


A rare case of metastatic atypical meningioma that highlights the shortcomings of treatment options at present

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Erik Kristian Maurice Wrange¹  and Stefan Markus Walbom Harders²

Abstract

We report a case of a locally invasive recurrent atypical meningioma in the temporal region with late onset of meningioma lung metastasis. The patient was diagnosed in early adolescence with an atypical meningioma believed to be radiotherapy induced following treatment of a benign pilocytic astrocytoma in the hypothalamus region at 6 years of age. Even though the patient underwent several surgical and radiotherapy treatments, the intracranial meningioma kept growing and was locally invasive. The patient received experimental treatment with bevacizumab, a vascular endothelial growth factor A (VEGF-A)-inhibitor, for 4 years from age 26. Treatment was withdrawn after proven tumor growth on routine control MRI. A DOTA-TOC PET-CT-scan was performed to evaluate the DOTA-TOC somatostatin receptor number for possible SSTR (somatostatin receptor targeted therapy). In the included scan plan multiple lung metastasis were detected and later verified. Genomic tumor sequencing was performed, but no targeted treatment options were found. Instead, the patient finally, as the last treatment option, underwent 4 series of SSTR-targeted therapy (Lutetium DOTA-TOC). Unfortunately, the intracranial tumor component significantly progressed during the final stages of the treatment and the patient died less than a year after treatment was withdrawn at age 32. This case story illustrates the shortcomings of atypical/anaplastic meningioma treatment strategies at present and highlights the possibility of extracranial metastasis.

Keywords (MESH)

Atypical meningioma, bevacizumab/therapeutic use, lung metastasis, magnetic resonance imaging, pilocytic astrocytoma, positron emission tomography, computed tomography, radiotherapy/therapeutic use

Non-mesh terms

Peptide receptor radiotherapy, Somatostatin receptor–targeted radionuclide therapy

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Introduction

Meningioma is the most common primary non-gliar brain tumor worldwide, accounting for more than 30% of all intracranial tumors in the United States.^{1–3} A meningioma is a solitary, well-defined tumor located to the skull base or the convexity of the brain. Meningiomas are classified into three types according to tumor differentiation and mitotic

¹Department of Radiology, Aarhus University Hospital, Aarhus, Denmark

²Department of Radiology, Odense University Hospital, Odense, Denmark

Corresponding author:

Erik Kristian Maurice Wrange, Department of Radiology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, Aarhus 8200, Denmark.

Email: erik_wrange@yahoo.se



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activity described in the World Health Organization's (WHO) classification system. WHO grade 1 is considered benign, grade 2 atypical, and grade 3 anaplastic or malignant. Grading is important for treatment, follow-up, and prognosis. Surgery and radiotherapy are first line and only standard treatments. Extracranial metastases are rare and almost solely reported in grade 3 meningiomas.¹

The incidence of extracranial metastases has been reported at <0.1% for grade 2 and 8.6% for grade 3.³ To our knowledge, the most substantial case series reported 6 cases of atypical meningiomas with extracranial metastases. These cases were retrospectively identified in patients admitted to John Hopkins Hospital during a 20-year period, emphasizing the rarity of this condition.³ Bevacizumab is considered an experimental treatment in higher grade meningiomas not responding to standard treatment. Bevacizumab is a VEGF-A-inhibitor of vascular endothelial growth. Being highly vascularized, in theory, a meningioma could benefit from this kind of angiogenic growth inhibition. However, there is limited clinical experience treating meningiomas with bevacizumab. In smaller clinical trials, the drug has been shown to shrink meningiomas and to reduce peritumoral brain edema.⁴ However, the withdrawal and reversal of VEGF inhibition have also been observed to rapidly increase regrowth of tumor vasculature.⁵

The most promising treatment option at present is the molecular targeted treatments. Several frequently mutated genes have been identified as targets. For example, NF2, KLF4, TRAF7, and TERT. Additional work correlating molecular signatures with risk of tumor growth and prognosis are needed.¹ Unfortunately, not all patients are candidates to molecular targeted treatments.

