Fine Needle Aspiration Cytology Of The Thyroid Following Carbimazole Therapy In Graves' Disease: A Case Report

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Citation

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Abstract

Fine needle aspiration cytologic (FNAC) findings of the thyroid in Graves' disease, following carbimazole therapy are rarely documented.

We present a case of 35-year-old female patient who clinically presented with thyromegaly and features of hyperthyroidism. A routine FNAC led to a diagnostic dilemma, with cytologic features indicative of Hashimoto's thyroiditis/colloid goiter with follicular hyperplasia, and in places raising even, a suspicion of malignant transformation. On further clinical details, it was found that the patient had defaulted carbimazole therapy for Graves' disease. Correlating the clinical and cytomorphologic features, a diagnosis of “therapy induced (carbimazole) changes in Graves' disease” was offered.

Therapy induced changes in Graves' disease can cause serious diagnostic dilemma on FNAC. The present case stresses the importance of obtaining history of therapy, when interpreting thyroid aspirates in patients with hyperthyroidism, in order to avoid unnecessary diagnostic confusions.

INTRODUCTION

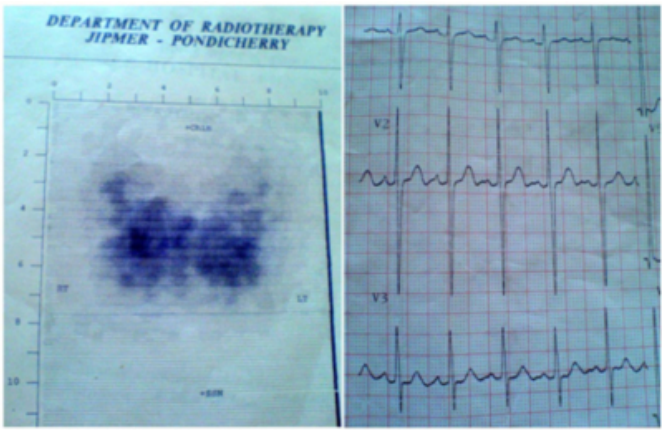
Graves' disease is an autoimmune thyroid disease which classically manifests in young females with thyromegaly, exophthalmos, and other features of thyrotoxicosis. The laboratory findings in patients with Graves' disease include an elevated T_4 and T_3 levels, along with an increased radioiodine uptake, in the presence of TSH levels less than 0.1mU/L. [1] The patients are treated with radioactive iodine (RaI) or, anti-thyroid drugs, or a subtotal thyroidectomy.[1,2,3] Histologically, radioactive iodine is known to induce changes that often simulate malignancy.[2, 3] Though rare, fine needle aspiration cytologic (FNAC) features of Graves' disease, following treatment with RaI, as well as, anti-thyroid drugs such as carbimazole have been described.[2, 4] In the absence of treatment history, these changes have led to a serious misinterpretation, sometimes, even as papillary thyroid carcinoma.[2, 4] Here, we report the FNAC findings of Graves' disease treated with carbimazole. The drug induced changes in the thyroid aspirates of our case caused a diagnostic dilemma.

CASE REPORT

A 35-year-old female patient, a known case of Graves' disease presented with a grade 3 thyromegaly of 1 year duration. She also complained of palpitation at rest, irritability, weight loss and an increased appetite. On examination, she had exophthalmos which was more prominent in the right eye than the left. Electrocardiogram (ECG) revealed sinus tachycardia; radioisotope studies demonstrated an increased radioiodine uptake, consistent with hyperthyroidism (figure1). Ultrasonogrm (USG) of thyroid showed diffuse enlargement of the lobes as well as isthmus, with altered echo-texture, and a few eccentric areas suggestive of cysts. Thyroid function tests revealed tri-iodothyronine (T_3) – 236pg/mL, thyroxine (T_4) - 16.3µg/dL, and thyroid stimulating hormone (TSH) - 0.0µIU/mL. Serologic test for anti-thyroperoxidase antibodies was negative. A clinical diagnosis of Graves' disease was made and the patient was referred to us for an FNAC.

