
Case report

Subcutaneous immunoglobulin therapy in an 11-year-old patient with common variable immunodeficiency and von Willebrand disease

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Background: Subcutaneous immunoglobulin (SCIG) is an option for replacement therapy in patients with humoral immune deficiencies.

Objective: To describe a patient with common variable immunodeficiency (CVID) and von Willebrand disease who tolerated immunoglobulin replacement via the subcutaneous route.

Methods: An 11-year-old boy receiving monthly intravenous immunoglobulin (IVIG) since 5 years of age presented to an academic medical center after moving to the area. The patient also had a history of von Willebrand disease. He had started receiving IVIG because of recurrent infections and an absent IgG subclass 3. Further immunologic assessment revealed a normal B-cell count, decreased IgM level, and an abnormal response to bacteriophage Φ X174. Given these findings and the lack of another cause, the patient was diagnosed as having CVID. Because of difficult intravenous access, a port was placed for IVIG administration in 1999. The initial port was removed because of infectious complications, and a second port was found to be distally displaced in the right atrium, requiring removal.

Results: Continued difficulties with intravenous access and the potential complications with maintaining a long-term indwelling catheter prompted consideration of alternative methods for immunoglobulin administration. After removal of the port, the patient was prescribed weekly SCIG infusions. He tolerated the infusions well without bleeding complications related to the von Willebrand disease and was able to transition to home infusions.

Conclusions: SCIG was well tolerated by a pediatric patient with CVID and von Willebrand disease without any significant bleeding complications.

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INTRODUCTION

Immunoglobulin replacement therapy has been a cornerstone of treatment for humoral immune deficiencies since it was first administered subcutaneously to a patient with agammaglobulinemia by Colonel Ogden Bruton in 1952.¹ Intravenous administration became the main route of therapy in the United States when intravenous immunoglobulin (IVIG) preparations were approved for human use in the 1980s.² Recently, subcutaneous immunoglobulin (SCIG) has received attention as an alternative to IVIG. SCIG offers the advantages of the possibility for self-administration at home, decreased systemic effects, and the lack of requirement for

venous access but has the disadvantages of more frequent dosing and possible local infusion site discomfort.² It is not known how well SCIG is tolerated in patients with bleeding disorders. We describe a pediatric patient with common variable immunodeficiency (CVID) and von Willebrand disease who has been treated successfully with SCIG.

CASE REPORT

An 11-year-old boy with a history of von Willebrand disease and an antibody deficiency presented to the Walter Reed Army Medical Center allergy/immunology clinic for continuation of IVIG therapy after moving to the Washington, DC, area. IVIG therapy was started in this patient at the age of 5 years because of recurrent infections and an absent IgG subclass 3. He had a good clinical response to IVIG with significantly decreased infections and an improvement in his quality of life. However, the immune system evaluation before starting IVIG therapy was not sufficient to make a specific diagnosis. Subsequent evaluation while the patient was receiving IVIG therapy revealed undetectable IgM levels, normal IgG and IgA levels, normal anergy panel results, and normal numbers and proportions of T, B, and NK cells on flow cytometry. To further characterize his ability to make

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specific antibodies while receiving IVIG therapy, he underwent further testing with 2 doses of the neoantigen, bacteriophage Φ X174. The results of this testing demonstrated a reduced antibody response and decreased antibody class switching from IgM to IgG, which are consistent with a defect in specific antibody formation.

Although the patient was tolerating IVIG, he had difficulty with venous access. Approximately 5 months into therapy, a venous access port device was placed. This was complicated by development of a vegetation that extended from the tip of his vascular port to the vena cava. After antibiotics were administered, the port was removed and a second port placed.

