartment syndrome of thigh	40 BU, 61 seconds	FVIII concentrates, IV steroids, immunoglobulins, antifibrinolytics, blood transfusions	Bleeding controlled for 3 weeks, patient died from unrelated complications
Vignes et al, 18	Subcutaneous hematomas	512 BU, 96 seconds	Oral and IV steroids, CYC, IV immunoglobulins	Improvement but not resolution of inhibitor
Carmassi et al, 19	Muscular and subcutaneous hematomas	25 BU, 100 seconds	FVIII concentrates, oral prednisone, IV immunoglobulins, azathioprine	Remission with undetectable levels of inhibitor

* APTT = activated partial thromboplastin time; BU = Bethesda units; IV = intravenous; CYC = cyclophosphamide.

itary FVIII deficiency, are unusual with acquired disease (10,11).

The diagnostic hallmark of acquired FVIII deficiency is prolongation of the APTT. Other conditions causing a prolonged APTT such as APS, von Willebrand's disease, and DIC must be excluded. The Bethesda assay establishes the diagnosis and quantifies the inhibitor titer. In this test, serial dilutions of patient plasma are incubated with pooled normal plasma for 2 hours, and then FVIII activity is measured. The reciprocal dilution of patient plasma that results in 50% FVIII activity is defined as 1 BU. The stronger the inhibitor, the greater the dilution required to allow for FVIII activity.

Treatment of acquired FVIII inhibitors consists of 2 essential components: control of bleeding and elimination of the inhibitor. Active bleeding can be controlled with agents such as desmopressin or by replacement with FVIII concentrates of human or porcine origin. Desmopressin is a synthetic vasopressin analog that causes vasoconstriction by directly stimulating the smooth muscle in the blood vessels. It also raises plasma levels of von Willebrand factor and FVIII (12). FVIII concentrates of porcine origin continue to be used because they have reduced cross-reactivity with anti-human FVIII antibodies. If human FVIII concentrates are used, these have to be given in quantities sufficient to overwhelm the inhibitor present in plasma. Therefore, replacement with FVIII concentrates is a good therapeutic option for patients with low titers of FVIII inhibitors (2,3).

A variety of immunosuppressive drugs have been used to eliminate or suppress the activity of the FVIII inhibitor. It should be noted that 30% of patients with an acquired FVIII inhibitor have spontaneous recovery over a mean period of 14 months (13). In a study of 31 patients with acquired FVIII inhibitors, 13 responded to prednisone, whereas a smaller number (8 patients) benefited from the addition of cyclophosphamide (CYC) (14). In another study of 12 patients with acquired FVIII inhibitors who failed to respond to FVIII concentrate infusions, 11 responded after 1–3 courses of a combination regimen of intravenous (IV) and oral CYC, IV vincristine, and oral prednisone, with disappearance of the inhibitor without recurrence after a followup of 2–5 years (15).

Rituximab is an anti-CD20 chimeric monoclonal antibody that binds specifically to the CD20 antigen in normal and malignant pre–B and B lymphocytes, but not to plasma cells, because the latter do not express CD20 (16). Several case reports and series have described the successful use of rituximab in patients with acquired FVIII inhibitors (1,17,18). In these series, 1 patient had RA; others had no associated rheumatologic conditions. Rituximab was generally successful in patients with low titers of FVIII inhibitors. Patients with high titers required repeated courses of rituximab infusions or concomitant treatment with CYC to achieve remission. A more recent case series described the successful use of rituximab in 4 patients with high titers of FVIII inhibitors ranging from 249 to 725 BU. However, it should be noted that all of these patients had only partial responses, 3 of whom relapsed and required concurrent treatment with CYC (17).

Four reports of FVIII inhibitors in patients with SS have been described in the literature and are summarized in Table 1. One patient presented with spontaneous ecchymosis and hematuria, an APTT of 65 seconds, and a FVIII inhibitor titer of 26 BU (3). Treatment with oral prednisone and azathioprine controlled the bleeding and normalized the APTT, and the patient remained in remission. The second patient presented with a compartment syndrome of the thigh after a fall (4), with an APTT of 61 seconds and a FVIII inhibitor titer of 40 BU, and was treated aggressively with FVIII concentrates, IV corticosteroids, immunoglobulins, antifibrinolytic agents, and blood transfusions; the patient's bleeding was controlled and the APTT was maintained below 40 seconds for 3 weeks. However, the patient died from complications of chronic obstructive pulmonary disease. Vignes et al described FVIII inhibitors in a patient with SS who presented with subcutaneous hematomas, an APTT of 96 seconds, and an FVIII inhibitor titer of 512 BU. The patient was treated with oral and IV steroids and CYC and IV immunoglobulin, which led to improvement but not resolution of the FVIII inhibitor (18). Carmassi et al reported a patient with SS with acquired

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FVIII and IX inhibitors who presented with extensive muscular and subcutaneous hematomas. The patient had an APTT of 100 seconds and FVIII and IX inhibitor titers of 25 and 7 BU, respectively, and was treated with FVIII concentrates, oral prednisone, IV immunoglobulins, and azathioprine, and achieved remission with undetectable FVIII and IX inhibitor levels (19). Our patient responded to a regimen of prednisone and rituximab, and on relapse was successfully treated with rituximab monotherapy.

In conclusion, we report the first case to our knowledge of a patient with SS with acquired FVIII inhibitor who achieved complete remission after treatment with rituximab. However, we would urge caution that B cell depletion therapy may not be effective in all instances of acquired FVIII inhibitors secondary to autoimmune disease. Our successful outcome may be due to the relatively low titer of acquired FVIII inhibitor (287 BU) in our patient at presentation. Bleeding secondary to acquired FVIII inhibitors is a rare complication of SS, and should be suspected in patients presenting with spontaneous ecchymoses or hematomas. Rituximab may be a safe, effective treatment in such patients and obviate the need for cytotoxic agents.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Ranganathan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Vintimilla, Joseph, Ranganathan.
Acquisition of data. Vintimilla, Joseph, Ranganathan.
Analysis and interpretation of data. Vintimilla, Joseph, Ranganathan.

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