Figure 1

Figure 1: Left: Radio iodide scan showing increased radio-iodine uptake; right: ECG showing sinus tachycardia



Cytologic findings: FNAC was performed using a 23gauge needle attached to a 10mL syringe. Aspirate was blood mixed. Air-dried and 95% ethanol fixed cytologic smears were stained with May-Grünwald-Giemsa (MGG) and Papanicolaou stains respectively. Smears were moderately cellular with discrete, as well as clusters of thyroid follicular cells exhibiting striking anisokaryosis, with moderate hyperchromasia, and a frayed-up nondescript cytoplasm, in a blood mixed colloid background, showing a few scattered hemosiderophages. A prominent Hurthle cell change with anisokaryosis, but bland chromatin was also noted. Some of the Hurthle cell clusters revealed infiltration by scattered lymphocytes (figure2). The most striking feature was the presence of many discrete, unusually large, hyperchromatic, naked nuclei, most of which were entangled in the blood clot (figure3). This varied cytomorphology caused a diagnostic dilemma. At the time of cytologic examination, a history of therapy was not provided to us; however on interrogation, it was found that the patient was on carbimazole therapy for 6 months and defaulted treatment, after having felt symptomatically better. Correlating the clinical and cytologic findings, a cytodiagnosis of “carbimazole induced change in Graves' disease” was given.

Figure 2

Figure 2: Hurthle cell change with lymphocytic infiltrate reminiscent of Hashimoto's thyroiditis; colloid background and a cyst macrophage are also seen (MGG stain, X400)

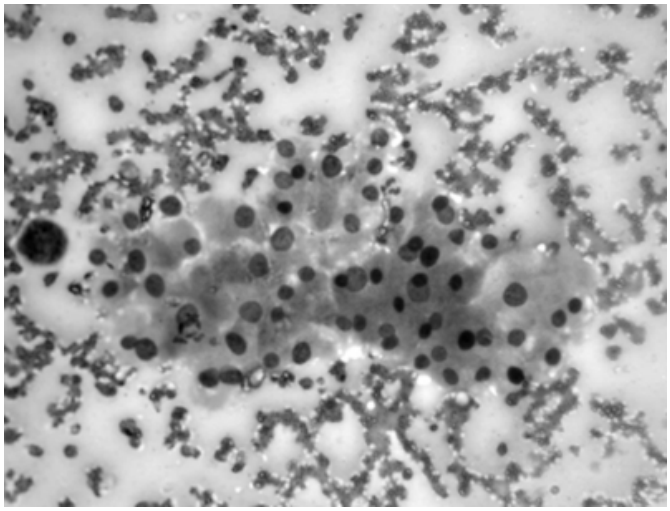
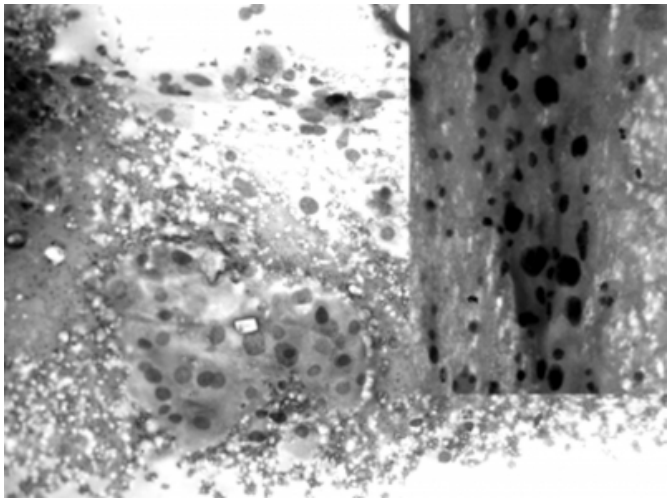


Figure 3

Figure 3: FNA smear showing anisonucleosis and Hurthle cell change and a few mild to moderately enlarged naked nuclei (MGG stain, X400); Inset shows huge hyperchromatic nuclei entangled in the blood clot (Papanicolaou stain, X400)



DISCUSSION

Graves' disease is considered among the autoimmune thyroid diseases together with Hashimoto's thyroiditis and idiopathic myxedema.[1] The changes resulting from different therapeutic modalities of thyrotoxicosis have been described by various authors.[1,2,3,4] Radioactive iodine (RaI) induced histologic patterns are not uniform, and range from loss of follicles to fibrosclerosis. Three patterns of histologic changes are described in patients treated with RaI. They are

(i) the radiation changes with follicular cell damage and fibrosis, along with the atrophic epithelium studded with enlarged and bizarre nucleated cells (ii) a progressive cellular metaplasia, usually of Hurthle cell type, and some times of glandular or squamous type and (iii) the changes reminiscent of Hashimoto's thyroiditis. In severe cases, the thyroiditis may be sclerosing with histologic pattern simulating that of an idiopathic myxedema.[3] The FNAC findings described in these cases include cellular enlargement, nuclear hyperchromasia, intranuclear pseudo-inclusions, cytoplasmic metaplasia, oxyphilia, and vacuolization. These changes are sometimes erroneously interpreted as papillary carcinoma, especially when the clinical data on prior RaI are not provided. [2]

