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Case Report

Isolated Extracranial Intraosseous Metastasis of an Intracranial Meningioma following Bevacizumab Therapy: Case Report and Review of the Literature

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Abstract

Meningiomas account for a significant proportion of all primary intracranial tumors; distant metastasis is quite rare. We report a patient with resected, atypical meningioma. The patient's clinical course over 5 years included two craniotomies, a course of radiation, and a shortened course of bevacizumab. Only 5 months after starting bevacizumab, the patient developed an isolated left clavicular pathological fracture attributable to metastatic anaplastic meningioma. This constitutes the first report of meningioma with isolated extracranial intraosseous metastasis in the modern English literature and highlights concerns associated with the use of anti-angiogenic agents in promoting more invasive tumor phenotypes upon disease recurrence.

Keywords: *Anaplastic meningioma, atypical meningioma, bevacizumab, extracranial intraosseous metastasis*

Introduction

Arising from meningothelial cells of the arachnoid membrane, meningiomas are generally benign tumors, accounting for approximately 15% of all primary central nervous system tumors.[1-7] Historically, meningiomas have been known to invade local venous sinuses, bone, or soft tissues of the scalp with an incidence of up to 32% in some series.[8,9] Distal metastases of meningiomas are much more rare, with the most common sites of such metastasis including the lungs, abdominal wall, liver, cervical lymph nodes, long bones, and vertebrae.[10-26] To date, only one reported case of meningioma metastatic to the clavicle has been reported in the literature, with that case predating modern adjuvant advances, such as the use of stereotactic radiosurgery and bevacizumab therapy, and presenting in a patient with widely disseminated disease.[27] We report a modern case of an 81-year-old man with progressive, recurrent meningioma with isolated metastasis to the left clavicle.

Case Report

An 81-year-old, right-handed, retired gardener with a distant history of prostatectomy for cancer presented with a 3-week history of right frontal headaches and left arm numbness without weakness. On the day prior to admission, the patient had a complex, partial motor seizure of the left face which progressed to left arm tonic then clonic activity treated by lorazepam and phenytoin. The patient had no secondary generalization but had a postictal period of confusion and sleepiness. Following this episode, the patient returned to his neurological baseline, including numbness of the left arm. Brain magnetic resonance imaging (MRI) demonstrated an approximately 3 cm, extra-axial mass along the right frontal convexity with some underlying edema and mild diffuse atrophy [Figure 1].

The patient underwent a right frontal craniotomy for tumor resection using frameless stereotaxy with formalin-fixed pathology demonstrating a 2.5 cm × 2.4 cm × 2.1 cm soft, tan-white, dural-based tumor with brisk mitoses focally (approximately 9–11/high powered field), rare small foci of necrosis, and hypercellularity, all consistent with a World Health Organization (WHO) Grade II or atypical meningioma [Figure 2]. There was a discussion with the patient and family over upfront focal radiation versus following closely with MRIs, and radiation was deferred.

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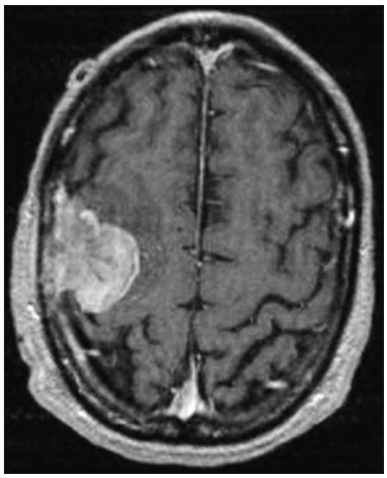

Figure 1: Initial brain magnetic resonance imaging demonstrating a 3 cm, extra-axial mass along the right frontal convexity with some underlying edema and mild diffuse atrophy

