Letter to the Editor

Atypical meningiomas with multiple extracranial metastases: a case description

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Introduction

Meningiomas are mostly benign tumors originating from the arachnoid cap cells, with an annual incidence of 5/100,000, which gradually increases with age. It is the most common benign brain tumor of the central nervous system in adults (1). Meningiomas are more common in women, with a male-to-female ratio of approximately 2–3:1. Meningiomas can present with a wide range of clinical symptoms. Although most meningiomas are not malignant, they can cause clinical symptoms when they grow large and compress important areas of the brain or spinal cord. The 2016 World Health Organization (WHO) classification of tumors of the central nervous system classifies meningiomas into 3 types: benign (WHO class I), atypical (WHO class II), and anaplastic/malignant (WHO class III). The revisions of the WHO classification in 2007 produced a marked increase in atypical meningiomas (AMs) from the previously reported 5% (2-4). AMs have biological characteristics that fall between benign and malignant and are highly heterogeneous and invasive. Multiple extracranial metastases of AMs are rare, occurring in about 0.1% of cases. Most reported cases of metastasis have been found in the lungs, liver, or spine (5). Only a few similar cases have been documented, involving multiple distant metastases of intracranial meningiomas with extensive pleural metastatic features (6-8). However, it is important to note that these meningiomas are mostly mesenchymal in nature and often accompanied by intracranial recurrences. In this study, we present a rare case of AM with multiple metastases to the thorax, abdomen, and bone, while noting the absence of intracranial recurrence. Additionally, we provide a comprehensive review and discussion of the histopathologic features and mechanisms of metastatic meningiomas. The main objective of this study was to assist clinicians in minimizing misdiagnosis, improving diagnostic clarity, and offering valuable insights for the postoperative management and treatment of AM patients.

Case presentation

A 64-year-old female patient presented to the Neurosurgery Department of The Second Affiliated Hospital of Nanchang University in September 2018 due to a 3-month history of headache. Brain magnetic resonance imaging (MRI) suggested a possible hemangiopericytoma (*Figure 1A-1D*). Chest computed tomography (CT) showed no obvious abnormalities (*Figure 1E*). With the assistance of neuro-navigation, the doctor opened the skull through the right midline frontotemporal flap and saw that the tumor was encroaching on the skull and eroding the capitellar tendon, with poorly defined tumor margins and extremely rich blood supply, and removed it completely after freeing the tumor margins. Postoperative follow-up head MRI showed complete resection of the right frontal lesion (*Figure 1F*). After discharge, the patient underwent brain MRI scans every 6 months during follow-up visits, and no signs of tumor recurrence were detected (*Figure 1G,1H*). All procedures performed in this study were in accordance with

