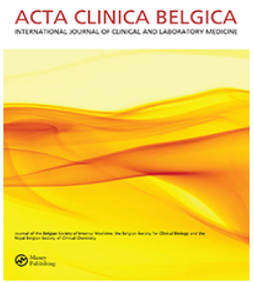

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CASE REPORT

Occurrence of sporadic medullary thyroid carcinoma in Graves' disease in association with a RET proto-oncogene mutation

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ABSTRACT

Background: Graves' disease may be associated with thyroid cancer, particularly differentiated thyroid cancer. Medullary thyroid cancer (MTC) is less common. The occurrence of sporadic MTC in Graves' disease in the presence of a RET proto-oncogene has never been reported.

Clinical presentation: A 63-year-old woman was referred for Graves' disease. A thyroid ultrasound disclosed five nodules, one of which was classified as Eu-Tirads 5 with a size of 6.7 × 6.5× 11 mm. Fine needle aspiration was reported as Bethesda class IV follicular neoplasm of a Hürthle cell subtype. Calcitonin level was found to be elevated. A total thyroidectomy confirmed the diagnosis of MTC and a bilateral cervical lymphadenectomy was performed, with four lymph nodes being infiltrated by MTC. Genetic testing revealed a M918T mutation in the RET proto-oncogene.

Conclusion: MTC may occur in Graves' disease, especially if a nodule is present. In this case, genetic testing should always be performed even if MTC is sporadic. Increased incidence of thyroid cancer in autoimmune thyroid diseases, as well as the link existing between autoimmunity, inflammation and carcinogenesis, leads us to hypothesize that the association here reported is not coincidental.

KEYWORDS

Medullary thyroid carcinoma; Graves' disease; endothelin; carcinogenesis

Background

Thyroid carcinoma, the most common endocrine cancer, may occur in Graves' disease with a mean event rate of 7% according to a recent meta-analysis [1]. Some studies have suggested an increased risk of differentiated thyroid cancer in patients with Graves' disease, especially in the presence of thyroid nodules [2–5]. Medullary thyroid cancer (MTC) is less common, with 15 cases having been reported since 1980 [6–10]. The RET proto-oncogene encoding the transmembrane receptor of the tyrosine kinase family has been shown to exhibit mutations in MTC either in inherited syndromes or in sporadic cases [11–13]. To our knowledge, in none of the previous cases, such a mutation has been studied or found to be in association with Graves' disease. Moreover, how Graves' disease could drive the occurrence of this cancer has never been addressed. We here describe a case of MTC occurring in Graves' disease in association with a RET mutation and discuss its characteristics as well as the possible links between both diseases.

Case report

A 63-year-old woman was referred to the endocrine clinic on suspicion of Graves' disease based on left exophthalmos with a retraction of the upper eyelid and episodes of eye irritation with a conjunctival injection. There was no family history of thyroid or other endocrine diseases. She gave a past history of Prinzmetal angina, hiatus hernia, Ehler Danlos syndrome and atrial fibrillation that was controlled with diltiazem. She complained of nervousness, palpitation and heat intolerance. On physical examination, there was a small goitre. Apart from the left exophthalmos, there were no other extra-thyroidal manifestations of Graves' disease. Blood pressure was 118/76 mmHg and heart rate 97/min. Biochemical investigations showed normal free thyroxine (T4) and free triiodothyronine (T3) levels with a thyroid-stimulating hormone (TSH) <0.02 mU/l (normal 0.46–4.68) consistent with subclinical hyperthyroidism. Thyrotropin receptor and anti-thyroid peroxidase antibody levels were increased to 2.69 UI/l (normal <0.55) and 37 UI/ml (normal <5.6), respectively, whereas anti-thyroglobulin antibodies were absent. Serum calcium and phosphorus were normal. A Technetium scan revealed a bilateral goitre that was more prominent on the right side. A thyroid ultrasound showed four spongiform right-sided nodules of less than 7 mm and a 6.7 × 6.5 × 11 mm hypoechoic nodule with irregular margins in the upper left lobe that was classified Eu-Tirads 5. Fine needle

