Table 1. Entry thyroid function and number of patients developing overt thyrotoxicosis according to aetiology of subclinical thyrotoxicosis

	GD	MNG	AN	Unknown	P*
Free T4 (pmol/l)	17·5 (14·5–20·8)	16·6 (14·0–19·3)	15·1 (11·5–18·3)	16·5 (13·5–18·0)	0·605
TSH (mU/l)	0·165 (0·087–0·243)	0·230 (0·115–0·405)	0·095 (0·063–0·258)	0·284 (0·223–0·390)	0·193
Number (%) developing OT	1 (25·0)	29 (48·3)	4 (50·0)	0	0·412

Data are expressed as median (interquartile range) and number of patients (percentage).
*Kruskal–Wallis nonparametric ANOVA for differences in free T4 and TSH; Fisher exact test for differences in percentages of patients developing overt thyrotoxicosis.
Abbreviations: GD, Graves' disease; MNG, multinodular goitre; AN, autonomous nodule; OT, overt thyrotoxicosis.

between aetiology and these variables. In addition, Kaplan–Meier curves for proportion of patients who developed overt thyrotoxicosis according to aetiology showed no significant differences ($P = 0{\cdot}557$; log-rank test).

Results obtained in our patients are similar to those reported by Rosario,[3] who found that progression to overt hyperthyroidism occurred in 20% of 30 women with Graves' disease and in 40% of 15 women with nodular disease. On the contrary, Woeber[4] found that only one of seven patients with Graves' disease and none of nine patients with nodular disease developed overt hyperthyroidism. We have performed a chi-square analysis of available data form Rosario's and Woeber's reports, and did not find any significant relationship between aetiology and progression to overt thyrotoxicosis ($P = 0{\cdot}174$ and $0{\cdot}438$ for Rosario's and Woeber's data, respectively; Fisher exact test). Discrepancies between these results and those recently reported by Schouten *et al.*[1] may be accounted for by differences in the number of studied subjects and the time of observation, and also by differences in iodine intake, geographical location and genetic background of patients.

It is our opinion that, although the aetiology of thyroid hyperfunction is essential in evaluating patients with thyrotoxicosis, the clinical relevance of the initial TSH should not be underestimated when assessing the risk of progression to overt thyroid disease. Furthermore, it should be noted that the presence of TSH < 0·10 mU/l has been associated with an increased risk of atrial fibrillation, cardiac dysfunction, and adverse effects on bone mineral density in postmenopausal women, and that most experts and scientific societies recommend therapy for older patients with TSH < 0·10 mU/l.[5]

In brief, we think that, in clinical practice, TSH concentration is a major factor in assessing the risk of progression to overt thyrotoxicosis. It is very probable that the aetiology of thyrotoxicosis is also a significant variable in the assessment of progression, but the importance of this variable might vary depending on geographic location of patients, iodine intake and possibly other variables.

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The first case report of diaphragmatic paralysis as a paraneoplastic syndrome of medullary thyroid carcinoma

Bilateral diaphragmatic paralysis is rare and usually caused by anatomical lesions or generalized neuromuscular diseases. Rare cases of bilateral phrenic nerve paralysis as a consequence of a paraneoplastic syndrome of breast or renal cancer have been described.

We describe the case of a patient with respiratory distress syndrome from bilateral diaphragmatic paralysis, due to medullary thyroid carcinoma (MTC). The bilateral diaphragmatic paralysis was mixed, compressive for the right phrenic nerve and paraneoplastic for the left. This is the first case of paraneoplastic diaphragmatic paralysis from MTC with recovery after thyroid surgery.

A 50-year-old man with a history of depression was admitted to the pneumology department with dyspnoea due to bilateral diaphragmatic paralysis. The chest radiograph showed a bilaterally raised diaphragm. Electroneuromyography (ENMG) showed isolated bilateral phrenic nerve paralysis, but no signs of generalised neuropathy, myopathy or motor neurone disease. Because of respiratory distress syndrome, the trachea was intubated for mechanical ventilation.

A brain and cervical scan and magnetic resonance imaging (MRI) of the medulla ruled out a central cause of the diaphrag-

matic paralysis. A scan of the chest showed normal lung parenchyma. Laboratory examinations showed an isolated increase in procalcitonin levels at 159 ($N < 0.6$) μg/l (C-reactive protein <3 mg/l, leucocytes 6600/mm^3, negative urine culture). Clinical examination revealed no fever and no sign of pulmonary, urinary, digestive, skin or neurological infection. The hypothesis of increased thyrocalcitonin (CT) and MTC was raised.

