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Case Report

Refractory Thyrotoxicosis in Oropharyngeal Squamous Cell Carcinoma Invading the Thyroid Gland

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ABSTRACT

Objective: Thyrotoxicosis from local invasion of the thyroid gland by an extrathyroidal malignancy is rare. We describe a patient with thyrotoxicosis secondary to invasion of the thyroid gland by an oropharyngeal squamous cell carcinoma (OPSCC). To our best knowledge, this has not been reported.
Case Report: A 62-year-old Indian man with histologically proven, p16-negative, cT3N3bM0 (stage IVb) posterior OPSCC was admitted for elective gastrostomy. Biochemical thyroid profile was normal before admission, and there was no thyroid invasion radiologically. The patient developed persistent fever and tachycardia associated with an elevated white cell count and C-reactive protein. This was treated as sepsis, and antibiotic therapy was initiated for 17 days without response. An extensive septic workup did not reveal any infection. A subsequent neck computed tomography revealed rapid progression of the OPSCC, with the invasion of bilateral thyroid lobes. Thyroid function tests revealed primary hyperthyroidism. Antibodies indicative of Graves' disease were negative. A tracheostomy was performed due to impending airway compromise. The patient showed minimal clinical improvement with medical management, and thyroid function continued to worsen. He died due to cardiorespiratory collapse due to tumor progression, new-onset atrial fibrillation, and poor underlying cardiac function.
Discussion: We report a rare observation of thyrotoxicosis secondary to thyroid gland invasion by OPSCC. This highlights the need for a high index of suspicion of malignancy-induced hyperthyroidism and evaluation of thyroid function early in febrile/tachycardic patients with locoregionally advanced head and neck SCCs. Urgent oncological treatment may be necessary to control thyrotoxicosis.

Introduction

To our best knowledge, thyrotoxicosis secondary to the local invasion of the thyroid gland by squamous cell carcinoma (SCC) has not been reported. We describe a patient with thyrotoxicosis secondary to a rapidly progressive oropharyngeal SCC (OPSCC).

Case Report

A 62-year-old Indian man with recently diagnosed posterior oropharyngeal wall SCC was admitted for elective feeding gastrostomy. His medical comorbidities included hypertension, hyperlipidemia, and ischemic heart failure (ejection fraction of 23%) for which he had an automated implantable cardioverter-defibrillator. His OPSCC was p16 negative on histology, clinically T3N3bM0, stage IVb (American Joint Committee on Cancer Staging, 8th Edition), and he had been a heavy smoker and alcohol user. He was planned for radical radiotherapy, as he was unfit for concurrent chemoradiotherapy due to the severity of his comorbidities. His biochemical thyroid profile was normal at the time of initial staging (Fig. 1).

Three weeks after an unremarkable gastrostomy, he developed fever, tachycardia, and stridor. Flexible nasolaryngoscopy showed near-complete obstruction of the oropharynx, and an emergency tracheostomy was performed. Examination under anesthesia revealed rapid progression of the OPSCC into a circumferential stricture of the oropharynx, whereas a month prior, the tumor involved only the posterior oropharyngeal wall, right tonsillar

Abbreviations: CT, computed tomography; OPSCC, oropharyngeal squamous cell carcinoma; SCC, squamous cell carcinoma.

