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Case Report

Medicine

Graves's Disease Is Associated with Pancytopenia and Splenomegaly Response to Steroid Therapy

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Abstract: Graves's disease is an autoimmune disease characterized by hyperthyroidism due to circulating autoantibodies. Thyroid-stimulating immunoglobulins (TSIs) bind to and activate thyroid-tropin receptors, causing the thyroid gland to enlarge and the thyroid follicles to produce more thyroid hormone. In certain individuals, Graves's disease may be a component of more widespread autoimmune conditions that affect several organs (such as polyglandular autoimmune syndromes). Pernicious anemia, vitiligo, diabetes mellitus type 1, systemic sclerosis, myasthenia gravis, Sjogren syndrome, rheumatoid arthritis, and systemic lupus erythematosus are all linked to Graves's disease. A few instances of this uncommon and little-known "entity" have been reported. Herein, I describe the association of Graves's disease associated with pancytopenia and splenomegaly response to steroid therapy. We suggest that such an association has been very rarely reported. Case study: A 55-year-old Sudanese male presented to us at ELmek Nimer University Hospital complaining of generalized fatigability with symptoms and signs of Graves ' disease. He also looked pale on the abdominal examination; there was a huge splenomegaly, a complete blood count showed features of pancytopenia, and all components of blood and cells were low. We diagnosed him with autoimmune thyroid disease associated with splenomegaly and started treatment with steroids, which showed improvement clinically and in the laboratory. In Graves' disease, four well-known thyroid antigens are known to be targets of B and T lymphocyte-mediated autoimmunity: thyroglobulin, thyroid peroxidase, sodium-iodide symporter, and thyrotropin receptor. Nonetheless, the thyrotropin receptor itself is the main autoantigen of Graves's disease, and it also results in hyperthyroidism. The immune responses specific to the thyroid antigen mediated by antibodies and cells are well-defined in this disease. The development of hyperthyroidism in healthy subjects by transfer of thyrotropin receptor antibodies in serum from patients with Graves's disease and the passive transfer of thyrotropin receptor antibodies to the fetus in pregnant women are direct indications of an autoimmune disorder mediated by autoantibodies. We recommend that steroid 'therapy' should be considered as one of the modalities in the management of pancytopenia, splenomegaly associated with Graves's disease, in combination with ant-thyroid treatment.

Keywords: Graves's disease, pancytopenia, splenomegaly and steroid therapy

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1. INTRODUCTION

Graves's disease is an autoimmune disease that affects multiple organs of the body and is characterized by different presentations according to the system involved. Graves's disease is a state of hyperthyroidism that can be associated with various hematological disorders. The prevalence of anemia among patients with hyperthyroidism ranged from 10 to 15%[1]. Slight leucopenia, neutropenia, and thrombocytopenia are common events in thyrotoxicosis and are usually of an autoimmune origin [2, 3]. Splenomegaly is also a rare event in Graves's disease and is generally of an autoimmune origin, which may cause peripheral pancytopenia. Boelaert et al. investigated the prevalence of and relative risks for coexisting autoimmune diseases in patients with Graves' disease (2791 patients) or Hashimoto thyroiditis (495 patients). The authors found coexisting disorders in 9.7% of patients with Graves' disease and 14.3% of those with Hashimoto thyroiditis, with rheumatoid arthritis being the most common of these (prevalence = 3.15% and 4.24% in Graves' disease and Hashimoto thyroiditis, respectively). Relative risks of greater than 10 were found for pernicious anemia, systemic lupus erythematosus, Addison disease, celiac disease, and vitiligo. The authors also reported a tendency for parents of patients with Graves's disease or Hashimoto's thyroiditis to have a history of hyperthyroidism or hypothyroidism, respectively. [3]

2. CASE STUDY

2.1 History

A 55-year-old Sudanese man with thyrotoxicosis was admitted to ELmek Nimer University Hospital and complained of generalized fatigue, generalized weakness, weight loss, insomnia, irritability, shortness of breath, and abnormal behavior. He also reported intermittent palpitation over the past few months. There was no history of fever, night sweats, or recent infection. He denied any significant bleeding episodes, bruising, or prior hematological disorders. The diagnosis was made in 2013, at which time the patient was treated with thioamides (carbimazole), 45 mg daily, and propranolol tablets, 40 mg twice per day. Because his condition improved, but the patient was in poor compliance with his medication, the patient presented with recurrent attacks of thyrotoxicosis crises.

