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Paraganglioma: an unusual tumour of the parathyroid gland

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Abstract
A case of paraganglioma arising within a parathyroid gland is reported. The lesion was an incidental finding in a block dissection of neck performed for squamous carcinoma of the pharynx. A well-circumscribed lesion, exhibiting the characteristic pathological features of a paraganglioma, was embedded within the right inferior parathyroid gland. Due to its location, the chief histological differential diagnosis was an unusual variant of parathyroid adenoma. Immunohistochemistry and electron microscopy assisted in reaching a diagnosis. This, as far as we are aware, is the first reported case of a paraganglioma of the parathyroid gland.

Key words: Paraganglioma; Parathyroid gland; Immunohistochemistry; Microscopy, electron

Introduction

Paraganglioma is a relatively rare, but well described, tumour that originates in the extra-adrenal paraganglia of the autonomic nervous system. These extra-adrenal paraganglia are widely dispersed collections of specialized neural crest cells that include the carotid and aortic bodies, the vagal body and small groups of cells associated with the thoracic, intra-abdominal and retroperitoneal ganglia (Enzinger and Weiss, 1988). Occasional cases of paraganglioma arising as a primary within the thyroid gland have been reported (Haegert *et al.*, 1974; Kay *et al.*, 1975; Buss *et al.*, 1980; Mitsudo *et al.*, 1987; Brownlee and Shockley, 1992) but, as far as we are aware, origin within a parathyroid gland has not been described. We report a case of paraganglioma arising within a parathyroid gland. Due to its location, the chief histological differential diagnosis was an unusual variant of parathyroid adenoma. Immuno-histochemistry and electron microscopy examination assisted in making the distinction.

Case report

A 66-year-old man, a heavy smoker, underwent a left hemilaryngectomy and block dissection of neck in 1987 for biopsy-proven squamous cell carcinoma of the left vocal cord. The left lobe of thyroid gland was removed. Histology confirmed a squamous cell carcinoma of the larynx with no histological abnormality of the thyroid gland. The left parathyroid glands were not identified histologically.

In March 1995 he was investigated for progressive dysphagia and weight loss. Examination revealed a mass in the posterior pharyngeal wall and hypopharynx, biopsy of which confirmed squamous cell carcinoma. A palpable mass was present in the neck in the region of the right lobe of thyroid. Clinically this was felt to be a thyroid nodule. Fine needle aspiration was not performed. He underwent laryngo-pharyngo-oesophagectomy with removal of the right lobe of the thyroid gland. Pre-operative electrolyte measurements, including serum calcium, were within the normal range.

Pathological findings

The surgical specimen comprised a laryngo-pharyngo-oesophagectomy together with the right lobe of the thyroid gland. A large indurated mass was present in the posterior pharyngeal wall and hypopharynx, histology of which confirmed squamous cell carcinoma. No metastatic carcinoma was present in any of several lymph nodes identified. The thyroid gland was extensively sampled and no histological abnormality was present.

A well-circumscribed 2.5 cm diameter, red-brown coloured lesion was present at the inferior pole of the right thyroid lobe. Histology showed this to be surrounded by an incomplete attentuated fibrous capsule (Figure 1a). A rim of compressed normal parathyroid tissue was present at one edge. The lesion was composed of polygonal epithelioid cells, largely arranged in small nests imparting a zelballen pattern (Figure 1b). Between cell nests the stroma was extremely vascular with numerous dilated, thin-walled capillary channels. Focally the stroma consisted of acellular eosinophilic hyalinized material which stained negatively with Congo-red. On high power examination, polygonal cells contained round to oval nuclei with abundant clear or granular eosinophilic cytoplasm. Nuclei were characteristically vesicular, but focally hyperchromatic. Occasional multinucleate giant cells were present. There were only scattered mitotic figures, the mitotic count being less than one per 10 high power fields. In areas with a typical zelballen appearance, spindle-shaped cells were arranged around the periphery

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FIG. 1a

Well-circumscribed, encapsulated lesion in which islands of normal parathyroid tissue (arrows) are embedded within tumour. (H & E; × 10).

