Case Report / *Olgu Sunumu*

Ege Journal of Medicine / *Ege Tıp Dergisi* 2026; 65 (3): 620-623

Co-existence of pancytopenia, autoimmune hemolytic anemia and hepatic dysfunction in intensive care unit patient: Graves' disease

Yoğun bakım hastasında pansitopeni, otoimmün hemolitik anemi ve hepatik disfonksiyon birlikteliği: Graves hastalığı

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ABSTRACT

Graves' disease (GD) may rarely present with hematologic findings and hepatic dysfunction. Diagnosis may be difficult, but early diagnosis is important to avoid delays in treatment. According to a recent literature review, the association of pancytopenia, autoimmune hemolytic anemia (AIHA) and hepatic dysfunction in GD has not been reported before. We report the case of a 57-year-old woman admitted to the intensive care unit with symptoms of heart failure and diagnosed as GD with pancytopenia, AIHA and impaired liver function tests. Corticosteroid and anti-thyroid treatment was initiated and clinical and laboratory findings improved within the first week. Pancytopenia, AIHA and hepatic dysfunction may occur as the first manifestation of the disease or may be seen in the course of Graves' disease. The occurrence of these severe findings is very rare and respond well to treatment.

Keywords: Graves' disease, pancytopenia, rare manifestation, hepatic dysfunction

ÖZ

Graves hastalığı, nadir de olsa hematolojik bulgular ve hepatik disfonksiyon ile prezente olabilir. Teşhisi zor olabilir ancak tedavide gecikme yaşamamak için erken teşhis önemlidir. Güncel literatür taramalarına göre Graves hastalığında pansitopeni, otoimmün hemolitik anemi (AIHA) ve hepatik disfonksiyonun birlikteliğine daha önce rastlanmamıştır. Kalp yetmezliği semptomları ile yoğun bakım ünitesine başvuran ve pansitopeni, AIHA ve karaciğer fonksiyon testlerinde bozulma ile seyreden ve Graves hastalığı tanısı alan 57 yaşında bir kadın olguyu sunuyoruz. Kortikosteroid, anti-tiroid tedavisi başlandı ve birinci hafta içinde klinik ve laboratuvar bulguları düzeldi. Pansitopeni, AIHA ve hepatik disfonksiyon hastalığın ilk belirtisi olarak ortaya çıkabileceği gibi Graves hastalığı seyrinde de görülebilir. Bu bulguların ortaya çıkması çok nadirdir ve tedaviye iyi yanıt verir.

Anahtar Sözcükler: *Graves hastalığı, pansitopeni, nadir görülen bulgu, karaciğer fonksiyon bozukluğu*

INTRODUCTION

Graves' disease (GD) is an autoimmune thyroid disorder that is resulted in stimulating antibodies to the thyroid-stimulating hormone (TSH) receptor on thyroid follicular cells. This condition leads to high levels of thyroid hormones in circulations. The most common cause of hyperthyroidism is GD and its prevalence is 20-30 cases per 100 000 individuals each year (1, 2).

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Application date: 29.05.2024 Accepted: 18.06.2026

The most common symptoms are palpitations, tremulousness, heat intolerance, weight loss and anxiety in GD. Tachycardia, proptosis, thyroid enlargement and tremor are the most common physical findings. Laboratory findings in GD could be rarely associated with hematological findings including pancytopenia and autoimmune hemolytic anemia (AIHA). Additionally, hepatic dysfunction ranges from asymptomatic laboratory abnormalities to hepatitis (3) .

Here we report a 57-year-old woman who had a history of GD and admitted to intensive care unit (ICU) with the symptoms of heart failure (HF) and

further diagnosed with AIHA, pancytopenia and hepatic dysfunction as a complication of GD.

CASE REPORT

A 57-year-old woman presented with fatigue, shortness of breath and lower extremity edema. She had a history of GD, HF and pulmonary hypertension (PHT). She had been using furosemide, spironolactone, metoprolol succinate and methimazole in her past medical history, but she discontinued methimazole for 6 months.

