Case Report

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Deciphering extracranial metastasis in high-grade meningiomas: insights from a case study and literature review

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Introduction and importance: These high-grade meningiomas have higher recurrence rates and poorer survival outcomes compared to benign variants. This study presents a case of metastasis in a high-grade meningioma and a comprehensive analysis of the literature published between 2000 and 2023, including only original studies focused on extracranial metastasis.
Case presentation: We report the case of a 45-year-old female who presented with progressive left-sided weakness and partial seizures. Imaging revealed a large, lobulated extra-axial mass in the right parietal parasagittal region, which was surgically resected and diagnosed as an anaplastic meningioma (WHO grade III). Despite an initial recovery, the patient experienced tumor recurrence with local invasion, multiple metastases to the contralateral brain, liver, lung, spine, and long bone. Various treatments, including radiotherapy, chemotherapy, and surgery, were employed, but the disease progressed, leaving the patient bed-bound at 8 years follow up.
Clinical discussion: In our literature review, encompassing 247 patients with extracranial metastasis of meningiomas from seven studies, the lungs and bones were the most common metastatic sites. Patients with grade III meningiomas had poorer survival outcomes than those with grade II. Gross total resection (GTR) was associated with improved progression-free survival, while recurrence markedly reduced overall survival, underscoring the aggressive nature of metastatic meningiomas and the importance of early, comprehensive treatment strategies.
Conclusion: Extracranial metastasis in high-grade meningiomas poses significant diagnostic and therapeutic challenges. Our analysis underscores the complexity of managing these cases and highlights the critical need for early identification of high-risk patients and tailored treatment protocols to improve long-term outcomes.

Keywords: extracranial, meningioma, metastasis

Introduction

Meningiomas are considered the most common primary brain tumor[1–5]. Traditionally, they arise from arachnoid cap cells, which are commonly found in the arachnoid membrane and arachnoid villi associated with the venous sinuses[1]. They show considerable variable morphological patterns; however, they are most commonly benign. A small proportion of meningiomas exhibit atypical aggressive behavior and are considered as high-grade lesions[6–17]. They are classified based on the basis of mitotic activity and a certain histological feature such as pleomorphism, cellularity, and necrosis[8–20]. Overall, the 5-year survival rate for benign meningiomas is 88.0%, while it is 63.5% for high-grade tumors[4,9,20–23]. For totally resected high-grade meningiomas, the local recurrence rate has been reported in 9% to 32% of cases[19,20].

Furthermore, the exact incidence of distant extracranial spread among meningioma is unknown, and it is estimated to be less than 1%[4,9,23]. Due to the rarity of extracranial spread in meningiomas, the most reported literature consists of isolated case reports and a few case series. The most frequent locations to be involved in extracranial spread are the lung, liver, and bone[10,17,23–27]. The risk factors and genomic makeup of metastasizing meningioma are poorly understood due to the scarcity of the literature. There are no established criteria for the prediction of extracranial metastasis of meningioma. In this article, we describe a high-grade meningioma with extracranial spread to different locations including the liver, lung, spine, and non-spine bone. We then systematically review the existing literature to summarize the findings of published case series of high-grade metastasizing meningioma.

Case description

History and physical examination

The disease course began when a 45-year-old female patient presented in 2016 with a progressive left-sided weakness and several episodes of partial seizure to the hospital over a duration of two years. Physical examination was notable for left-sided weakness of grade 3/5 and a positive Babinski sign. Besides this, fundoscopy demonstrated stage II papilledema. Other systemic examination findings were unremarkable.

