

A report of three cases of untreated Graves' disease associated with pancytopenia in Malaysia

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Abstract:

Generally, clinical presentations of Graves' disease range from asymptomatic disease to overt symptomatic hyperthyroidism with heat intolerance, tremor, palpitation, weight loss, and increased appetite. However, atypical presentation of Graves' disease with hematological system involvement, notably pancytopenia, is distinctly uncommon. Hereby, we present and discuss a series of three untreated cases of Graves' disease clinically presented with pancytopenia and the hematological abnormalities that responded well to anti-thyroid treatment. With resolution of the thyrotoxic state, the hematological parameters improved simultaneously. Thus, it is crucial that anti-thyroid treatment be considered in patients with Graves' disease and pancytopenia after a thorough hematological evaluation.

Keywords: Graves' disease, hyperthyroidism, thyrotoxicosis, pancytopenia

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1. Introduction

Graves' disease belongs to the category of autoimmune thyroid diseases. It was first described by Robert J. Graves, MD, in the 1830s (1). Pathophysiologically, it is due to auto-antibodies' binding to the activated thyrotropin receptors and leads to high levels of circulating serum thyroid hormones (2). Commonly, patients with Graves' disease exhibit symptoms of hyperthyroidism, e.g., fatigue, heat intolerance, weight loss, increased appetite, increased gastrointestinal motility, palpitation, irritability, and restlessness (3). Single-cell lineage haematological abnormalities, such as anemia, leucopenia, and thrombocytopenia, although uncommon, could be part of the clinical manifestations in patients with Graves' disease (4). However, it is extremely rare for pancytopenia to accompany Graves' disease (5–8). Only a handful of patients with Graves' disease and pancytopenia have been reported in the literature (5–8). Here, we report three patients with Graves' disease who presented with pancytopenia, and the hematological parameters responded well to anti-thyroid therapy. The cases illustrate the importance of initiating anti-thyroid therapy in patients with Graves' disease in association with pancytopenia. Written informed consents were obtained from the respective patients for publication of their cases.

2. Case presentation

2.1. Case 1

A 56-year-old woman presented to the medical department with fever for six days, and the fever was accompanied by myalgia and arthralgia with no concomitant respiratory or gastrointestinal symptoms. Her physical examination

was unremarkable, and she was treated for viral fever. However, her full blood count revealed that she had persistent pancytopenia (total white cell count of $2.9 \times 10^9/L$, neutrophil count of $1.1 \times 10^9/L$, hemoglobin of 10.6 g/dL, and platelet count of $110 \times 10^9/L$) despite her recovery from viral fever. Subsequently, the cause of pancytopenia was investigated. Bone marrow aspiration and trephine biopsy (BMAT) showed normocellular marrow. Serum vitamin B12 and folate levels were normal. There were no thyroid disorders in her family history.

Further reassessment revealed that the patient had experienced intermittent palpitations with weight loss in recent months with profuse sweating. Subsequently, the investigations that were ordered proved that she had Graves' disease (free T4 37.8 pmol/L, thyroid stimulating hormone < 0.01 mU/L, detection of anti-microsomal antibodies and anti-thyroglobulin antibodies). The decision was made to treat her hyperthyroidism with 100 mg of propylthiouracil (PTU) twice daily. Table 1 shows the trends of her thyroid function test, full blood count, and dose of medication.

With anti-thyroid therapy, the patient's thyroid function test results showed consistent improvement and resolution of pancytopenia was stable with the treatment of hyperthyroidism. There were minimal reductions of her neutrophil count during follow-up but without any clinical significance. In a clinical review, the patient's hyperthyroidism symptoms had resolved, and she experienced significant weight gain.

