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CLINICAL VIGNETTE

Graves' Disease: An Overview of Diagnosis and Management

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Case Presentation

A 54-year-old Asian female with hyperlipidemia, history of endometrial adenocarcinoma stage III status post TAH/BSO, chemotherapy and radiation therapy was found to have enlarged thyroid nodules on surveillance chest CT. Subsequent ultrasound showed a 3 cm complex nodule in the left lobe and a 1.38 cm complex cystic lesion with calcifications and irregular borders in the right lobe. FNA of her nodules revealed atypia of undetermined significance of the right nodule and normal left nodule. She had normal thyroid function test. She returned 8 months later, with 4 weeks of frequent palpitation at 110-120 beats per minutes along with chest pain, shortness of breath and nausea during these episodes. She also had increase shakiness and tremor. Patient denied anxiety, fatigue, caffeine intakes, diarrhea, weight loss, or mood change. There is no family history of thyroid disease.

Physical exam revealed heart rate of 115 with regular rhythm, enlarged non-tender thyroid with palpable left nodule and right-sided fullness. Her exam was otherwise unremarkable.

Diagnostic Tests

TSH < 0.02 (N: 0.3-4.7 mIU/ml)
Free T4: 5.7 (N: 0.8-1.7 ng/dL)
Free T3: 2022 (N: 222-383 pg/dl)
Thyroid stimulating immunoglobulin (TSI): 136 (N: < 122 %)
Thyrotropin Binding Inhibitory Immunoglobulin (TBII): 32 (N<16% Inhibition)
Thyroid peroxidase antibody (TPO AB): 15 (< 20 IU/ml)
Thyroglobulin antibody 49.8 IU/ml (<4.0 IU/ml)
WBC 2.4 (N: 4-10 x 10³/uL)
Absolute neutrophil count of 1.0 (N: 1.56-6.13 x 10³/uL)
Absolute lymphocyte count of 0.75 (N: 1.18-3.74x 10³/uL)
Normal hemoglobin/ hematocrit and Platelet counts
EKG: sinus tachycardia at 107, otherwise normal EKG.

Discussion

Graves' disease (GD) is an autoimmune disorder of the thyroid gland that contributes to 80% of hyperthyroid cases.¹ The triad of exophthalmos, palpitations and goiter was initially described by Dr. Robert James Graves in 1835.¹ The syndrome includes additional hyperthyroid symptoms, goiter, ophthalmopathy and dermopathy. It results from increased thyroid-stimulating hormone receptor antibodies (TRAb) that bind to TSH receptor and stimulate thyroid follicular cells, which lead to abnormal

thyroid growth, thyroid hormones synthesis and release.² Because thyroid hormones, thyroxine (T4) and triiodothyronine (T3), have major physiologic effect on multiple organ systems, patients present with extensive clinical manifestation owing to imbalance in these hormone levels. This paper will present an overview of the Graves' disease and management options in non-pregnant patients.

Graves' disease typically presents in patients age of 40-60 years old with higher prevalence in female.³ Hyperthyroidism is the most common feature affecting nearly all GD patients. The TRAb are the driving force behind the disease but underlying mechanisms are not completely understood. TRAb is specific for Graves' disease unlike antibodies to thyroglobulin and thyroid peroxidase.⁴ TRAb can have stimulatory, blocking or neutral effect on thyroid gland. Stimulating antibodies mimic the action of TSH result in increased synthesis of Na-Iodide symporter and subsequent increase iodide uptake by thyroid tissue causing hyperthyroidism. In addition, TRAb stimulates subtypes of G proteins with increased protein kinase A and thyroid adenylate cyclase activities result in increased thyroid hormone synthesis, secretion, and thyroid cell proliferation.^{5,6} Blocking TRAb prevents binding and action of TSH and may lead to hypothyroidism. GD can have mixture of both blocking and stimulating TRAb thus clinic presentation is based on the amount of each types.^{5,6} Genetic predisposition, infection, vitamin D and selenium deficiency, thyroid injury, radiation, stress, pregnancy and immunomodulating drugs are suspected as causes for increase TRAb in patients with GD.⁷

