CASE REPORT

Aggressive thyroid cancer associated with toxic nodular goitre

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Reports of concurrent thyrotoxicosis and thyroid cancer have appeared in the last three decades. While most of the tumours have been clinically inconsequential, it has been suggested that thyroid carcinomas arising in patients with Graves’ disease tend to behave aggressively, while those associated with toxic nodular goitre follow a more benign course. We report a contrary clinical experience with four cases of thyrotoxicosis associated with metastatic thyroid cancer, two of which were fatal. All four patients had toxic nodular goitre. Thyroid eye signs were uniformly absent. Two patients had received 131I therapy: none had another history of irradiation to the head or neck. Antimicrosomal and antithyroglobulin antibodies were absent in all four patients. Thyroid-stimulating immunoglobulin, which was measured in one patient, was also absent. Histopathological examination of the resected thyroid glands revealed two papillary cancers, one mixed anaplastic/papillary and one anaplastic cancer. All four patients had cervical node involvement and one had pulmonary metastases. Both patients with anaplastic carcinoma succumbed to their disease within 6 months; neither of the patients with papillary cancer had disease recurrence after 2 and 4 years, respectively. The experience reported here of aggressive thyroid cancer associated with toxic nodular goitre may represent a coincident occurrence or, alternatively, may represent the early recognition of a change in the natural history of toxic nodular goitre.

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Prior to 1960 it was generally accepted that thyrotoxicosis and thyroid cancer rarely occurred together (1) and it was postulated that thyrotoxicosis might ensure against thyroid malignancy (2). Recent studies have challenged this view, reporting an incidence of thyroid cancer in surgically treated thyrotoxic patients of 2.5–9.0% (3–6). However, the majority of the tumours identified at surgical resection were occult and clinically inconsequential. Where aggressive thyroid carcinoma has occurred in association with thyrotoxicosis, it has been in the setting of Graves’ disease rather than toxic nodular goitre (7). We report four cases of toxic nodular goitre associated with metastatic thyroid cancer, two of which were fatal.

Case 1

A 29-year-old woman presented to another institution in January 1993 with classical features of thyrotoxicosis. Physical examination revealed a diffusely enlarged thyroid gland with no palpable nodules. There was no evidence of exophthalmos. The serum free thyroxine level (FT4) was 73.1 pmol/l (reference range 9.0–20.6), the serum triiodothyronine concentration (T3) was 3.69 nmol/l (reference range 0.8–2.4) and the serum thyrotrophin (TSH) level was < 0.01 mU/l (reference range 0.15–3.2). Antimicrosomal, antithyroglobulin and thyroid-stimulating antibodies were absent. No imaging procedures were performed. Following introduction of carbimazole the patient’s symptoms resolved. FT4 fell to 26.6 pmol/l, T3 fell to 2.9 nmol/l and the TSH level remained suppressed at < 0.05 mU/l. Four months later she developed a 6 × 3 cm mass in the right posterior triangle, which was cystic on ultrasound examination, and was referred to this institution. A technetium scan of the thyroid demonstrated reduced uptake inferiorly in the right lobe. Surgical exploration of the posterior triangle revealed a nodal mass that histologically demonstrated extensive replacement of lymph nodes (Fig. 1) and soft tissue by a metastatic well-differentiated papillary thyroid carcinoma. A total thyroidectomy was performed, at which a 2-cm papillary thyroid carcinoma was identified in the left lobe in addition to a multinodular colloid goitre. The resected thyroid gland showed no evidence of lymphoid infiltration. Postoperatively, suppressive treatment with 0.2 mg of l-thyroxine daily was instituted. This was followed by ablative therapy with 150 mCi of 131I, because of the presence of residual thyroid tissue. The radiotherapist to whom she was referred for ablative 131I therapy subsequently elected to give external radiation to the
cervical nodes. She has no evidence of disease recurrence after 2 years. While the classification of this patient poses some difficulty, given the diffuse nature of the goitre, we feel that the absence of thyroid eye signs and thyroid antibodies and the histopathological findings favour multinodular goitre rather than diffuse toxic goitre.

