Graves’ thyrotoxicosis soon after hemithyroidectomy for low-risk papillary thyroid carcinoma

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SUMMARY
Hyperthyroidism is a medical problem that is commonly encountered by emergency physicians, internists and endocrinologists. The development of hyperthyroidism in the postoperative setting of hemithyroidectomy is quite rare. Reported causes include destructive thyroiditis and inappropriate thyroid hormone replacement. Here we report a case of Graves’ disease causing thyrotoxicosis soon after surgery in a woman who underwent hemithyroidectomy for low-risk papillary thyroid carcinoma.

BACKGROUND
Graves’ disease (GD) is the most common cause of hyperthyroidism worldwide. It is an autoimmune disease that results from autoantibodies directed against the thyroid-stimulating hormone receptor (TSHR) that stimulate production and secretion of thyroid hormones. The disease reflects a dysregulated immune response for the interaction of a genetic predisposition and environmental factors. The main treatment modalities include antithyroid drugs, radioiodine therapy and surgery. The incidental finding of thyroid cancer with histological examination of the surgical specimen of GD is not uncommon. However, new-onset GD developing after hemithyroidectomy to treat suspicious thyroid nodules is very rare with only a small number of cases being reported.

CASE PRESENTATION
A woman in her 40s was referred for an enlarging thyroid nodule known for 2 years. She has no other medical history and was not taking any medications. She denied a family history of thyroid cancer or disease. Ultrasonographic thyroid interrogation showed a left solid, hypoechoic nodule that measured 1.3 cm in maximum diameter. Fine needle aspiration biopsy was performed and was positive for papillary thyroid carcinoma (PTC). In the context of a low-risk profile for disease recurrence, the decision was made to perform a hemithyroidectomy. The surgery was uncomplicated, and the patient was discharged home on the same day. Pathology described a classic PTC that measured 1 cm in maximum diameter with no aggressive or invasive features. It also showed evidence of mild chronic lymphocytic thyroiditis.

One month after her surgery, during a regular follow-up visit, the patient complained of palpitations. The thyrotropin (TSH) was 0.01 (0.35–5.0 mU/L), free thyroxine (fT4) 24.6 (12–22 pmol/L), free tri-iodothyronine (fT3) 10.2 (3.4–5.9 pmol/L), thyroglobulin 136 (10–65 µg/L) with negative antithyroglobulin antibodies. Under the assumption that the entire thyroid was removed, her family physician prescribed desiccated thyroid extract soon after surgery.

DIFFERENTIAL DIAGNOSIS
With this initial clinical picture, the top differential diagnosis was thyrotoxicosis due to exogenous thyroid hormone replacement. However, her TSH remained suppressed (0.01 mU/L) and fT3 elevated (9.3 pmol/L) with a normal fT4 (19.7 pmol/L) 6 weeks following cessation of desiccated thyroid extract.
hormone. At this point, we considered a diagnosis of destructive thyroiditis which in this clinical context could be due to a viral illness (eg, COVID-19) or palpation thyroiditis secondary to surgery. The thyrotoxicosis in our patient persisted for more than 12 weeks which is not classic for thyroiditis where the usual thyrotoxic phase lasts for 4–12 weeks. This scenario prompted further work up for the suspected diagnosis of GD. Thyroid ultrasound revealed an increase in the vascularisation of the remnant right lobe ‘thyroid inferno’ (figure 1). The TSH receptor antibody (TRAB) titre was elevated, 17.56 (0.00–1.75 mU/L) and thyroid scintigraphy showed diffuse uptake in the right thyroid lobe consistent with GD (figure 2).

**TREATMENT**

The patient was started on methimazole 5 mg two times per day.

**OUTCOME AND FOLLOW-UP**

The patient developed mild proptosis and lid swelling, consistent with mild Graves’ orbitopathy, noted approximately 4 months after surgery. She was started on selenium and artificial tears. Her thyroid function tests improved rapidly after 4 weeks of therapy and accordingly, the dose of methimazole was decreased to 5 mg once daily. The trend of her thyroid function tests before and after treatment is shown in table 1.

**DISCUSSION**

The most common cause for thyrotoxicosis after thyroidectomy is iatrogenic due to exogenous thyroid hormone replacement. Another important cause is palpation thyroiditis which was reported after thyroid and neck surgeries and is thought to be secondary to intraoperative thyroid manipulation, trauma and thyroid hormone leakage. Other causes include residual functional thyroid nodules, functional thyroid metastases, other medications (eg, amiodarone) and GD. In our patient, the persistence of thyrotoxicosis for weeks after stopping the desiccated thyroid hormone excluded an exogenous cause and warranted further work up. The results of the thyroid scan, thyroid ultrasonography and TSHR antibodies ruled out other causes and established the diagnosis of GD.

