Successful Management of an Auto-Immune Hematologic Disorder in a Child with Velo-Cardio-Facial Syndrome

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Abstract

Velo-cardio-facial syndrome (VCFS) is the most common microdeletion syndrome in humans, caused by a hemizygous deletion from the long arm of chromosome 22 at the q11.2 band. Autoimmune disease is a known complication of VCFS but does not typically involve auto-immune attack on the immune system itself. In this report we describe a patient with VCFS who developed auto-immune thrombocytopenia, anemia, neutropenia and CD4-penia who was successfully managed with immunosuppressive therapy including Rituximab infusions and immunoglobulin replacement.

Keywords: Velo-cardio-facial syndrome, VCFS, autoimmune disease, thrombocytopenia, neutropenia, Rituximab

Introduction

Velo-cardio-facial syndrome (VCFS) is the most common microdeletion syndrome in humans with an expansive and highly variable phenotypic expression. VCFS is caused by a hemizygous deletion from the long arm of chromosome 22 at the q11.2 band. In most cases, the deletion spans three million base pairs containing approximately 40 genes. Immune abnormalities are part of the phenotypic spectrum of VCFS and may vary from complete thymic aplasia, immune deficiency, to more subtle immune dysfunction or even apparently normal immunity. A variety of autoimmune diseases are known to occur in VCFS including autoimmune thrombocytopenia, thyroiditis, juvenile rheumatoid arthritis (JRA), and psoriasis[1]. In this report we describe a patient with VCFS who developed auto-immune thrombocytopenia, anemia, neutropenia and CD4-penia who was successfully managed with immunosuppressive therapy including Rituximab infusions and immunoglobulin replacement.

Case Report

This caucasian male was first seen at our institution at 11 years of age with a history of worsening recurrent respiratory infections, splenomegaly and thrombocytopenia. His past medical history was significant for muscular VSD (repaired elsewhere at 4 weeks of age), seizures, cognitive delay, recurrent ear infections, and asthma with environmental allergies. An episode of transient immune thrombocytopenic purpura (ITP) six years previously had been treated successfully. There was no significant family history of recurrent or severe infections or other immune abnormalities. He had a recurrence of frequent nose bleeds that led to a diagnosis of pancytopenia and a referral to the hematology service. Bone-marrow biopsy was normal with no evidence for malignancy. He was followed for one year with a stable course until he developed recurrent febrile episodes and splenomegaly. In January 2008 evaluations for Hemophagocytic Lymphohistiocytosis (HLH) and other infectious causes of marrow suppression were negative. Laboratory studies demonstrated a total IgG level of 1730mg/dL, IgA of 214mg/dL and IgM 162mg/dL. Five months later, fever, splenomegaly and pancytopenia recurred. He had a positive Coombs test and antibodies directed against neutrophils and platelets were detected. Additional immune evaluation demonstrated negative antibody responses to vaccine antigens of tetanus and MMR, but positive responses to varicella, hepatitis B virus, diphtheria and 3 of 14 pneumococcal serotypes.

Initial management of his thrombocytopenia consisted of oral steroids and high-dose (6gm/kg) immunoglobulin (IVIG) as an immune-modulator. He responded initially to this approach and was maintained on IVIG 1gm/kg every 2 weeks, but within 2 months he had an exacerbation of thrombocytopenia requiring another

course of oral steroids. An evaluation for Autoimmune Lymphoproliferative Syndrome (ALPS) was negative (ALPS score 2/4, negative TNFRSF6 gene mutation analysis). Several immunologic parameters suggested significant thymic dysfunction. CD45RA/RO analysis showed a near-complete lack of CD45RA+ T lymphocytes in both the CD4 and CD8-positive lineages, suggesting a lack of naïve T-cells, as an indirect measure of thymic integrity. In addition, the patient showed a reduced number of FOXP3+ T-cells, as defined by FOXP3 expression on CD4 T-cells expressing bright CD25 (normal range for age: >27 cells/UL). This cell population is also of thymic origin. As a newborn, the diagnoses of VCFS had been considered but ruled out clinically because of the absence of some key clinical features. Following our evaluation, the diagnosis was considered and fluorescence in situ hybridization was performed that confirmed a deletion from chromosome 22 at the q11.2 band.

He was transitioned to subcutaneous IG, but this was insufficient to control his disease process, and he required several short-term high-dose courses of steroids and occasional platelet transfusions to maintain safe platelet counts above 20,000 per microliter. He required three hospital admissions for febrile respiratory infections or severe thrombocytopenia secondary to hypersplenism. He also began to develop severe neutropenia due to anti-neutrophil antibodies. At the lowest point his laboratory evaluations revealed a platelet count as low as 6000/microliter and an absolute neutrophil count of zero.

