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Clinical Record

Rapid thyrotoxicosis in anaplastic thyroid carcinoma

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Abstract

We present the case of a 71-year-old man with anaplastic thyroid cancer. On presentation, his thyroid function was normal, but he subsequently developed sudden, rapid thyrotoxicosis. Thyrotoxicosis in anaplastic thyroid carcinoma is very rare, but in all previously reported cases the patient was thyrotoxic at presentation. Our case is unusual as our patient presented euthyroid, and thyrotoxicosis developed subsequently. We challenge current ideas regarding the biochemical pathophysiology of rapid thyrotoxicosis in anaplastic thyroid carcinoma and provide an alternative explanation.

Key words: Thyroid Neoplasms; Anaplastic Carcinoma; Thyrotoxicosis

Case report

We present the case of a 71-year-old man who presented to our ENT clinic with a one week history of right neck swelling. This was associated with mild hoarseness and dysphagia; there were no airway symptoms.

On the right side, there was a large neck mass measuring 15 × 12 cm which occupied both the anterior and posterior triangles of the neck. On the left side, there was a neck mass measuring 8 × 6 cm. Fibre-optic laryngoscopy revealed distortion of the larynx to the left. There was slight restriction of the glottis, but both vocal folds were mobile.

At presentation, thyroid function tests, measured on an Advia Centaur (Bayer Diagnostics, Newbury, United Kingdom) analyser, revealed a free thyroxine concentration of 24 pmol/l (reference range 9–19 pmol/l), with a thyroid-stimulating hormone (TSH) concentration of 1.2 mIU/l (reference range 0.25–5.0 mIU/L).

A core biopsy of the neck mass was taken, and the sample demonstrated 'features consistent with an undifferentiated carcinoma and in keeping with a primary tumour of the thyroid gland'.

Three days later, thyroid function tests revealed a raised free thyroxine concentration of 45 pmol/l and a suppressed TSH of <0.1 mIU/L. As the thyroid function test results seemed at variance with the clinical picture, these results were then confirmed using an alternative assay technique (AutoDelfia; Perkin-Elmer, Wellesley, USA) in another laboratory. As routine free thyroxine assays have been subject to criticism regarding their ability to truly measure free hormone, free thyroxine was also measured by equilibrium dialysis, which remains a 'gold standard' technique. The free thyroxine concentration, measured in this way, was 118 pmol/l (reference range 10–30 pmol/l). A thyroid receptor antibody test (Brahms; Brahms Diagnostica GMBH, Berlin, Germany) revealed a thyroid receptor antibody concentration of 0.8 IU/l; this was within normal limits (reference range 0–1 IU/L) and therefore did not suggest the presence of Graves' disease.

A computed tomography (CT) scan at presentation revealed a large neck mass extending into the upper mediastinum, with encasement of vascular and bony structures. No thyroid tissue was visible separate from the mass. The appearances represented very extensive, locally infiltrative thyroid malignancy. Associated extensive bilateral cervical lymphadenopathy was also noted.

Treatment was palliative, and, sadly, the patient died a month after presentation.

Discussion

Anaplastic thyroid carcinoma has been reported to represent between 1.6 and 7.5 per cent of all thyroid malignancies.[1,2] Incidences vary depending on geographical location, but generally a decline in frequency has been noted over the last 40 years. The association between anaplastic thyroid carcinoma and a thyrotoxic state is very rare. To date, eight other cases of this association have been reported.[3–10] These cases are summarised in Table I.

Thyrotoxicosis has been reported with other thyroid malignancies such as lymphoma[4] and metastatic breast carcinoma,[5] and from other non-thyroid locations, as with gonadal and trophoblastic tumours.[6,7] Thyrotoxicosis in these situations has been described as 'malignant pseudothyroiditis', especially when the clinical syndrome mimics subacute or chronic thyroiditis.[8]

In previously reported cases of thyrotoxicosis in anaplastic thyroid carcinoma, the authors excluded Graves' disease, autonomously functioning thyroid nodules and metastatic carcinoma to the thyroid gland, by histological, biochemical and radiological means; this was also true of our case.

