ORIGINAL ARTICLE

Cytomorphological Profile of Graves' Disease and its Co-relation with anti-TPO Antibody

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ABSTRACT

Objective: Thyroid diseases are major health problems in our society, which are manifested by alteration in hormone secretion, enlargement of the thyroid gland. FNAC plays a significant role in the diagnosis of thyroid lesions due to its simplicity and low cost and with a diagnostic accuracy rate of 92%. This study was designed to cytomorphological profile of Graves' disease and its co relation with anti TPO antibody. **Materials and Methods:** This is a prospective analytical study of fifty patients with clinically enlarged thyroid gland presenting at STG Hospital, Haldwani, Nainital during Oct 2019 to Oct 2022. FNAC smears of these patients were studied and correlated with cytomorphological findings of different types, grades of thyroiditis and hormone level of T4, T3 and T.S.H. **Results:** Females were mostly affected by thyroid diseases than males. Female patients were 39 (78%) and male patients were 11 (22%). In the present study, patients were in the age group of 13 to 74 years of age. High T3 levels were noted in 80% high T4 levels were found in 90%. Low TSH level was found in only 64%, normal TSH level found in 34% and 2% presented with high TSH level. 34 patients (68%) found high anti-thyroid peroxidase antibody titre >34 U/ml. Cytomorphology revealed moderate to high cellularity in 88% cases, mild to moderate nuclear atypia in 86% and presence of marginal vacuoles in 82%. Lymphocytic infiltrate found in 24% cases and epithelioid cell granuloma in 14% cases. **Conclusion:** Thyroid cytology proves to be a reliable, simple, and cost-effective first-line diagnostic procedure with high patient acceptance and with rare, usually easily treated and not life-threatening complications. We recommend further studies with a larger population to validate our study.

KEY WORDS: Thyroiditis, Graves' Disease, Malignancy Goiter, Histopathology.

Introduction

Thyroid diseases are major health problems, that manifested by alteration inhormone secretion, enlargement of the thyroid gland. The mostprevalent thyroid diseases are goiter, hypo or hyperthyroidism, thyroiditis andneoplasms[1,2]. The incidence and prevalence of thyroid diseases in a community are variables which depends on various factors[3].

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The presence of thyroid peroxidase (TPO) antibody is a feature of autoimmune thyroiditis and hyperthyroid variant is closely related to Graves' disease on gross examination and microscopic appearance[4]. Thyroid-stimulating hormone (TSH) receptor antibodies confirm the diagnosis of GD in such cases[5]. The autoimmune process involves an underlying genetic predisposition and a trigger (s) that initiate the cascade of events. The identified triggers are infections, life stress, iodine intake, smoking, medications such as amiodarone, interferon, radiation and environmental toxicants[6,7].

GD is most common in women, the spectrum of clinical presentation ranges from asymptomatic, large goiter to an atrophic gland, euthyroidism, hypothyroidism and rarely hyperthyroidism.

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This disease tends to be geographical, seasonal and is most common in summer and fall[8,9]. The pathologic changes include marked lymphocytic infiltration of the thyroid with germinal center formation, atrophy of the thyroid follicles accompanied by oxyphil metaplasia, absence of colloid, and mild moderate fibrosis[10].

Fine needle aspiration cytology (FNAC) is a widely accepted screening procedure in diagnosis of diffuse and solitary thyroid nodules and it is a simple, cost effective, minimally invasive and quick to perform procedure[11]. Widespread use of FNAC has reduced number of patients requiring surgery by more than 50%. FNAC not only prevents unnecessary thyroid surgery for benign nodules, but also has increased malignancy rate in resected nodules from 14% to 50%[12]. However, the procedure has its own limitations since accuracy is lower in suspicious cytology and in follicular neoplasms[13]. FNAC is considered superior as well as more cost-effective in diagnosing than antibody screening[14].

