Primary Seeding of Myxopapillary Ependymoma: Different Disease in Adult Population? Case Report and Review of Literature

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Key words
- Cauda equina
- Conus
- Myxopapillary ependymoma
- Primary seeding
- Spinal myxopapillary ependymoma
- Spine

Abbreviations and Acronyms
MPE: Myxopapillary ependymoma
MRI: Magnetic resonance imaging

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Myxopapillary ependymoma (MPE) is a slow-growing tumor, occurring most often in adults. It originates from the filum terminale in the area of the conus medullaris and cauda equina and is considered a benign lesion. Despite this classification, however, recurrence after both partial and gross total resection is well known. In the pediatric population, primary MPE seeding and generally more aggressive clinical course is well documented and treated through gross total resection, if possible, followed by irradiation. In adults, however, primary MPE seeding is rarely seen. There are few prior reports describing primary metastases into multiple spinal locations in an adult before resection of an MPE. The reason for this difference among pediatric and adult MPE remains unclear. We present the case of a 32-year-old man with primary seeding of an MPE into multiple lumbosacral areas. The patient underwent gross total resection of the lesions and had an uneventful postoperative course. Primary seeding could be a sign of aggressive behavior in this tumor. Complete craniospinal magnetic resonance imaging studies should be done before and after surgery in patients who present with a multifocal primary MPE. Furthermore, patients with a history of primary tumor seeding of MPE should be thoroughly evaluated radiologically. Unlike in pediatric populations, the need for postoperative irradiation in adults is less clear and further studies—particularly genetic ones—are warranted.

INTRODUCTION

Myxopapillary ependymoma (MPE) is a slow-growing tumor that most frequently occurs in adults. It originates from the filum terminale in the area of the conus medullaris and cauda equina. MPE was first described as a subtype of ependymoma in 1932 by J. W. Kernohan.[1] It is considered a benign lesion and is classified as a grade I tumor by the World Health Organization.[2] Despite this classification, recurrence after both partial and gross total resection is well documented.[3]

Secondary seeding (metastasis) of lumbosacral MPEs after surgery has been described in detail with reports as early as the 1950s.[4-10] Overall, however, metastasis of an MPE is uncommon and usually occurs in patients undergoing subtotal resection.

Primary seeding of MPEs in the pediatric population, with generally more aggressive clinical behavior, has also been well described.[3,11-13] To our knowledge, there are only 13 English-language reports of primary metastases into multiple cerebrospinal locations in adults before resection of the MPE.[10,14-23]

Herein, we present the case of a 32-year-old man with primary seeding of an MPE into multiple lumbosacral areas. We emphasize the possibility of primary MPE tumor seeding in adults and highlight the difference in the frequency of occurrence of this phenomenon in pediatric and adult populations. We also discuss multiple diagnostic and therapeutic implications, as well as particular areas of genetic research needed to further elucidate this phenomenon.

CASE REPORT

A 32-year-old Caucasian man with no significant medical history presented to our neurosurgical clinic on referral from his primary care physician. The patient stated he had developed progressive urinary incontinence over the previous 2 years and was currently catheterizing himself. He had no bowel incontinence, numbness, pain, or leg weakness, and his sexual function was intact. Physical examination revealed no neurologic deficit other than bladder areflexia, which was confirmed with urodynamic studies.

Magnetic resonance imaging (MRI) of his lumbar spine showed 3 distinct lesions (Fig. 1), and the patient was referred to the neurosurgical service. These lesions appeared to be intradural extramedullary. MRI studies with and without contrast of the brain and the cervical and thoracic spine showed no abnormality. The differential diagnosis was neoplastic and included ependymoma and schwannoma. The patient underwent surgical resection and was monitored with intraoperative neurophysiologic monitoring, including somatosensory evoked potentials, motor evoked potentials, electromyography, train of 4, and electroencephalography.

