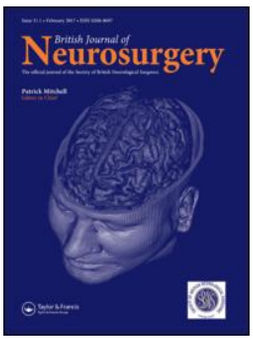

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SHORT REPORT

Supratentorial primary paraganglioma with good long-term outcome following radical excision

Abhijit Goyal-Honavar[a], Geeta Chacko[b] and Ari G. Chacko[a]

[a]Section of Neurosurgery, Christian Medical College, Vellore, India; [b]Section of Neuropathology, Department of Neurological Sciences, Christian Medical College, Vellore, India

ABSTRACT

Background: Paragangliomas are tumours of extra-adrenal paraganglia. They may metastasize to the brain but primary paragangliomas are exceedingly rare in the supratentorial region and long-term outcomes after surgery is largely unknown. This description of an excellent outcome 13 years following surgery in a 40-year-old gentleman with a primary paraganglioma near the falx provides an important perspective on the value of gross total resection in these tumours. We also review the options for adjuvant therapy in tumours that cannot be excised completely.

Case description: We describe a supratentorial paraganglioma in the parasagittal region in a 40-year-old gentleman who presented with clinical and radiological features suggestive of a right parafalcine meningioma. Histopathological examination following gross total excision of the tumour revealed histological and immunochemical features of a paraganglioma. A detailed search for a systemic primary was negative and the patient remains disease-free 13 years after the surgery.

Conclusions: Differentiating between tumours arising primarily and those that are metastatic deposits in the central nervous system requires long-term follow-up and monitoring for the appearance of occult primary tumours. Gross total resection is likely to provide good long-term outcomes.

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KEYWORDS
Supratentorial; paraganglioma; primary; long-term; follow-up

Case report

Clinicoradiological

A 40-year-old gentleman had one generalized tonic-clonic seizure a month prior to admission. He had received therapy for migraine headaches for 7 years with good relief. His ocular fundi and visual fields were normal. There were no other neurological deficits. The magnetic resonance image (MRI) of the brain showed a well-defined $5 \times 4 \times 5$ cm mass in the parietal interhemispheric region near the falx on the right side. No normal brain could be seen between the tumour and falx. It was isointense on the T1w image (Figure 1(a)) while on the T2w images (Figure 1(b)) there were areas of hyperintensity in the center, the periphery being hypointense. Also significant on the T2w images was the extensive white matter edema. There was uniform enhancement with gadolinium except in a few small cystic areas within the mass with no dural tail visible. (Figure 1(c,d)). With a preoperative diagnosis of a falx meningioma, we did a right parietal craniotomy in the right lateral position and opened the dura based medially. After releasing the arachnoid adhesions between the brain and the falx the parietal lobe fell away due to the position enabling excellent tumour exposure without brain retraction. The tumour was primarily extraaxial with a flimsy dural attachment to the falx, though anteriorly, because of the poor tumour-brain interface and pial transgression, it appeared parenchymal. The tumour, that was fibrous and hard, moderately vascular with a few small cysts, but no areas of necrosis, hemorrhage or calcification was radically excised with a 0.5 cm dural margin.

Histopathology

The light microscopic picture was that of a tumour composed of prominent cell clusters separated by delicate fibrovascular septa (Figure 2(a)). The tumour cells were moderately sized epithelioid cells with the nuclei containing salt-and-pepper chromatin. Scattered mitotic figures were seen. The Zellballen architecture was particularly well visualized with a reticulin stain (Figure 2(b)). A spindle cell morphology was seen in foci. Immunohistochemically the tumour cells displayed strong positivity for synaptophysin (Figure 2(c)) and neuron-specific enolase and a lack of reactivity for GFAP, S100 protein, Epithelial membrane antigen, Cytokeratin AE1/AE3, Cytokeratin 5/6, Cytokeratin 7, Cytokeratin 20 and Cam 5.2. S100 protein positivity was seen focally at the periphery of the cell clusters (Figure 2(d)). Focal faint positivity was noted with Cytokeratin 8 (Figure 2(e)). A MIB-1 immunostain showed a low tumour labeling index (Figure 2(f)). The light and immunohistochemical features were those of a neuroendocrine tumour and within this category, as the features were most consistent with a paraganglioma, the case was diagnosed as a supratentorial paraganglioma. A systemic workup and imaging studies ruled out a paraganglioma in any other location. Postoperatively, the patient did well and did not have any new neurological deficits, in particular, the visual fields were normal. At his 13-year follow-up the patient was asymptomatic and the MRI brain with contrast showed no recurrence (Figure 3).

