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Graves Disease (Thyroid Storm) with Polyautoimmune Disorders (Autoimmune Hemolytic Anemia and Probable Autoimmune Hepatitis)

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ABSTRACT

Graves' disease is caused by IgG antibodies that bind to the Thyroid Stimulating Hormone (TSH) receptor on the surface of the thyroid gland. These bonds drive the growth of stimulated thyroid follicular cells causing the glands to enlarge and increase the production of thyroid hormones. Previous studies mention the association of HLA-B8 and HLA-DR3 with Graves' disease and the Cytotoxic T-lymphocyte-associated-4 (CTLA-4) gene on chromosome 2q33 as a result of reducing T-cell regulation, resulting in autoimmune disease. Autoimmune thyroid disease is often found together with other autoimmune disorders (polyautoimmune). A 51-year-old male complained of dyspnea, yellowing of the body, and a lump on the neck. One year ago, he was diagnosed with hyperthyroidism. Graves' disease was suspected due to a score of 22 for the Wayne index, FT4 96.9 pmol/L, TSHs <0.01 µIU/mL, TRAb 10.8 IU/L, thyroid uptake test for toxic diffuse struma. In addition, the patient had atrial fibrillation and a thyroid storm with a Bruch Wartofsky index score of 65. Laboratory examination found normocytic normochromic anemia, thrombocytopenia, reticulocytosis, direct coomb test and auto control results positive one, SGOT 87 U/L, SGPT 59 U/L, alkali phosphatase 166 U/L, total bilirubin 38.13 mg/dL, direct bilirubin 16.59 mg/dL, indirect bilirubin 21.54, LDH 318 U/L, establishing the diagnosis of Autoimmune Hemolytic Anemia (AIHA). Autoimmune hepatitis score: 15, so a diagnosis of probable autoimmune hepatitis was made.

Keywords: Graves' disease, polyautoimmune, autoimmune hemolytic anemia, probable autoimmune hepatitis

INTRODUCTION

Graves' Disease (GD) is the most common cause of hyperthyroidism. This disease is a syndrome with an enlarged and overactive thyroid gland (hyperthyroidism due to circulating antibodies), a high heart rate, and eye abnormalities. The etiology of GD is the existence of IgG antibodies bound to the receptors of Thyroid Stimulating Hormone (TSH) on the surface of the thyroid gland. The binding stimulates the growth of thyroid follicle cells, causing the gland to enlarge and the production of thyroid hormones to increase. Autoimmune on GD forms anti receptors of TSH autoantibody, which are produced by B-cells. Furthermore, Immune tolerance attacks thyroid antigen and produces Thyroid Peroxidase (TPO) and or thyroglobulin antibody (Tg).[1,2]

The diagnosis of GD is confirmed through signs and symptoms of thyrotoxicosis. The Wayne index will be helpful to quantify the thyroid state of the patient clinically.[3] In a laboratory examination, it is identified that TSH concentrations are low and FT4 increases. T3 analysis is needed when physical examination leads to GD, but the laboratory results show a low value of TSH, with a normal FT4. The Examination of Thyroid-Stimulating Hormone Receptor Antibodies (TRAb) is performed when other examinations do not support the GD diagnosis.[4]

Some researchers found a connection between HLA-B8 and HLA-DR3 with GD. The HLA mechanism of autoimmune disease is when HLA molecules present T-cells that recognize antigen and interact with complex peptide antigen are compromised. HLA allele will have different affinity types for peptide autoantigen. When bound to specific HLA, the autoantigen will be presented on T-cells that have lost tolerance. In thyroid autoimmunity, HLA-DR will easily bind the autoantigenic thyroid peptide. The titer of HLA-B8 and HLA-DR3 is not related to the antibody titer in GD.[5] Graves' disease is also linked with the Cytotoxic T-lymphocyte-associated-4 (CTLA-4) gene on the 2q33 chromosome, which can lower the regulation

of T-cell that mediate autoimmune diseases. In addition to that, CTLA-4 also encodes T-cell receptor, which hampers the production of CD28-dependent interleukin. [2,6]

Autoimmune thyroid disease is often found along with another autoimmune disease, called polyautoimmune. The etiology of polyautoimmune itself is presumed from the body's failure in responding to the tolerance to cells from the body itself.[7] Some diseases, which may occur due to polyautoimmune on endocrine glands are shown in Table 1.