The characteristic cytomorphologic features of untreated toxic goiters include a fine cytoplasmic granularity with fire-flare like vacuoles, and a distinct anisonucleosis; these features are better appreciated on MGG stained smears.[4] Using toluidine blue staining Šmejkal et al have demonstrated an increased number of nucleoli in these cases; they also described the cytoplasmic positivity of hyperplastic cells for acid phosphatase. These features are said to indicate an increased proteosynthetic activity. The variation in nucleolar morphology is considered as a factor in determining the growth and activity of the thyroid follicular cells. Ring shaped nucleoli are indicative of a reversible inhibition of ribonucleic acid (RNA) synthesis, and therefore, a low proteosynthetic activity; compact nucleoli with homogeneous distribution of RNA indicate an increased activity of growth or secretion. Small compact nucleoli are demonstrated in thyrotoxic goiter, while large compact nucleoli are seen in cancer cells, or in a proliferating benign adenoma.[4]

The cytologic change described in toxic goiters treated with carbimazole is the presence of extraordinarily large nuclei, which are often irregular in contour. Diameter of some of these nuclei may be as large as 30µm.[4] Cytologically, Šmejkal et al demonstrated ring shaped nucleoli by toluidine blue staining, and the cytoplasmic negativity for acid phosphatase in the follicular cells of Graves' disease patients treated with carbimazole. These changes were similar to those of benign conditions, and were noted even in large, bizarre nuclei, indicating that a malignant origin of such nuclei was unlikely. It was also noted that these changes did not have any relation to the length of treatment, the age of the patient, or the dose of the drug used.[4]

Aspirate in our case showed a varied cytomorphology. Presence of colloid background with cyst macrophages, and anisonucleosis of follicular cells suggested a possibility of colloid goiter with hyperplasia, while prominent Hurthle cell metaplasia with lymphocytic infiltrate suggested a Hashimoto's thyroiditis. The other striking feature noted was the presence of extraordinarily enlarged, hyperchromatic nuclei, similar to those described in dyshormonogenetic goiter, [5], [6] as well as, in rare cases of follicular carcinoma in anaplastic transformation. [7] Though, there was a slight suspicion of malignant change, overall cytologic picture easily excluded any such possibility. Moreover, the macronucleoli, described in cases of cancers, [4], [7] or a proliferating adenoma [4] were not encountered in the cytologic smears of our case. However, we did not use toluidine blue staining for the demonstration of nucleolar morphology. We also excluded the possibility of a dyshormonogenetic goiter by the mode of clinical presentation, such as, age of the patient and features of thyrotoxicosis, and a colloid background of the cytologic smears. Dyshormonogenetic goiter, which is a form of thyroid hyperplasia due to enzymatic defects in hormone synthesis, manifests in younger age group (6-12years), with hypothyroidism; histologically, it is characterized by scanty colloid.[6]The therapy induced cytologic change in Graves' disease,[2], [4] as well as, a dyshormonogenetic goiter may often simulate malignancy, [5], [6] in which case, knowledge of complete clinical picture with hormonal levels is highly essential for an accurate interpretation and diagnosis. In our case, hormonal levels and radioisotope studies were indicative of primary thyrotoxicosis, though; serologic test for anti-thyroperoxidase antibodies was negative. As we were aware of the fact that the patient was a known case of Graves' disease, an attempt to obtain further clinical details was made, and we learnt that the patient had defaulted carbimazole treatment for Graves' disease. Thus, a final cytodiagnosis of “carbimazole induced changes in Graves' disease” could be rendered.

The cytologic changes described in our case were somewhat similar to those described for RaI induced change, [2] though; our patient had not received RaI. The bizarre nuclei are the only finding described in Graves' disease treated with carbimazole, [4] which of course, was seen in our case too. Despite the clinical and laboratory findings of thyrotoxicosis, surprisingly, the cytologic features indicative of hyperfunction such as fire flares were not found in our case. Though, we assume that this finding could be the

reflection of defaulted carbimazole therapy, a more meaningful explanation, and perhaps, further studies are required in this regard.

To conclude, a varied cytomorphology occurring as a result of carbimazole therapy in Graves' disease may result in a serious diagnostic dilemma. A careful cytologic interpretation, with complete clinical details, including that of hormonal levels, and the treatment history, can avoid unnecessary cytologic interpretive confusions.

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