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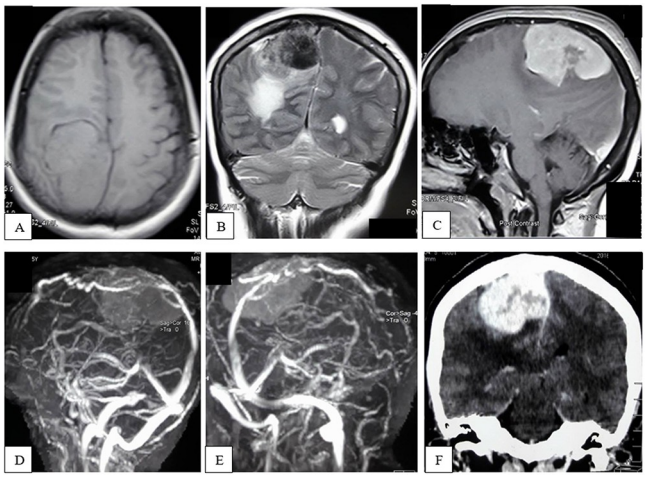

Figure 1. MRI of the brain, done in 2016, demonstrated a large, lobulated extra-axial T1WI hypointense, T2WI heterogeneously hyperintense mass lesion measuring about 5 cm in cranio-caudal, 6 cm in antero-posterior, and 4.4 cm in transverse diameter, which is noted in the parasagittal location in the right parietal region with moderate perilesional edema. The mass effect was evident by compression over adjacent sulci, posterior horn of the right lateral ventricle and the midline shift (MLS) of 8 mm towards left (A, B). After IV contrast (Gd-DTPA) administration, strong homogeneous enhancement was noted with few non-enhancing hypointense areas representing necrosis (C). The MRV-TOF sequence demonstrated that the superior sagittal sinus (SSS) was compressed at its middle part with multiple dilated tortuous vessels surrounding the mass, representing collateral circulation. Other cerebral venous sinuses showed a normal course, caliber, and flow pattern (D, E). A post-contrast CT scan demonstrated an intense heterogeneously contrast enhancing parasagittal lesion with moderate MLS.

Imaging

A gadolinium-enhanced MRI was performed and revealed a fairly large, lobulated extra-axial T1WI hypointense, T2WI heterogeneously hyperintense mass lesion, measuring about 5 cm in cranio-caudal, 6 cm in antero-posterior, and 4.4 cm in transverse diameter, which is noted in the parasagittal location in the right parietal region with moderate perilesional edema. The mass effect was evident by compression over adjacent sulci, posterior horn of the right lateral ventricle and the midline shift of 8 mm toward left (Fig. 1A, 1B). After IV contrast (Gd-DTPA) administration, strong homogeneous enhancement was noted with few non-enhancing hypointense areas representing necrosis (Fig. 1C). Besides this, the MRV-TOF sequence demonstrated that the superior sagittal sinus was compressed at its middle part with multiple dilated tortuous vessels surrounding the mass, representing collateral circulation. Other cerebral venous sinuses showed a normal course, caliber, and flow pattern (Fig. 1D, 1E). A CT scan of the brain, post-contrast sequence, was consistent with features of the parasagittal meningioma depicting intense heterogenous contrast enhancement with no features of overlying hyperostosis or osteolysis (Fig. 1F).