CASE

A 51-year-old male came with shortness of breath one week before admittance. The shortness of breath mainly happened during activities. He also

Table 1. Polyautoimmune endocrine syndromes, including thyroid disease

Clusters	Proposed Pathogenic Mechanism
Autoimmune polyglandular syndromes Type I (autoimmune polyglandular syndrome type I or Whitaker syndrome): mucosal and cutaneous *Candida* infections, Addison's disease, hyposplenism, hypoparathyroidism, and multiple autoimmune presentations (that is, hypothyroidism, hypogonadism, vitiligo, alopecia, pernicious anemia, and chronic autoimmune hepatitis)	Mutation of autoimmune regulator (AIRE)gene involved in central tolerance development. Phenotype possibly affected by human leukocyte antigen (HLA) subtypes.
Type II (Schmidt's syndrome): Addison's disease and hypothyroidism or type 1A diabetes as well as pernicious anemia, primary hypogonadism, vitiligo, celiac disease,and myasthenia gravis (by some further classified in types III and IV according to specific entities above)	Polygenetic with increased risk of illness linked to specific HLA-DR and HLA-DQ genotypes.
Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome Immune dysfunction, enteropathy, dermatitis, autoimmune endocrinopathies (often type 1 diabetes and autoimmune thyroid disease), autoimmune skin diseases (that is, bullous pemphigoid), and multiple organ involvement	Mutation of FOXP3 gene on the X chromosome
Multiple autoimmune syndromes	
Type I: myasthenia gravis, thymoma, polymyositis, and giant cell myocarditis	
Type II: Sjögren's syndrome, rheumatoid arthritis, primary biliary cirrhosis, scleroderma, and autoimmune thyroid disorders	
Type III: autoimmune thyroid disease, myasthenia and/or thymoma, Sjögren's syndrome, pernicious anemia, idiopathic thrombocytopenic purpura, Addison's disease, insulin-dependent diabetes, vitiligo, autoimmune hemolytic anemia, and systemic lupus erythematosus	Genetic predisposition, with phenotype HLA B8 and/or DR3 or DR5 seeming to be an essential factor
Thyrogastric cluster autoimmune thyroiditis, chronic gastritis/pernicious anemia, and autoimmune adrenalitis (Addison's)	Polygenetic
Lupus-associated cluster autoimmune hemolytic anemia, immune thrombocytopenia, systemic lupus erythematosus, rheumatoid arthritis, autoimmune hepatitis, and Sjögren's syndrome	Polygenetic
Trisomy 21 and Turner syndrome chronic thyroiditis, type 1A diabetes, and others	Chromosomal abnormalities
Kearns-Sayre syndrome external ophthalmoplegia, retinal degeneration, diabetes, thyroiditis, and hypoparathyroidism	Mitochondrial myopathy

Source: Bliddal *et al.*, 2017[7]

experienced palpitations accompanied by swelling in both legs. Another complaint was the yellowish appearance in both eyeballs and skin. The patient had a history of hyperthyroid before, but he did not take his medicine regularly.

The patient had compos mentis awareness with a blood pressure of 110/70 mmHg, a respiratory rate of 22x/minute, a pulse of 118x/minute, and a temperature of 37.30C. The patient's physical examination showed icteric skin, pale palpebral conjunctiva, and icteric sclera on both eyes (Figure 1A). There was thyroid gland enlargement on neck palpation with less than 5 cm diameter in size with smooth surface and soft consistency (Figure 1B). From the thorax examination, there was/were 1-2 irregular sounds from the heart and a pan-systolic murmur grade 3/6 that spread to the axilla with rhonchi on both lungs. Extremity examination showed pitting edema on both legs.

