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Evans Syndrome- Rare Cause of Abdominal Pain: A Case Report

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Abstarct- Evan's syndrome is a rare and chronic autoimmune disease characterized by autoimmune hemolytic anemia and immune thrombocytopenic purpura with a positive Coomb's test in the absence of an underlying etiology. There is no preferential distribution of Evans syndrome by age, gender, or ethnic group. The best treatment options for Evans syndrome depend on many factors, including the severity of the condition; presence of signs and symptoms and person's response to therapies. We present a case of a 12 year old adolescent girl with abdominal pain, diagnosed as a case of Evans syndrome based on the clinical features, Coombs test, hemolytic anemia and thrombocytopenia.

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Evans Syndrome- Rare Cause of Abdominal Pain: A Case Report

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Abstract- Evan's syndrome is a rare and chronic autoimmune disease characterized by autoimmune hemolytic anemia and immune thrombocytopenic purpura with a positive Coomb's test in the absence of an underlying etiology. There is no preferential distribution of Evans syndrome by age, gender, or ethnic group. The best treatment options for Evans syndrome depend on many factors, including the severity of the condition; presence of signs and symptoms and person's response to therapies. We present a case of a 12 year old adolescent girl with abdominal pain, diagnosed as a case of Evans syndrome based on the clinical features, Coombs test, hemolytic anemia and thrombocytopenia.

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I. Introduction

Evans syndrome is an uncommon condition defined by the combination (either simultaneously or sequentially) of direct antiglobulin test positive autoimmune haemolytic anaemia (AIHA), immune thrombocytopenia (ITP) and/or immune neutropenia in the absence of a known underlying etiology. There is evidence to support abnormalities in both cellular and humoral immunity in Evans syndrome[1]. Its chronic course is characterized by recurrent relapses and remissions. Evans syndrome is a diagnosis of exclusion. This means that a diagnosis is made in people with Coombs positive haemolytic anaemia and thrombocytopenia related to an abnormal immune response, other conditions with similar signs and symptoms have been ruled out. Various blood tests and in some cases, a bone marrow may be needed to exclude other conditions.

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II. Case Report

Maria,12 years old adolescent girl, 2nd issue of non consanguineous parents, admitted into Pediatric Gastroenterology and Nutrition department with the complaints of severe, agonizing, epigatric pain without any radiation and relieved slightly after leaning forward for 5 days, associated with non projectile, non bilious vomiting. She had no H/O of fever, cough, oral ulceration, joint pain, alopecia, but she had malaise, fatigue for last 15 days. Maria was severely pale, moderately icteric, no lymphphadenopathy, stigmata of chronic liver disease was absent. Maria had tenderness in epigastric region with just palpable spleen and no other organomegaly or ascites. Laboratory findings:

- CBC: ESR=120 mm, Hct= 23.5%, Hb=7.5gm/dl, MCV=84.5fL, MCH=27 pg, MCHC=31.9gm/dl, RDW- CV=14.6%, WBC=4500/cmm, N=63%, L=30%, M=05%, E=02%, B=00%, Platelet=80000/μL.
- PBF showed features consistent with immune haemolytic anaemia with thrombocytopenia and marked roulaeux formation.
- Reticulocyte count was about 4.79%.
- Direct Coomb's test (DAT) was positive, Indirect coomb's test (IAT) was negative.
- LDH-2905 U/L
- Hemoglobin electrophoresis revealed normal finding
- Serum bilirubin was 8.4 mg/dl, serum ALT-23 U/L, ceruloplasmin-44 mg/dl, s.albumin-4.35 g/dl,INR-1.12
- Serum Lipase-86 U/L,
- Fasting lipid profile , RBS, Serum electrolytes and Creatinine were within normal range
- Viral markers for Hepatitis A, B, C and E were negative
- IgG was14.3 g/l
- ANA, Anti –ds-DNA, Anti smooth muscle antibody and anti LKM1 were negative
- Flow cytometry for PNH evaluation was not consistent with a diagnosis of PNH
- S. Iron= 208.98 μgm/dl (raised); S. Ferritin=443.0 ngm/ml (raised); TIBC= 295 μgm/dl (Normal).
- *Urine* R/M/E showed Color=straw, Albumin=trace, Urobilinogen= 1+, Bilirubin- +++, Pus cell=2-4, RBC=plenty.