Surgery and follow-up

With all aseptic precaution, the patient underwent right-sided parietal parasagittal craniotomy and Simpson grade II resection of a tumor in the similar year. She had an uneventful post-operative recovery. There was no new neurological deficit, and she discharged from the hospital at the fifth post-operative day. A histopathology report was consistent with anaplastic meningioma (WHO grade III), which showed a cellular tumor composed of sheets of polygonal cells having round to oval nuclei and a moderate amount of clear cytoplasm. Nuclear pleomorphism was mild to moderate with frequent mitoses (6-10/HPF), whereas ocassional cells showed intranuclear pseudoinclusion. Surgery was followed by extensive rehabilitation with gradual resolution of the previously described neurologic symptoms. Due to economic constraint and familial issues, she denied any additional investigations or adjuvant chemoradiation. A follow-up CT scan in 2021 was consistent with no sign of recurrence with encephalomalachic changes in the parietal lobe (Fig. 2A, 2B). However, there were no signs of progression until 2022, when she seeks medical attention for progressively increasing localized headache for which the follow-up MRI of the brain was done, which demonstrated a small recurrence of a tumor in the previously resected area following the territory of the superior sagittal sinus (Fig. 3). She again denied undergoing any surgical intervention and adjuvant chemoradiation. In 2023, she experienced several episodes of convulsion despite having antiepileptic medication. Her contralateral weakness became aggravated for which repeat MRI demonstrated multilobulated tumor growth around the superior sagittal sinus, falx cerebri, distal subgaleal spread, and metastasis of the C2 spinous process (Fig. 4A, 4B). Additionally, the patient was discovered to have several metastatic lesions affecting the liver. The patient received 3D CRT: brain: 3000 cGy in 10 fractions, dorsal: 800 cGy in 1 fraction, lumber: 2000 cGY in 5 fractions, pelvis: 800 cGy in 1 fraction from 15 May 2023 to 5 June 2023. After that, she was on tab ponatinib till now. In December, 2023, she had pathological fracture of the shaft of the right femur and underwent open reduction and internal fixation surgery. Biopsy from the surgical site was consistent with metastasis of anaplastic meningioma. Due to aggravation of hemiparesis and a surgical procedure, she became completely bed-bound from January, 2024. The work has been reported in line with the SCARE 2023 criteria[28].

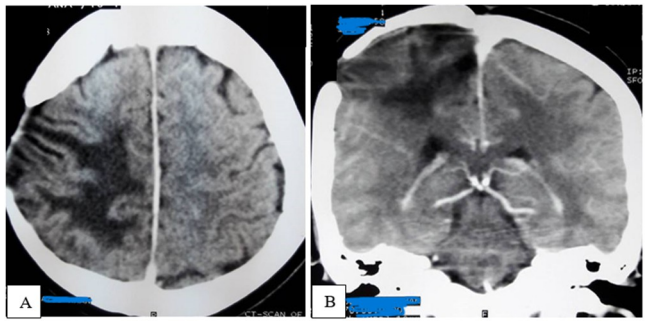

Figure 2. Follow-up CT scan of the brain and axial (A) and coronal (B) section after 5 years demonstrated no evidence of recurrence with encephalomalachic changes involving the right parietal lobe.

Analysis of patients from reviewed literature

Table 1 summarizes data of a total of 247 patients from seven original studies conducted between 2000 and 2023. The patient population is diverse, with both male and female patients

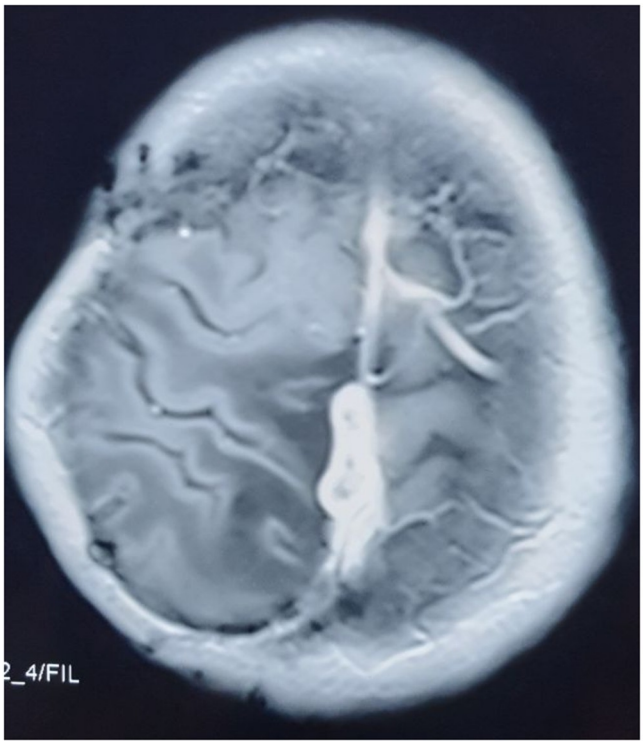

Figure 3. Follow-up MRI of the brain, done in 2022, post-contrast axial section demonstrated a small recurrence following the territory of SSS.

