Commentary: Association of autoimmune hepatitis and Evans syndrome in children
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ABSTRACT

Autoimmune hepatitis (AIH) is a chronic liver disease that may be associated with extrahepatic autoimmune disorders. Evans syndrome (ES) is an autoimmune disorder that is characterized by a combination of immune thrombocytopenia and autoimmune hemolytic anemia. Association of autoimmune hepatitis with Evans syndrome is rare, especially in children. We reported a 3-year-old-female with pre-existing Evans syndrome who developed AIH type 1. This commentary reviews this case along with other reported cases of AIH and ES.

Introduction

AIH is a chronic necroinflammatory liver disease that is associated with circulating autoantibodies and hypergammaglobulinemia. AIH occurs predominantly in females (female: male ratio = 3:1) and most patients are diagnosed before the age of 18 years with a peak incidence prior to puberty. AIH type 1 is diagnosed for patients exhibiting seropositivity for smooth muscle and/or anti-nuclear antibodies while AIH type 2 is defined for those with liver kidney microsomal antibodies and/or liver cytosol antigen. AIH type 1 accounts for two-thirds of the cases and presents usually during adolescence, whereas AIH type 2 presents at a younger age especially during infancy. In children, AIH is more likely to present acutely with a more aggressive course than in adults. If left untreated, it may progress rapidly to cirrhosis and end stage liver disease.

ES is a rare autoimmune disease that was first described in 1951, characterized by a combination of immune thrombocytopenia (ITP) and autoimmune hemolytic anemia (AIHA). Both diseases are mediated by autoantibodies, though in some cases it is considered a T-lymphocyte disorder. As typical of other auto-immune disorders, ES has a chronic and relapsing course and treatment requires prolonged immunosuppressive therapy since it is associated with a higher mortality risk than AIHA alone. Although approximately half of patients with ES have no other associated immune disorders, ES has been reported in association with other conditions such as systemic lupus erythematosus, common variable immune deficiency, or autoimmune lymphoproliferative disorder. ES in children is considered a serious condition because the risk of life threatening hemorrhage is greater than in classic ITP.
AIH has also been reported with other autoimmune disorders such as systemic lupus erythematosus, rheumatoid arthritis, Sjögren’s syndrome, chronic thyroiditis, ulcerative colitis, celiac disease, connective tissue diseases, membranoproliferative glomerulonephritis, myasthenia gravis and immune thrombocytopenia. The association of AIH with ES is rare, especially in children. We reported the case of a child with AIH and ES1. We speculate that autoimmune diseases, such as AIH and ES, may share genetic susceptibility factors.

Case Report

A previously healthy two-year-old African American female was diagnosed with ES after a two-month history of epistaxis and easy bruising1. Laboratory evaluation was significant for anemia with hemoglobin 8.4 g/dl, and thrombocytopenia with a platelet count of 61,000/µl. Testing for associated viral infection with hepatitis A, B, or C, cytomegalovirus, Epstein-Barr virus, parvovirus, or herpes simplex virus was negative. Her antiplatelet antibody, direct Coomb’s test and anti-compliment factor 3 antibody were positive and her anti-nuclear antibody (ANA) was negative. She responded to treatment with a single 1g/kg dose of intravenous immunoglobulin (IVIg) followed by oral prednisone at 2mg/kg/day.

One year later, she developed AIH presenting with jaundice, pruritus, hepatomegaly, transaminitis with aspartate aminotransferase (AST) 547 IU/L and alanine transaminase (ALT) 600 IU/L, hypoalbuminemia with albumin 2.6 g/dl, with normal total serum protein of 7.9 g/dl. She had cholestatic jaundice with a total and direct bilirubin of 10.2 mg/dl and 8.8 mg/dl, respectively. The serum alpha-1-antitrypsin and ceruloplasmin concentrations were normal. Autoimmune markers were positive for ANA (1:40), smooth muscle antibody (1:40), and F actin antibody (39 units) with hypergammaglobulinemia (total serum IgG 1,090 mg/dl). Her anti-liver-kidney-microsome antibody, anti-HAV-IgM, HBsAg, anti-HBc and anti-HCV were negative. Liver biopsy confirmed histologic evidence of AIH with interface hepatitis of a mixed inflammatory infiltrate including lymphoid cells, eosinophils, neutrophils, histiocyte cells and plasma cells in addition to periportal fibrosis with rare portal-portal septa (stage 2 fibrosis) along with canalicular and hepatocytic cholestasis. Immunologic screening tests showed normal immunoglobulin concentrations, normal absolute lymphocyte counts and sub-set populations (including CD3, CD4, CD8, CD56, no double negative T cells) via flow cytometry without evidence of an autoimmune lymphoproliferative disorder. She responded to treatment with corticosteroids and azathioprine. During her hospitalization for AIH, she had an Evans syndrome exacerbation, with a drop in hemoglobin to 4.9 g/dl and elevated reticulocyte count up to 44% with normal platelet count which was treated with intravenous rituximab 375 mg/m² weekly for four doses followed by IVIg monthly for six months. She responded with an increased hemoglobin to 14 g/dl, and a reticulocyte count of 4.7% with normal white blood cell and platelet counts.

Association between autoimmune hepatitis and Evans syndrome

To our knowledge, the case report summarized above was the first case report of a pre-school aged child with a combination of AIH and ES. Tokgoz et al reported a 12-year-old female with ES, AIH and nephrotic syndrome in addition to lymphopenia, leukopenia, low IgA, IgG and IgM levels, CD3, CD4, CD8 along with low TCR alpha/beta expression, leading to a diagnosis of CD3γ (gamma) deficiency9.

There are other case reports of an association of AIH and ES in adults. Korkmaz et al reported a 53-year-old female with transaminitis, anemia and thrombocytopenia who was ultimately diagnosed with AIH-primary biliary cirrhosis overlap syndrome concomitant with ES10. Another case report described a 59-year-old female with AIH and Hashimoto’s thyroiditis in association with Hodgkin lymphoma who developed ES one year later11. Another case reported12 was a 47-year-old female with autoimmune myelofibrosis associated with AIH and concomitant ES who responded to treatment with prednisolone and rituximab similar to our case report1.

Treatment of AIH and ES

Patients with ES are difficult to manage. Although ES may initially respond to corticosteroids, it is a chronic condition with periods of exacerbation and remission. Due to side effects of chronic corticosteroid therapy, non-steroidal therapies are often employed. The first line of treatment of ES is IVIg or corticosteroids. The second-line immunosuppressive therapies include rituximab, azathioprine, cyclosporine and mycophenolate mofetil. Other intravenous agents that have been reported as treatments for ES in adults include romiplostim and eltrombopag13. However, there is limited evidence on the use of these agents for treatment of ES and AIH in children. The efficacy of rituximab for treatment of ES in adults has been reported in a number of cases14-16. One systemic review showed 11 (67%) of 17 ES in children achieved response, and 9 (52.9%) achieved a complete response to rituximab17.
Lastly, long-term treatment of pediatric AIH is usually required, with only 20% of AIH type 1 patients able to discontinue therapy successfully. We reported a 2-year-old girl with AIH and ES who responded well to rituximab weekly for 4 weeks, following a short-term response to IVIg, corticosteroids, and azathioprine. Currently, there are no randomized controlled trials to determine the most effective treatment for concomitant AIH and ES in children.

Summary

To our knowledge, this is the first report of a pre-school age child with concurrent AIH and ES. We conclude that since ES may evolve over a period of time, observation for associated autoimmune conditions should be considered in these patients. Further study is needed in order to better understand the optimum management of ES and AIH in children and adults.

References