

Familial malignant retroperitoneal paraganglioma

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Summary: Paragangliomas are neuroendocrine tumours and those occurring in the head and neck have well recognized familial association. Retroperitoneal paragangliomas are uncommon and we present two cases of familial malignant retroperitoneal paraganglioma. Review of the literature revealed marked differences in the incidence and malignant potential of familial and non-familial paraganglioma. In contrast to the cases reported here, familial tumours are generally benign, though they may occur at multiple sites. Familial and non-familial paragangliomas may indeed be different disease entities.

Introduction

Paragangliomas are rare tumours and fewer than 50 cases of retroperitoneal paraganglioma have been reported. A review of the literature showed 13 cases of malignant retroperitoneal paraganglioma. We present 2 cases of malignant retroperitoneal paraganglioma occurring in sisters; to our knowledge, this is the first report of cases with a familial link.

Case reports

Case 1

A 27 year old woman presented with a lump on the left side of her neck, weight loss and low back ache. Two of her grandparents had died of unknown malignancy.

Examination showed non-tender, fixed, lymphadenopathy confined to the left supraclavicular region. She had smooth hepatomegaly extending 3 cm below the costal margin with splenomegaly. A large, irregular, non-tender mass was palpable in the left loin anteriorly.

X-ray of pelvis showed bone erosion. Intravenous urogram revealed the right kidney displaced by a soft tissue mass. Whole body computed tomography showed no abnormality above the diaphragm. A large, mixed density, tumour filled most of the upper abdomen, extending from just below the diaphragm to the pelvic brim and from the right lateral abdominal wall across the midline, displacing the right kidney, involving both aorta and inferior vena cava.

Biopsy of neck nodes was reported as anaplastic carcinoma of uncertain origin. At laparotomy a large mass arising from the posterior abdominal wall was found. Debulking proved impossible and biopsy showed non-chromaffin paraganglioma.

She was treated with adriamycin and cisplatin with no response. She subsequently received local radiotherapy for bone pain and further chemotherapy with adriamycin, cyclophosphamide and vincristine.

Following a pathological fracture, she died two years after initial presentation.

Case 2

A 24 year old woman, sister of our first patient, presented with a 10-month history of aching pain in the right leg. This occurred suddenly when the patient was at 36 weeks gestation. Following normal delivery she developed backache and progressive weight loss.

Examination revealed a firm, non-tender, ballotable mass 6 cm in diameter in the left iliac fossa and left loin. There was no lymphadenopathy or hepatosplenomegaly. Chest X-ray was normal. X-ray of pelvis showed lytic bone lesions. Bone scan showed areas of increased activity in the ribs, thoracic spine, pelvis and skull. Abdominal ultrasound showed a large pelvic mass and moderate splenomegaly.

At laparotomy, a highly vascular tumour arising from the ilium was found on the right side. Biopsies obtained at laparotomy and from previous needle biopsy showed non-chromaffin paraganglioma. Biochemical profile showed it to be a non-functioning paraganglioma.

She was offered symptomatic treatment. Subsequently she developed cord compression and metastatic paraganglioma was removed during laminectomy.

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tomy. She had radiotherapy for bone secondaries but died a few months later, two and a half years after initial presentation.

Pathological findings

Biopsy specimens from the two patients showed similar histological appearances. The partially encapsulated tumour masses were composed of nests and anastomosing sheets of regular eosinophilic cells with small nuclei and indistinct margins producing a syncytial-type appearance. Vascular spaces were prominent within the tumours (Figures 1 and 2). Mitotic figures were inconspicuous and there were foci of tumour necrosis. The tumour cells exhibited strong immunohistochemical reactivity with a polyclonal antibody to neurone-specific enolase (NSE) (Figure 3). Electron microscopy revealed membrane bound, neurosecretory type granules and bundles of densely aggregated filaments.

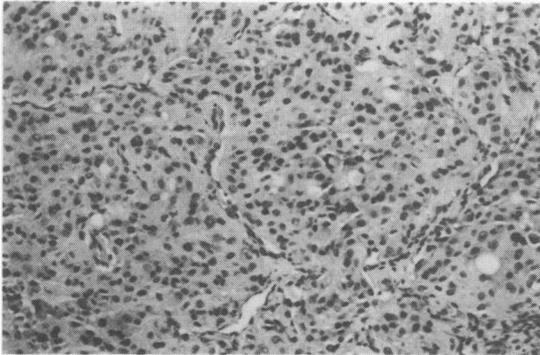


Figure 1 The tumours were composed of a syncytial network of regular nests of cells with intervening vascular spaces (H & E \times 102.4).

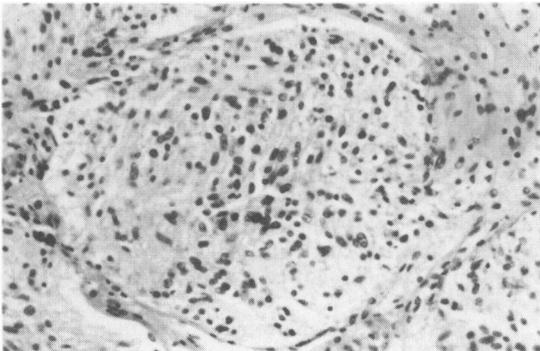


Figure 2 High power view of a cell nest (H & E \times 160).

