Case Report and Review of Literature

Hashimoto's thyroiditis associated Evans syndrome: A rare case report on the clustered autoimmune disease triad

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ABSTRACT

Evans syndrome is a rare combination of autoimmune hemolytic anemia and immune thrombocytopenia. Their association with autoimmune thyroid diseases has been reported by few authors; however, a sequential development of the Evans syndrome in cases of Hashimoto's thyroiditis is extremely rare. The clustering of these autoimmune diseases might share a common pathogenic pathway. We present the fourth such case in world literature, of a 34-year-old female diagnosed with Hashimoto's thyroiditis in 2006, who has been taking synthetic thyroid hormone since then. Her condition is now clinically complicated with the development of the Evans syndrome.

Key words: Autoimmune hemolytic anemia, hashimoto's thyroiditis, immune thrombocytopenia

Introduction

The simultaneous or sequential development of autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP) and/or immune neutropenia in the absence of any underlying cause was described as the Evans syndrome (ES) by Evans *et al.*, in 1951.[1] Since its first description, ES was considered as an idiopathic condition, and mainly as a diagnosis of exclusion. However, few case reports showed a common association of ES with other diseases, such as, systemic lupus erythematous, lymphoproliferative disorders, and immunodeficiency, which warranted the classification of ES into primary and secondary.[2] Only three case reports of the association of Evans syndrome with Hashimoto's thyroiditis were found in the literature review, and to the best of our knowledge, this is the fourth case, with a complete evaluation.[3-5]

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Case Report

A 34-year-old female, who is a known case of Hashimoto's thyroiditis, on synthetic thyroid hormone intake (50 μg/day) since five years, presented with high-grade intermittent fever associated with chills and rigors, headache, and breathlessness. There was no significant family history of thyroid disease and she was on no other medication except for the thyroxine intake. On examination, the patient was disoriented, looked pale with anemic conjunctiva, and icteric sclera. Her blood pressure was 110/90 mm of Hg, body temperature was 101°F, and pulse rate was 120 per minute. She had minimal, firm thyromegaly, tenderness in the right hypochondrium, and mild splenomegaly, on an ultrasound scan of the abdomen. There were neither enlarged peripheral lymph nodes nor any enlargement of them on the abdominal ultrasound scan. There were no signs or symptoms of overt hypothyroidism. Further investigations were negative for malaria, hepatitis B surface (HBs) antigen, hepatitis C virus (HCV) antibody, Dengue, HIV, Syphilis, and Leptospirosis. Antinuclear antigen

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(ANA) and "Anti-ds DNA" were negative. She had low hemoglobin, hematocrit, red blood cells (RBC), and platelet count along with high mean corpuscular volume (MCV). Peripheral blood smear examination showed a marked anisocytosis comprising of macrocytes, polychromatic cells, and microspherocytes. A high percentage of nucleated RBC and thrombocytopenia were also seen [Figure 1]. There were no hemoparasites or abnormal cells.

Bone marrow aspiration was done to rule out any underlying lymphoproliferative conditions and the slides showed only hypercellular marrow with erythroid hyperplasia and increased megakaryopoiesis [Figure 2]. The overall impression on hematological examination was hemolytic anemia with thrombocytopenia and reactive marrow hyperplasia. We performed a further workup and the results are shown in Table 1. To summarize, the patient had a positive direct antiglobulin test, evidence of hemolysis in the form of reticulocytosis, elevated indirect bilurubin, and serum lactate dehydrogenase (LDH). She also had increased anti-thyroid peroxidase antibody levels. The constellation of the clinical and laboratory data suggested that the patient was a case of Hashimoto's thyroiditis complicated by Evans syndrome. The patient was put on corticosteroids and she showed a significant improvement. She was now on a followup for six months**.** Her present hemoglobin is 13.2 grams% and total serum bilirubin is 0.8 mg/dl.

Discussion

Autoimmune diseases comprise of a heterogeneous group of disorders and are sometimes defined as a clinical syndrome caused by alterations in the immune system such as activation of T cells or B cells or both, resulting in a spectrum of diseases that can target specific organs or affect the body systemically.[6] Autoimmune thyroid diseases, thus comprise of a series of interrelated conditions including hyperthyroid Graves disease, Hashimoto's thyroiditis, atrophic autoimmune hypothyroidism, postpartum thyroiditis, and thyroid-associated ophthalmopathy.