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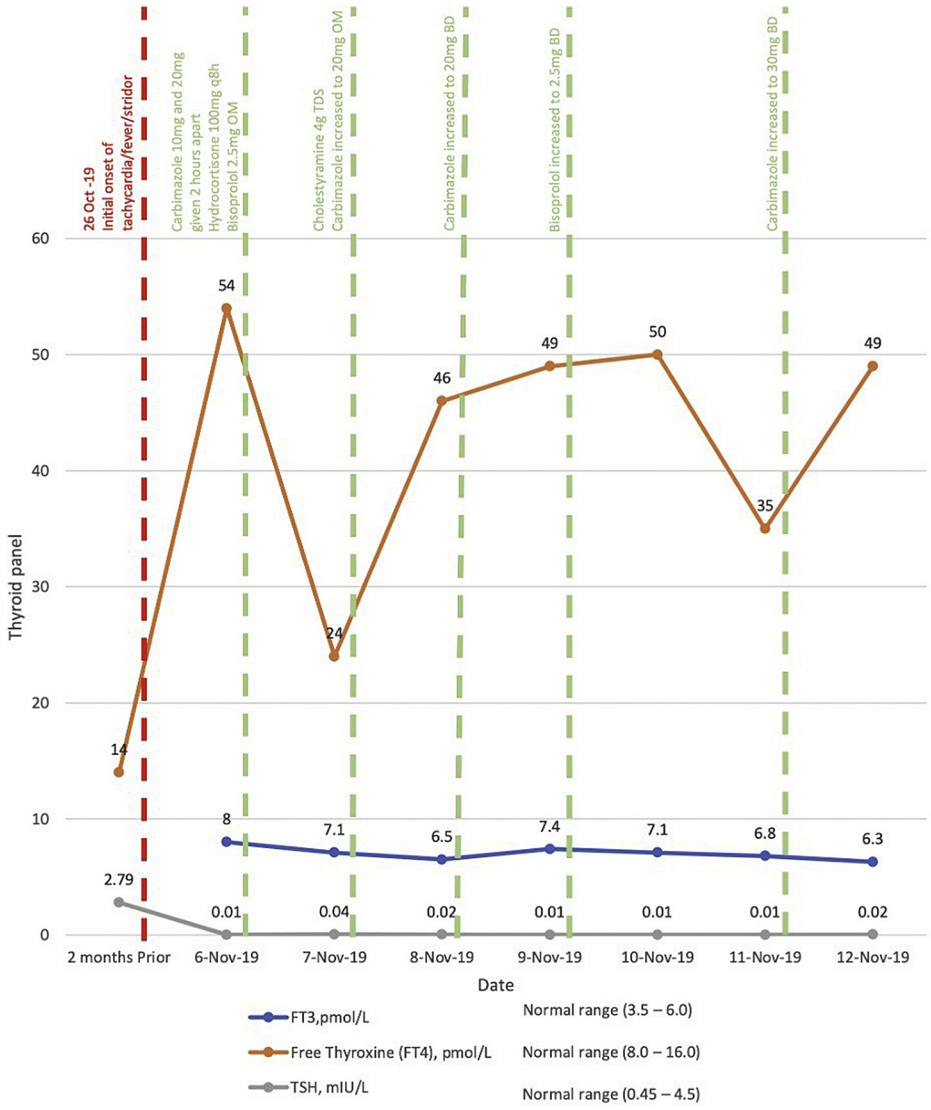

Fig. 1. Change in thyroid hormone levels over time. *BD* = twice a day; *FT3* = free triiodothyronine; *FT4* = free thyroxine; *OM* = once in the morning; *TDS* = three times a day; *TSH* = thyroid-stimulating hormone.

fossa, and pyriform sinus. Fever workup showed elevated C-reactive protein levels (243.3 g/L) and an elevated total white blood cell count (18 400) with a neutrophilic predominance of 75.1% (lymphocyte, 13.9%; monocytes, 10.4%; eosinophils, 0.1%; basophils, 0.5%). Extensive workup to elucidate the source of infection was negative. This included sets of aerobic and anaerobic blood cultures on 4 separate occasions, urine cultures, sputum cultures (including a polymerase chain reaction test for *Mycobacterium tuberculosis*, acid-fast bacilli smear and cultures), gastrostomy site cultures, human immunodeficiency virus and cryptococcal serology, 2-dimensional echocardiography to exclude infective endocarditis, and computed tomography (CT) of the brain to exclude brain abscess. Chest radiography revealed only a small right pleural effusion. We treated the patient empirically for sepsis and administered piperacillin-tazobactam for 17 days. However, his fever and tachycardia were unyielding, with a maximum temperature of 39.6 °C and a heart rate of 110 to 120 beats/min.