The hematology examination showed the following results; normocytic normochromic anemia (Hb 9.2 g/dL, MCV 95.4 fL, MCH 33.8 pg), thrombocytopenia (thrombocyte 92.103/uL), and reticulocytosis (2.83%). The peripheral blood smear displayed minimal erythrocyte agglutination, normocytes, and polychromatic cells. Both direct Coomb test and auto control result was a positive one. The examination of cold and warm agglutinin was performed with negative results (Figure 2).

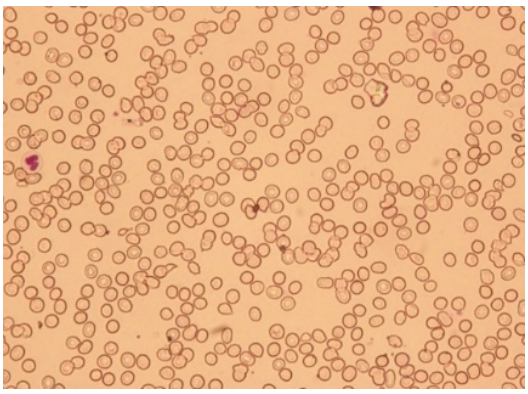
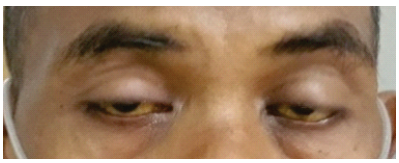
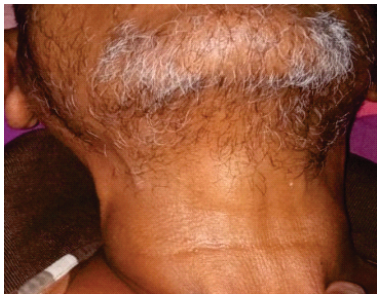


Figure 2. Peripheral blood smear with 400x magnification



A



B

Figure 1. A. Icteric sclera B. Localist status showed a lump on the neck suspected as thyroid enlargement

Table 2. Hyperthyroid score using Wayne's index

Symptoms (Acute Onset or Increased Severity)	Score	Signs	Score	
			(+)	(-)
Dyspnea on effect	(+) 1	Palpable thyroid	(+) 3	(-) 3
Palpitations	(+) 2	Bruit	(+) 2	(-) 2
Tiredness	(+) 2	Exophthalmos	(+) 2	
Preference for heat	(-) 5	Lid reaction	(+) 2	
Preference for cold	(+) 5	Lid lag	(+) 1	
Excessive sweating	(+) 3	Hyperkinesis	(+) 4	(-) 2
Nervousness	(+) 2	Hands hot	(+) 2	(-) 2
Appetite: increase	(+) 3	Hands moist	(+) 1	(-) 1
Appetite: decrease	(-) 3	Atrial fibrillation	(+) 4	
Weight increased	(-) 3	Heart rate > 80/minute	(-)	(-) 3
Weight decreased	(+) 3	> 90/minute	(+) 3	
Total score interpretation > 19 = hyperthyroid, 11-19= equivocal, < 11= euthyroid/normal				

Source: Naraintran *et al.*, 2018[3]

The clinical chemistry examination showed an increase of liver enzymes SGOT 87 U/L, SGPT 59 U/L, Alkaline Phosphatase 166 U/L), hyperbilirubinemia (total bilirubin 38.13 mg/dL, direct bilirubin 16.59 mg/dL, indirect bilirubin 21.54), and of LDH 318 U/L. The hematology and clinical chemistry examination led to suspicion of Autoimmune Hemolytic Anemia (AIHA) disease.

Thyroid blood work-up showed the following results; FT4 96.9 pmol/L, TSHs <0.01 uIU/mL, TRAb 10.8 IU/L, and the thyroid uptake test concluded with toxic diffuse goiter, which supported the diagnosis of GD.