Table 1. Summary of Case 1 Characteristics and Treatment

Date	May 22, 2013	June 5, 2013	June 26, 2013	July 10, 2013	August 14, 2013	October 23, 2013	January 15, 2014
Free T4 (pmol/L)	37.8	22.3	13.5		15.0	12.9	12.1
Free T3 (pmol/L)			3.1		3.2		
TSH (mU/L)	<0.01	<0.01	<0.01		<0.01	0.92	3.98
TWCC ($10^9/L$)	2.9	5.54	4.62	5.00	4.05	4.84	5.01
Neutrophil count ($10^9/L$)	1.1	2.72	2.13	2.14	1.44	2.01	1.92
Hb (g/dL)	10.6	10.4	11.0	11.3	11.4	13.1	12.8
Platelet ($10^9/L$)	110	166	163	173	152	184	166
Treatment	PTU 100mg BD	PTU 100mg BD	PTU 50mg BD	PTU 50mg BD	CBZ 10mg OD	CBZ 5mg OD	CBZ 2.5mg OD
Weight (kg)	58.5	59.0	60.4	63.1	62.0	68.6	71.1

TSH: Thyroid stimulating hormone; TWCC: Total white cell count; Hb: Hemoglobin; PTU: Propylthiouracil; CBZ: Carbimazole; OD: Once daily; BD: Twice daily; TDS: Three times a day

2.2. Case 2

A 57-year-old woman presented to Otolaryngology Department for loss of appetite and difficulty swallowing with 9 kg weight loss over the past two months. Investigations conducted in the Otolaryngology Department were unremarkable. Subsequently, the patient was referred to the endocrinology team because she had a private laboratory test of thyroid function that revealed a total T4 of 365.1 pmol/L and thyroid stimulating hormone (TSH) of < 0.01 mIU/mL. Otherwise, she did not manifest any other symptoms of hyperthyroidism. She had no family history of thyroid disease. Clinical examination revealed absence of goiter and she was clinically euthyroid.

Her thyroid function test was repeated on May 7, 2013, and showed suppressed TSH of < 0.01 mIU/mL and free T4 of 20.5 pmol/L. Incidentally, her full blood count during admission revealed the presence of pancytopenia, total white cell count of $3.8 \times 10^9/L$ with neutrophil count of $1.5 \times 10^9/L$, hemoglobin of 11.6 g/dL, and platelet count of $110 \times 10^9/L$. Despite this, her loss of appetite and difficulty swallowing diminished within three days of admission to the ward without any medical therapy. No treatment was initially instituted for her, and she subsequently was discharged with a scheduled review in the clinic in two weeks. The patient continued to be asymptomatic during review in clinic on May 22, 2013. The thyroid function test was repeated on the same day, and it revealed persistently suppressed TSH < 0.01 mU/L with significant elevation of free T4 at 33.1 pmol/L. Her total white cell count remained low at $3.19 \times 10^9/L$ with neutrophil count of $1.32 \times 10^9/L$ with hemoglobin of 9.5 g/dL and platelet count of $108 \times 10^9/L$. Serum vitamin B12 and folate levels were normal. Anti-microsomal antibodies and anti-thyroglobulin antibodies were detected.

A decision was made to treat her for Graves' disease and treatment with 15 mg of carbimazole daily was initiated. In view of logistic reasons, she could only be reviewed in the endocrine clinic at intervals of four to eight weeks. During her review in the clinic on September 25, 2013, analysis of the patient's blood revealed elevated TSH (79.32 mU/L) with low free T4 (2.5 pmol/L), indicating overtreatment with carbimazole, and, subsequently, the medication discontinued until December 11, 2013.

Unfortunately, full blood count results were missing for October 23 November 14, and December 11, 2013, because the blood was drawn at a district hospital, and the blood samples were clotted. However, the test results on February 14, 2014, revealed improving thyroid function and resolution of neutropenia and anemia with improving thrombocytopenia with anti-thyroid therapy. The patient is still undergoing medical therapy because she was opposed to definitive radioactive iodine therapy. Tables 2a and 2b show the trends of her thyroid function tests, full blood counts, and dose of medication.

