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Case Report

Delayed intracranial and bony metastasis of paraganglioma

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Abstract

Background: Paragangliomas are tumors of neural crest origin that arise from the extra-adrenal paraganglia. In contrast with the often quoted 10% rule of malignancy for pheochromocytomas, the rate of malignancy as defined by local invasion or distant metastasis has been reported to be from 20% to as high as 50% in some case series with the most common sites of distant metastases being the liver, lungs, and bones. Here we present the case of a patient who presented with a rare case of intracranial metastasis from abdominal paraganglioma.

Case Description: Our patient was a 48-year-old male with a distant history of multiple resections of abdominal paraganglioma in 1975 who presented with left shoulder, and left occipital metastasis 35 years after his original paraganglioma operations.

Conclusions: Intracranial metastasis of paraganglioma is rare. There are unfortunately no known criteria to assess the risk of metastatic potential and given the long possible latency period between the resection of the primary tumor and the discovery of metastatic disease, patients with paragangliomas require lifelong monitoring. The optimal interval of monitoring has not been elucidated but follow-up every 5–10 years seems warranted.

Key Words: Intracranial metastasis, paraganglioma, neuroendocrine tumor

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INTRODUCTION

Paragangliomas are tumors of neural crest origin that arise from the extra-adrenal paraganglia.[2,4,10,13] They have sometimes been referred to as "extra-adrenal pheochromocytomas" and represent approximately 10–18% of chromaffin-associated tumors.[13] These tumors may be discovered due to symptoms secondary to mass effect, symptoms due to hypersecretion, incidentally, or as part of a family screening program. Head and neck paragangliomas are most often diagnosed incidentally or due to mass effect while abdominal paragangliomas are most often associated with the classic symptoms of palpitations, tremor, headache, and diaphoresis related to episodic catecholamine secretion.[2,4,10,13] Eight-five percent of paragangliomas are found in the retroperitoneum.[2,7] In contrast with the often quoted 10% rule of malignancy for pheochromocytomas, the rate of malignancy as defined by local invasion or distant metastasis has been reported to be from 20% to as high as 50% in some case series with the most common sites of distant metastases being the liver, lungs, and bones.[2,10] Here we present the case of a patient who presented with a rare case of intracranial metastasis from abdominal paraganglioma. To our knowledge, only two other reports of intracranial metastasis of paraganglioma have been reported in the literature.[4,14]

CASE REPORT

Our patient is a 48-year-old African American male who was referred to UCLA after an incidental discovery of an intracranial mass while undergoing metastatic workup for a shoulder mass. The patient had a distant history of retroperitoneal paraganglioma that was discovered at the age of 10 as a painless expanding abdominal mass. The patient underwent seven abdominal surgeries over the course of the next 4 years with the last operation occurring in 1975 and was found to be disease free at 5-year follow-up. The patient reported that he never underwent chemotherapy or radiation therapy prior to or after his abdominal operations. He reported that he was symptom free for the next 34 years with no reported episodes of diaphoresis, palpitations, headaches, arrhythmias, or other symptoms concerning for catecholamine secretion. The patient reported that his only health problem in this interval was hypertension that was managed with three hypertensive medications.

However, in the winter of 2009, the patient began noticing an expanding, painful, erythematous swelling in his left shoulder. A workup at an outside hospital found a large expansile left acromial mass that was biopsied and initially read as possible sarcoma. However, upon referral to UCLA and repeat biopsy, the diagnosis was determined to be consistent with metastatic paraganglioma. Microscopic examination demonstrated "packets of bland-appearing round blue cells present in nests lining numerous pericytoma-like vascular proliferation" that were found to stain positive for chromogranin, S100, synaptophysin, and neuron-specific enolase (NSE). During his oncologic workup, CT and MRI of the brain were performed, which demonstrated a large left extra-axial occipital lesion measuring 2.9 × 4.5 cm compressing the torcula, left transverse sinus, and posterior sagittal sinus with the invasion of and through the occipital calvarium into the soft tissues of the scalp [Figure 1]. Urine metanephrines were within normal limits but serum chromogranin A levels were elevated to 20 times the normal range suggesting a nonfunctioning neuroendocrine tumor. CT of the abdomen was negative for abdominal recurrence. The patient was neurologically intact with no neurologic deficits other than 3/5 weakness of his left shoulder. Distal extremity strength was intact.

