CASE REPORT

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SPURIOUS T3 TOXICOSIS IN MULTIPLE MYELOMA: A CASE REPORT

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ABSTRACT

Alteration of thyroid function tests (TFT) may be seen in apparently healthy individuals in the presence of many drugs, chemicals, and vitamins in abnormal concentration in blood. Presence of plasma protein in high concentration (e.g., paraprotein) may affect the TFT by altering the binding capacity, giving rise to high concentration of total triiodothyronine (TT3) and total thyroxine (TT4) with normal concentration of free hormones (FT3, FT4).Here is a case report of a 25-year-old clinically euthyroid man without previous personal or family history of thyroid disease.He was referred to the endocrinologist for evaluation of inappropriately high TT3>8.0 ng/ml (Reference range: 0.6-1.81) in the presence of normal TSH, TT4 concentration. He was diagnosed as a case of multiple myeloma (MM)five months back,receiving chemotherapy (Bortezomiband cyclophosphamide).The patient was clinically euthyroid, and his free T3 (FT3) was checked and was found to be within the normal reference range (FT3=3.03 pg/ml; reference range 2.3-4.2). He was not taking any drugs (e.g., Tamoxifen, Biotin, Estrogen, Clofibrate, 5-Fluorouracil, Methadone) concomitantly that may interfere with the thyroid function test reports. He had normal liver function test reports with mild impairment of renal function (Serum Creatinine level: 1.48mg/dl, eGFR:58 ml/min/1.73m^2). The patient was on follow-up without specific treatment for abnormal TFT, ensuring that the abnormal TFT report was due to paraproteinemia, which must be interpreted cautiously in such a situation.

Keywords: Spurious T3 Toxicosis, Euthyroid hypertriiodothyroninemia, Multiple Myeloma, Paraproteinemia.

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INTRODUCTION

The thyroid gland is the largest endocrine gland, secreting predominantly T4, with a small amount of T3[1]. More than 99% of secreted thyroid hormones are present in serum as bound form with plasma protein, and only 0.04% of T4 and 0.4% of T3 are present in plasma as free form, producing their physiological actions[2]. There are three major thyroid hormone transport proteins: thyroxine-binding globulin (TBG), transthyretin, and albumin. The plasma protein binding permits blood delivery of the iodothyronines, which are otherwise poorly soluble in water. High-binding affinity of TBG for T4 and T3 allows it to carry about 70% of circulating thyroid hormones. Transthyretin binds 10% of circulating T4. Its affinity for T4 is 10-fold greater than for T3.

The dissociation of T4 and T3 from transthyretin is rapid, so that transthyretin is a source of readily available T4. Ectopic production of transthyretin, which has been reported to occur in patients with pancreatic and hepatic tumors, causes euthyroid hyperthyroxinemia. Albumin binds to T4 and T3 with lesser affinity than TBG or transthyretin, but its high plasma concentration results in its transport of 15% of circulating T4 and T3[2]. Alteration of plasma protein alters the total hormone concentration, keeping the free hormone within the normal reference range to maintain its normal physiological functions. Some physiological conditions, drugs, and diseases (e.g., Multiple myeloma) produce very high concentrations of plasma protein, which increase the binding capacity of plasma protein and produce euthyroid hyperthyroxinemia[2,3].

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Here a case is being reported of multiple myeloma with very high TT3 in the presence of normal TSH, TT4 concentration, which was finally diagnosed as spurious T3 toxicosis or euthyroid hypertriiodo-thyroninemia due to Immunoglobulin G (IgG) paraproteinemia.

CASE REPORT

Our patient is a 25 years old man who was diagnosed as a case of MM (IgG Kappa, International Staging system, ISS- Stage 3) five months back based on clinical features of hyper-viscosity syndrome (ischemic stroke, abnormal behavior), immune-dysfunction (e.g., recurrent pneumonia, septicemia), moderate to severe bone pain and back pain with evidence of renal damage (serum creatinine:1.48mg/dl) without history of taking anytoxic drugs. The diagnosis was supported by positive laboratory parameters[Beta 2 microglobulin:26055mg/L (normal range, NR:0.8 to 3.0); Kappa Free Light Chain:5200mg/L (NR:3.3-19.4); Serum IgG:7374.90mg/dl (NR:7-16); Serum Total Protein:14.71g/dl (NR:6-8.3); and Gamma Globulin:8.5 g/dl (NR:0.7-1.6)] and Cytogenetic study [Polymerized Chain Reaction/Fluorescent In situ Hybridization (PCR/FISH)- Positive Deletion 13q, Immunoglobulin Heavy Chain (IGH) (4,14), Fibroblast Growth Factor Receptor 3/Immunoglobulin Heavy Chain (FGFR3/IGH)]. The patient was receiving chemotherapy (Bortezomib and cyclophosphamide) for the last three months. On routine follow-up, treating physician prescribed TFT, which revealed a very high TT3 level of >8.0 ng/ml (NR: 0.6-1.81) by Indirect Chemiluminescent assay despite normal TSH (3.01µIU/ml, NR: 0.35-5.5) and TT4 (5.63µg/dl, Normal: 5.53-11.0). So, the physician referred the patient to endocrinologist for further evaluation.