The expression of somatostatin receptor 2 in meningiomas can not only be used to discriminate healthy tissue from meningiomas in the diagnostic process with PET-CT, but also as a pathway for targeted radionuclide treatments. The so-called chelator site on DOTA-D-Phe1-Tyr3-octreotate (DOTATATE) or DOTA-D-Phe1-Tyr3-octreotide (DOTA-TOC) can be used to attach a radiation emitting radioisotope for local radiation treatment of the meningiomas with a high count of somatostatin 2 receptors. This treatment has been shown to be generally well tolerated. To our knowledge, the most substantial study showed for 20 patients with progressive atypical meningioma disease at baseline to PRRT, a 57% progression free period for a median of 17 months. A high level of somatostatin 2 receptor expression was in this study associated with stable disease at 6 months follow-up, but did not correlate to WHO grading.⁶ Written informed consent was acquired from the patient with the acceptance of the case report including images being published.

Case history

At the age of six, the patient presented with abnormal growth. He was diagnosed with a 5 cm tumor in the hypothalamus region consistent with a chiasm glioma. The tumor was subtotally resected. Pathology revealed a pilocytic astrocytoma grade 1. Following surgery, the patient received radiotherapy. Blindness on the left eye, right sided deafness, and headache were his main complaints during childhood and early adolescence. Following combined surgery and radiotherapy, the original tumor remnant was stationary on interval MRI examinations.

As a young adult in 2006, MRI revealed a new contrast enhancing skull base tumor in the left temporal region. (Figure 1) The new tumor was subtotally resected and followed by concurrent radiotherapy after pathology revealed an atypical meningioma subsequently believed to be radiotherapy induced. Over a course of the next 8 years, the patient underwent subtotal surgery several times due to continued tumor growth. He received radiotherapy once more in 2010. In 2016, the patient started experimental bevacizumab treatment, a vascular endothelial growth factor inhibitor, hoping to halt the growth of the meningioma.

He received bevacizumab for approximately 4 years until it was ultimately withdrawn due to significant tumor growth despite the therapy. (Figure 2)

Because of relentless tumor progression despite surgery, radiotherapy, and bevacizumab therapy, the patient received Ga-68-DOTA-TOC PET/low dose CT to evaluate the (somatostatin) DOTA-TOC receptor number and thus the potential for DOTA-TOC treatment. Surprisingly, the PET-CT revealed several highly PET positive lung nodules. A CT scan of the thorax and abdomen verified the presence of multiple small lung nodules. (Figure 3) A core biopsy from one of these nodules verified the diagnosis of lung metastases from an atypical meningioma. The pathology report from this core lung biopsy described massive tumor infiltration in bigger map like areas with anastomosing solid islands of tumor cells. Immunohistochemical tests showed tumor cells slightly but convincingly positive for EMA and CD56, but negative for low and high molecular keratin and cytokeratin 7. Negative for S-100, TTF-1, Napsin A, and P63. Clearly, elevated proliferative activity evaluated on Ki-67 and some mitosis figures. Pathology report concluded findings of a meningioma metastasis. After this revelation, the patient finally underwent thorough genetic testing and sequencing as part of a personalized targeted treatment regimen at our regional University Hospital. Unfortunately, no genetic targets were identified.

Radiotherapy maps from 1996 and 2010 were reevaluated, but acknowledging that the skull base had received more than 100 Gy and the brainstem about 60 Gy, further