Clinical manifestation of Graves' disease can range from mild to full blown thyrotoxicosis. Goiter is a common physical finding. Patient may have classical hyperthyroid presentation. Younger patients have more overactive symptoms such as anxiousness, tremor, palpitations, and hyperactivities. Older patients with thyrotoxicosis tend to manifest with cardiovascular symptoms and weight loss. In the elderly, they can have apathetic hyperthyroidism with depression, lethargy, weight loss and muscle wasting.⁸ Atrial fibrillation develops in 20% of patients. In patients 70-79 years old, 15 % developed atrial fibrillation within 30 days of GD diagnosis.⁹ Other findings specific to GD include ophthalmopathy, thyroid dermopathy and thyroid acropachy.² Graves' orbitopathy occurs in 24% of GD. It includes proptosis, periorbital edema, slow eyelid retraction and diplopia.¹⁰ Thyroid dermopathy characterized by thickened hyperpigmented skin, primarily in the pretibial area

and can occur in 4% of GD.¹⁰ Acropachy clubbing of the fingers and toes is a rare extrathyroidal manifestation of GD..^{10,11}

Clinical and biochemical features of hyperthyroidism with elevated TRAb, ophthalmopathy, or diffuse increase on radioactive iodine uptake scan confirm the diagnosis of GD.³ Serum TSH, T4 and T3 measurements distinguish between subclinical from overt hyperthyroidism. Thyrotropin-binding inhibitory immunoglobulin (TBII) and thyroid-stimulating immunoglobulin (TSI) assays are used to measure TRAb level. TRAb is a good diagnostic measurement of GD with 97% sensitivity and 99% specificity and it is useful in predicting patients at risk for post treatment relapse.² The thyroid radioactive iodine uptake test can help differentiate causes of hyperthyroidism. It shows diffusely increased uptake in Grave's disease, normal or high uptakes with irregular pattern in toxic multinodular goiter, localized and focal pattern in toxic adenoma.² Thyroid ultrasound assesses thyroid blood flow, presence of nodules, and size of the gland. It can distinguish between GD from painless thyroiditis. Thyroid carcinomas are 5 times more likely to occur in GD patients with thyroid nodules.¹² Eighty-eight percent of cancers are papillary with solitary papillary microcarcinoma (< 10mm) made up 23% of all detected thyroid cancer.¹² Hyperthyroidism can cause mild leukopenia, anemia or thrombocytopenia and in rare cases pancytopenia.¹³ An observational cohort study found thyroid disease as the most common disorder among patients with mild to moderate neutropenia.¹⁴ The incidence of GDs in neutropenic patients is considerably higher than in the healthy population.¹⁴

The treatments for GD involve symptom control and correcting the underlying cause. B-blockers are used for rapid symptom relief of palpitation, tremor, anxiety and heat intolerance before thyroid hormone reach normal level from treatment. Glucocorticoids can decrease conversion of F4 to T3, lowering T3 hormone levels to treat acute hyperthyroid symptoms.¹ The three main treatment options for GD are antithyroid drugs (ATDs), radioactive iodine ablation (RAI) and surgery. The choice of treatment is based on severity of hyperthyroidism, age, size of the goiter, response of treatments and other comorbidities.¹⁵

Two types of ATDs are propylthiouracil (PTU) and methimazole. PTU decreases the conversion of T4 to T3 in peripheral tissue by inhibiting the outer ring deiodinase of T4. Methimazole inhibits the oxidation of iodine in the thyroid gland. ATD is effective and safe; therefore, it is the first choice of treatment in most GD patients.¹⁶ Methimazole has better efficacy, once daily dosing schedule and less severe side effects than PTU, which can have significant liver toxicity.² The starting dose of methimazole depends on the severity of the hyperthyroidism and the size of the thyroid gland. Thyroid function should be checked 4-6 weeks after initiation of therapy and every 2-3 months once euthyroidism is achieved.¹⁵ Once euthyroid, a low maintenance dose should be continued for 12-18 months to minimize relapse, which is more frequent within first 6 months post treatment but uncommon after 4 years.¹⁷ Minor side effects of ATDs occur in about 5% of patients, which include pruritus,

arthralgia and gastrointestinal distress. Major side effects are rare but consisted of agranulocytosis, aplastic anemia, thrombocytopenia, hypoprothrombinemia and hepatotoxicity.¹⁸ Agranulocytosis with absolute granulocyte count less than 500 cells/mm³ is the most frequent major side effect and is life threatening. It can occur within 1 month after start of therapy.¹⁹ ATD should be discontinued if the ANC count is less than 1000 cells/mm³.¹⁷ GD can have underlying cytopenias. One in seven GD patients has associated neutropenia at time of diagnosis especially in non-Caucasians and those with higher thyroid hormone levels. Treatment with ATD can lead to reduction in thyroid hormone concentration and normalization of cytopenias without the side effect of agranulocytosis.^{20,21} Hepatotoxicity and vasculitis can occur with PTU. Patient can develop acute liver failure vasculitis kidney failure from PTU treatment. Thus methimazole is preferred over PTU.¹⁸