The patient underwent excisional biopsy of his occipital tumor. Microscopic examination revealed an infiltrating neoplasm composed of nests of round blue cells with round-to-ovoid nuclei, smudgy chromatin, moderate amount of eosinophilic cytoplasm, and distinct cytoplasmic border with no necrosis appreciated, and rare mitotic figures which were determined to be consistent with metastatic paraganglioma [Figure 2]. The patient tolerated all procedures well, had an uncomplicated postoperative course, and was discharged on postoperative day 3 at his neurologic baseline.

Following his discharge, the patient underwent an outpatient metaiodobenzylguanidine (MIBG) scan that demonstrated an abnormal tracer activity in the left occiput and left scapula corresponding to the known residual tumor and shoulder mass as well as small foci of abnormal activity in the left upper arm proximal to the elbow and left thigh proximal to the knee. Follow-up MRI of the left humerus and left femur demonstrated intramedullary masses that are consistent with metastatic paraganglioma. The patient later underwent successful gross total resection of his large left scapular mass with orthopedic surgery. Treatment for his left humeral and left femoral masses remains to be determined.

DISCUSSION

Paraganglia are neural crest-derived neuroendocrine

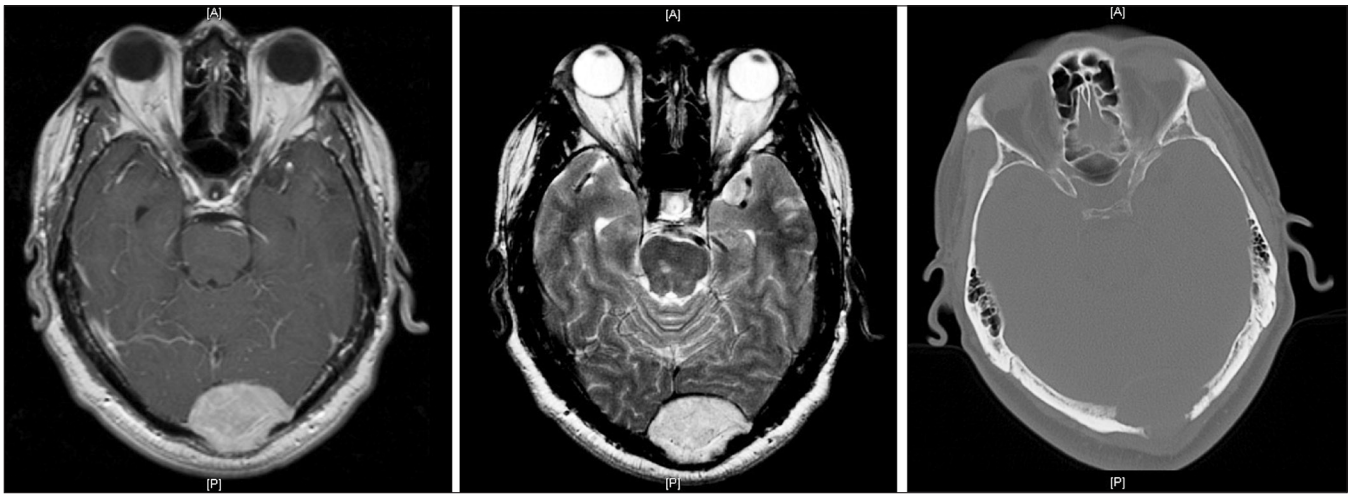

Figure 1: MRI of the intracranial torcular metastatic paraganglioma showing contrast enhancement on T1, hyperintensity on T2, and bony erosion without hyperostosis on CT images

