Spinal drop metastasis in myxopapillary ependymoma: a case report and a review of treatment options

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Abstract

Myxopapillary ependymoma (MPE) is a World Health Organization grade I ependymoma that is quite rare and generally thought to be benign. Possible drop metastasis from MPE has been reported three times in the literature; in each case there were cotemporaneous additional MPE lesions. We report the case of a man who had a piecemeal gross total resection of a MPE at L1-L3 followed by adjuvant external beam radiotherapy (EBRT) who presented sixteen months later with a lesion in the thecal sac consistent with drop metastasis. A subtotal resection and adjuvant EBRT were performed. The patient has been disease-free in follow-up 27 months from the second surgery. A review of the literature regarding the treatment for MPE showed that gross total resection is optimal initial management. Several retrospective studies supported the role of adjuvant radiotherapy in enhancing local control and progression-free survival. Chemotherapy has a minimal role in the management of MPE.

Introduction

Myxopapillary ependymoma (MPE) is a relatively rare low-grade glioma, specifically classified as a WHO grade I histologic subtype of ependymoma. MPE most frequently occurs in the conus medullaris, cauda equina, or filum terminale, though can also develop elsewhere within the central nervous system.[1] The most common presenting symptoms of spinal MPE include pain, weakness, and sensory changes. Symptoms of bowel, bladder, and/or sexual dysfunction are not common.[2] Metastatic spread of MPE is infrequent and, when it does occur, the disease tends to spread in the rostral direction within the central nervous system.[3] Published reports of drop metastases in patients with MPE are scarce; what is reported describes cases in which drop metastases were discovered simultaneously with the primary tumor.[4,5] In this case report, we discuss an adult patient who presented with secondary MPE drop metastases following an initial piecemeal resection and post-operative radiotherapy of the tumor bed of a primary MPE.

Case Report

Initial presentation and treatment

A 21-year-old Hispanic male presented initially with increased pain in the middle back that radiated to both legs. A thorough neurologic exam was otherwise normal and a complete review of systems was negative. An magnetic resonance imaging (MRI) scan of the lumbar spine without contrast showed a well-defined lesion extending from the middle of the L1 vertebrae to the top of the L3 vertebrae as shown in Figure 1A. A laminectomy of the inferior portion of L1, all of L2, and the superior portion of the L3 lamina was performed. Upon opening the dura, unencapsulated tumor was found. Superficial tumor was removed and a deep dissection was performed revealing a deep tumor capsule that was removed in its entirety. Intraoperative pathology confirmed the diagnosis of myxopapillary ependymoma. Deep to the encapsulated portion, further unencapsulated tumor was found surrounding several nerve roots. A careful dissection was performed with intermittent, but not prolonged, firing of the gastrocnemius and anal sphincter noted on free-run electromyography (EMG). All visible tumor was eventually removed and a gross total resection (GTR) was presumed. Further histologic analysis showed no mitotic figures and no necrosis in the sample. After an uncomplicated post-operative course, the patient was discharged from the hospital on post-operative day 2.

Given that the piecemeal rather than *en bloc* GTR increased our concern for microscopic residual tumor, as well as the reported benefits of radiotherapy for MPE (discussed below), the patient was offered adjuvant radiotherapy. He was prescribed a total of 52 Gy in 26 fractions, using a dose painting approach in which the clinical target volume (CTV, defined as the post-operative cavity/pre-operative cranial-caudal extent of tumor) was prescribed 52 Gy in 26 fractions, and the planning target volume (PTV, defined as the CTV plus a 2 cm margin which encompassed the thecal sac from L1 to L3) was prescribed 49.4 Gy in 26 fractions. Radiotherapy was planned and delivered with the Tomotherapy® system (Accuray Inc., Sunnyvale, CA, USA) which allows the planning and delivery of intensity modulated radiotherapy (IMRT) via a helical delivery of megavoltage (MV) energy radiation, akin to a standard computed tomography (CT) scanner expect that therapeutic megavoltage radiation is delivered as opposed to kilovoltage diagnostic radiation, using a hydraulically controlled collimator to achieve modulation of the beam. This system also allows a MV CT scan to be performed prior to treatment to optimize accuracy of patient set-up. The external beam radiotherapy (EBRT) was completed within 3 months following the initial surgery. Follow-up MRI scans of the lumbosacral spine were obtained 1, 6, 10, and 14 months postoperative. No scans showed any sign of recurrent or metastatic disease.

