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Malignant vagal paraganglioma

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Abstract
Vagal paraganglioma is a rare usually benign tumour of neural crest origin. The malignant form of this tumour is very uncommon and the diagnosis is made on the basis of its clinical behaviour rather than its histological appearance. We report a case of vagal paraganglioma metastatic to adjacent cervical nodes and discuss the diagnosis and management of this tumour.

Key words: Paraganglioma; Glomus tumour; Vagus nerve; Neoplasm metastasis

Introduction

Paragangliomas are rare, usually benign, tumours that arise from paraganglia, small neural-crest derived neuroectodermal structures distributed throughout the body usually in close relation to autonomical structures and ganglia and/or vascular structures. Paraganglia have been found in association with the carotid body, aortic body, vagal ganglion, auricular branches of the ninth and tenth cranial nerves, superior and recurrent laryngeal nerves, iliac vessels and pineal body (Batsakis, 1974). Some of these cells have a known physiological function such as the carotid and aortic bodies while others such as the vagal body have no known function.

White (1935) was the first to describe chemoreceptor cells resembling the carotid body in the perineurium of the vagus nerve below the nodose ganglion in man. In the same year Stout (1935) published the first report of a tumour arising from the nodose ganglion of the vagus nerve which he termed 'pigmented malignant paraganglioma'. This tumour has been called by various names including non-chromaffin paraganglioma (Lattes and Waltner, 1949), chemodectoma (Mulligan, 1950), vagal body tumour (Birrell, 1953) and glomus vagale tumour. The first case of a vagal paraganglioma considered to be malignant was reported by Lattes in 1950 while the first case of a widely metastasising vagal paraganglioma was described by Burman in 1955.

Vagal paragangliomas (VP) usually arise from one of the three ganglia of the vagus nerve in the first 2 cm of its extracranial course, all above the carotid bifurcation (Lawson, 1980). Tumours arising from the inferior ganglion (ganglion nodosum) or just inferior to it are usually spindle-shaped and represent the commonest site of origin of these tumours. The tumour may arise within the nodose ganglion (intravagale) or less commonly in juxtaposition to it (juxtavagale) (Trail and Chambers, 1970). Tumours arising from the middle ganglion are usually cone-shaped with the base attached to the skull base while tumours arising from the superior (jugular) ganglion are usually dumb-bell-shaped with both intracranial and cervical components.

VPs account for approximately five per cent of all head and neck paragangliomas (Trail and Chambers, 1970; Lawson, 1980; Chen *et al.*, 1985). They are rare as evidenced by the fact that fewer than 190 cases have been reported in the English literature (Urquhart *et al.*, 1994). The incidence of metastasis or malignancy in a vagal paraganglioma (MVP) is estimated to be approximately 10 per cent (Kahn, 1976; Lack *et al.*, 1977; Lawson, 1980; Davidson and Gullane, 1988) which is higher than that in carotid body (six per cent) and glomus jugulare (four per cent) tumours (Kahn, 1976). Metastatic or malignant paragangliomas (MVP) are unusual in that, unlike malignant tumours elsewhere, they are diagnosed on the basis of their clinical behaviour and not their histological appearance. There is no histological difference between the benign (VP) and malignant (MVP) forms of this tumour (Lawson, 1980). We report a further rare case of MVP which was successfully treated by balloon occlusion of the carotid artery followed by excision of the tumour and its metastases.