Table 2a. Summary of Case 2 Characteristics and Treatment (May-July 2013)

Date	May 7, 2013	May 22, 2013	June 26, 2013	July 31, 2013
Free T4 (pmol/L)	20.5	33.1	-	21.5
TSH (mU/L)	<0.01	<0.01	-	<0.01
TWCC ($10^9/L$)	3.80	3.19	2.86	4.60
Neutrophil count ($10^9/L$)	1.50	1.32	1.11	1.67
Hb (g/dL)	11.6	9.5	10.2	11.0
Platelet ($10^9/L$)	110	108	102	121
Treatment (CBZ dose)	-	-	15mg OD	15mg OD
Weight (kg)	55	54.4	50.8	53.5

TSH: Thyroid stimulating hormone; TWCC: Total white cell count; Hb: Hemoglobin; PTU: Prophylthiouracil; CBZ: Carbimazole; OD: Once daily; BD: Twice daily; TDS: Three times a day

Table 2b. Summary of Case 2 Characteristics and Treatment (September 2013-February 2014)

Date	September 25, 2013	October 23, 2013	November 14, 2013	December 14, 2013	February 12, 2014
Free T4 (pmol/L)	2.5	8.9	22.8	27.7	18.1
TSH (mU/L)	79.32	3.01	0.07	0.02	0.03
TWCC ($10^9/L$)	3.9				6.0
Neutrophil count ($10^9/L$)	1.4				2.4
Hemoglobin (g/dL)	12.2				12.3
Platelet ($10^9/L$)	122				133
Treatment (CBZ dose)	Medication withheld	Medication withheld	Medication withheld	5mg OD	5mg OD
Weight (kg)	54.0	55.5	-	57.5	62.8

TSH: Thyroid stimulating hormone; TWCC: Total white cell count; Hb: Hemoglobin; PTU: Prophylthiouracil; CBZ: Carbimazole; OD: Once daily; BD: Twice daily; TDS: Three times a day

2.3. Case 3

A 58-year-old female presented to us with diarrhoea for five days and drastic weight loss over three months. She also complained of dry cough for two weeks prior to admission. She had a history of type 2 diabetes mellitus and hypertension for the past 10 years. She denied palpitation, tremors, sweating, heat intolerance, or visual problems. The stool was loose and more frequent, up to six times per day. Upon further enquiry, she admitted to being more lethargic, emotional, and moody for the past few months. There was no fever, chest pain, shortness of breath, haemoptysis, night sweats, or contact with tuberculosis patients. Her appetite was good despite the dramatic loss of weight. She was postmenopausal for eight years and not aware of any lumps or bumps on her body. She had no family history of thyroid disease.

Clinically, she was a small-framed woman, pale, afebrile, and her blood pressure was 150/90 mmHg; her heart rate was 130 beats per minute-. Fine tremors were seen upon outstretching of hands, and her palms were not sweaty. There was no thyroid acropachy, thyroid ophthalmopathy, or pretibial myxedema. She had a nodular goitre, non-

tender, no associated bruit, and no retrosternal extension. She had no other features to suggest any other associated autoimmune disease. Cardiovascular, respiratory and abdominal examinations were unremarkable.

Investigations revealed persistent pancytopenia with normal renal and liver functions. Electrocardiography (ECG) showed sinus tachycardia, and her chest radiograph was normal. She remained afebrile in the ward. Ultrasound of the neck showed multinodular goitre with the largest lesion in the left thyroid lobe, echocardiogram showed normal chamber size, good left ventricular function with ejection fraction of 62% and normal valve morphology. Glycated haemoglobin (HbA1c) was 5.5% with fasting plasma glucose of 6 mmol/L. Both anti-microsomal antibodies and anti-thyroglobulin antibodies were detected. The initial free T4 on May 2012 was 58.6 pmol/L with suppressed TSH < 0.01 mU/L. Complete blood count (CBC) examination showed normochromic normocytic anemia and bone marrow aspiration, and trephine revealed normocellular cells with no blast seen. She was started on propylthiouracil, which was then changed to carbimazole. Table 3 shows the series of her blood results.

The thyroid functions improved temporarily after the antithyroid medication was commenced, and the pancytopenia also improved simultaneously. However, in July 2012, she had a relapse of hyperthyroidism on a tapering dose of antithyroid drug, which led to the decision of administering radioiodine therapy. She received 10 mCi of radioiodine therapy in September 12 and responded well. However, she had another relapse in January 2013, and it was clearly demonstrated that the pancytopenia had recurred. The second radioiodine therapy of 15 mCi was given in May 2013, and she was rendered hypothyroidism. The pancytopenia improved following the resolution of hyperthyroidism. Then, she was started on thyroxine replacement, and, currently, she is clinically and biochemically euthyroid.

