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CASE DISCUSSION

X-linked lymphoproliferative syndrome: An X-cellent question

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Here, we pose the question of which patient presentations should appropriately be evaluated for X-linked lymphoproliferative syndrome (XLP) to three experts in the field.

Case 1: A 4-year-old boy, who has had mild hypogammaglobulinemia and has been on IVIG replacement, develops intestinal Burkitt's lymphoma.

Case 2: A 3-year-old boy, who has been well, is admitted for pancytopenia, hepatitis and fever. He has had 2 weeks of fever prior to admission and is found to have very high circulating EBV DNA.

Case 3: A 12-year-old boy, whose much older maternal step-brother died of hyper IgM syndrome, comes in with a history of recurrent infections. An evaluation reveals an IgG of 135 mg/dl and IgA <5 mg/dl and an IgM of 21 mg/dl. His T cell and B cell numbers are completely normal.

Case 4: A 15-year-old boy has been evaluated several times for recurrent infections. He developed very severe EBV positive mononucleosis requiring a brief hospitalization as a 10-year-old. An immunologic evaluation including immunoglobulin levels and titers was normal at that time. As a 12-year-old, he developed a very prolonged viral illness complicated by bone marrow suppression. He required transfusions but after several months regained his health. An immunologic evaluation at that time was also normal. Recently, he has had two episodes of pneumonia and has required antibiotics for several other infections. At his most recent evaluation, he had an IgG of 350 mg/dl and IgA of 17 mg/dl and an IgM of 45 mg/dl. He had no titers to diphtheria and tetanus, which had previously been protective.

Case 5: A 23-year-old man, who has been treated for common variable immune deficiency with IVIG replacement for the past 5 years, was recently evaluated for a neck mass and found to have lymphoma.

Commentary from Dr. Alexandra Filipovich

Practicing immunologists suspect that XLP is underdiagnosed. If true, this is likely due to several factors. Among these is the variability of clinical presentations some of which are not obviously associated with lymphoproliferation or can be seen in other genetic immune defects (e.g. hypogammaglobulinemia), and even occur in presumed immunocompetent persons (e.g. non-Hodgkin lymphoma). The second reason may be the broad age span at which initial symptoms develop, with a significant proportion of patients seeking medical attention from internists unfamiliar with genetic immunodeficiencies. Thirdly, most medical practitioners, if they have heard of XLP, associate it exclusively with life-threatening EBV infection.

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Too often, a careful family history is not or cannot be obtained. Finally, frequently performed tests of immune function such as lymphocyte subsets, response to mitogens, or standard NK function testing may be normal, especially in patients who are not experiencing a severe viral infection.

The five vignettes presented here illustrate some of these diagnostic challenges. Cases 1 and 5 present the important clue of two clinical problems in the same patient pointing to the diagnosis of XLP: hypogammaglobulinemia, or CVID, and non-Hodgkin lymphoma (NHL). While the risk of developing NHL is increased in CVID overall, this association in a male under 50 should prompt an evaluation for XLP. Both these complications are seen in patients with XLP who are EBV naive as well as those who have survived severe EBV infection (case 4). Many NHL tumors in patients with XLP are EBV negative.

Case 3 demonstrates the usefulness of obtaining a family history—in that the finding of hypogammaglobulinemia, CVID, or hyper IgM syndrome in maternally related males argues strongly for the need to rule out XHIGM and XLP, both conditions which might benefit from timely hematopoietic cell transplantation. However, screening for XLP in males with sporadic CVID has been reported to be of low yield, 1/60, with the affected individual later found to have a relevant family history [1].

Cases 2 and 4 illustrate the link with EBV infection, which is the most commonly reported and often rapidly fatal complication of XLP. During EBV infection, and other viral illnesses as well, the invading pathogens are not adequately controlled by any of the Signaling Lymphocytic Activation Molecule [SLAM]-associated protein (SAP) deficient cytotoxic cells. The "lymphoproliferation" of CD8 T cells which is observed results in markedly elevated levels of cytokines (cytokine storm) responsible for the life-threatening hepatitis and hemophagocytic syndrome. In a retrospective genetic analysis of males with severe EBV-associated disease in Japan, 10/40 patients were found to have XLP—five of them were sporadic cases [2]. A rapid screening test for XLP is now available in the clinical setting. It uses flow cytometry to detect intact intracellular SAP in cytotoxic cells [3]. It is particularly useful in the critical cases of fulminant infectious mononucleosis where the prompt institution of chemotherapy in addition to steroids and Rituxan can be life-saving.