Case report

A 31-year-old woman presented to another ENT department with a three-month history of hoarse voice and a left-sided neck mass. Her father had died of a malignant phaeochromocytoma 15 years previously. Examination showed a left-sided adductor vocal fold palsy and a fixed hard 3 × 2 cm mass in the left anterior triangle below the angle of the mandible. Cranial nerve function was normal. Routine blood tests, chest X-ray and panendoscopy were normal and aspiration cytology was not contributory. Magnetic resonance imaging (MRI) showed a mass in the left parapharyngeal space which extended from the carotid bifurcation to the jugular foramen at the skull base and enveloped the left internal (ICA) and external (ECA) carotid arteries and compressed the internal jugular vein (IJV) (Figure 1). Multiple

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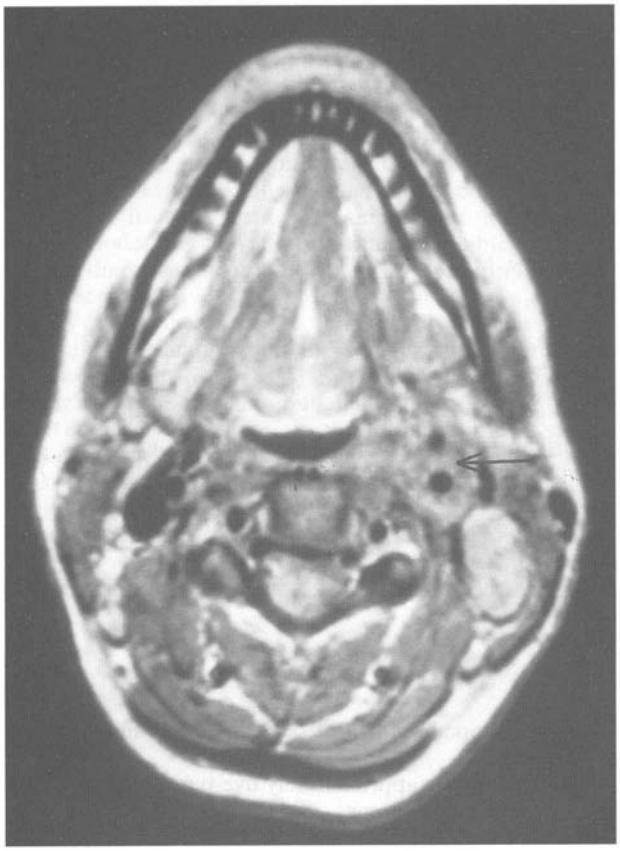

FIG. 1

MRI scan (axial view) of the neck showing a left parapharyngeal mass (arrow) surrounding the ICA and ECA and compressing the EJV.

adjacent upper deep cervical lymph nodes were also seen. Left-sided neck exploration showed a vascular mass surrounding the major vessels and through which ran the last four cranial nerves. It extended to but was not adherent to the skull base. Frozen section biopsy showed findings consistent with a paraganglioma. The mass was not resectable because of its vascular encroachment and the patient was referred to our department for further assessment.

Digital subtraction angiography showed a highly vascular mass situated above the carotid bifurcation with feeding vessels from the occipital and ascending pharyngeal arteries (Figure 2) and it displaced the ICA and ECA anteriorly. Carotid doppler ultrasonic angiography showed normal blood flow along the ICA and CCA (Figure 3a) with no apparent connection between the mass and the vessels (Figure 3b). Cerebral doppler ultrasonic angiography showed good cross-flow from the right to left cerebral circulation. Twenty-four hour urinary vanillylmandelic acid (VMA) levels were normal. A MRI scan did not show any evidence of multicentric tumours.

Balloon occlusion of the petrous part of the left ICA was undertaken via the transfemoral route under general anaesthesia in the X-ray department. On the same day the patient underwent a left radical neck dissection with excision of the tumour, ICA, ECA and sacrifice of the last four cranial nerves. The histological features together with the clinical findings were diagnostic of malignant vagal paraganglioma (MVP).

Post-operatively the patient underwent a radical course of radiotherapy. She has a residual left-sided Horner's syndrome and palsies of the ninth to twelfth cranial nerves. Intensive speech therapy was not helpful and so she underwent an Isshiki type I thyroplasty under local anaesthesia. Post-operative swallowing was not a problem. Follow-up at three years showed no evidence of recurrence.