2.2 Physical examination

The man was an overactive person with a tall stature, irritable, drowsy, and semi-conscious. His pulse rate was 120 per minute regularly, respiratory rate was 24 per minute, and blood pressure was 110/70. Conspicuous exophthalmos and other ophthalmic signs like lead-lag, lead retraction, and ophthalmoplegia of thyrotoxicosis were observed (Figure No 1). The thyroid gland was diffusely enlarged, and a bruit was audible in the region of the gland. (Figure No 2). There was a fine tremor of the outstretched hands; also, there was sweating and hotness on both palms of the hands. There are hypo-pigmented areas in both dorsums of the hands, called vitiligo (Figure No 3). There was pretibial myxedema on both anterior aspects of the legs (Figure No 4). The spleen was palpable 6 cm below the left costal margin, the liver not palpable, and no ascites or lymph nodes palpable Figure 5. Neurological examination showed hyperreflexia.

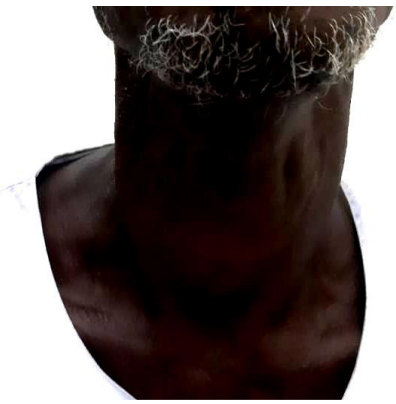

Fig 1: Conspicuous exophthalmos. **Fig 2: Diffusely enlarged thyroid gland**

Fig 3: Vitiligo

Fig 4: Pretibial myxedema

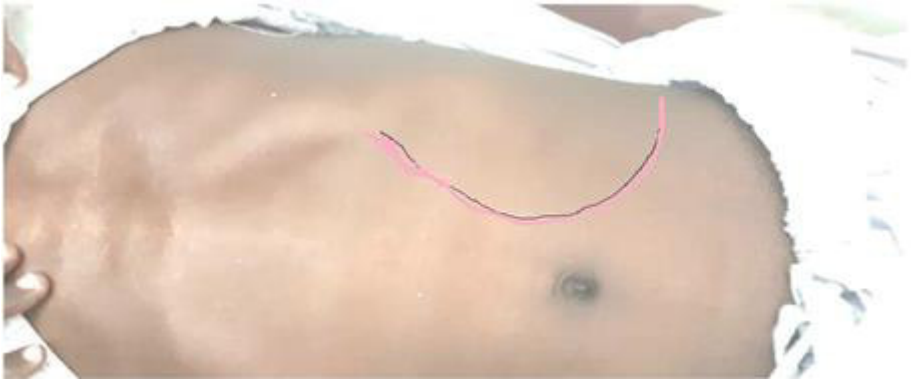

Fig 5: Splenomegaly

2.3 Initial laboratory finding

2.3.1 Complete blood cell count showed.

Complete blood count during admission revealed pancytopenia Hb was 7.5 g/dl, RBCs were 3.4 mili/cum, WBCs were 2.1 cells/cum, and the platelet count was 88.000 cells/cum. The peripheral blood picture revealed thrombocytopenia and normocytic norm chromic RBCs. Table 1

2.3.2 Thyroid function test revealed: Table 2

2.3.3 The radiological result

The abdominal ultrasound conducted in April 2022 revealed a significantly enlarged spleen measuring 19 cm, with a normal homogenous echo pattern, no focal lesion, and a normal splenic vein. By May 26, 2022, the spleen size had reduced to 16 cm. However, when the procedure was repeated on October 20, 2022, and again on November 30, 2022, the Spleen size increased to 17 cm, likely due to the patient discontinuing steroid therapy.

Diagnosis: Based on the clinical findings, laboratory results, and radiological evidence, the patient was diagnosed with Graves's disease complicated by pancytopenia and splenomegaly.

2.4 Hospital course

The patient received I.V. fluid, pressure wash, and Paracetamol infusion on the first hospital day as needed. He is already on a carbimazol tablet of 15 mg. Then "I" started oral steroid (prednisone 1 mg/kg) and proton pump inhibitor. The patient showed excellent improvement in both his clinical manifestations and laboratory findings after the first two weeks of fluid from starting management; unfortunately, the patient stopped the treatment, his condition deteriorated, and his hemoglobin dropped. We introduced the management again and then discharged in good condition. Table 1