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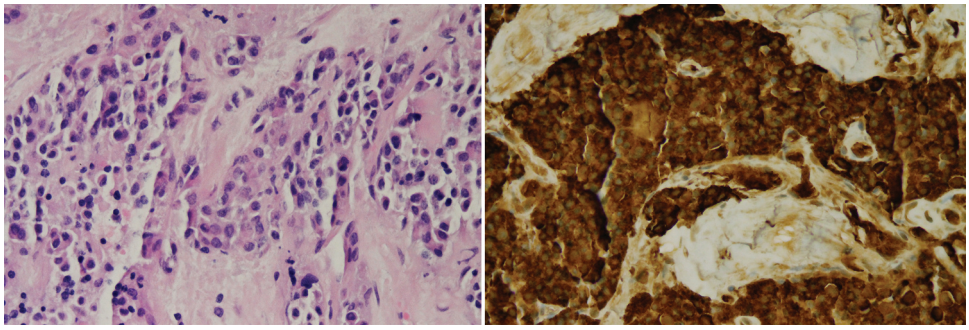

Figure 1. Section of the thyroid showing the medullary thyroid carcinoma stained with haematoxylin and eosin on the left and with a strong immunostaining for calcitonin on the right (magnification x40). The tumour is surrounded by typical thyrocytes of Graves' disease. The tumour shows a solid growth pattern with sheets of cells separated by a fibrous stroma. The cells are oval or polyhedral with irregular and hyperchromatic nuclei. Their cytoplasm is relatively abundant and eosinophilic.

aspiration (FNA) of this nodule was reported as Bethesda class IV follicular neoplasm of a Hürthle cell subtype. Serum calcitonin was then measured at 124 pg/ml (normal <10). A 24-hour urine collection revealed normal excretion of adrenaline, noradrenaline, dopamine, metanephrines and normetanephrines. Treatment with methimazole was initiated to achieve a euthyroid state, as well as selenium administration for Graves' ophthalmopathy. A total thyroidectomy was then performed with intraoperative confirmation of MTC. This justified a bilateral central and lateral cervical lymph node dissection. A 9 mm lesion was found in the left lobe that was confirmed to be a MTC expressing calcitonin on immunohistochemistry (Figure 1). Four ipsilateral out of 39 dissected lymph nodes were infiltrated by MTC. After DNA extraction from tumour tissue, a genetic screening of 22 genes found a p.(Met918Thr) mutation in the RET proto-oncogene. Five months after the operation, serum calcitonin was 24.6 pg/ml. The thyroid ultrasound did not show any abnormality.

Discussion

We here report the case of a patient in whom MTC occurred in Graves' disease in the presence of a RET proto-oncogene mutation. In the above-mentioned meta-analysis comprising 33 studies, the incidence of thyroid cancer in Graves' disease was roughly 2.5 times the overall global figures [1]. Eighty-eight percent were papillary, 10% follicular and only 0.6% medullary. A large-scale nationwide cohort study also found that the overall incidence of cancer in Graves' disease was 1.37-fold higher than in a matched control cohort [4]. After adjusting for sex, age and comorbidities, the hazard ratio for developing thyroid cancer was 10.4-fold higher in patients with Graves' disease. Moreover, the risk was higher in older patients. In other studies, coexisting thyroid nodules were found to increase the risk of thyroid carcinoma [1,2,5] and thyroid cancer was more aggressive in Graves' disease [3]. These were the features we observed in our patient. The pathogenic role of thyrotropin receptor antibodies (TRAb) in thyroid cancer has been controversial. One study suggested that TRAb may play a role in determining the high aggressiveness of thyroid cancer in Graves' disease [3] whereas another failed to find an association between TRAb levels and cancer outcome [14]. Some authors observed that initial TRAb measured in eight patients with micropapillary cancer were not different from those in a control group without cancer [15]. However, it is well known that thyrotropin stimulates proliferation in normal thyrocytes and thyroid cancer cells and that TSH-suppressive doses of thyroid hormone therapy reduce the recurrence and cancer-related mortality in patients with differentiated thyroid cancer [16]. Therefore, further studies are required to evaluate the effect of TRAb on thyroid cancer cells. It is to note that the above studies concern differentiated thyroid carcinoma but that our case report focusses on MTC. As already mentioned, 15 cases of MTC associated with Graves' disease have been previously published [6–10]. Among them, 67% were females [10], which was also the sex of our patient. Given the rarity of MTC in general and in Graves' disease in particular, it is difficult to establish if such an association is coincidental or not.

Interestingly, our patient was the carrier of a p.Met918Thr (M918T) mutation in the RET proto-oncogene. In the previous cases of concurrent MTC and Graves' disease, only two papers studied the RET gene without finding any mutation. However, somatic RET mutations are identified in 40% to 50% of sporadic MTC, the most common mutation being M918T [12,13]. This mutation also occurs in 95% of the MEN 2B syndrome that could be ruled out in our patient who had no phaeochromocytoma nor the typical clinical phenotype of the syndrome nor a family history of the syndrome. Of note, a meta-analysis including 23 studies and 964 sporadic MTC showed that the presence of a somatic RET mutation is a strong indicator of aggressive tumours with a poor survival [13]. The discovery of invaded lymph nodes in our patient at an early stage is thus not surprising.

