Case Report

Atypical Thyrotoxicosis Relapse after Carbimazole Discontinuation: A Case Report with Pharmacological View

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Abstract

A 15-year-old girl who presented with pyrexia of unknown origin of 3 month's duration was evaluated and examined. She had two palpable axillary lymph nodes associated with mild hepatosplenomegaly and leukopenia (white blood cell count - 1700/cmm). Later was assessed for systemic infection, hematological malignancies and autoimmune disorders. All investigations showed no cause pertaining leukopenia and fever. There was moderate sized goiter in midline of neck with past history of hyperthyroidism associated with tachycardia, tremors, weight loss and thyroid hormone profile suggesting hyperthyroidism, which prompted to think about thyrotoxicosis associated autoimmunity leading to lymphadenopathy, hepatosplenomegaly and leukopenia. Patient improved rapidly in 3 days after initiation of anti-thyroid drug.

Keywords: Hyperthyroidism, Leucopenia, Pyrexia, Thyrotoxicosis.

INTRODUCTION

Thyrotoxicosis presents with numerous varying combinations of systemic manifestations, especially in young females. Hematological system involvement leads to changes in all the three cell line lineage by immune and non-immune mechanisms. Leukopenia has been known as a rare manifestation of thyrotoxicosis, which responds well to anti-thyroid medications. Leucopenia is commonly seen co-exist with other diseases, or may present just as differential diagnosis in which clinicians may be faced such a problem where their diagnostic and therapeutic decision-making may be put to test plus dilemma regarding management of patient cannot be easily decided. The main causes of low serum thyroid stimulating hormone (TSH) concentrations are overt thyrotoxicosis, non-thyroidal illness, secondary (central) hypothyroidism, physiological causes, and subclinical thyrotoxicosis.[1] Hypothyroidism is a common disorder, easily treated with thyroxine therapy. Thyroid stimulating hormone level assay can detect under- or overtreatment.[2]

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CASE REPORT

A 15-year-old girl presented with complaints of intermittent, moderate degree of fever with occasional chills of 2 months duration. Patient complained about loss of appetite, weight loss, generalized weakness, insomnia and fatigability. She also complained to have palpitation and anxiety. No history of cough, abdominal pain, rash, joint pain, menstrual disturbance or altered bowel habits were present. She had been diagnosed as having primary hyperthyroidism 2 years back and was treated with anti-thyroid drugs (carbimazole [CBZ]) for 6 months. Later she discontinued the anti-thyroid drugs on her own without follow-up. She took self-medication by a course of broad spectrum antibiotic and anti-malarial drug without any improvement before getting admitted here.

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On general physical examination, she was febrile (102°F), had tachycardia (118 beats/min), and other vital parameters were normal. She had two solitary, firm, mobile and non-tender palpable lymph node in the right axilla, measuring 1.5 cm and 1.2 cm respectively. No bony tenderness, petechiae or purpura seen. Liver was palpable (1 cm) with normal span and spleen tip was mildly palpable. She had a moderate sized goiter without in the left lobe of the thyroid with minor ophthalmopathic manifestation. Other systemic examinations were normal.

On laboratory investigations (Table 1), her complete blood picture showed only leucopenia. Fine needle aspiration cytology of two lymph nodes showed reactive hyperplasia (Figure 1) consecutively. Bone marrow aspiration revealed mild hypocellularity with normal cell maturation.

Thyroid profile suggested of hyperthyroidism. Tc99m pertechnate thyroid scan showed low uptake and immunological test of thyroid microsomal antibody was positive (65.3 IU/ml). All other investigation findings were negative.

The patient was prescribed CBZ for 6 months only and then discontinued. Fever subsided in 3 days and total leukocyte count came to normalcy in 2 weeks. Follow-up showed no relapse.

Table 1: Results of laboratory investigations done

Hb	11.6 g/dl
ESR	8 mm/h
TLC (on day 1/2/3/4/5, after 1 week, and 2 weeks)	1750/1800/2150/2500/3050/3800/6550 per cmm
Differential count	N-68%, L-28%, E-3%, M-1%
PCV	37%
Erythrocyte count	4.3 millions/uL
MCV	86% fL
MCH	30 pg/cell
MCHC	35 g/dL
Platelet count	3.98 lakh/cmm
Blood and urine culture	Showed no growth and sterile
Urine routine examination	Normal findings
Chest radiograph	Normal findings
Widal test	Negative
Viral markers (HIV I and II, HbsAg, HCV)	Negative
ANA estimation	Normal
IgM for *Brucella*	Negative
Bone marrow finding	Normocellular, M: E=3:4, no granuloma seen
FNAC (both axillary lymphnodes)	Showed reactive hyperplasia
Thyroid assay	TSH<0.02 mU/L, T4=17 mcg/dL, T3=229 ng/dL
Thyroid scan (Tc99m Pertechnate)	Showed low uptake
Thyroid microsomal antibody	65.3 IU/mL (N<34 IU/mL)