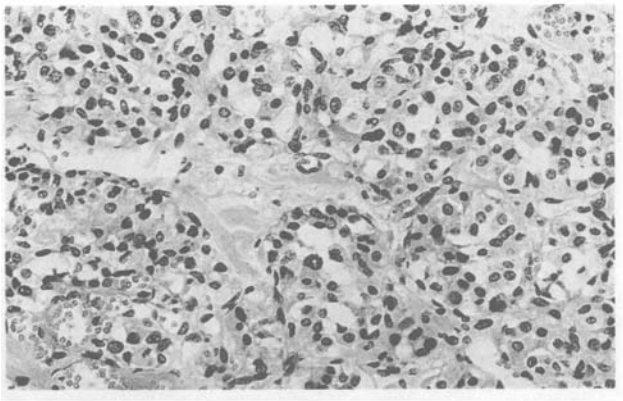

FIG. 1b

High power view showing tumour cells arranged in groups creating a zelballen appearance. (H & E; × 40).

of cell nests. Areas of necrosis were not seen and there was no evidence of vascular invasion by tumour. Focally, especially around the periphery but also within the centre of the tumour, parathyroid tissue consisting of normal parathyroid chief cells was present.

Immunohistochemical staining of tissue sections was performed using a standard streptavidin-biotin peroxidase method. Antibodies employed were chromogranin A (monoclonal, Dako), protein gene product 9.5 (PGP 9.5) (monoclonal, Ultraclone), neurone-specific enolase (NSE) (monoclonal, IncStar), calcitonin (monoclonal, Signet), CAM 5.2 (monoclonal, Becton Dickinson), S-100 protein (monoclonal, Diagnostic Products Ltd.), carcinoembryonic antigen (CEA) (monoclonal, Dako), and factor VIII-related antigen (monoclonal, Signet).

Tumour cells exhibited strongly positive immunohistochemical staining with PGP 9.5 and NSE and were weakly positive with chromogranin A. Parathyroid tissue, around the periphery and within the tumour, was weakly positive with chromogranin A and negative with PGP 9.5 and NSE. There was positive immunohistochemical staining with S-100 protein of spindle-shaped cells at the periphery of cell nests but no staining of polygonal cells or of parathyroid tissue. With CAM 5.2 there was strongly positive staining of parathyroid tissue, but no staining of tumour cells. All cell types were negative with calcitonin and CEA. Factor VIII-related antigen highlighted the stromal vascularity but there was no staining of other cell types.

Specimens of formalin-fixed tissue were processed routinely for electron microscopy. Ultrastructural examination showed groups of cells surrounded by basal lamina material. The principal cell type was polygonal with a round nucleus and abundant cytoplasm containing a range of cell organelles. These cells contained varying numbers of small dense-core neuroendocrine granules, 100–150 nm in diameter (Figure 2). Adjacent cells were joined by well-formed adhesion specializations. A second cell type (corresponding to the spindle-shaped cells seen on light microscopy) was present around the periphery of cell groups. These cells contained elongated tapering cell processes and were devoid of cytoplasmic dense-core granules.

Discussion

The paraganglia are dispersed collections of specialized cells that arise in association with autonomic ganglia throughout the body and are derived from the neural crest. They include the adrenal medulla, chemoreceptors (e.g. carotid and aortic bodies), the vagal body and groups of cells that are associated with the thoracic, intra-abdominal and retroperitoneal ganglia.

Most paraganglia situated in the region of the head and neck are composed of two cell types. Round or polygonal cells (type 1 or chief cells) form nests which are surrounded by delicate spindle-shaped cells (type 2 or sustentacular cells) creating a nest-like or zelballen appearance. Chief cells are neurosecretory in type while sustentacular cells have a presumed supportive function and are of Schwann cell derivation.

The nomenclature of paragangliomas (tumours arising from paraganglia) is confusing but current terminology is to designate tumours arising from paraganglia within the adrenal medulla as phaeochromocytoma while extra-adrenal tumours are designated paraganglioma and named according to their anatomical site (Glenner and Grimley, 1974). The most common tumours within the latter group are the carotid body paraganglioma (chemodectoma, carotid body tumour), jugulotympanic paraganglioma (glomus jugulare tumour), vagal paraganglioma (vagal body tumour), mediastinal paraganglioma (aortic body tumour) and retroperitoneal paraganglioma. However, paragangliomas have been described in many diverse organs including larynx, orbit, nasopharynx, urinary bladder, gallbladder, duodenum, kidney and heart. Generally, paragangliomas show a close morphological resemblance to normal paraganglia, being composed of a mixture of chief cells and sustentacular cells creating a zelballen appearance.