Histological examination

Macroscopic examination of the neck dissection specimen showed a firm pale tumour measuring 30 × 40 × 25 mm which encased the carotid vessels, with a separate nodule medially measuring 25 × 10 × 10 mm which had the appearance of a lymph node. A further 27 lymph nodes were identified in the specimen. Microscopy showed the typical appearance of a paraganglioma: on low-power magnification the tumour had a nested pattern (Figure 4) with intervening stroma (there is artefectual retraction of the stroma from the cell nests). The tumour was intimately associated with the compressed nerve trunks. High-power examination showed the nests to be composed of polygonal cells with a moderate amount of granular pink cytoplasm and round to oval nuclei with a finely stippled chromatin pattern and nuclear pleomorphism (Figure 5). These are the neoplastic chief cells. Note the presence of some central vacuolar change and only occasional mitoses were seen.The separate nodule was a lymph node largely replaced by metastatic tumour and tumour was seen in only one of the 27 other nodes (Figure 6). Immunohistochemical analysis showed positivity in the polygonal cells with the neuroendocrine markers neurone specific enolase (NSE) and PGP 9.5. The epithelial marker CAM 5.2 was negative. Occasional cells were positive with S100,

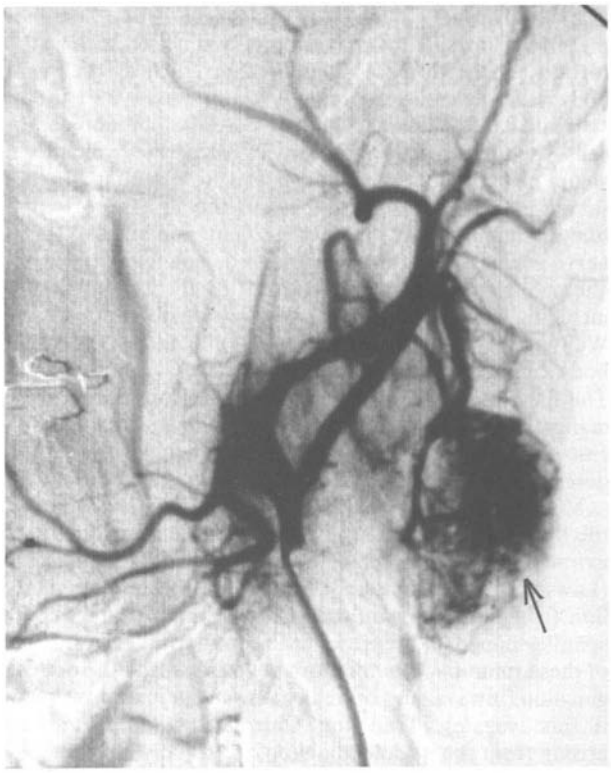

FIG. 2

Digital subtraction angiogram of the left ECA showing a vascular mass (arrow) situated above the carotid bifurcation, arising from the ascending pharyngeal and occipital arteries and displacing the ECA anteriorly.

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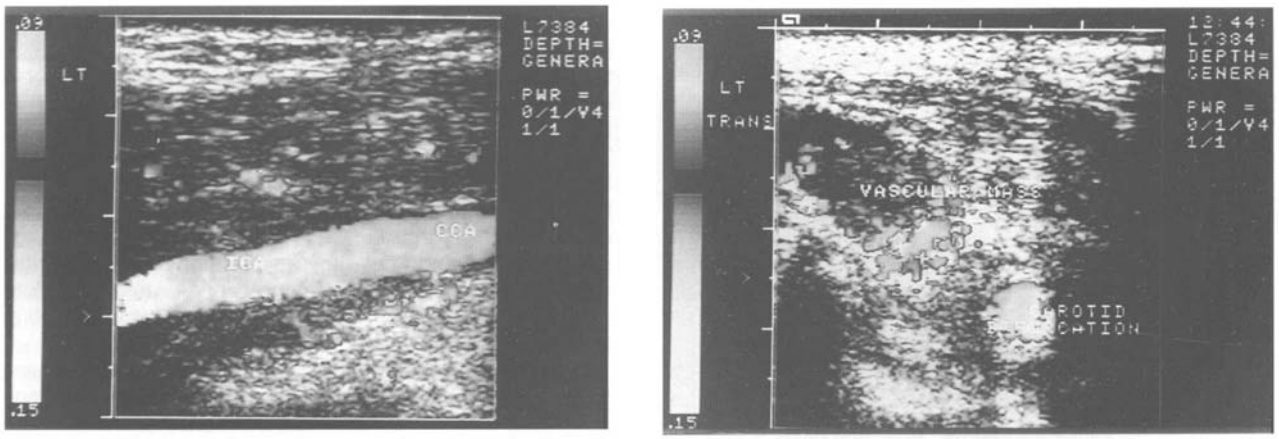