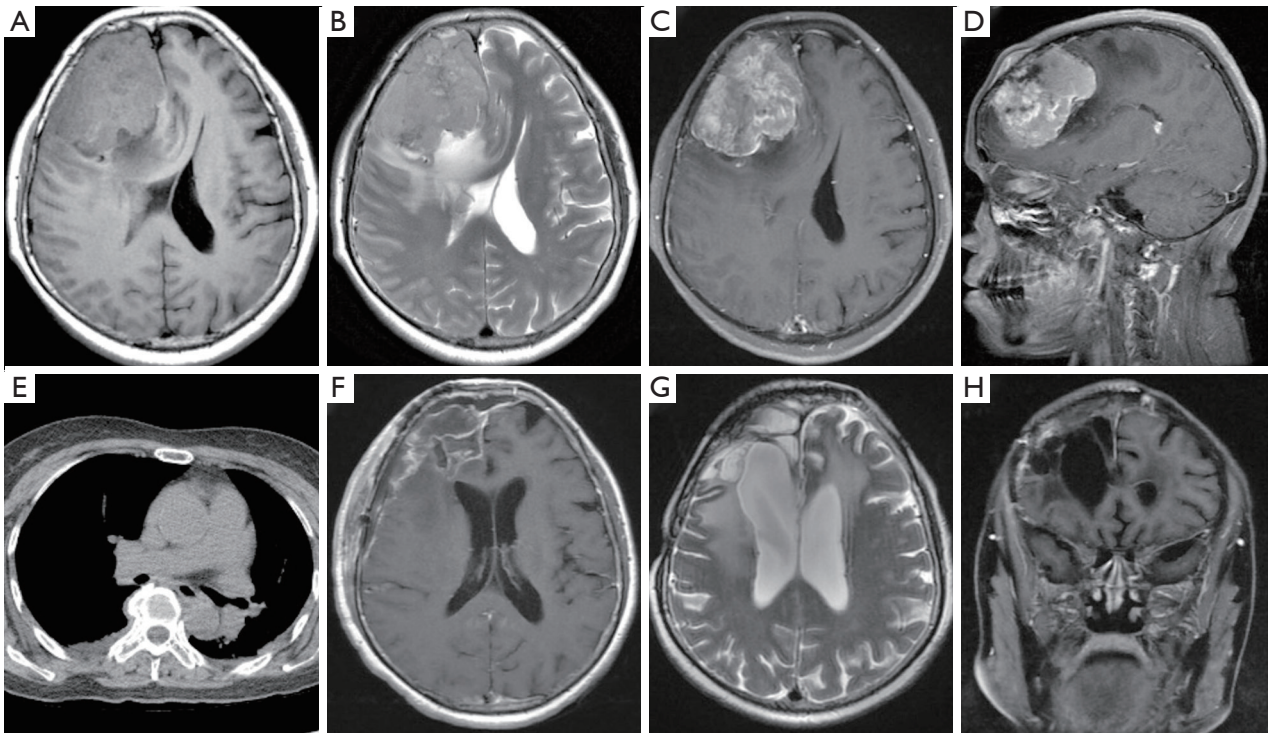

Figure 1 Preoperative and postoperative imaging data of patients. (A-D) MRI of the patient's brain before surgery in 2018, showing a large lobulated mass in the right frontal region (6.1 cm × 5.6 cm × 5.6 cm): (A) the T1-weighted image is mainly iso-intensity, and multiple spots and patchy low-intensity can be seen inside; (B) lesions that appeared iso- to hyper-intense on T2WI, multiple spots and flaky high signal can be seen inside. In addition, multiple vessels flow void sign can be seen around and inside the lesion; (C,D) transverse and sagittal T1-enhanced images, indicating that the mass has a rich blood supply, involves the adjacent frontal bone and grows extracranially, with cerebral herniation. (E) Preoperative chest CT plain scan showed no obvious abnormalities. (F) Postoperative transverse T1-enhanced image. (G,H) Brain MRI was re-examined 3 years after surgery (October 2021), and there was no clear sign of tumor recurrence. MRI, magnetic resonance imaging; T2WI, T2-weighted imaging; CT, computed tomography.

the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was provided by the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

In October 2021, the patient was admitted to the hospital due to persistent chest pain. Enhanced CT of the chest revealed the presence of multiple masses of varying sizes adjacent to the spine and pleura, extending into the abdominal cavity. The enhancement was significantly uneven, and the border between the liver parenchyma and right kidney was blurred (*Figure 2A-2D*).

Some abnormalities in the combination of lung cancer markers (*Table 1*) and no abnormalities were found in other electrolytes and routine blood tests. Whole-body bone scan revealed an abnormally active metabolism in the left posterior rib of the 7th and the right anterior ribs of the 7th and 8th vertebrae. The patient's physical status (PS) score was 1 point, and the numerical rating scale (NRS) was 1 point.

Immunization combined with targeted therapy was used for treatment, with camrelizumab for injection 200 mg day 1, oral administration of anlotinib hydrochloride 10 mg days 1–14, supplemented by symptomatic treatment such as antiemetic and stomach protection. After 6 cycles of treatment, the patient's symptoms improved and imaging showed a reduction in lesions compared to before surgery, indicating that the treatment was effective (*Figure 2E-2H*).

