Malignant pheochromocytoma with cerebral and skull metastasis: A case report and literature review

Jun-Chen Chen, Dong-Zhou Zhuang, Cheng Luo, Wei-Qiang Chen

Abstract

BACKGROUND
Malignant pheochromocytoma with cerebral and skull metastasis is a very rare disease. Combining our case with 16 previously reported cases identified from a PubMed search, an analysis of 17 cases of malignant cerebral pheochromocytoma was conducted. This literature review aimed to provide information on clinical manifestations, radiographic and histopathological features, and treatment strategies of this condition.

CASE SUMMARY
A 60-year-old man was admitted with a progressive headache and enlarging scalp mass lasting for 3 mo. Radiographic images revealed a left temporal biconvex-shaped epidural mass and multiple lytic lesions. The patient underwent a left temporal craniotomy for resection of the temporal tumor. Histopathological analysis led to identification of the mass as malignant pheochromocytoma. The patient’s symptoms were alleviated at the postoperative 3-mo clinical follow-up. However, metastatic pheochromocytoma lesions were found on the right 6th rib and the 6th to 9th thoracic vertebrae on a 1-year clinical follow-up computed tomography scan.

CONCLUSION
Magnetic resonance spectroscopy and histopathological examination are necessary to make an accurate differential diagnosis between malignant cerebral pheochromocytoma and meningioma. Surgery is regarded as the first choice of treatment.

Key Words: Malignant pheochromocytoma; Catecholamine-secreting; Cerebral metastasis; Skull metastasis; Meningioma; Magnetic resonance spectroscopy; Case report

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**Core Tip:** Malignant pheochromocytoma with cerebral and skull metastasis is a very rare disease. We present the case of a 60-year-old male patient with malignant cerebral and skull pheochromocytoma who underwent surgical resection. A literature review was performed to provide information on clinical manifestations, radiographic and histopathological features, and treatment strategies of this condition. Clinical features may be similar between malignant cerebral pheochromocytoma and meningioma because they have a strong relationship in terms of genetic origin. Magnetic resonance imaging spectroscopy and histopathological examination are necessary to make an accurate differential diagnosis between malignant cerebral pheochromocytoma and meningioma. Different treatment strategies are discussed, including surgery, radiotherapy, and chemotherapy.

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**INTRODUCTION**

Pheochromocytomas are rare catecholamine-secreting neuroendocrine tumors that originate from the chromafin cells of the sympathoadrenal system[3,4]. The incidence of pheochromocytoma in the general population ranges from 0.0002% to 0.0008%[5]. Most pheochromocytomas are located in the adrenal gland due to this location having the largest collection of chromaffin cells[2,3]. Similar to pheochromocytomas, paragangliomas are catecholamine-secreting tumors that arise from extra-adrenal sites along with tumors of the sympathetic nervous system and/or pheochromocytomas (such as the neck, mediastinum, abdomen, and pelvis)[5,6]. Accumulating evidence suggests that the possible mechanism of pheochromocytomas is related with germline mutations in known susceptibility genes, such as NF1 and VHL[7]. In the case of malignant pheochromocytomas, metastases are present in aberrant endocrine tissue without chromaffin cells[5,28]. In general, approximately 2%-26% of pheochromocytomas and paragangliomas are malignant[5]. These metastases are usually located in the bones, liver, lungs, kidneys, and lymph nodes[5,28].

However, malignant pheochromocytomas with cerebral and skull metastasis are even more uncommon. This report describes a case of malignant pheochromocytoma with cerebral and skull metastasis and reviews 16 previously documented cases to gain a better understanding of malignant pheochromocytomas with cerebral and skull metastasis, including the mechanisms of pathogenesis, histopathological and immunohistochemical characteristics, clinical manifestations, radiographic features, and treatments. Furthermore, we also compared malignant pheochromocytoma and meningioma. This study was reviewed and approved by the Ethics Committee of The First Affiliated Hospital of Shantou University Medical College (B-2020-222).

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**CASE PRESENTATION**

**Chief complaints**
A 60-year-old man was admitted with a progressive headache and enlarging scalp mass.

**History of present illness**
The patient’s symptoms started 3 mo ago with a progressive headache and enlarging scalp mass.

