**Name of Journal: *World Journal of Hepatology***

**Manuscript NO: 33476**

**Manuscript Type: Case Report**

**Association of autoimmune hepatitis type 1 in a child with Evans syndrome**

Jarasvaraparn C *et al*. Autoimmune hepatitis and Evans syndrome

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**Author contributions:** All authors contributed to the acquisition of data, writing, and revision of this manuscript.

**Institutional review board statement:** This case report was exempt from the Institutional Review Board standards at University of South Alabama.

**Informed consent statement:** Our patient’s legal guardian provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** The authors have no conflicts of interest to disclose.

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**Manuscript source:** Unsolicited manuscript

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**Telephone:** +1-251-4343919

**Received:** February 10, 2017

**Peer-review started:** February 15, 2017

**First decision:** April 17, 2017

**Revised:** June 27, 2017

**Accepted:** July 7, 2017

**Article in press:**

**Published online:**

**Abstract**

Autoimmune hepatitis (AIH) is a progressive liver disease that is often associated with extrahepatic autoimmune disorders. Evans syndrome (ES) is a rare autoimmune disorder, which is characterized by immune thrombocytopenia and autoimmune hemolytic anemia.Association of AIH with ES is rare, especially in children. We report a 3-year-old female with a past medical history of ES who presented with jaundice and significant transaminitis due to AIH type 1. She required multiple treatments with steroids as well as azathioprine, intravenous immunoglobulin and a course of rituximab.

**Key words:** Autoimmune hepatitis type 1; Evans syndrome; Child

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**Core tip:** We report a 3-year-old female with a past medical history of Evans syndrome (ES) who presented with jaundice and significant transaminitis due to autoimmune hepatitis (AIH) type 1. To our knowledge, this is a rareassociation of concurrent AIH and ES in a child who responded well to rituximab. The patient also demonstrated short-term response to intravenous immunoglobulin, methylprednisolone, azathioprine and oral prednisone. We conclude that ES may evolve over a period of several months therefore evaluation for associated autoimmune conditions should be considered in these patients.

Jarasvaraparn C, Imran H, Siddiqui A, Wilson F, Gremse DA. Association of autoimmune hepatitis type 1 in a child with Evans syndrome. *World J Hepatol* 2017; In press

**INTRODUCTION**

Autoimmune hepatitis (AIH) is characterized by chronic necroinflammatory liver disease of unknown cause, circulating non organ-specific autoantibodies and increased levels of immunoglobulin G. The epidemiology of pediatric AIH is unknown. Most patients are diagnosed before the age of 18 years and 75% are girls- the peak incidence being prior to puberty. Currently two types of AIH are recognized according to seropositivity for smooth muscle and/or anti-nuclear antibody for AIH type 1 or liver kidney microsomal antibody and/or to a liver cytosol antigen for AIH type 2. 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[1]. Liver biopsies remain essential for diagnosis and evaluation of disease severity in patients with AIH. In children, AIH often presents acutely and has a more aggressive course than in adults[2]. If left untreated, it generally progresses rapidly to cirrhosis and liver failure.

Evans syndrome (ES) is a rare autoimmune disease, which is characterized by 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. It was first described in 1951. The incidence of ES in children has not been calculated[3]. ES has a chronic and relapsing course, and patients usually depend on prolonged immunosuppressive treatments. ES is more difficult to treat and has a higher mortality than AIHA alone[4]. In approximately half of those diagnosed with ES, no other immune disorder is recognized but in rest of the patients it may be a manifestation of systemic lupus erythematosus, common variable immune deficiency[5], autoimmune lymphoproliferative disorder[6] or another immune disorders[7]. The first line of treatment is intravenous immunoglobulin or steroids. The second-line immunosuppressive therapies are rituximab, azathioprine, cyclosporine and mycophenolate mofetil. ES in children should be considered a severe disease because the risk of life threatening hemorrhage is greater than in classic ITP[3].

AIH cases have been reported concomitantly with extrahepatic immune disorders such as systemic lupus erythematous, rheumatoid arthritis, Sjögren's syndrome, chronic thyroiditis, ulcerative colitis, celiac disease, connective tissue disorder, proliferative glomerulonephritis, Myasthenia Gravis or ITP. Association with ES is rare, especially in children. We report a child with past medical history of ES who presented with jaundice and significant transaminitis due to AIH type 1.

