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BIRC4 mutation: An important rare cause of uveitis

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Abstract

We report a 6 year old male with chronic severe recalcitrant bilateral anterior uveitis and a remote history of hemophagocytic lymphocytic histiocytosis (HLH) secondary to Epstein Barr Virus infection. The patient was treated for idiopathic uveitis after an initial extensive evaluation failed to reveal a specific diagnosis. The patient failed to achieve sustained inactive disease with multiple monotherapies including topical glucocorticoid, methotrexate, infliximab, mycophenolate mofetil and cyclosporine. Disease control was finally attained with a combination of cyclosporine and adalimumab. After more recent testing, he was found to have a novel deletion on the baculovirus inhibitor of apoptosis repeat containing protein 4 (BIRC4) gene, the causative gene for X-linked Lymphoproliferative Syndrome (XLP) type 2. We conclude that male patients with chronic idiopathic uveitis should be questioned about a history of HLH during their work-up and screened for BIRC4 mutation if appropriate.

Keywords

Uveitis; BIRC4 Mutation; XIAP Deficiency; XLP 2

Case

A 6 year old Caucasian male presented for evaluation and treatment of bilateral anterior uveitis initially manifested by decreased visual acuity. He was examined and had 20/600 vision, band keratopathy, 360 degree synechiae with bound pupil, and 3+ flare in the right eye and trace flare in the left eye. He was referred to Rheumatology for systemic therapy since topical glucocorticoids were not providing adequate control. He had no morning stiffness, arthralgias, myalgias, fever, rash, abdominal complaints or other systemic symptoms.

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Conflict of Interest Statement

The authors report no conflicts of interest.

Author Contributions

All authors were involved in the drafting and/or revising of the important content and all author approved the final version to be published.

Past medical history

At age 3 he had a prolonged hospitalization for hemophagocytic lymphocytic histiocytosis (HLH) secondary to Epstein Barr Virus infection. While hospitalized he had a liver biopsy for transaminitis which showed steatohepatitis and a bone marrow biopsy showing hemophagocytosis. During hospitalization he became coagulopathic, required hepatic artery embolization, and was intubated for severe respiratory distress. His work-up revealed normal immunoglobulin A, G and M levels and a decreased natural killer (NK) count with normal function measured using chromium release comparing NK cells to target cells. Familial HLH workup including SH2 domain protein-1A gene (SH2D1A), protein unc-13 homolog D (MUNC 13-4), and perforin mutation analyses were negative. He was treated with glucocorticoids, intravenous immunoglobulin, and rituximab (2 doses). After discharge his NK cell numbers returned to normal. He had no further episodes of HLH and uveitis was not present until we first evaluated him at 6 years of age.

Clinical course

The patient's uveitis improved with initiation of systemic therapy with methotrexate (25 mg subcutaneous weekly) and infliximab (10 mg/kg every 4 weeks). Two months after starting the regimen he developed vomiting and diarrhea for 3 days followed by a fever to 103 Fahrenheit for 1 week. Labs were drawn and significant for thrombocytopenia (73K), anemia (11.6 Hgb), elevated AST and ALT (214 and 87, respectively), hyperferritinemia (15,000), normal white count, mildly elevated CRP of 1.4 mg/dL, elevated d-dimer (3.23 ug/mL), high LDH (7844), normal erythrocyte sedimentation rate, negative anti-nuclear antibody, negative angiotensin converting enzyme, negative serum lysozyme and negative toxoplasma serologies. Polymerase chain reaction testing for cytomegalovirus was positive with 8,600 copies/ML detectable on quantitative analysis. His exam was significant for mild splenomegaly, diffuse abdominal tenderness, and myalgias. Given his remote history of HLH responsive to IVIG, he was treated with 2g/kg IVIG once and 30 mg/kg of methylprednisolone for 3 days; he improved and was discharged with infliximab, a prednisolone taper and methotrexate held. He was admitted several weeks later for transaminitis (AST and ALT 1285 and 792, respectively) on the day he was due to restart his infliximab. He had low-grade fevers the day before with vomiting. Notable labs included a normal white count, hemoglobin, and platelet count, d-dimer of 2.6 µg/mL, ferritin of 6848 ng/mL, negative hepatitis A/B/C serologies, negative liver autoimmune panel, ebstein-barr VCA IgG positive, ebstein-barr DNA PCR negative, CMV DNA PCR revealed 547 copies. He was again treated with 2 g/kg once of IVIG, 30 mg/kg of methylprednisolone and a prednisolone taper with good response.