Table 1: Hematological investigations: Hematology profile

	06/08/ 2012	28/01/ 2014	12/07 /2017	16/01/ 2018	01/02/ 2018	13/03 /2019	20/03 /2019	28/03/ 2019	11/04 /2019	27/06 /2019	22/9/20 19	Normal range
Hb g/dl	8.6	8.8	8.8	8.6	8.8	7.5	9	7.1	6.9	12.8	13.3	12-16
Hb%	57%	59%	59%							88%	91%	
RBCs (mili/cumm)	3.30		4.1	3.6	3.7	3.4	4.0	3.6	3.00	5.42	5.7	3.8-5
PCV	26.3%	31.6%	29.0%	25%	26.0%	25.0%	38.0%	29.0%	24.0%	43.0%	43.7%	36-46
RBCs indices												
MCV (fl)	79.7		70.0	23.0	70.0	74.0	80.0	79.0	79.0	79.51	77.3	78-98
MCH (pg)	26.7		21.0		23.0	22.0	30.0	19.0	23.0	23.6	23.4	27-32
MCHC (g/dl)	32.7		31.0	33.0	33.0	30.0	33	24	29.0	29.7	30.4	30-37
RDW												
Platelet Count (cells/cumm)	81000	135000	76000	71000	64000	88.000	367000	92000	91000	123000	126000	150000-450000
MPU												
WBCs (cells/cumm)	2.2	3100	1800	2100	2400	2.1	5.600	4.300	1.000	3.500	3000	4000-11000
WBCs Differential count												
Segmented Neutrophils	0.9%	56%	72%	76%	75%	70%[3.3]	34%	85%	70.0%[6.7]	70%	72%	
lymphocytes	0.5%	34%	23%	14%	15%	20%[1.5]	56%	08%	20%[1.7]	25%	22%	
Monocytes	0.6%	2%	05%	10%	10%	10%[0.5]	10%	07%	10%[0.7]	03%	04%	
Eosinophils	0.2%	8%						4%		01%	02%	
Basophils		0								01%	00%	
Peripheral Blood picture												
RBCs	Normocytic norm chromic cells	Normocytic norm chromic cells	Microcytic Hypochromic cells	Microcytic Hypochromic cells	Microcytic Hypochromic cells	Normocytic norm chromic cells	Normocytic norm chromic cells	Normocytic norm chromic, target cells		Normocytic norm chromic cells	Erythrocytosis, with microcytic hypochromic	
WBCs	Normal morphology	Normal morphology	leucopenia	Leucopenia	leucopenia	Normal morphology	lymphocytosis	Normal morphology		Normal morphology	Normal morphology	
Platelets	thrombocytopenia	Slightly Reduce	thrombocytopenia	thrombocytopenia	thrombocytopenia	thrombocytopenia	adequate	thrombocytopenia		Reduce	Slightly Reduce	
ESR	38											

Normal range: Hemoglobin (12.0-16.0)g/dl, RBCS (3.8-5.0)milli/cumm, TWBC (4.000-11000) cells/cumm, PCV (36-46.0), MCV (78.0-98.0) FL, MCH (27.0-32.0) pg, MCHC (30.0-37.0)g/dl, platelet count (150.000-450.000) cells/cumm.

Table 2: Thyroid function test

	06/08/2012	29/01/2014	12/07/2017	16/01/2018	01/02/2018	18/04/2019	22/09/2019	Re-value
TSH	0.01 ulU/ml	0.01 ulU/ml	0.01 ulU/ml	0.01 ulU/ml	0.01 ulU/ml	0.01 ulU/ml		0.38-4.3ulU/ml
T3		750ng/ml	1.0ng/ml NR(0.79-1.58)ng/ml	1.1ng/ml NR(0.79-1.58)ng/ml	2.1ng/ml NR(0.79-1.58)ng/ml			79-159ng/ml
T4		24ng/dl	7.8 ng/dl	3.1 ng/dl	5.5 ng/dl	5.4 ng/dl		4.0-11ng/dl
FT4	2.8ng/dl						44.5pmol/L NV(10.6-21.0)Pmol/L	0.82-1.63ng/dl
FT3	11.6ng/ml							2.1-3.8ng/ml

Thyroid Stimulating Hormone (TSH) triiodothyronine (T3) thyroxine (T4) Free thyroxine (FT4) Free triiodothyronine (FT3)

Table 3 Reported pancytopenia induced by hyperthyroidism and recovered by treatment

Year	Author	Sex	Age	Causes	Treatment
1981	Talasky	F	48	Graves'	I-131
1983	Iguchi	F	51	Graves'	Methimazole
1995	Duquene	F	72	Toxic adenoma	I-131
1995	Duquene	F	66	Graves'	I-131
1995	Duquene	F	83	Graves'	I-131
1998	Bertola	F	63	Graves'	I-131
2000	Masuoka	F	45	Graves'	Methimazole
2001	Soeki	M	49	Graves'	Methimazole, then thyroidectomy
2002	Shaw	M	46	Graves'	Carbimazole
2005	Kebapcilar	F	53	Graves'	Propylthiouracil, then I-131
2006	Lima	M	71	Graves'	Methimazole, then I-131
2006	Lima	F	35	Graves'	Methimazole
2006	Lima	M	39	Graves'	Methimazole
2006	Lima	F	18	Graves'	Propylthiouracil, then I-131
2007	Akoun	F	65	Graves'	Methimazole
2008	Hegazi	F	43	Toxic multinonular goiter	Carbimazole
2008	Ohtsuka	F	48	Graves'	Carbimazole
2009	Low	F	56	Graves'	Methimazole
2012	Raina	M	27	Graves'	Methimazole
2017	Elayne Christinne Marcelino e Silva	F	46	Graves'	Propylthiouracil, then I-131