The patient's medical history was also remarkable for von Willebrand disease diagnosed at the age of 5 years, a few months before starting IVIG therapy. The patient was diagnosed as having type 1 von Willebrand disease based on an abnormal platelet function assay, abnormalities in the ratio of von Willebrand antigen to both factor VIII and ristocetin cofactor activity, lack of response to desmopressin, and family history of type 1 von Willebrand disease in his 2 sisters. He required factor replacement on 2 occasions. The first occasion, which occurred when the patient was 6 years old, resulted after an injury to his elbow while he was playing outside and required therapy with antihemolytic factor–von Willebrand factor complex in the emergency department. At the age of 10 years, the patient had a knee abrasion while playing, which eventually required 2 doses of antihemolytic factor–von Willebrand factor complex to stop the bleeding. Recently, he reported occasional bruising but had not had any significant bleeding episodes. He also had a history of seizures, recurrent headaches, and attention-deficit/hyperactivity disorder. He had no history of pneumonia or opportunistic infections.

His family history was remarkable for possible early deaths in his paternal uncle (at the age of 2 years) and paternal cousin (at the age of 23 years) because of infections, but no further information was available. His father had had unclear episodes of sepsis as a child, which did not recur after adolescence. The patient's father was no longer involved with the patient, so further details were not available. The patient's 2 sisters also had type 1 von Willebrand disease.

At presentation, his medications included intravenous immune globulin, 15 g every 3 weeks (approximately 430 mg/kg per dose); prophylactic amoxicillin, 500 mg/d; and lamotrigine for the seizures. Prophylactic amoxicillin therapy was started before the initiation of IVIG therapy and had been continued. He reported no drug allergies and his vaccinations were up to date, including live viral vaccines, which he tolerated without difficulty.

In our overall evaluation of the patient, the recurrent infections were certainly suggestive of a primary immune deficiency. The lack of other diagnoses, undetectable IgM, and abnormal production of specific antibodies, as shown by testing with bacteriophage Φ X174, were suggestive of CVID, although a decreased IgG level could not be demonstrated because he was receiving IVIG.³ The presence of lymphoid

tissue and normal B-cell counts made the diagnosis of X-linked agammaglobulinemia less likely. Treatment with IVIG was continued, but the interval was changed to 15 g monthly and the prophylactic amoxicillin therapy was stopped. The risks of maintaining a vascular access port device were discussed with the patient's mother. However, she wanted to keep the port in place. A subsequent echocardiogram to verify resolution of the prior vegetations revealed that the port was too distal and located in the right atrium. Removal was recommended. The patient was admitted to the hospital, and after the patient received therapy with antihemolytic factor–von Willebrand factor complex, the port was removed without complication. At this point, options for immunoglobulin replacement included continuing IVIG with a new intravenous tube placed for each administration, placing a new port with continuation of IVIG, and starting SCIG.

The patient's history of von Willebrand disease was a concern regarding the consideration of SCIG. This issue was discussed with the family and the patient's pediatric hematologist. Venous access remained difficult, and risks with maintaining a vascular port were significant. A trial of SCIG was considered reasonable given the relatively mild severity of the von Willebrand disease and the superficial tissue layers involved in SCIG.

After discussion of the options and the risks and benefits associated with each, the patient was prescribed SCIG. His dose was changed to immune globulin, 4 g subcutaneously weekly (equivalent to 114 mg/kg per week). His first infusion was administered in our clinic under physician observation. Other than some local discomfort, the patient tolerated the infusion well, without any bleeding or bruising complications. The next few infusions were administered at home under the direct guidance of a home health nurse. Currently, the patient's mother administers the infusions to the patient. The patient has tolerated SCIG well and remains without bruising or bleeding complications. He has maintained appropriate trough IgG levels and has had no recent infections. Overall, the patient and his family have been satisfied with the SCIG.

DISCUSSION

This case involves a patient with both CVID and von Willebrand disease. A literature review revealed no other reports of patients with both CVID and von Willebrand disease. A family who had 3 members with humoral immunodeficiency, cleidocranial dysplasia, and von Willebrand disease was described by Kelkar and Ten in 2001.⁴ These patients had normal immunoglobulin and IgG subclasses but were found to have defective responses to polysaccharide pneumococcal antigens. This syndrome and the humoral immune system abnormalities described in this report differ from our patient.

