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GRAVE'S DISEASE: STUDY OF CLINICAL PRESENTATION, HORMONAL, BIOCHEMICAL AND RADIOLOGICAL INVESTIGATIONS ALONG WITH CYTOLOGICAL PARAMETERS

Radiology

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ABSTRACT

Grave's disease accounts for 60-80% cases of thyrotoxicosis. Diagnosis of Grave's Disease is based on clinical findings, thyroid function tests, USG, radioactive iodine thyroid scan and presence of anti-thyroidal antibodies. Fine needle aspiration cytology of thyroid is necessary in selected cases. We studied cytological findings in 25 cases of Graves' disease, where FNAC was indicated because of nodularity or cold areas on scan. All cases had elevated serum T3, T4 with high anti-TPO titers seen in majority of cases.Fire flares and lacy cytoplasm were significant cytomorphological features. Combined evaluation of clinical presentation, hormonal status, anti-thyroid antibodies and RAIU scans along with cytological parameters can correctly interpret Grave's disease.

KEYWORDS

Fire Flares, Grave's Disease, F.n.a.c. Thyroid

INTRODUCTION

Grave's disease (GD), an autoimmune disorder is the most common cause of hyperthyroidism in iodine-sufficient areas, with prevalence of 0.5%.[1]Patient's usually present with nervousness, fatigue, tremors, palpitations, tachycardia, increased appetite, loss of weight. It may include Ophthalmopathy and dermatological manifestation. The thyroid gland shows bilateral symmetrical enlargement. Lobulations and nodules can also occur. [2]

Increased levels of free T4 and decreased TSH are usually confirmatory for diagnosis of GD. Levels of FT4 and FT3 are increased more than T3 and T4, but these tests are expensive and have more chances of laboratory errors. [3] Antibodies against thyroid peroxidase are found in 90% patients with GD. [4][5] Ultrasonography is noninvasive and sensitive technique, in which thyroid gland appears diffusely enlarged and hypoechoic: In GD, RAIU is diffusely increased.[3] FNAC in GD is performed in selected cases and shows hyperplastic changes with fire flare appearance [6]

AIMS AND OBJECTIVES

To evaluate indications of F.N.A.C. and cytomorphological findings in Graves disease diagnosed by clinical, hormonal, biochemical and radiological profile

MATERIAL AND METHODS

Study of Thyroid FNAC done in a tertiary care hospital over a period of four and half years. All cases of GD where F.N.A.C. was performed, were included in this study.

***FNAC Procedure*:**[7]

FNAC done by 23 gauze needle with non-aspiration technique. Aspiration was from nodule and surrounding thyroid in case of solitary nodules. Alcohol fixed smear and air dried smears were prepared and stained with Papanicolaou (Pap) and MGG stain. For non-palpable nodules-USG guided FNAC was performed. Clinical findings,TFT's, USG, Thyroid scan and Anti-TPO antibodies were noted wherever available. Cytological parameters were studied in detail.

RESULTS

Majority of patients were in 3rd to 5th decade (68%). Male: female ratio was 1:2 with 68% being females. All the patients presented with neck swelling and palpitations. Tremors (95%) and weight loss (65%) were other common finding .All the 25 cases were functionally hyperthyroid (↑T3, T4 and ↓ TSH). On USG, multinodular goiter was observed in 69.6% cases and 30.4% presented as solitary thyroid nodule. None showed classical diffuse enlargement of thyroid. Thyroid scan findings were available in 18 cases and all showed increased trapping with occasional cold area. Anti-TPO titers were raised in 18 cases Cytology was indicated in these cases due to nodularity or cold areas on scan. (table1)

Table 1: Cytological parameters in Grave's disease (n=25)

Cytological parameters	No. of cases	% of cases
Follicles	20	80%
Clusters	23	92%
Papillae	3	12%
Hurthle cells	3	12%
Lacy cytoplasm	16	64%
Fire flares	18	72%
Background sparse lymphocytes	9	36%
Anisonucleosis	19	76%
Blood mixed scant colloid	21	84%

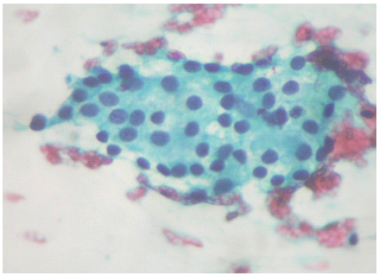

Figure 1- Hyperplastic changes- Lacy cytoplasm [Pap 400X]

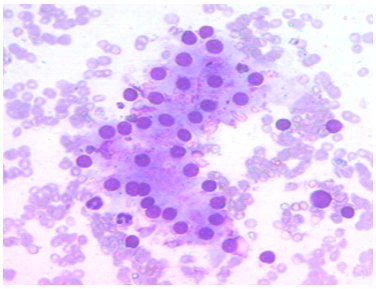

Figure 2: Hyperplastic epithelium with fire flares (arrow) [MGG 100X]

DISCUSSION

Classical cases of GD are diagnosed on the basis of clinical features,

thyroid function tests, antibody titres and thyroid scan. Cytological evaluation is required in selected cases to distinguish from Hashitoxicosis or cases where cold nodules are noted on scan. In the present study, 25 cases of Grave's disease were cytologically assessed, all with nodularity on USG and 18 with cold nodules on scan.

Majority of our cases were seen to occur in 4th and 5th decade (32% and 36% respectively) with 8% of cases occurring in elderly individuals. Literature describes GD to manifest classically in 4th to 6th decade; it can also occur in children and elderly.[8]

Grave's disease is about 5-10 times more common in females.[9] In our study, females were predominant (68%) with approximate M: F ratio of 1:2.