Case 2
A 72-year-old woman presented in October 1990 with atrial fibrillation and was found to have a 3 x 5 cm nodule in the right lobe of thyroid. Thyroid eye signs were absent. The FT₄ level was 15.9 pmol/l, T₃ was 3.6 nmol/l and TSH was <0.05 mU/l. Ultrasound examination confirmed the presence of a solitary, right-sided nodule. A technetium scan demonstrated a large hot nodule in the right lower lobe with suppression of uptake in the remainder of the thyroid gland. She was treated with carbimazole for 1 year, after which she received 13.5 mCi of ¹³¹I. Thyroid function was monitored closely following ¹³¹I therapy and between 9-12 months later she was noted to be hypothyroid. Replacement with 0.1 mg of l-thyroxine daily was instituted and the TSH value returned to and subsequently remained within the normal range. In April 1993 the patient developed a rapidly enlarging painful mass in the right side of her neck. Ultrasound examination revealed a complex 6-cm mass extending into the right anterior triangle and an isotope scan showed no uptake in the right lobe. Percutaneous needle biopsy of the mass obtained tissue composed of anaplastic thyroid carcinoma with a small focus of differentiated papillary carcinoma (Fig. 2). She received palliative radiotherapy and died from her disease 6 months following diagnosis.

Case 3
A 66-year-old women presented in March 1990 with weight loss and atrial fibrillation. Physical examination revealed a multinodular goitre with a dominant nodule in the right lobe. Thyroid eye signs were absent. Ultrasound examination confirmed the presence of a large nodule in the right lobe and in addition demonstrated two small nodules in the left lobe. Following treatment with carbimazole the FT₄ level fell from 43 to 10.8 pmol/l, T₃ fell from 4.8 to 1.8 nmol/l and TSH...
increased from < 0.05 to 0.12 mU/l. In July 1992 she complained of hoarseness and painful neck swelling and was found to have a 4 × 5 cm fixed mass in the right lobe of the thyroid. The FT$_4$ level was 14.5 pmol/l. T$_3$ was 2.3 nmol/l and TSH was < 0.05 mU/l. An ultrasound scan demonstrated a marked increase in the size of the right lobe compared to the previous examination and a technetium scan showed it to be non-functioning. Percutaneous needle biopsy yielded tissue that was composed of poorly differentiated carcinoma. The patient died 2 months later and at post-mortem examination an anaplastic thyroid carcinoma with pulmonary metastases was diagnosed.

Case 4

A 52-year-old woman presented in 1963 with a toxic multinodular goitre. Thyroid eye signs were absent. Antimicrosomal and antithyroglobulin antibodies were absent. She was treated with 5 mCi of $^{131}$I initially and a further 6 mCi 3 years later for relapse. In 1967 she became hypothyroid and was commenced on 0.1 mg of L-thyroxine daily. Periodic monitoring of thyroid function over the next 20 years revealed normal levels of FT$_4$ and TSH. She remained well until 1988 when she developed pain and swelling on the right side of her neck. On examination the right lobe of the thyroid was hard and enlarged threefold and there was a 2 × 2 cm palpable cervical node. The FT$_4$ level was 10.5 pmol/l and the TSH level was 18.3 mU/l. Ultrasound examination revealed a multinodular goitre predominantly involving the right lobe. Histological examination of a resected lymph node revealed metastatic papillary carcinoma. A total thyroidectomy was performed. A locally invasive 3 cm papillary tumour was identified in the right lobe of the thyroid. Post-operatively a total body $^{131}$I scan demonstrated uptake in the cervical and thoracic regions and external radiation was administered to the affected area. Suppressive treatment with L-thyroxine 0.1 mg was then initiated. The patient enjoyed good health until 4 years later when she was found to have metastatic renal carcinoma to which she succumbed within 3 months.

