

CASE REPORT

Extra-adrenal paraganglioma: presentation in three uncommon locations

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Abstract

Extra-adrenal paragangliomata are uncommon entities. They can be classified into four basic groups according to their anatomical sites, i.e. branchiomeric, intravagal, aorticosympathetic and visceral autonomic. Similar tumours may arise in sites away from the usual distribution of the sympathetic and parasympathetic ganglia, e.g. orbit, nose, small intestine and even in the pancreas. We report three instructive cases of extra-adrenal paraganglioma which were found in unusual sites such as urinary bladder, thyroid gland and on the wall of the inferior vena cava.

Keywords: extra-adrenal paraganglioma, urinary bladder, thyroid gland, inferior vena cava

INTRODUCTION

Extra-adrenal paragangliomata are uncommon entities. They can be classified into four basic groups according to their anatomical sites, i.e. branchiomeric (head and neck), intravagal, aorticosympathetic and visceral autonomic.¹ The two most frequent sites of these tumours are the jugulotympanic and carotid body areas (branchiomeric), followed by vagal and aortic lesions.² Similar tumours may arise in sites away from the usual distribution of the sympathetic and parasympathetic ganglia, e.g. orbit, cauda equine, nasal cavity, nasopharynx, small intestine and even in the pancreas.³

We report three cases of extra-adrenal paragangliomata which were found in unusual sites such as urinary bladder, thyroid gland and on the wall of the inferior vena cava. Recognition and awareness of such paraganglioma are important for the surgical pathologist who has to make an accurate diagnosis so that proper treatment may be instituted.

CASE HISTORIES

Case 1

A 40-year-old Chinese woman presented with recurrent multinodular goitre. Ultrasound showed enlarged right and left thyroid lobes with a separate nodule in the right upper pole

of the thyroid gland. She gave a history of having had right hemithyroidectomy seven years ago. Subsequently a total thyroidectomy was performed. Histology of the left lobe of the thyroid gland showed multiple benign colloid nodules. The remnant right thyroid lobe showed an intrathyroid nodule which measured 2.5cm across in the largest dimension and weighed 15gms. It was fleshy, vascular, and surrounded by a thin fibrous capsule. The tumour cells were uniform, bland and polygonal, with dense nuclei and abundant granular cytoplasm, and were arranged in clusters segregated by haemorrhagic fibrovascular tissue (figure 1). There was no discernible necrosis, mitosis or vascular invasion. The adjacent thyroid parenchyma showed colloid-filled benign thyroid follicles of varying sizes.

Case 2

A 43-year-old Indian man was found to have an inferior vena cava tumour which was located just below the junction of the renal vein. Pre-operative radiological images showed that the kidney was separate from the tumour. At laparotomy, the tumour was found to be attached to the wall of the inferior vena cava, just below the junction of the renal vein. The tumour was completely excised. Grossly, the tumour was brownish, focally encapsulated, measured 6cm diameter and weighed 50gms. Cut sections showed a dark

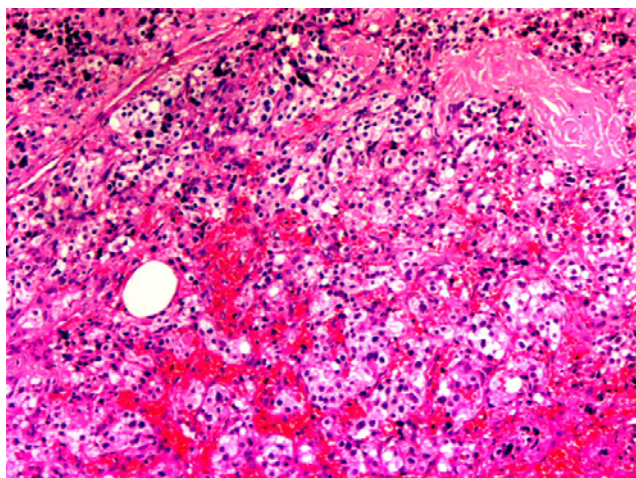


FIG. 1: Intrathyroidal paraganglioma comprising nests of chief cells. Adjacent thyroid follicles are not visible in this view (H&E x100)

brownish, lobulated and vascular tumour, with central fibrosis (figure 2). Microscopy revealed nests of large uniform polygonal cells with clear cytoplasm. The nuclei were hyperchromatic and focally pleomorphic. An occasional giant nucleus and multinucleated tumour cells was present. No mitoses or vascular involvement was detected. The capsule, as well as the cauterised margin, was invaded by tumour cells in areas. There was hardly any necrosis

Immunocytochemical stains done on the tumours in Cases 1 & 2 showed the tumour cells to be positive for chromogranin (figure 3) as well as synaptophysin. S100 antigen-positive cells

were present between the tumour cell clusters (figure 4). At the time of writing, both these patients were well and showed no evidence of tumour recurrence.