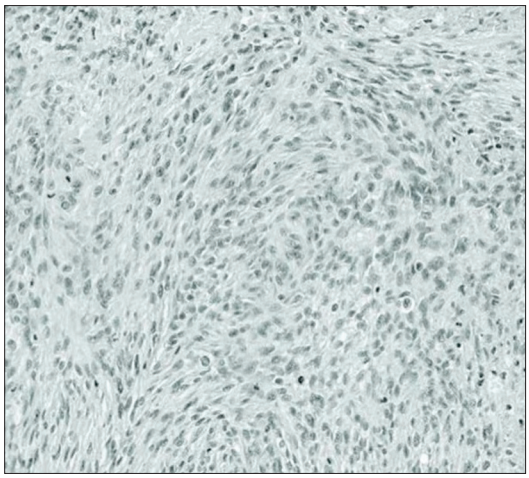

Figure 2: Formalin-fixed pathological specimen with brisk mitoses, small foci of necrosis rarely, and hypercellularity, all consistent with a World Health Organization Grade II or atypical meningioma

From the immediate postoperative period through approximately 2 years postoperatively, the patient continued to have some left-handed numbness as well as some mild difficulty with memory and word-finding difficulties but was otherwise asymptomatic and independent with a Karnofsky performance score of 90. Routine postoperative MRI imaging 2 years after resection demonstrated a new right frontal dural-based enhancing mass measuring <1 cm in diameter and associated with some modest new surrounding edema as well as residual postoperative changes.

Given the patient's advanced age and the relatively small size of the recurrent lesion, the patient underwent gamma knife radiosurgery with a treatment consisting of two 14 mm collimator isocenters with 18 gray to the 75% isodose line using trunnions. This procedure was tolerated without complication and repeat MRI imaging approximately 6 months following the procedure demonstrated a smaller right frontal lesion.

Although his symptoms remained stable, routine MRI imaging every 6 months eventually demonstrated the further growth of the right frontal parasagittal lesion 2 years following the patient's initial gamma knife radiosurgery. Thus, the patient underwent a second round of gamma knife radiosurgery consisting of two 14 mm collimator isocenters and two 8 mm collimator isocenters with 13 gray to the 50% isodose line. There was a portion of the tumor that had an unusual shape inferiorly, however, and thus hypofractionated stereotactic radiosurgery using a 7-field IMRT approach was used to treat this area of the tumor.

Over the subsequent year, the patient's clinical course was complicated by a deep vein thrombosis and focal seizures involving the left arm, for which he was started on levetiracetam. Approximately, 1½ years after his preceding last dose of radiosurgery, the patient developed slurred speech and a significantly unsteady gait due to worsening left sided weakness. Subsequent MRI demonstrated a large right-sided extra-axial mass with extension through the patient's craniotomy defect, consistent with a recurrent meningioma. Thus, the patient was taken to the operating room for right-sided craniotomy for recurrent tumor resection. Of note, some elements of the tumor were invading the skull. Pathology demonstrated an extensively necrotizing WHO Grade III malignant meningioma with a sarcomatoid growth pattern and up to 80 mitotic figures per square millimeter, nuclear sheeting, and nucleolar prominence. Following surgical resection, the patient additionally underwent broader field 25 gray radiotherapy delivered in five fractions and was started on bevacizumab therapy.

Approximately 5 months later, the patient began to develop persistent left clavicular pain after a mechanical fall. Plain X-ray imaging of the clavicle was notable for a mass lesion and adjacent pathological fracture [Figure 3]. The patient underwent an incisional biopsy of the left clavicle with internal fixation and bone grafting to correct the pathological fracture. Pathology demonstrated an unencapsulated neoplasm with nests of epithelioid and spindle cells along with prominent nucleoli, entrapping, and infiltrating skeletal muscle and bone trabeculae, consistent with a metastatic anaplastic meningioma.

Following this orthopedic procedure, the patient's clavicular pain abated. His bevacizumab therapy was halted as he had developed tumor progression while on chemotherapy, coupled with his significant preceding history of deep vein thrombosis. Radiation to the clavicle was discussed with the family, but given the patient's deteriorating condition, his family opted for hospice care.

