Abstract:
Graves’ disease, first described in 1825, is an autoimmune disease characterized by antibodies against the TSH receptor. The prevalence of concomitant thyroid carcinoma with Graves’ disease has been reported to be 2.3 percentage. We report a 36 year old female who presented with palpitations, exophthalmos, weight loss and a diffuse neck swelling for 1 year duration. Her TSH was undetectable and T4, T3 were elevated. A diagnosis of Graves’ disease was made and the patient was started on antithyroid drugs. After 4 months of treatment she returned to euthyroid status. Her TSH was undetectable and T4, T3 were elevated. A diagnosis of Graves’ disease was made and the patient was started on antithyroid drugs. After 4 months of treatment she returned to euthyroid status. Total thyroidectomy was done. Her HPE report showed two Papillary microcarcinomatous nodules. Her post op USG showed two tiny nodes in level III and VI. Her TSH was 30, Tg was 10 and Anti Tg Ab was 80.36. A whole body Radioactive 131I uptake study showed 8 percentage residual thyroid tissue in thyroid bed. Rest of the body showed normal tracer uptake. RAI ablation was done and the patient was put on suppressive dose of Eltroxin. A repeat USG done after 2 months showed no nodes and a normal TFT. She is on regular follow up. We also report a comprehensive review of literature of incidental Papillary carcinoma in Graves’ disease patients. 

Keyword: Graves’ disease, Papillary thyroid carcinoma

INTRODUCTION:
Graves’ disease which was first described by Dr. Caleb Hillier Parry in 1825, Dr. Robert James Graves in 1835, and Dr. Carl A. Von Basedow in 1840 [1] is an autoimmune thyroid disease that is characterized by hyperthyroidism due to stimulatory antibodies directed against the thyroid-stimulating hormone (TSH) receptor. Patients with Graves’ disease present with symptoms of hyperthyroidism and may have a diffuse goiter, ophthalmopathy, proximal...
muscle weakness and pretibial myxedema [2]. The prevalence of thyroid carcinoma in patients with Graves’ disease has been reported as 2.3% [7]. The most commonly encountered thyroid cancer is papillary cancer. When these two diseases coexist the clinical behavior has been described as ranging from benign [5] to very aggressive [6]. Thyroid cancers occurring in combination with Graves’ disease have a variable presentation and it can be classified as incidental thyroid cancer and nonincidental thyroid cancer [8]. Incidental thyroid carcinomas are nodules that usually measure less than 1 cm hence the name, thyroid microcarcinomas [7]. They are rarely palpated during physical examination. Non-incidental thyroid cancer refers to patients with Graves’ disease who also have a thyroid nodule or cancer during the pre-operative workup. These thyroid cancers are usually larger than 1 cm.

**CASE REPORT:**
A 36 year old female presented to our outpatient department with palpitations, tremors, exophthalmos and a swelling in front of the neck for the past 1 year. She had lost 8 kgs of weight in the last 6 months (from 56 kgs to 48 kgs). She did not complain of any compressive neck symptoms like dysphagia, hoarseness or shortness of breath. She did not have any proximal muscle weakness or pretibial myxedema. She consumed iodised salt. She had neither a past history of irradiation to head and neck nor any family history of thyroid disease. Physical examination revealed her pulse rate to be 96 beats / min which was regular and a blood pressure of 130/80 mm of Hg. A painless diffuse swelling of size 12 X 10 cm was present in the thyroid region which was soft in consistency and moved with deglutition. The surface over the swelling was smooth and no nodules were palpable. No lymphnodes were palpable in the neck or supraclavicular region. No bruit was heard on auscultation. She had lid lag, lid retraction, starring look, infrequent blink, exophthalmos and was unable to converge her eyeballs (Figure 1). She did not have ophthalmoplegia or chemosis.

