Graves Disease Causing Pancytopenia: Case Report and Literature Review

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ABSTRACT

BACKGROUND: Graves disease or other causes of thyrotoxicosis are frequently associated with cytopenia. Although anemia is the most common, other cell lineage can be affected. Pancytopenia is a rare complication of thyrotoxicosis.

CASE PRESENTATION: We report a case of a 33-year-old Chinese man who presented a nonsevere pancytopenia in the context of a newly diagnosed Graves disease. Restauration of euthyroid state led to progressive correction of pancytopenia.

CONCLUSIONS: Literature review shows other rare cases of pancytopenia. It is usually nonsevere with just extremely rare cases of transfusion reported. Evolution was always favorable after achievement of euthyroid state. Its mechanism remains poorly understood, especially because those patients have no vitamin or iron deficiency. The exact physiopathological process remains unclear but 2 causes seem to overlap: reduced production of hematopoietic cells from the bone marrow and increased destruction or sequestration of mature hematopoietic cells. Despite unclear mechanism, the presence of hematologic abnormalities including pancytopenia must not be considered as a contraindication to antithyroid drug therapy.

KEYWORDS: Graves disease, pancytopenia, hyperthyroidism, antithyroid drug therapy

Background

Graves disease or other causes of thyrotoxicosis are frequently associated with cytopenia. Anemia is the most common, but other cell lineage can be affected.1–3 Pancytopenia, however, is rare. This can raise a therapeutic dilemma with antithyroid drug therapies known for hematologic side effects.

Case Presentation

A 33-year-old Chinese man with no past medical history presented to the emergency department with bilateral leg edema and progressive dyspnea over 1 month. He also complained of neck swelling, palpitations, hand tremor, nycturia, stomach aches, and diarrhea since childhood, testicular and penile edema, and involuntary weight loss (12 kg) over 4 months despite a good appetite. He has lived in Switzerland for the past 10 years and had no history of professional or recreational drug therapies known for hematologic side effects.

Physical examination demonstrated a voluminous thyromegaly, with leg edema from the feet to the hips, dermatitis, and a raised jugular venous pulse. Cardiac auscultation revealed an irregular heart rate, with a cardiac murmur (5/6) at Erb’s point, radiating to the carotids. Pulmonary auscultation revealed pulmonary crackles in the lung bases. The abdomen was distended with a fluid thrill sign, but pain free. On genital examination, there was a translucid painless testicular edema. He had no exophthalmia.

Laboratory tests revealed pancytopenia with a nonregenerative anemia (hemoglobin = 97 g/L [normal range = 117-157 g/L], reticulocytes = 12 G/L [normal range = 25-75 G/L]), thrombocytopenia (T = 74 G/L [normal range = 150-400 G/L]), and leukopenia (L = 3.4 G/L [normal range = 4-10 G/L]) without agranulocytosis (neutrophil count = 1.7 G/L [normal range = 2-7.5 G/L]). Anemia workup showed no vitamin B12 or folic acid deficiency, normal haptoglobin. A blood smear showed no abnormality. The NT-proBNP was 1664 ng/L (normal range < 300 ng/L).

Thyroid function test detected abnormally high levels of thyroid hormones: l-triiodothyronine (T3) > 50 pmol/L (normal range = 3.5-6.5 pmol/L), l-tyroxine (T4) > 100 pmol/L (normal range = 10-23 pmol/L), thyroid-stimulating hormone (TSH) < 0.01 (normal range = 0.5-4.70 mIU/L). Later, immunology revealed TRAK levels > 30 U/L (normal range < 1.8 U/L) and antithyroperoxydase antibodies = 1508 kUI/L (normal range < 35 IU/mL). An electrocardiogram showed atrial fibrillation (cardiac frequency = 135/min), and transthoracic ultrasound (US) showed cardiomegaly with no ventricular dysfunction. Cervical US revealed an enlarged thyroid gland (total volume = 22 mL [normal range = 5.7-17 mL]) with bilateral heterogeneous enlarged lobes, without any focal suspect lesion. Color Doppler showed a highly increased “inferno” type of vascularization. Thorax X-ray showed a pulmonary edema with small pleural effusions on both sides.

He was hospitalized. Treatment was started with carbimazole (15 mg, 3 times a day) with furosemide (40 mg/d) to treat global cardiac failure. Anticoagulation with rivaroxaban was also started to prevent embolisms due to atrial fibrillation. To reduce the heart beat fibrillation, metoprolol was given, with perindopril for pressure control. With treatment, symptoms
improved within 5 days: the tremor stopped and he had a normal bowel transit. Spontaneous cardioversion to a normal sinus rhythm lead to the regression of the edemas and weight loss (−6 kg). Within several days, restauuration of a euthyroid function was linked to the correction of hematologic values (Table 1). After discharge, the pancytopenia resolved completely and remained stable without any blood product transfusion.