Common signs and symptoms like palpitations, tremors and weight loss as described in literature were also seen in our cases.[3][2] Diffuse goitrous enlargement is the classical presentation in GD.[10] It can be nodular in patients with iodine deficiency where nodular goiter pre-exists before the onset of Grave's disease.[3] These cases need to be differentiated from toxic MNG and toxic adenoma on the basis of percentage of thyroid uptake and USG findings.

In our study, all cases had hyperthyroid profile (raised serum T3 and T4 levels with decreased TSH levels) as reported in many studies in literature.[10] However, patients of GD may have either isolated T3 toxicosis with elevated FT3 levels and normal FT4 or they may have isolated T4 toxicosis with elevated FT4 and normal FT3.[3]

The classical diffuse enlargement of thyroid was observed by Jayaram et al in majority of their cases.[10]In present study, multinodular goitre was seen in 69.6% of cases followed by STN in 30.4% of cases. This nodularity can be explained by goitrous nodularity of iodine deficiency pre-existing in our patients before GD developed. In GD, the thyroid gland appears diffusely hypoechoic on USG.[11]Such diffuse or micronodular hypoechoic enlargement may be seen in lymphocytic thyroiditis too. Colour flow Doppler ultrasonography is useful to distinguish between Grave's disease and thyroiditis as the causes of thyrotoxicosis.[12][13]It is also useful in distinguishing nodular variants of GD from non-autoimmune toxic multinodular goitre.[14]Doppler study findings were not available in any of our cases.

Detection of antithyroid antibodies is useful in confirming autoimmunity .Antibodies against thyroglobulin and thyroid peroxidase are found in patients with Hashimoto's thyroiditis as well as in GD .Modern immunoassays and bioassays for TSHR-Ab help in determining the precise etiology of hyperthyroidism.[15] TSHR-Ab assay is very sensitive and specific (upto 98%) for the diagnosis of Grave's disease. It is a useful indicator of the degree of disease activity and can also predict the prognosis of GD. There are more chances of relapse in patients with persistently high TSHR-Ab level after cessation of antithyroid drugs.[16] However, it is very expensive and not widely available. In the present study, anti-TPO titres were available in 18 cases (72%) and were raised in all indicating autoimmune process.

Radioactive iodine uptake (RAIU) is not required in each and every case of GD, but is useful in excluding thyrotoxicosis caused by thyroiditis (Hashitoxicosis), toxic MNG and toxic adenoma. In Grave's disease there is diffuse and high uptake, whereas patchy localized uptake is seen in toxic adenoma or toxic MNG. In patients with thyroiditis there is decreased uptake.[3] In our study, thyroid scans available in 18 cases showed diffusely increased uptake on RAIU scans with cold nodule in one of lobes. One Case showed cold as well as hot nodule on scan. In this case, presence of classic clinical presentation, raised antibody titres and hyperplastic changes (lacy cytoplasm and fire flares) noted on cytology helped in arriving at diagnosis of GD.

Classical cases of GD need no cytological confirmation. It is usually performed in patients with nodular thyroid enlargement or when suspicious cold nodules are detected on USG and scan, as were the indications for F.N.A.C. in our study.

In present study, thyroid follicular cells were mainly arranged in clusters (92%), follicles (80%) and papillary pattern in 12% of cases. Lacy cytoplasm was noted in 64% of cases (Figure 1).The most characteristic feature of GD is the presence of marginal vacuoles (fire flares) in the follicular cells (Figure 2). This feature may be a focal phenomenon in other non-neoplastic and neoplastic lesions of thyroid, but it is found most consistently in GD. In untreated cases of GD, almost 80-100% of follicular cells show a fire-flare appearance.[17] In our study, fire flares were noted in majority (72%) of cases on Giemsa stained smears. Jayaram G et al have described fire flares in 27.8% of their cases.[10]

Hurthle cells observed in 12% of cases, were relatively less compared to 46.3% as observed by Jayaram G et al.[10]Hurthle cell change may be prominent in cases of GD who have received radioactive iodine. No such treatment history was available in our cases.[18]

Moderate anisonucleosis was seen in 76% of cases. Cells with indistinct cell borders, hyperchromatic nuclei and moderate pleomorphism may raise suspicion of neoplasm. However such cytomorphological features may be focally seen in cases with Neomercazole treatment.[19]

Blood mixed scant colloid was seen in 84% of cases. As thyroid gland is very vascular in GD, blood often dilutes the cellularity of the smear. Hence rapid completion of FNAC is recommended.

In our study, cytological overlap was seen between chronic lymphocytic thyroiditis and Grave's disease due to presence of hurthle cells and sparse background lymphocytes as seen in 12% and 36% cases of GD respectively. This cytological overlap is mostly seen, since both of them are closely related in their etiopathogenesis. Absence of significant lymphoid cells in background, low lymphoid to epithelial cell ratio and absence of follicular infiltration by lymphocytes were useful in differentiating these cases from thyroiditis.

Conclusion- Classic diffuse thyroid enlargement with symptoms of hyperthyroidism, hyperthyroid hormonal profile usually clinch the diagnosis of GD. Raised anti-TPO titers when interpreted along with diffuse increased uptake on RAIU scan,USG with colour Doppler findings and hyperplastic changes on cytology can correctly diagnose Grave's disease in cases with nodular thyroid enlargement and help to rule out other differentials.

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