Discussion

Meningiomas are a relatively common intracranial tumor, accounting for up to 20% of all primary neoplasms.[28]

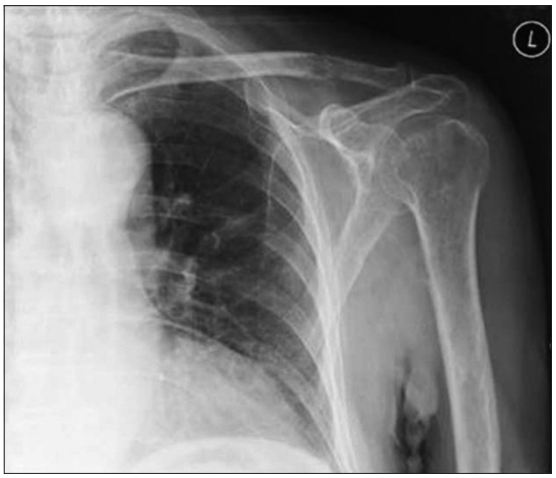

Figure 3: Plain X-ray of the left clavicle demonstrating a mass lesion and adjacent pathological fracture

Although generally benign, recurrence is not uncommon for atypical or anaplastic variants, with 5 years recurrence rates of 38% and 78% for atypical and anaplastic variants, respectively.[29] Even among higher grade meningiomas with recurrence, metastasis is rare, reaching approximately 5% for atypical meningiomas and 30% for anaplastic or malignant meningiomas.[30]

Several histological parameters are predictive of rapid recurrence, including high cellularity, mitotic rate, nuclear pleomorphism, and invasion of adjacent structures.[31-33] According to one case series, such features also seem to predict distant metastatic spread.[34] Many such features were present in the current case, particularly after transformation into an anaplastic meningioma.

Unique in this case report, however, is the location of the distant metastasis. While meningiomas are thought to metastasize distantly via the spread of cerebrospinal fluid or the venous system predominantly to the lungs, pleura, and liver, this case is only the second reported in the literature to metastasize to the relatively avascular clavicle, far from any source of potential cerebrospinal fluid spread. The only prior report of distant metastasis of a meningioma to the clavicle was reported in a patient with markedly diffuse distant disease. Though it is unclear the particular mechanism by which this meningioma may have spread to the clavicle, it is important to note that currently postulated mechanisms of spread, namely via cerebrospinal fluid or the venous system, may have played a role. Neuro-oncologists and neurosurgeons should remain aware of the possibility of distant, often isolated spread of atypical or anaplastic meningiomas. For patients with meningiomas, especially aggressive meningiomas, metastasis to the bone is a possible though rare entity. Providers should have an index of suspicion for such patients presenting with referred skeletal pain.

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor, is Food and Drug Administration-approved for the treatment of a variety of malignancies, including recurrent glioblastoma. There are also several case reports that suggest activity against recurrent or progressive meningiomas.[35-37] One of the theoretical concerns of treatment with an anti-angiogenic agent such as bevacizumab is the potential for promoting a more invasive tumor phenotype. Several reports contend that glioblastoma patients treated with bevacizumab are more likely to present with infiltrative or multifocal disease at recurrence.[38-40] It is reasonable to hypothesize that the risk of promoting tumor invasion may apply to other aggressive types of brain tumors, such as anaplastic meningioma. Ultimately, in this case, it is not completely clear whether concurrent bevacizumab therapy contributed to distant metastasis, but the possibility cannot be excluded.

Conclusion

This case report constitutes the first report of a meningioma with isolated osseous metastasis to the clavicle in the English literature. Clinicians should be aware of the potential for atypical or anaplastic meningiomas to metastasize extracranially, particularly when using anti-angiogenic agents such as bevacizumab.

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Conflicts of interest

There are no conflicts of interest.

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