**Discussion and Conclusions**

In our case, the patient came to the emergency department because of heart failure symptoms. They were further related to the Graves disease. Pancytopenia was identified in the initial workup. With no vitamin or iron deficiency, the cause of pancytopenia was unclear. Furthermore, because the blood smear was normal, with a well-tolerated, non-severe pancytopenia, no bone marrow biopsy was performed, and the response to antithyroid treatment was assessed on repeated blood tests.

Resolution of pancytopenia occurred simultaneously with the return of a euthyroid state (Table 1).

It is known that isolated anemia, thrombopenia, or leukopenia can be associated with thyrotoxicosis. It appears that anemia is the most associated cytopenia (10%-34%) of patients with thyrotoxicosis.1–3 Leukopenia is reported in 15% to 30% of untreated thyrotoxicosis, and thrombocytopenia is rarely observed in 2% to 5% of thyrotoxicosis cases.1,3 The association between thyrotoxicosis and pancytopenia is a rarely described in the literature (Table 2). Two major points seem relevant. First, it appears that pancytopenia is usually chronic and well tolerated. Over the 23 cases reported in the literature (Table 2), 5 were transfused with red blood cells, and 2 also received platelet transfusion. In those cases, transfusion was mainly done because of tachycardia with cardiac failure related to thyrotoxicosis, which could be worsened by anemia. We found no case report of ischemia or other severe complication of anemia, nor bleeding because of thrombocytopenia, nor synchronous infection due to leukopenia. Only 2 cases were close to agranulocytosis with 0.5 G/L neutrophils; however, none of them required growth factor treatment. Second, in all cases reported, hematologic values were corrected with correction of the thyrotoxicosis. Choice of treatment (propylthiouracil, methimazole, radioidine therapy, or even surgery) did not matter, and normalization of the thyroid hormones values was followed by correction of the blood cell counts.

These reports indicate an association between thyrotoxicosis and pancytopenia, although the underlying physiopathology remains unclear.

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. Indeed, thyroid hormones are known for their effect on erythropoiesis, through hyperproliferation of immature erythroid progenitors and increased secretion of erythropoietin.3 This leads to an exaggerated consumption of iron, folic acid, and vitamin B12 and can generate various forms of anemia (normochromic-normocytic, hypochromic-microcytic, or macrocytic). In the cases we reviewed, only 2 cases reported severe vitamin B12 deficiency.3,6,7 Nevertheless, a large part of patients received anyway a substitution in iron, folates, or vitamin B12 without deficiency to support the erythropoiesis. No auto-immune anemia was reported, and peripheral hemolysis was ruled out by normal values of indirect bilirubin, haptoglobin, and negative Coombs.3 Several authors3,6,9,15,17 reported association of hyperthyroidism with splenomegaly that is known to be correlated with a reduction in the erythrocyte life span with hypersplenism.6 After treatment and achievement of the euthyroid status, splenomegaly returned to normal size.

The cause of leukopenia is also poorly understood. On one hand, granulopoiesis is limited by a reduced marrow granulocyte reserve,9 on the other hand, the hypothesis of immunologic destruction mechanisms has been suggested, as antineutrophil antibodies were detected in the serum of patients with thyrotoxicosis.19 Moreover, a relative lymphocytosis with cross-antigenicity between human TSH receptors and polymuclear neutrophils has been described with formation of a characteristic blood finding of Graves disease called Kocher blood picture.1 EMA Kyritsi et al20 found that thyroidopathy represents the most common disorder among apparently healthy patients with mild-to-moderate neutropenia. They showed significant patterns of parameters and markers of immunity and remarkable correlations between T3 levels and absolute neutrophil counts, TSH levels and absolute CD4+ counts, T4 levels and absolute CD4+ counts.

In addition, antplatelet antibodies have been detected in the serum of patients with Graves disease and Hashimoto thyroiditis.3,6 Hypersplenism is implicated in the same way in the reduction in lifetime of the thrombocytes.

Finally, it is known that antithyroid drug therapy can cause severe hematologic disorders. Therefore, a complete blood

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**Table 1. Hematologic values.**

|        | D1  | D3  | D5  | D7  | D9  | D11 |
|--------|-----|-----|-----|-----|-----|-----|
| Leukocytes, G/L | 3.4 | 2.8 | 3.1 | 3.3 | 3.4 | 4.7 |
| Hemoglobin, g/L  | 97  | 98  | 102 | 105 | 102 | 112 |
| Thrombocytes, G/L | 74  | 77  | 78  | 95  | 104 | 148 |
Table 2. Literature review.