On clinical evaluation, our patient denied heat intolerance, palpitation, tremor, although he lost several pounds of weight due to his primary disease and chemotherapy-related side effects. He has no personal or family history of thyroid disorders before this report. On examination, there was no palpable goiter, the patient was mildly anemic (Hemoglobin-9.3g/dl, Normal Range:13-18 g/dl). He was not currently taking any drugs (e.g., Tamoxifen, Biotin, Estrogen, Clofibrate, 5-Fluorouracil, Methadone) that may alter plasma protein, abnormally raise the TT3 concentration, or interfere with the laboratory assay of TT3. Since his TSH and TT4 were within normal limits, we considered measurement of FT3, which was completely normal (FT3:3.03 pg/ml, Normal Range: 2.3-4.2pg/ml). Considering the circumstantial evidence, we confirmed the diagnosis of spurious T3 toxicosis. The patient was on regular follow-up without any specific treatment for these abnormal TFT reports, which are expected to be normal after normalization of plasma protein. Informed consent was obtained from the patient for online publication of the case in a medical journal, provided that the patients' identity was kept confidential.

DISCUSSION

Spurius T3 toxicosis is a well-recognized condition in paraproteinemia. In one study, which included newly diagnosed 105 MM patients, the prevalence of euthyroid hypertriiodothyroninemia(high T3) was seen in 13 (12.38%) cases, of which 12 were IgG type. Higher serum globulin and lower albumin levels and more advanced disease were found to be associated with this condition. The study also reported 100% normalization of the conditions after completion of antimyeloma chemotherapy[4].

Our patient had IgG type monoclonal gammopathy, with a very high level of serum globulin (8.5g/dl) and an advanced stage of disease (ISS-3). We observed isolated high TT3 despite normal total T4 and TSH, which is similar to the finding observed by Pan et. al [4].

Presence of paraprotein in serum affects the test reports in different ways, e.g., changing turbidity and viscosity of serum, interfering with assay constituents, hook effects, and increasing binding capacity of paraprotein. In MM, a very high level of IgG, IgA act as a high-capacity, low-affinity binding protein for T3 and T4, resulting in an increase in the total hormone concentration without increasing the free hormones[5].Generally, it is expected that a high level of paraprotein (IgG, IgA) would increase both the TT3 and TT4, but it depends on the type of paraprotein predominantly found in plasma. In IgG monoclonal gammopathy, a study reported an isolated rise of TT3 sparing the TT4; it is due to the high

affinity of IgG protein with T3[6]. However, Monoclonal gammopathy with IgA predominance showed a rise of both TT3 and TT4 due to its affinity to both hormones[3]. Spurious T3 toxicosis may be seen in patients taking high doses of biotin[7]. Our patient is not taking any form of biotin supplementation. TSH-secreting pituitary adenoma, Thyroid Hormone Resistance syndrome (THRS) may produce high serum T3 with normal TSH. in case of TSH-secreting pituitary adenomana, the patient usually presents with thyrotoxicosis. Here our patient was clinically euthyroid.In case of THRS, although patient is euthyroid,free hormones (FT3) are expected to be high.This patient had high total T3 but normal FT3 .The presence of heterophile antibodies may also cause similar types of reports[8]. Isolated high T3 may be the first presentation of MM., where retrospective investigation of serum protein electrophoresis confirmed the diagnosis of paraproteinemia [6]. Therefore, we should be careful about interpreting the TFT reports when it does not match the clinical scenario.

CONCLUSION

In MM, TSH should be screened as an initial screening test; if it is found abnormal, then we should check free hormones (FT4, FT3) rather than total hormones (T3, T4). In a normal person with normal TSH but high total T3 or T4, abnormal plasma protein must be screened, and MM should be ruled out.

CONFLICT OF INTEREST

There is no conflict of interest.

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