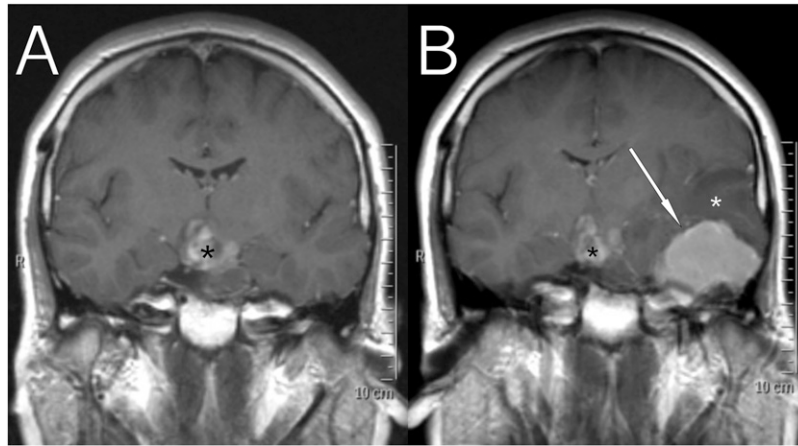


Figure 1. MRI T1 Coronal + IV contrast Gadolinium showed A: In 2005, remnant of the pilocytic astrocytoma in the hypothalamus region that had remained unchanged since early childhood (black asterisk). B: In late 2006, pt. debuted with a meningioma in the left temporal region (white arrow) with mass effect and edema (white asterisk).

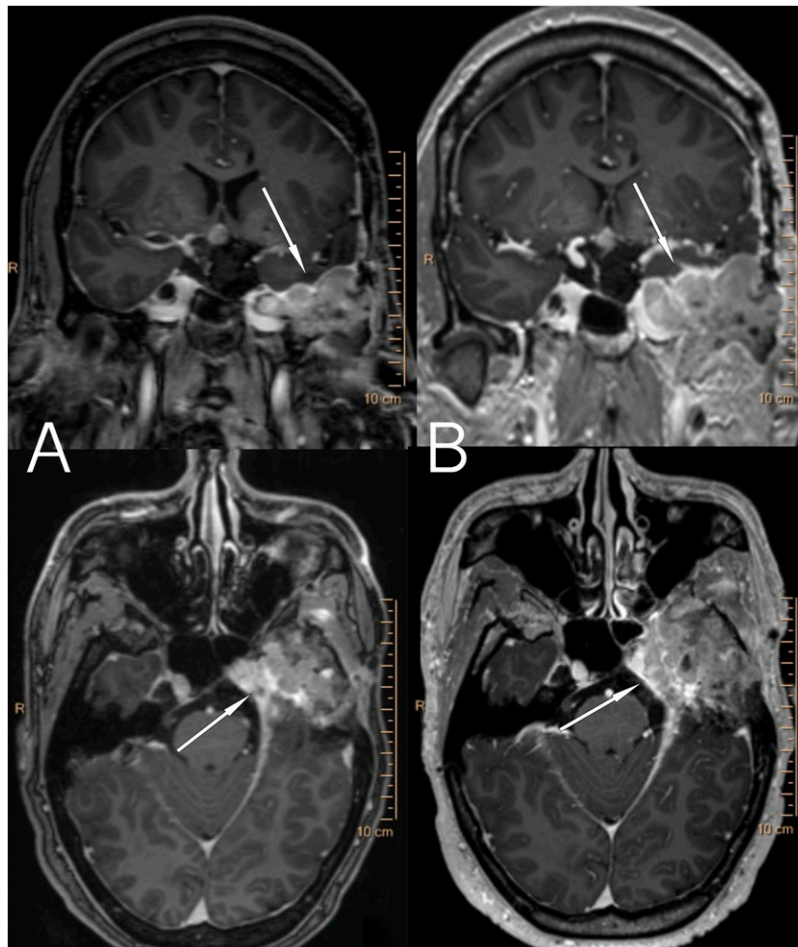


Figure 2. MRI T1 Coronal and axial sequences + IV contrast Gadolinium: A. Baseline MRI in 2016 prior to bevacizumab treatment. B. Meningioma tumor growth shown on routine control MRI in late 2019. The meningioma (white arrow) was locally invasive with tumor growth into the left temporal craniotomy area and into the cavernous sinus.