(a) (b)

FIG. 3

Left-sided carotid doppler ultrasonography showing normal ICA and CCA blood flow (Figure 3a) with no apparent connection between the vascular mass and the carotid bifurcation (Figure 3b).

representing the sustentacular cells which are found in paraganglia and paragangliomas alike.

Discussion

The fact that such a small number of cases of metastatic or malignant vagal paraganglioma (MVP) have been reported in the literature to date may be partly due to the fact that the criteria used for inclusion in the past were too strict (Druck *et al.*, 1976; Heinrich *et al.*, 1985). The diagnosis was made on the basis of histological evidence of cervical lymph node metastasis or the clinical detection of distant metastasis. The criteria set by Jackson (1993) are more widely accepted now. Malignancy in a paraganglioma is suggested by:

(1) the presence of lesions at sites other than where this specialized type of tissue occurs. This encompasses cervical node and distant metastasis but excludes multicentric tumours and multiple endocrine neoplasia (MEN) syndromes (Nilssen and Wormald, 1996).

(2) Local recurrence of a vagal paraganglioma (VP).

(3) Aggressive behaviour of the tumour.

The significance of vascular invasion is unclear as long-term survival has been reported in several cases showing this feature (Stout, 1935; Lattes, 1950) with the patients remaining free of recurrence or metastatic disease. VPs have a propensity towards local infiltration e.g. involvement of the carotid artery, erosion of the skull base and intracranial spread through the jugular foramen even in the absence of metastasis (Someren and Karcioglu, 1977). The presence of extensive local invasion is not indicative of malignancy.

The most comprehensive review of MVP was by Heinrich *et al.* in 1985. He reviewed the 14 cases reported in the English literature and reported another one. The demographic features and the clinical presentation of patients with MVP are similar to those of patients with VP (Druck *et al.*, 1976; Heinrich *et al.*, 1985). There was a slight female preponderance (F:M = 8:7) and the average age at the time of diagnosis was 50 years (range: 23–70 years). These are slow growing tumours as evidenced by the long duration of symptoms before diagnosis: 3.7 years (range: six months–16 years). Their characteristic clinical presentation results from their location in the parapharyngeal space. The presence of the base of the skull superiorly, the mandible laterally and the vertebral bodies posteriorly forces the tumour to grow inferiorly and medially i.e. present as a mass below the angle of the mandible or as an oropharyngeal mass. It may involve any of the structures in this space i.e. ICA, ECA, IJV, cervical sympathetic chain and cranial nerves 9–12. The commonest symptoms were a neck mass (71 per cent) and cranial nerve dysfunction (64 per cent): dysphagia, dysphonia and vasovagal symptoms were the cranial nerve symptoms in descending order of frequency.