Rereading of the cervical scan revealed a suspiciously nodular thyroid and a voluminous right cervical mass. Cervical ultrasound examination showed a right thyroid nodule and a swollen cervical lymph node on the right side of the neck. These two cervical examinations revealed no lymph nodes on the left side of the neck. A fine-needle aspiration biopsy of the lymph node was performed. Ganglionic metastasis of an MTC was diagnosed. A high level of CT was observed (2855 ng/l, $N < 8.4$). The level of carcino-embryonal antigen was 41.3 μg/l ($N < 5$).

The hypothesis of type 2 multiple endocrine neoplasia was raised. Urinary catecholamines and metanephrines measured on 3 consecutive days were negative. Serum calcium, adjusted to levels of albuminemia (2.23 mmol/l) and parathormone (25 ng/l) were normal.

Total thyroidectomy with central and bilateral compartment lymphadenectomy was performed. Macroscopic resection of the neoplasic tissue was complete. The right phrenic nerve was massively invaded by the cervical node and was not spared by the node resection. The left phrenic nerve was not invaded by lymph node. The two recurrent laryngeal nerves were not invaded by lymph node and were intact after surgery.

Tracheostomy was performed. Histology of the surgical specimen confirmed medullary carcinoma of the right lobe of the thyroid with massive right node invasion. The patient's respiratory function recovered and the tracheostomy was removed 2 months after the thyroid surgery. ENMG of the diaphragm confirmed functional recovery of the left phrenic nerve. The right phrenic nerve was still paralysed 2 months after surgery. The CT level was 133 ng/l and the procalcitonin level was 5.14 μg/l.

This case calls to mind the need to measure thyrocalcitonin when an isolated increase in procalcitonin occurs in the absence of clinical or biological signs of infection.[1] MTC is a rare thyroid cancer (5–10% of thyroid cancers). MTC is usually sporadic and diagnosed by exploring a thyroid nodule. It can be also discovered in a context of multiple endocrine neoplasia type 2 (MEN2), in the presence of suggestive clinical signs. The association between MTC and bilateral diaphragmatic paralysis has never been described.

Many aetiologies of unilateral diaphragmatic paralysis have been reported[2]: iatrogenic (cervical or heart surgery), post-traumatic, thoracic neoplasia, infection, toxic, autoimmune diseases, generalized neuromuscular diseases. Fewer cases of bilateral diaphragmatic paralysis have been described and these usually occurred as a consequence of anatomical lesions of both phrenic nerves or generalized neuromuscular diseases (amyotrophic lateral sclerosis, multiple sclerosis, poliomyelitis, spinal muscular atrophy, myasthenia gravis and muscular dystrophy).[3] Bilateral diaphragmatic paralysis has already been reported in association with mediastinal radiotherapy for the treatment of Hodgkin's lymphoma.[4] The association of paraneoplastic syndrome and bilateral diaphragmatic paralysis has been reported in only four cases of breast or renal cancer.[5–8] The association with MTC has never been described to our knowledge.

In our patient there was no surgical or traumatic history and no treatment before hospitalization. There was no evidence in the neurological or neurophysiological examinations of a generalized neuromuscular disease. The right phrenic nerve paralysis was caused by compression of the nerve by the ganglionic mass. This nerve was not spared by the node resection and remained paralysed after surgery. The left phrenic nerve was found to be intact during the surgery and no extrinsic compression was found. The first ENMG showed isolated bilateral diaphragmatic paralysis and complete recovery of the left phrenic nerve was confirmed by ENMG after resection of the neoplastic tissue. Because recovery of the left phrenic nerve has followed curative resection of the MTC, we believe that the left diaphragmatic paralysis was a consequence of a paraneoplastic syndrome. To our knowledge, paraneoplastic diaphragmatic paralysis has only been reported with other types of carcinoma such as breast and renal.[5–8] Involvement of only the phrenic nerve may be explained by an antigenic mechanism or through a neurotransmitter mechanism present only in the phrenic nerve.

We suggest that medullary thyroid carcinoma should be added to the list of aetiologies for paraneoplastic diaphragmatic paralysis. The association of paraneoplastic syndrome with diaphragmatic paralysis has previously been reported in only cases of carcinoma. The mechanism is still unknown. The dual aetiology of compressive and paraneoplastic bilateral phrenic nerve paralysis is original.

Disclosure

None of the authors of this work have any financial conflicts of interest to disclose. All authors had access to the data and a role in writing the manuscript.

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