The thyroid is an endocrine organ composed histologically of 20-40 thyroid follicles. They produce hormones triiodothyronine (T3) and thyroxin (T4) which are in turn regulated by thyroid stimulating hormone produced by anterior pituitary gland[15]. The lesions of thyroid can be categorized in hypothyroid, euthyroid or hyperthyroid condition based on the assessment of the level of T3, T4 and TSH[16]. Thyroid cancers are divided into papillary carcinomas, follicular carcinomas and medullary thyroid carcinomas (MTCs), anaplastic carcinomas, primary thyroid lymphomas and primary thyroid sarcomas[17]. The present study aims to assess the complete clinical examination and cytomorphological features of GD and its co relation with anti TPO antibody and its association with clinical and thyroid hormone status of patients.

Methodology

It contained fifty patients with GD (11 male and 39 female), patients were selected Kumaon region hill area and nearby industrial area belt of endemic goiter, iodine deficiency and so many environmental issues. Patients diagnosed from by specialist doctor team in tertiary care referral hospital, otorhinolaryngology (ENT) Outpatient Department (OPD) in Dr. Susheela Tiwari Government Hospital, Haldwani, Nainital, Uttarakhand. The GD was diagnosed by documented clinical and biochemical hyperthyroidism with presence of diffuse goiter. For all subjects, phenotype was determined with the clinician blinded to the individual's genotype.

Physical examination of graves patients

The physical examination can be grouped under three main categories, examination of the goiter and the surrounding structures, and identifying clinical signs and symptoms of hyperthyroidism specific to GD.

Data collection procedure

All the caregivers of the patients were explained about the purpose of the study and were assured strict confidentiality. Written informed consents were taken from each of them prior to the study. We examined all cases by detailed clinical history, family history, residence, food habits and drug intake with special emphasis on onset, duration and rate of thyroid swelling and particularly any irradiation in the head and neck region in the recent or distant past. In female patients, an enquiry was made about reproductive health too. FNAC was done in all the cases as an OPD procedure with other non-invasive procedures, viz. X-Ray chest PA and Ultrasound, when required. GD sample of FNAC were sent to the Department of Pathology with correct labeling for cytopathological study.

Procedure followed in Fine Needle Aspiration Cytology

The study period included from Oct 2019 to Oct 2022. All the patients with thyroid swellings were referred by ENT OPD to department of pathology for FNAC as well as thyroid hormone assay. FNAC was performed in total fifty cases of thyroid swellings using non aspiration or aspiration techniques by 23 G needle with 20 mL syringe. Cytomorphologic features were reviewed and reported according to "The 2017 Bethesda System for Reporting Thyroid Cytopathology (TBSRTC)" and other parameters eg. presence of granuloma, Hurthle cells, degree of anisonucleosis and giant cells.

Thyroidectomy specimens were fixed in 10% formalin for 12-18 h after gross morphological features were documented and the submitted tissue sections were processed for paraffin embedding. Thereafter 3-5- micron thick tissue sections were obtained and stained with H&E stain. Special stains such as PAS (Periodic Acid-Schiff) and Congo red were used as and when required. The cytological and histopathological findings were correlated.

T3, T4 and TSH were analyzed by electrochemiluminescence (ECLIA) immunoassay by Cobas e411 automated analyzers (Roche Diagnostics, Mannheim, Germany). Normal reference range for T3 was taken as (0.85-2.02 ng/ml); for T4 from (5.13-14.06 ug/dl) and TSH the normal range was (0.27-4.20uIU/ml test were performed on patients' serum.

Anti-TPO assays were evaluated on the automated analysers Roche Cobas e411. Which uses an electrochemiluminescence immunoassay (ECLIA) technology. The reagents, calibrators and controls were used in this study Elecsys Kit. Calibration for anti-TPO were performed weekly. Anti TPO Positive reference range High (>34 U/ml) Anti TPO reference range Negative Normal (< 34 U/ml). Anti-TPO assays were performed on patients' serum.

