CASE REPORT

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Evan's Syndrome with Autoimmune Thyroiditis: A Rare Clinical Presentation

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Abstract

The association between Idiopathic Thrombocytopenic Purpura (ITP) and Autoimmune Haemolytic Anaemia (AIHA) was first described by Evans* et al *in 1951 and this entity was named as Evans Syndrome. Later it was found that there is close association of autoimmune haemolytic anaemia with other autoimmune disorders and Hashimoto's disease is one such disorder[1]. They seem to have same overlapping immunological mechanism. The syndrome presents with positive Coomb's test along with other autoantibodies. Very few cases showing association of Evans syndrome with Hashimoto's disease have been reported in the literature where patient presents with high Anti-Thyroid Per Oxidase (TPO) Antibodies and Coomb's Positive Haemolytic Anaemia, and our case is one of them.

Here we report a case of a 55-year-old female who presented in emergency room with severe anaemia, jaundice and bradycardia. Investigations showed anaemia, thrombocytopenia, indirect hyperbilirubaenaemia and a positive Coomb's test, indicative of an autoimmune haemolytic pathology. Thyroid profile revealed a very high Thyroid Stimulating Hormone (TSH) and anti TPO antibody titers. Hall mark of our case was presentation of the patient with cardiac involvement in the form of conduction blocks with severe bradycardia along with above features, probably due to uncontrolled hypothyroidism. Patient was given an immediate treatment with temporary pacemaker implantation and simultaneously treated with thyroid replacement therapy along with low dose steroids to which patient showed a remarkable recovery.

Introduction

The association between Idiopathic Thrombocytopenic Purpura (ITP) and Autoimmune Haemolytic Anaemia (AIHA) was first described by Evans *et al* in 1951 and this entity was named as Evans syndrome. Most people accept there is some pathophysiological co-relation between ITP and AIHA. Since then, there have been many cases reported with association of Evans syndrome and some other autoimmune disorder like Systemic Lupus Erythamatosus (SLE), Sjögren syndrome, etc.

Hashimoto's disease is one of the common endocrinal autoimmune disorders which is associated with other non endocrine autoimmune disease like Evans syndrome[1]. This disease presents with anti-TPO antibodies and Coombs positive haemolytic ansemia. There is a belief that autoimmune thyroiditis and Evans syndrome have same overlapping immunological mechanism[1].

Here we report a case of Evans syndrome associated with Hashimoto's thyroiditis, in a 55-year-old female who presented in ER with anaemia, jaundice and severe bradycardia.

Case report

A 55-year-old female patient from a remote village of Kumaon presented to our emergency room, with history of yellowish discolouration of sclera, easy fatigability and progressive distension of abdomen for 15 - 20 days. She also had past history of repeated episodes of jaundice over the period of last two years recovering on its own. On admission patient was drowsy, having slow response to verbal commands, pale, icteric and oedematous. Jugular venous pressure was raised, pulse rate was 28/minute, irregular (Fig. 1). Blood pressure was 90/70 mmHg. On per abdominal examination there was mild splenomegaly with ascites, cardiovascular examination revealed a short systolic murmur at left third parasternal area. Respiratory and neurological examination were grossly normal.

An urgent ECG done revealed A-V dissociation with heart block (Fig. 2). A temporary pacemaker was inserted urgently to control the heart rate after consultation with the cardiologist. This was followed by an echocardiography which revealed a dilated cardiomyopathy, mild pericardial effusion, mild mitral regurgitation, no regional wall motion abnormality with severe systolic dysfunction – LVEF 30%.

Meanwhile blood investigations revealed haemoglobin of 4.3 gm/dl, platelet count of 75,000/mm^3, total leucocyte count 8,200/mm^3. Peripheral smear revealed microcytic hypochromic cells, anisopoikilocytosis, tear drop cells, target cells and pencil cells along with thrombocytopenia.