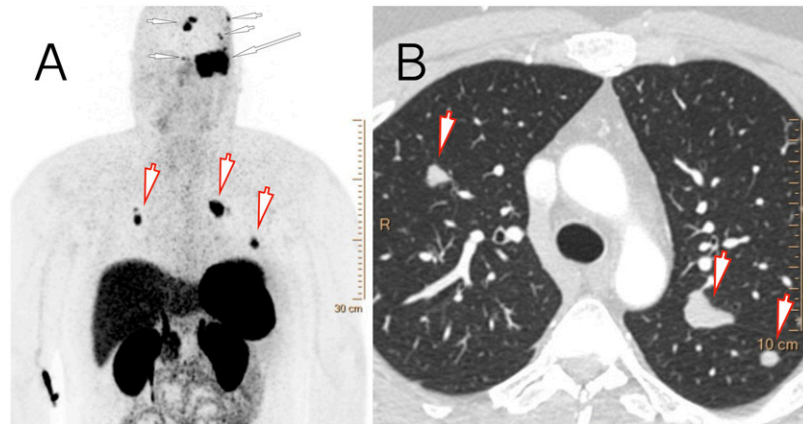


Figure 3. In April 2020, A: (maximum intensity projection image) PET Ga-68-DOTA-TOC showed surprisingly meningioma lung metastasis (red and white arrowheads). Also shown is the large temporal meningioma (white arrow), several meningiomas satellites, and the involvement at the craniotomy border (white arrowheads). B: (Axial image) Contrast-enhanced CT thorax abdomen and pelvis showed the bilateral meningioma lung metastasis. (Red and white arrowheads) Histology verified the imaging findings.

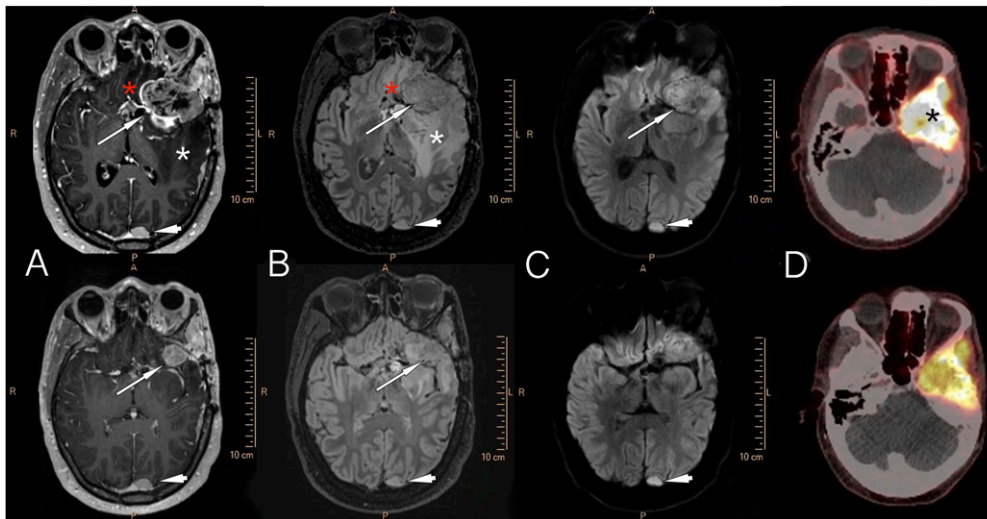


Figure 4. A. MRI T1 axial sequence + IV contrast Gadolinium B. MRI FLAIR sequence C. MRI DWI sequence D. PET-CT low dose DOTA-TOC: Images shown below represent the baseline studies performed in August 2020 prior to PRRT. Images above show tumor growth on studies performed briefly after the final PRRT. Progression of the left frontotemporal meningioma (white arrows) with mass effect, a significant midline shift to the right (red asterisks), and heavy peritumoral edema/infiltration shown as FLAIR hyperintensity areas (white asterisks). The DWI sequences remained without areas demonstrating diffusion restriction. Occipital small meningioma (white arrowhead) and the other smaller meningiomas and lung metastasis (not shown here) remained unchanged. Also, PET DOTA-TOC activity remained unchanged. Image D represents the unchanged meningioma DOTA-TOC activity in the left side of the skull base (black asterisks).

