Melanin-producing medullary carcinoma of the thyroid gland

A case report

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Summary

A case of melanin-producing medullary carcinoma of the thyroid gland is reported. The histological characteristics of the tumour were typical of medullary carcinoma, immunohistochemical testing for calcitonin was positive, and neurosecretory granules were found to be present on ultrastructural examination. In addition the tumour was producing melanin and melanosomes were identified in the same cells which contained neurosecretory granules, suggesting that the tumour arose from a common precursor cell of neural crest origin capable of producing both calcitonin and melanin.

Thyroid medullary carcinoma was categorized as a distinct type of thyroid carcinoma by Hazard in 1959. The tumour often produces an amyloid stroma and the cells produce calcitonin, which is normally secreted by the parafollicular C cells from which the tumour is derived. It is also known to produce a number of ectopic substances such as serotonin, kallikrein and prostaglandins, adrenocorticotropic hormone (ACTH), histaminase, carcino-embryonic antigen, corticotrophin-releasing factor with prolactin production-stimulating activity, somatostatin, substance P and nerve growth factor. It is also known to produce a single report of a case of medullary carcinoma which was not associated with any other endocrine disturbance or diarrhoea was elicited, and both the past and family histories were non-contributory. On examination a smooth, non-tender thyromegaly was found, the right lobe measuring 5 x 10 cm and the left lobe 3 x 5 cm. There were no enlarged lymph nodes and no bruit was heard over the thyroid gland. General examination was unremarkable and salient negative features included normal cardiovascular and respiratory systems and no clinical evidence of abnormal thyroid or parathyroid activity, Cushing's syndrome, subcutaneous nodules or neuromas.

Results of thyroid function tests were normal and thyroid antibodies were not detected. A thyroid scintiscan showed a 'cold' zone within the right thyroid lobe with normal uptake of the isotope throughout the remainder of the gland. Ultrasonography demonstrated a homogeneous and solid gland, with no evidence of a focal lesion within the right thyroid lobe. Results of all other diagnostic tests were within normal limits; serum calcium, phosphate and glucose levels were normal, urinary vanillylmandelic acid and 17-ketosteroid values were within normal limits, and liver and bone scans revealed no focal lesions. Serum calcitonin and serotonin assays were unfortunately not carried out pre-operatively.

A right total and left subtotal thyroidectomy was performed. Postoperative recovery was uncomplicated and the patient's voice returned to normal shortly after surgery. Six months postoperatively she was still asymptomatic.

Material and methods

For light microscopic examination, formalin-fixed paraffin-embedded blocks of tumour were sectioned and stained with haematoxylin and eosin, Congo red and crystal violet, Masson-Fontana stain for melanin, Grimelius stain for argyrophilic granules and reticulin stain. Immunoperoxidase staining was performed using the peroxidase-antiperoxidase method for calcitonin, carcino-embryonic antigen, somatostatin, vaso-intestinal polypeptide (VIP) and muramidase. One-millimetre blocks of formalin-fixed tumour were re-fixed in gluteraldehyde, post-fixed in 1% osmium tetroxide, rinsed in Millonig's buffer, pH 7.4, dehydrated in graded ethanols, impregnated with propylene oxide and embedded in araldite-epon mixture. Sections were stained with uranyl acetate and lead citrate.

Pathological examination

The mass was firm and partially encapsulated, and measured 8 cm in diameter. The cut surface showed small areas of necrosis, and the colour varied from grey-white to brownish-black.

Microscopic examination revealed a neoplasm surrounded by normal thyroid tissue. The majority of the neoplastic cells were lying in sheets and trabeculae, some areas having an organoid...
pattern, with a delicate fibrovascular stroma. Abundant melanin pigmentation was present within many of the tumour cells (Fig. 1). The tumour cells were rounded, oval or spindle-shaped and contained abundant eosinophilic granular cytoplasm; their borders were indistinct. The nuclei showed variable pleomorphism and mitotic activity (Fig. 2). In most areas mitoses were sparse, but large amounts of morphologically normal mitoses were seen in foci. Extracellular amyloid was present in some areas but was not widespread (Fig. 3). Capsular invasion was present in focal areas, but no definite vascular invasion was observed. The surrounding thyroid gland showed no evidence of C-cell hyperplasia, but contained a small neoplastic focus.

 Immunoperoxidase staining showed diffuse positivity for calcitonin and carcino-embryonic antigen (Fig. 4) but did not reveal the presence of somatostatin, ACTH, VIP or muramidase. Grimelius staining revealed abundant argyrophilic granules.

 Electron microscopy showed numerous membrane-bound neurosecretory granules up to 400 nm in diameter. The larger pleomorphic cells contained neurosecretory granules, and some also had compound mature and immature melanosomes within the cytoplasm which varied in density and quality and which consisted of lamellar ellipsoid structures, confirming the light microscopic findings (Figs 5 and 6).

Discussion

Medullary carcinoma is characteristically composed of oval to spindle-shaped eosinophilic cells arranged in an organoid, diffuse or trabecular fashion. Few mitoses are seen, the stroma contains amyloid, and focal areas of calcification are often evident. The lesion originates from C cells, which produce calcitonin, and belongs to the APUD group of tumours. Between 6% and 10% of thyroid neoplasms are medullary
carcinomas.13 They may be familial or sporadic and may be associated with a number of syndromes, particularly multiple endocrine neoplasia (MEN) types 2A and 2B.17 Although a variety of morphological and anaplastic18 variants have been described and although a number of ectopic hormone substances may be produced by the tumour, this is only the second reported case of melanin-producing medullary carcinoma. In the case described by Marcus et al.11 there was evidence only of scanty melanin production by bland dendritic cells having no neurosecretory granules, but in our case cells containing both neurosecretory granules and compound melanosomes were present. The melanin was abundant and present in all areas of the neoplasm.

We agree that the tumour may arise by polyclonal evolution of a common neoplastic precursor cell, able to produce both melanin and calcitonin, by evolution of a precursor cell of the neural crest, having melanocytic and C-cell characteristics within a single cell, or by a mixed phenotypic expression in an oncogenic setting. It is well known that a number of other neural and endocrine-related tumours may produce melanin, such as schwannomas,19 adrenal tumours,20 ganglioneuroblastoma,21 thymic and bronchial carcinoids,22-24 and others. Whether or not the production of melanin in this tumour and the degree of pleomorphism will influence the biological behaviour remains to be seen.

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REFERENCES