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A Rare Case of Graves' Disease with Splenomegaly and Pancytopenia

CASE REPORT

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Abstract

Introduction: Splenomegaly and pancytopenia are rare complications of Graves' disease with few reports in the literature about this association. The pathogenesis is unknown and immunological mechanisms seem to be involved. The possibility of hyperthyroidism should always considered in patients with pancytopenia.

Objective: Describe a clinical case of association between Graves' disease, splenomegaly and pancytopenia.

Method: This is a case report, obtained through data from medical records of a reference hospital located in the city of Juazeiro do Norte, Ceará, Brazil.

Case Report: Patient, 46 years old, female, sought treatment at a reference hospital with abdominal pain that started two days earlier, prevalent in mesogastric region and left hypochondrium very intense and recurrent, associated with significant consumptive syndrome (loss of 10 kg in 4 months), asthenia, dyspnea on minimum exertion, irritability and fine tremor in extremities. She denied fever, palpitations, heat intolerance, skin or eye changes. A diffuse thyroid enlargement with the presence of thrill and murmur, digital clubbing, fixed and bright look, light exophthalmos and splenomegaly about 6 cm below the left costal margin were observed after physical examination. Ultrasound examination (USG) of the abdomen and CT scan showed moderate splenomegaly. Laboratory tests showed normocytic and normochromic anemia, leukocytosis and mild thrombocytopenia. Thyroid USG showed characteristic features of Graves' disease, a bone marrow biopsy revealed maturation preserved in all strains and lack of fibrosis and megakaryocytes present in normal number without atypia. Treatment was set with propylthiouracil 300 mg a day and

after the first revaluation after hospital discharge three weeks later a regression of splenomegaly has been observed. Five months after initiation of treatment, there was normalization of pancytopenia.

Conclusion: This case illustrates the rare association between hyperthyroidism and splenomegaly with pancytopenia.

Keywords
Graves' Disease; Splenomegaly; Pancytopenia.

Introduction

Graves' disease (GD) is a syndrome characterized by hyperthyroidism, diffuse goiter, eye disease, and occasionally a pretibial myxedema. It is caused by autoantibodies of the thyrotropin receptor (TRAb) that activate the receptor, stimulating the synthesis and secretion of thyroid hormones, as well as the diffuse growth of the gland [1-3]. These modifications are well described in the literature, however the existence of pancytopenia or splenomegaly is treated as a rare complication of the disease [4].

Hematological abnormalities are commonly described in patients with hyperthyroidism, but what is usually found is an isolated presentation of anemia, leukopenia, thrombocytopenia and abnormalities in coagulation factors [5]. The mechanisms involved in these isolated strains are related to reduced circulation time for some and the autoimmune reactions for others. Pancytopenia, which may be related to cell sequestration caused by splenomegaly, was rarely reported and all cases were fully reversible with properly performed antithyroid drug treatment [6].

Despite numerous effects related to Graves' disease and the association of clinical signs and symptoms already described in the literature, there are gaps about the development of rare complications such as splenomegaly and pancytopenia. Thus, this case study aims to describe the rare occurrence of splenomegaly and pancytopenia associated with Graves' disease.

Case Report

Female patient, 46 years old, previously healthy sought treatment at a reference hospital in September 2014 with abdominal pain that started two days before admission, prevalent in mesogastric region and left hypochondrium very intense and recurrent associated with significant consumptive syndrome (loss of 10 kg in 4 months), irritability, asthenia and fine tremor in extremities. She denied fever, palpitations, heat intolerance, skin or eye changes, previous comorbidities, medication use, alcoholism or smoking. She reported having family members with hyperthyroidism.

Diffuse thyroid enlargement with the presence of thrill and murmur, digital clubbing, fine tremor of the extremities, tachycardia, mild jaundice, fixed and bright look, light exophthalmos and splenomegaly of about 6 cm below the left costal margin were observed with physical examination.

In previous history, the patient denied comorbidities, denied use of medications, denied alcoholism and smoking.