Results

Current study included a total of 50 patients with signs and symptoms of hyperthyroidism and clinical suspicion of GD. All relevant data was collected for evaluation of clinical characteristics. Thyroid function tests (T3, T4 and TSH), Anti-thyroid peroxidase (Anti-TPO) antibody assay and cytomorphology were done for further evaluation. In the present study, patients were in the age group of 13 to 74 years of age. Youngest patient encountered was 13 years and oldest was 74 years. The median age of the study population of 37 years. Females were mostly affected by thyroid diseases than males. Female patients were 39 (78%) and male patients were 11 (22%). Most of the patients presented with diffuse enlargement of thyroid gland and unexplained weight loss with fatigue. A total of 45 patients (90 %) complained of diffuse enlargement of thyroid gland, 44 patients (88%) complained of unexplained weight loss with fatigue and 41 patients (82%) complained of sweating (Figure 1).

Thyroid function test was done by electrochemiluminescence immunoassay method. 40 patients (80%) presented with elevation of T3 levels and 45 patients (90%) with elevation of T4 levels. Low TSH level was found in only 32 patients (64%), normal TSH level found in 17 patients (34%) and 1 patient (2%) presented with high TSH level. Variation in thyroid function was occur due to most of the patients (38 patients, 76%) were known hyperthyroid for a long time and on therapy for more than 1year. (Figure 2).

Anti-thyroid peroxidase (Anti-TPO) antibody assay was done in all patients. Anti-thyroid peroxidase antibody assay was done by electrochemiluminescence immuno assay method. Normal range of anti-thyroid peroxidase antibody was < 34U/ml. Out of 50 patients, 34 patients (68%) found high anti-thyroid peroxidase antibody titre >34 U/ml (Figure 3). Our results are similar with previous study (Table 1).

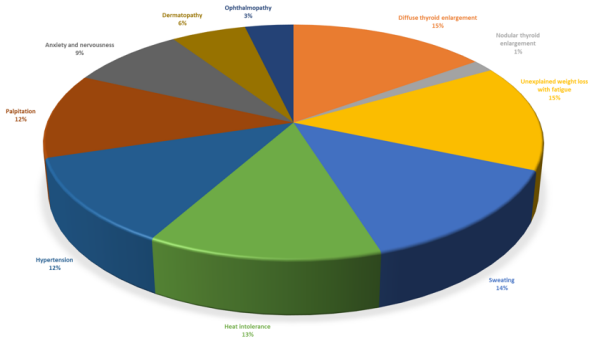

Figure 1: Clinical characteristics in GD patients

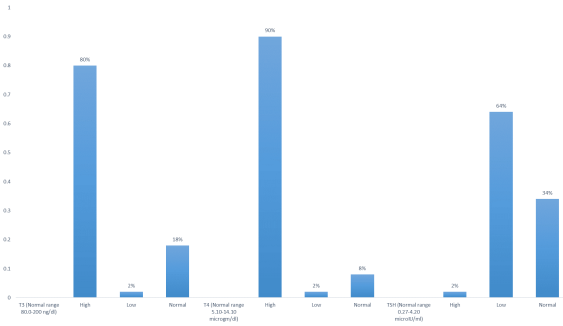

Figure 2: Thyroid function of GD patients

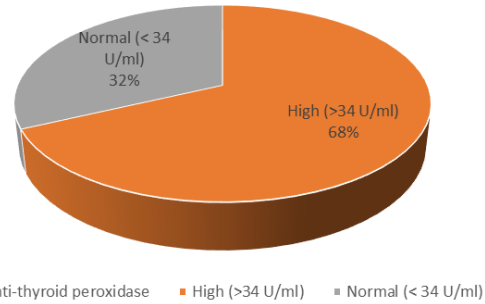

Figure 3: Anti-thyroid peroxidases of GD patients

FNAC was done in all patients and cases reported according to "The 2017 Bethesda System for Reporting Thyroid Cytopathology (TBSRTC)". All cases were categorised in Bethesda category 2. Thyroid smears with good cellularity, presence of 6 cell groups with atleast s10 thyroid follicular cells in each group, were defined as adequate smears. This constituted to all 50 cases. Cytomorphology revealed cellular smears & showed follicular cells in groups, clusters and flat monolayered sheet against a hemorrhagic background. Follicular cells were showing finely granular cytoplasm, mild nuclear atypia, vesicular chromatin and inconspicuous to conspicuous nucleoli. Fair number of follicular cells are showing marginal cytoplasmic vacuoles with pink red frayed edges.