CONTACT Geeta Chacko geetachacko@cmcvellore.ac.in Section of Neuropathology, Department of Neurological Sciences, Christian Medical College, Vellore 632004, India

Discussion

Paragangliomas are tumours of extra-adrenal paraganglia, regardless of location.[1] While in the craniospinal axis these usually arise in the cauda equina,[2,3] intracranial paragangliomas have been reported in the pineal region,[4] cerebellum[5,6] cerebellopontine angle[7,8] and sella turcica.[9,10] Primary parenchymal supratentorial paragangliomas are rare with one case report of an intracerebral paraganglioma attached to the middle cerebral artery (MCA),[11] one in the insular region[12] and another of a primary intracerebral paraganglioma in the frontal lobe.[13] Due to the rarity of these tumours, our first impression on histopathology was that of a tumour with neuroendocrine features given the microscopic appearance of well-defined nests of cuboidal cells containing abundant granular basophilic cytoplasm and separated by highly vascularized fibrous septae. With a provisional diagnosis of a metastatic neuroendocrine carcinoma, we proceeded with further staining. This tumour was negative for epithelial markers and showed focal faint positivity for Cytokeratin 8. Antibody to Cytokeratin 8 labels a low molecular weight cytokeratin found in non-squamous epithelium and is reactive with neuroendocrine tumours. Paragangliomas of the cauda equina and a few in the head and neck region have expressed focal to strong immunopositivity for cytokeratin markers AE 1/3 and CAM 5.2.[14–16] The present case was negative for these cytokeratins. A thorough systemic search in our case did not reveal any evidence of a primary tumour. Therefore, the clinical, histological and immunohistochemical features appeared to be most consistent with a primary paraganglioma. In addition, at long-term follow-up of 13 years, we did not detect any distant tumour, indicating that the supratentorial paraganglioma indeed arose primarily at that site rather than a manifestation of an occult primary source extracranially.

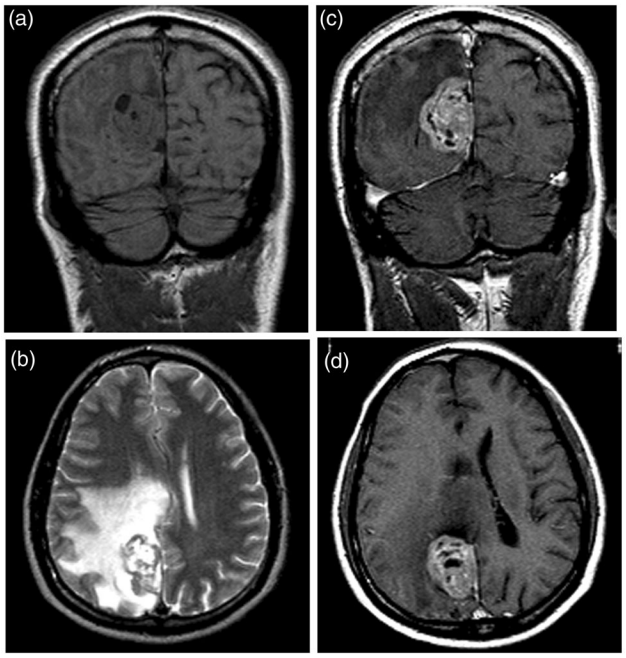

Figure 1. Preoperative MRI brain: (a) T1w coronal image showing the tumour isointense with brain (b) T2w axial image showing white matter edema in the adjacent brain (c,d) post-contrast coronal and axial images showing a $5 \times 4 \times 5$ cm well-defined enhancing mass with a broad surface abutting the falx in its middle third.