On clinical examination; she was conscious, looked tired and had lower extremity edema. There was no tremor and she did not have a visible or palpable goiter. No exophthalmos detected.

Blood pressure was 107/ 57 mmHg, heart rate was 98 beats/minute, respiratory rate was 24/minute, body temperature was 37°. She was admitted to internal medicine ICU with a preliminary diagnosis of HF. On admission; liver function tests, urea and electrolytes were normal. Total bilirubin was 1,56 mg/dl (reference range: 0.1-1mg/dl) and direct bilirubin was 1.33 mg/dl (reference range < 0.25 mg/dl). Lactate dehydrogenase was 325 U/L (reference range 135-225), N-terminal pro hormone B-type natriuretic peptide (NT-proBNP) was 1921 ng/dl (reference range < 125 ng/dl) C-reactive protein (CRP) was 6.25 mg (reference range 0-5 mg/dl) and erythrocyte sedimentation rate (ESR) was 79 mm/ 1 h (reference range <30). Full blood count revealed pancytopenia.

In examinations for etiology of anemia, hemoglobin was 7,6 mg/dL (reference range 11.7-16 g/dL) and direct Coombs test was 2 positives. Iron, B12 and folate deficiencies were not detected. In peripheral blood smear, there were decreased number of platelets, hyper-segmented neutrophils and erythrocytes features were hypochromic and microcytic. Serum TSH was <0.005 mU/L (reference range 0.27- 4.2 mU/L), serum free T4 (fT4) was 2.51 ng/dl (reference range 0.89-1.76 ng/dl) and serum fT3 was 5.56 ng/dl (reference range 2-4.4 ng/ dl). She was investigated for hyperbilirubinemia; viral and autoimmune hepatic markers were negative. Also, there wasn't any pathology in biliary tracts in abdominal ultrasound (USG). Laboratory findings at admission are summarized in (Table-1). There was severe cardiomegaly in chest radiograph.

She was treated with furosemide infusion for HF and methylprednisolone for AIHA. Bone marrow aspiration (BMA) and biopsy was performed with the pre-diagnosis of hematological malignancy. BMA showed hypocellularity and normal of trilineage hematopoiesis. In clinical follow-up, leukopenia and thrombocytopenia did not improve despite methylprednisolone. In addition, bilirubin raised to 4.05 mg/dL. AIHA, hyperbilirubinemia and cytopenia in this patient were thought to be related to GD. Propylthiouracil (PTU) was started with 100 mg / day.

After a week; pancytopenia improved and bilirubin decreased. The patient was discharged with PTU 100mg/day, furosemide 80mg/day, metoprolol succinate 50 mg/day and methylprednisolone 16 mg/day by tapering. The laboratory findings during follow-up are summarized in (Table-1).

Table-1. Laboratory findings of the patient at admission and follow-up.

Laboratory test	On admission	On following	First week after treatment	Reference Range
AST	20	29	29	<31 U/L
ALT	14	26	26	< 34 U/L
ALP	89	81	79	35-104 U/L
GGT	36	19	21	< 38 U/L
T.bilirubin	1, 56	4, 05	1,97	0. 1 -1 mg/dL
D.bilirubin	1, 33	2,83	1,52	<0. 25 mg/dL
WBC	2.07 x10^3	1.32 x10^3	5.91 x10^3	4.5- 11 x10^3/µL
PMNL	0.91 x10^3	1.06x10^3	4.87x10^3	2.02-7.46 x10^3/µL
Hb	7, 6	7, 8	8, 1	11.7-16 g/dL
Platelet	62 x10^3	27x10^3	126x10^3	150-450 x10^3/µL
TSH	<0.005			0.27- 4.2 mU/L
fT4	2, 51			0.89-1.76 mU/L
fT3	5,56			2-4.4 mU/L