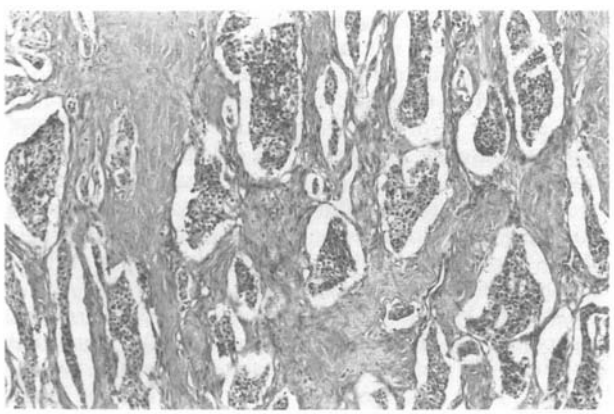

FIG. 4

Tumour cell nests (zellballen) set in a fibrous stroma. (H & E; × 100).

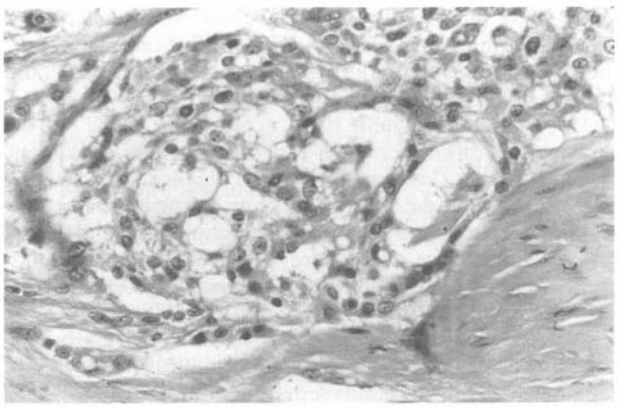

FIG. 5

Cells with round to oval nuclei and a stippled chromatin pattern. Note the absence of mitotic activity and the presence of pale vacuolar change. (H & E; × 200).

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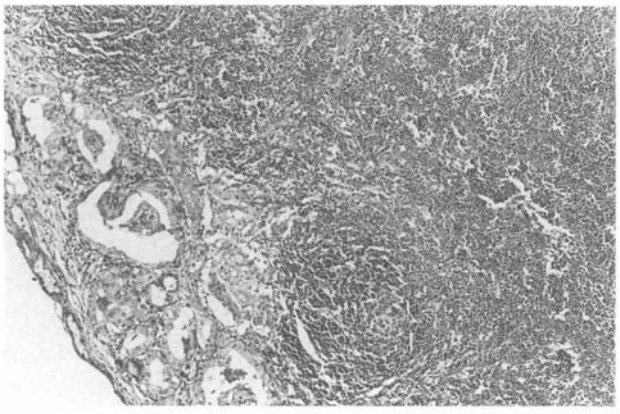

FIG. 6
Lymph node with a deposit of metastatic tumour. (H & E; × 100).

There is a slight predilection for the tumour to be located on the right side. The commonest examination findings in cases of MVP were a neck mass (92 per cent), neck and oral masses (62 per cent), oral mass alone (eight per cent) and a cranial nerve palsy (54 per cent). The commonest nerve involved was the tenth (47 per cent) followed by the ninth (40 per cent) and twelfth (33 per cent) (Heinrich *et al.*, 1985). There were no cases of Horner's syndrome. Cranial nerve palsy can used as a predictor of metastasis in VP. A patient with an isolated tenth nerve palsy has a 10 per cent risk, a patient with two or more palsies has a 20 per cent risk while a patient with an isolated ninth nerve palsy has a 36 per cent risk of metastasis (Kissel *et al.*, 1976).

It is estimated that the incidence of multicentricity in head and neck paragangliomas is 10 per cent (Spector *et al.*, 1975; Endicott and Maniglia, 1980; Lawson, 1980). This figure rises to 35 per cent in familial cases (Parkin, 1981; Van Barrs *et al.*, 1981). It is important that these are not confused with metastatses. VPs and MVPs may be familial but only a few cases have been reported in the literature to date (Linn and Proctor, 1956; Kahn, 1976).