Bilateral L1, L2, and partial L3 laminectomies were done by the senior author (KA), as well as a partial L5/S1 laminectomy. The dura was opened in the

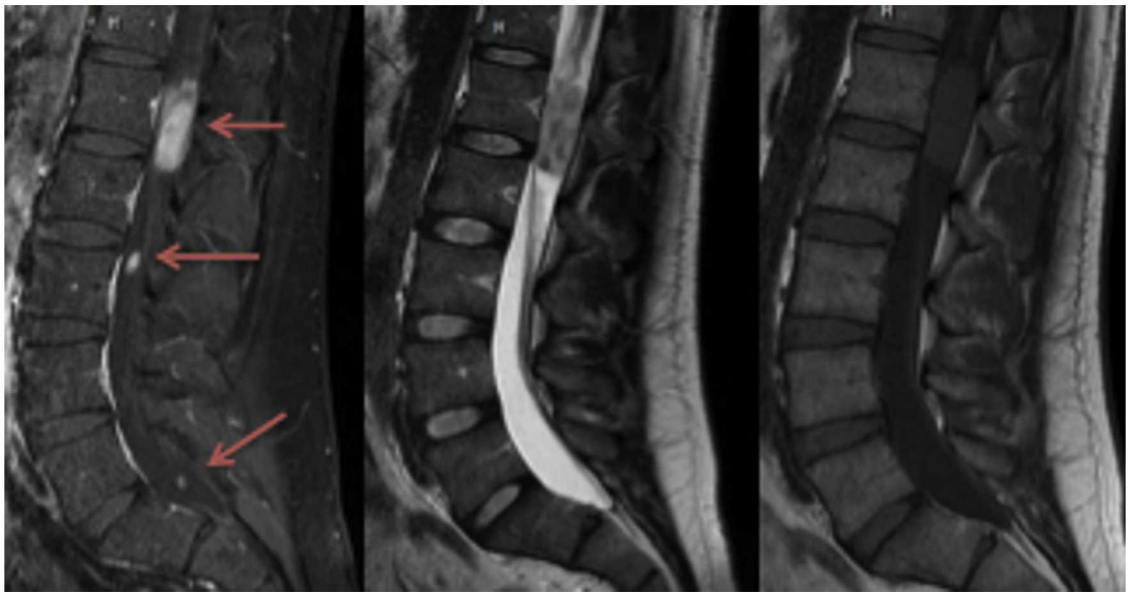

Figure 1. Magnetic resonance imaging studies: T1 with contrast (left), T2 without contrast (middle), and T1 without contrast (right). These images show 3 distinct, intradural, extramedullary lesions that enhance with contrast *(red arrows)*.

midline at L1–L2, and a large, vascularized tumor was found attached proximal and distal to the filum terminale. The tumor was dissected in 1 piece from the exiting nerves after the filum terminale was divided both proximally and distally. The dura was closed at this level and then opened at the level of L3 in the midline. Again, a vascularized tumor was dissected from the spinal nerves and removed. Through a separate incision, the third lesion—similar to the previous 2—was found and removed from the sacral nerve roots. The pathologic findings for all 3 lesions showed myxopapillary ependymoma (Fig. 2).

The patient had no disturbances of neurophysiologic monitoring during surgery and had no new postoperative neurologic deficits (Fig. 3). His postoperative course was uncomplicated, and he was discharged from the hospital on the third day. Immunostaining was positive for glial fibrillary acidic protein. A full genetic work-up was done to identify any genetic abnormality that might explain the atypical presentation of this disease and possibly predict possible aggressive behavior. This workup included 592 genes most commonly associated with cancer. Of these, 569 had no mutation. One gene (*cMET*) had a mutation, and the findings from another 23 genes were indeterminate. *EGFR*, *FGFR*, and *CDKN2* showed no mutation. The patient remains neurologically intact and disease free at 6-month follow-up.