The prevalence of both immunodeficiency and coagulopathy, in general, including therapeutic coagulopathy such as with heparin or warfarin therapy, is likely much more common. However, the exact prevalence of the coexistence of these 2 disorders has not been defined, and no reports of

SCIG therapy in patients taking anticoagulants currently exist.

Regarding the immune status of patients with von Willebrand disease, a single study evaluated the immune system in patients with various forms of bleeding disorders.⁵ Three patients with severe von Willebrand disease were found to have increased immunoglobulins compared with controls but reduced lymphocyte counts, lymphocyte function (as determined by phytohemagglutinin stimulation tests), and classic complement pathway activity. Although the number of patients was small, this finding suggests a lack of association of von Willebrand disease with humoral immune deficiencies.

SCIG has become a viable alternative to IVIG replacement therapy in patients with humoral immune deficiencies.² The efficacy of SCIG is comparable to IVIG or intramuscular immunoglobulin.^{6–10} SCIG allows for the possibility of home infusions, which may improve the overall quality of life^{6,10,11} and offers the advantage of not requiring intravenous access. This was the main reason for pursuing SCIG in our patient.

The 2005 Practice Parameter for the Diagnosis and Management of Primary Immunodeficiency states that “central venous access devices for the sole purpose of administering IVIG should be discouraged.”³ Our patient had maintained a central venous access port for 6 years and experienced life-threatening complications with the development of an infection and formation of a vegetation. Clearly, the risks of maintaining a port outweighed the benefits in his case. Venous access, however, remained a significant difficulty. SCIG provided a viable alternative for continuation of immunoglobulin replacement without the need for venous access. This case illustrates the value of SCIG in patients who require immunoglobulin replacement but have difficulty with venous access.

A concern in our patient with starting SCIG therapy was the risk of bleeding given his history of von Willebrand disease. The most common local reactions in SCIG are swelling, erythema, tenderness, and induration.^{6–8,12,13} Gardulf et al¹³ noted that bruising was reported by 24 (16%) of 152 patients receiving SCIG. However, infusion volumes per site reached up to 40 mL. Other studies that used infusion volumes of 10 to 20 mL per site did not report bruising as an adverse effect.^{6,7,12} Bleeding has not been reported as an adverse event associated with SCIG. The risk of bleeding with SCIG in our patient was discussed with pediatric hematologists. Given that the patient’s von Willebrand disease was clinically mild and considering the risks and benefits of the immunoglobulin therapeutic options, starting SCIG was considered reasonable. The patient was monitored closely for any bleeding during his first infusion in the clinic. Since no bleeding complications were noted, the patient was able to transition the SCIG infusions to home and now enjoys the freedom of home therapy, although monitoring for bleeding remains important with each infusion.

Given the wide spectrum of bleeding risks and complications in patients with von Willebrand disease, the decision to administer subcutaneous therapies such as SCIG should be

individualized. Bleeding in von Willebrand disease typically manifests as easy bruising and prolonged bleeding from mucosal surfaces, although the severity of these symptoms may vary.¹⁴ von Willebrand disease consists of 3 major types.¹⁴ Type 1 von Willebrand disease is the most common type and manifests as mild to moderate bleeding symptoms, although some patients are asymptomatic. Type 2 von Willebrand disease consists of 4 subtypes, which range from moderate to severe bleeding complications. Type 3 disease is rare and typically has severe bleeding symptoms. The patient’s bleeding risk with von Willebrand disease involves both the determination of the type of von Willebrand disease and a thorough evaluation of the individual patient’s bleeding history. Since subcutaneous therapies are administered to the superficial tissue layers of the skin, they may be well tolerated in patients with mild von Willebrand disease. As the severity of von Willebrand disease increases, the risk-benefit ratio should be fully evaluated with close monitoring for bleeding complications with any subcutaneous therapy administered.

This case describes a pediatric patient with type 1 von Willebrand disease who had an immunodeficiency suggestive of CVID and required immunoglobulin replacement therapy in the face of difficult venous access. SCIG provided a viable option that allowed the avoidance of vascular access port placement and was tolerated well without any bruising or bleeding complications. This case illustrates that SCIG may be well tolerated in patients with mild bleeding disorders.

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