Neck CT at this point (6 weeks after initial staging) revealed rapid progression of the OPSCC—with worsening of the pharyngeal primary, cervical, and mediastinal lymphadenopathy and development of new bilateral lung nodules suspicious for distant metastases. Significantly, the primary tumor displayed radiological features of invasion into bilateral thyroid lobes without abscess formation (Fig. 2). Examination revealed tenderness of his central neck without a palpable goiter. Thyroid function tests revealed primary hyperthyroidism of new onset—elevated triiodothyronine level of 8.0 pmol/L (reference, 3.5-6.0) and free thyroxine level of 54 pmol/L (reference, 8.0-16.0) and suppressed thyroid-stimulating hormone level of 0.01 mIU/L (reference, 0.45-4.5). Autoimmune thyroid antibodies including antithyroid peroxidase, thyroid-stimulating hormone receptor antibody, and thyroid-stimulating immunoglobulin were negative. Sonography of his thyroid gland showed reduced vascularity without thyroidal abscess. Thyroid uptake scan was withheld because the patient was hemodynamically unstable and had undergone recent iodine-contrasted scans.

He was managed for thyrotoxicosis with impending storm given his tachycardia (atrial fibrillation with rapid ventricular response), high fever, and tachypnea. Intravenous hydrocortisone, enteral carbimazole, cholestyramine, and bisoprolol were initiated. Despite this, he remained thyrotoxic (Fig. 1). Neck irradiation with palliative intent was expedited but could not be administered due to severe orthopnea. Unfortunately, the patient died due to cardiorespiratory collapse 5 days after the onset of atrial fibrillation.

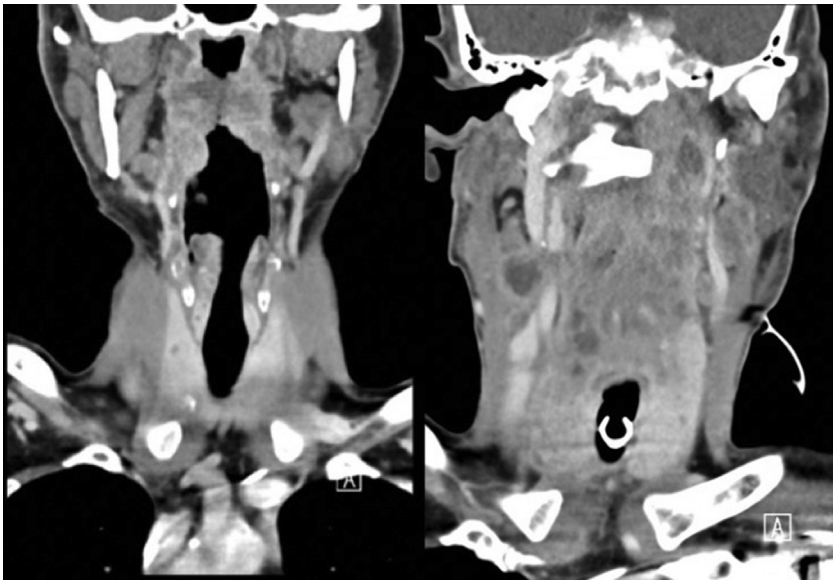

Fig. 2. Interval computed tomography (CT) of the neck demonstrating rapid invasion of the thyroid gland. Left panel, initial staging neck CT, with no evidence of thyroid invasion. Right panel, 6 weeks after initial staging showing evidence of oropharyngeal squamous cell carcinoma invasion into bilateral thyroid lobes

Discussion

Various studies have reported instances of primary thyroid malignancy leading to hyperthyroidism.[1–6] Thyroid metastases from nonthyroidal malignancy have also reportedly caused hyperthyroidism, most being lung, breast, or hematologic in origin.[7] Our literature search on PubMed revealed no reports of hyperthyroidism from local invasion of the thyroid gland secondary to oropharyngeal, hypopharyngeal, or laryngeal SCC, except for 1 patient with laryngeal carcinoma who also had hyperthyroidism secondary to Graves' disease.[8] Moreover, the 2016 American Thyroid Association Guidelines on hyperthyroidism did not mention nonthyroidal malignancy as a cause of thyrotoxicosis.[9]