**CASE REPORT**

A previously healthy two-year-old African American female presented with a two-month history of epistaxis and easy bruising. She was admitted to the University of South Alabama Children’s and Women’s hospital in May 2015. Examination was remarkable for few healing bruises without hepatosplenomegaly. Laboratory tests (Table 1) showed hemoglobin of 8.4 g/dL, mean corpuscular volume of 75 fL, white blood cell count of 14800/µL, platelet count of 61000/µL and reticulocyte count of 8%. Her aspartate aminotransferase (AST) was 387 IU/L and alanine aminotransferase was 449 IU/L. Coagulation studies were normal and the viral panels including anti-HAV-IgM, HBsAg, anti-HBc, anti-HCV, CMV-IgM, EBV-VCA-IgG, EBV-VCA-IgM, EB early Ag, EBnA, Parvovirus, and HSV-IgM were negative. Further laboratory evaluations yielded a negative anti-nuclear antibody, positive antiplatelet antibody and direct Coomb’s test positive for both Immunoglobulin G (IgG) and anti-compliment factor 3 antibody. Thus, a diagnosis of ES was made. After treatment with single 1 g/kg dose of intravenous immunoglobulin (IVIg) followed by oral prednisone at 2 mg/kg per day, her hemoglobin improved from 8.4 to 10.9 g/dL and corticosteroids were discontinued but she was lost to follow up overtime. She was hospitalized a few times for intravenous antibiotics due to a bacterial pneumonia and acute bacterial sinusitis. Her ES remained stable during this time. Immune work up showed normal immunoglobulin levels. (Immunoglobulin G 1.090 mg/dL, Immunoglobulin A 114 mg/dL, Immunoglobulin M 86 mg/dL and Immunoglobulin E 148 kU/L), normal absolute lymphocyte counts and sub-set population (including CD3, CD4, CD8, CD56, no double negative T cells) *via* flow cytometry without evidence of autoimmune lymphoproliferative disorder.

One year later, she developed jaundice and pruritus, hepatomegaly with a liver span of 13-cm and increased echogenicity without gallstones on abdominal ultrasound. Her laboratory findings included AST 547 IU/L, alanine transaminase (ALT) 600 IU/L, albumin 2.6 g/dL, total protein 7.9 g/dL, total bilirubin 10.2 mg/dL and direct bilirubin 8.8 mg/dL, prothrombin time (PT) 13.5 seconds, partial thromboplastin time (aPTT) 31 s, International Normalized Ratio (INR) 1.02, positive anti-nuclear antibody (1:40), positive smooth muscle antibody (1:40), positive F actin antibody (39 units) and elevated total serum IgG (1090 mg/dL). The anti-liver-kidney-microsome antibody, anti-HAV-IgM, HBsAg, anti-HBc and anti-HCV were all negative. The serum alpha-1-antitrypsin and ceruloplasmin concentrations were normal. Prior to percutaneous liver biopsy, she received packed red blood cell (for associated AIHA flare with Hb 4.9 g/dL and reticulocyte count 44%) and fresh frozen plasma. Her pre-biopsy hemoglobin was 11.5 g/dL with platelet count 101000 /mcL, PT 10.9 s, INR 1.0, and aPTT 31 s. She received high doses of intravenous methylprednisolone (30 mg/kg per day for 3 d) and oral ursodiol after percutaneously liver biopsy due to suspected AIH type 1. She was discharged with oral prednisone therapy after liver biopsy. Before discharge, her AST was 677 IU/L and ALT 1094 IU/L.

Liver biopsy revealed interface hepatitis with a mixed inflammatory infiltrate including lymphoid cells, eosinophils, neutrophils, histiocytic cells and plasma cells in addition to periportal fibrosis with rare portal-portal septa (stage 2 fibrosis) along with canalicular and hepatocytic cholestasis, indicating AIH. One month later after a high dose of methylprednisolone and oral prednisone, her AST improved to 194 IU/L and ALT to 424 IU/L. Shortly after, she was started on oral azathioprine at a dose of 1.5 mg/kg per day. Currently (4 mo after diagnosis of AIH), her AIH is controlled very well with oral azathioprine and oral prednisone, her present AST is 87 IU/L and ALT is 104 IU/L.