He developed significant Cushingoid symptoms as a result of chronic steroid use and an alternative approach was undertaken using a steroid-sparing agent (mycophenolate mofetil - MMF) and Rituximab, an anti-CD20 monoclonal antibody, to remove peripheral B cells. Rituximab was administered via intravenous infusion weekly for 4 weeks at a dose of 375mg per meter-squared. MMF was dosed at 750mg twice daily (conventional pediatric dose for a body-surface-area under 1.5m squared).

Over the course of several months we were able to successfully wean the oral steroids with complete resolution of the Cushingoid side effects and no evidence for recurrence of thrombocytopenia or neutropenia. We continued the subcutaneous IG as a replacement therapy in the context of B cell depletion from the Rituximab. His platelet counts normalized to a steady-state of 130-150 thousand per microliter and his absolute neutrophil counts were safely maintained above 1500 per microliter. His splenomegaly completely resolved as the platelet counts normalized and the previously debilitating respiratory symptoms did not recur. Approximately 6 months later he began to experience increased fatigue, decreased appetite, and progressive splenomegaly. Weekly blood counts revealed declining platelet counts

and ANC's and mild anemia. Lymphocyte subsets confirmed a return of CD20+ B cells and a second course of Rituximab was given with an excellent response.

We have since repeated Rituximab treatments on 5 occasions, with an interval of about 6-7 months between courses. We have observed that at approximately 6 months posttreatment his B cells become detectable, and within a month his platelet count begins to decline. Once the platelet count reaches 100,000 per microliter it drops precipitously and he becomes symptomatic (decreased energy and appetite) with hypersplenism and severe neutropenia and thrombycytopenia. Treatment with Rituximab pre-emptively once the platelet count reaches 100K/microliter has prevented further decline after the first dose of the series. We have elected not to perform a splenectomy in favor of maintaining protection against encapsulated bacterial pathogens.

His lymphocyte subset analyses have shown persistently low CD4+ T cells while on therapy with Rituximab and MMF (~170 per microliter), although he has not demonstrated any clinical signs of cellular immune deficiency (e.g. Severe or recurrent viral or opportunistic infections). There is no firm evidence in the literature that patients with VCFS have similar cellular dysfunction to that seen in HIV infection, but we suspected that the low counts together with the MMF therapy put him at a theoretical risk for opportunistic infections. We have elected to initiate prophylaxis against pneumocystis jirovecii pneumonia with trimethoprim-sulfamethoxazole.

DISCUSSION

This report describes a complicated case of VCFS with autoimmune thrombocytopenia and neutropenia, successfully managed with Rituximab B cell ablation and replacement SCIG. Individuals with VCFS are often found to have compromised immune systems, with primarily a cellular defect due to thymic agenesis or dysplasia[1-3]. VCFS also has a well-described association with auto-immune disease of various types[1, 4-14]. Perhaps these autoimmune abnormalities are related to a lack of appropriate T cell tolerance of self-antigens, but it is unusual to see an auto-immune attack of the immune system itself. The aggressive approach of removing the antibody-producing cells from the circulation is not without risks, but the most dangerous risks associated with Ritixumab do not apply to our patient: there is no risk for tumor lysis syndrome as he does not have a large tumor cell burden, and we are replacing his immunoglobulins with SCIG so he likely remains immune competent. The primary Rituximab adverse effect in our patient has been infusion reactions with the first dose of the 4-dose series. These are

typically managed with antipyretics, an antihistamine and in one instance a dose of solumedrol, along with meperidine to control rigors and a slower infusion rate. Subsequent doses resulted in no adverse effects. The interval between treatment series with Rituximab varies between patients, but typically is between 3 and 12 months. In keeping with this, our patient demonstrates return of B cells on lymphocyte subset analysis consistently 6-7 months after a treatment course.

This case also highlights the difficulty in diagnosing immune deficiency disorders in children, as well as the importance of recognizing the full phenotypic spectrum in VCFS. The average age for diagnosis of an immune deficiency is approximately 12 years, as it was in our patient. The cardiac defect should have prompted appropriate molecular genetics testing for VCFS in infancy. Although complex congenital heart disease, such as tetralogy of Fallot, interrupted aortic arch or truncus arteriosus typically prompt diagnostic work-up for VCFS, it must be kept in mind that VSD is the most common heart anomaly seen in VCFS[15]. His history of frequent otitis media infections and developmental delays are also consistent with VCFS. Although his immunologic abnormalities appeared in his second decade of life, one could argue that a more timely initiation of appropriate therapy could have limited some of his clinical manifestations.

This case not only has lessons about the evaluation of an immune abnormality in a pediatric patient, but also has implications for the management of severe antibodymediated autoimmune disease. It serves as a warning to physicians caring for other patients with VCFS that such immune abnormalities can occur and as a framework upon which therapy might be based. Since we began treating this patient, Rituximab was formally approved for the treatment of autoimmune thrombocytopenia.

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