Primary versus metastatic paragangliomas

Glenner and Grimley[17] divided paraganglia into four 'families', branchiomeric, intravagal, aortico-sympathetic and visceral autonomic. Raftopoulos[18] suggested a fifth 'family' that included paraganglionic cells scattered throughout the central nervous system (CNS) that give rise to primary paragangliogliomas in the CNS. The CNS location is probably due to aberrant migration of paraganglion cells along the tympanic or ciliary nerves or branches of the glossopharyngeal nerve[19,20] or from embryonic remnants paraganglion cells entrapped in or near the pituitary gland.[9,19] There are a few reports of primary paragangliomas in the cerebellar parenchyma[5,6] and cerebellopontine angle[7,8,20] and one from the pineal gland.[4]

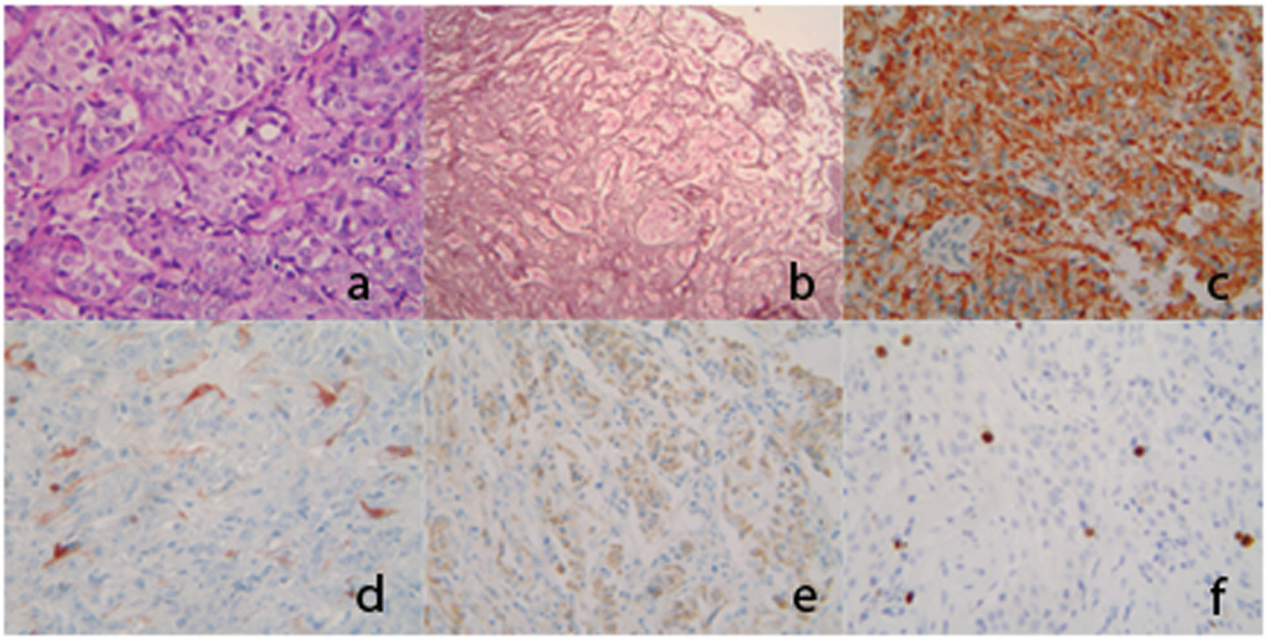

Figure 2. Photomicrograph of the paraganglioma with well-defined nests of epithelioid cells. (a) Hematoxylin and Eosin. (b) Reticulin stain, (c) Immunopositivity for synaptophysin, (d) S100 positivity in the sustentacular cells, (e) Faint positivity for Cytokeratin 8, and (f) Low MiB-1 labeling index.

