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Case report

Biopsy proven metastatic meningioma: A case report and review of the literature

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ABSTRACT

Meningiomas are the most common type of benign tumor found in the brain and are typically benign, slow-growing lesions. The current standard of care consists of surgical resection and subsequent postoperative radiotherapy to prevent local recurrence. Because of their indolent nature, meningiomas are rarely found to spread extracranially and develop distant metastases. We present the clinical, imaging, and pathologic features of a patient who had meningioma with multiple local recurrences, who was incidentally found to have metastatic disease in the lungs. In addition, we discuss details of this case in the context of the previously reported literature.

1. Introduction

Primary meningiomas are among the most common intracranial tumors in adults, representing 14–19% of all cases.[1] The World Health Organization (WHO) classifies meningiomas into three types: benign (WHO grade I), atypical (WHO grade II), and anaplastic/malignant (WHO grade III).[2] These tumors are typically benign and slow growing, with atypical and anaplastic tumors accounting for less than 5% of all meningiomas.[3,4] For patients undergoing definitive therapy for localized meningioma, complete surgical resection has been advised, but there is a significant subset of patients who cannot be managed by surgery alone.[5] Complete resection may not be possible due to intricate anatomy and there exists a potential for recurrence following subtotal resection or gross total resection.[6,7]

Local recurrences are the predominant mode of failure; distant metastases are especially rare, occurring in 0.1% of patients.[4] Among the most frequent sites of metastases are the lungs, accounting for 60% of cases.[4] Currently, there is no

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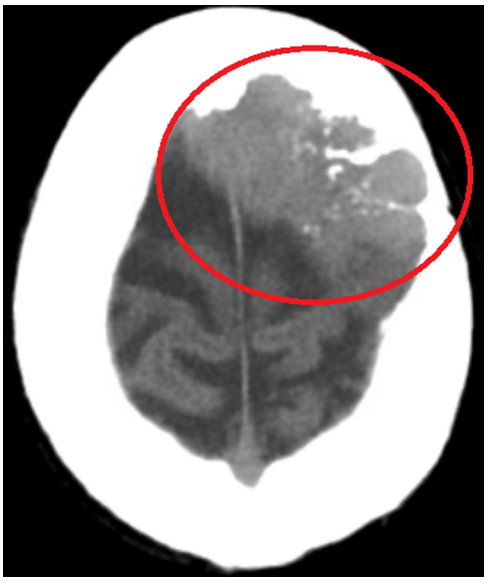

Fig. 1 – CT imaging showing the initial presentation of the meningioma (red oval). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

standard treatment for metastatic meningioma.[3] We present a case of anaplastic meningioma status post multiple courses of surgery and radiation who developed metastatic disease. In addition, we discuss this case in the context of previously reported literature.

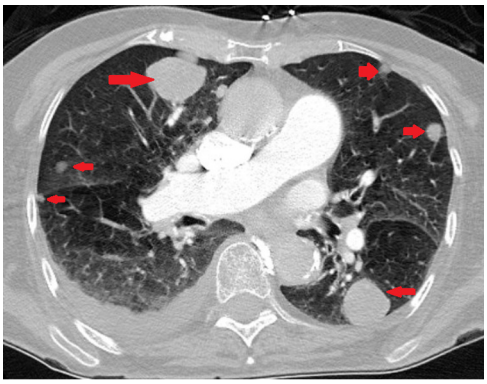

Fig. 3 – CT imaging showing multiple pulmonary nodules (red arrows). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2. Case presentation

A 91-year-old female was originally diagnosed with meningioma in November 2014. CT scan noted a lytic, left frontoparietal mass with extension through the dura (Fig. 1). She underwent craniotomy; pathology showed a WHO grade III, anaplastic meningioma with a Ki-67 (MIB-1) of 20–30% (Fig. 2A and B). Postoperative imaging showed residual disease. She was not referred for postoperative radiotherapy. Surveillance imaging over the next year showed an increase in size of the residual disease with subsequent invasion of the superior sagittal sinus. She then underwent a repeat surgical resection; a complete resection could not be performed so the