represented across a broad age range. The studies predominantly focus on patients with grade II and grade III meningiomas, which are known for their higher likelihood of aggressive behavior and potential for extracranial metastasis. Our analysis also reflects a near-equal gender distribution, with 128 male patients (51.8%) and 119 female patients (48.2%). The age of patients spans a wide range, which indicates that metastasis can occur at various stages of life; specifically, 158 patients (64%) were between the ages of 30 and 60. However, the data do not allow for a clear determination of whether age is a significant factor in the likelihood of extracranial metastasis.

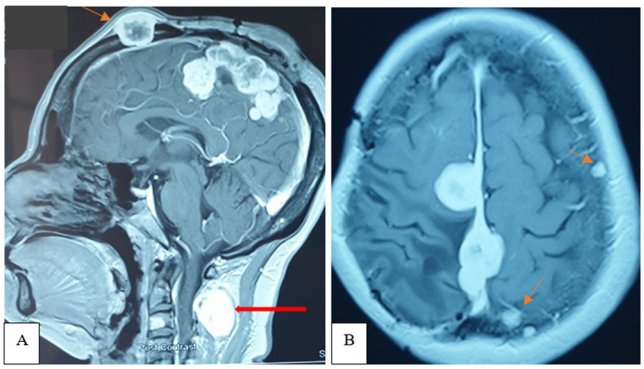

Figure 4. Repeat MRI of the brain in 2023 post-contrast sagittal (A) and axial (B) section demonstrated multiple recurrences with local invasion (marked by orange arrowhead) and metastasis to a C2 spinous process (marked by red arrowhead).

The primary locations of meningiomas in these patients include various regions of the brain, such as the cranial vault, falx, convexity, and parasagittal regions. Among the patients, 149 (60.3%) had grade II meningiomas, while 98 (39.7%) had grade III meningiomas. Grade III meningiomas are generally associated with higher metastatic potential, which is reflected in the data where these patients often had more severe outcomes. The primary locations of meningiomas included various regions of the brain. The cranial vault was the most frequently reported site, noted in 143 patients (57.9%). Other locations included convexity (15.8%), falx (12.6%), and parasagittal regions (13.7%). The varying primary locations suggest that while the exact origin site may influence metastatic pathways, it does not limit the potential for metastasis to extracranial sites.

The table highlights the diverse extracranial sites affected by metastasis, including the lungs, bones, liver, and other organs. The lungs and bones were the most frequently reported sites of metastasis, occurring in 176 patients (71.3%) and 132 patients (53.4%), respectively. This pattern may be due to the rich vascular supply to these regions, facilitating the dissemination of tumor cells. In 82 patients (33.2%), metastasis was observed in multiple extracranial sites, indicating an advanced stage of disease with widespread dissemination. These cases underline the aggressive nature of certain meningiomas, particularly those that have undergone multiple recurrences or are of higher histological grade.

The studies detail various surgical and adjuvant therapies used in the management of these metastatic meningiomas. The extent of surgical resection varied, with some patients undergoing gross total resection (GTR) and others subtotal resection (STR) or even just biopsy. Among the patients, 152 (61.5%) underwent gross total resection (GTR), while 85 (34.4%) had subtotal resection (STR), and 10 (4.0%) underwent biopsy only. The degree of resection often correlates with survival outcomes, where more complete resection generally leads to better prognosis, although this is not uniformly the case. Radiotherapy (RT) was employed in 167 patients (67.6%), particularly in cases with incomplete resection or recurrence. Chemotherapy was used less frequently, noted in 48 patients (19.4%), often reserved for more aggressive or recurrent cases. The varying use of these therapies reflects the lack of a standardized treatment approach for metastatic meningiomas, with decisions often made on a case-by-case basis.