Considering the presence of a suspicious nodule and the possible pitfall for MTC on FNA [17], calcitonin was measured. This allowed to make a diagnosis of MTC before the operation. Common causes potentially increasing calcitonin levels were ruled out, such as proton pump inhibitors, renal failure and hypercalcemia. In any case, a value >50 pg/ml was highly indicative of MTC, as previously suggested [18]. The question of measuring calcitonin in the assessment of a thyroid nodule is still controversial, some of the reasons being no proven cost-effectiveness or the unavailability of the pentagastrin stimulation test in the US and other countries. In 2015, a Task Force of the American Thyroid Association revised the management guidelines for patients with thyroid nodules but could not recommend either for or against the routine measurement of serum calcitonin because of insufficient evidence and no uniform agreement [18]. However, in our case, a measurement of calcitonin proved to be useful. Indeed, calcitonin levels are directly related to tumour mass with a practical impact on preoperative work-up and on the extent of cervical lymph node dissection [19].

Assuming that a link might exist between Graves' disease and MTC, would a common pathogenic mechanism make obvious such a link? A possible role of TRAb has already been discussed in differentiated thyroid carcinoma. Regarding MTC, a study demonstrated an expression of TSH receptors on C-cells at both mRNA and protein levels as well as their functionality [20]. Moreover, human MTC cells exhibit a very positive signal for TSH receptors that can be co-localized with calcitonin. Using Northern blot analysis, a study also showed that some MTC cells express TSH receptor mRNA [21]. Moreover, the presence of TSH receptor transcript was confirmed in neoplastic cells by in situ hybridization [21]. Therefore, a stimulating effect of TRAb on MTC cells may not be excluded, but this deserves further studies.

Another important path worth exploring is the well-known link existing between autoimmunity, inflammation and carcinogenesis [22,23]. The extremes of thyroid autoimmune diseases are Graves' disease and Hashimoto's thyroiditis which also share common features such as lymphocytic infiltration of the thyroid and anti-thyroglobulin, and anti-peroxidase antibodies. In Hashimoto thyroiditis, a higher risk of thyroid cancer has also long been recognized [23–25]. The mechanisms underlying the link between inflammation and thyroid cancer are numerous [22,23]. For instance, in papillary thyroid cancer (PTC), cytokines and chemokines may predispose to RET/PTC rearrangement in follicular cells, leading to the development of thyroid cancer. The RET/PTC rearrangement itself may contribute to maintaining an inflammatory reaction [26]. Endothelin-1 (ET-1) is another factor that could play a role in carcinogenesis, notably by inducing cellular proliferation and survival, angiogenesis and bone metastases [27]. Several interleukins and tumour-necrosis-factor alpha that are released in Graves' disease are potential stimuli of endothelin-1. In Graves' disease, a study suggested that the autoimmunologically induced inflammatory response of the thyroid gland was responsible for increased ET-1 plasma levels [28]. We previously showed that papillary and follicular carcinoma cells express all components of the ET-1 axis and that ET-1 receptor A (ET_A R) antagonism exerts antiproliferative effects [29]. Additionally, we studied 12 patients with MTC and demonstrated an overexpression of ET-1, of its mitogen receptor ET_A R and of ET-1-converting enzyme [30]. Therefore, among multiple pathogenic factors, endothelin may also be a candidate linking MTC and Graves' disease.

In conclusion, we have reported the first case of MTC occurring in Graves' disease in association with a RET proto-oncogene mutation. Clinicians should be aware that a thyroid nodule in Graves' disease may harbour a cancer including MTC. In this case, genetic testing should always be performed even if the case appears as sporadic. Multiple mechanisms, including thyrotropin receptor antibodies, inflammation, cytokines and chemokines released by lymphocytes infiltrating the thyroid, might play a role in the occurrence of MTC in Graves' disease.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Author contribution

All authors made substantial contribution to the conception and design and/or acquisition of data and/or analysis and interpretation of data, participated in drafting the article or revising it critically for important intellectual content and gave their final approval for the version to be submitted and any revised version.

Statement of ethics

Written informed consent was obtained from the patient for publication of this case report.

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