As stated earlier, occasional cases of paraganglioma arising primarily within the thyroid gland have been described (Haegert *et al.*, 1974; Kay *et al.*, 1975; Buss *et al.*, 1980; Mitsudo *et al.*, 1987; Brownlee and Shockley, 1992). One of these behaved in a malignant fashion (Mitsudo *et al.*, 1987), and another was associated with bilateral carotid body paragangliomas (Haegert *et al*, 1974). The probable source of such tumours is small paraganglia located in, or immediately beneath, the thyroid capsule (Zak and Lawson, 1972). As far as we are aware, paraganglioma arising primarily within a parathyroid gland has not been described previously. A single report of parathyroid tissue within a paraganglion in the neck (Michal, 1993) was interpreted as ectopic parathyroid tissue within a neck paraganglion.

Although the histological features in the present case were characteristic of paraganglioma, a number of alternative diagnoses were considered due to the unusual site. Immunohistochemistry and electron microscopy were of value in reaching a definitive conclusion. The main alternative diagnosis considered was an unusual histological variant of parathyroid adenoma. Positive immunohisto-

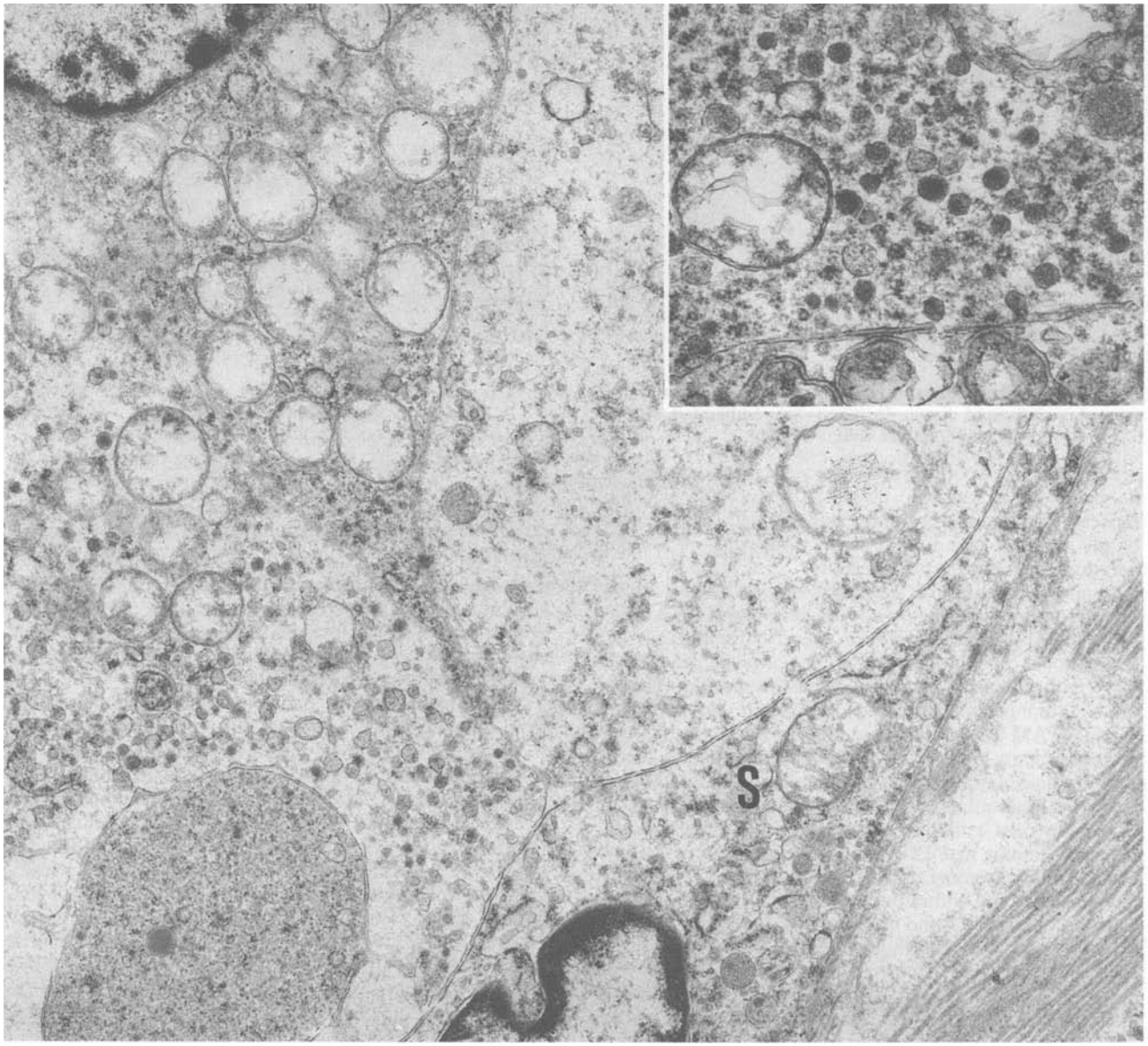

FIG. 2

Electron micrograph showing tumour cell containing small cytoplasmic granules. The cell process of a sustentacular cell is also present (S) × 16 000 (Insert – high power view of dense-core neuroendocrine granules × 30 000).

chemical staining of tumour cells for the neuroendocrine markers PGP 9.5 and NSE together with negative staining with the cytokeratin epithelial marker CAM 5.2 was consistent with a paraganglioma. Residual parathyroid tissue exhibited a converse pattern of staining, cells being positive with CAM 5.2 but negative with PGP 9.5 and NSE. A potential source of confusion was positive staining of tumour cells, as well as residual parathyroid tissue, with the neuroendocrine marker chromogranin A. However, positive staining with chromogranin A has been described in normal and pathological parathyroid tissue (Wilson and Lloyd, 1984) and thus this antibody is of no value in the distinction of paraganglioma from parathyroid adenoma. Immunohistochemistry for S-100 protein was of value, highlighting a second or sustentacular population of spindle-shaped cells, located at the periphery of cell nests. Positive staining with S-100 protein would not be expected in a parathyroid adenoma. Electron microscopy assisted in confirming a diagnosis of paraganglioma with two cell types identified. The