

Graves' Disease with Pancytopenia and Hepatic Dysfunction: A Rare Case Presentation

Abstract

Pancytopenia due to thyrotoxicosis is a rare but serious complication. In this report, we describe a rare case of Graves' disease confirmed on thyroid scintigraphy presented with coexisting pancytopenia and liver dysfunction. There was complete recovery of blood counts and hepatic enzyme level to normal after antithyroid treatment and radioiodine ablation.

Keywords: Anemia, Graves' disease, liver dysfunction, pancytopenia, thyrotoxicosis

Introduction

Autoimmune thyroid disorder is the most common form of autoimmune disorder affecting 5% of the general population.^[1] Graves' disease (GD) is an autoimmune disorder. It is characterized by autoantibody binding to the activated thyrotropin receptors, which leads to high levels of thyroid hormones in the circulation.^[2] This causes a variety of thyrotoxic manifestation such as heat intolerance, weight loss, tremor, palpitation, and exophthalmos. However, GD is not always present with typical signs and symptoms in clinical practice. Less commonly, GD may present with single-cell lineage hematological abnormalities such as anemia, leukopenia, and thrombocytopenia.^[3] We present a case of GD-induced pancytopenia associated with elevated liver enzymes and the role of thyroid uptake scan, antithyroid drugs (ATD), and radioiodine therapy in patient management.

Case Report

Clinical symptoms and signs

A 31-year-old woman presented with palpitation and dyspnea on exertion with weight loss of approximately 10 kg over a period of 12 months. She also noticed swelling of the neck for the last 1 year which she informed was progressively increasing in size. On clinical examination,

she looked tired and afebrile and had a pulse rate of 124 beats/min, blood pressure of 104/58 mmHg, and respiratory rate of 20/min. She had mild exophthalmos, raised jugular venous pressure, diffuse goiter with positive bruit, and bilateral pedal edema. She was anemic, but there was no icterus. Her abdominal examination was unremarkable with no tenderness or organomegaly.

Blood investigations

Table 1 shows the blood investigations. The prothrombin and activated partial thromboplastin time were within normal limits. She was investigated further for autoimmune hepatitis. However, immunological markers such as ANA, AMA-M2, LKM-1, LC-1, and SLA/LP were negative. Although she was positive to HBsAg, the HBV DNA titer was within normal limits. Direct and indirect Coombs test was negative.

Bone marrow examination

The patient had pancytopenia, and hence a bone marrow aspirate (BMA) was done. BMA showed hypercellularity with erythroid hyperplasia [Figure 1]. There was significant dyserythropoiesis in the form of binucleation, nuclear budding, nuclear membrane irregularity, and maturation arrest. However, there were no ring sideroblasts. Megakaryocytes were adequate in number, but there was no dysplasia. There was normal maturation of neutrophils. Neutrophils showed hypolobation and hypogranularity. Perl's

**Kishore Kumar
Behera,
Kanhaiyalal
Agrawal¹,
Amit Kumar Adhya²**

Departments of Endocrinology,
¹Nuclear Medicine and
²Pathology, All India Institute of
Medical Sciences, Bhubaneswar,
Odisha, India

Address for correspondence:

Dr. Kanhaiyalal Agrawal,
Department of Nuclear
Medicine, All India Institute
of Medical Sciences, Sijua,
Bhubaneswar - 751 019,
Odisha, India.

E-mail: nucmed_kanhaiyalal@aiimsbhubaneswar.edu.in

Access this article online

Website: www.ijnm.in

DOI: 10.4103/ijnm.IJNM_134_18

Quick Response Code:



How to cite this article: Behera KK, Agrawal K, Adhya AK. Graves' disease with pancytopenia and hepatic dysfunction: A rare case presentation. Indian J Nucl Med 2019;34:38-41.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