**History of past illness**
The patient’s family reported that he had a history of left adrenal pheochromocytoma, which presented as paroxysmal hypertension and was finally surgically removed at another hospital 5 years prior. The patient also had a 15-year history of gout.
**Personal and family history**

No pertinent family history was identified, including von Hippel-Lindau syndrome, multiple endocrine neoplasia type 2, and neurofibromatosis type 1.

**Physical examination**

The blood pressure was 138/86 mmHg, and the heart rate was 83 beats per minute. The neurological and physical examinations revealed a left temporal scalp mass (6.0 cm × 4.0 cm × 2.0 cm), which was hard and fixed. Other physical findings were unremarkable.

**Laboratory examinations**

Routine laboratory tests and preoperative hemodynamic and cardiovascular assessments were ordered. The 24-h urinary vanillylmandelic acid (VMA) and metanephrine levels were within normal limits.

**Imaging examinations**

Magnetic resonance imaging (MRI) revealed a biconvex-shaped epidural mass (6.0 cm × 4.0 cm × 3.4 cm) that compressed the left temporal lobe with extracranial and intracranial extension (Figure 1A-D). The mass showed mixed hypo-and hyperintensity on T1-weighted imaging (T1WI) and T2-weighted imaging (T2WI). After gadolinium injection, the homogeneous enhancement of a well-defined lesion with a dural tail sign was observed. Cranial computed tomography (CT) demonstrated multiple lytic lesions in the left temporal bone (Figure 1E and F). The abdominal CT findings were unremarkable, with adrenal lesions. Based on the above findings, our differential diagnosis of this mass lesion included malignant meningioma, skull neoplasm, and even rare malignant pheochromocytoma.

**FINAL DIAGNOSIS**

Malignant pheochromocytoma with cerebral and skull metastasis.

**TREATMENT**

The risk of surgical intervention and general anesthesia was high because of the size and abundant blood supply of the tumor. In consultation with the anesthesiologist, adequate preoperative preparations were proposed: Standard blood pressure control (below 160/90 mmHg) and no S-T segment changes or T-wave inversions on electrocardiography. Adequate red blood cells and frozen plasma preparations were also recommended.

The patient underwent a left temporal craniotomy for resection of the temporal tumor. After making an incision in the skin, we found that the tumor had invaded the musculi temporalis. The mass was tightly attached to and infiltrating the underlying bone. Bony decompression (approximately 7 cm × 7 cm) was achieved to completely resect the lesion. After decompression, tumor tissue was found in the epidural space with a blood supply from the underlying dura. Direct tumor manipulation and coagulation and debulking of the supplying blood vessels resulted in significant alterations in blood pressure (70-230/40-110 mmHg). Four units of red blood cells and 400 mL of fresh-frozen plasma were transfused to counteract the blood loss during the operation. The tumor and surrounding dura were completely resected, and no remaining mass was seen in the subdural space. Then, dural grafting was performed with artificial dura. Finally, the outer layers were sutured step-by-step to achieve anatomical reduction. After surgery, the patient was transferred to the intensive care unit and placed under close surveillance.

Histopathological analysis led to identification of the mass as malignant pheochromocytoma. Grossly, the surgical specimen was separated into the extracranial part (the musculi temporalis) and the intracranial part (the epidural mass with adhered temporal bone) (Figure 2A and B). Both of these parts were grayish-yellow in color on the cut section. Microscopically, the specimens revealed nested and trabecular arrangements of neoplastic cells surrounded by a labyrinth of capillaries. Granular cytoplasms and round-to-oval nuclei with prominent nucleoli were noted in the neoplastic cells. Immunohistochemical analysis revealed strong, diffuse immunoreactivity for vimentin, Syn, and CgA but negative nuclear and cytoplasmic
Figure 1 Radiographic images of the presenting case. A: Magnetic resonance imaging (MRI) T1-weighted imaging showed an isointense left temporal lobe mass; B: MRI T2-weighted imaging showed a mixed hypointense and hyperintense left temporal lobe mass; C: Homogeneous enhancement of well-defined lesion was showed on axis MRI after intravenous contrast material; D: Coronal MRI showed the left temporal lobe mass after intravenous contrast material; E: Unenhanced computed tomography (CT) scan indicated the left temporal lobe mass; F: Multiple lytic lesion of the left temporal bone was noted on CT scan.

immunoreactivity for S-100, EMA, and CD10. The P53 labeling index was approximately 1%, while the Ki-67 labeling index was 20% (Figure 2C-F).