Cytomorphology revealed moderate to high cellularity in 44 cases (88%) and low cellularity in 06 cases (12%). Most frequent cellular pattern was small to large flat monolayered sheet in 43 cases (86%), micro or macrofollicular pattern in 31 cases (62%) and 13 cases (26%) showed avascular papillary infoldings. Mild to moderate nuclear anisokaryosis found in 43 cases (86%) and marginal vacuoles; fire flares in 41 cases (82%). Lymphocytic infiltrate was found in 12 cases (24%), epithelioid cell granuloma in 07 cases (14%), multinucleated giant cells in 05 cases (10%) and pseudo giant cells in 04 cases (08%). Background colloid was scant or minimal in 44 cases (88%) and abundant colloid seen in only 06 cases (12%) (Figures 4, 5 and 6).

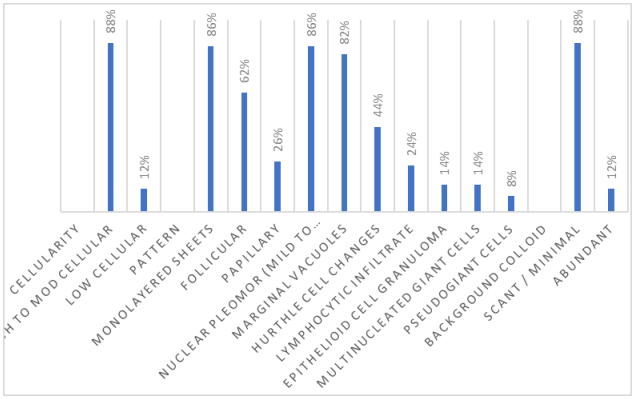

Figure 4: Cytopathological features in GD Patients

Hemi-thyroidectomy or thyroid lobectomy was done in only 2 cases with diffuse enlargement of thyroid gland. Histopathology revealed hyperplastic thyroid follicles with focal papillary infoldings and vascular congestion. Follicles were lined by tall columnar

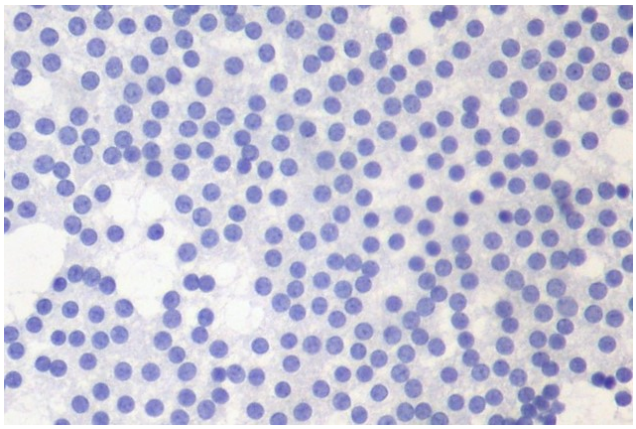

Figure 5: Graves' disease,Cellular smears and show follicular cells in flat monolayered sheets. (PAP Stain 100X)

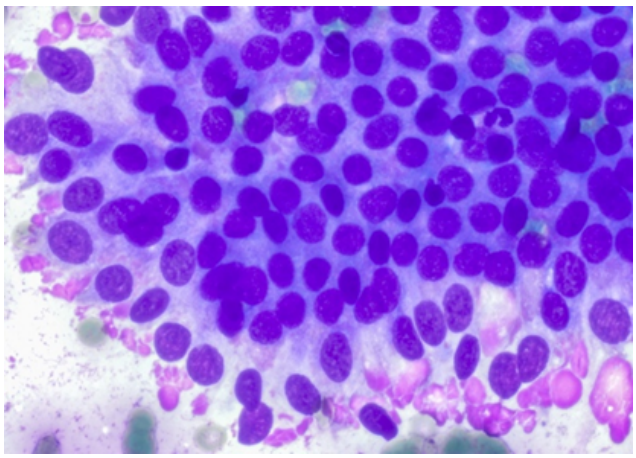

Figure 6: Graves' disease, Follicular cells are showing finely granular cytoplasm,mild nuclear atypia, vesicular chromatin and inconspicuous to conspicuousnucleoli. Fair number of cells are showing marginal cytoplasmic vacuoles withpink red frayed edges (MGG Stain 400X)