Pathological features: pathological findings of patients after the operation suggested an AM (WHO grade II) (*Figure 3A*). Puncture of the pleural mass, hematoxylin and

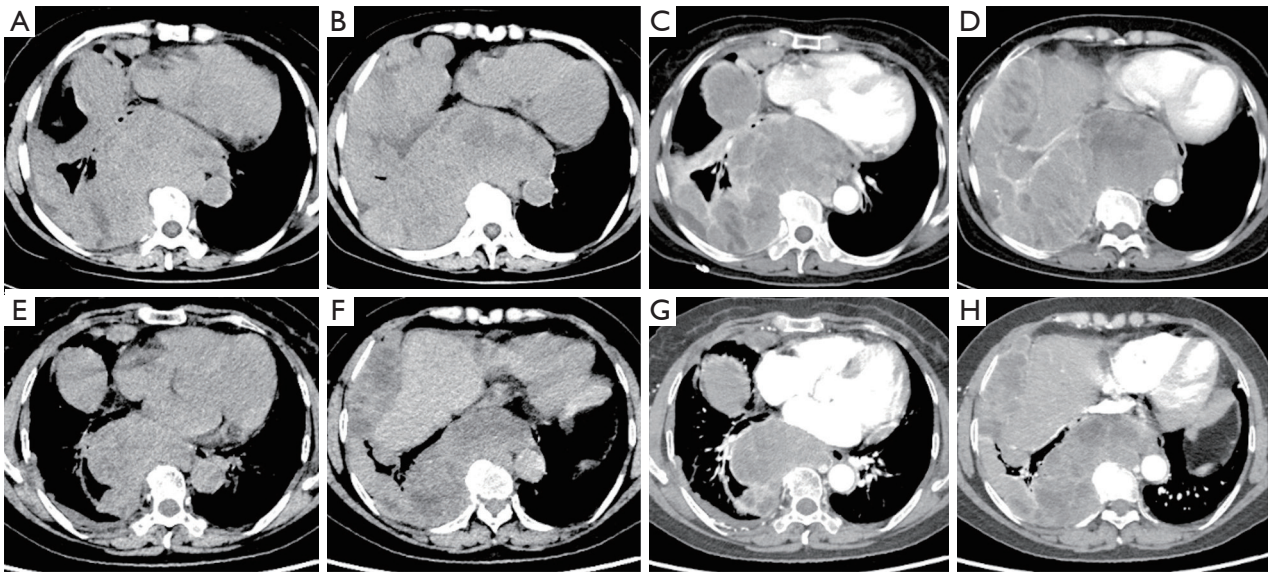

Figure 2 Chest CT of the patient with pleural metastases before treatment and after targeted therapy. (A-D) Three years after surgery (October 2021) review chest CT: (A,B) chest CT plain scan revealed multiple masses of various sizes in the paravertebral posterior mediastinum and the right pleura, extending to the abdominal cavity; (C,D) chest CT enhanced scan showed the mass with obvious heterogeneous enhancement. (E-H) After targeted therapy (January 2022), the plain and enhanced chest CT scan showed that multiple masses in the paravertebral posterior mediastinum and right pleura had shrunk compared to before. CT, computed tomography.

Table 1 Some experimental results and reference indicators of patients

Indicator	Test result	Reference value
CEA (ng/mL)	1.23	0–5.09
CA-199 (U/mL)	13.04	0–37
SCCA (ng/mL)	3.24↑	<2.5
NSE (ng/mL)	52.13↑	<10
Cytokeratin 19 fragment (ng/mL)	1.40	<3.3

↑ indicates that the corresponding indicator is higher than the normal range. CEA, carcinoembryonic antigen; CA-199, carbohydrate antigen-199; SCCA, squamous cell carcinoma antigen; NSE, neuron-specific enolase.

eosin (HE)-stained tumor cells were spindle-shaped or oval, arranged in a swirl shape, infiltrative growth, and extensive necrosis (*Figure 3B*). Immunohistochemical results: the patient's epithelial membrane antigen (EMA) (*Figure 3C*), vimentin (*Figure 3D*), and cluster of differentiation 34 (CD34) (*Figure 3E*) were all positive, and the Ki-67 proliferation index was high (hot spot >20%) (*Figure 3F*). Combined with the patient's right frontal AM medical history, the final pathological diagnosis was metastatic meningioma after biopsy and immuno-omics examination of the pleural lesion.