OUTCOME AND FOLLOW-UP

Neither fluctuating blood pressure nor cardiac dysfunction parameters were noted in the postoperative course. One week after the operation, the patient’s headache was alleviated. He did not receive chemotherapy, radiotherapy, or targeted therapy.

Based on the postoperative 3-mo clinical follow-up, the patient had a favorable outcome, reporting that symptoms were diminished, with normalized blood pressure and catecholamine values and no relapse of the mass on follow-up cranial MRI examinations (Figure 3A and B). However, metastatic pheochromocytoma lesions were found on the right 6th rib and the 6th to 9th thoracic vertebrae on a 1-year clinical follow-up CT scan (Figure 3C).

DISCUSSION

Preoperative clinical manifestations

Malignant pheochromocytomas with cerebral and skull metastasis have preoperative clinical manifestations that vary among patients. According to previous studies, headache, vomiting, and cognitive deterioration are the most frequent symptoms in these patients and are related to the mass effect on the brain parenchyma. Another important symptom is hypertension (including paroxysmal hypertension), which does coincide well with the features of typical pheochromocytomas because of the excess catecholamine secretion. In contrast to the above symptoms of functioning tumors, nonfunctioning malignant pheochromocytomas with cerebral and skull metastasis are usually clinically silent or just painless scalp masses. Some cases were found due to regular radiographic surveillance[16,23]. Silent clinical manifestations may delay the accurate diagnosis, and some patients may develop symptoms because of the
Malignant cerebral pheochromocytoma

Typically, the diagnosis of pheochromocytomas should be based on the findings of different examinations, including clinical, laboratory, and imaging examinations. Preoperative symptoms might be significant signs of deterioration in those with a previous history of pheochromocytoma. We recommend regular radiographic surveillance for pheochromocytoma patients so that malignant metastatic growth can be detected early.

Malignant cerebral pheochromocytoma vs meningioma

We considered meningioma as a differential diagnosis of malignant pheochromocytoma because they share comparable complaints, clinical manifestations, and imaging features, as observed in our case. Previous studies have indicated that malignant pheochromocytoma has a strong relationship with meningioma in terms of genetic origin. Pheochromocytoma and meningioma originate from a common embryological tissue — the neural crest. The cells of the meninges, the adrenal medulla, and paraganglionic tissue are derived from the neural crest. This feature can be strengthened by evidence of “neurocristopathies” (disorders of the neural crest). For example, pheochromocytoma may exist in von Hippel-Lindau disease, and metastatic growth of the tumor, which may make subsequent therapy a challenge.

Figure 2 Histopathological appearances of the left temporal lobe mass. A: The extracranial part (the musculi temporals) of the gross surgical specimen; B: The intracranial part (the epidural mass with adhered temporal bone) is showed; C: Neoplastic cells arranged in a nested and trabecular fashion and surrounded by a labyrinth of capillaries are demonstrated (hematoxylin and eosin, × 40); D: Hematoxylin and eosin, × 100; E: Hematoxylin and eosin, × 400; F: Immunohistochemical analysis revealed strong diffuse immunoreactivity for CgA.

Figure 3 Follow-up radiographic images of the presenting case. A: No relapse of mass was showed on 3-mo follow-up magnetic resonance imaging (MRI) T1-weighted imaging; B: Cerebral edema was presented on the left temporal lobe on 3-mo follow-up MRI; C: Metastasis of pheochromocytoma was noted on the rib and vertebra on 1-year clinic follow-up computed tomography.
According to the literature review, 12 of 17 patients underwent surgical resection for the treatment of malignant pheochromocytoma with cerebral and skull metastasis. Decompressive surgery was performed in only one patient for relief of the increased intracranial pressure (Table 1). Good clinical outcomes were found in 9 of 12 patients who underwent surgical resection on follow-up. It seems that surgical resection is the primary curative treatment for those patients. Most metastatic cerebral and skull lesions of malignant pheochromocytoma are superficial to the cerebral hemispheres and easier to remove than tumors in deep parts of the central nervous system. First, complete surgical resection can reduce anatomical complications, such as headaches due to mass effects and cerebral edema. Second, removal of the tumor can reduce or even abolish excess catecholamine secretion such that the normalization of blood pressure and relief of hormonal manifestations can be achieved. Third, the opportunity for distant metastasis can be reduced. Last but not least, surgical resection reduces the tumor burden and is beneficial for subsequent radiotherapy because fewer doses of irradiation are needed, which thus reduced the potential for complications of radiation (i.e., bone marrow suppression).