The inheritance pattern is autosomal dominant with variable penetrance. In the series of cases of MVP reviewed by Heinrich *et al.* (1985) the diagnosis of malignancy was reached by the finding of cervical lymph node metastasis in 67 per cent, distant metastasis alone in 26 per cent and cervical lymph node and distant metastasis in seven per cent. The commonest site of distant metastases were lung, bone, liver and brain in descending order of frequency. Lung metastases were diagnosed 1.5 to three years later and bone metastases two to four years after the initial diagnosis. The sites of these metastases indicate that these tumours are capable of both lymphatic and haematogenous spread (Urquhart *et al.*, 1994).

Most authors would now agree that there is no histological difference between benign and malignant paragangliomas (Lawson, 1980). The diagnosis of a specific paraganglioma is determined by considering its anatomical location, clinical presentation and radiological and histological appearance. They are highly vascular tumours consisting of nests of uniform polygonal cells (zellballen) with a rich intervening capillary network. The location of the tumour within the vagus nerve may lead to a capsule or pseudocapsule of perineural tissue containing nerve trunks together with fibrous bands separating tumour clumps. The latter feature is supposed to distinguish VPs and carotid body tumours. The presence of ganglion cells within or adjacent to the tumour is well described (Glenner and Grimley, 1974). Ultrastructural studies of the main cell type (chief cell) in VPs have shown the presence of spherical membrane-bound dense core neurosecretory type granules in some of them, suggesting a neurohumoral function (Kahn, 1976). Sustentacular cells may be identified by their positive reaction with S100 protein antibody. Their presence and the usual absence of positive cytokeratin staining helps distinguish paragangliomas (whether benign or malignant) from carcinomas showing neuroendocrine differentiation. The latter tumours, usually of pulmonary origin in this site, are of endodermal derivation while paragangliomas are of neural crest or neuroectodermal origin. A chest X-ray is mandatory to exclude such a tumour.

The criteria commonly used for diagnosing malignant tumours elsewhere, including nuclear and cellular pleomorphism and perineural or vascular invasion are not reliable indicators of malignancy in VPs (Johnstone *et al.*, 1990; Barnes and Taylor, 1991; Urquhart *et al.*, 1994). The value of mitotic counts is more controversial. Mitotic figures are sparse in VPs and while some authors (Lack *et al.*, 1979) suggest that their presence is associated with malignancy others suggest that there is no direct relationship (Kliewer and Cochran, 1989; Barnes and Taylor, 1991). A recent study of 120 paragangliomas showed that mitotic figures were more commonly found in malignant tumours but the differences were not statistically significant (Linnoila *et al.*, 1990). Tissue markers of proliferative activity e.g. argyrophilic nucleolar organiser regions (AgNOR) have limited predictive value for malignancy in VPs (Gee *et al.*, 1992).

The diagnostic procedure of choice in the past has been bilateral carotid angiography (El Gammal, 1971). It delineates the extent of tumour accurately (Hesselink *et al.*, 1981), shows its blood supply, excludes the presence of occult multicentric tumours and carotid artery invasion and it can assess the contralateral ICA flow and cerebral cross-flow. However, it is invasive and ipsilateral vertebral angiography is often required if its full blood supply is to be appreciated. Some authors believe that MR imaging (Som *et al.*, 1987) or dynamic CT scanning (Som *et al*, 1984) are just as effective with the advantage that they are not invasive. However, these fail to give an accurate assessment of the arterial supply and venous drainage both of which are vital factors in the management of these lesions. Carotid and cerebral doppler ultrasonic angiography allow a non-invasive means of assessing ICA/ECA patency and cerebral cross-flow but are not totally reliable. Test occlusion is more accurate, but even this is not failsafe as a delayed stroke may develop some days later. Nilssen and Wormald (1996) recommend the use of MIBG scintigraphy, which identifies ectopic neuroendocrine tissue, to exclude concomitant primaries or metastatic deposits especially if urinary VMA levels are elevated. However, not all tumours accumulate MIBG and so a negative scan cannot exclude other lesions. Twenty-four hour urinary VMA levels should be measured in all suspected cases of paraganglioma (Chaudry *et al.*, 1979), however, there have been only five reported cases of functional VP in the literature (Levit *et al.*, 1969; Sundaram and Cope, 1976; Bogdasarian and Lotz, 1979; Tannir *et al.*, 1985; Karusseit and Lodder, 1987). Open biopsy of these tumours is no longer recommended.