Presentation at recurrence

Nineteen months after the initial operation, the patient presented for routine follow-up with no complaints, a negative review of systems, and no abnormal physical exam findings. Spinal MRI with contrast showed the development of an enhancing lesion at the S1-S2 level at the tip of the thecal sac consistent with drop metastases; also noted was stable appearance of a linear enhancing lesion at the L2-L3 level as shown in Figure 1B. The last spinal MRI was five months prior and showed no evidence of this lesion. This new lesion developed far inferior to the previous radiation field.

Surgery after recurrence

The patient underwent a lumbosacral laminectomy from L5-S2. Following removal of

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Key words: ependymoma, myxopapillary, drop metastasis, adjuvant radiotherapy.

Contributions: JB, CP, manuscript writing; JB, CP, GY, TL, DR, data collecting and analysis; MM, KW, GY, manuscript reviewing and references searching.

Conflict of interests: the authors declare no potential conflict of interests.

Received for publication: 26 March 2014.
Revision received: 19 May 2014.
Accepted for publication: 27 May 2014.

Licensee PAGEPress, Italy
Rare Tumors 2014; 6:5404
doi:10.4081/rt.2014.5404

the lamina between L5-S2 and the ligamentum flavum between L5 and S1, a firm tumor nodule was palpated between S1 and S2. An attempt to dissect the tumor was made, however, the tumor capsule had significant arachnoid adhesions involving multiple sacral nerve roots. This complicated the resection. Alternative angles of dissection were pursued, however sacral nerve adhesions were again found. The tumor was debulked, however, the capsule was unable to be removed due unacceptably high levels of intraoperative free-run EMG activity in the sphincter muscle. The dura was closed with visual tumor left behind. Pathology showed small bland cells forming perivascular pseudorosettes with intervening myxoid material, shown in Figure 2. The morphology was similar when compared to previous resection material and determined to be consistent with recurrence. A Ki-67 stain showed a tumor proliferative index of 4-9 percent. The patient remained in the hospital for three days and at the time of discharge had no neurological deficits.

Adjuvant radiotherapy after recurrence

One month following the operation, the patient started his second course of EBRT; at that time, he felt well, with absolutely no symptoms and no neurological deficits on physical examination. He was again treated with Tomotherapy®; the CTV was prescribed a dose of 54.0 Gy in 27 fractions, while the PTV was prescribed a dose of 50.5 Gy. The PTV extended from inferior lumbar region to the superior two-thirds of the sacrum, with the superior extent of the PTV at the middle of the L4 vertebral body. IMRT was used to minimize dose to nearby sacral nerve roots that could potentially result in bladder incontinence, impotence, or bowel incontinence. During EBRT he developed nausea, as an expected complication, that was treated with prochlorperazine. Otherwise treatment was well tolerated and he completed as planned.

Follow-up

Five months following the completion of radiotherapy, the patient followed up with radiation oncology. The patient had no complaints and a negative review of systems, including no bowel or bladder incontinence reported. A physical exam showed no abnormalities. An MRI with contrast noted the initial laminectomy at L2-L3 was unchanged, with a linear intradural enhancement seen consistent with MRI taken prior to surgery and radiotherapy. Fatty marrow changes were seen in lumbar vertebrae and attributed to post-radiation change. Evidence of the L5-S2 laminectomy was noted with an irregular heterogeneous enhancement seen at the surgical site. No definite residual mass was seen at the S1-S2 level. The patient is now over 48 months since initial diagnosis and 27 months since his second surgery and has no radiological or symptomatic evidence of tumor progression on continued follow-up.

