Grumpy? Recognizing and treating the return of Graves’ disease

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CASE

Mrs. RS, a previously healthy 60-year-old lady, was referred to the Endocrinology clinic by her family physician for assessment of low TSH and elevated free T4. Over the last 2 months, she had been experiencing a sensation of neck tightness, mild dysphagia, hoarse voice, dry nose and some blood in her sputum every week. She also complained of frequent epistaxis ranging from blood in mucous to frank red blood from her nose with dizziness. Her appetite was increased and she believed that her body “doesn’t absorb anything well”. She had no weight loss. Mrs. RS does not have cold or heat intolerance. Her other complaints included fatigue, feeling anxious and irritable, and blurry vision when reading at night-time with the occasional white flash. Her last optometry visit was 7 years ago.

She admitted to having seasonal allergies that have been improving over the last 10 years, for which she took over-the-counter allergy medications in the past. She has also used Nasonex for her nose in the past, prescribed by her family doctor. Her current medications include vitamins, Fosamax, calcium, magnesium and glucosamine. She denied taking any herbal supplements. She has no known drug allergies.

Her past medical history is significant for thyroid disease 10 years ago. She was unsure of the type of disease, but recalls taking medications for 2 years and stopping when her disease subsided. She also had a history of osteoarthritis (OA) in her hands for 8 years.

Her family history is significant only for OA in her mother. She denied any family history of thyroid disease. Mrs. RS has also had no surgeries or hospitalizations.

Her social history revealed that Mrs. RS is originally from the Philippines, of Chinese decent, and immigrated to Canada 20 years ago. She lives with her husband, her son, her daughter-in-law and her 2 grandsons. She works part-time in a coffee shop. She has never smoked cigarettes or used recreational drugs, and only has one drink at Christmas.

On examination, Mrs. RS sat comfortably in no apparent distress. Her weight was 100 lbs with a height of 5 feet 5 inches. Heart rate was 72 beats/minute and regular with a blood pressure of 110/60 mmHg and a respiration rate of 16 breaths/minute. Upon head and neck exam, she had full ocular movements with no lid lag, retraction or proptosis. Her thyroid was normal to palpation, with no lumps or enlargement. There was a soft painless lymph node in her right posterior cervical chain that measured under 1 cm. Auscultation of her thyroid revealed no bruits. Nasal conchae look red and dry with dried blood.

Her lab results from her referral showed a TSH <0.05 mIU/L, free Tdried blood.

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DISCUSSION

Graves’ disease is increasing in prevalence, affecting about 1% of Canadians, and more common in women than men. Thyroid stimulating IgG antibodies (TSI) circulate in the body and activate the thyrotropin receptor resulting in follicular hyperplasia and hypertrophy. This enlarges the thyroid and increases thyroid hormone (T3 and T4) production. Excess T3 and T4 work on the pituitary, the heart, the liver, bone, reproductive organs, fat and muscle resulting in manifestations of thyrotoxicosis, summarized in Table 1.

Diagnosis of Graves’ disease can be made clinically by evaluating patients for hyperthyroidism signs and symptoms. Symptoms include weight loss, heat intolerance, insomnia, tremor, increased defecation, proximal muscle weakness, irritability, menstrual irregularity and erectile dysfunction with decreased libido and possible gynaecomastia in men. Signs include tachycardia, “Graves’ stare”, lid lag, proptosis, goiter, resting tremor, hyperreflexia, warm and moist skin. Rarely, patients can present with pretrial myxedema and thyroid-induced clubbing. Usually, patients will report increased appetite and food intake with paradoxical weight loss.

The case patient, Mrs. RS, did not present to clinic with overt hyperthyroidism symptoms and only reported similar anxiety and irritability that she experienced during her past thyroid problems. Notably, the irritability was “out of her control” and was starting to impact her home and work environments. Otherwise, her history and physical were within normal parameters. This “apathetic hyperthyroidism” is more typical in older patients who present with weight loss or depression. Compared to younger patients, they are less likely to exhibit tachycardia, tremor, goiter, exophthalmos or increased appetite.
Be useful in some patients; however, they are not necessary for further testing for TSI antibodies and radioactive uptake scans may be useful in some patients; however, they are not necessary for diagnosis or management of Graves’ disease. In Graves’ patients, TSI antibodies would be present in the blood and the thyroid would have elevated uptake of radioactive iodine homogeneously.\(^2\) As such, with TSH <0.05 and free \(T_4\) elevated, the case patient RS has Graves’ disease.