Adequate preoperative management is key to successful surgical resection. Consistent with benign pheochromocytoma, in malignant pheochromocytoma, patients need to achieve good control of hypertension using alpha- and beta-
# Table 1 Summary of malignant pheochromocytomas with cerebral and/or skull metastasis

| Ref.     | Year | Age (yr)/sex | Symptoms and signs                                | Location                                      | Surgery            | Immunohistochemical presentation | Adjuvant treatment | Clinical outcome                  | Others                                         |
|----------|------|--------------|---------------------------------------------------|-----------------------------------------------|--------------------|-----------------------------------|--------------------|------------------------------------|------------------------------------------------|
| Spatt et al[10] | 1948 | 51/F         | Headaches, falls, poor memory, drowsiness and convulsions | Multiple lesions in peduncles, cerebellum, pons, and cerebrum | Right subtemporal decompression | NR                               | None                             | Died 8th day postadmission          | NR                                             |
| Melicow et al[11] | 1977 | 61/M         | Headaches, convulsions, sweating, palpitation and hypertension | NR                                            | None                | NR                               | None                             | Died 6th week postadmission          | Metastases to liver and carcinoid of ileum |
| Ferrari et al[12] | 1979 | 47/M         | Progressive cognitive deterioration               | Multiple lesions in frontal, parietal, temporal, and occipital lobes and cerebrum | None               | NR                               | None                             | Died 22nd day postadmission         | NR                                             |
| Grabel et al[13] | 1990 | 43/F         | Painless scalp mass                               | Left parietal lesion                          | Surgical resection | Chromogranin and neuron-specific enolase and negative for prekeratin | Preoperative chemotherapy | Relieved                           |                                                 |
| Mornex et al[14] | 1992 | 49/M         | NR                                                | NR                                            | NR                 | NR                               | None                             | Died after 8 yr                      | Lung, lymph node metastases            |
| Gentile et al[15] | 2001 | 31/F         | Partial motor crisis                              | Right frontal lesion                          | Surgical resection | Neuro-specific enolase, S100 protein and chromogranin; negative for anti-calciton | None                             | No relapse of disease in 4-yr follow-up | MEN type 2a                             |
| Liel et al[16] | 2002 | 47/M         | Radiographic surveillance                        | Right frontotemporal                          | Surgical resection | Chromogranin, negative for progesterone receptors and epithelial membrane antigen | Postoperative MIBG therapy | Relieved                           | Coexistence of recurrent meningioma in the left hemisphere |
| Mercuri et al[17] | 2005 | 46/F         | Headaches, vomiting, hypertension                 | Right temporoparietal extra-axial lesion with inner table skull infiltration. Epidural and subdural | Surgical resection | Neuro-specific enolase, chromogranin A, synaptophysin; negative for anti-calciton | None                             | No relapse of disease in 6-yr follow-up | First primary meningeal pheochromocytoma |
| Kowalska et al[18] | 2009 | 60/F         | Hypertension                                      | Left frontal and parietal                     | Surgical resection | NR                               | Brain radiotherapy               | Relapse in the left front cerebral lobe and right cerebellar meningeoma | Coexistence of left temporal meningioma |
| Schaefer et al[19] | 2010 | 53/M         | Headaches, cognitive impairment, visual loss and shortness of breath | Left occipital                                | Surgical resection | Neuron specific enlase and chromogranin A, negative for keratin, somatostatin, and S-100 | Preoperative chemotherapy and postoperative radiotherapy | Relieved                           | Differing from the primary PCC only by loss at 18q on CGH analysis |
| Kharlip et al[20] | 2010 | 23/F         | Altered mental status                            | Left occipital, left parietal, and right frontal lobes | None               | NR                               | Chemotherapy and radiotherapy     | Relieved                           | Chemotherapy and radiotherapy                             |
| Schulte et al[21] | 2012 | 73/M         | Loss of cognitive function, a homonymous hemianopsia and left sided dysmetria | Right parietal lobe                           | Surgical resection | NR                               | Adjuvant whole brain radiotherapy | Relieved                           | First description of a cystic CNS metastasis |