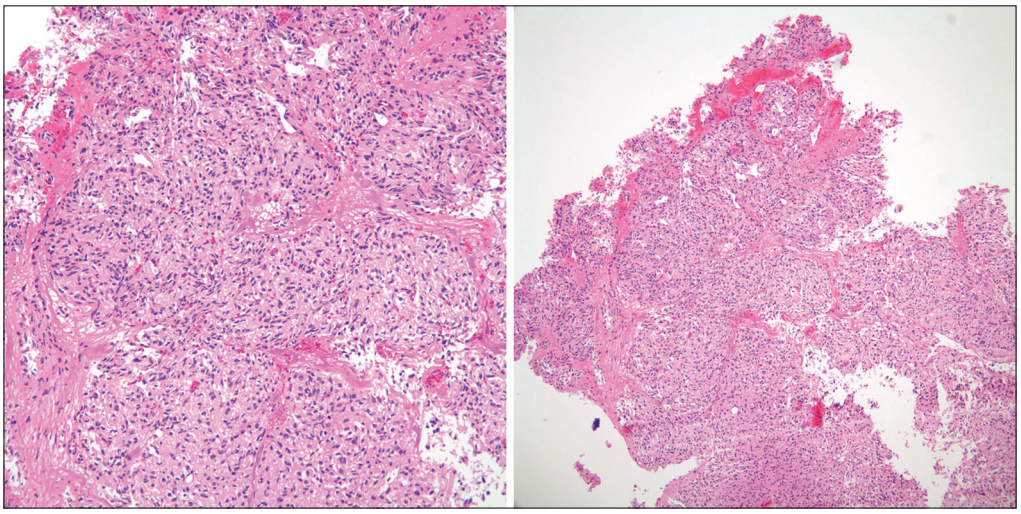

Figure 2: Representative area of the tumor stained with (H and E, ×10 and ×20), illustrating nests of round blue cells with round-to-ovoid nuclei and distinct cytoplasmic borders

organs that secrete catecholamines or indolamine hormones.[7,13] They are divided into two types with the first type being sympathetic paraganglia which lie along a paravertebral distribution and secrete catecholamines in response to an increased sympathetic drive.[7] The second type is the parasympathetic paraganglia which are primarily associated with the vascular structures supplying the IX and X cranial nerves and serve as chemoreceptors.[7]

Paragangliomas are rare tumors with an estimated incidence of 1 per 100,000.[7,10] Ninety percent of these tumors are sporadic, as in the case of our patient who had no family history of neuroendocrine tumor, but 10% can be associated with familial syndromes such as MEN 2A/2B, neurofibromatosis type 1, von Hippel-Lindau, and Sturge–Weber.[2,7] Malignancy is even rarer and depends on the site of the primary neoplasm with intra-adrenal tumors having a <10% chance of metastasis.[10] However, in patients like ours who have a history of extra-adrenal abdominal paraganglioma, reported rates of malignancy have varied between 15% and 35%.[7,10,14] Currently, no microscopic or laboratory criteria exist to reliably predict metastatic potential. However, malignant tumor is more often associated with a greater dry weight of the primary tumor, confluent necrosis, and presence of local invasion.[3,7]

The assessment for metastatic disease is performed via various imaging techniques. Besides standard MRI and CT imaging, functional nuclear medicine tests have increasingly been used to assess the extent of disease of neuroendocrine tumors. The most common nuclear medicine test for pheochromocytoma/paraganglioma is the MIBG scan.[2] Radio-labeled MIBG is a molecular analog of norepinephrine that has gained popularity due to its highly specific uptake into the tissue of neural crest origin by plasma membrane norepinephrine transporters.[11] A recent prospective multicenter trial performed by Wiseman *et al*. estimated the sensitivity and specificity of this test at 82–88% and 82–84%, respectively.[11] While MIBG scanning remains the mainstay, other functional studies such as octreotide scanning are being actively investigated and compared to MIBG results. Radio-labeled octreotide is an analog of the naturally occurring hormone somatostatin that has been found to be useful in imaging neuroendocrine tumors due to its specific binding to somatostatin receptors on tumor cells of this subgroup.[6] Interestingly, octreotide scanning may be superior to MIBG scanning depending on the location of the tumor, with one study by Koopmans *et al*. suggesting that octreotide scanning may be superior to MIBG scanning for the detection of primary head and neck paragangliomas.[6]

Defining the extent of disease is important as surgical resection is the mainstay of treatment even for metastatic disease. If the disease is not resectable, chemotherapy and/or application of therapeutic levels of I-131 MIBG for radiotherapy may be considered.[9] Given the small numbers of patients with metastatic paraganglioma, there is a paucity of data with regard to optimum chemotherapy. However, the cyclophosphamide, vincristine, and dacarbazine (CVD) protocol is the only chemotherapy regimen that has been used more than sporadically and is thus the treatment protocol of choice by default because of its more extended clinical experience.[1,9]

Hallmarks of diagnosis of a functional tumor are plasma and urine metanephrines. The sensitivity of urinary fractionated metanephrines for diagnosis of functional paraganglioma is approximately 97% and the specificity of urinary vanillylmandelic acid is approximately 95%.[2] Our patient had normal levels of urine metanephrines

but had highly elevated levels of serum chromogranin A which is a major component of neurosecretory granules and thus is highly suggestive of neuroendocrine tumor.[7]