to cuboidal follicular cells exhibiting vacuolated cytoplasm, finely granular cytoplasm, mild to moderate nuclear anisokaryosis, vesicular chromatin and inconspicuous to conspicuous nucleoli. Numerous follicles were showing colloid reabsorption droplets. At places stroma were showing patchy lymphoid infiltrate (Figures 7 and 8).

Discussion

The average age of onset is between thirty and fifty years of age, the commonest age group to be the 3rd to 4th decade[18]. In our study most cases fall in between 18 to 40 years, with female predominance. This increase in incidence has been linked to excess iodine intake and residence in

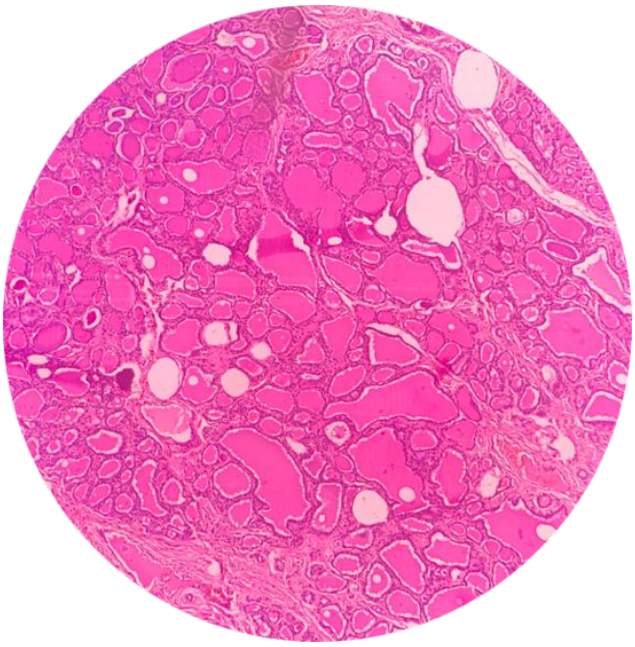

Figure 7: Histopathology revealed hyperplastic thyroid follicles with focal papillary infoldings and vascular congestion. Follicles were lined by tall columnar to cuboidal follicular cells. Stroma were showing mild lymphoid infiltrate. (H&E Stain 40 X)

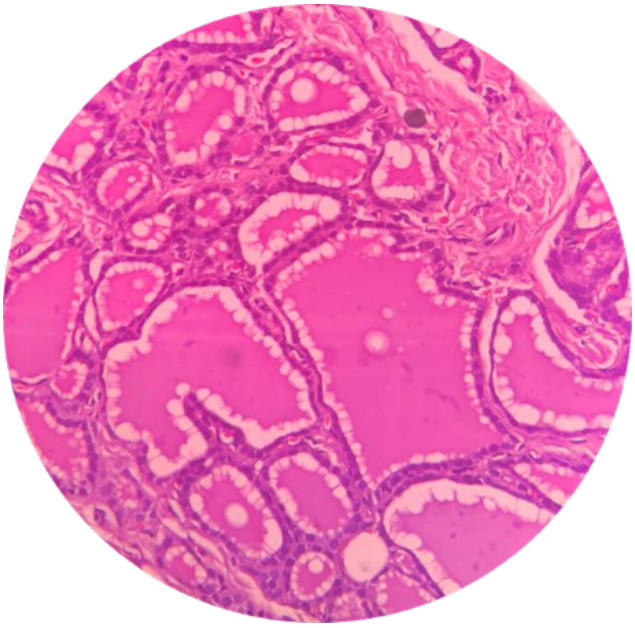

Figure 8: Histopathology revealed hyperplastic thyroid follicles lined by tall columnar follicular cells and exhibiting colloid reabsorption droplets (H&E Stain 100 X)