Risk factors for GD include female sex, infections, stress, pregnancy, iodine and iodine-containing drugs, radiation and immune-modulating agents. GD can often be diagnosed clinically based on signs and symptoms. Low TSH and high T4 in addition to high TSHR antibodies can establish the diagnosis. If the antibodies are negative, thyroid uptake scan is performed to confirm the diagnosis. The main treatment modalities for GD include antithyroid drugs, radioiodine therapy and surgery. GD results from a dysregulated immune response to an extrinsic or intrinsic factor in a genetically predisposed individual. As mentioned above, the causes and risk factors for GD are variable. In our case, the patient was euthyroid before surgery and developed signs of GD 4 weeks after surgery. New GD developing after hemithyroidectomy is very rare and only a small number of cases has been reported. In most of these cases, GD developed years after surgery and the relation of GD to the surgery is tenuous.

The mechanism whereby GD develops following partial thyroidectomy is not established and remains speculative. Broadly, one theory proposes that injury to the thyroid follicular cells releases autoantigens which then elicit an immune response. Specifically, antigen presenting cell (APC) induce a T helper cell humoral response (Th2) and ultimate TRAB production. The tight temporal relationship of the hemithyroidectomy, TRAB production, typical Graves’ thyrotoxicosis and orbitopathy in this case supports this mechanism. The TRAB status before the hemithyroidectomy in our case is unknown; however, the preoperative biochemical euthyroid state leads us to speculate that either the levels increased significantly (incipient GD) or appeared de novo postoperatively. To that end, chronic lymphocytic thyroiditis was reported on the final surgical specimen possibly indicating pre-existing subclinical autoimmune thyroid disease. It has been reported that subclinical GD is present before the onset of hyperthyroidism in most patients with GD. This was evident by detecting TRABs before the occurrence of hyperthyroidism in a group of patients with GD.

Another theory focuses on induced immune dysregulation of the effector cells in genetically predisposed individuals by either an intrinsic (stress) or extrinsic (surgery, general anaesthesia, virus) factor. Specifically, either the APC and/or the TH2 effector cell activation lead to TRAB production and GD. Of note, we considered the role that desiccated thyroid hormone, an animal thyroid extract, could have played in triggering the immune system and causing GD, but we could not find any evidence to support such a role.

Autoimmune thyroid disease should be considered in the preoperative care of patients with suspicious or malignant nodules prior to hemithyroidectomy. In addition to a basic thyroid panel as recommended by the American Thyroid Association guidelines, sonographic interrogation of the entire gland should be scrutinised for signs of autoimmune thyroid disease, including GD. Preoperative findings of a diffuse goitre with a hypechogenic heterogenous texture and especially a diffuse increased colour flow doppler signal should prompt further investigations for GD, that is, TRABs or thyroid scintigraphy.

In conclusion, we reported a case of GD developing soon after hemithyroidectomy for low-risk papillary thyroid carcinoma. Our case highlights the importance of regular follow-up after surgery that includes repeating thyroid function tests. A broad differential diagnosis should be considered in cases of transient thyrotoxicosis secondary to infection or altered immune state.

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**Table 1** The trend of the thyroid function tests

|            | Preop | Weeks after surgery | 4     | 10    | 14    | 18 (methimazole start) | 22    | 26    |
|------------|-------|---------------------|-------|-------|-------|------------------------|-------|-------|
| TSH (0.5–4.5 mU/L) | 1.50  | 0.01                | 0.01  | 0.01  | 0.01  | 6.21                   | 1.4   |       |
| fT4 (10–25 pmol/L) | 8.9   | 24.6                | 19.7  | 18.9  | 26.9  | 5.3                    | 10.9  |       |
| fT3 (3.5–7.0 pmol/L) | 4.1   | 10.2                | 9.3   | 8.5   |       | 2.7                    |       |       |
| Tg (10–60 µg/L) | 136   |                     | 130   |       |       |                        |       |       |
| TgAb       | 15    |                     | 18    |       |       |                        |       |       |
| TRABs      |       |                     |       |       |       |                        | 17.56 |       |

fT3, free tri-iodothyronine; fT4, free thyroxine; Tg, thyroglobulin; TgAb, thyroglobulin antibodies; TRABs, TSH receptor antibodies; TSH, thyrotropin.
Hyperthyroidism. Further research is needed to understand the mechanism of GD following thyroid surgery.

Learning points

► Hyperthyroidism developing after hemithyroidectomy has multiple causes.
► Major causes are inappropriate thyroid hormone replacement, destructive thyroiditis (eg, palpation) and less commonly Graves’ disease.
► Graves’ disease can occur early in the postoperative course following partial thyroid surgery.
► Subtle signs of autoimmune thyroid disease especially Graves’ disease should be searched for during sonographic interrogation of the entire thyroid gland in the preoperative setting of a thyroid nodule.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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