AST: aspartate transaminase, ALT: alanine transaminase, ALP: alkaline phosphatase, GGT: gamma-glutamyltransferase, T: total, D: direct, WBC: white blood cell, PMNL: Polymorphonuclear Leukocytes, Hb: hemoglobin, TSH: thyroid-stimulating hormone, fT4: free thyroxin, FT3: free triiodothyronine

DISCUSSION

Tachycardia, proptosis, thyroid enlargement and tremor are most common symptoms in patients with GD, however; hematologic and hepatic dysfunctions have been reported. Hematopoietic system can be affected variously in hyperthyroidism including anemia, thrombocytopenia and leukopenia. However, pancytopenia is a very rare occurrence in GD (3,4).

Anemia can be seen 12-34% cases in hyperthyroidism. Hyperthyroidism can increase erythrocyte counts leading to tissue hypoxia which stimulates erythropoietin from kidneys. However, anemia can be associated with simultaneous increase in plasma volume, shortening of erythrocyte turnover, deficiency of iron, vitamin B12, or folate [5]. In untreated patients with hyperthyroidism, leukopenia and neutropenia can be seen in %15-30 (5). It is suspected to various mechanisms including decreased granulocyte reserves, decreased leukocyte circulation time and immunological destructions. Thrombocytopenia is rarely seen in 2-5% patients with hyperthyroidism. It is supposed to be due to increasing destruction of platelets secondary to splenic sequestration of antiplatelet antibodies (6). AIHA rarely can accompany to GD. In the current literature; 5 cases with GD were reported to be associated with AIHA. Although the certain pathophysiology remains unclear, it seems to be associated hyperthyroidism with autoimmunity (7,8).

In our case, hematologic involvement was first presented with AIHA and in the clinical follow-up pancytopenia developed. The causes that make cytopenia were excluded, malignancy was not found in bone marrow aspiration and biopsy. There was no history of new drugs that could result in AIHA, and no signs of infection were found. Therefore, it was thought that AIHA and pancytopenia were related to GD in the patient.

GD patients have got various ranges of hepatic dysfunction including asymptomatic biochemical abnormalities to severe hepatitis with hepatic or cholestatic injuries. ALP elevation is the most common hepatic enzyme and it is seen in 25-64% patients with hyperthyroidism. In hyperthyroidism patients, hepatic dysfunctions could become due to be relative hypoxia with deteriorating of splanchnic blood supplies, cholestasis in hepatocytes, deteriorating of bilirubin metabolism, congestive heart failure or autoimmune hepatic disease. Moreover, there has been cases in the literature that CHF has made worsening of hepatic dysfunctions in patients with hyperthyroidism [9]. In our case, ALP levels were normal but bilirubin levels were high. Since the autoimmune hepatitis and viral hepatitis markers were negative in our patient and biliary tract and parenchymal pathology were not observed; we determined high bilirubin levels in our case due to the coexistence of CHF and hyperthyroidism.

In the management of hematologic and hepatic involvement, clinical findings are severe, fortunately treatment is usually promising. Glucocorticoids are first agents against AIHA. However, AIHA can be treated successfully with only antithyroid medications in some patients. With the initiation of antithyroid therapy, hematologic and hepatic dysfunction resolve rapidly after euthyroid state is achieved (9,10). In our case methylprednisolone 1mg/kg/day was started for AIHA. Her anemia resolved, but since her cytopenia deepened in the follow-up and the current clinical statement was related to GD, PTU was added to the treatment at dose of 100 mg/day. The patient improved in the follow-up.

CONCLUSION

In conclusion; diseases may not always present with common symptoms. Endocrine pathologies should be also considered in the ICU patient followed up with organ failure including cytopenias. If GD is considered in the differential diagnosis in patients presenting with multi-organ involvement, the treatment is promising. To the best of our knowledge; it is also the first case where pancytopenia, AIHA and hepatic dysfunction were reported simultaneously.

Ethical Approval: Not applicable

Informed Consent: The patient provided informed consent to publish of this report.

Conflicts of interest: Authors declared no conflict of interest.

Funding: None

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