- Bone marrow shows Dimorphic erythroid and megakaryocytic hyperplasia.
- USG of whole abdomen – periportal echogenicity of Liver is increased. Parenchymal echogenicity is decreased. Multiple ill defined hyperechoic areas are noted in the right lobe of Liver.
- CT scan of whole abdomen with contrast- Hepatosplenomegaly with multiple hepatic SOLs and irregular heterogenous enhancement of spleen with abdominal lymphadenopathy.

She received total 3 bags blood within 10 days for correction of anaemia but her condition was deteriorating. Her general condition was improved after Injection Methyl Prednisolone 30 mg/kg/day for 5 days followed by oral prednisolone 1.5 mg/kg/day continued up to normalization of CBC then slow tapering. Follow up CBC after 7 days showed increased haemoglobin and platelet level without blood transfusion.CBC: ESR=5 mm, Hct= 24.0%, Hb=12.1 gm/dl, MCV=87.3fL, MCH=27.6 pg, MCHC=31.7 gm/dL, RDW- CV=16.4%, WBC=6000/cmm, N=50%, L=42%, M=05%, E=03%, B=00%, Platelet= 180000/μL and USG of whole abdomen revealed no mass lesions in liver but spleen is enlarged in size with altered echotexture in inferior pole. Maria was diagnosed as Evans syndrome on the basis of clinical picture and laboratory investigations.

III. Discussion

Autoimmune hemolytic anemia (AIHA) is an immune disorder which is characterised by circulating antibodies against antigens on the red blood cells (RBCs) membrane resulting in shortened life span of the RBC [2]. Robert Evans first described an association between idiopathic thrombocytopenic purpura and autoimmune hemolytic anemia in 1951. It was characterized by simultaneous destruction of the body's own red blood cells, white blood cells, platelets, neutrophils which causes Autoimmune Hemolytic Anemia (AIHA) and Idiopathic Thrombocytopenia Purpura (ITP) or immune neutropenia in absence of any cause [3].

Evans syndrome is predominantly a disease of pediatric age group[4]. There is evidence to support abnormalities in both cellular and humoral immunity in Evans syndrome. Both CD4 and CD8 lymphocytes were reduced; increased constitutive production of interleukin-10 and interferon-y caused activation of autoreactive, antibody-producing B cells. Despite the frequency of haemopoietic cell-specific autoantibodies in patients with Evans syndrome, there is very little information about the identity of target antigens.

Patients may present with AIHA or ITP either separately or concomitantly. Neutropenia occurs in up to 55% of patients at presentation, or pancytopenia (14%). The development of the second cytopenia may occur months to years after the first immune cytopenia and may delay diagnosis. Usual features of haemolytic anaemia i.e: pallor, lethargy, jaundice, heart failure in severe cases; and features of thrombocytopenia i.e: petechiae, bruising, mucocutaneous bleeding may be present. The lymphadenopathy and organomegaly (hepatomegaly and/or splenomegaly) may be chronic or intermittent and in some cases may only be apparent during episodes of acute exacerbation[2-6].

A full blood count will confirm the presence of cytopenias and a blood film should be examined for features of AIHA (polychromasia, spherocytes) and to exclude other underlying diagnoses (malignancies, micro angiopathic haemolytic anaemia, congenital haemolytic and thrombocytopenic conditions).

Features of haemolysis should be sought including a raised reticulocyte count, unconjugated hyperbilirubinaemia and decreased haptoglobins. The direct antiglobulin test (DAT) is almost invariably positive (although often weakly so), even in the absence of haemolytic anaemia, and may be positive for IgG and/or complement (C3)[3-6]. The indirect antiglobulin test may also be positive in 52-83% of patients[5,10].