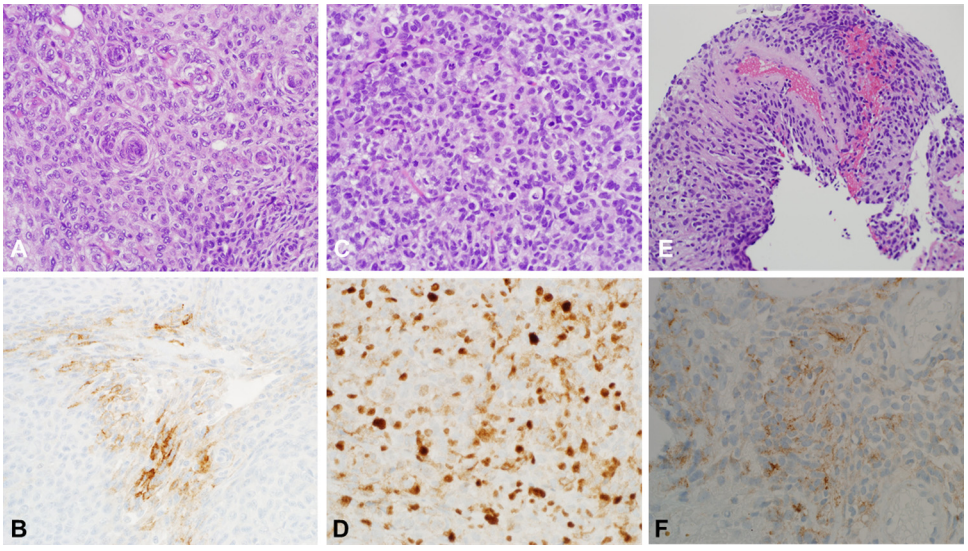

Fig. 2 – (A) Hematoxylin and eosin (H&E) stain from the initial resection showing many syncytial nests of atypical tumor cells with oval to spindled, hyperchromatic nuclei, prominent small nucleoli and occasional intranuclear inclusions. Brisk mitotic activity is seen. (B) Epithelial Membrane Antigen (EMA) immunostaining from the initial resection is positive, consistent with meningioma. (C) H&E stain from the repeat resection showing mitotically active and hypercellular meningothelial neoplasms with vague tumor nests and whorls. (D) EMA immunostaining from the repeat resection is again positive. (E) H&E stain from the lung biopsy showing a high grade spindle neoplasm. (F) EMA immunostaining from the lung biopsy is positive, consistent with metastatic meningioma.

Table 1 – Characteristics of patients with metastatic meningioma.

Age at metastasis diagnosis, sex	WHO grade	Time from initial primary diagnosis (yrs)	Follow-up after metastatic disease presentation (mos)	Primary tumor location	Number of resections performed	Number of SRS courses	Number of EBRT courses	Location(s) of metastatic disease	Treatment of metastatic disease
69, F	III	5.4	5.1	Cerebellum	1	2	1	Lung, liver	No intervention
75, F	II	9.2	1.4	Falx, parasagittal	2	0	1	Lung	No intervention
54, F	IIII	4.7	3.7	Falx	3	2	1	Liver	Hydroxyurea
64, F	III	10.8	13.3	Parasagittal	3	4	1	Mediastinum	Hydroxyurea, EBRT
82, F	II	26.2	55.4	Convexity	4	0	2	Sacrum, pubic ramus	Resection, EBRT
53, F	II	26.2	1.3	Falx, parasagittal	2	1	1	Liver	EBRT
50, M	II	27.6	158.3	Sphenoid wing, orbital	3	2	1	Lung, liver	No intervention
69, M	II	31.0	7.9	Sphenoid wing, orbital	2	0	1	Liver	Hospice

Adapted from Dalle Ore et al.[17]

SRS = stereotactic radiosurgery, EBRT = external beam radiation therapy.

residual disease remained. Pathology confirmed a WHO grade III, anaplastic meningioma with a Ki-67 (MIB-1) exceeding 50% in some areas of the tissue specimen (Fig. 2C and D). She was referred for and received postoperative radiotherapy to the surgical bed and residual disease. The patient received 54 Gy in 27 daily fractions. She then developed multiple recurrences (with disease-free intervals of 2, 6, and 3 months, respectively), each at the margins of the previous radiation field(s) and subsequently treated with additional courses of radiotherapy (each course consisted of 32 Gy in 8 fractions, delivered every other day). She tolerated each radiotherapy course well, with minimal symptoms.

During her last radiation course, the patient was hospitalized for atrial fibrillation. The atrial fibrillation was controlled with medication, but chest X-ray performed at the time showed multiple lesions in her chest concerning for metastatic disease. Subsequent CT scan (Fig. 3) showed multiple pulmonary nodules, the largest measuring approximately 7.4 cm in size, indicative of lung primary versus metastatic disease. She underwent biopsy of one of the lung nodules; histopathology showed a high-grade lesion consistent with metastatic anaplastic meningioma (Fig. 2E and F). The patient was recommended sunitinib daily as systemic therapy. On sunitinib, she developed failure to thrive and treatment was discontinued. Her systemic therapy was changed to immunotherapy with pembrolizumab. Unfortunately, her performance status did not improve and active oncological treatment was discontinued.