Discussion

AM is an aggressive form of meningioma, with a recurrence rate of 30–60% at 5 years after surgery, which poses a central and important issue in the management of AM patients (9-12). The pathogenesis of distant metastases from meningiomas is unknown and may be related to the following causes: (I) meningioma tumor cells located in the venous sinus shed into the cortical vein or invade the sagittal sinus, and metastasize to the extracranial through venous blood; (II) surgical resection increases the risk of tumor cell dissemination and implantation along the cerebrospinal fluid pathway; (III) Intraoperative salvage autotransfusion; (IV) metastases involving the spine and kidneys may be related to the metastasis of the paravertebral venous plexus; (V) extracranial metastasis by invading the lymphatic system around the cranial nerve (13-17).

In general, maximal safe resection is the recommended first-line treatment for all meningiomas (18,19). In order to prevent recurrence, Simpson I–II grade resection is often used clinically to completely remove the tumor

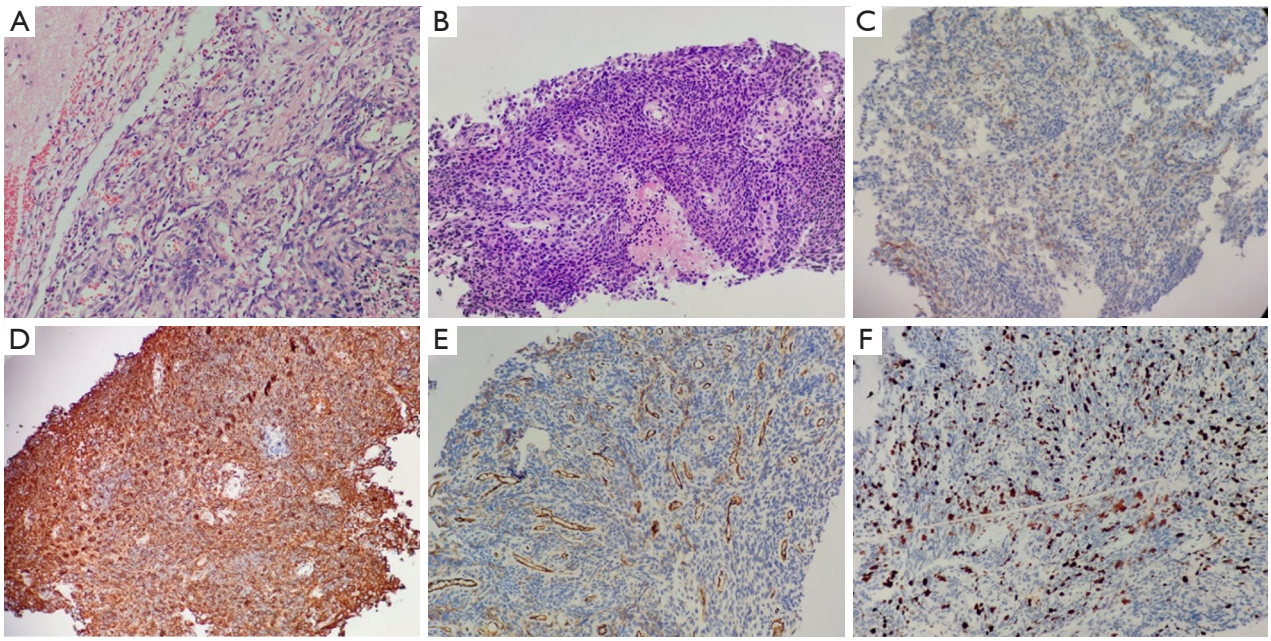

Figure 3 Histopathological and immunohistochemical examinations of intracranial and pleural masses. (A) In 2018, the patient's intracranial tumor surgery pathological results confirmed that it was an atypical meningioma, WHO grade II, the tumor cells were arranged in sheets, the cells were atypical and invaded the skull tissue, and focal necrosis could be seen (HE stain, 200×). (B) Pathology after puncture of the right pleural mass in October 2021, the tumor tissue was arranged in nests and swirls (HE stain, 200×). (C-E) Immunohistochemistry: positive for EMA, vimentin, and cluster of CD34, respectively (EnVision method, 200×). (F) Ki-67 positive index in lesions is 20%. Combined with medical history and immunohistochemistry, the right pleural mass was found to be a metastatic meningioma (EnVision method, 200×). WHO, World Health Organization; HE, hematoxylin and eosin; EMA, epithelial membrane antigen; CD34, differentiation 34.

within a safe range. The patient underwent Simpson I grade resection and postoperative adjuvant radiotherapy, but still had distant metastasis 3 years later. In most cases, patients with AMs should receive adjuvant radiotherapy after surgery; however, some studies have shown that there is no significant difference in progression-free survival whether or not radiotherapy is given after surgery (8,20). It has also been suggested that histopathological criteria could be reconsidered according to risk stratification for stronger prognostic value (i.e., 2 out of 3: absence of psammoma bodies, presence of necrosis, and/or ≥4 mitoses per 10 high-power fields) (21).