Table 1: Laboratory findings

Parameter	Reference range	Result
Red blood cell ($\times 10^6/\mu L$)	3.5-4.5	1.27
White blood cell ($\times 10^3/\mu L$)	4-11	8.5
Platelet ($\times 10^3/\mu L$)	150-450	73
Hemoglobin (g/dL)	11-16	5.0
Hematocrit (%)	34-46	14.0
Mean corpuscular volume (fL)	75-95	110
Mean corpuscular hemoglobin (pg)	26-32	39.2
Mean corpuscular hemoglobin concentration (g/dL)	31-36	35.6
Reticulocyte count (%)	0.5-2.0	40
Total bilirubin (mg/dL)	0.2-1.0	11.3
Indirect bilirubin (mg/dL)	0.2-0.8	10.2
Lactate dehydrogenase (U/L)	65-155	2706
Urine hemosiderin	Negative	Negative
Direct Coombs' test	Negative	3+
Indirect Coombs' test	Negative	Negative
Anti-nuclear antibodies (ratio)	Negative:<1.0	Negative (0.21)
Anti ds-DNA (U/ml)	Up to: 100	2.0
Alkaline phosphatase (U/L)	50-136	95
Aspartate transaminase (U/L)	15-37	79
Alanine transaminase (U/L)	30-65	62
Thyroid stimulating hormone (μIU/mL)	0.35-5.5	4.05
Total thyroxine (μg/dL)	3.2-12.6	8.3
Total triiodothyronine (ng/mL)	0.6-1.81	0.38
Anti-thyroid peroxidase antibody (U/mL)	<60.00	195.6
Serum sodium (mmol/L)	135-145	135
Serum potassium (mmol/L)	3.5-5.0	3.3
PT (seconds)		14.9
APTT (seconds)		37.19
Albumin (g/dL)	3.4-5.0	4.3

APTT: Activated partial thromboplastin time PT: Prothrombin time, DNA: Deoxyribonucleic acid

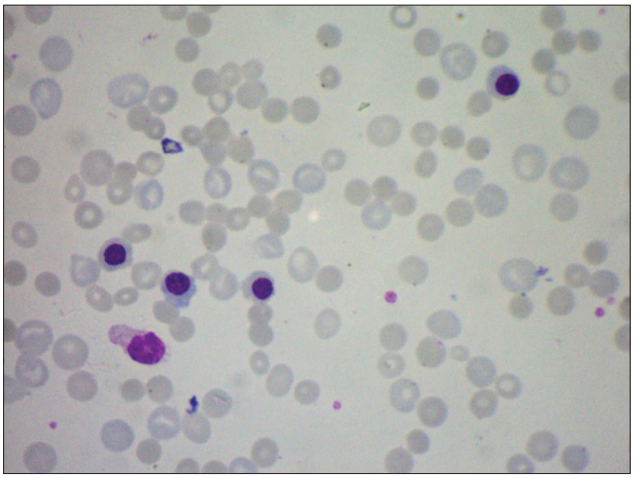

Figure 1: Peripheral blood smear shows features of hemolysis manifested as spherocytes, macrocytosis, nucleated RBC, and polychromatic cells along with thrombocytopenia (×400)

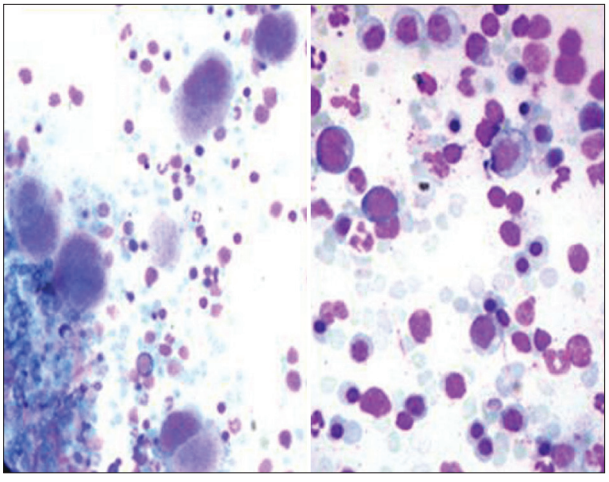

Figure 2: Bone marrow aspiration smear shows features of erythroid hyperplasia and increased megakaryopoiesis (×400)

These manifestations can occur synchronously and most frequently as a combination.[7] The initiation of autoimmune events in Hashimoto's thyroiditis may be caused by a molecular mimicry mechanism, abnormal antigen-specific induction of T cells due to abnormal human leukocyte antigen (HLA)-related genes, mutation of T cells to form abnormal clones, or an immune defect causing reduced induction of T-suppressor cells by specific antigens.[8] The detection of anti-thyroid peroxidase (TPO) is one of the reliable diagnostic tests for Hashimoto's thyroiditis (HT) and our patient showed a high antibody level.