Figure 1: Patient image before treatment
Laboratory data (Table 1) revealed a virtually undetectable TSH level of < 0.01 µIU/ml (reference range: Other routine blood tests were unremarkable. Her Chest X ray and X ray neck did not show any tracheal deviation or calcification. Her indirect laryngoscopy showed B/L mobile vocal cords. Her Echocardiogram and ECG were normal. A diagnosis of Graves’ disease was made and the patient was started on T. Neomercazole 15 mg tds and T. Propranolol 40 mg bd. Flurbiprofen and Lacrygel eyedrops were given for her ophthalmopathy. Gradual reduction of doses was done. After four months of antithyroid medications she achieved an euthyroid state (Table 1). A repeat USG of the neck also showed the same features. A Total Thyroidectomy was performed and the specimen was sent for histopathological examination. In the post-operative period no clinical hypocalcemic symptoms were noted. Antithyroid drugs and -blockers...
The histopathology report was as follows. The measurements were a right lobe of size 9 x 8 x 2 cm and a left lobe of size 5 x 4 x 2 cm. On section, the right lobe showed a grey white area of size 0.9 cm and the left lobe showed another grey white area of size 0.7 cm surrounded by normal appearing thyroid parenchyma filled with colloid. Both grey white lesions showed a neoplasm arranged in papillae with fibrovascular core. The cells were polygonal with nuclear clearing (Orphan Annie Eyed) and nuclear grooving. Also seen were intranuclear inclusions. Lymphovascular invasion was present. Adjacent thyroid showed colloid filled follicles lined by flattened follicular epithelial cells and the surrounding septa shows lymphocytic infiltrate. The impression was Papillary carcinoma Thyroid (Figures 3, 4 & 5).
<table>
<thead>
<tr>
<th>Authors</th>
<th>Sample Size</th>
<th>Microcarcinoma (%)</th>
<th>Type of Carcinoma</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meliere et al [21]</td>
<td>345</td>
<td>8(1.7%)</td>
<td>Papillary microcarcinoma</td>
<td>100%</td>
</tr>
<tr>
<td>Ozoux et al [22]</td>
<td>88</td>
<td>4(4.5%)</td>
<td>Papillary microcarcinoma</td>
<td>100%</td>
</tr>
<tr>
<td>Rieger et al [23]</td>
<td>84</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ozaki et al [6]</td>
<td>743</td>
<td>19(2.6%)</td>
<td>15 Papillary (6 microcarcinoma), 4 follicular</td>
<td>42%</td>
</tr>
<tr>
<td>Befiore et al [3]</td>
<td>132</td>
<td>2(1.5%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hales et al [5]</td>
<td>886</td>
<td>16(1.3%)</td>
<td>15 Papillary (14 microcarcinoma), 1 follicular</td>
<td>88%</td>
</tr>
<tr>
<td>Kasuga et al [24]</td>
<td>847</td>
<td>29(3.4%)</td>
<td>24 Papillary (23 microcarcinoma), 5 follicular</td>
<td>79%</td>
</tr>
<tr>
<td>Miccoli et al [16]</td>
<td>140</td>
<td>10(7.1%)</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Linos et al [25]</td>
<td>112</td>
<td>8(5%)</td>
<td>5 Papillary, 1 medullary</td>
<td>0%</td>
</tr>
<tr>
<td>Razack et al [26]</td>
<td>82</td>
<td>3(4.9%)</td>
<td>Papillary microcarcinoma</td>
<td>100%</td>
</tr>
<tr>
<td>Pellegri et al [27]</td>
<td>316</td>
<td>13(4.1%)</td>
<td>-</td>
<td>-</td>
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<td>Angusti et al [4]</td>
<td>1586</td>
<td>0</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Krampe et al [28]</td>
<td>557</td>
<td>21(3.8%)</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Barakate et al [41]</td>
<td>1387</td>
<td>29(2.1%)</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Cappelli et al [26]</td>
<td>145</td>
<td>2(1.4%)</td>
<td>Papillary microcarcinoma</td>
<td>100%</td>
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<tr>
<td>Weber et al [27]</td>
<td>48</td>
<td>3(6.25%)</td>
<td>Papillary microcarcinoma</td>
<td>100%</td>
</tr>
<tr>
<td>Phitayakorn et al [7]</td>
<td>89</td>
<td>2(2.2%)</td>
<td>Papillary microcarcinoma</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>8204</strong></td>
<td><strong>186(2.3%)</strong></td>
<td><strong>85 Papillary (57 microcarcinoma), 10 follicular, 1 medullary</strong></td>
<td><strong>42%-100%</strong></td>
</tr>
</tbody>
</table>

**Figure 3:** Papillary Carcinoma Thyroid - Low power field

**Figure 4:** Papillary Carcinoma Thyroid - High power field
A repeat USG was done which showed two nodes in level III & VI each of size 4 x 3 mm and 6 x 5 mm. Her thyroid function tests (Table 1) were repeated post surgery and the TSH was 30 µIU/ml, T3 was 46ng/dl, T4 was 5.00 µg/dl, Thyroglobulin was 10 ng/ml and Anti TgAb was 80.36. A whole body Radioactive 131I uptake study showed 8% residual thyroid tissue in thyroid bed. Rest of the body showed normal tracer uptake. RAI ablation was done using 85.09 Mci of I-131. Post procedure the patient had no complications. Two focal increased concentration of tracer was noted in the thyroid bed region. No abnormal uptake of tracer was found elsewhere in the body. The patient was put on suppressive dose of T. Eltroxin. After 2 months a repeat USG neck was performed which showed no nodes. Her thyroid function test was also within normal limits (Table 1) and is on regular follow up.