Table 1: Blood investigations

Parameters	At initial diagnosis	6 weeks after ATD
Hemoglobin (g/dL)	6.5	9.2
RBC count (million/cumm)	3.23	4.02
WBC count (per cumm)	2270	8500
Platelet (per cumm)	54,000	231,000
Alkaline phosphatase (U/L)	497	912
Total bilirubin (mg/dL)	2.2	0.6
Direct bilirubin (mg/dL)	0.8	0.2
Indirect bilirubin (mg/dL)	1.4	0.4
FT3 (normal: 2.3-4.3 pg/ml)	20	5.41
FT4 (normal: 0.89-1.76 ng/dl)	12	2.08
Serum TSH (normal: 0.5-4.7 mIU/L)	0.001	0.01

WBC: White blood cell, RBC: Red blood cell, TSH: Thyroid-stimulating hormone, ATD: Antithyroid drugs, FT4: Free thyroxine, FT3: Free triiodothyronine

stain for iron demonstrated absent iron stores. Overall features were consistent with pancytopenia induced due to thyrotoxicosis. Bone marrow biopsy [Figure 2] showed similar features as shown in BMA.

Imaging

Ultrasonography of the abdomen revealed no hepatic and splenic enlargement. She underwent technetium-99 m thyroid uptake scan [Figure 3], which showed diffusely increased homogeneous tracer uptake in the enlarged thyroid gland, suggestive of diffuse toxic goiter. The tracer uptake at 20 min was very high at 46.5% (normal 0.3%–4.5%).

Management

She was treated with tablet carbimazole initially. The hematologic and liver parameters were monitored. On follow-up after 6 weeks, the patient was clinically better; the thyroid function test had improved with improvement in blood counts [Table 1] and decrease in total bilirubin level. As ATD itself can induce pancytopenia, the patient was further treated with radioiodine (Iodine-131).

Discussion

The present case was unusual as it presented with GD, pancytopenia, and hepatic dysfunction. The blood counts and hepatic enzyme levels were normalized promptly after improvement in thyroid hormone level.

GD with pancytopenia has been described rarely in literature.^[4-9] Single-lineage abnormalities are more common in patients with hyperthyroidism. In hyperthyroidism, anemia, leukopenia, or thrombocytopenia occurs in approximately 34%, 5.8%, and 3.3% of patients, respectively.^[6,10] The anemia in GD is usually anemia of chronic disease.^[6] Bone marrow examination usually shows hypercellularity (as in the present case) or normocellularity, but rarely hypoplastic changes. The pathogenesis of GD-induced pancytopenia is not clearly

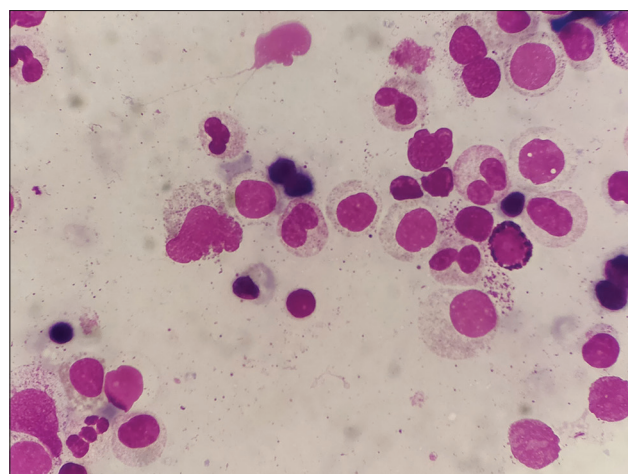


Figure 1: Bone marrow aspirate showing trilineage hematopoiesis and mild dysplasia in the erythroid series, (May–Grünwald–Giemsa, ×400)

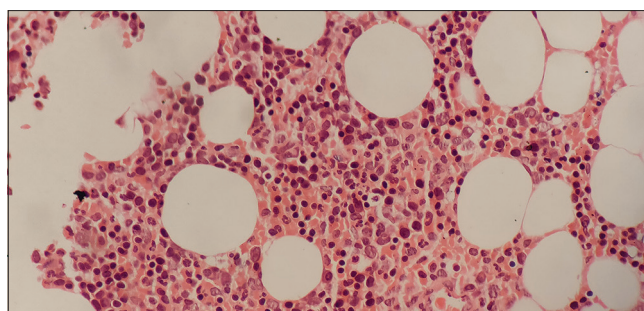


Figure 2: Bone marrow biopsy showing mild hypercellularity with erythroid hyperplasia, and normal trilineage hematopoiesis (H and E, ×400)

