

Autoimmune Thyroiditis: Correlation of Cytomorphology with Drug History and Clinical Implications

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Abstract. Background: The cytopathologist plays an important role in the evaluation of thyroid cytomorphology in various neoplastic and non-neoplastic conditions. However, thyroid cytomorphology and the clinical implications of drug usage have rarely been discussed. Nonetheless, drugs used for different non-thyroid conditions may influence the hypothalamic-pituitary-thyroid axis and cause diverse cytomorphological patterns on aspiration smears. Clinicians should be informed of the presence or absence of specific underlying thyroid abnormalities detected on cytospreads which may warrant complete drug withdrawal, dose reduction, or change to different drug combinations. Besides these outcomes, interpreting thyroid cytomorphology, without a prior knowledge of antithyroid drug therapy, can be challenging and lead to misdiagnoses of neoplasm or malignancy. **Cases:** We present the thyroid cytomorphology of 3 different patients, each of whom was receiving a different drug (amiodarone, carbimazole, and carbamazepine) with biochemical, serological, and ultrasound correlations. We also briefly review the relevant literature. We conclude that a proper drug history is important while interpreting thyroid cytology in different clinical settings.

Keywords • Amiodarone • Carbimazole • Carbamazepine • Cytomorphology • Drugs • Thyroid

Introduction

Thyroid autoimmunity encompasses two extremes: at one end, the diffuse hyperplasia and hyperfunctioning gland of Graves' disease; and at the other, total destruction of the gland with hypothyroidism (as in Hashimoto's thyroiditis).

Hashimoto thyroiditis is the most common cause of hypothyroidism in iodine sufficient areas of the world.^[1] Fine needle aspiration cytology of thyroid is a safe and accurate procedure for the initial evaluation of thyroiditis. This is especially true when correlated with serology, hormone profile, colour Doppler ultrasonography, and radionuclide parameters.^[2-6]

However, drug induced cytological changes in thyroid fine needle aspiration, their diagnostic pitfalls, and clinical implications are rarely described in the literature.

Amiodarone, a class III antiarrhythmic drug, pro-

duces thyroid dysfunction (both hyper and hypothyroidism) in its users with or without underlying thyroid abnormalities. Amiodarone-induced hypothyroidism is amenable to thyroid replacement therapy whereas amiodarone-induced thyrotoxicosis (type 1 & 2) leads to a difficult therapeutic approach. Proper evaluation of thyroid function is, therefore, important both prior to the start and during amiodarone use in cardiology practice.^[7-10] Even more problematic is the scenario of unnecessary overdiagnosis of a neoplasm or malignancy in fine needle aspiration smears in patients of untreated Graves' disease or those receiving radioiodine ablation or antithyroid drugs (carbimazole, a pro-drug converted after absorption to the active form, methimazole).^[11-15]

An association of autoimmune thyroiditis during the course of or following antiepileptic therapy is rare, and that after carbamazepine therapy has not been reported in English literature. However, there

Table 1. Clinical characteristics, prescribed drugs, cytological diagnosis of goitre and impact on further management in three different patients.

Age/sex	Department Primary Diagnosis Drug therapy	Secondary presentation (duration)	Cytological diagnosis	New therapy	Remark
48/M	Cardiology CRHD, MR, AF x 6 months tab amiodarone 200 mg x 6 months	Diffuse goitre x 1 month Palpitation, hand tremor, weight loss x 15 days	Diffuse toxic goitre	C+P+D stoppage of amiodarone	Withdrawal of amiodarone due to risk of development of type 1 AIT ^[7,8]
40/M	Endocrinology Graves' disease x 1 year Tab carbimazole 20 mg x 1 year	Reduction in size of goitre, weight loss, heat intolerance present	Toxic goitre, Autoimmune thyroiditis	Tab carbimazole 20mg contd.	TIC, suspicion of neoplasm, diagnostic pitfall. ^[12,15]
26/F	Neurology Seizure disorder x 9 years Tab carbamazepine (Cz) 200 mg TDS x 9 years	Diffuse Goitre (L > R) x 2years Cold intolerance, menorrhagia, hoarseness of voice, weight gain x 2 months	Hashimoto thyroiditis	Cz+T	Possible association of autoimmunity ^[16] (significance ?)