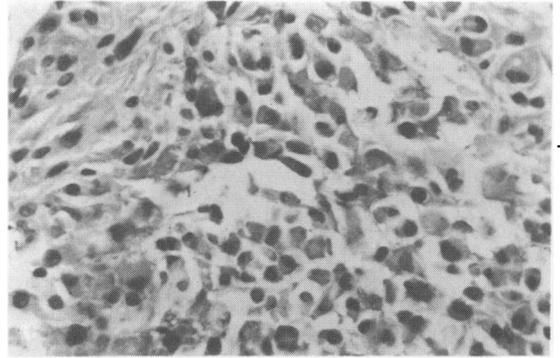


Figure 3 Tumour cells showed dense immunohistochemical reactivity for neurone-specific enolase. (Immunoperoxidase \times 160).

Discussion

Paraganglionic cells originate from the neural crest and migrate in close association with ganglion cells of the autonomic nervous system.¹ They are present in the aortic and carotid bodies where they act as chemo-receptors, and in the adrenal medulla which functions as a neuro-endocrine organ. However, they have been identified at various other sites where their function is not known.

Tumours originating from paraganglia are called paragangliomas and they are known to occur in the aortic, carotid and vagal bodies, jugulo-tympanic area, nasopharynx, base of skull, Zuckerkandle bodies, mediastinum, lung, heart, pancreas, duodenum, retroperitoneum, and cauda equina.² Tumours of adrenal medulla form a distinct group and are known as pheochromocytomas.

Microscopy shows small, round to polyhedral cells, arranged in nests surrounded by a delicate capillary network (Zellbellern formation). The cells are amorphous with abundant eosinophilic cytoplasm. Areas of haemorrhagic necrosis and ganglionic differentiation are occasionally seen. Histologically, benign and malignant paragangliomas cannot be differentiated.³

On electron microscopy two groups of cells are seen – light and dark – but these are thought to be merely a reflection of cellular hydration. The cells are arranged in clusters, closely apposed and joined by intercellular desmosomal junctions. Membrane bound neurosecretory granules may be demonstrated by specific stains. Reactivity to antibodies against neurofilament neurone-specific enolase and S-100 protein is usually seen.^{4,5}

Patients with non-malignant retroperitoneal gang-

lioma are usually asymptomatic until the tumour reaches sufficient size to produce symptoms of compression on adjacent organs. In contrast, patients with malignant retroperitoneal ganglioma may present with signs and symptoms of local and/or distant metastatic spread.

Usually laparotomy is necessary to obtain sufficient tissue for histology to make a firm diagnosis.⁶ Computed tomographic scan is the investigation of choice, both to demonstrate the retroperitoneal mass and infiltration into surrounding tissues. The tumour is highly vascular and angiography is useful to demonstrate large feeding vessels.⁷ Needle biopsy sometimes provides sufficient material for histological diagnosis but may lead to profuse arterial bleeding.⁸

Pre-operative assessment should include estimation of urinary metanephrines as pharmacological intervention may be necessary if the tumour is functional.⁹ In addition, a search should be made for paraganglioma at other sites. Radical excision, when feasible, is the treatment of choice.¹⁰ Though paragangliomas are generally resistant to treatment with radiotherapy and chemotherapy, Mikhail described one patient in 13 previously reported who showed excellent response to chemotherapy using cyclophosphamide, vincristine, doxorubicin and DTIC.¹¹

Over 2,000 cases of paragangliomas have been reported, more than 90% of which are tumours of carotid body and glomus jugulare.¹² About 150 cases of vagal body tumour and 53 cases of paraganglioma of cauda equina have been described. Retroperitoneal paraganglioma is rare and less than 50 have been reported so far. A review of the literature revealed only 13 cases of malignant retroperitoneal paraganglioma.¹¹

Carotid body tumour is the commonest paraganglioma.¹ There is an increased incidence in populations living at high altitude¹³ and it is also associated with diseases causing chronic hypoxia.¹⁴ Analysis of 923 cases showed a familial incidence of 9.5%. These

tumours were bilateral in 31.8% of familial cases and 4.4% in non-familial. Contrary to earlier reports, the incidence is equal in males and females. However, second primary tumours in familial and non-familial forms showed a 2:1 female preponderance. Twelve percent of non-familial and 2.5% of familial tumours were malignant.²

Malignancy of vagal body tumours occurs in 10 to 16% of cases and familial cases have been reported.^{5,8} Paragangliomas of cauda equina show a slight male preponderance and recur in 10% of cases after surgical excision.⁴ In general, sporadic cases of paraganglioma have a much higher incidence of malignancy than familial cases,² in contrast to the cases here reported.

Paraganglioma originate from the neural crest and may be a part of the amine precursor uptake and decarboxylase system. Neurocristopathies have been described in various combinations in multiple endocrine neoplasia. Familial paragangliomatosis may also be viewed as a form of neuro-endocrine neoplasia.¹⁵

All cases of malignant retroperitoneal paraganglioma, except one case with a familial history of carotid body tumour¹¹ and our two cases, were sporadic. Because they are relatively common, carotid body tumours may be used to demonstrate familial incidence. Grufferman noted that equal distribution of familial carotid body tumours among males and females is suggestive of autosomal transmission.² Variable penetrance or delayed mutation model may explain skipping of generations and occurrence of carotid body tumour in first cousins with no prior family history of carotid body tumour.¹⁶ As familial tumours are characterized by increased family risk, early age of onset and involvement of multiple sites,¹⁷ it has been suggested that familial and non-familial paraganglioma may be regarded as distinct entities.²

Acknowledgement

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