3. DISCUSSION

In our case, the patient was hospitalized due to anemic symptoms; a complete blood count during admission revealed pancytopenia despite the patient having been on treatment with anti-thyroid management for more than 6 years; and splenomegaly was detected 6 cm below the left costal margin. As pancytopenia was associated with hypersplenism when splenomegaly and normal blood smears were present, no further tests were performed, including iron profiles, vitamin and iron profiles, or bone marrow assays. Instead, the response to steroids was evaluated through repeated blood tests. It is known that isolated anemia, thrombopenia, or leucopenia can be associated with thyrotoxicosis. Anemia appears to be the most associated cytopenia (10%-34%) of patients with thyrotoxicosis.1-3 Leukopenia is reported in 15% to 30% of untreated thyrotoxicosis, and thrombocytopenia rarely occurs in 2% to 5% of thyrotoxicosis cases.1, 3 The mechanism seems to be plural, mainly on 2 paths: reduced production of hematopoietic cells from the bone marrow and increased destruction or sequestration of mature hematopoietic cells. Thyroid hormones affect erythropoiesis by increasing erythropoietin secretion and hyperproliferating immature erythroid progenitors. 3. This causes an excess of iron, folic acid, and vitamin B12 to be consumed, resulting in normochromic-normocytic, hypochromic-microcytic, or macrocytic anemia. 4,5. Several 15 authors, [3, 6, 7, 8, 9, 10], reported an association of hyperthyroidism with splenomegaly that is known to be correlated with a reduction in the erythrocyte lifespan with hypersplenism.6 After treatment and achievement of the euthyroid status, splenomegaly returned to normal size. Even rare, the association of pancytopenia with hyperthyroidism has been previously described in the literature.[11, 19] Table 3. About 14 reports and 19 cases were reported from 1981 to 2012 [8-10]. All patients had GD, except for two cases caused by toxic nodular disease [9-11]. As in the described case, all showed regression after the establishment of the euthyroid state. But in our case, despite management with antithyroid treatment, there was no response in both cytopenia and splenomegaly. When starting treatment with steroid therapy, showed excellent response to all parameters of complete blood cells and regression of the spleen. The cause of leukopenia is also poorly understood. On the one hand, a decreased granulocyte reserve in the bone marrow limits granulopoiesis. Antineutrophil antibodies, on the other hand, have been found in the serum of thyrotoxicosis patients,

supporting the theory of immunologic destruction mechanisms. [18, 19] Furthermore, a relative lymphocytosis with cross-antigenicity between polynuclear neutrophils and human TSH receptors has been reported, leading to the development of the Kocher blood picture, a distinctive blood finding associated with Graves's disease. 1 EMA Kyritsi et al., 20 found that choroidopathy represents the most common disorder among apparently healthy patients with mild-to-moderate neutropenia. Notable associations were observed between TSH and absolute CD4+ counts, T4 and absolute CD4+ counts, and T3 and neutrophil counts. They also displayed noteworthy patterns of immunity-related parameters and markers. Furthermore, antiplatelet antibodies have been found in individuals suffering from Hashimoto thyroiditis and Graves' disease serum. [3, 6] Similar implications apply to hypersplenism and the decrease in thrombocyte lifespan.

4. CONCLUSION

This case illustrates that pancytopenia in Graves' disease is related to hypersplenism, which is a part of autoimmune disease, and showed excellent response to steroid therapy when combined with antithyroid therapy and postponed splenectomy. Steroid therapy was effective in this case; however, pancytopenia and autoimmune reactions are immunological mechanisms that contribute to the pathophysiology of the association between splenomegaly, pancytopenia, and Graves' disease.

5. AUTHORS CONTRIBUTION STATEMENT

The MIA consultant physician was involved in making the decisions regarding the patient's treatment in the intensive care unit. He was the patient's primary consultant physician. He reviewed the manuscript critically and approved it for final submission.

6. CONFLICT OF INTEREST

Conflict of interest declared none.

7. ETHICAL CONSIDERATIONS

Informed consent from patient

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