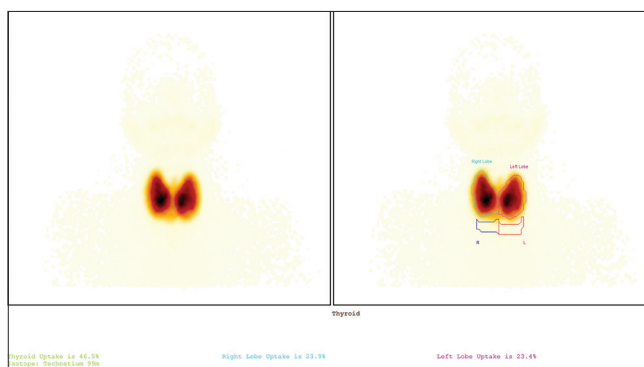


Figure 3: Technetium-99 m thyroid uptake scan shows severely increased but diffuse homogeneous tracer uptake in the enlarged thyroid gland with faintly visualized salivary glands suggestive of diffuse toxic goiter. Technetium 99 m pertechnetate uptake at 20 min is 46.5%

understood. The various proposed pathogeneses are (a) direct effect of thyroid hormones on hematopoiesis, (b) reduction in blood cell lifespan caused due to autoimmunity, and (c) toxicity of thyroid hormone to bone marrow stem cells.^[11-13] However, in most of the cases, there is prompt improvement in blood cell counts with normalization of thyroid status, which suggests that there is some direct effect of thyroid hormones. Further, pancytopenia has also been reported with hyperthyroidism

forms other than GD such as multinodular goiter^[11] and even with overdosing of levothyroxine.^[7] This further indicates probable nonimmunological mediated theory. To add, in the existing reported cases, there was no severe complication of anemia or thrombocytopenia such as ischemia or bleeding.

The hepatic dysfunction in GD patients ranges from asymptomatic biochemical abnormalities to overt hepatitis with either hepatitis or cholestatic injury. Alkaline phosphatase (ALP) is the most common hepatic enzyme to be raised in hyperthyroid patients at diagnosis (25%–64%).^[6] However, initial rise in ALP level may be of hepatic or bone origin. Hence, to diagnose hepatic dysfunction, it is important to check other hepatic markers.^[14] The possible hypothesis for liver dysfunction could be relative hypoxia due to increased oxygen demand with unchanged splanchnic blood supply, which leads to hepatic dysfunction and cholestasis in the centrilobular hepatocytes, congestive heart failure, or associated autoimmune liver disease.^[6] In the present case, all the immunological markers for autoimmune hepatitis were negative. Therefore, possibly, the hepatic dysfunction was due to cholestasis. However, the bilirubin level normalized, but there was an increase in ALP level. This may be due to an increase in osteoblast activity.^[15]

Thyroid uptake scan in the present case showed unusually high tracer uptake. This along with very high FT3 and FT4 level shows high severity of GD. Hence, very high thyroid uptake on scintigraphy may suggest the need of hematological and hepatic parameter evaluation.

The main challenge in this patient was the treatment as thionamides are known to cause agranulocytosis and are also hepatotoxic. However, the incidence of pancytopenia with thionamides is rare and incidence of agranulocytosis with ATD is 0.1%–0.5%.^[16] On the other hand, radioiodine ablation initially may lead to thyroid storm. Therefore, we preferred to treat the patient with ATD for 3 months initially and then radioiodine ablation was done. We carefully monitored the patient's hematological and hepatic parameters during the ATD. There was an improvement in hematological and hepatic parameters with ATD and radioiodine (except ALP level as described). As in the present case, in all the reported cases, pancytopenia was corrected after correction of thyrotoxicosis irrespective of the chosen treatment modalities.^[17]