The score obtained from the thyroid scoring examination using Wayne's index (Table 2) was 22 to conclude that the patient had hyperthyroid.

The score obtained from Bruch Wartofsky's index (Table 3) for thyroid crisis was 65, which showed that the patient was in thyroid crisis. An electrocardiogram showed atrial fibrillation. Echocardiography with mild-moderate mitral valve regurgitation and mild tricuspid valve regurgitation; Left Ventricular Ejection Fraction (LVEF) was 61% left atrial dilatation showed thyroid crisis and thyroid heart disease. Chest X-Ray results were cardiomegaly, and ultrasonography showed hepatomegaly with dilatation of hepatic vein.

Screening of other autoimmune diseases was done, and clinical chemistry results showed globulin serum was 1.7 g/dL, ANA test was negative (5.0 U), and scoring for autoimmune hepatitis (Table 4) was performed

The score obtained from the calculation of autoimmune hepatitis was 12 showing probable autoimmune hepatitis. During the treatment period, the patient got medication, transfusion, and Radioactive Iodine 131 (RAI 131). Unfortunately, due to a recurrent thyroid crisis, the patient passed away.

Table 3. Thyroid score using Bruch Warsofsky's index

Diagnostic Criteria					
Thermoregulatory dysfunction				Cardiovascular tachicardia	
Temperature	99.9 (^{0}F)	37.2-37.7 (^{0}C)	5	Tachycardia 99-109	5
	100-100,9	37.8-38.2	10	110-119	10
	100-101,9	38.3-38.8	15	120-129	15
	102-102,9	38.9-39.2	20	130-139	20
	103-103,9	39.3-39.9	25	>140	25
	>104	≥ 40.0	30		
Central nervous system disturbance				**Heart failure**	
Absent			0	Absent	0
Mild (agitation)			10	Mild	5
Moderate (delirium, psychosis, extreme lethargy)			20	Moderate	10
Severe (come, seizure)			30	Severe	15
				Atrial fibrillation	
				Absent	0
				Present	10
				Precipitant history	
				Negative	0
				Positive	10
Gastrointestinal-hepatic dysfunction				**Total score**	
Absent			0	>45	Thyroid storm
Moderate	(diarrhea, nausea/vomiting / abdominal pain)		10	25-44	impending storm
Severe	(unexplained jaundice)		20	<25	Storm unlikely

Source: Jacuzzi *et al.*, 2017[8]

Table 4. Autoimmune hepatitis scoring system

Category	Score	Comments	Category	Score	Comments
Female	+2		Liver histology		Biliary changes refer to bile duct patterns of injury typical of PBC or PSC with ductopenia in an adequate biopsy. Other features are any suggesting an alternative etiology, e.g., non-alcoholic fatty liver disease.
AP: AST (or ALT) ratio			Interface hepatitis	+3	
<1.5	+2		Lymphoplasmacytic hepatitis	+1	
1.5-3.0	0		Hepatocyte rosette pattern of regeneration	+1	
>3.0	-2		Other features	-5	
Serum globulin or IgG above normal			Biliary changes	-3	
>2.0	+3		Other features	-3	
1.5-2.0	+2		Other autoimmune disorders, inpatient or first degree relatives	+2	
1.0-1.5	+1		Optional parameters in patients who are seronegative for ANA, SMA, an LKM-1:		Other defined antibodies are those with published evidence of relevance
<1.0	0		Seropositivity from another autoantibody	+2	to AIH, and include pANCA, anti-LC1, anti-SLA/LP, anti-ASGPR
Autoantibodies (ANA, SMA, or LKM-1)		The low titer is considered	HLA DR3 or DR4	+1	
>1:80	+3	significant in children and should be scored +1	Response to therapy		
1:80	+2		Complete	+2	
1:40	+1		Relapse	+3	
<1:40	0				
Hepatitis viral markers		The patient should be tested markers hepatitis A, B, C, infection such as EBV and CMV may be considered.	**Interpretation of aggregate scores**		
Positive	-3		Pre-treatment		
Negative	+3		Definite AIH	>15	
Drug history			Probable AIH	10-15	
Positive	-4	Recent use of known suspected hepatotoxic drugs	After treatment		
Negative	+1		Definite AIH	>17	
Average alcohol consumption			Probable AIH	12-17	
Low (<25g/day)	+2				
High (>60g/day)	-2				