Abbreviations: M; males, F; female, CRHD; chronic rheumatic heart disease, MR; Mitral regurgitation, AF; atrial fibrillation, TDS; three times daily, mg; milligram, L; left, R; right, C; Carbimazole, P; Propranolol, D; Digoxin, Cz; Carbamazepine, T; L-Thyroxine (50 microgram), AIT; Amiodarone induced thyrotoxicosis, TIC; therapy induced changes in cytosmear.

are reports to suggest that anticonvulsants may induce or exacerbate autoimmune mechanisms in certain thyroid diseases, the exact pathogenesis of which still not known.^[16]

The aim of the present article is to highlight various issues related to drug therapy and thyroid cytomorphology. By doing so, we hope to create awareness among cytopathologists and guide clinicians to more effective patient management.

Case Histories

The 3 cases described in this report involved clinical presentation and fine needle aspiration cytology of the thyroid glands from three different patients (2 male, 1 female). Each patient received a different category of drug (1 antiarrhythmic, 1 anti-thyroid, and 1 antiepileptic). The cytologies are presented in Table 1 and 2, respectively.

Discussion

Amiodarone, a class III antiarrhythmic drug, has a strong structural resemblance to the thyroid hormones. It contains two iodine atoms, which constitute 37.5% of its mass. Daily intake of 200 mg of amiodarone increases the iodine level in the circulation 20-to-40 times compared to the general population. The excessive load of iodine causes alteration in thyroid hormone metabolism. Thyroid dysfunction, both

hypothyroidism and hyperthyroidism occurs in up to 25% of users. Amiodarone-induced hypothyroidism occurs more commonly in females in iodine sufficient areas. Their hypothyroidism results from the Wolf-Chaikoff effect with blockage of hormone secretion or as a consequence of chronic autoimmune thyroiditis due to iodine excess. The patient with amiodarone-induced hypothyroidism should undergo thyroid hormone replacement therapy. Amiodarone withdrawal is not always necessary.^[7,8]

Amiodarone may induce autoimmune thyrotoxicosis more commonly in males in iodine deficient areas 4 months to 3 years after initiating therapy. Type 1 amiodarone-induced thyrotoxicosis is defined as hyperthyroidism occurring in patients with underlying thyroid disease, with or without positive thyroid hormone (Jod-Basedow effect). Patients do not have peroxidase antibody titre. The hyperthyroidism is due to increase synthesis and release of thyroid hormone.

Type 2 amiodarone-induced thyrotoxicosis is a drug-induced destructive thyroiditis that occurs in patients without underlying thyroid disorder. Anti-thyroid drugs such as propylthiouracil/methimazole with withdrawal of amiodarone are the treatment of choice in type I and type 2 amiodarone-induced thyrotoxicosis. Patients respond rapidly to glucocorticoid therapy.^[7-10]

In view of potential interaction of amiodarone with the thyroid gland and consequent therapeutic implications, interpretation of thyroid cytomorphol-

Table 2. Cytomorphology of thyroid, hormone profile, serology, ultrasound finding in three different patients on medications for different conditions.

Cases/drug	Cytomorphology	Serology	Thyroid hormone	CD-USG thyroid	Diagnosis
1 Amiodarone (antiarrhythmic)	Cellular, pseudopapillae, fire flare, dense cytoplasm, paravacuolar granules, thin colloid, no inflammation.	Anti TPO + ve	Hyperthyroid (undetectable serum TSH)	B/L enlarged gland, heterogenous echotexture, Increased colour flow	Diffuse Toxic Goitre Suggestive of GD ^[6] (Figure-1A,B)
2 Carbimazole (antithyroid)	Cellular, monolayer sheet, microfollicles pseudopapillae, plenty of bare nuclei, sudden bizarre pleomorphic nuclei, coarse chromatin, occasional paravacuolar granules, mild Hurthle cell change, minimal lymphocytes, absent colloid.	Anti TPO + ve	Euthyroid	Not available at the time of FNAC	Therapy induced changes, suspicious of neoplasm. ^[11-15] (Figure 2)
3 Carbamazepine (antiepileptic)	Moderate cellularity, Prominent Hürthle cell change, folliculolysis, giant cells, epitheloid cells, prominent lymphocytic infiltration, crushed tissue fragment, ^[4] scant thick colloid.	Anti TPO + ve	Hypothyroid (elevated TSH)	B/L asymmetrically enlarged gland, nodular outline, heterogenous echotexture, no calcification. Decreased blood flow	Hashimoto thyroiditis. ^[2-4] (Figure-3A,B,C)

Abbreviations: TPO; thyroid peroxidase antibody, TSH; thyroid stimulating hormone, CD-USG; Colour Doppler ultrasonography, B/L; bilateral, FNAC; fine needle aspiration cytology, GD; Graves' disease.