Laboratory data on admission **(Table 1)** showed normocytic and normochromic anemia (Hb = 6.1 g/dl), leukocytes: 2,062/mm³ and mild thrombocytopenia: 99,000/mm³. Hypoalbuminemia (3.76 g/dl) and indirect hyperbilirubinemia (1.32mg/dl) were also found in the biochemical evaluation. Reticulocytes were 0.8% (14,800/mm³), lactate dehydrogenase (LDL) was high (472 U/L) and indirect Coombs test result was negative. There was elevated ferritin (517.4 ng/ml), normal iron serum (51.8µg/dl) redu-

Table 1. Summary of lab results during first evaluation and six months after.

Lab test	First admission (pancytopenia)	Six months after
TLC (3,600-11,000/µl)	2,062/µl	4,800/µl
DLC		
Polymorphs	62	58
Lymphocytes	28	35
Monocytes	10	3
Eosinophils	0	6
Hemoglobin (11,5-16,4 g/dl)	6.1g/dl	10.6g/dl
MVC (80-98 fl)	95.7fl	91.8fl
MCH (25-32 pg)	32.1	28.6
MCHC (28-36 g/dl)	33.5	31.1
Platelets (15-45 x 10^4 µl)	9.9 x 10^4µl	16.1 x 10^4µl
Reticulocytes (2-20%)	0,8%	10%
TSH (0.5-5 µU/ml)	0.008µU/ml	5.27
Free T_4	2.61ng/ml	1.8ng/ml

TLC: Total leucocyte count, DLC: Differential leucocyte count, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobina concentration, TSH: thyroid stimulating hormone.

ced haptoglobin (7 mg/dl), high folic acid (19.8ng/ml) and regular vitamin B12 dosage besides 152 alkaline phosphatase and gamma glutamiltranspeptidase level of 55. The abdominal ultrasonography revealed homogeneous splenic parenchyma, increased volume and spleen index of 144. The USG revealed a normal liver.

Hormonal evaluation showed hyperthyroidism with TSH: 0.008µU/ml, Free T4: 2.61ng/dl, Total T3 616.4ng/dl, anti-thyroperoxidase: 600, anti-thyroglobulin <20.

Ultrasound examination (USG) of the abdomen and CT scan showed moderate splenomegaly. Thyroid USG showed thyroid parenchymal disease with increased volume of the gland (70cm³) and its vascularization, a characteristic feature of Graves' disease.

The bone marrow biopsy was performed, resulting in the estimated cellularity of 60%, compared with granulocyte/eosinophil of 4:1, preserved maturation in all lineages and no fibrosis. Megakaryocytes present in normal number without atypia.

The case occurred in an endemic area for visceral leishmaniasis, for this reason the patient was also investigated for this condition, but presented negative serology for K39 and bone marrow biopsy which showed no protozoan.

The patient received treatment with propylthiouracil 300 mg/day, plus Propranolol 80mg/day to control tremors. The abdominal symptoms, tremors, jaundice and asthenia gradually regressed with the treatment. The patient was discharged and continued as an outpatient. Iodotherapy therapy was indicated in the month following the discharge because of the distance from her residence to the reference center and the fear of accompanying loss.

The healing of pancytopenia was observed after 5 months and regression almost complete of the splenomegaly started from the third week of use of antithyroid drugs. The euthyroid state was assured after 6 months of treatment. Abdominal ultrasonography was performed to monitor the splenomegaly and after eight months the patient showed significant regression.

Discussion

During hospitalization, our patient was diagnosed with Graves' disease, splenomegaly and pancytopenia which are considered rare manifestations of this disease. She did not use drugs before hospitalization and laboratory tests showed no signs of myelodysplastic syndrome, visceral leishmaniasis or any other conditions that could explain the spleen and blood disorders. These results, coupled with the unexpected response to treatment carried out

Table 2. 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'	Propylthiouracil, then I-131
2006	Lima	F	18	Graves	Methimazole
2007	Akoun	F	65	Toxic multinonular goiter	Carbimazole
2008	Hegazi	F	43	Graves'	Carbimazole
2008	Ohtsuka	F	48	Graves'	Methimazole
2009	Low	F	56	Graves'	Methimazole
2012	Raina	M	27	Graves'	Carbimazole

only with antithyroid drugs suggest that pancytopenia and splenomegaly were caused by hyperthyroidism.