Table 3. Summary of Case 3 Characteristics and Treatment

Time (month)	Free T4 (pmol/L)	TSH (mU/L)	TWCC (X 10 ⁹ /L)	Neutrophil Count (X 10 ⁹ /L)	Hb (g/dL)	Platelet (X 10 ⁹ /L)	Treatment
Initial	58.6	<0.01	3.22	1.48	8.6	72	PTU 100mg TDS
1	15.9	<0.01	4.68	2.19	10.9	132	CBZ 15 mg OD
2	29.2	<0.01	4.6	2.3	9.9	157	CBZ 15 mg OD
3	26.9	<0.01	4.2	1.5	10.6	109	First RAI
4	27.4	<0.01	4.2	1.9	10.6	122	
5	5.2	39.89	3.4	1.9	10.2	93	
6			5.6	3.6	12.1	140	
7	27	0.03	4.7	3	11.3	122	CBZ 10 mg OD
8	18.2	0.01	4	2.4	11.2	92	CBZ 5 mg OD
9			3	1.3	10.9	99	
10	16.7	0.01	4	2	11.2	103	Second RAI
11			3.51	1.61	11.8	121	
12	12.9	0.2	3.6	1.7	11.7	125	
13			3.7	1.8	12	114	
14	7.9	>75	4.1	2.25	12	119	Thyroxine
16	13.6	47.38	4.78	2.76	13.1	144	Thyroxine
17	19.2	2.74	5.2	2.9	13.9	160	Thyroxine

TSH: Thyroid stimulating hormone; TWCC: Total white cell count; Hb: Hemoglobin; PTU: Propylthiouracil; CBZ: Carbimazole; RAI: Radioiodine therapy; OD: Once daily; BD: Twice daily; TDS: Three times a day

3. Discussion

The similarities of the cases were that the three patients are female in their 50s and had no thyroid disorders in the family history. The patients in Case 1 and Case 2 responded well to oral anti-thyroid therapy, whereas the patient in Case 3 required radioiodine therapy to achieve the euthyroid state. The findings for the three cases were consistent with other case reports reported in the literature; the resolution of pancytopenia occurred simultaneously with the achievement of the euthyroid status. Pancytopenia has been described in association with a wide variety of

conditions. These conditions include bone marrow disorders (marrow failure syndromes, marrow space-occupying lesions, and ineffective marrow production), peripheral destruction of blood cells, infections, and drugs (9). However, its association with hyperthyroidism has been observed in only a very small number of case reports (5–8). Although the pathogenesis of pancytopenia associated with hyperthyroidism is still not fully elucidated, it has been postulated that this condition probably is due to the reduction of the lifespan of blood cells that results from the immunological mechanism and increased destruction or sequestration of peripheral blood cells. Excess thyroid hormones can lead to ineffective haematopoiesis, and the autoimmune process has the potential to induce antineutrophil or antiplatelet antibodies (7, 8). The coexistence of pancytopenia and Graves' disease is uncommon, and no consensus exists as to the most appropriate treatment. Moreover, the delivery of standard anti-thyroid medication may be delayed based on the concern about drug-induced cytopenia (10). In fact, pancytopenia resolved in most of the patients after they achieved the euthyroid state with the initiation of anti-thyroid treatment.

4. Conclusions

Even though association between Graves' disease and pancytopenia is uncommon, the possibility of Graves' disease or hyperthyroidism should be kept in mind when clinicians encounter a patient with unexplained pancytopenia. Pancytopenia in patients with Graves' disease largely responds well to anti-thyroid treatment with reversal of hyperthyroidism. The administration of anti-thyroid treatment should be considered in patients with Graves' disease and pancytopenia after a thorough haematological evaluation. In our case studies, it was fascinating to observe the association between hyperthyroidism and pancytopenia, which later resolved with the successful treatment of hyperthyroidism. The observation of this association could be the basis for future research to explore the mechanisms involved in Graves' disease and haematological abnormalities.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

This work was conducted with the collaboration of all of the authors. Abdullah Noor Rafhati conceived the work and wrote the first draft of the manuscript. All authors participated equally in the preparation of the manuscript, and each read and approved the final manuscript.

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