Acquired factor VIII deficiency is a well-characterized hematologic disorder that involves spontaneous production of circulating IgG autoantibodies to human factor VIII. Although many patients go into remission with immunosuppression therapy alone, several studies have shown efficacy of combining factor VIII with immunosuppression therapy when patients are unresponsive to immunosuppression alone.\(^1,2\) We present the case of a man with multiple minor migratory ecchymoses who was subsequently diagnosed with acquired factor VIII deficiency and treated with porcine factor VIII infusion and cyclophosphamide after his factor VIII inhibitor levels did not initially resolve with immunosuppressive therapy alone. This article reviews the epidemiology, etiology, and pathophysiology of acquired factor VIII deficiency and illustrates the success of using porcine factor VIII followed by pulse-dose cyclophosphamide in a patient with an extremely high Bethesda titer inhibitor level.

**CASE PRESENTATION**

**Patient Presentation**

A 64-year-old man recently diagnosed with acquired factor VIII deficiency presented to the hematology clinic with a right olecranon hemorrhagic bursitis (Figure 1). Factor VIII levels had not improved after treatment with immunosuppressive therapy.

**History and Prior Management**

Four months prior, the patient noticed a bruise on his left hand while ocean fishing. He presented to a hospital internal medicine clinic because he saw the bruising slowly progressing up his left arm. The patient’s past medical history was significant only for rheumatoid arthritis. Initial laboratory results revealed a normal complete blood count, blood chemistry profile, liver-associated enzymes, and urinalysis. However, a coagulation panel returned abnormal with a partial thromboplastin time (PTT) of 73 sec (normal, 24–34 sec). The patient was consequently referred to the hematology clinic for further evaluation.

Further evaluation by a hematologist revealed an abnormal mixing study (PTT did not normalize with a 1:1 mix of normal and patient plasma) and low levels of factor VIII activity (2%). Initial factor VIII inhibitor levels returned at 81 Bethesda units (BU) (normal < 0.4 BU). The patient was diagnosed with acquired factor VIII deficiency and consequently started on 70 mg of prednisone daily.

Throughout the next few weeks, the patient continued to experience minor migratory ecchymoses involving his right arm and left periorbital area. None of the ecchymoses were life-threatening, and their frequency began to diminish over the ensuing 1 to 2 months following treatment initiation. However, during an attempt to taper his prednisone dosage 1 month prior to the current presentation, the patient suffered from a subcutaneous abdominal hemorrhage as a result of coughing paroxysms associated with an evolving upper respiratory tract infection (Figure 2). He was consequently admitted to the hospital for treatment and further evaluation.

After 4 days in the hospital, the patient’s abdominal hematoma stabilized, and his hematocrit level did not significantly decrease. Factor VIII replacement was not deemed necessary at this point, and the patient was discharged on a daily course of 70 mg of prednisone and 150 mg of cyclophosphamide.

**Current Presentation**

The patient had been doing well until the current
presentation when he presented again to the hematology clinic with a right olecranon hemorrhagic bursitis associated with the lack of improvement of factor VIII levels (Figure 1). As prior screening had revealed negative cross-reactivity between porcine factor VIII and human factor VIII, the patient was treated with 2 infusions of porcine factor VIII and 1500 mg of pulse-dose cyclophosphamide for 2 cycles. The patient’s factor VIII levels normalized, factor VIII inhibitor levels resolved, and no recurrent hemorrhagic events have occurred (Figure 3).

DISCUSSION

Acquired Factor VIII Deficiency

Acquired factor VIII deficiency, also known as acquired hemophilia, is a well-characterized hematologic disorder that involves the spontaneous production of circulating IgG autoantibodies to human factor VIII. The resulting factor VIII inhibition is frequently complicated by serious hemorrhages that may be life-threatening. Unlike congenital factor VIII deficiency, in which hemarthroses are relatively common, acquired factor VIII deficiency tends to more frequently involve soft tissue, retroperitoneal, and gastrointestinal bleeding.

Epidemiology and Etiology

Although extremely rare, acquired factor VIII deficiency is the most common acquired factor deficiency, occurring in 1 person per million each year. It has been associated with a variety of other autoimmune disease states such as systemic lupus erythematosus, Sjögren’s syndrome, and rheumatoid arthritis. In addition, it has been shown to be associated with the post-partum state, medications (eg, penicillin), and hematologic and nonhematologic malignancies (eg, B cell lymphoma; acute lymphocytic leukemia; monoclonal gammopathies; lung, colon, pancreas, and prostate cancers). However, 46% of cases have no known underlying etiology.