Untreated hyperthyroidism may be associated with anemia (34%) [7], leukopenia (5.8%) and thrombocytopenia (3.3%) [6]. According to Soeki, the prevalence of anemia in these patients has increased in recent years. Classically, the most common anemia is the one that is common to chronic diseases, but anemia caused by iron deficiency, pernicious anemia and hemolytic anemia have also been well described [4,7]. Our patient had no findings suggestive of nutritional or hemolytic anemia.

Even rare, the association of pancytopenia with hyperthyroidism has been previously described in the literature **(Table 2)**. A total of 14 reports, 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.

The pathogenesis of pancytopenia in hyperthyroidism still presents few studies, but it has been speculated that may occur because of a reduced hematopoietic cell production [9, 11, 12] or reduction of lifetime of the blood cells caused by hypersplenism induced by hyperthyroidism [4].

Immunological mechanisms seem to be involved also in reducing the lifetime of hematopoietic cells, antineutrophil cytoplasmic and antiplatelet antibodies can be found. Too much thyroid hormone also exerts an inhibitory effect of hematopoiesis and hyperthyroidism investigation in patients with pancytopenia without apparent cause is therefore importante [9, 12, 13].

Beyond pancytopenia, another finding that deserves more emphasis here was the presence of noticeable splenomegaly on physical examination. The association between this clinical sign and Graves' disease is rarely reported, although it is a common finding in other autoimmune diseases, particularly in cases of rheumatoid arthritis [14, 15].

Splenomegaly is a diagnostic challenge since almost all associated diseases are extrinsic to the spleen. The various diseases associated with splenomegaly depend on geographic location for their diagnosis and even the time of its occurrence [16]. In a study performed by O'Reilly in the period between 1913 and 1962, 2505 patients with splenomegaly were studied.

Among the inflammatory causes, the hyperthyroidism in 60% of cases, was the main cause. The study showed that 60% of patients with this association were suffering from Graves' disease (GD), which contrasts with other studies conduc-

ted between 1983 and 1993 which showed that GD was found in only 1 case of 170 patients with splenomegaly. Nowadays we see little about the relationship between hyperthyroidism and hypersplenism and the persistence of splenomegaly in patients with hyperthyroidism is linked to inadequate treatment of GD [16].

The direct relationship of hyperthyroidism, excluding other autoimmune diseases, with splenomegaly, was found in only two studies in the last twenty years. Kimura et al (1989) described the case of subacute thyroiditis with increases in serum levels of acute phase proteins and erythrocyte sedimentation rate. It also showed signs of liver dysfunction [alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl transpeptidase (GGT) and leucine aminopeptidase (LAP) increased slightly], mild anemia, glucose intolerance, increased pancreatic enzymes, splenomegaly and an increase in peripheral cells [17].

Akasheh (1994) describes a case involving splenomegaly, lymphadenopathy and hypochromic microcytic anemia. Thyroid hormones stimulate erythropoietin production through increased overall metabolism, resulting in an increase in oxygen consumption. This series of hematological changes, in this case described, Graves' disease mimicked traits of thalassemia, confusing diagnosis [5].

Besides the description of splenomegaly in adults with hyperthyroidism, two cases in which women with hyperthyroidism gave birth to children with manifestations of thyrotoxicosis and splenomegaly with regression at three months of age were also described [18, 19].

Conclusion

In both the above cases, treatment for hyperthyroidism were also successful in the treatment of the complications described and the case mentioned is an example.

In conclusion, pancytopenia and splenomegaly are possible complications of hyperthyroidism. The underlying mechanisms are unclear but there is regression after treatment with antithyroid drug. Further studies are needed to clarify the real nature of this association and the assessment of thyroid status should be included in the evaluation of unexplained pancytopenia and splenomegaly.

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