Discussion

Ependymal tumors are rare, with an incidence of approximately 0.2 per 100,000 person-years with a slight predominance in men and Caucasians. However, there is a slight trend of increasing incidence over the past 35 years. Only 0.5% of all ependymomas are classified as myxopapillary, suggesting an incidence of approximately 0.01 per million person-years.[6] No specific risk factors for the development of ependymoma have been identified, though associations with neurofibromatosis type 2, SV-40 polyomavirus exposure, and lack of maternal consumption of prenatal vitamins have been suggested.[1] The prognosis for World Health Organization (WHO) grade I ependymoma, of which, MPE is a sub-type, is very good. The 1-year and 10-year cause-specific survival rates for WHO Grade I ependymoma are 100% and 93% respectively.[1]

In single institution retrospective studies postulated poor prognostic factors for patients with ependymoma include younger age, higher tumor grade, supratentorial location, and failure to achieve GTR.[1,2,7] In a large population-based study from the Surveillance, Epidemiology, End Results database older age rather than younger age was associated with a poorer prognosis.[8] Recent investigations have begun to develop pathologic and immunohistochemical markers of prognosis. A study has shown increased mitotic index, increased cellularity, presence of Ki-67, and presence of cyclin D1 as independent markers of mortality in ependymomas.[9] However, no such studies have focused solely on MPE.

As a grade I tumor, MPE is generally considered benign. However, metastatic behavior has been reported in the medical literature. Intracranial metastasis is the most common site for MPE spread. A recent review described 19 such cases and found a variety of intracranial sites involved including the telencephalon, the brainstem, and the cerebellum. The time span to presentation of metastasis also varied wildly, from 1 month to 13 years following primary tumor resection in one series.[10] Metastases have been reported up to 20 years after initial treatment, emphasizing the role for extremely long-term follow up in patients treated for MPE.[11] One case reported drop metastases from a T11-L2 primary MPE to the distal thecal sac, similar to the patient reported here, however this patient was a 13 year old girl and the metastasis was found on the initial MRI scan.[4] An additional case report describes a 22-year-old man who presented with MPE lesions in the third ventricle and sacral spinal canal who was hypothesized to have a drop metastasis by the

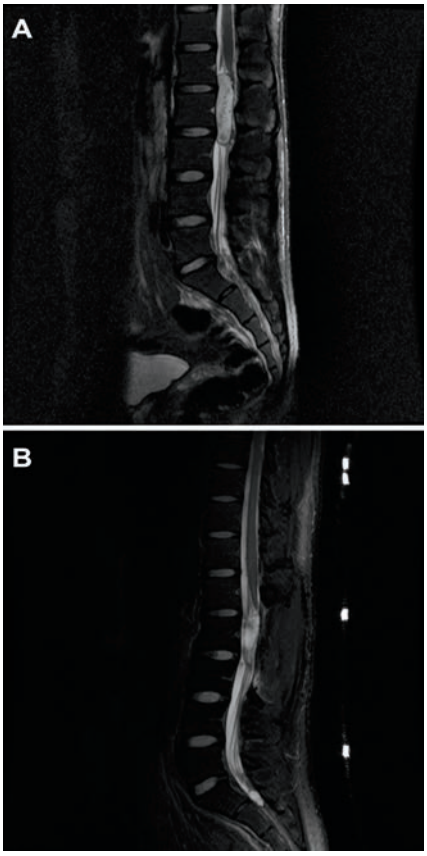

Figure 1. A) Sagittal T2 magnetic resonance imaging (MRI) without contrast of initial lesion from L1-L3 prior to surgery. B) Sagittal T2 MRI without contrast 16 months after completion of initial radiotherapy showing new lesion at S1-S2 level.

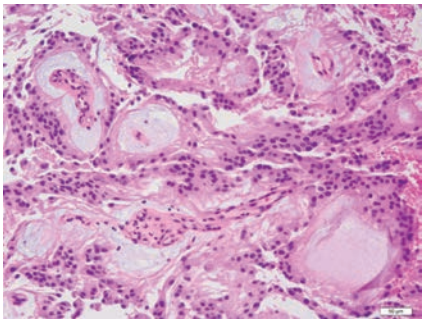

Figure 2. Hematoxylin and eosin-stained photomicrograph showing perivascular pseudorosettes containing bluish myxoid material characteristic of myxopapillary ependymoma.

Table 1. Summary of recent studies regarding the use of adjuvant radiotherapy in spinal myxopapillary ependymoma.