| YEAR | AUTHOR (REFERENCE) | SEX | AGE, Y | PATHOLOGY | HEMOGLOBIN, G/DL NORMAL RANGE = 117-157 G/L | PLATELET COUNT, G/L NORMAL RANGE = 150-400 G/L | WBC, G/L NORMAL RANGE = 4-10 G/L | NEUTROPHIL COUNT, G/L NORMAL RANGE = 2-7.5 G/L | TRANSFUSION | RECOVERY AFTER THE THERAPY | VITAMIN B12 DEFICIENCY |
|------|---------------------|-----|--------|-----------|------------------------------------------|---------------------------------------------|---------------------------------|----------------------------------------|-------------|---------------------------|-----------------------|
| 2014 | Rafhati et al,4 Case 1 | F   | 56     | GD        | 10.6                                      | 110                                         | 2.9                             | 1.1                                     | No          | Yes                       | No                    |
| 2014 | Rafhati et al,4 Case 2 | F   | 57     | GD        | 11.6                                      | 110                                         | 3.8                             | 1.5                                     | No          | Yes                       | No                    |
| 2014 | Rafhati et al,4 Case 3 | F   | 58     | GD        | 8.6                                       | 72                                          | 3.22                            | 1.48                                    | No          | Yes                       | No                    |
| 2012 | Raina et al P       | M   | 27     | GD        | 9.5                                       | 80                                          | 2.4                             | —                                       | No          | Yes                       | No                    |
| 2009 | Boon-Hua Low and Kok | F   | 56     | GD        | 5.7                                        | 59                                          | 2.05                            | —                                       | No          | Yes                       | Yes                   |
| 2013 | Peyman Naji et al2   | M   | 70     | GD        | 9                                         | 80                                          | 2.5                             | —                                       | No          | Yes                       | No                    |
| 2013 | Loh Hui Heng and Tan7 | M   | 48     | GD        | 8.7                                        | 48                                          | 3.2                             | 1.16                                    | RBC T       | Yes                       | Yes                   |
| 2006 | Lima et al,3 Case 1  | M   | 71     | GD        | 7.3                                        | 23                                          | 2.5                             | 0.9                                     | RBC T       | Yes                       | Yes                   |
| 2006 | Lima et al,3 Case 2  | F   | 35     | GD        | 9.5                                        | 75                                          | 2.8                             | 1.6                                     | No          | Yes                       | No                    |
| 2006 | Lima et al,3 Case 3  | M   | 39     | GD        | 11.9                                       | 96                                          | 3.9                             | —                                       | No          | Yes                       | No                    |
| 2006 | Lima et al,3 Case 4  | F   | 38     | GD        | 4                                          | 10                                          | 3                               | 0.5                                     | RBC T       | Yes                       | No                    |
| 2015 | Subrata Chakrabarti8 | F   | 38     | GD        | 8.6                                        | 78                                          | 3.1                             | —                                       | No          | Yes                       | No                    |
| 2013 | Tae Hoon Kim et al1  | F   | 69     | GD        | 8.4                                        | 17                                          | 3.1                             | 1.7                                     | No          | Yes                       | No                    |
| 2014 | Garcia et al9        | F   | 54     | GD        | 9.5                                        | 137                                         | 2.1                             | 0.5                                     | No          | Yes                       | No                    |
| 2002 | Shaw and Mehta10      | M   | 46     | GD        | 9.7                                        | 22                                          | 2.2                             | 1                                       | RBC T + P T | Yes                       | —                     |
| 2015 | Imai et al11         | F   | 33     | HT        | 9.8                                        | 105                                         | 3.5                             | —                                       | No          | Yes                       | No                    |
| 2014 | Jha et al12          | F   | 62     | GD        | 7.4                                        | 91                                          | 3.4                             | —                                       | RBC T       | Yes                       | No                    |
| 2009 | Chen et al13         | F   | 36     | GD        | 9.1                                        | 69                                          | 1.6                             | —                                       | No          | Yes                       | —                     |
| 1995 | Ladwig et al14       | F   | 25     | GD        | 4.1                                        | 44                                          | 5.2                             | —                                       | No          | 0                        | No                    |
| 2001 | Soeki et al15        | M   | 49     | HT        | 6.5                                        | 48                                          | 2.87                            | 1.87                                    | No          | Yes                       | No                    |
| 2008 | Hegazi et al16       | F   | 43     | GD        | 7.3                                        | 55                                          | 3.2                             | —                                       | No          | Yes                       | No                    |
| 2017 | Silva et al17        | F   | 46     | GD        | 6.1                                        | 99                                          | 2.06                            | —                                       | No          | Yes                       | No                    |
| 2007 | Das et al18          | F   | 10     | GD        | 4.7                                        | 22                                          | 3.5                             | —                                       | RBC T + P T | Yes                       | No                    |

Abbreviations: GD, Graves disease; RBC, red blood cell.
count with reticulocyte rate seems important when hyperthyroidism is diagnosed. Identification of initial cytopenia or pancytopenia correlates with the thyrotoxicosis. This will help, in the future, to disqualify them from adverse effect of antithyroid drug therapy.

If there is no agranulocytosis (contraindication to start antithyroid drugs), the presence of initial hematologic abnormalities, including pancytopenia, must not be considered as a contraindication to antithyroid drug therapy. Daily monitoring of hematologic values must be done.

Pancytopenia is a rare complication of thyrotoxicosis. It is usually not severe and resolves with the restoration of euthyroid state. Extremely rare cases need transfusion.

Author Contributions
LP provided medicine for the patient. LP and FG wrote the manuscript. All authors read and approved the final manuscript.

Availability of Data and Materials
The author can be contacted for data requests.

Consent for Publication
Written informed consent was obtained from the patient for publication of this case report.

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