The current theory is that acute thyrotoxicosis is the result of rapid leakage of thyroid hormone from thyrocytes. It is this concept that we find hard to support, for two reasons. Firstly, if this were a natural consequence of infiltrative anaplastic disease, it would seem peculiar that only eight cases have been reported in the world literature to date. Secondly, thyrotoxicosis in our patient developed after he presented euthyroid, and his CT scan showed no demonstrable thyroid tissue to 'leak' thyroid hormone. Historically, there has been interest in thyroiditis as a cause of thyrotoxicosis. Some authors have proposed that thyroiditis associated with thyroid carcinoma is secondary to the neoplasm and in most cases represents the reaction induced by an antigen from the neoplasm itself.[9,10]

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TABLE I

PREVIOUS CASES OF THYROTOXICOSIS ASSOCIATED WITH ANAPLASTIC THYROID CARCINOMA

Author	Year	Age (years)	Sex	Metastasis?	Graves'?	Toxic nodule(s)?	Thyroid status on presentation
Mangla *et al.*	1967	46	M	Yes	Unknown	Yes	Thyrotoxic
Oppenheim *et al.*	1983	48	M	No	No	No	Thyrotoxic
Murakami *et al.*	1989	55	M	Unknown	No	No	Thyrotoxic
Alagol *et al.*	1999	55	F	Yes	No	No	Thyrotoxic
Basaria *et al.*	2002	51	M	Yes	Unknown	Unknown	Thyrotoxic
Villa *et al.*	2004	76	F	Yes	No	No	Thyrotoxic
Heymann *et al.*	2005	74	M	No	No	No	Thyrotoxic
Kumar *et al.*	2005	65	M	Yes	No	No	Thyrotoxic
Present case	2007	72	M	Yes	No	No	Euthyroid

TABLE II

EXPLANATIONS FOR THYROTOXICOSIS IN ANAPLASTIC THYROID CARCINOMA

Graves' disease[17]
Autonomous thyroid nodules[18]
Metastatic carcinoma to the thyroid gland[11,12]
Silent thyroiditis[19]
Subacute thyroiditis[20]
Rapid tissue destruction by the primary tumour[4]
Widespread, thyrotrophin-sensitive metastasis[20]

Autoimmune thyroiditis has also been implicated, but, once again, these theories rely on the presence of viable thyroid tissue.[6]

Insular carcinoma has previously been considered a variant of anaplastic thyroid carcinoma; it has also been referred to as a solid variant of follicular carcinoma or a poorly differentiated type of papillary carcinoma.[11] A unique case has demonstrated autonomous production of thyroid hormone, with clinical thyrotoxicosis, due to an active mutation of the thyrotrophin receptor.[12] A similar explanation has been given in a case of metastatic follicular thyroid cancer.[13] A possible explanation for why some metastatic follicular thyroid carcinomas are functional and cause thyrotoxicosis while others are non-functional may be the presence of thyroid-stimulating immunoglobulins.[14] Some investigators believe that thyroid-stimulating immunoglobulins stimulate the TSH receptors on metastatic tissue and activate adenylate cyclase, causing growth of tumour tissue and stimulation and secretion of thyroid hormone production, thus resulting in hyperthyroidism.[15,16] Explanations for thyrotoxicosis in anaplastic thyroid carcinoma are listed in Table II.

Russo *et al.* documented the case of an activating TSH receptor gene mutation in a hyperfunctioning, poorly differentiated thyroid carcinoma and its lymph node metastasis.[12] A base substitution at codon 633 of the TSH receptor gene was identified. Mutations at this codon have been reported to constitutively activate the cyclic adenosine monophosphate cascade.

- **Thyrotoxicosis in anaplastic thyroid carcinoma is very rare**
- **A number of explanations have been given to explain this phenomenon in previous cases**
- **The most popular theory to date is that of rapid tissue destruction and thyrocyte leakage**
- **The authors propose that thyrotoxicosis in anaplastic thyroid carcinoma may be due to hyperfunctioning metastasic tumour**

On reviewing the current hypotheses surrounding thyrotoxicosis with anaplastic thyroid carcinoma, none are compatible with the clinical, radiological and biochemical findings of the present case. Our case did not undergo TSH receptor gene analysis. However, in the absence of any other logical explanation for this phenomenon, we propose that thyrotoxicosis in anaplastic thyroid carcinoma may be due to an alternative mechanism, and in cases of poorly differentiated carcinoma, in which gene mutations are common, thyrotoxicosis is likely to be produced from hyperfunctioning metastases.

Conclusion

There have been eight previously reported cases of thyrotoxicosis due to anaplastic thyroid cancer. In these cases, the thyrotoxicosis was thought to be due to the rapid destruction of thyroid tissue and subsequent release of thyroid hormone. Due to the way our case presented, and after careful consideration of the radiological findings, we feel that the current hypothesis must be challenged, and we propose that this phenomenon may be due to an alternative mechanism.

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