radiotherapy to the primary tumor was considered futile due to tumor size and the risk for serious complications such as osteonecrosis and liquor fistulation. A national multidisciplinary team conference instead suggested PRRT treatment since the atypical meningioma tumor and metastasis showed a high somatostatin receptor count. The patient received four treatments of PRRT, with doses at each treatment of 4.5 GBq Y-90-DOTA-TOC. There was no significant measurable intra- or extracranial tumor growth

after the first three treatments, but shortly after the fourth and final treatment, significant intracranial tumor growth was proven on control MRI. (Figure 4) The patient tolerated the PRRT treatment well, but after the second treatment over a few weeks he developed loss of eyesight on the right eye, which progressed to almost blindness, probably due to tumor progression and not the treatment. Symptoms and tumor progressed over the next 10 months after which the patient died age 32.

Discussion

A retrospective chart review with a summarizing table of all case reports on atypical meningiomas with extracranial metastasis can be found in this cited article.³ As for now, limited non-standardized treatment options are available for patients with atypical and anaplastic meningiomas after primary surgery and radiotherapy have failed. Especially, patients with a secondary to radiotherapy grade 2 and 3 meningioma are a challenge as in our case, since radiotherapy in the first place is a limited option because of risks due to high cumulative doses. At the time of treatment, adjuvant radiotherapy was an accepted primary treatment method for pilocytic astrocytoma in children. However, today we know that radiotherapy induces age-related cerebral vulnerability with a high level of radiation sensitivity, significantly increasing the risk of radiation-induced primary brain tumors such as an atypical or malignant meningioma worsening the prognosis. Further, repetitive surgery and radiotherapy has shown to induce a vicious cycle promoting event further tumor growth and proliferation. A hypothesis that can explain how extracranial metastasis in meningiomas evolve is through sarcomatous metaplasia that appears to be a possible mechanism of extracranial metastasis of intracranial primary malignant brain tumors. Irradiation may cause sarcomatous metaplasia of tumor cells and help the cells acquire the necessary extracellular matrix proteins for vascular invasion and hematogenous dissemination to distant extracranial sites.⁷ Sarcomatous metaplasia was not reported in the pathology report in our case. Surgical resection has been shown to increase the risk of iatrogenic metastasis in histologically aggressive meningioma. Metastasis has been shown even without prior surgery.³

Our patient was treated with the VEGF-A-inhibitor bevacizumab for several years. Long-term use followed by subsequent withdrawal and reversal of VEGF inhibition has been observed to rapidly increase regrowth of tumor vasculature.⁵ Thus, there is a possibility that the long-term use of bevacizumab and withdrawal of treatment in this case may have contributed to progressive deterioration and extracranial metastasis. Perhaps, bevacizumab treatment should have been withdrawn earlier on.

Molecular target agents are promising but if no targets are identified very limited options are available as in our case. An interesting aspect of this case is the finding of the incidentally discovered bilateral lung metastases on Ga-68-DOTA-TOC PET. The discovery of lung metastasis 16 years after the initial diagnosis of atypical meningioma was made while the patient was treated with an angiogenesis inhibitor. The patient's somatostatin receptor count was high in both the primary tumor area, the local and in the lung metastasis. Even though smaller studies have shown an association between somatostatin 2 receptor expression and

stable disease during inner radiotherapy, little is known about the efficacy of PRRT in patients with atypical meningiomas especially in a heavy pretreated population as in our case.

In conclusion, this case highlights the possibility of rare lung metastasis in atypical meningioma especially in a pretreated population. Evidence is limited, but one can consider radiotracer whole-body imaging for possible PRRT if no molecular targets are identified. This case is very illustrative of the shortcomings of present treatment options for patients with radiotherapy induced atypical meningiomas, and highlights the need to search for new treatment strategies.

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ORCID iD

Erik Kristian Maurice Wrangé  <https://orcid.org/0000-0002-6203-6346>

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