Given his improving, but persistently elevated transaminases after hospital discharge, methotrexate and infliximab were discontinued. Insurance would not approve adalimumab so mycophenolate mofetil 750 mg twice daily was started. His transaminases slowly improved and his uveitis was controlled. Six months after presentation he had removal of a cataract on his right eye. Two months after the right eye surgery he developed uveitis in the left eye that was persistent despite topical ophthalmic drops and maximized dose of mycophenolate mofetil. Mycophenolate mofetil was replaced with cyclosporine with a goal trough level of 100-200 mcg/L. The patient's uveitis came under control with cyclosporine.

Two years after starting cyclosporine the patient's uveitis flared in both eyes. The uveitis resolved once the dose of cyclosporine was adjusted for weight-gain over the prior 2 years. Two and half years after his last uveitis flare cyclosporine was discontinued to see if he had established long-term remission. Within 4 weeks of stopping the cyclosporine he developed bilateral uveitis that was not controllable with topical glucocorticoids. He also developed loose and non-bloody stools, abdominal pain, 10-lb weight loss, arthralgias and a sinus infection. He had no fevers or rashes and was started on ciprofloxacin for sinusitis by his primary care physician. Labs at that time were notable for normal transaminases, normal white count, hemoglobin and platelet count, normal urinalysis, negative blood culture, ferritin of 164, normal fibrinogen and erythrocyte sedimentation rate of 45. Cyclosporine was restarted along with systemic glucocorticoids. His abdominal symptoms quickly resolved but his uveitis remained very active with significant flare, cells and declining vision in his right eye. Weekly subcutaneous injections of adalimumab 40mg (now approved by insurance) were added to his cyclosporine regimen and the uveitis came under control. Adalimumab was spaced to every other week with maintenance of remission. Around this time, a phenotype was described in males with severe uveitis in the face of EBV-induced familial HLH as the consequence of a mutation on the baclovirus inhibitor of apoptosis repeat containing protein 4 (BIRC4) gene the disease causative gene for X-linked Lymphoproliferative Syndrome (XLP) type 2.[1] Our patient was initially tested at a CLIA certified laboratory by gene sequencing and the inability to amplify exon 4 for sequencing suggested a deletion in this region of BIRC4. Subsequent CLIA certified clinical testing for BIRC4 protein expression showed the complete absence of protein by flow cytometry and a 7.45kb deletion of encompassing exon 4 of the BIRC4 gene was found by comparative genomic hybridization, confirming the diagnosis (Figure 1). This particular deletion has not been previously reported, but in conjunction with absent protein by flow cytometry is consistent with a clinically meaningful mutation. His family is clinically asymptomatic for the BIRC4 phenotype. His mother is a carrier with a deletion on the BIRC4 gene. His female maternal relatives and sister have not been tested at this time, but seek medical insurance approval to do so.

The patient had done well on 40 mg of adalimumab biweekly and cyclosporine for approximately 18 months before having a uveitis flare that abated after several weeks. The adalimumab was increased to 40 mg weekly in addition to topical prednisolone ophthalmic drops until the inflammation came under control. We plan to continue adalimumab and cyclosporine indefinitely.

Discussion

Uveitis is a relatively common pediatric inflammatory condition that is managed by pediatric rheumatologists. While it is most often encountered in the context of Juvenile Idiopathic Arthritis, many patients with idiopathic uveitis are also cared for in pediatric rheumatology clinics as well. While it is important to screen for other conditions associated with uveitis (e.g., sarcoidosis, infection, vasculitis) which may reveal an underlying cause, many uveitis patients remain without definitive diagnosis and are labeled idiopathic.

An important form of genetically inherited childhood uveitis is Blau Syndrome which is caused by mutation of the NOD2 gene. [2] Intriguingly BIRC4 has recently been identified as a NOD2 interacting protein and patients with BIRC4 mutations have been reported to develop uveitis as well as Crohn's disease-like granulomatous colitis as part of their clinical presentation. [1] BIRC4 binds to the NOD2 signalosome via interaction with RIP2, and in epithelial cells BIRC4 has been shown to be required for NOD2 mediated NF κ B activation. [3] NOD2 mutations in Crohn's are often inactivating [4] in contrast to the mutations associated with Blau syndrome which are activating. [5] Thus, it appears that either overactivation or underactivation of this pathway can lead to granulomatous pathology. Interestingly, the genotype of BIRC4 mutation does not seem to predict the presence of either uveitis or colitis, suggesting a complex relationship between this regulator of NOD2 signaling and clinical phenotype.[1]