Assays for antiplatelet and antigranulocyte antibodies have shown varied results[11]. In a report of 32 adult patients with AIHA, showed antiplatelet antibodies in 91% (demonstrated by thromboagglutination and indirect antiglobulin consumption tests) and leucocyte antibodies in 81% (demonstrated by a cytotoxicity test). Common variable immunodeficiency (CVID) and IgA deficiency, which have been reported to develop acquired cytopenias[12,13], and also as a baseline prior to immunomodulatory therapy.

As Evans syndrome is a diagnosis of exclusion so other confounding factors such as malignancies, infections and rhematological disorders should be ruled out. A bone marrow examination (aspiration/biopsy) necessary to rule out causes of aplastic anemia or an infiltrative disorder. Bone marrow aspiration usually shows a mild to moderate erythroid hyperplasia. Megakaryocytes may be normal to increased in number which indicates an increased destruction of platelets in the peripheral blood as the cause of thrombocytopenia[6].

Our patient Maria presented with abdominal pain, vomiting, generalized weakness and jaundice. Her CBC showed severely anaemic, thrombocytopenia, PBF showed features consistent with immune haemolytic anaemia with thrombocytopenia and marked roulaeux formation. Reticulocyte count and LDH was raised. Direct Coomb's test (DAT) was positive and Hemoglobin electrophoresis revealed normal finding. Liver function test was normal except bilirubin. Viral, autoimmune and Wilson disease markers for Hepatitis was negative. Serum Lipase, Fasting lipid profile, RBS, Serum electrolytes and Creatinine were within normal range. Flow cytometry for PNH evaluation was not consistent

with a diagnosis of PNH. Urine R/M/E showed plenty of RBC. Bone marrow showed Dimorphic erythroid and megakaryocytic hyperplasia. USG of whole abdomen – periportal echogenicity of Liver was increased. Parenchymal echogenicity was decreased. Multiple ill defined hyperechoic areas were noted in the right lobe of Liver. CT scan of whole abdomen with contrast showed Hepatosplenomegaly with multiple hepatic SOLs and irregular heterogenous enhancement of spleen with abdominal lymphadenopathy.

Our patient's general condition was improved after injection methyl prednisolone 30mg/kg/day for 5 days followed by oral prednisolone 1.5 mg/kg/day continue upto normalization of CBC then slow tapering. Follow up CBC after 7 days showed increased haemoglobin and platelet level without blood transfusion and USG of whole abdomen revealed no mass lesions in liver but spleen is enlarged in size with altered echotexture in inferior pole.

Evans syndrome is managed by Corticosteroids and/ or intravenous immunoglobulins as the first-line therapy. Most patients respond to this line of treatment although relapses are quite common. The second line therapy includes immunosuppressive drug. Recently, some patients have been treated with rituximab. Rituximab is one such drug that can be tried in cases of refractory Evans syndrome. Rituximab is a chimeric anti-CD20 monoclonal antibody with human IgG1 and k constant regions and murine variable regions [8,9]. It causes selective depletion of B cells through complement and antibody-dependent cell-mediated cytotoxicity and induction of apoptosis.

In long-term follow-up most authors described more frequent episodes of ITP compared with episodes of AIHA. Causes of death were mainly related to haemorrhage or sepsis and reassuringly, given the degree of immune dysregulation seen in many patients, none of the patients described in these long-term studies (mainly of children) developed malignancy.

Splenectomy may also be considered although long-term remissions are less frequent than in uncomplicated ITP. For severe and refractory cases, stem cell transplantation (SCT) offers the only chance of long-term cure. A fully developed Evans syndrome should be associated with a Coomb's positive hemolytic anemia which is essential for definitive diagnosis. Although rare, Evans syndrome should be suspected and investigated for in patients presenting with autoimmune haemolytic anaemia or autoimmune thrombocytopenia concurrently or sequentially. Patients of either of these disorders individually should therefore be thoroughly investigated for the other so as not to miss a diagnosis of Evans syndrome. Long term follow up is essential in such cases as the patient is at a risk of developing other auto immune problems [4].

IV. Conclusion

Although a rare disorder, Evans syndrome should always be considered in cases presenting with AIHA or AITP occurring simultaneously or in follow up after excluding the causes of unknown etiology. Hence the early diagnosis, knowledge of its presentation and constant follow up is crucial for this syndrome.

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