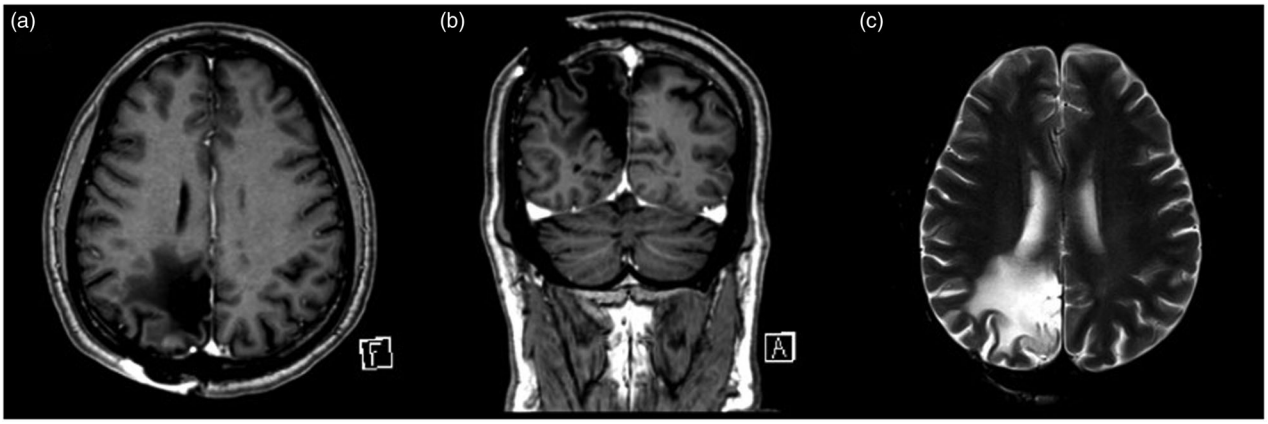

Figure 3. Postoperative T1w axial (a) and coronal (b) MR images with gadolinium and T2 flair image (c), showing no tumour recurrence after 13 years but persistence of gliosis.

Primary supratentorial paragangliomas are rare with only three cases reported. A 40-year-old male with a tumour located in the Sylvian fissure that had an attachment to the middle cerebral artery (MCA),[11] a 48-year old lady with a right-sided insular mass[12] and a frontal parenchymal tumour in a 40-year-old man.[21] In the first two cases, the autonomic nerves on the MCA may be postulated as a possible source for the paraganglia cells from which the tumours arose. With a follow-up of less than 1 year in all three cases it is not possible to establish convincingly that these were indeed primary and not metastatic tumours. Abou Chaar et al.[21] report an extraaxial frontal paraganglioma invading the orbit and paranasal sinuses with coexistent pleural metastases. From the data provided in their case it is likely that the frontal paraganglioma represented one of the many metastatic deposits and cannot be classified as a primary supratentorial paraganglioma.

Biological behavior and surveillance

Surgery is the treatment of choice and a gross total resection can provide long term disease free survival,[22] as exemplified in our patient who is disease free for 13 years. Profuse bleeding from highly vascular tumours, on the other hand, might preclude radical excision,[6,10,23] that can lead to local recurrence.[21,24] While a small number of partially excised tumours subjected to adjuvant radiation have remained stable at follow-up, the long-term efficacy of radiation is unknown.[6,23] Given the slow growth rates of these tumours, long-term follow up is mandatory.[21] As primary and metastatic paragangliomas demonstrate a high density of somatostatin receptor 2 (SSTR-2) positivity, the search for an occult primary tumour can be conducted using ^{68}Ga-DOTATOC PET/CT that has greater sensitivity and specificity than somatostatin receptor scintigraphy with octreotide (Octreoscan) and ^{18}F-FDG PET/CT.[25,26] Metastatic, residual or inoperable disease treated with radionuclide therapy has shown encouraging results.[25,27] Combination chemotherapy with cyclophosphamide, vincristine and dacarbazine in malignant paragangliomas might be indicated in symptomatic patients or in those in whom reduction in tumour size is desirable.[28]

Conclusion

The present report highlights the existence of intracerebral paragangliomas and the good long-term disease-free survival with gross total resection. The absence of an extra-CNS tumour and the fact that no new disease developed over the 13-year follow-up period, in this case, argues for a primary CNS origin and against metastasis.

Author contributions

All authors contributed to the preparation of this manuscript.

Disclosure statement

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria, educational grants, participation in speakers' bureaus, membership, employment, consultancies, stock ownership, or other equity interest, and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

ORCID

Abhijit Goyal-Honavar http://orcid.org/0000-0001-5564-2690

Data availability statement

The data that support the findings of this study are available from the corresponding author, Geeta Chacko, upon request.

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