Treatment of Graves’ disease includes three options: antithyroid medications, radioactive iodine ablation and surgical management.\(^4\) Antithyroid medications include the thionamides, propylthiouracil (PTU) and methimazole (MMI), which inhibit thyroid peroxidase and subsequent thyroid hormone synthesis.\(^4\) MMI is more effective than PTU and with less adverse reactions even on higher doses.\(^5\) PTU is favoured during pregnancy as MMI is rarely associated with teratogenicity: aplasia cutis and gastrointestinal defects. Thionamides are generally started until patients are euthyroid, then withdrawn for remission of Graves’ disease. However, the estimated recurrence rate of Graves’ on thionamides is estimated to be 50-60%,\(^6\) as was in the case of Mrs. RS. Thionamide-induced hypothyroidism correlates to a higher remission rate.\(^6\) Radioiodine (I-131) ablation is used to induce hypothyroidism to prevent recurrences of Graves’ disease and is 80% effective. Least often, surgical thyroidectomy can be used but is reserved for patients with complications of antithyroid medication, those who decline radioiodine and those with large goiters or thyroid nodules.\(^2\) Total thyroidectomy has similar complications as subtotal thyroidectomy, however ST has a 30% recurrence rate for Graves’ and thus total thyroidectomy is preferred.\(^6\) Generally, in non-pregnant patients without hepatic disease, the initial treatment for Graves’ disease is MMI.

Recurrence of Graves’ disease is treated similar to naïve Graves’ disease. However, some patients may need definitive treatment with radioiodine or thyroidectomy. These patients are usually hypothyroid post-treatment and are treated with L-thyroxine until their TSH values are within normal parameters.

### CONCLUSIONS

Graves’ disease is a common problem presenting to family physicians and endocrinology clinics. Despite the typical textbook presentations of Graves’ disease, individual patients’ signs and symptoms are varied and one needs to seek context with laboratory confirmation to make the diagnosis. Treatment is also individualized to patient needs and can include antithyroid medication, radioiodine (RAI) ablation or thyroidectomy. Recurrence rates are 50-60% with antithyroid drugs, 20% in RAI ablation, 30% in subtotal thyroidectomy and <1% in total thyroidectomy. Recurrences are treated similarly to naïve disease. Recognition and treatment of recurrences of Graves’ disease are important to reduce complications and increase patients’ quality of life.

Resources for patients with Graves’ disease: National Graves’ Disease Foundation (www.Ngdf.org), the American Thyroid Association (www.thyroid.org/patients/patients.html) and the Thyroid Foundation of Canada (www.thyroid.ca).

### Table 1: Thyroid hormone action and resulting manifestations of thyrotoxicosis

<table>
<thead>
<tr>
<th>System</th>
<th>Action of thyroid hormones</th>
<th>Manifestations of thyrotoxicosis</th>
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<tbody>
<tr>
<td>Pituitary</td>
<td>Suppress TSH production</td>
<td>Decreased TSH in labs</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Increased channel expression, increased (a)-MHC and decreased (\beta)-MHC expression, increased serum atrial natriuretic peptide</td>
<td>Increased heart rate and contractility</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Increased D1 deiodinase, LDL and VLDL receptors, lipase, and liver metabolism enzymes</td>
<td>Increased peripheral T(_3) production, reduced total cholesterol, LDL cholesterol and lipoprotein((a))</td>
</tr>
<tr>
<td>Skeletal</td>
<td>Increased osteocalcin, alkaline phosphatase</td>
<td>Increased bone turnover, osteopenia, osteoporosis and fractures</td>
</tr>
<tr>
<td>Reproductive</td>
<td>Male: increased sex hormone globulin and reduced free testosterone</td>
<td>Male: erectile dysfunction, decreased libido</td>
</tr>
<tr>
<td></td>
<td>Female: antagonism of estrogen action, impaired gonadotropin regulation</td>
<td>Female: irregular menses</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Increased fatty acid oxidation and sodium-potassium ATPase</td>
<td>Increased thermogenesis and oxygen consumption</td>
</tr>
<tr>
<td>White fat</td>
<td>Increased adrenergic lipolysis</td>
<td>Reduced fat mass</td>
</tr>
<tr>
<td>Muscle</td>
<td>Increased SERCA activity, and serum creatinine kinase</td>
<td>Proximal muscle weakness, fatigue</td>
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REFERENCES