Case 3

A 25-year-old Chinese man presented with painless haematuria. Cystoscopy showed a solid tumour in the lateral wall of the urinary bladder. It was removed piecemeal. Gross appearance showed fragments of brownish haemorrhagic tissue, measuring 3 cm in aggregate. Histology revealed a haemorrhagic tumour composed of nests of relatively uniform

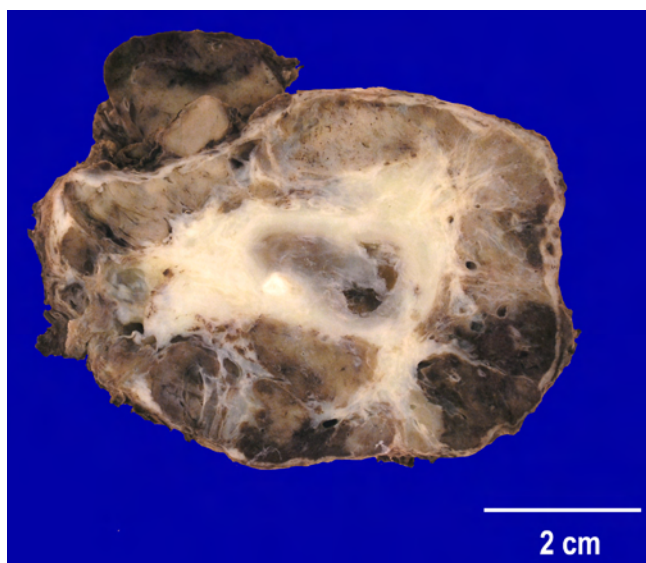


FIG. 2: Inferior vena cava paraganglioma with dark brownish colour, lobulated, vascular appearance and central fibrosis.

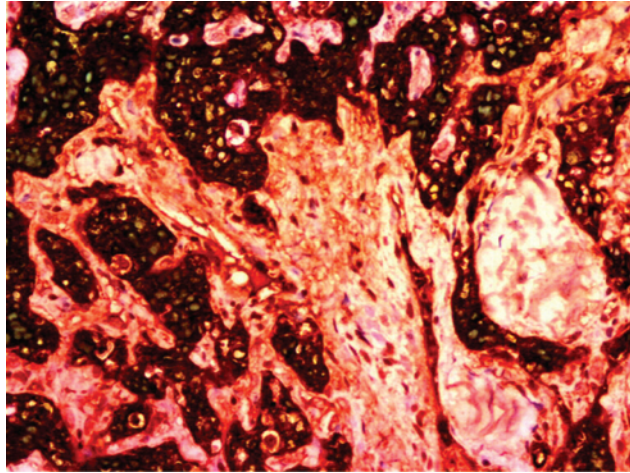


FIG. 3: Intrathyroidal paraganglioma strongly expressing chromogranin (chromogranin A x200)

round to polygonal tumour cells, with moderate nuclear pleomorphism, occasional mitoses (one to two mitotic figures per high power field in some areas) and abundant eosinophilic granular cytoplasm. This tumour had invaded into the urinary bladder submucosa and muscle wall. There was no discernible capsule surrounding the fragments of this tumour. Focal necrosis was evident. There was no obvious vascular invasion. The tumour cells in this case expressed vimentin and synaptophysin. At the time of writing, we were informed that this patient had gone to China and was lost to further follow-up.

DISCUSSION

A paraganglioma is essentially an extra-adrenal pheochromocytoma.³ When these tumours arise in the adrenal medulla, it is

called a pheochromocytoma. However, when paraganglioma-like tumours outside the adrenal medulla demonstrate chromaffin reaction (dusky colour change which occurs when tumour tissue is immersed in a solution of chromate salts or a weak oxidising agent) and clinical evidence of epinephrine and/or norepinephrine secretion, the tumour is preferentially called an extra-adrenal pheochromocytoma rather than a paraganglioma.⁴ A chemodectoma, on the other hand, refers to a paraganglioma arising from a paraganglia with chemoreceptor function. A chemodectoma is therefore used only when a paraganglioma originates from the carotid and aortic bodies.