Conclusion

In all patients with thyrotoxicosis, at initial diagnosis, hematologic and hepatic evaluation should be considered. This is more important when these patients are treated with ATD as close follow-up will be needed. ATD and radioiodine ablation can be used in patients with GD associated with hepatic dysfunction and pancytopenia;

however, close follow-up of hematological and hepatic parameters is essential. If there is no prompt improvement in hematological parameters with improvement in thyroid function test, further evaluation for pancytopenia must be considered. Finally, thyrotoxicosis should be considered in the rare differential diagnosis of pancytopenia.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Davies TF. Graves' diseases: Pathogenesis. In: Braverman LE, Utiger RD, editors. *Werner and Ingbar's the Thyroid: A Fundamental and Clinical Text*. Philadelphia, PA: Lippincott Williams and Wilkins; 2000. p. 518-30.
2. Jacobson EM, Tomer Y. The CD40, CTLA-4, thyroglobulin, TSH receptor, and PTPN22 gene quintet and its contribution to thyroid autoimmunity: Back to the future. *J Autoimmun* 2007;28:85-98.
3. Hamsch K, Herrmann F, Fischer H, Langpeter D, Maller P, Sorger D, *et al.* Changes in the blood picture in hyperthyroidism. *Z Gesamte Inn Med* 1989;44:300-6.
4. Lima CS, Zantut Wittmann DE, Castro V, Tambascia MA, Lorand-Metze I, Saad ST, *et al.* Pancytopenia in untreated patients with Graves' disease. *Thyroid* 2006;16:403-9.
5. Garla VV, Abdul Salim S, Yanes-Cardozo LL. Pancytopenia: A rare complication of Graves' disease. *BMJ Case Rep* 2018;2018. pii: bcr-2017-223887.
6. Baagar KA, Siddique MA, Arroub SA, Ebrahim AH, Jayyousi AA. Atypical complications of Graves' disease: A case report and literature review. *Case Rep Endocrinol* 2017;2017:6087135.
7. Talansky AL, Schulman P, Vinciguerra VP, Margouleff D, Budman DR, Degnan TJ, *et al.* Pancytopenia complicating Graves' disease and drug-induced hypothyroidism. *Arch Intern Med* 1981;141:544-5.
8. Shaw B, Mehta AB. Pancytopenia responding to treatment of hyperthyroidism: A clinical case and review of the literature. *Clin Lab Haematol* 2002;24:385-7.
9. Kebapcilar L, Yeşil S, Bayraktar F, Saklamaz A, Demir T, Güngör O, *et al.* Recovery from pancytopenia and liver dysfunction after administration of propylthiouracil for Graves' disease. *N Z Med J* 2005;118:U1615.
10. Jung RS, Parghane RV, Sood A, Bhattacharya A, Mittal BR. Primary autoimmune thrombocytopenia and co-existing Graves' disease: Role of radioiodine-131. *Indian J Nucl Med* 2014;29:195-6.
11. Jha P, Singh YP, Ghimire B, Jha BK. Pancytopenia in a surgical

- patient, a rare presentation of hyperthyroidism. *BMC Surg* 2014;14:108.
12. Rafhati AN, See CK, Hoo FK, Badrulnizam LB. A report of three cases of untreated Graves' disease associated with pancytopenia in Malaysia. *Electron Physician* 2014;6:877-82.
 13. Garcia J, França LD, Ellinger V, Wolff M. Marrow hypoplasia: A rare complication of untreated Grave's disease. *Arq Bras Endocrinol Metabol* 2014;58:953-7.
 14. Doran GR. Serum enzyme disturbances in thyrotoxicosis and myxoedema. *J R Soc Med* 1978;71:189-94.
 15. Sarinnapakorn V, Noppavetchwich P, Sunthorntepwarakul T, Deerochanawong C, Ngongamrut S. Abnormal liver function test in Graves' disease: A prospective study of comparison between the hyperthyroid state and the euthyroid state. *J Med Assoc Thai* 2011;94 Suppl 2:S11-6.
 16. Cooper DS. Drug therapy: Anti-thyroid drugs. *N Engl J Med* 2005;352:905-17.
 17. Pincet L, Gorostidi F. Graves disease causing pancytopenia: Case report and literature review. *Clin Med Insights Case Rep* 2018;11:1179547618781090.