Source: Mann's *et al.*, 2015[9]

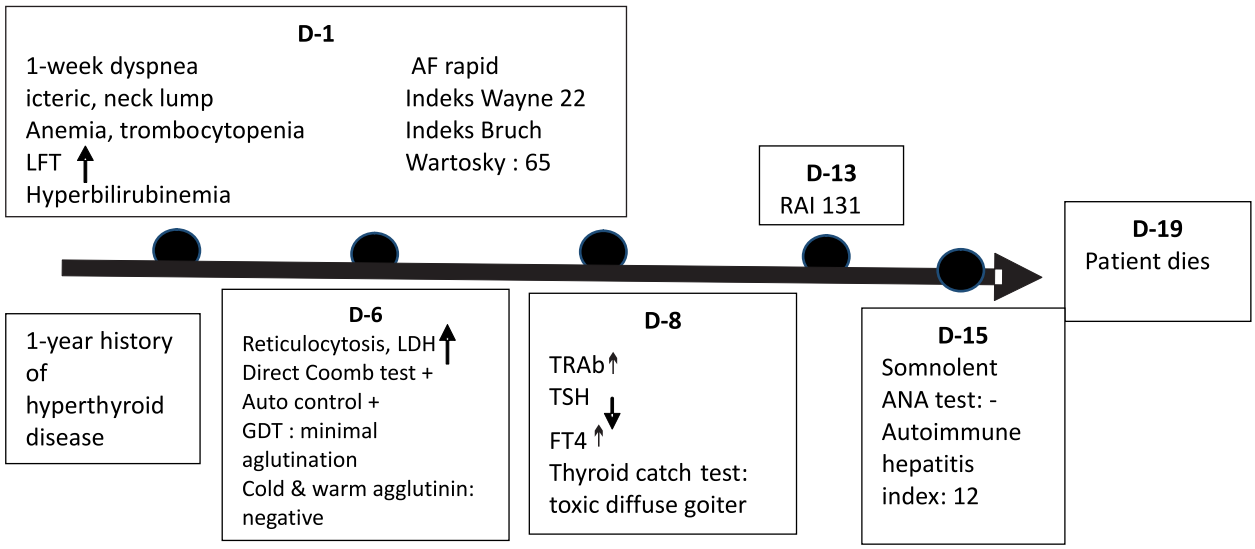


Figure 3. The course of the disease

DISCUSSION

T-lymphocytes in GD are stimulated antigen inside the thyroid gland, stimulating B lymphocytes and synthesizing antibodies against the antigen. The synthesized antibody known as TSH-R will react with the TSH receptor inside the thyroid cell membrane stimulating the growth and function of the thyroid cells. An autoimmune mechanism is an essential factor in the pathogenesis of hyperthyroid, ophthalmopathy, and dermopathy in GD.[10]

A patient with GD can experience a thyroid crisis. The exact etiology of the thyroid crisis has not yet been identified. A patient with a thyroid crisis is an emergency and can increase the death risk. When a thyroid crisis happens, thyroid hormones are released excessively into the tissue. Circulating T4 and T3 are caught by cell cytoplasm. T4 is subsequently changed to its active form, which is T3. T3 approaches the cell's nucleus and is bound to thyroid hormone receptors leading to activation of genes and transcription. Tissue stimulation occurs upon the binding of the receptor and thyroid hormones.[11]