**DISCUSSION:**

Graves' disease was originally described by the Welsh physician Caleb Parry in a posthumous article in 1825, but is known as Graves' disease after Robert Graves, an Irish physician who described three patients in 1835. Graves' disease is by far the most common cause of hyperthyroidism, accounting for 60 to 80% of cases. It is common in the age group of 40 to 60. Female gender has a higher incidence of 5:1. It is an autoimmune condition due to stimulatory antibodies to TSH-Receptor. Graves' disease is characterized by thyrotoxicosis, diffuse goiter, and extrathyroidal conditions including ophthalmopathy, dermopathy (pretibial myxedema), thyroid acropathy, gynecomastia, and other manifestations. The incidence of papillary thyroid cancer along with Graves' disease is an indisputably rare combination.

Different studies around the world have confirmed this rare coexistence of Graves' disease and thyroid cancer. The prevalence of thyroid carcinoma in Graves' disease has been reported to range from 0 – 10 % [3, 4] and the exact prevalence is 2.3 % [7] and this difference in prevalence of incidental thyroid carcinoma in Graves' disease and clinical significance may be caused by the clinical situation in which a carcinoma is diagnosed . The most commonly encountered thyroid cancer is papillary cancer. When these two diseases co-exist the clinical behavior has been described as ranging from benign [5] to very aggressive [6]. Based on the World Health Organization's classification of thyroid cancer, a papillary microcarcinoma is defined as a papillary carcinoma 10 mm or less [10]. Up to 30% of all cases of papillary thyroid carcinoma are papillary microcarcinomas [11]. Previous autopsy studies have noted a prevalence of papillary microcarcinomas of 1.0% to 35.6% in individuals who died from non–thyroid related illnesses [12, 13] depending on pathologic sectioning techniques, different diagnostic criteria, as well as different environmental or population-based genetic factors [11]. The clinical aggressiveness of thyroid cancer with concomitant Grave's disease is still an enigma. As TSH stimulates growth of metastatic differentiated thyroid cancer expressing the TSH receptor TSHR), it is possible to hypothesize that high levels of anti-TSHR antibodies of Graves’ patients might stimulate thyroid cancer growth and early metastatic spread, thus negatively affecting patient outcome [14]. However, other studies do not support the suggestions that thyroid cancer in patients with Graves’ disease is more aggressive than in either patient with toxic nodular goiter or euthyroid subjects ([5, 15] as antithyroid antibodies may be able to recognize these malignant cells and destroy them in the same way as
they destroy the normal cells contributing to the low rate of clinical progression of these lesions. Thyroid nodules are common in patients with Graves’ disease and raise concern about the possible presence of thyroid malignancy. Early detection of thyroid nodules has recently become possible by ultrasonography, and the increasing use of thyroid ultrasonography has revealed greater numbers of thyroid nodules that are not palpable. Small thyroid cancers are being discovered as incidental findings in Graves’ disease patients. Although most cases of papillary hyperplasia of Grave’s disease can be differentiated from papillary carcinoma based on histological and cytological features, some cases of Graves’ disease may simulate papillary carcinoma. In these patients Cytokeratin 19 may help in differentiating the two conditions. Table 2 shows the prevalence and clinical significance of incidental thyroid carcinoma in patients with Graves’ disease in the literature. The table shows that the majority is papillary microcarcinoma. The best treatment is Total thyroidectomy as there are no pre-operative investigations to exclude malignancy with certainty. Most Papillary cancers have an indolent course and only a very minimal progress to distant metastasis and lead to death [32].

CONCLUSIONS:
Patients with Graves’ disease should be carefully monitored for the detection of thyroid nodules. Ultrasonography is the best modality to detect such nodules. Total thyroidectomy is the treatment of choice in these patients. Since no case has been reported from India a prospective case control study is necessary to determine the prevalence and the nature of Papillary carcinoma in Graves’ disease in the Indian sub-continent.

REFERENCES:


