Intracranial meningioma with vertebral or intraspinal metastasis: report of 2 cases and review of the literature

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Extracranial meningioma metastases (EMM) occur in 0.1% of intracranial meningioma patients and are more commonly seen in those with atypical and anaplastic histologies. While the lungs and pleura are the most common site of EMM, intraspinal and vertebral EMM also occur and are not well described in the literature. Although the presence of EMM can worsen prognosis, no standard of care has been established for EMM management.

All patients treated for recurrent atypical/anaplastic meningiomas between January 1985 and July 2014 at Memorial Sloan Kettering Cancer Center were screened for intraspinal and vertebral EMM. Of these patients, 2 were identified as having recurrent meningioma complicated by vertebral or intraspinal EMM. A review of the literature was also conducted. The PubMed database was screened for intraspinal and vertebral EMM cases reported in the literature from 1985 to 2015. Nineteen articles were identified from the literature and included 24 individual cases with a total of 34 vertebral or intraspinal EMM. Forty-two percent (10/24) of patients with vertebral or intraspinal EMM had WHO Grade I tumors. Furthermore, 25% (6/24) of vertebral and intraspinal EMM occurred after the primary tumor but prior to any recurrence.

This paper highlights that vertebral and intraspinal EMM can occur in patients with WHO Grade I meningiomas and can occur before tumor recurrence. This challenges the notion that EMM are seen primarily in high-grade atypical and anaplastic meningiomas.

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KEY WORDS extracranial meningioma metastasis; intraspinal meningioma metastasis; recurrent meningioma; vertebral meningioma metastasis; oncology

EXTRACRANIAL meningioma metastases (EMM) occur in 0.1%–0.2% of meningioma cases, with the lungs and pleura being the most common sites followed by liver, lymph nodes, and osseous involvement of long bones and the vertebral column.^{3,5,15,17,19,24,36,38} While rare overall, EMM are more common with atypical (WHO Grade II) or anaplastic (WHO Grade III) meningiomas.^{15,21,36} Although EMM can complicate treatment and worsen prognosis, no standard of care has been established for management.^{17,19} Recent work has highlighted the clinical, radiological, molecular, and cytogenetic profiles of primary meningiomas that metastasize, but has been focused primarily on EMM to the lungs.^{3,5,16,17,19,36,38} In this case report, clinical, radiological, and histopathological findings are presented from 2 patients with meningiomas that metastasized to the spine and vertebral

column. Twenty-four additional cases of intraspinal and vertebral EMM in meningiomas were identified in the literature and are also presented. These cases and literature review may aid clinicians in identifying patients with meningiomas that are at risk for spine metastases with appropriate clinical presentation.

Methods

All patients treated for recurrent atypical/anaplastic meningiomas between January 1985 and July 2014 at Memorial Sloan Kettering Cancer Center were screened. A total of 918 patients were screened, of whom 81 had recurrent disease. For all patients with original pathology reports dated before 2000 or initial surgery performed at an outside institution, the slides were retrospectively re-

ABBREVIATIONS EMM = extracranial meningioma metastases; STR = subtotal resection.

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TABLE 1. Case report summary

Case No.	Age (yrs), Sex	WHO Grade	Tumor Location	Primary Tumor Tx	Time to EMM (mos)*	EMM Detected After	Location of EMM	EMM Tx
1	58, F	II	Lt middle cranial fossa	Op	40	1st recurrence	T7–10 vertebrae, L-4 vertebra, S-2 to Lt upper sacral foramina, spinal cord	RT
2	57, F	I→II†	Rt frontal lobe	Op	74	3rd recurrence	Multiple vertebrae, distal Lt clavicle, proximal Lt humerus	RT

RT = radiation therapy; Tx = treatment.

* All times are calculated from the time of diagnosis of initial meningioma to the date of MRI that confirmed recurrence or EMM.

† Primary tumor was WHO Grade I, but upgraded to Grade II after first recurrence.

viewed to confirm diagnosis and update tumor grading in accordance with current WHO guidelines.²⁸ Two patients were identified as having recurrent cranial disease complicated by vertebral or intraspinal EMM and were included in this case report (Table 1). Inpatient and outpatient charts were reviewed to collect clinical, radiographic, and pathological data. This study was approved by the Institutional Review Board of Memorial Sloan Kettering Cancer Center.

A literature review was also performed. The PubMed database was screened for intraspinal and vertebral EMM cases from 1985 to 2015 using the following key terms: “meningioma intraspinal metastasis,” “meningioma intraspinal metastases,” “meningioma vertebral metastasis,” and “meningioma vertebral metastases.”

Results

Case 1

A 58-year-old woman with a homogeneously enhancing dural-based mass in the left middle cranial fossa (Fig. 1A) underwent a Simpson Grade III resection. Tumor histology revealed an atypical meningioma (WHO Grade II) with increased mitotic activity. At 24 months, a large, multicompartamental recurrence infiltrating the orbit and brainstem was treated using subtotal resection (STR) and intensity-modulated radiation therapy with 54 Gy. At 34 months, STR was performed to remove tumor growth extending intracranially and superficially into the soft tissue of the face. At 40 months, the patient experienced worsening radicular pain in the left S-1 distribution without neurological deficit. MRI revealed a large, expansile osseous lesion in the left hemisacrum, narrowing the central canal and encroaching on the neural foramina (Fig. 1B and C). Additional lesions were seen in the L-4 and T7–10 vertebral bodies. EMM were confirmed with CT-guided needle biopsy of the sacral lesion, which revealed anaplastic meningioma (WHO Grade III). The patient was offered palliative pain management and died 45 months after initial diagnosis.

Case 2

A 57-year-old woman with a right frontal meningioma (Fig. 2 left) underwent resection at an outside hospital. Tumor histology revealed a benign meningioma (WHO Grade I). At 24 months, a recurrence required STR and postoperative conventional radiation therapy with 54 Gy. At 60 months, a second recurrence underwent resection

and intraoperative P-32 brachytherapy with 10 Gy. Tumor histology revealed an atypical meningioma (WHO Grade II). At 72 months, a third recurrence received courses of bevacizumab and hydroxyurea. Shortly after, the patient experienced left upper-extremity and low-back pain. MRI revealed a lytic bone lesion in the distal left clavicle, a small lesion in the proximal left humerus, and multilevel multifocal osseous lesions in the spine (Fig. 2 right). EMM were confirmed with CT-guided core biopsy of a T-11 vertebral body lesion revealing spindle cell neoplasm with necrosis and positive epithelial membrane antigen immunostaining. Palliative care was provided until the patient's death, 84 months after initial diagnosis.

Literature Review

A total of 128 articles were screened. The included articles contained histological diagnosis of the primary intracranial meningiomas with vertebral or intraspinal EMM. Histological diagnosis of EMM was not required for inclusion. Nineteen articles met the inclusion criteria, representing 24 cases with 34 vertebral or intraspinal EMM (Table 2). The median age at diagnosis of the primary intracranial meningioma was 51 years (range 14–87 years) with a female predominance (14 females and 10 males). Forty-two percent (10/24) of reported vertebral or intraspinal EMM cases occurred in patients with WHO Grade I primary tumors. The remaining 58% (14/24) of vertebral or intraspinal EMM occurred in higher-grade meningiomas.

The median time to EMM was 78 months (range 3–168 months), with 25% (6/24) of the EMM occurring after the primary tumor, and the remaining 75% (18/24) of EMM occurring after the first recurrence of the primary lesion. Seventy-five percent (18/24) of vertebral or intraspinal EMM presented with symptoms, with pain being the most common symptom. Other presenting symptoms included reduced sensation, paresthesias, lower-extremity weakness, and reduced deep tendon reflexes. Thirty-eight percent (9/24) of vertebral or intraspinal EMM cases had EMM to other organs.

Treatment of the primary intracranial meningioma included surgery alone in 58% (14/24) and surgery plus radiation therapy in 25% (6/24) of cases. Treatment of the primary lesion was unknown in the remaining cases. Treatment of the vertebral or intraspinal EMM varied, but generally included surgery alone, radiation therapy alone, surgery plus radiation therapy, or chemotherapy.

FIG. 1. Case 1. **A:** Axial T1-weighted postcontrast image of the brain showing a large left middle cranial fossa meningioma. **B and C:** Axial T1-weighted images of the sacrum showing a large left sacral metastasis with narrowing of the neural foramina (arrows).

FIG. 2. Case 2. **Left:** Axial FLAIR image of the brain demonstrating a right frontal meningioma with surrounding edema and mass effect. **Right:** Sagittal fat-saturated T1-weighted postcontrast image of the thoracic spine, demonstrating multilevel multifocal osseous EMM involving the vertebral bodies (arrows) and posterior elements.

Discussion

Meningiomas account for 15%–35% of all primary intracranial and intraspinal tumors, with 70%–80% being benign (WHO Grade I) on histopathological grading.⁴¹ Atypical and anaplastic meningiomas together account for a significant minority of all intracranial meningiomas and display an aggressive clinical behavior, including high rates of recurrence. Atypical meningiomas (WHO Grade II) show 4 or more mitotic figures per 10 hpf, or express 3 or more atypical features such as hypercellularity, necrosis, cell pleomorphism, and brain invasion. Anaplastic meningiomas (WHO Grade III) have 20 or more mitotic figures per 10 hpf or lack of differentiation with a carcinomatous or sarcomatous-like appearance. WHO Grade II meningiomas can be further subtyped into chordoid and clear cell, while WHO Grade III meningiomas can be further subtyped as papillary or rhabdoid.

Atypical and anaplastic meningiomas (WHO Grade II and Grade III) are associated with higher rates of recurrence and metastases, and consequently have poor clinical outcome.^{35,37} In this case report, one patient had an initial diagnosis of atypical meningioma (WHO Grade II), while the other patient had a WHO Grade I meningioma that recurred with atypical histology. High-grade meningiomas that progress from low-grade tumors may have a different clinical course than high-grade meningiomas that arise *de novo*, but any potential differences are not fully characterized at present.³⁰

While the per case incidence of EMM is low, intracranial meningiomas are common and knowledge of EMM is clinically useful. Forty-two percent (10/24) of reported vertebral or intraspinal EMM cases identified in the literature review occurred in patients with WHO Grade I primary tumors, challenging the notion that EMM are seen mostly in atypical/anaplastic meningiomas. Given this surprising finding, it may be clinically useful to closely follow low-grade meningioma patients as regularly as high-grade meningioma patients with radiological imag-

ing and clinical examinations to identify vertebral and intraspinal EMM.

Time to EMM can vary from a few months to several years.^{19,29,36,37} In the presented case reports, time to vertebral or intraspinal EMM ranged from 40 to 74 months. The median time to vertebral or intraspinal EMM in the literature review was 78 months and ranged from 3 months to 14 years. In the case reports, EMM occurred after the last recurrence. Surprisingly, in the literature review 25% (6/24) of vertebral and intraspinal EMM occurred after the primary tumor and prior to any recurrence, which challenges the notion that EMM is an end-stage phenomenon in disease progression. In 4 of these 6 cases, the primary tumor was high grade, suggesting that perhaps high-grade meningiomas tend to metastasize earlier than low-grade meningiomas. Therefore, clinical suspicion for vertebral and intraspinal EMM may be warranted not only after meningioma recurrence, but also after the primary tumor, especially in high-grade meningiomas.

While the majority of meningioma cases tend to have EMM to one organ, as many as 31% of cases can have EMM to multiple organs.³⁷ In total, 6 EMM were identified between the 2 cases presented, with EMM occurring in different organs in one of the cases. The most common site of EMM in the literature is lung (37.2%), followed by bones (16.5%), intraspinal (15.2%), and the liver (9.2%).^{5,12,16,17,37,38} In the case reports, several EMM were noted in the vertebral bodies, spinal cord, and other bones. In the literature review, 38% (9/24) of vertebral or intraspinal EMM cases had EMM to other organs. Therefore, if vertebral or intraspinal EMM are suspected and identified, whole-body imaging may be recommended to screen for EMM to other organs.

In the case reports, EMM were identified after the patient presented with symptoms, usually pain localized to the EMM. In the literature review, the majority (18/24) of vertebral or intraspinal EMM cases were identified

TABLE 2. Clinical data of published vertebral and intraspinal meningioma metastasis between 1985 and 2015

Authors & Year	Age (yrs), Sex	WHO Grade	Primary Tumor Location	Primary Tumor Tx	Time to EMM (mos)*	EMM Presenting Symptoms	EMM Detected After	Location of EMM	Multiorgan EMM	EMM Tx
Zaghouni et al., 2014	51, F	III	Lt parietotemporal convexity	Op, RT	60	Back pain	Primary tumor	T-3 transverse process		RT
Kuroda et al., 2009	48, F	I	Lt cerebellopontine angle	Op	88	LE paraparesis, sensory disturbance below T-11	5th recurrence	T-2, T11-12, L-2 intradural		Op
Chuang et al., 2006	52, M	II	Lt frontal lobe	Op, RT	3	Back pain, LE weakness, decreased DTRs, unsteady gait	Primary tumor	Cervical spine, lower thoracic spine, lumbar spine	Rt & Lt ilium, Lt ischium, rt acetabulum, rt & Lt proximal femurs	None
Delgado-Lopez et al., 2006	37, M	I	Lt occipital intraventricular	Op	84	Dorsolumbar pain	1st recurrence	T-11		Op
Tournat et al., 2006	52, M	II	Lt frontal lobe	Op, RT	3	Back pain, LE weakness, decreased DTRs, unsteady gait	Primary tumor	Cervical, T-12, L-1, S-1 VBs	Rt & Lt ilium & humerus	Op
Ghodsian et al., 2005	14, F	III	NA	Op	48	Lt LE radiating pain & spasm	Primary tumor	S-1 VB, lung	Lung	RT
Pinsker et al., 2005	71, M	II	Rt parasagittal	Op	59	Neck pain, hemiparesis & paresthesias	2nd recurrence	C3-4 VBs & extradural space		Op
Chamberlain & Glantz, 2005	50, F	I	Bi-hemispheric	Unk	102	Unk	2nd recurrence	Spinal cord	Cervical lymph node	Chemo
	24, F	I	Rt cerebral hemisphere	Unk	15	Unk	5th recurrence	Spinal cord		Chemo
	78, F	I	Bi-hemispheric	Unk	78	Unk	1st recurrence	Spinal cord		Chemo
	87, F	I	Lt frontal convexity	Unk	168	Unk	1st recurrence	Spinal cord	Cervical lymph node	Chemo
Fuentes et al., 2002	53, F	II	Rt parietal lobe	Op	120	Neck pain	1st recurrence	T-1 VB		Op
Lee et al., 2002	48, F	I	Rt frontal convexity	Op	31	Lumbar pain, Lt LE sciatica, reduced sensation, decreased DTRs	1st recurrence	Lt sacrum	Lt ilium	Op
Conrad et al., 2001	31, F	I→III†	Frontotemporal	Op	96	Lumbosacral pain	5th recurrence	L5-S1 dural attachment		Op
					104‡	Perineal pain	5th recurrence	L-4 & S-3 dural attachment		Op
Adlakha et al., 1999	17, F	III	Lt parietooccipital	Op, RT	81	Unk	1st recurrence	Vertebrae		NA
Lee & Landy, 1998	59, M	III	Lt frontal lobe	Op	31	Lumbar pain radiating to rt leg	3rd recurrence	Cauda equina		RT
	65, M	III	Foramen magnum	Op, RT	62	Back pain, urinary incontinence	4th recurrence	Lumbosacral region intradural		RT
	43, M	III	Bifrontal	Op	105	Low-back pain, Lt LE weakness	5th recurrence	Thoracolumbar junction intraspinal		RT
Enam et al., 1996	73, F	II	Midline frontoparietal	Op	24	Abdominal pain, Brown-Séquard syndrome	2nd recurrence	T-10 VB	Liver	Op+RT

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TABLE 2. Clinical data of published vertebral and intraspinal meningioma metastasis between 1985 and 2015

Authors & Year	Age (yrs), Sex	WHO Grade	Primary Tumor Location	Primary Tumor Tx	Time to EMM (mos)*	EMM Presenting Symptoms	EMM Detected After	Location of EMM	Multiorgan EMM	EMM Tx
Tominaga et al., 1994	41, F	I	Rt parasagittal	Op	156	Unk	Primary tumor	C-2 VB		Op
Olson et al., 1994	70, M	II	Lt frontal lobe	Op	11	Back pain	Primary tumor	T-6, T-11 VB		NA
Palmer et al., 1994	43, M	II	Rt posterior fossa	Op	144	Lumbar pain	1st recurrence	L-5 VB & lt pedicle	Lung	RT
Akimura et al., 1992	53, F	III	Lt frontal lobe	Op, RT	44	Back pain, paraparesis	2nd recurrence	T-1 intradural		Op
Asai et al., 1988	52, M	I	Tentorial	Op	96	Pain in posterior legs & buttocks	1st recurrence	T-1, T-10, T-11 vertebral arches; L-4, L-5 VBs	Rib, ilium	RT

Chemo = chemotherapy; DTR = deep tendon reflex; LE = lower extremity; NA = not available; unk = unknown; VB = vertebral body.

* All times are calculated from the time of diagnosis of primary meningioma to the date of MRI that confirmed recurrence or EMM.

† Primary tumor was WHO Grade I, but upgraded to Grade III after first recurrence.

‡ Patient had a recurrence of an EMM.

after the patient presented with symptoms, usually pain with associated neurological impairment. Contrarily, in a recent literature review of EMM cases, Surov et al. found that 31.3% of EMM were clinically silent and were discovered incidentally.³⁷ However, since Surov et al. assessed all EMM cases, their findings may be true of EMM in general, but not representative of vertebral or intraspinal EMM specifically. Given the anatomical location of EMM in the vertebrae or spine, the patient is more likely to have associated symptoms. Treated meningioma patients should therefore be advised to promptly undergo follow-up if they experience back pain, loss of sensation in extremities, loss of muscle tone, or muscular spasms, as these could indicate an underlying vertebral or intraspinal EMM.

Identifiable risk factors for EMM include previous craniotomy, venous sinus invasion, local recurrences, and histological malignancy, namely, papillary morphology, hypercellularity, cellular heterogeneity, high mitotic activity, nuclear pleomorphism, and necrosis.^{1,15,18,19,38} While our 2 patients had most of the identifiable risk factors for EMM, the literature review brings these risk factors under question as applied specifically to vertebral or intraspinal EMM. Notably, a significant number of cases of vertebral or intraspinal EMM occurred in patients with WHO Grade I meningiomas, and EMM occurred in patients prior to any tumor recurrence.

While the exact route of metastasis is unknown, hematogenous, lymphatic, and CSF routes, along with seeding from resection, have been suggested.^{6-8,14} It is appealing to suspect that CSF spread may account for intraspinal EMM and hematogenous spread for vertebral EMM; however, this is difficult to validate without further laboratory investigation. Recent work has also highlighted several molecular and cytogenetic markers that may predict EMM. Scognamiglio and colleagues reported high expression of CD90 in cases of EMM.³⁶ CD90, a protein associated with aberrant activation of the self-renewal machinery that is normally restricted to stem cells, has been previously observed in glioblastomas and may play a role in the formation of tumor vasculature and tumor progression, making it a potential marker for meningioma metastatic potential.^{23,34} Using a comparative cytogenetic analysis, Frydrychowicz and colleagues reported deletions affecting chromosomes 22 and 1 in primary atypical meningiomas and their EMM, arguing that chromosomal instability may be associated with metastatic spread.¹⁹

Conclusions

This case report and literature review highlight that vertebral and intraspinal EMM can occur in patients with WHO Grade I meningiomas and can occur before tumor recurrence. Unlike EMM to other organs, vertebral and intraspinal EMM are usually symptomatic. Therefore, patients with low-grade and high-grade meningiomas should be followed regularly with imaging after primary tumor treatment for accurate and timely identification of vertebral and intraspinal EMM. Furthermore, patients should be advised to undergo follow-up if they begin experiencing symptoms suggestive of vertebral or intraspinal EMM,

such as back pain, loss of sensation in extremities, loss of muscle tone, or muscle spasms.

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Disclosures

The authors report no conflict of interest concerning the materi-

als or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Chohan, Singh, Ryan, Bilsky. Acquisition of data: Singh, Ryan, Tisnado, Hadjigeorgiou. Analysis and interpretation of data: Chohan, Singh, Ryan, Tisnado, Hadjigeorgiou. Drafting the article: Chohan, Singh, Ryan, Tisnado, Bilsky. Critically revising the article: Chohan, Singh, Ryan, Hadjigeorgiou, Bilsky. Reviewed submitted version of manuscript: Hadjigeorgiou, Bilsky. Approved the final version of the manuscript on behalf of all authors: Chohan. Study supervision: Chohan.

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