[Downloaded free from http://www.saudiannals.net on Sunday, December 12, 2010, IP: 62.193.94.5]

case report

Pancytopenia related to Graves' disease

Mohammed Hegazi,[a] Ramesh Kumar,[a] Zouheir Bitar,[a] Eman Ibrahim[b]

From the Departments of [a]Medicine and [b]Hematology, Al Adan Hospital, Riqah, Ahmadi, Kuwait

Correspondence and reprints: Mohammed Hegazi · Al Adan Hospital, Riqah, Ahmadi 64029 Kuwait · T: +9653940600/1543 F: +9653941638 · mommh@hotmail.com · Accepted for publication April 2007

Ann Saudi Med 2008; 28(1): 48-49

Pancytopenia is a serious hematological disorder that, apart from primary marrow failure, may be secondary to several other conditions. These include infection, radiation, drugs (especially cytotoxic drugs), and certain metabolic diseases.[1] Among the latter, the association between hyperthyroidism and pancytopenia is reported least commonly.[2] The pathogenesis of such an association is not clearly understood, though hypotheses of immunogenic and toxic mechanisms have been advocated.[3] The response of pancytopenia to treatment of hyperthyroidism confirms the casual relationship and may preclude any other treatment modalities of pancytopenia.

CASE

A 43-year-old female presented with dizziness, dyspnea, and bilateral lower limb edema. Clinical examination showed marked pallor and signs of congestive heart failure. There was no lymphadenopathy or hepatosplenomegaly. Biochemical investigations, except for raised hepatic enzymes (AST=233 IU/L, ALT=80 IU/L), which were attributed to hepatic congestion, essentially showed normal findings. Hematological parameters before treatment are shown in Table 1. A blood smear showed a microcytic hypochromic picture with no polychromasia or normoblasts. The reticulocyte count was 2%, serum iron was 34.3 µmol/L, serum transferrin was 1.5 g/L, serum ferritin was 43 ng/mL, serum vitamin B12 was 378 pg/mL (normal, 148-443 pmol/L), and serum folate was 6.2 ng/mL (normal, >2 ng/mL). Hematologically, pancytopenia because of a microcytic hypochromic picture with an increased iron status was puzzling. Paroxysmal nocturnal hemoglobinuria (PNH) was suspected, but could not be supported by specific testing. Bone marrow examination, including trephine biopsy was performed. It showed a hypercelluar marrow with normoblastic hyperplasia, normal granulopoiesis and normal megakaryopoiesis. With these findings, pancytopenia was considered either immune-based or related to a bone marrow stem cell disorder like myelodysplastic syndrome, though no suggestive morphological findings could be observed. A direct antiglobulin test and auto-immune profile (ANA, anti-DNA, C3, and C4) were normal.

While hematological aspects were being debated, the results of thyroid function tests were received and showed a markedly reduced TSH (0.01 µIU/mL) with a raised free T4 64.8 pmol/L (normal range), a surprising finding indicating marked hyperthyroidism. Retrospective clinical examination showed mild bilateral exophthalmos and a mild diffuse thyroid prominence with a significant bruit over the thyroid gland. Unfortunately, these findings had been missed in the earlier clinical examination. The diagnosis of Graves' disease was confirmed by thyroid scan and iodine I 131 uptake studies showing diffusely increased activity. Congestive cardiac failure was considered to be related to both anemia and hyperthyroidism. For Graves' disease, treatment with carbimazol (30 mg/day) was started, and hematological management was given in the form of blood transfusion for anemia and antibiotic cover for neutropenia. No specific hematinic therapy was given. With resolution of the thyrotoxic state and a return to euthyroid status, the hematological parameters (Table 1) improved simultaneously and soon returned to normal.

DISCUSSION

An association of pancytopenia with hyperthyroidism is of rare occurrence. Only 7 case reports have been recorded in the literature.[2-8] All, except one case that showed toxic adenoma,[3] had Graves' disease. The fact that pancytopenia resolved with reversal of hyperthyroidism in all the reported cases including our case provides ample testimony to the causal relationship between the two conditions. In all, except one case of aplasia, reported by Das et al,[4] the bone marrow was hypercellular. Hematologically, pancytopenia in the presence of a hypercellular marrow could be related to either of the three mechanisms, either organ sequestration such as observed in hypersplenism, an enhanced removal of peripheral circulating blood cells by an immune or toxic mechanism, or hemopoietic stem cell dysfunction such as myelodysplasia. One or both of the latter two

[Downloaded free from http://www.saudiannals.net on Sunday, December 12, 2010, IP: 62.193.94.5]

Table 1. Hematological findings before and after treatment of Graves' disease with carbimazole.