However, local invasion of the thyroid gland in advanced head and neck SCCs is not uncommon. Especially in hypopharyngeal and laryngeal SCCs, 10% to 15% show evidence of thyroid invasion in surgically resected specimens. The overall rate of thyroid invasion in head and neck SCCs is likely higher as not all such cancers are treated by surgery and thyroidectomy is not routinely performed even in the resection of these cancers.[10–14] Moreover, thyroid function was not routinely reported in most studies—with an occasional mention of patients being euthyroid or hypothyroid perioperatively.[12,13,15] Thus, the rate of hyperthyroidism in patients with thyroid invasion secondary to head and neck SCCs is unknown.

Before concluding that the thyrotoxicosis of our patient was caused by thyroid invasion secondary to OPSCC, we considered the differential diagnosis of subacute thyroiditis, given the mild tenderness on neck examination, reduced vascularity of the thyroid gland on ultrasonography, and elevated C-reactive protein levels. Empirically, we commenced the patient on hydrocortisone, but a rapid rebound of free thyroxine within 48 hours suggested that subacute thyroiditis was unlikely the sole cause of thyrotoxicosis in this patient. Moreover, leukocytosis and neutrophilia in our patient were also not typically seen in subacute thyroiditis. Acute suppurative thyroiditis became a plausible differential, but the lack of an abscess on neck CT and sonography suggests otherwise. Furthermore, the lack of pus in the thyroid isthmus at the time of tracheostomy and lack of bacterial growth on multiple blood cultures, including one that was performed before the start of antibiotic therapy, also decreased the likelihood of acute suppurative thyroiditis. Hyperthyroidism from surgical manipulation or direct trauma to the thyroid gland during tracheostomy could also be possible,[16] but unlikely as the patient displayed signs of hyperthyroidism before tracheostomy, and there was minimal manipulation of the gland intraoperatively.

Therefore, we postulate that the mechanism of thyrotoxicosis in our patient could be follicular and stromal disruption of the thyroid parenchyma from local invasion by OPSCC. The rapid growth of the cancer could cause necrosis of the thyroid follicles, resulting in the loss of its integrity in a mechanism analogous to subacute thyroiditis,[4,7,15] thereby releasing thyroxine and triiodothyronine into the circulation. This was termed "malignant pseudothyroiditis" in the context of primary thyroid carcinoma by Rosen et al.[17] The OPSCC, being p16 negative on immunohistochemistry, likely factored in its rapid progression and invasion.[18] The resultant swift destruction of thyroid follicles could be a reason why the initial response of the patient's thyrotoxicosis to medical treatment was not durable and why the thyrotoxicosis was unresponsive to increasing dosage of carbimazole. As the thyrotoxicosis in this patient was refractory to medical treatment, alternative therapeutic options including plasmapheresis, palliative chemotherapy, and thyroidectomy were considered. These were deemed to be unsuitable in view of the patient's comorbidities and hemodynamic instability.[19] Surgical resection could have controlled the thyrotoxicosis, as suggested in patients with hyperthyroidism from primary thyroid malignancy.[20] However, total thyroidectomy in our patient would require transection through the tumor, risking a nonhealing malignant fistula.

Conclusion

We report a rare observation of thyrotoxicosis secondary to thyroid gland invasion from OPSCC. This highlights the need for a high index of suspicion for hyperthyroidism in febrile or tachycardic patients with locoregionally advanced head and neck SCCs. Against the rapid progression of this patient's OPSCC, thyrotoxicosis

was refractory to medical management. Thus, urgent oncological treatment may be needed in this situation.

Disclosure

The authors have no multiplicity of interest to disclose. The authors consulted the National Healthcare Group, Singapore Domain Specific Review Board (institutional review board equivalent), and a waiver of consent was obtained for this publication. This was endorsed by the Head of Department, Department of Otorhinolaryngology, Tan Tock Seng Hospital, Associate Professor Yeo Seng Beng as well as the Chairman, Clinical Research Committee, Tan Tock Seng Hospital, Associate Professor Tan Cher Heng.

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