nearby industrial area[19]. The ratio of total T3 to total T4 is commonly used for differentiating the etiology of thyrotoxicosis between GD and subacute thyroiditis. The ratio of T3 to T4 was useful for distinguishing the cause of thyrotoxicosis. The low sensitivity of the cutoff value of T3/T4 ratio, we chose to use high specificity for the diagnosis of GD[20]. FNAC is highly sensitive in diagnosing GD, by characteristic features of mononuclear cells infiltrate consisting of lymphocytes, plasma cells, histiocytes impinging on follicular cells, multinucleated giant cells and hurthle cell change with a diagnostic accuracy rate of 92%. Diagnosis of GD is likely to be missed in cases of nodular goiter that can be differentiated by the absence of multinucleated giant cells and epitheliod cells and lymphoid cells impinging on follicular cells[21].

Anti-TPO antibodies are the most common anti-thyroid autoantibody, present in approximately 90% of Hashimoto's thyroiditis, 75% of GD and 10–20% of nodular goiter or thyroid carcinoma[22].

Carvalho et al., anti-TPO Abs were present in about 80% of patients,[23] Samsudin et al., anti-TPO Abs were present in about 62% of patients,[24] Almomin et al., 2019 anti-TPO Abs were present in about 60.4% of patients,[25] Siriwardhane et al., anti-TPO Abs were present in about 59.8%. of patients,[26] Sulejmanovic et al., anti-TPO Abs were present in about 71% of patients,[27] and Alhubaish et al., anti-TPO Abs were present in about 58.9% with GD[28] .

GD is revealed by presence of hypercellular colloid free smear showing columnar type follicular cells in monolayered sheets. Cytoplasm is abundant, vacuolated with larger marginal vacuoles (fire flares). Hurthle cells, lymphocytes and multinucleated giant cells are rarely seen and have done cytological grading on FNAC smears for the first time using predefined sets of criteria, where they tried to correlate the lymphoid density withclinical, radiological and biochemical parameters[29]. The importance of presence of eosinophils and high eosinophil: neutrophil ratio for making diagnosis of GD and to differentiate it from colloid goiter[30]. It is important to diagnose GD because patients subsequently become hypothyroid and require lifelong thyroxine supplementation, genetic factor and environmental factors such as iodine intake, exposure to certain drugs, smoking habits, stressful life events and a number of infectious agents have all been found associated with GD[31]. It could have been better if we

Table 1: Anti TPO antibodies study in Graves diseases patients

S.No.	Researcher Team	Anti TPO Positive High (>34 U/ml)	Anti TPO Negative Normal (< 34 U/ml)
1.	Carvalho et al., 2013 [23]	80%	40%
2.	Samsudin et al., 2014 [24]	62%	38%
3.	Almomin et al., 2019 [25]	60.4%	39.6%
4.	Siriwardhane et al., 2019 [26]	59.8%	40.2%
5.	Sulejmanovic et al., 2020 [27]	71%	29%
6.	Alhubaish et al., 2023 [28]	58.9%	41.1%
7.	Current Study 2023	68%	32%

had done US and computed tomography (CT) scan guided FNAC that have a higher probability of higher accuracy along with any wet stain (H and E, Pap stain).

Conclusion

A correct cytological diagnosis was achieved in the majority of cases and rejecting the need for a surgical intervention and provided lifelong hormonal therapy in justified cases. A careful and diligent search for various cytological features and accurate sampling can help in reducing the number of indeterminate, false-positive and false-negative diagnoses. FNAC is highly sensitive and specific technique in diagnosing GD and other types of thyroiditis. Patients with high serum anti-TPO levels seem to be at an increased risk and require frequent evaluation. Further well-designed larger community studies are required to have a clearer picture of the current situation.

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Ethical clearance

Ethical approval: The study was approved by the Institutional Ethics Committee.

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