Study	Year	Patients	Patients treated with radiotherapy	Field	Dose	Fractionation	Results
Akyurek *et al.*[14]	1968-2002	35	22	Primary and 3-5 cm margin (17), craniospinal axis (5)	50.4 Gy (44.3-56)	1.8 Gy (1.5-2)/fraction	Radiation improved PFS and local control
Pica *et al.*[15]	1970-2007	85	47	Primary and one vertebral body above and below (17), Primary and >1 vertebral body above and below (28), craniospinal axis (1)	50.4 Gy (25.2-59.4)	1.8 Gy (1.5-2.0)/fraction	Improved PFS in patients receiving RT, with high-dose (>50.4 Gy) having better PFS than low-dose (<50.4 Gy)
Chao *et al.*[16]	1974-2007	37	Initial: 9 Recurrence: 6	-	Initial: 50.2 Gy (45-58) Recurrence: 50.4 Gy (45-54)	-	RT on first recurrence lengthened time to second recurrence

Gy, Gray; PFS, progression-free survival; RT, radiotherapy.

authors, though both lesions were again found simultaneously.[5] Peripheral metastasis has also been described, including one case of local tumor reoccurrence forty years after initial therapy with concomitant metastases in the lungs, liver, and lymph nodes.[12]

The gold standard first-line therapy for all spinal ependymomas, including MPE, is *en bloc* GTR, especially in cases without evidence of metastasis.[13] The role of adjuvant radiotherapy is less clear in cases of MPE. Table 1 presents several radiotherapy regimens from various studies regarding the role of radiation in the treatment of patients with spinal MPE.[14-16]

Studies whose patient population includes only those with MPE show improved outcomes with the use of adjuvant radiotherapy. In a study of 35 patients with MPE treated at the M.D. Anderson Cancer Center, a statistically significant improvement in progression-free survival and local control was shown in those treated with surgery and adjuvant radiotherapy versus surgery alone.[14] A multi-institution study of 85 patients with MPE showed that postoperative high-dose radiotherapy was the only independent predictor of progression-free survival in their study; no cases of radiation-induced myelopathy occurred in patients receiving adjuvant radiotherapy.[15] A study of 37 patients with recurrent MPE treated at the Cleveland Clinic showed that patients who received radiotherapy as salvage therapy after an initial tumor recurrence had a statistically significant longer time to second recurrence. Further, no long-term side effects in patients receiving radiotherapy were found.[16] A recent meta-analysis showed that in a combined population of pediatric and adult cases, adjuvant radiotherapy had no impact on recurrence rate regardless of the totality of the initial tumor resection.[13] An additional meta-analysis found that in patients under 20, adjuvant radiotherapy was associated with an improved progression-free survival on multivariate analysis.[17] The sum of these studies suggests that radiotherapy is both efficacious and safe as a first-line adjuvant therapy for MPE and should be considered regardless of completeness of surgical resection, especially in younger patients.

Chemotherapy has been used in the treatment of ependymoma to decrease tumor burden before resection, to delay radiotherapy delivery (primarily in infants with intracranial ependymoma in whom late effects of radiation can be more severe), and in cases of recurrent disease.[1] Platinum-based therapies have been shown to improve response rate, but have no benefit on overall or progression-free survival.[18] Molecularly targeted chemotherapy may play a role in the treatment of MPE. A small retrospective case series showed radiographic response in patients with recurrent MPE treated with bevacizumab.[19] A single case report showed that imatinib was effective in the treatment of recurrent spinal ependymoma.[20] Another case report showed that sorafenib induced disease stabilization in a patient with extraneural MPE metastases.[11] These reports suggest targeted chemotherapy may have a promising role in the future treatment of ependymoma.

Conclusions

MPE is a rare subtype of ependymal tumor that is most frequently considered benign. MPE rarely metastasizes, and when it does, secondary sites typically include the cerebellum, brain stem, and telencephalon. Spinal drop metastasis is exceedingly rare with only three other cases reported in the medical literature, all of which were discovered simultaneously with the primary tumor. We have discussed a case of drop metastasis that presented two years following surgery for primary MPE in which a piecemeal rather than *en bloc* GTR was performed. Therapy for any recurrence or metastasis should include an attempt at GTR and adjuvant radiotherapy, which has been shown to increase time to second recurrence.