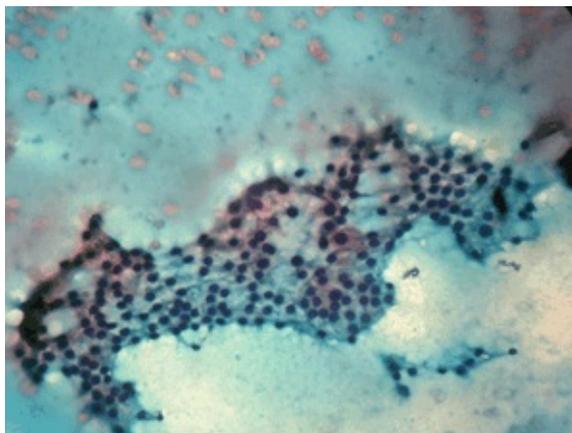


Figure 1A. Cytosmears from thyroid in Case 1 showing sheets of follicular epithelial cells with marginal vacuoles (fire flare appearance) over a background of thin colloid (Papanicolaou stain, 400X). These features are that of a hyperfunctioning state and with a positive serology suggestive of Graves' disease

ogy is important. Cytological features such as fire-flare appearance of the thyrocytes, dense cytoplasm, paravacuolar granules with thin colloid are suggestive of a hyperfunctioning state, whereas Hürthle cell morphology, folliculolysis, lymphocytic infiltration, epitheloid cells, plasma cells, and scant to absent colloid are strongly suggestive of Hashimoto's hyperthyroiditis.^[2-6] The presence of positive serology, undetectable serum TSH, and cytomorphology was suggestive of hyperthyroidism in Case 1. Complete withdrawal of the drug was necessary to prevent possible development of type 1 autoimmune thyrotoxicosis.

Worrisome cellularity and nuclear atypia in Graves' disease, with or without prior therapy, can be a potential source of misdiagnosis of neoplasm. Irradiated follicular epithelial cells, following radioiodine therapy, may show focal regenerative cellular and nuclear atypia, oxyphil or squamous metaplasia or cytoplasmic vacuolization. Bizarre cells with markedly enlarged and cells with nuclear pseudo inclusions may lead to a false positive diagnosis of malignancy. Similar morphology has been described in patients with untreated Graves' disease or those receiving carbimazole therapy.^[11-15]

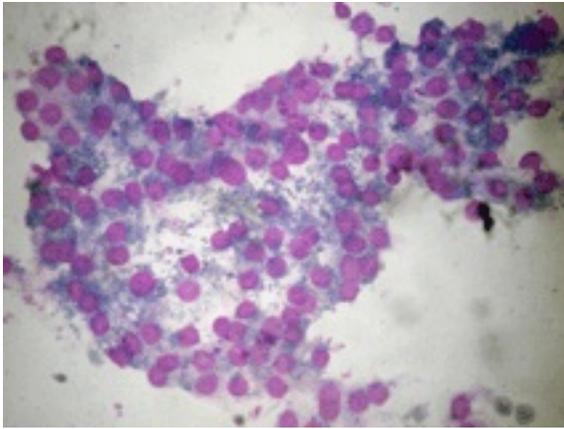


Figure 1B. Bluish green paravacuolar cytoplasmic granules in thyroid follicular epithelial cells indicative of hyperfunctioning state. No evidence of thyroiditis was seen (Leishmann stain, 400X).

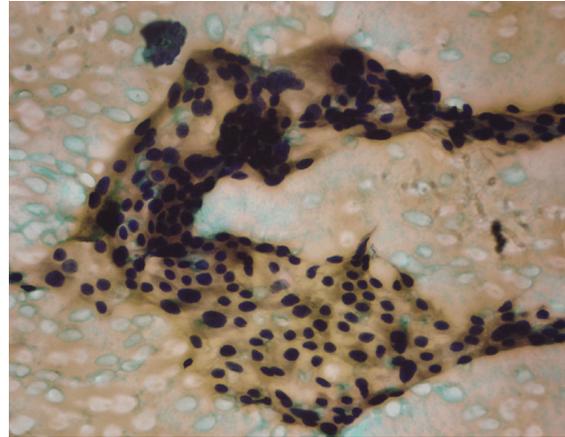


Figure 2. Changes suspicious of neoplasm induced by therapy.