Although VPs are usually benign and slow growing, surgery is the mainstay of treatment as significant symptoms will result from the mass effect of the tumour (Lawson, 1980; Van der Mey *et al.*, 1992; Browne *et al.*, 1993 and early surgery may prevent intracranial extension and the development of metastases (Someren and Karcioglu, 1977). The treatment of choice of MVPs is excision of the primary tumour and the regional lymph node

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metastases. Complete surgical removal can be difficult particularly if there is widespread infiltration of the skull base or intracranial involvement. Tumours that lie in the parapharyngeal space without invasion of the jugular foramen (Stage I) can be removed safely through a transcervical incision while tumours that invade the jugular foramen (Stage II) and middle ear/carotid canal (Stage III) require a Fisch infratemporal fossa A approach for adequate exposure (Browne *et al.*, 1993). Involvement of the ICA does not preclude surgery as it can either be resected or bypassed with a saphenous vein graft. If the tumour invades the ICA near or within the temporal bone then balloon occlusion of the petrous part facilitates resection (Browne *et al.*, 1993). Selective embolization of the feeding vessels pre-operatively reduces tumour vascularity intra-operatively (Wong *et al.*, 1987; Davidson and Gullane, 1988; Browne *et al.*, 1993). Some authors believe that embolization also has a role to play as a palliative modality in elderly debilitated patients and in patients with inoperable tumours (Ogura *et al.*, 1978). Surgery carries a significant risk of morbidity. In cases of MVP all involved nerves must be excised potentially resulting in deficits of cranial nerves 9–10 together with Horner's syndrome. Undue traction on the vagus nerve intra-operatively should be avoided as it may induce bradycardia or cardiac arrest (Wong *et al.*, 1987). Swallowing difficulties can be minimized by considering a cricopharyngeal myotomy at the time of surgery and dysphonia/aspiration symptoms may be helped by a teflon injection or thyroplasty.

The use of radiotherapy in the treatment of paragangliomas is controversial (Konefal *et al.*, 1987; Arts and Fagan, 1991). Radiotherapy causes extensive fibrosis and collagen deposition but tends to have little effect on the chief cells or tumour vasculature and, therefore, tumours do not usually regress (Spector *et al.*, 1975). Some authors believe that paragangliomas involving the temporal bone are, to some degree, radiosensitive (Jackson *et al.*, 1982) but the long-term effects of radiotherapy on the skull base cannot be overlooked particularly if surgery becomes necessary several years later. Nevertheless, it may be indicated post-operatively if there is incomplete excision, if metastatic disease is present or if there is extensive infiltration. In addition it may be used if the patient is unfit, if the tumour is unresectable or for recurrent disease. The therapeutic role of meta-iodobenzylguanidine (MIBG) is currently being assessed. So far only anecdotal evidence of response exists. However, it has been shown to control the disease and reduce metastatic bony pain in malignant phaeochromocytoma (Cornford *et al.*, 1992). Malignant vagal paraganglioma have a worse prognosis than vagal paraganglioma although the follow-up of all reported cases to date is too short to accurately assess this (Heinrich *et al.*, 1985).

Conclusion

We report a rare case of familial malignant vagal paraganglioma which was successfully treated by surgery and post-operative radiotherapy. Once a diagnosis of vagal paraganglioma is suspected it is important to exclude the presence of multicentric tumours, metastases and assess the degree of local infiltration accurately prior to treatment. In addition it should be ensured that it is non-functioning and that no other members of the family are similarly affected.

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