In this case, the patient had atrial fibrillation that was a manifestation of thyroid hormones on muscle ion of atrial myocytes. Research performed on mice stated that thyroid hormones (T3) increase Kv 1.5 mRNA and decrease type L calcium channel, while Kv 4.2 mRNA expression does not change. Action Potential Duration (APD) becomes short during hyperthyroid causing atrial fibrillation in GD.[12,13]

Autoimmune Hemolytic Anemia (AIHA) is defined as the increase of red blood cell destruction caused by anti-erythrocyte autoantibody with or without complement activation. An autoantibody is produced by tissue and self-reacting circulation of B lymphocytes collaborating with T helper lymphocytes. Autoantibodies are capable of destructing red blood cells through cell-mediated cytotoxicity-cell-mediated cytotoxicity antibody (ADCC) mediated by T-cell CD8 + cytotoxic and Natural Killer (NK), which carry membrane Fc receptors from Immunoglobulin G (IgG). The Macrophages actively carrying the Fc receptor can recognize and phagocytize erythrocytes covered by autoantibody and complements. Some researches stated the existence of an association of HLA B8, DR 3 with various organ diseases and systemic autoimmune diseases (type-1 DM depending on insulin, Hashimoto's thyroiditis, GD, multiple sclerosis, myasthenia gravis, pemphigus vulgaris, systemic lupus erythematosus, rheumatoid arthritis, and ankylosing spondylitis), but the exact HLA association has not yet been identified in AIHA development.[14,15]

Autoimmune hepatitis is a chronic liver inflammation marked by autoantibodies and hypergammaglobulinemia accompanied by hepatitis symptoms on a liver biopsy. Antibodies on autoimmune hepatitis are ANA, Smooth Muscle Antibody (SMA), and Anti Liver Kidney Microsomal (LKM). Still, if those antibodies cannot be found, the diagnosis can be performed through autoimmune hepatitis scoring.[9,16]

Autoimmune hepatitis in GD is rarely found, and its' diagnosis is somewhat confusing because thyroid hormones also destroy the liver. Liver destruction is

caused by long-term exposure to thyroid hormones to the liver. Hypermetabolism in a patient with hyperthyroid and thyrotoxicosis quickly causes glycogen and protein decomposition. The appearance of autoimmune hepatitis in GD is related to gene polymorphism of Cytotoxic T-lymphocyte antigen-4 (CTLA-4) in both of these autoimmune diseases.[6,17,18] Further research is still necessary to find the relation between autoimmune hepatitis and thyroid autoimmune disease.

This case is interesting because it happened to a male patient (who should rarely be autoimmune) experiencing several autoimmune diseases simultaneously, namely GD, AIHA, and probable autoimmune hepatitis, which is rarely found. Polyautoimmune is defined as the appearance of two or more autoimmune diseases in one patient. Some patients who suffer from an autoimmune disease may suffer from other autoimmune diseases. Polyautoimmune in Autoimmune Thyroid Disease (AITD) is the most common cause. Polyautoimmune can also occur in several glands simultaneously.[7] Case reports by Kandinata *et al*. in 2020 reported the emergence of GD and AIHA in a 29-year-old female. This patient was previously diagnosed with severe anemia, but on examination, they found clinical symptoms such as tachycardia, exophthalmos, bilateral diffused goiter, decreased TSH, increased FT4 and TRAb, which led to GD.[19]

CONCLUSION

According to the anamneses, physical examination, and supporting examinations, it can be concluded that the patient had a thyroid crisis of GD and was polyautoimmune (autoimmune hemolytic anemia and probable autoimmune hepatitis). An autoimmune disease is commonly followed by other autoimmune disorders (polyautoimmune), which may occur due to the failure of the body to recognize its own body cells'(self-intolerance). However, establishing the diagnosis of the polyautoimmune disease is not easy because most patients are already in the severe phase of the illness when hospitalized. Therefore, although it rarely happens, screening and monitoring for the chance of polyautoimmune in a patient who has previously been diagnosed with an autoimmune disease are necessary.

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