3. Discussion

Although meningiomas are often thought of as benign, they metastasize in 0.1% of patients.[4] Currently, histopathological criteria cannot be used to predict metastasis.[2] However, histological parameters indicating aggressive behavior may confer greater risk of metastasis. Higher grade primary tumors, such as atypical and anaplastic tumors, confer higher risk of recurrence and metastatic spread, although metastasis from benign lesions can occur, too.[8] Histologic variables of greatest prognostic significance include indicators of high proliferation, such as high mitotic index (>20 mf per 10 HPF).[9] A similar predictor of metastasis is immunohistochemical staining of Ki-67 (MIB-1), a nuclear protein related to cellular proliferation. The Ki-67 proliferative index has been shown to be significantly higher in metastatic meningiomas (14.7%) when compared to benign ones (1%).[10] Our patient's meningioma had a Ki-67 labeling index of 20–30% on initial pathology and a Ki-67 exceeding 50% on repeat resection. This finding aligns with the multiple local recurrences and eventual development of metastatic disease.

The most common sites of metastases are the lungs, followed by the liver, lymph nodes and bones.[4] The underlying mechanism of metastasis has not been yet determined; proposed routes include hematogenous, lymphatic, or via cerebrospinal fluid (CSF).[1] Hematogenous spread to the pulmonary circulation may occur via metastasis through the dural venous sinuses and cranial veins.[1] Our patient had a lytic mass with extension through the dura, with invasion of the superior sagittal sinus occurring after initial resection. This behavior may have provided a mechanism for metastatic spread. Symptoms of metastatic disease depend on the site of metastasis. Pulmonary metastases, however, rarely cause symptoms.[11] In the case of our patient, multiple pulmonary nodules indicative of metastatic disease were found incidentally.

Primary treatments for localized (non-metastatic) anaplastic meningioma include resection and adjuvant radiotherapy.[12] Studies by Orton et al. and Garzon-Muvdi et al. demonstrated adjuvant radiotherapy improved overall survival and clinical outcomes for patients with anaplastic meningioma.[13,14] Although surgical resection is the mainstay of treatment for a localized meningioma, complete resection may not be possible in all circumstances. Some patients have increased risks due to intricate anatomy and the potential for recurrence following subtotal resection or gross total resection.[6,7] Furthermore, surgical resection of the tumor may confer the risk of iatrogenic metastatic disease.[15] Despite residual grade III disease being present in our patient, she was not referred for postoperative radiotherapy, as is recommended by the NCCN guidelines. If she received postoperative radiotherapy after her initial resection, she might have not developed multiple recurrences and metastatic disease. Adjuvant radiotherapy is not without toxicity; however, especially in a 91-year-old patient. A recent trial of adjuvant radiotherapy for meningioma reported a rate of acute grade 2 toxicity of 10.9% and a rate of late grade 2 toxicity of 25.6%; no grade 3–5 toxicities were seen.[16] Unfortunately, no breakdown of toxicities based on age has been reported. Our patient tolerated her radiotherapy courses well. Instead, she suffered significant morbidity from her multiple recurrences, which may have been prevented if she received a proper upfront treatment of adjuvant radiotherapy after her initial surgery.

Due to the rarity of metastatic meningioma, there is minimal information on effective treatment options. A brief summary of the literature is given in Table 1.[17] Limited clinical trials have been done assessing the efficacy of the systemic therapy for metastatic disease. Previous studies of hydroxyurea have produced mixed results.[18,19] A phase II trial reported sunitinib to be efficacious in patients with localized anaplastic meningiomas.[12,20] In this trial, the median progression free survival (PFS) was 5.2 months, with 42% of patients free of progression at 6 months. Overall, 14% of patients had grade 3 or higher toxicity and 32% of patients required dose reduction. We felt daily sunitinib was a reasonable treatment option for our patient given her good performance status. Unfortunately, she did not tolerate sunitinib; a trial of pembrolizumab was started before an active oncological treatment was finally discontinued.

4. Conclusion

We report a case of metastatic meningioma with multiple pulmonary nodules. For localized (non-metastatic) meningioma, surgery is the standard of care but can be difficult in areas of eloquent anatomy. Postoperative radiotherapy for residual disease and higher-grade disease is an appropriate course of treatment. If metastatic disease does develop, systemic

therapy with sunitinib is an option. A very well calculated clinical plan must be followed not only to enable early detection, but also to prevent recurrence and further malignant transformation. Our case report demonstrates the importance of proper upfront diagnosis, management, and treatment planning.

Conflict of interest

None declared.

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