Progression-free survival (PFS) rates varied widely across the studies, with 58% of grade II meningioma patients achieving a 5-year PFS compared to only 32% of grade III patients. The presence of metastasis was consistently identified as a significant negative prognostic factor. The overall survival (OS) data showed considerable variability depending on the grade of the tumor and the treatment approach. Grade II patients tended to have longer survival times, with a 10-year OS of 55%, compared to 22% for grade III patients. The use of adjuvant therapies such as RT appeared to improve survival in some cases, though the impact was not uniform across all studies. A significant number of patients, 102 out of 247 (41.3%), experienced recurrence, which was strongly associated with reduced survival times. This finding underscores that recurrence is a critical factor in the management of meningiomas, particularly those with metastatic potential.

Table 1

Summary of the original studies reported extracranial metastasis of meningiomas till date

Author	Year	Pt's no	II/III	No of pt reported mets	Age/ sex	location	Site of metastasis	Risk factors for metastasis	Resection status	Adjuvant therapy	Recurrence	PFS/OS
Hug *et al*[11]	2000	31	15/ 16	3	3 F	10 convexity 11 skull base 4 parasagittal 6 others	Bone-3, lung-2, abdomen-1, multiple sites-2	Failure of local control-2	GTR-8 STR-21 Biopsy-2	II-6, RT III-10,RT	Present (n = 15)	OS: II-89% (5 years) II-89% (8 years) III-51% (5 years) III-51% (8 years)
Wang *et al*[24]	2012	23	15/8	2	1 M/ 1 F	9 skull base 8 convexity 1 parasagittal 5 others	Lung-2	NM	GTR-11 STR-11 Unknown-1	II,III-9,RT	Present (n = 10)	PFS: II,III-54.5% (10 years) OS: 58.3%(with RT) 52.6%(without RT)
Andric *et al*[2]	2012	9	9/0	2	1 M/ 1 F	4 convexity 3 skull base 2 parasagittal	Lung-1 Stomach-1	NM	GTR-6 STR-3	II-2, RT	Present (n = 8)	OS: II- 43 months II- 219 months Average: 133.4 months
Frydrychowicz *et al*[7]	2015	166	148/ 18	2	2 F	1 covexity 1 parasagittal	Lung -2	Sinus invasion-2 Chrosomal abnormality-2	GTR-2 (only metastatic cases mentioned)	II-1, RT II-1, RT (only metastatic cases)	Present, no. not mentioned	NM
Kessler et al[14]	2017	6	2/6		3 F/ 3 M	NM	Lung, mediastinum, liver, spine	NM	NM	Doxorubicin, hydroxyurea, bevacizumab, temozolomide	Present (n = 7)	II (15 y) III (5 y) III (32 y) III (3 y) III (10 y) II (7 y)
Garzon-Muvdi *et al*[8]	2020	6	3/3	3/3	3 F/ 3 M	1 convexity 1 parafalcine 1 Falcine 3 Multiple locations	NM	Sinus invasion-2 Scalp invasion-4	GTR-86(2) STR-62(3) Missing (1)	3, RT	Present (n = 4)	126 months (non specified for each grade)
Himič et al[9]	2023	6	3/3	1-8	2 F/ 4 M	3 convexity 1 parasagittal 1 skull base 1 falx	Vertebrae, iliac bone, acetabulum, sternum, femur, Parotid, Breast, Liver, peritoneum, Lung, colon, thyroid	NM	NM	II-3, RT III-3, RT	Present (n = 4)	II- (20 years) III- (NM) II- (3 years and two months) II- (3 years and two months) III- (NM) III- (NM)

M: male, F: female, Pt: patient, Mets: metastasis, GTR: gross total resection, STR: subtotal resection, NM: not mentioned, RT: radiotherapy, CT: chemotherapy, PFS: progression-free survival, OS: overall survival.