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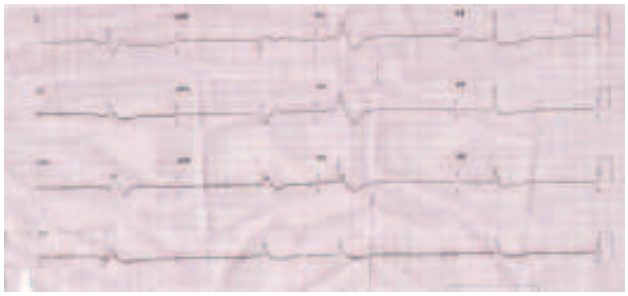

Fig. 1:

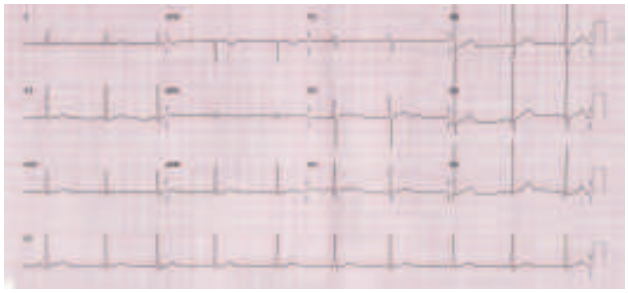

Fig. 2:

Reticulocyte count was 3.5%. Total serum bilirubin was 12.50 mg% with indirect hyperbilirubinaemia of 11.30 mg% and normal SGOT, SGPT and ALP. Serum LDH was 817 units/liter indicative of haemolysis. Viral markers including HIV were non reactive. Bone marrow examination was later done to rule-out any other haematological disorder which was suggestive of erythroid hyperplasia. Ultrasound abdomen showed mild hepato-splenomegaly with moderate ascites.

On the basis of above investigations and keeping a possibility of haemolysis a Coombs test was done which came out to be positive. Simultaneously thyroid profile and anti thyroperoxidase antibodies titers were done which revealed a high values of TSH - 106 U/ml and positive anti TPO antibodies > 1,000 U/L. Autoimmune markers including ANA, ds DNA and rheumatoid factor were done which came out to be negative. Megaloblastic anaemia was ruled-out by a normal vitamin B_{12} level of 312 pg/ml and normal folate level of 10 ng/ml.

Overall, the clinical presentation and investigations were suggestive of haemolytic anaemia, thrombocytopenia probably of autoimmune pathology as Coombs was positive, in association with a high TSH and anti-thyroperoxidase antibody titers suggesting similar immunological pathology. A cardiac involvement could be explained with an uncontrolled and overt hypothyroidism.

Patient was started on thyroxine in a dose of 75 microgram/day and 2 units of blood transfusion was given. She was also put on low dose steroid of 10 mg/day along with furosemide and spironolactone. Patient started responding, her heart rate was closely monitored on temporary pacemaker with repeated ECG's and pacemaker was later removed on day 13. Slowly her alertness and anaemia improved.

Patient stayed with us for a period of 21 days and on discharge patient was conscious and alert, with a heart rate of 62/min and the ECG showed a normal sinus rhythm. Investigations revealed haemoglobin 8.2 gm/dl, total leucocyte count 4,800/mm^3, platelet 1.2 lakhs/mm^3 (Table I).

Table I: Investigations of the patient at the time of admission and discharge.

Investigation	On admission	On discharge
Hb	4.3 gm%	8.2 gm%
TLC	8,200/mm^3	4,800/mm^3
Platelet	75,000/mm^3	1,20,000/mm^3
Total bilirubin	12.50 mg%	7.80 mg%
Direct bilirubin	1.20 mg%	1.0 mg%
Indirect bilirubin	11.30 mg%	6.80 mg%
Retic count	3.5%	
LDH	817 U/L	
TSH	106 U/ml	
Anti-TPO	> 1,000	
Vit B12	312 pg/ml	
Serum folate	10 ng/ml	
ANA/RF/dsDNA	Negative	
Coombs test	Positive	

Discussion

Evans syndrome is a rare haematological abnormality characterised by Coombs-positive AIHA and ITP without any known underlying cause. This condition may be idiopathic or associated with other diseases. The diagnosis is made in people with Coombs-positive haemolytic anaemia and thrombocytopenia related to an abnormal immune response once other conditions with similar signs and symptoms are ruled-out[1]. Its association with other immunological disorders like SLE, Antiphospholipid syndrome, Sjögren syndrome is well known. 100% of people present with haemolytic anaemia and thrombocytopenia both of which are of autoimmune pathology. Patient may also have associated autoimmune neutropenia, petechiae and easy bruising[2].

The association of Evans syndrome with Hashimoto's thyroiditis has been reported in the literature in very few case reports and the manifestations most frequently occur

in combination[3]. Mechanism of molecular mimicry has been suggested to explain their association. There might be an associated specific gene with Evans syndrome, which may amplify the autoimmune mechanism in the thyroid gland[1].