The diagnostic features of autoimmune hemolytic anemia include a combination of clinical and laboratory signs of RBC hemolysis, together with the detection of autoantibodies, as represented mostly by a positive direct antiglobulin test; which has been demonstrated in our case. The formation of autoantibodies in autoimmune hemolytic anemia (AIHA) may be due to the break down in T-cell regulation of B cells, with the emergence of a hostile clone of immunocytes, or to a change in the structure of the antigen on the patient's red cells, which is then recognized as non-self by its immune system.[9]

A rise in serum bilirubin greater than 5 mg/dl seldom occurs in uncomplicated hemolysis unless hepatobiliary disease is also present, however, increased bilirubin with normal alkaline phosphatase suggests constitutional hyperbilirubinemias or hemolytic crisis.[10] An elevated aspartate transferase (SGPT) alone can be of nonspecific etiology, such as, anemia. Patients with isolated unconjugated hyperbilirubinemia (Gilbert's syndrome) may develop more pronounced hyperbilirubinemia in intercurrent illness, such as, febrile illness.[11] Autoimmune hemolytic anemia in Gilbert's disease has been reported.[12] We attribute the high bilirubin and altered serum glutamic pyruvate transaminase (SGPT) noted in our patient to hemolytic crisis and anemia. We could not evaluate the hepatic conjugating enzyme uridine diphosphate glucuronyl transferase in our case, to exclude Gilbert's disease. The clinical presentation of febrile illness, hyperbilirubinemia, and hemolytic crisis, with relatively normal liver function tests, as a scenario in our case, has provocated us to exclude a previously unrecognized Gilbert's syndrome in the follow-up.

There is a diversity of autoimmune mechanisms in idiopathic thrombocytopenic purpura (ITP), such as, antiplatelet antibodies and B-cell, and T-cell tolerance. Platelet antibodies are only detected in approximately 60% of the patients and failure to detect may be due to limited test specificity or undetected antigens. The immune tolerance defects in ITP can arise during early development (central tolerance defects), due to differentiation blocks with skewed peripheral B-cell subsets or peripheral tolerance defects arising in the setting of immune stimulation.[13] A negative antiplatelet antibody in our case may be due to the above-mentioned reasons and in cases of concomitant active AIHA, the presence of mild splenomegaly is not an exclusion criterion for ITP.

Approximately 2% of the patients with ITP have coexisting immune hemolytic anemia (Evans syndrome).[13] However, in clinical practice true cases of ES may show a variety of underlying diseases, and thus, ES should be classified as primary or secondary.[2] There is an increased susceptibility for people with one autoimmune disease to develop another. The increased relative risk of acquiring a second autoimmune disease may be due to a genetic susceptibility that affects both diseases, the alteration of the body's homeostasis by one disease that creates a susceptibility to another or some as-yet undefined shared mechanism.[14] The present case is a rare clustering of three autoimmune diseases; Hashimoto's thyroiditis, autoimmune hemolytic anemia, and immune thrombocytopenia, and can be attributed to any of the above-mentioned causes.

Polyglandular autoimmune syndromes (PGAS) are rare immune endocrinopathies characterized by the coexistence of at least two endocrine gland insufficiencies, and associations with nonendocrine immune diseases may occur.[15] The serum electrolytes and glucose levels of the patient had been normal, thus ruling out adrenal insufficiency in our case. Organ-specific autoantibody screening facilitates the identification of those that are at risk of developing PGAS. In view of financial constraints we have not been able to screen for all the organ-specific autoantibodies, but the patient is kept under regular follow-up.

Conclusion

A Hashimoto's thyroiditis – Evans syndrome association is extremely rare and may share a common immunopathogenic pathway. Detection of such cases needs close collaboration and good communication between the laboratory physician and the clinician. Patients with clustered autoimmunological diseases necessitate evaluation over time, and detection of various organ-specific antibodies as well as *HLA*-gene polymorphisms, will broaden the entities under autoimmune polyendocrine syndromes.

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