Discussion

We have analyzed data from 247 patients across seven studies (Table 1) on extracranial metastasis in meningiomas. These patients predominantly had either grade II (atypical) or grade III (anaplastic/malignant) meningiomas. The lung and bones were the most common sites for metastasis, with additional sites including the abdomen, liver, mediastinum, spine, parotid, breast, and peritoneum. Despite recent advances in targeted therapies, surgical resection remains the best treatment option for malignant meningioma, particularly for grade III, where gross total resection combined with radiotherapy is standard. Recent clinical trials have explored newer treatments, including chemotherapy, immunotherapy, small molecules, and radiation therapy protocols[15,16,21,22]. Kessler *et al* described a case series of six patients with histologically confirmed metastatic disease from atypical and anaplastic meningiomas. The metastases were found in the lung, mediastinum, pleura, spine, and liver. All patients had a history of recurrent meningioma after multiple surgical resections, suggesting a possible correlation with extracranial spread[14].

Our presented case with anaplastic meningioma (WHO grade III) highlights several unique and clinically significant aspects of metastatic behavior in high-grade meningiomas. This case demonstrates an aggressive pattern of metastasis, including multiple extracranial sites such as the liver, lungs, spine, and long bones, which is rarely observed. Recurrence involves the superior sagittal sinus, subsequent systemic metastases, and pathological fracture due to bone metastasis which is a unique progression. The pattern of metastasis and disease progression observed in this case not only expands the understanding of meningioma metastases but also highlights the challenges of effective treatment protocols in resource-constrained settings. The findings reinforce the necessity of integrating advanced molecular profiling and imaging strategies into routine follow-ups to identify high-risk patients earlier and improve therapeutic outcomes.

Factors favoring metastasis

Risk factors for extracranial metastasis in meningiomas are multifaceted and significantly impact the likelihood of metastatic spread. Key factors include sinus and scalp invasion, which markedly increase the chances of metastasis. Recurrent tumors also show a higher propensity for spreading beyond the primary site. Several established factors influencing metastatic spread include a history of atypical or anaplastic meningioma, local tumor recurrences or incomplete tumor resections, tumors located near the venous sinuses, and molecular signs of increased chromosomal instability. Previous studies revealed that multiple recurrences are strongly associated with the development of metastatic disease in meningioma patients. Research also showed scalp invasion as a significant factor for systemic metastasis and recommended screening with systemic imaging in patients with multiple recurrent meningiomas to detect systemic spread early[8,9,14].

Biczok *et al* analyzed tumors from five patients with meningioma metastases using methylome and next-generation sequencing, finding BAP1 gene mutation as the most frequent, followed by losses of NF2 and PTEN. These findings underscore the need for robust mutational analyses and large-scale sequencing studies to determine the genetic signature that drives metastasis in meningioma patients[3,4].

Currently, there are no documented guidelines supporting routine scanning for metastatic disease in meningioma patients. A proposed grading system based on tumor recurrence frequency, local scalp invasion, proximity to vascular structures, and molecular signs of chromosomal instability could help identify patients who should be screened for metastatic disease. Published data suggest that metastatic spread often occurs late in the disease course, with latencies of months, years, or even decades between the initial intracranial meningioma and subsequent metastases, with pulmonary metastasis occurring 5 to 11 years post-surgery[2,7,9,24]. To address these complexities, larger, multicentric studies involving multiple institutions are necessary to pool robust data and improve our understanding and management of metastatic meningiomas.

Diagnosis and treatment strategy

Diagnosing and treating extracranial metastasis in meningiomas presents unique challenges due to its rarity and the lack of standardized guidelines. Several diagnostic and treatment strategies have been explored. Fine needle aspiration biopsy, FDG positron emission tomography (PET), and somatostatin-receptor scintigraphy are used to detect distant metastases.

The treatment approach for metastatic meningiomas primarily involved GTR combined with RT, which remains the standard. Thoracotomy may be performed for complete tumor resection. Surgical resection remains the mainstay of treatment for malignant meningiomas. Gross total resection (GTR) combined with radiotherapy (RT) is the standard approach, particularly for grade III tumors. Subtotal resection (STR) is also common in metastatic cases[11,25-27,29-37].