BIRC4 mutation (XIAP deficiency) has been classically described to result in XLP type 2. XLP is a rare, inherited immunodeficiency characterized by recurrent episodes of HLH, hypogammaglobulinemia, and lymphoma. In the initial genetic analysis the classic XLP patients were found to have a signaling lymphocytic activation molecule (SLAM) associated protein (SAP) deficiency with an X-linked pattern of inheritance, but this was only seen in 55-60% of the XLP phenotype. [6-8] In 2006 Rigaud and colleagues examined 12 patients from 3 families with the XLP phenotype without a SAP deficiency. Patients from all 3 families had a gene mutation encoding and leading to a deficiency in BIRC4/XIAP. [9] It is important to note although Rigaud described a similar phenotype to the SAP patients, he specifically observed recurrent splenomegaly in the BIRC4 patients which is not typical of SAP deficiency which preferentially manifest with splenomegaly in the acute phase[10]. XIAP deficiency testing has previously been done by protein expression and apoptosis testing. However, these tests can be highly variable and some mutations do not cause complete XIAP deficiency, limiting the sensitivity of this screening.[11] With the availability of clinical genetic sequencing for the BIRC4 gene, we suggest that mutation analysis of BIRC4 be included in the evaluation of XLP2 for chronic idiopathic uveitis. Screening with for protein expression would be an advisable first step as this will identify most patients within hours of testing, however has the potential to miss some true cases as mentioned above.[1]

Uveitis is not a feature of SAP deficient patients, but has recently been described in XIAP deficiency. Speckmann described a German cohort of male patients with HLH, reduced or normal XIAP expression and EBV-induced HLH who were screened for BIRC4 mutations. They described 13 complex BIRC4 mutations and most importantly characterized several unique presenting manifestations not seen in the SAP patients including uveitis and Crohn-like bowel disease, both previously recognized as NOD2 associated diseases [1]. Thus, BIRC4 deficiency in some sense can be thought of extending the NOD2 phenotype of granulomatous uveitis or colitis into hemophagocytic syndrome. There has been an additional case of uveitis reported in association with BIRC4 deficiency beside the Speckmann article presenting in a 2 month old Caucasian male.[12]

Thus, BIRC4 deficiency and subsequent XLP2 should be on the differential diagnosis for children with "idiopathic" uveitis. This is particularly true for male patients that present with

a systemic inflammatory phenotype including splenomegaly or severe EBV infections. Our patient only had one remote history of EBV induced hemophagocytic syndrome, for which a work up at the time was unrevealing. Subsequently, no further episodes of clinically significant hemophagocytic syndrome were present, with uveitis being his major manifestation of disease. This highlights the importance of identifying potential hemophagocytic episodes in the past medical history for diagnosis, as the patients may only present to a rheumatologist's care long after such an episode and may no longer exhibit these more characteristic features of XLP2. We therefore advocate for BIRC4 mutation testing and XIAP protein expression for any male patient with idiopathic uveitis and one of these extended phenotypes on the basis of current disease or remote history. It should be stressed that the uveitis is unique to XLP2 and testing for other hemophagocytic syndromes is not necessarily warranted in this population. It is critical to make this diagnosis as these patients will likely need indefinite immunosuppression if uveitis is part of their disease process and monitored closely for HLH flares particularly if exposed to EBV. It is unclear what the overall prevalence of uveitis is in the BIRC4 mutation, but if they do not have it at presentation, frequent ophthalmologic evaluations would seem essential. There are no specific gene therapies available, but there are reports in the literature of hematopoietic stem cell transplantation being curative in the XIAP deficient patients who manifested with Crohn-like disease.[1, 13-15] Stem cell transplantation is a risky undertaking for a multitude of reasons with the potential for graft versus host disease being the most feared. As a result the prospect of stem cell transplant complications may not outweigh the risk of not undergoing the procedure. If nothing else the diagnosis of XLP type 2 provides the family and clinician with prognostic information and a reason for uveitis beyond the unsatisfying moniker "idiopathic" as well as the potential for future therapeutic intervention.

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Figure 1. Results of BIRC4 deletion testing

A-C. Flow cytometric analysis of XIAP expression. In all panels, the top plot represents the patient sample and the bottom plot represents the same day healthy control. In A, gating strategy is shown for CD3+CD4+ and CD3+CD8+ T-cells. In B, XIAP expression is shown in CD3+CD4+ T-cells. In C, XIAP expression is shown in CD3+CD8+ T-cells. Similar differences in XIAP expression were seen in CD3-CD19+ B-cells, CD3-CD56+ NK cells, and monocyte and granulocyte populations identified by forward and side scatter plots (data not shown). D) Map of the BIRC4 gene showing region of deletion. Exons are depicted as black boxes and labeled 1-6. The 3' untranslated region (UTR) is shown as a white box. Introns are depicted as diagonal lines connecting the exons. The region found to be deleted by CGH, extending an approximately 7.45 kilobase section encompassing the entirety of exon 4, is shown. This map is drawn to scale, with the scale bar in the upper right measuring 5 kilobases.