NR: Not recorded
Malignant cerebral pheochromocytoma

| Authors | Year | Gender | Symptoms | Location | Treatment | Outcome | Other Information |
|---------|------|--------|----------|----------|-----------|---------|------------------|
| Miyahara et al. | 2017 | 58/M | Headache, right hemiparesis, aphasia, and dysarthria | Left parietal lobe | Surgical resection positive for chromagranin A, synaptophysin, and S100 | Preoperative Stereotactic radiosurgery | No recurrence for 1 yr |
| Boettcher et al. | 2018 | 24/M | Radiographic surveillance | Right posterior parietal, epidural lesion | Surgical resection Chromogranin, synaptophysin | None | Died several weeks later |
| Cho et al. | 2018 | 52/M | Headache, dizziness and motor aphasia | Multiple (more than 10) masses in the bilateral cerebral hemisphere and right pons | Surgical resection Synaptophysin, S100 | Radiotherapy | Died due to progressed intraabdominal cancer |
| Kammoun et al. | 2019 | 29/F | Headache, vomiting, hypertension | Extradural lesion attached to the tentorium | Surgical resection Chromogranin, synaptophysin, NSE | Postoperative whole brain radiotherapy | Death 1 month after second surgery. No other metastases found |
| Presenting case | 2020 | 60/M | Headache and enlarging scalp mass | Left temporal | Surgical resection Vimentin, Syn and CgA, negative for S-100, EMA and CD10 | None | No relapse of cranial mass |

CGH: Comparative genomic hybridization; CNS: Central nervous system; EMA: Epithelial membrane antigen; F: Female; M: Male; MEN: Multiple endocrine neoplasia; NR: No reported; PCC: Pheochromocytoma; SDHB: Succinate dehydrogenase subunit B.

In addition, an appropriate fluid and electrolyte balance is needed[3,32]. The introduction of opioids, antiemetics, neuromuscular blockage, or sympathomimetics and tumor manipulation could lead to a massive intraoperative outpouring of catecholamine, accompanied by fluctuating blood pressure and arrhythmia[34]. Endovascular embolization treatment may be beneficial for surgical resection[22]. It might reduce the blood loss and excess release of catecholamine during the operation. These adequate preoperative managements have a good impact on the process of anesthesia and surgery.

**Radiotherapy**: Based on our review of case reports on PubMed, 7 of 17 patients underwent radiotherapy or stereotactic radiosurgery[14,15,22,24,25]. The question of whether radiotherapy is beneficial to patients is still open. Kharlip et al.[20] reported success in a case in which the cerebral metastasis was nearly eliminated by radiotherapy, and the patient remained free of neurological symptoms without surgery. They suggested that radiotherapy at a dose of 3500 cGy to 4000 cGy should be a treatment option recommended for patients with cerebral metastatic lesions of pheochromocytoma. In the case presented by Cho et al.[24], postoperative radiotherapy partially decreased the size of multiple metastatic cerebral lesions on follow-up MRI[24]. Contrary to these two cases, radiotherapy and stereotactic radiosurgery showed poor effects in some other cases[22,24]. 

**Chemotherapy**: Chemotherapy is considered a choice for malignant pheochromocytoma patients who are not suitable for surgery. The cyclophosphamide, vincristine,
and dacarbazine regimen is usually used for neuroblastoma patients but is also used in malignant pheochromocytoma patients because neuroblastoma and pheochromocytoma share a common embryological tissue—the neural crest[8,9]. Only 3 of 17 patients had received adjuvant chemotherapy[28,29]. There is still a lack of systematic studies evaluating the value of chemotherapy because of the rarity of this pathology.

CONCLUSION

Malignant pheochromocytoma with cerebral and skull metastasis is extremely rare. It is noteworthy that malignant cerebral pheochromocytoma shares similar clinical manifestations with meningioma because both originate from a common embryological tissue—the neural crest. The different features on MRS and histopathological examination might help to make an accurate diagnosis. Although radiotherapy was effective in two cases, the summary of 17 cases indicates that surgery is the first treatment choice for malignant cerebral pheochromocytoma. Further studies are needed to gain better knowledge on the origin and treatment of malignant cerebral pheochromocytoma.

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