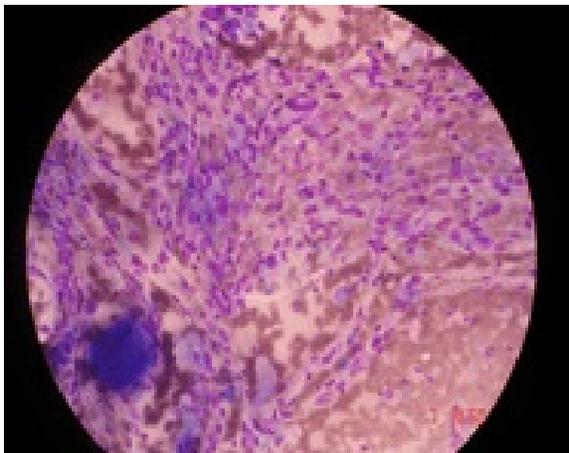


Figure 3C

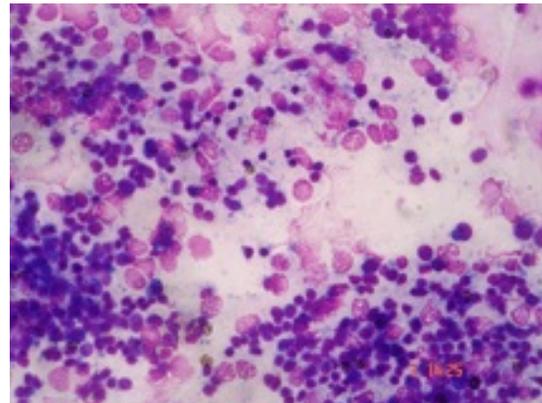


Figure 3A

Figures 3A, 3B, and 3C. Moderately cellular cytosmears from thyroid in Case-3 showing (A) intense lymphocytic infiltration into the epithelial cells, (B) Hürthle cell change), and (C) crushed cellular fragments with epitheloid cells over a hemorrhagic background devoid of colloid. These cytological features are diagnostic of autoimmune thyroiditis (Hashimoto thyroiditis) (Leishmann, 200X, 400X).

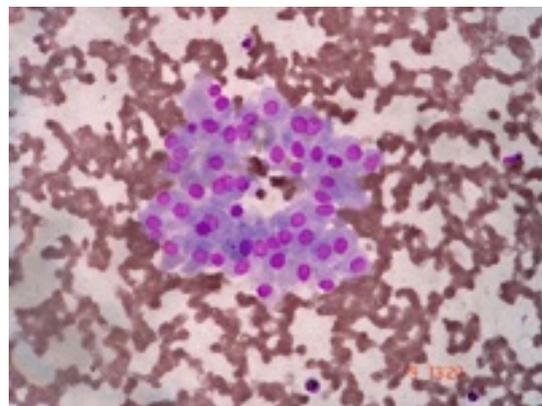


Figure 3B

Demonstrating nucleolar features with toluidine blue stain can be helpful in these cases.^[12] Obtaining a drug possible development of type 1 amiodarone-induced history with serological, hormonal, and radiological correlation can avoid unnecessary misdiagnosis as in Case 2.

Association of autoimmune thyroiditis with the use of antiepileptic drugs has been rarely documented in the research literature.^[16,17] Goitrous hypothyroidism with increased anti-thyroglobulin antibodies and anti-mitochondrial antibodies has been reported in two adolescent girls 1-to-3 years following antiepileptic (ethosuximide) therapy. Replacement of ethosuximide with valproate in one, and discontinuation of therapy with thyroxine replacement in the other, led to reduced antibody titres with restoration of euthyroid status.^[16]

In a recent study by Allison Gandey et al.,^[17] it was found that 32% of patients with epilepsy taking antiepileptic drugs in mono or polytherapy have thyroid hormone abnormalities. From a study of 300 epileptic patients, “the most relevant,” report, “was the increase of thyroid stimulating hormone (TSH) in patients taking valproate monotherapy (61.5%; TSH level > 6.6; $p < 0.001$).” It is an increase, they caution, that can lead to subclinical hypothyroidism. Forty-eight percent of carbamazepine users and 17% phenytoin users had thyroid abnormalities. Carbamazepine in polytherapy significantly decreased thyroxine levels below 62.01 ($p = 0.008$). These observations suggest that anticonvulsants may induce or exacerbate autoimmune mechanisms in certain thyroid diseases. Autoimmune thyroiditis following the use of carbamazepine in a young female (case 3) in the present series may just be an association, the clinical significance of which is yet to be ascertained. Hence, more cases with similar findings must be studied in order to reach a rational conclusion.

Conclusion

To conclude, interpretation of thyroid cytomorphology can be challenging in various clinical settings. Obtaining a proper drug history is essential while interpreting cytosmears in order to guide the clinicians for better therapy options.

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