	Before carbimazole therapy	After recovery from hyperthyroidism
Hemoglobin (gm/L) (112-157 gm/L)	73.00	121.00
White blood cell (WBC) count ($\times 10^9$/L) (3.9-10$\times 10^9$/L)	3.20	5.40
Platelets ($\times 10^9$/L) (182-369$\times 10^9$/L)	55	199.00
Mean corpuscular volume (MCV) (fL) (74.9-94.8 fL)	62.10	80.00
Mean corpuscular hemoglobin (MCH) (pg) (25.6-32.2)	19.90	26.00
Thyroid stimulating hormone (TSH) (μIU/ml) (0.27-4.2 μIU/ml)	0.01	1.15
T4 (thyroxine) (pmol/L) (7-21 pmol/L)	64.80	5.17

mechanisms could be responsible for pancytopenia related to hyperthyroidism. Whatever the mechanism of pathogenesis, it is recommendable that all cases of pancytopenia should be evaluated for hyperthyroidism even though it may not be clinically obvious in the first instance. Conversely, the CBC findings in patients with hyperthyroidism should be closely checked for pancytopenia, and if indicated, bone marrow examination should be considered before starting anti-thyroid therapy. Also, in such cases, it is not necessary to institute specific therapy for pancytopenia immediately. Initially, the treatment may only be supportive.

Pancytopenia related to hyperthyroidism is much less commonly reported than single lineage abnormalities.[2] Iguchi et al reported a case of pancytopenia due to Graves' disease with recovery on methimazole therapy, though neutropenia showed a prolonged persistence due to a drug side effect.[5] Duquenne et al published a report, including 3 cases of pancytopenia with hyperthyroidism, 2 with Graves' disease and one with toxic adenoma; all hematological disorders disappeared when patients became euthyroid.[3] Soeki et al reported a case of primary hyperthyroidism with pancytopenia that recovered after methimazole therapy, but later needed a subtotal thyroidectomy to control hyperthyroidism.[6] Shaw et al reported a case of post-bone marrow transplant pancytopenia that was found to be related to hyperthyroidism; the patient recovered on antithyroid therapy.[2] Das et al reported a case of remission of aplastic anemia induced by treatment of Graves' disease in a pediatric patient.[4] Kebapcilar et al reported a case of recovery from pancytopenia and liver dysfunction after administration of propylthiouracil for Graves' disease.[7] Lima et al reported 4 patients with Graves' disease who presented with pancytopenia at diagnosis, three of whom recovered on antithyroid drug therapy.[8]

Pancytopenia is a recognized complication of hyperthyroidism. Though the mechanism is still unclear, recovery from hyperthyroidism is associated with a simultaneous reversal of pancytopenia. It is recommendable that evaluation of the patient's thyroid status should be included among the investigations for pancytopenia, even though hyperthyroidism may not be clinically evident at the first instance. Conversely, hematological abnormalities in patients with hyperthyroidism should be carefully analyzed in view of the reported association between the two conditions. Specific treatment for pancytopenia in such cases should be deferred until the effect of anti-thyroid treatment is observable.

REFERENCES

1. Neal S Young. Differential diagnosis of pancytopenia (table 94-1). Harrison's Principles of Int Med 16th ed. 2005; Chapter 94:617.
2. B Shaw, A B Mehta. Pancytopenia responding to treatment of hyperthyroidism: a clinical case& review of literature. Clinical & Laboratory Haematology.2002 ; 246:385-387.
3. Duquenne M, Lakomsky D, Humbert JC, Hadjadi S, Weryha G, Leclere J. Pancytopenie resolutive par le traitment d'une hyperthyroidie. La Presse Medicale 1995; 24(17): 807-810.
4. Das P D, Wherrett D, Dror Y. Remission of aplastic anemia induced by treatment of Graves' disease in a pediatric patient. Pediatr Blood Cancer. 2006 Feb 2; [Epub ahead of print]. PMID: 16456859
5. Iguchi H, Nakano M. Case of hyperthyroidism with pancytopenia Nippon Naibunpi Gakkai Zasshi. 1983 Aug 20; 59(8):1117-1122.
6. Soeki T, Tamura Y, Kondo N, Shinohara H, Tanaka H, Bando K, Fukuda N. A Case of thyrotoxicosis with pancytopenia. Endocr J. 2001 Jun; 48(3):385-389.
7. Kebapcilar L, Yesil S, Bayraktar F, Suklamaz A, Demir T, Gungor O, Alacacioglu I, Comlekci A. Recovery from pancytopenia and liver dysfunction after administration of propylthiouracil in Graves' disease.Journal of the New Zealand Medical Association 2005 Aug 12; 118(1220):U1615.
8. Lima C S P, Wittmann D E Z, Castro V, Tambascia M A, Lorand-Metze I, Saad S T O, Costa F F. Pancytopenia in untreated patients with Graves' disease. Thyroid 2006 Apr; 16(4):403-409.