In recent years, more research has been conducted on the pathogenesis, development, and treatment of meningioma using molecular techniques, and monosomy 22 and NF2 inactivating mutations are genetic alterations that have been identified (22). Ongoing studies are focused on molecular characterization of gene mutations, such as *SMO*, *TERT*, *TRAF*7, and DNA methylation profiles. Sahm *et al.* conducted a genome-wide methylation pattern analysis and discovered that different methylation types were significantly correlated with tumor growth and recurrence patterns. They proposed a new classification system for meningiomas based on methylation category (23); however, the sample size of the study was too small and may be heterogeneous. Unfortunately, next-generation DNA/RNA sequencing and methylome analysis have not yet been performed in our patient; we believe that genetic testing can help to determine adjuvant treatment options for patients with meningioma metastases, and we will continue to follow up on the results of the patient's testing in the future.

The report indicates that metastases exhibited anaplastic characteristics, including cellular pleomorphism, nuclear atypia, and a high Ki-67 index. Immunohistochemistry and molecular pathology methods have been effectively utilized in the grading and typing of meningiomas. The markers EMA and vimentin are preferred auxiliary diagnostic markers for meningioma, specifically for identifying epithelial and mesenchymal tissue. These markers are used to differentiate between different types of meningiomas

and aid in diagnosis (24). An immunohistochemical marker alone may not accurately predict prognosis and needs to be used in conjunction with an indicator of cell proliferative activity, and Ki-67 is strongly correlated with the degree of malignancy, metastasis, or prognosis of meningiomas. Barrett reported that AMs with high expression of Ki-67 and mitotically active mitosis were prone to recurrence after surgery (25). The patient in this case report had a pleural metastasis with a Ki-67 hotspot of >20%, indicating that the tumor cells were highly malignant and proliferated rapidly.

In summary, our findings emphasize the importance of careful re-evaluation of patients with a history of intracranial meningeal tumors, especially patients with WHO grade II–III meningiomas, for early detection and treatment of any distant metastases, even if such metastases are rare, with the aim of maximizing the long-term prognosis of the patient. Recommend regular brain MRI to exclude *in situ* or borderline recurrence, as well as whole-body imaging to identify metastases, and genetic testing is also necessary to determine subsequent treatment options. In addition, the extracranial metastases in this patient were significantly reduced/shrunk with immunotherapy combined with targeted therapy, and future clinical trials, prospective studies, and further molecular studies are needed to reliably determine whether this treatment regimen is an effective treatment for extracranial metastases of meningiomas.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-565/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was provided by the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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