Hb: Hemoglobin, ESR: Erythrocyte sedimentation rate, TLC: Total leukocyte count, PCV: Packed cell volume, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, HIV: Human immunodeficiency virus, HbsAg: Hepatitis B surface antigen, ANA: Anti-nuclear antibody, IgM: Immunoglobulins M, FNAC: Fine needle aspiration cytology, TSH: Thyroid stimulating hormone

DISCUSSION

Subclinical thyrotoxicosis is defined as a low serum thyrotropin (TSH) concentration in an asymptomatic patient with normal serum free thyroxine (T_4) and triiodothyronine (T_3) concentrations. The secretion of TSH gets suppressed even in the presence of normal serum thyroid hormone levels. This reflects the highly sensitive response that the pituitary gland mounts to minor changes in serum free T_4 and T_3 concentrations inside the normal range of the population is exemplified by the log-linear relation between serum TSH and thyroid hormone concentrations.[1] Some patients having non-thyroidal illnesses may have low serum TSH concentrations. This is invariably associated with low serum concentrations of T_3 and often T_4. Although the pathogenesis of the reduction in serum TSH in these patients remains uncertain, decreased secretion of thyrotropin-releasing hormone, increased secretion of somatostatin, cortisol, or cytokines, and inhibition of TSH secretion by drugs such as dopamine or glucocorticoids may contribute. In addition to a low serum TSH concentration, secondary (central) hypothyroidism is often associated with other pituitary hormone deficiencies, and may be accompanied by neurological abnormalities related to the local effect of a hypothalamic-pituitary tumor.[1]

The causes of subclinical thyrotoxicosis, in which TSH secretion is suppressed, but the concentrations of circulating thyroid hormones remain normal - Albeit in the upper-normal range - can be divided as exogenous and endogenous. Drug-related subclinical thyrotoxicosis may occur, as in the administration of supraphysiological doses of thyroid hormone, and in drug-induced thyroiditis (amiodarone, α interferon, iodine in patients with multinodular goiter).

Over treatment with thyroid hormones may be intentional, as in patients with thyroid carcinoma in order to reduce TSH secretion to below normal, or unintentional, as in approximately one-quarter of hypothyroid patients receiving treatment.[2]

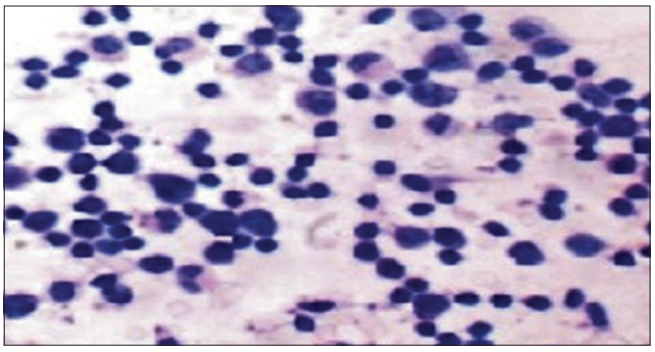

Figure 1: Fine needle aspiration cytology lymphnodes showing reactive changes

CBZ-dependent antibodies against the neutrophil-specific Fc gamma receptor IIIb have been previously detected in the sera patients who had been treated with CBZ for hyperthyroidism.[3] These drug-dependent antibodies can be a cause leukocytopenia. In a study of humoral autoimmunity assessed by quantitative determination of serum immunoglobulins and thyroglobulin autoantibodies estimation in patients of Grave's disease before and after treatment with CBZ, it was found that the thyrotoxic patients presented high values of serum immunoglobulins G and M which did not significantly change after 6 months of treatment.[4] Persistence of high levels of autoantibodies may have led to relapse in this patient.

It has been reported that thyrotropin receptor antibodies (TRAb) levels and T-cell subset abnormalities returned toward normal in patients receiving CBZ and the return towards normalcy was rapider when compared with propylthiouracil. These results indicate that the effects of CBZ on TRAb levels and T cell subset abnormalities are not due solely to its action in controlling the biochemical features of Graves' disease and provide indirect evidence of an action on the immune system *in vivo*.[5] McGregor, 1984 reported that low doses of methimazole (the active metabolite of CBZ) were found to inhibit thyroid-autoantibody production in cultured lymphocytes. Since thyroid lymphocytes are a major site of thyroid-antibody synthesis in Graves' disease and methimazole is concentrated in the thyroid during treatment, a local action of the drug on antibody production seems likely. This possibility could be important in the use of CBZ to control hyperthyroidism.[6] Our findings are also in concordance with an earlier study, which showed that after 3 or 6 months of CBZ therapy, both total T cells and helper/inducer T cells returned to a normal level.[7]

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