RAI ablation therapy can be used as first line treatment for patients that failed the ATD treatment. It is contraindicated during pregnancy, breastfeeding, planning pregnancy or inability to follow radiation safety recommendation.² In addition, it is not recommended for patients with suspicious thyroid nodules or thyroid cancer, as surgical intervention is the therapy choice.¹⁵ RAI has been shown to cause de-novo development or worsening of orbitopathy. It should be avoided in patients with moderate to severe Graves' ophthalmopathy.^{15,22} Thyroid function should be monitored 1-2 months after RAI and treatment with levothyroxine if hypothyroidism develops.² Acute thyroiditis occurs in 1% of patients post RAI treatment and can last for weeks. Treatment includes NSAIDs or glucocorticoids for severe cases and B-blockers for associated hyperthyroidism symptoms.²

Total thyroidectomy is the main surgical option and the most successful treatment for Graves' hyperthyroidism.^{23,24} It is recommended for patient with compressive symptom from goiter, low uptake on thyroid scanning, malignant or suspicious cytology, large thyroid nodule >4 cm, hyperparathyroidism, or failed ATD/RAI treatment.^{1,13,24} Surgical risks are bleeding, paralysis of the vocal cord and hypocalcemia, which are minimized when performed by experienced thyroid surgeons. For patients with overt hyperthyroidism, pretreatment with ATD reduces the risk of perioperative thyroid storm, while B-blocker control hyperthyroid symptoms. Pretreatment with inorganic iodide such as potassium iodide can be used to reduce thyroid hormone release and thyroid vascularity with decreased intraoperative blood loss.^{23,24} Before surgery, a euthyroid state is recommended but not an absolute requirement.^{24,25} Post-operatively, levothyroxine replacement should be started and TSH level monitored 6-8 weeks. Oral calcium and calcitriol supplementation are used for prevention of postoperative hypocalcemia.¹⁵

Patients with GD may experience relapse after stopping ATD or post RAI treatments. The relapse rate is highest in ATD group. Relapse episode is associated with occurrence of ophthalmopathy, smoking, thyroid volume and goiter size, FT4, FT3, and TRAb levels.¹ Keeping the ATD regimen for 12-18

months is recommended to prevent relapse. Patients can undergo repeat RAI therapy after post RAI relapse or persistent hyperthyroidism after 6 months. Relapse is rare in surgical treated patients. Vitamin D supplement, selenium and smoking cessation may be beneficial to prevent relapse.²⁶

Case Treatment and Follow Up

The patient exhibited overt hyperthyroidism with palpitations, tremor and elevated FT3 level. The elevated TSI and TBII confirmed Graves' disease. Given her neutropenia and lymphopenia state, ATD was not the first treatment choice due to high risk for agranulocytosis. The presence of large thyroid nodules with indeterminate cytology and increase risk of thyroid carcinoma in GD patient, total thyroidectomy was recommended over RAI ablation. Because of extremely elevated T3 level, patient was at risk of thyrotoxicosis peri-operatively. After coordinating with her oncologist, low dose methimazole was started along with weekly monitoring of her blood count with goal to bring her close to euthyroid state. Propranolol and prednisone treatment temporarily improved of her hyperthyroid symptoms. Patient underwent successful total thyroidectomy 1 month later when her T3 level was below 800pg/dl. Final pathology of the gland showed fully encapsulated microscopic papillary carcinoma < 1mm in size of the right thyroid lobe and lymphocytic thyroiditis with nodular hyperplasia of the left lobe. Because the papillary thyroid carcinoma was clinically insignificant, no additional treatment was needed and there was no need to suppress TSH for carcinoma management. At 6 months follow up post thyroidectomy, patient's hyperthyroid symptom had resolved. Her WBC normalized with normal neutrophil and lymphocyte counts. Her thyroglobulin antibody decreased to 4 IU/ml from 49.8 and thyroglobulin < 0.1 mg/ml. Her thyroid function tests were in normal range with daily levothyroxine treatment.

Conclusion

Graves' disease is a common cause of hyperthyroidism with multitude of clinical manifestations. Early detection and treatment can prevent adverse outcomes. It is important to consider ATD, RAI and surgical treatment options based individualized patient specific factors. ATD is the treatment of choice mild clinical sign and symptoms. RAI ablation should be considered after failed ATD treatment. It is important to screen for nodules in GD patient due to risk of thyroid carcinoma and the presence of thyroid nodule will determine the need for thyroidectomy.

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