Discussion

The incidence of thyroid cancer reported in surgically treated thyrotoxic patients is 2.5–9.0% (3–6). The
incidence of clinically detected thyroid cancer in a southern Irish population is approximately 20 per million (8). Because the thyroid glands from thyrotoxic patients undergoing surgery were screened specifically for thyroid cancer, the appropriate control group is found in autopsy subjects whose thyroid glands were also screened for cancer and in whom occult carcinomas were identified in up to 13% cases (9). In the surgical series the majority of tumours associated with toxic nodular goitre were either occult or small, well-differentiated carcinomas with no evidence of local invasion or distant metastases (6, 7, 10). Thus, the previously reported data suggest that the incidence of clinically significant thyroid cancer is no greater in individuals with toxic nodular goitre than in the general population. The four cases of toxic nodular goitre associated with thyroid cancer described here are therefore unusual, in that all had evidence of metastatic spread and two died of their disease within 6 months of diagnosis. These four cases were collected over a 30-year period from a referral population of approximately 0.5 million. With an annual incidence of thyroid cancer in Ireland of 20 per million, one would expect to see approximately 300 cases of thyroid cancer in our institution over that time period. Therefore, the risk of developing thyroid cancer over 30 years is 0.06%. With an annual incidence of thyrotoxicosis of 1/1000 (13) the risk of developing thyrotoxicosis in the same population over the same time period is 3%. Therefore, the risk of developing both thyrotoxicosis and thyroid cancer is 0.0018%. We, however, observed four cases of thyrotoxicosis out of a possible 300 cases of thyroid cancer (1.3%), this is 1000-fold greater than anticipated. Based on these calculations we feel that the occurrence of thyrotoxicosis and thyroid cancer is unlikely to be mere coincidence. However, given the diversity of clinical presentation, it is also unlikely that there is a single causal link common to all four cases.

Possible mechanisms underlying the association of thyrotoxicosis and thyroid cancer include coincidental occurrence (11), autonomous synthesis and excessive secretion of thyroid hormone by well-differentiated thyroid tumours (11), thyroid-stimulating immunoglobulin (TSI) acting as a promoter in the pathogenesis of both thyroid cancer and thyroid hypersecretion (12) or radioactive iodine treatment for thyrotoxicosis triggering malignant change in susceptible thyroid cells (4).

In case 1, it is possible that the thyroid cancer was contributing to the thyrotoxic state, given its hot appearance on isotope scanning, its high degree of differentiation and the short interval between presentation with thyrotoxicosis and the diagnosis of metastatic thyroid cancer. There is increasing evidence that Graves’ disease influences the development and behaviour of thyroid carcinoma (7, 12, 14). However, none of our patients had clinical evidence of Graves’ disease and thyroid autoantibodies were uniformly absent. While TSI was only measured in case 1, it is unlikely to have been present in the other three patients, given the absence of thyroid autoantibodies with which it is almost invariably associated (15). While it is known that TSH may stimulate growth of thyroid cancer in a manner analogous to TSI (16), the transient hyperthyroidism seen in two of our four patients is unlikely to have played a significant role in the evolution of their thyroid cancer. Three large epidemiological studies that have examined the association of radioactive iodine therapy and thyroid cancer, found no increased risk of thyroid malignancy with 131I therapy (17–19). However, it is interesting to note that in case 4, who had received 131I therapy, there was a small focus of differentiated papillary cancer in the anaplastic tumour.

The experience reported here of aggressive thyroid cancer associated with toxic nodular goitre may either represent coincidence or the conditions may be interrelated, although the former appears to be unlikely. This report may represent the recognition of a changing pattern.

References


Table 1. Data on four patients with toxic nodular goitre and thyroid cancer.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age at diagnosis of thyroid cancer (years)</th>
<th>Clinical classification of goitre</th>
<th>Histological appearance</th>
<th>Metastases</th>
<th>History of [131I]</th>
<th>Years between thyrotoxicosis and cancer</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>Case 1</td>
<td>F</td>
<td>29</td>
<td>Diffusely enlarged</td>
<td>Papillary cancer with colloid goitre</td>
<td>Cervical nodes</td>
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<td>0.5</td>
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<td>Case 2</td>
<td>F</td>
<td>72</td>
<td>Solitary nodule</td>
<td>Anaplastic cancer with papillary focus</td>
<td>Cervical nodes</td>
<td>13.5 mCi</td>
<td>3</td>
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<td>Case 3</td>
<td>F</td>
<td>66</td>
<td>Multinodular</td>
<td>Anaplastic cancer</td>
<td>Lung</td>
<td>None</td>
<td>2</td>
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<td>Case 4</td>
<td>F</td>
<td>76</td>
<td>Multinodular</td>
<td>Papillary cancer in multinodular goitre</td>
<td>Cervical nodes</td>
<td>11 mCi</td>
<td>25</td>
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14. Mazzaferrri EL. Thyroid cancer and Graves' disease [editorial]. J Clin Endocrinol Metab 1990;70:826–9

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