As with most autoimmune disorders, susceptibility to autoimmune hypothyroidism is determined by a combination of genetic and environmental factors. HLA-DR polymorphisms are the best documented genetic risk factors, especially HLA-DR3, -DR4, and -DR5 in caucasians. Both of these genetic associations are shared by other autoimmune diseases as well which may explain the relationship between autoimmune hypothyroidism and other autoimmune diseases[4].

The thyroid lymphocytic infiltrate in autoimmune hypothyroidism is composed of activated CD4+ and CD8+ T-cells as well as B-cells. Cell destruction is primarily mediated by the CD8+ cytotoxic T-cells, which destroy their targets by either perforin-induced cell necrosis or granzyme B–induced apoptosis. In addition, tumour necrosis factor (TNF), IL-1, and interferon, may render thyroid cells more susceptible to apoptosis.

The diagnosis of the syndrome is done on the basis of clinical and laboratory findings suggestive of haemolysis, along with detection of autoantibodies. Our case clinically had anaemia, jaundice, hepatosplenomegaly and investigations revealed anaemia, thrombocytopenia, indirect bilirubinaemia with normal SGOT, SGPT, ALT. Raised retics and LDH along with peripheral blood smear changes were in favour of haemolysis and a positive direct antiglobulin test was suggestive of autoimmune origin. Though the corrected retic count was very low, but evidence of increased serum LDH with indirect hyperbilirubinaemia and Coombs test positive were strong indicators for ongoing haemolysis. Reticulocytosis may be absent in patients with ongoing autoimmune phenomenon[5]. Hashimoto's thyroiditis was supported by high anti TPO antibodies tires. Oedema and ascites can have dual pathology of congestive heart failure and long standing anaemia.

The hall mark of our case was uncontrolled hypothyroidism with its cardiac involvement in the form of bradycardia, conduction blocks, dilated cardiomyopathy, mild pericardial effusion and severe systolic dysfunction – LVEF 30%. Cardiac involvement in hypothyroidism is known and it is associated with decreased cardiac contractility, increased systemic vascular resistance and decreased cardiac output. Its manifestations are insidious and subtle in its progression and clinical behaviour. Dilated cardiomyopathy may be caused by various factors including metabolic/endocrine disturbances. Thyroid hormones act on the cardiac myocytes and peripheral vasculature. The genomic and non-genomic effects of thyroid hormone are related to the cardiac function and cardiovascular haemodynamics. To explain their possible genomic effects, it has been proposed that they are involved in the regulation of the mRNA transcription of genes associated with the contractile system. They have a non-genomic effects on the ionic channels of cardiomyocyte's membrane[6,7].

Most consistent cardiac abnormality recognised in patients with overt hypothyroidism is impairment of LV diastolic function which is characterised by slowed myocardial relaxation and impaired early ventricular filling[8,9]. Bhupathi *et al*[10] found that systolic time intervals like pre-ejection period and ejection time and diastolic functions like isovolumic relaxation time were affected in hypothyroid children. In the study by Di Paolo *et al*[11], acute hypothyroidism was associated with left ventricular systolic dysfunction, probably due to pre- and afterload alterations rather than to an impaired myocardial contractility. The diastolic function was not significantly modified.

First-line therapy is immunosuppression, while second-line therapy includes danazol and splenectomy[12,13]. Various immunosuppressive therapies, including *Vinca* alkaloids, androgens, corticosteroids, intravenous immunoglobulin, and splenectomy, have been used to treat Evans syndrome. However, both medical and surgical treatments have been rather unsuccessful in treating refractory cases of Evans syndrome[14,15]. Some patients require lifelong immunosuppression to keep the disease in remission. Rituximab is a chimeric human/mouse monoclonal antibody that targets CD20 on B lymphocytes and is increasingly used for a variety of autoimmune disorders, including Evans syndrome[12,13]. For cases that are very severe and difficult to treat, a stem cell transplant may be used to provide a long-term cure. Autologous and allogeneic stem cell transplantation have been used in a small number of patients (14 patients aged 5 - 52 years), with mixed results[16].

Patient was started on low dose thyroxine as it is recommended that patients with heart failure should be started on low dose thyroxine therapy and gradually up titrate the dose[4]. Steroid was started on low dose and patient showed remarkable improvement.

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