Treatment

The treatment approach for acquired factor VIII deficiency has been well studied. Immunosuppressive therapy was introduced as the primary treatment approach during the latter half of the 20th century because of the disease’s autoimmune involvement. Numerous studies have shown the efficacy of corticosteroids and other immunosuppressive agents (eg, cyclophosphamide, azathioprine) in suppressing factor VIII inhibition. In addition, the efficacy of human and porcine factor VIII replacement has been well established as the primary treatment for episodes of acute bleeding.

Spontaneous remission of such acquired inhibitors has been documented; however, remission occurs in a minority of patients, and the cumulative evidence over the years has generally shown a poor prognosis in untreated patients.

Although many patients will go into remission with immunosuppression alone, some cases are refractory to immunosuppressive treatment and warrant different approaches. Several studies have shown the efficacy of combining factor VIII replacement with immunosuppression to suppress factor VIII inhibitors.

The theoretical basis for inhibitor suppression in this manner involves immunocyte “priming” by the initial factor VIII infusion. This mechanism depends upon the presence of minimal antigenic cross-reactivity between human and porcine factor VIII, which has been well documented. Porcine factor VIII is sufficiently
unlike human factor VIII (the target of the immune reaction) that it draws little to no affinity from the inhibitor, although it still retains the ability to prime the monoclonal subset of CD20+ B cells responsible for inhibitor production, making the B cells susceptible to lympholytic properties of cytotoxic agents. It is this lack of crossover with porcine factor VIII, along with the immune-modulating effects that cytotoxic agents possess, that quashes the immune reaction and controls hemorrhage.

Although some patients have responded to this treatment approach, there are few documented cases of success using chemotherapy alone. Furthermore, there have been no cases to date that have shown the efficacy of cyclophosphamide combined with factor VIII replacement in a patient with an initial Bethesda titer as high as was seen in the case patient (ie, 81 BU). The success of combining chemotherapy with factor VIII replacement was first illustrated by Green1 after observing a patient with a factor VIII inhibitor fail to respond to prednisone or cyclophosphamide alone but respond when the two immunosuppressive agents were administered following factor VIII infusion. This observation was later followed up by Lian and colleagues,2 who analyzed a series of cases of acquired factor VIII deficiency treated with combined cyclophosphamide, vincristine, and prednisone (CVP). Of 12 nonhemophilic patients, 11 patients responded after 1 to 3 courses of factor VIII infusion combined with CVP. However, 11 of 12 patients had an initial Bethesda titer inhibitor level of less than 46 BU. Furthermore, the one patient who had a Bethesda titer greater than 46 BU failed to respond to the CVP regimen.

The current case supports using combined chemotherapy and factor VIII infusion in treating acquired factor VIII inhibition. Although immunosuppression alone has been shown to be successful in treating acquired factor VIII deficiency, success is usually dependent on a prolonged course of immunosuppressive therapy. This may lead to a variety of untoward side effects, including an increased risk for opportunistic infections. Treatment with combined short-term pulse chemotherapy following factor VIII infusion may allow for inhibitor suppression without further prolonged immunosuppression. In addition, this case illustrates the efficacy of a single chemotherapeutic agent (cyclophosphamide) following factor VIII infusion in suppressing factor VIII levels. This may not only apply in cases with low Bethesda titer inhibitor levels, but also in those cases in which the Bethesda titer is extremely elevated. Thus, although prior cases have demonstrated the efficacy of a multi-chemotherapeutic regimen, successful suppression of factor VIII inhibitors may be attained with a single-drug regimen as described previously by Green,1 thereby

Figure 3. Successful treatment of acquired factor VIII inhibition with 2 infusions of porcine factor VIII followed by pulse cyclophosphamide (CP) in the case patient.
avoiding the increased risk for opportunistic infections and adverse side effects that accompany a multidrug regimen.

CONCLUSION

Acquired factor VIII deficiency has been well described in the literature. It is a rare disorder and has no standard approach to treatment. Additionally, high-titer inhibitors represent only a fraction of all cases, and we demonstrate successful treatment of this unique clinical entity with both porcine factor VIII replacement therapy and cyclophosphamide. Although larger controlled clinical trials to further investigate the efficacy of combined single chemotherapeutic agents with factor VIII infusions would be beneficial, the rarity of this disorder may make this effort difficult.

REFERENCES