During her hospitalization for AIH, she also had a flare up of ES, with a drop in hemoglobin to 4.9 g/dL and elevated reticulocyte count up to 44% but stable normal platelet counts. She eventually received intravenous rituximab 375 mg/m2 every week as an outpatient for four doses and she is currently on a replacement intravenous immunoglobulin (IVIg) course once a month for six months. Her present labs show hemoglobin of 14 g/dL, reticulocyte count of 4.7% and a normal white blood cells and platelets count. She has not been hospitalized since starting Rituximab and IVIg for 7 mo.

**DISCUSSION**

This report describes an unusual case of ES and AIH type 1 in a child. The diagnosis of ES preceded that of AIH for over a year. Patients with ES have a relapse rate of 74%, with a median delay of eight months (41 d to 9.5 years). Among those, 52% relapse with ITP and AIHA, 40% with ITP alone and 8% with AIHA alone[3]. In a French study ES was found to be secondary to an underlying disease in 10% of patients. No secondary disease was diagnosed over the entire course of study in 30% of children[3]. In addition, 60% of patients with ES demonstrated other associated immune manifestations such as autoimmunity and lymphoproliferation. This suggests that ES occurs within the context of a poorly understood autoimmune dysfunction[3]. Tokgoz *et al*[8] published a case report of a 12-year-old female presenting with ES, AIH and nephrotic syndrome. She differed from our patient by having lymphopenia, leukopenia, low IgA, IgG and IgM levels; low CD3, CD4, CD8 and low TCR alpha/beta expression. Finally, she was diagnosed with CD3γ (gamma) deficiency. CD3 chain deficiency is a heterogeneous group of immunodeficiencies responsible for a small proportion of Severe Combine Immune Deficiency (SCID). Our patient had a history of recurrent infections but her immunoglobulin levels were not low, CD3, CD4 and CD8 were also unremarkable. Flow cytometry also showed no evidence of autoimmune lymphoproliferative disorder. Therefore, our patient demonstrated AIH and ES without evidence of CD3γ deficiency.

Patients with ES are difficult to manage. Although ES may initially respond well to corticosteroids, it usually runs a chronic course with intermittent exacerbations. Interestingly, the effectiveness of rituximab for adults in ES has been established in a number of cases[9,10]. The effects of a weekly infusion with rituximab for four weeks would be effective for up to one year[11]. Experience with the use of Rituximab for treatment of concurrent ES and AIH is limited, especially in children. Carey *et al*[11] reported successful treatment of refractory AIH and ES with rituximab in an adult. Rituximab has been explored in children for a number of hematologic conditions including treatment of AIHA, ITP, factors VIII and IX inhibitors in patients with hemophilia, post-transplant lymphoproliferative disease, Burkitt’s lymphoma and so on. It is overall well tolerated except for occasional symptoms of chills, fever, headache, occasional dyspnea, nausea, pruritus, angioedema, and/or hypotension[12].

Lastly, long-term treatment of pediatric AIH is usually required, with roughly 20% of AIH type 1 patients able to discontinue therapy successfully[1]. Interestingly, our case had elevated levels of immunoglobulin G during diagnosis of AIH type 1. Immunoglobulin G is usually raised at presentation in both types of AIH, although 15% of AIH types 1 and 25% of AIH type 2 have normal levels[13].

To our knowledge, this case report is a rare concurrent association of AIH and ES in a child who responded well to rituximab. The patient also demonstrated short-term response to IVIg, methylprednisolone, azathioprine and oral prednisone. We conclude that ES may evolve over a period of several months therefore evaluation for associated autoimmune conditions should be considered periodically in these patients. Most of the published literature consists of either case reports or small case series. International collaboration is essential in order to better understand the association and treatment of ES and AIH in children and adults**.**

**COMMENTS**

***Case characteristics***

A 2-year-old African American female with past medical history of Evans syndrome (ES) presented with jaundice and significant transaminitis.