Commentary from Dr. Mary Ellen Conley

The spectrum of clinical and laboratory findings in patients with X-linked lymphoproliferative syndrome (XLP) is unusually broad [4—7]. The most common presentation is rampant Epstein—Barr virus infection resulting in fulminant infectious mononucleosis. Affected patients develop fever, massive lymphadenopathy, hepatic necrosis, coagulopathy, and bone marrow failure. The old literature suggests that about 60% of patients with XLP die of fatal EBV infection at less than 10 years of age [7]. However, before the gene responsible for XLP was identified in 1998 [8—10], it was difficult to make the diagnosis of XLP in the absence of fulminant infectious mononucleosis or a positive family history of disease. There are no routine clinical laboratory tests that are consistently abnormal in patients with XLP. In addition, as is true with all X-linked disorders that are lethal in the absence of medical intervention, about 50% of patients with XLP have no family history of disease because they are the first manifestation of a new mutation. Sporadic patients with atypical findings are unlikely to be diagnosed as having XLP.

The identification of SH2D1A as the defective gene in XLP has made it obvious that not all young males with fatal infectious mononucleosis have XLP and many patients with mutations in SH2D1A have findings that are not specific to XLP. All five cases described above could have XLP. Case 2 presents with a constellation of findings consistent with aggressive EBV infection and hemophagocytosis or bone marrow failure. This is quite typical of XLP; however, mutations in SH2D1A have not been found in as many as 40% of males with fulminant EBV infection [11]. Patients in whom mutations are not found may have mutations that are difficult to identify, a few may have defects in perforin or other proteins required for cytotoxic granule function [12], and some may have unrelated genetic diseases or multifactorial disease. Cases 1, 3, 4, and 5 all have hypogammaglobulinemia and an additional finding that suggests the diagnosis of XLP. Approximately 30% of patients with XLP develop hypogammaglobulinemia at some point during the course of their disease [7]. Case 1 is particularly suspicious because of the development of intestinal Burkitt's lymphoma. B cell lymphomas can be seen in about 25% of patients with XLP, and ileo-cecal Burkitt's lymphoma is the most typical tumor [13]. Although case 5 could have XLP, my index of suspicion is not quite as high with this patient because the site of the tumor is a little unusual for XLP.

In case 3, the history of hyper IgM syndrome in a maternal half-brother indicates the presence of an X-linked immunodeficiency in this family. That elevated IgM makes the diagnosis of X-linked agammaglobulinemia highly unlikely. Both CD40 ligand deficiency (X-linked hyper IgM syndrome) and XLP should be considered. I would favor the diagnosis of XLP because elevated serum IgM can be seen in XLP, but low serum IgM, as reported in the patient, would be unexpected in a patient with CD40 ligand deficiency. Furthermore, most patients with CD40 ligand deficiency have additional problems, such as neutropenia or opportunistic infections [14,15]. The progressive B cell deficiency, coupled with the severe EBV infection reported in case 4, is strongly suggestive of XLP.

Making the diagnosis of XLP would be expected to influence the care of the patient and help in genetic counseling of the family. An affected patient may have asymptomatic brothers who are vulnerable to the fatal complications of XLP. The SH2D1A gene is relatively small, 4 exons, and can be screened for mutations by a variety of techniques. In addition, cytoplasmic staining for SH2D1A in CD3+CD8+ cells is generally absent in patients with XLP, making this a quick and useful test [16].

Commentary from Dr. Kim Nichols

The male patients described in these five clinical vignettes have medical histories notable for varying combinations of dysgammaglobulinemia, malignant lymphoma, and bacterial or viral infections. These patterns of clinical features suggest the diagnosis of a primary immunodeficiency, such as common variable immunodeficiency (CVID), X-linked lymphoproliferative disease (XLP), X-linked hyper IgM syndrome