Therefore, the histomorphology of a paraganglioma and a pheochromocytoma are virtually indistinguishable. Grossly, a

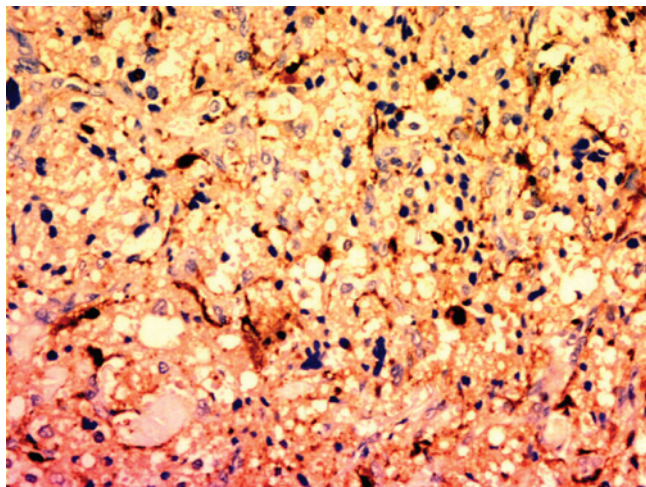


FIG. 4: Intrathyroidal paraganglioma with sustentacular cells expressing S100 antigen (S100 antigen x200)

paraganglioma is a solid tumour which may be fully or partially encapsulated. The cut surface may appear pale yellow to tan to dark red. The colour may be homogeneous or variegated, the latter due to foci of haemorrhage, fibrosis and degeneration. The size of these tumours is variable, with dimensions ranging from several millimetres to a mass as large as 22cm. An example of such large paraganglioma was a rare ovarian paraganglioma reported by McCluggage and Young.⁵

Microscopically, these tumours are composed of uniform to highly pleomorphic, even bizarre, neoplastic chief cells arranged in well-defined "Zellballen" nests. The chief cells are often cuboidal and have abundant granular cytoplasm. In some cases, intracytoplasmic brownish pigments have been noted. As with most endocrine tumours, pleomorphism and vascular invasion do not necessarily indicate malignant behaviour. Mitotic activity, however, is uncommon and frequent mitoses are usually associated with a malignant nature. The intervening stroma is frequently highly vascularised and contains a second cell population, the sustentacular cells. Occasionally, the stroma may be hyalinised and may even overwhelm the tumour cell clusters.^{3,4,6}

Immunohistochemically, the chief cells express common neuroendocrine markers, e.g. chromogranin and synaptophysin, whereas the sustentacular cells are positive for S100 antigen and glial fibrillary acidic protein (GFAP).³

Primary intrathyroidal paragangliomas are rare. A Medline search revealed twelve reported cases of such tumours.^{7, 8, 9, 10, 11} These tumours present serious difficulties in terms of diagnosis and the differential diagnoses that were entertained in these cases included medullary carcinoma, carcinoid tumour, intrathyroidal parathyroid adenoma trabecular hyalinising adenoma and metastatic neuroendocrine tumour. Immunohistochemistry will usually identify neoplasms of thyroid origin as these tumours will express calcitonin, thyroglobulin, thyroid transcription factor (TTF) -1 and carcinoembryonic antigen (CEA).^{10, 11}

A retroperitoneal paraganglioma may arise anywhere along the paravertebral chain. Even so, a Medline search revealed that most reported cases of such tumours are actually bona fide pheochromocytomas. The actual number of true paragangliomas which directly involved the inferior vena cava is approximately four.^{12,13,14,15} This number included a paediatric case where the patient was a 10-year-old boy.¹⁵ Paragangliomas

in this site pose serious problems in terms of management as surgery may require *en bloc* resection of the inferior vena cava and complex reconstruction procedures. In our patient (Case 2), the tumour was easily resected as it did not infiltrate the major vessel's wall.

Paraganglioma in the urinary bladder, while more frequently seen compared to primary intrathyroid tumours, are also relatively uncommon. In the United States of America, mesenchymal tumours of the urinary bladder made up approximately 5% of primary bladder neoplasms. Of these, the most common were rhabdomyosarcoma (especially in children) and leiomyosarcoma (in adults). Rarer are tumours such as lymphoma, leiomyoma, solitary fibrous tumour and paraganglioma.¹⁶ Patients with urinary bladder paraganglioma may present with suspicious symptoms like haematuria, post-micturition headache, palpitation and cold sweats.¹⁷ Some patients do not exhibit any symptoms at all and the tumour is found incidentally while investigating for other diseases.¹⁸ Case 3 presented with only painless haematuria. While the two previous paragangliomas were deemed benign, this tumour was suspected to have a more sinister nature as there were increased mitoses, necrosis and widespread local invasion. However, it is well-known that paragangliomas of the urinary bladder may exhibit increased cytological atypia, mitosis and even local invasion, without actually being malignant.⁴ Two cases of malignant urinary bladder paraganglioma have been reported.^{19, 20}

Paraganglioma may arise in any part of the body and the histomorphology may be confused with many other neoplasms, both benign and malignant. Complicating matters is the propensity of endocrine tumours to behave in a benign fashion despite a bizarre cytology and invasion. A careful review of the histology, with the help of immunostains where applicable and aided by careful clinical history will usually lead to the correct diagnosis. Recognition and awareness of such paraganglioma are important for the surgical pathologist who has to make an accurate diagnosis so that proper treatment may be instituted.

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