***Clinical diagnosis***

A two-month history of epistaxis and easy bruising at diagnosis of ES and one year later she developed jaundice, pruritus, and hepatomegaly.

***Differential diagnosis***

Viral hepatitis, cholelithiasis, alpha-1-antitrypsin deficiency, Wilson’s disease, glycogen storage disease or congenital hepatic fibrosis.

***Laboratory diagnosis***

Aspartate aminotransferase (AST) 547 IU/L, alanine transaminase (ALT) 600 IU/L, albumin 2.6 g/dL, total protein 7.9 g/dL, total bilirubin 10.2 mg/dL and direct bilirubin 8.8 mg/dL, prothrombin time 13.5 s, partial thromboplastin time 31 s, International Normalized Ratio 1.02, positive anti-nuclear antibody (1:40), positive smooth muscle antibody (1:40), positive F actin antibody (39 units) and elevated total serum IgG (1090 mg/dL). The anti-liver-kidney-microsome antibody, anti-HAV-IgM, HBsAg, anti-HBc and anti-HCV were all negative. The serum alpha-1-antitrypsin and ceruloplasmin concentrations were normal.

***Imaging diagnosis***

Abdominal ultrasound showed a liver span of 13-cm and increased echogenicity without gallstones.

***Pathological diagnosis***

Liver biopsy revealed interface hepatitis with a mixed inflammatory infiltrate including lymphoid cells, eosinophils, neutrophils, histiocytic cells and plasma cells in addition to periportal fibrosis with rare portal-portal septa (stage 2 fibrosis) indicating autoimmune hepatitis (AIH).

***Treatment***

High doses of methylprednisolone (30 mg/kg per day for 3 d) and then oral prednisone, oral ursodiol, oral azathioprine, intravenous immunoglobulin and intravenous rituximab.

***Related reports***

AIH is characterized by chronic necroinflammatory liver disease of unknown cause, circulating non organ-specific autoantibodies and increased levels of immunoglobulin G. AIH cases have been reported concomitantly with extrahepatic immune disorders. Association with ES is rare, especially in children.

***Term explanation***

ES may evolve over a period of several months therefore evaluation for associated autoimmune conditions should be considered periodically even if negative initially, especially AIH.

***Experiences and lessons***

This is the rarecase report of concurrent AIH and ES in a child who responded well to rituximab. The patient also demonstrated short-term response to intravenous immunoglobulin, methylprednisolone, azathioprine and oral prednisone. International collaboration is essential in order to better understand the association and treatment of ES and AIH in children and adults.

***Peer-review***

Authors report an interesting case of 3-year-old child with ES associated with type 1 AIH.

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**P-Reviewer:** Carbone M, He ST, Shi Z **S-Editor:** Ji FF **L-Editor: E-Editor:**

**Specialty type:** Gastroenterology and hepatology

**Country of origin:** United States

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C, C

Grade D (Fair): 0

Grade E (Poor): 0

**Table 1 Laboratory tests during the disease course**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Laboratory tests** | **0 mo** | **12 mo** | **13 mo** | **14 mo** | **16 mo** |
| Hemoglobin (g/dL) | 8.4 | 4.9 | 9.6 | 9.8 | 14 |
| Reticulocyte count (%) | 8 | 44 | 34.2 | 32 | 4.7 |
| Platelet (cells/µL) | 61000 | 187000 | 303000 | 327000 | 502000 |
| Albumin (g/dL) | 2.7 | 2.6 | 3.5 | 3.7 | 4.1 |
| Aspartate aminotransferase (IU/L) | 387 | 547 | 45 | 49 | 87 |
| Alanine transaminase (IU/L) | 449 | 600 | 51 | 188 | 104 |
| Total bilirubin (mg/dL) | 0.8 | 10.2 | 1.3 | 0.5 | 0.4 |

0 mo: Diagnosis of Evans syndrome; 12 mo: Diagnosis of autoimmune hepatitis; 13 mo: One month after treatment of methylprednisolone and oral prednisolone; 14 mo: Prior to rituximab; 16 mo: Present.