Chemotherapeutic agents were also utilized, particularly for grade III tumors. These including hydroxyurea, temozolomide, irinotecan, interferon-alpha, imatinib, erlotinib, and gefitinib have been used with varying success. Individual treatment trials with somatostatin-receptor-targeted octreotide acetate combined with different chemotherapeutic agents have shown promise in some cases. Despite these interventions, the recurrence rates were notably high, especially for grade III meningiomas, underscoring the aggressive nature of these tumors. The findings emphasize the complexity and challenges in managing extracranial metastasis in meningiomas. Agents used included single agents, that is, Doxil or a combination of multiple substances such as vincristine, adriamycin, and cyclophosphamide. The significant variation in survival outcomes and high recurrence rates highlight the need for further research to better understand the underlying mechanisms and develop more effective management strategies[12,13,18,25].

Progression-free survival and overall survival

The progression-free survival (PFS) and overall survival (OS) outcomes for patients with metastatic meningiomas vary significantly across studies, reflecting the complexity of managing this condition. High recurrence rates are noted, especially for grade III meningiomas, underscoring the aggressive nature of these tumors[26]. For example, Hug *et al* reported an 8-year PFS of

19% for grade II and 17% for grade III meningiomas, with 8-year OS rates of 89% for grade II and 51% for grade III[11].

Studies indicate substantial variability in survival outcomes. For instance, Garzon-Muvdi *et al* observed no significant difference in the median overall survival between patients with metastases, which was 126 months, much less than that in patients without metastases who had a median overall survival of 158 months; however, this difference was not statistically significant ($P = 0.33$)[8]. Himič *et al* reported up to 20 years of OS for grade II patients, while Kessler *et al* reported an OS range of 3 to 32 years. Patients with metastases have a median OS of 126 months, compared to 158 months for those without metastases, although this difference was not statistically significant ($P = 0.33$)[9].

The findings emphasize the importance of early identification and tailored treatment protocols to improve long-term outcomes for patients affected by this rare manifestation of meningiomas. For instance, Hug *et al* reported an 8-year progression-free survival (PFS) of 1% [8] for grade II and 17% for grade III meningiomas, while the 8-year overall survival (OS) rates were 89% for grade II and 51% for grade III[11]. Wang *et al* indicated a 10-year PFS of 54.5%, with RT improving outcomes. The overall survival data showed substantial variability, with some patients achieving long-term survival[24]. Himič *et al* reported up to 20 years of OS for grade II patients, although the OS for grade III patients was not specified[9]. Kessler *et al* highlighted a broad range of OS from 3 to 32 years, reflecting the diverse outcomes in metastatic meningioma cases[14]. Tomas Garzon Muvdi *et al* noted a median OS of 126 months (approximately 10.5 years), underscoring the severe impact of extracranial metastasis on patient prognosis[8].

A limitation of our case is the absence of molecular profiling, such as analyses for BAP1, NF2, and PTEN mutations, due to resource limitation. Alterations in BAP1 and NF2 are associated with increased chromosomal instability and aggressive tumor behavior, which may predict extracranial spread[3,4]. The lack of such data in this case limits a deeper exploration of the genetic underpinnings that could explain the observed widespread metastasis. Incorporating molecular profiling into the diagnostic workflow for future cases is essential to stratify patients based on their metastatic risk and guide precision medicine approaches.

Conclusion

Extracranial metastasis in high-grade meningiomas poses significant diagnostic and therapeutic challenges. Our analysis underscores the complexity of managing these cases and highlights the critical need for early identification of high-risk patients and tailored treatment protocols to improve long-term outcomes.

Ethical approval

Not applicable.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author's contribution

All authors have contributed equally in formation of manuscript.

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Data availability statement

Not applicable.

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