The most common sites for metastatic spread are bone, liver, and lung in order of decreasing frequency.[5] Only a few reports of intracranial metastasis for pheochromocytoma exist and to our knowledge, only two other cases of intracranial metastasis have been reported for paraganglioma.[4,8,14] Although Zhang *et al*. have reported a single case of intraparenchymal involvement of metastatic disease from a paraganglioma, our patient and all other reports of intracranial metastasis demonstrated extra-axial lesions that often involved the skull table. The prognosis of metastatic disease depends on the location of metastasis with lung and liver metastasis having the worst prognosis. Bony metastasis such as that in our patient seems to have a slower growth and progression rate.[12] Some case series have reported that the average time between primary resection and the discovery of metastasis is approximately 9 years.[2] Wen *et al*. recently reported a series of 67 patients with retroperitoneal paraganglioma where 9 of 67 patients eventually developed metastatic lesions. However, the latest metastasis was discovered only 5 years after the resection of the primary tumor.[10] Mercuri *et al*. have reported a meningeal pheochromocytoma that was discovered 23 years after the initial resection of the adrenal primary tumor.[8] By comparison, our patient had metastatic disease discovered 34 years after his last abdominal resection which represents the longest reported disease-free period prior to the discovery of metastatic disease in the literature. Given the long possible latency period between primary disease and discovery of metastasis or disease recurrence, long-term follow-up appears warranted.

CONCLUSIONS

Paragangliomas are rare tumors of neural crest origin. Metastatic disease is uncommon and intracranial metastasis is among the rarest forms of metastasis. There are unfortunately no known criteria to assess the risk of metastatic potential, and given the long latency period between the resection of primary tumor and the discovery of metastatic disease, patients with paragangliomas require lifelong monitoring. The optimal interval of monitoring has not been elucidated but follow-up every 5–10 years seems warranted.

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REFERENCES

1. Averbuch SD, Steakley CS, Young RC, Gelmann EP, Goldstein DS, Stull R, *et al*. Malignant pheochromocytoma: Effective treatment with a combination of cyclophosphamide, vincristine, and dacarbazine. Ann Intern Med 1988;109:267-73.
2. Disick G, Palese M. Extra-adrenal pheochromocytoma: Diagnosis and Management. Curr Urol Rep 2007;8:83-8.
3. Fritzsche FR, Bode PK, Koch S, Frauenfelder T. Radiological and pathological findings of a metastatic composite paraganglioma with neuroblastoma in a man: A case report. J Med Case Reports 2010;4:374.
4. Gezen F, Ziyal IM, Baysefer A, Kahraman S, Ciklatekerlioglu O. Calvarial metastasis of a paraganglioma: Case report and review of the literature. Surg Neurol 2000;53:61-3.
5. Grabel JC, Gottesman RI, Moore F, Averbuch S, Zappulla R. Pheochromocytoma presenting as a skull metastasis with massive extracranial and intracranial extension. Neurosurgery 1990;27:134-7.
6. Koopmans KP, Jager PL, Kema IP, Kerstens MN, Albers F, Dullaart RP. 111In-octreotide Is superior to 123I-metaiodobenzylguanidine for Scintigraphic detection of head and neck paragangliomas. J Nucl Med 2008;49:1232-7.
7. McNicol AM. Differential diagnosis of pheochromocytomas and paragangliomas. Endocr Pathol 2001;12:407-15.
8. Mercuri S, Gazzeri R, Galarza M, Esposito S, Giordano M. Primary meningeal pheochromocytoma. J Neurooncol 2005;73:169-72.
9. Scholz T. Clinical review: Current treatment of malignant pheochromocytoma. J Clin Endocrinol Metab 2007;92:1217-25.
10. Wen J, Li H, Ji ZG, Mao QZ, Shi BB, Yan WG. A decade of clinical experience with extra-adrenal paragangliomas of retroperitoneum: Report of 67 cases and a literature review. Urol Ann 2010;2:12-6.
11. Wiseman GA, Pacak K, O'Dorisio MS, Neumann DR, Waxman AD, Mankoff DA, *et al*. Usefulness of 123I-MIBG scintigraphy in the evaluation of patients with known or suspected primary or metastatic pheochromocytoma or paraganglioma: Results from a prospective multicenter trial. J Nucl Med 2009;50:1448-54.
12. Yoshida S, Hatori M, Noshiro T, Kimura N, Kokubun S. Twenty-six-years' survival with multiple bone metastasis of malignant pheochromocytoma. Arch Orthop Trauma Surg 2001;121:598-600.
13. Young WF. Paragangliomas: Clinical overview. Ann N Y Acad Sci 2006; 1073:21-9.
14. Zhang L, Li F, Zhang Y, Zhu S. A rare paraganglioma with skull and brain metastasis. J Clin Neurosci 2010;17:644-6.