References

1. Reni M, Gatta G, Mazza E, Vecht C. Ependymoma. Crit Rev Oncol Hematol 2007;63:81-9.
2. Armstrong TS, Vera-Bolanos E, Bekele BN, et al. Adult ependymal tumors: prognosis and the M. D. Anderson Cancer Center experience. Neuro Oncol 2010;12:862-70.
3. Davis C, Barnard RO. Malignant behavior of myxopapillary ependymoma. Report of three cases. J Neurosurg 1985;62:925-9.
4. Fassett DR, Pingree J, Kestle JR. The high incidence of tumor dissemination in myxopapillary ependymoma in pediatric patients. Report of five cases and review of the literature. J Neurosurg 2005;102:59-64.
5. Wang M, Wang H, Zhou Y, et al. Myxopapillary ependymoma in the third ventricle area and sacral canal: dropped or retrograde metastasis? Neurol Med Chir (Tokyo) 2013;53:237-41.
6. McGuire CS, Sainani KL, Fisher PG. Incidence patterns for ependymoma: a surveillance, epidemiology, and end results study. J Neurosurg 2009;110:725-9.
7. McLaughlin MP, Marcus RB Jr., Buatti JM, et al. Ependymoma: results, prognostic factors and treatment recommendations. Int J Radiat Oncol Biol Phys 1998;40:845-50.
8. Milano MT, Johnson MD, Sul J, et al. Primary spinal cord glioma: a surveillance, epidemiology, and end results database study. J Neurooncol 2010;98:83-92.
9. Zawrocki A, Izycka-Swieszewska E, Papierz W, et al. Analysis of the prognostic significance of selected morphological and immunohistochemical markers in ependy-

momas, with literature review. Folia Neuropathol 2011;49:94-102.
10. Chakraborti S, Govindan A, Alapatt JP, et al. Primary myxopapillary ependymoma of the fourth ventricle with cartilaginous metaplasia: a case report and review of the literature. Brain Tumor Pathol 2012;29:25-30.
11. Fegerl G, Marosi C. Stabilization of metastatic myxopapillary ependymoma with sorafenib. Rare Tumors 2012;4:e42.
12. Graf M, Blaeker H, Otto HF. Extraneural metastasizing ependymoma of the spinal cord. Pathol Oncol Res 1999;5:56-60.
13. Feldman WB, Clark AJ, Safaee M, et al. Tumor control after surgery for spinal myxopapillary ependymomas: distinct outcomes in adults versus children: a systematic review. J Neurosurg Spine 2013;19:471-6.
14. Akyurek S, Chang EL, Yu TK, et al. Spinal myxopapillary ependymoma outcomes in patients treated with surgery and radiotherapy at MD Anderson Cancer Center. J Neurooncol 2006;80:177-83.
15. Pica A, Miller R, Villa S, et al. The results of surgery, with or without radiotherapy, for primary spinal myxopapillary ependymoma: a retrospective study from the rare cancer network. Int J Radiat Oncol Biol Phys 2009;74:1114-20.
16. Chao ST, Kobayashi T, Benzel E, et al. The role of adjuvant radiation therapy in the treatment of spinal myxopapillary ependymomas. J Neurosurg Spine 2011;14:59-64.
17. Kukreja S, Ambekar S, Sin AH, Nanda A. Cumulative survival analysis of patients with spinal myxopapillary ependymomas in the first 2 decades of life. J Neurosurg Pediatr 2014;13:400-7.
18. Brandes AA, Cavallo G, Reni M, et al. A multicenter retrospective study of chemotherapy for recurrent intracranial ependymal tumors in adults by the Gruppo Italiano Cooperativo di Neuro-Oncologia. Cancer 2005;104:143-8.
19. Green RM, Cloughesy TF, Stupp R, et al. Bevacizumab for recurrent ependymoma. Neurology 2009;73:1677-80.
20. Fakhrai N, Neophytou P, Dieckmann K, et al. Recurrent spinal ependymoma showing partial remission under Imatimib. Acta Neurochir (Wien) 2004;146:1255-8.