principal cell type contained cytoplasmic dense-core neuroendocrine granules and a second, non-granulated population of spindle-shaped cells located at the periphery of cell nests was ultrastructurally consistent with sustentacular cells. In addition to the immunohistochemical and ultrastructural evidence, normal pre-operative serum calcium measurements would also mitigate against a diagnosis of parathyroid adenoma.

A third alternative diagnosis considered on morphological grounds was a medullary carcinoma of the thyroid gland which had secondarily invaded the adjacent parathyroid. This possibility was excluded due to negative staining of tumour cells with calcitonin and CEA, both of which are expected to be positive in medullary carcinoma. Positive staining with S-100 protein would also be inconsistent with medullary carcinoma. Stromal amyloid is commonly found in medullary carcinoma and negative staining of eosinophilic stromal material for Congo-red helped to exclude this diagnosis in the present case. Moreover, no lesion was identified within the thyroid gland and the location of a well-circumscribed tumour within the parathyroid without extraglandular extension would rule against tumour invasion from the adjacent thyroid.

The majority of paragangliomas of the head and neck region behave in a benign fashion but a small proportion

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exhibit malignant behaviour, as indicated by the development of metastasis. The incidence of metastasis has been estimated at six per cent to nine per cent (Lack *et al.*, 1977; Lack *et al.*, 1979). In general, as with many neuroendocrine tumours, it is difficult or impossible to predict potentially metastasizing tumours on morphological grounds alone because many are virtually devoid of histological features suggestive of malignancy. It has been suggested that the presence of large numbers of sustentacular cells, as demonstrated by S-100 protein positivity, is indicative of a benign tumour with little propensity for metastasis, since in malignant tumours the sustentacular cell population may be lost (Achilles *et al.*, 1991). In the present case, sustentacular cells were easily identified, being present in substantial numbers.

In summary, we report a case of a paraganglioma arising primarily within a parathyroid gland. This, as far as we are aware, is the first case described in the literature. The likely source of the tumour is a small paraganglion located in the region of the thyroid capsule.

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