DISCUSSION

Ependymal tumors originate from ependymal cell-rests in the filum terminale located in the area of the conus medullaris and cauda equina. These tumors are uncommon with an incidence of 0.2 per 100,000 person-years.[1] Fifty percent of ependymomas are spinal and—within this group—50% are MPEs. MPE is a slow-growing tumor most frequently found in adults between 30 and 50 years of age.[24] Despite its classification as benign,[9] recurrence after both subtotal and gross total resection is well documented.[3] The recommended treatment for patients with MPE is gross total resection, and patients undergoing subtotal resection usually also undergo radiotherapy.[3] In 1985, a series of 77 patients documented improved outcomes with radiotherapy in adults who had subtotal resection or metastasis.[25]

"Seeding," "metastasis," and "tumor dissemination" are terms used interchangeably and present a known phenomenon that describes many tumors of the central nervous system.[26] Surgical or secondary seeding of MPE after surgery is a described, although uncommon, phenomenon and usually occurs after subtotal resection. Reports as early as the 1950s and 1970s describe this phenomenon in detail.[7-9] When MPE metastasizes, it tends to spread rostrally in the central nervous system.[1,6,9,14]

The literature contains many reports of primary metastasis of an MPE in the spine in pediatric patients.[4,12,13] In 2000, a study by Merchant et al[13] found 4 in a series of 5 pediatric patients (80%) with disseminated MPE at presentation. In 2005, Fassett et al[3] reported primary drop metastases of MPE in the spinal cords in 4 of 5 pediatric patients (80%). In 2008, De Falco[12] described the case of a 16-year-old male with a midthoracic MPE and a sacral MPE. There is also 1 report of 9 pediatric patients in a 30-year series who had leptomeningeal dissemination on presentation.[11] Primary seeding of MPEs with a higher incidence of local dissemination and decreased incidence of radical surgical resection has been well described in the pediatric population. Furthermore, recurrence in adults usually happens at the site of primary resection, whereas in the pediatric population, recurrence in the

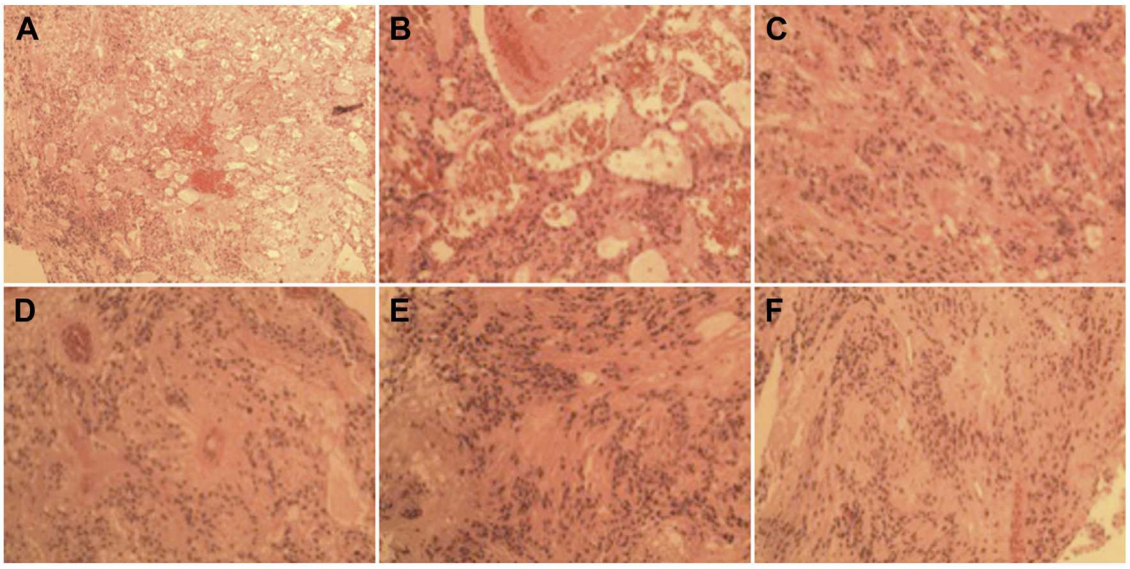

Figure 2. Histopathologic images: (**A**) Low-power (40×) hematoxylin-eosin (H&E) stain showing microcystic spaces characteristic of myxopapillary ependymoma (MPE). (**B**) Intermediate power (100×) H&E stain showing microcystic spaces characteristic of MPE. (**C**) Intermediate power (100×) H&E stain showing radial perivascular cell processes. (**D**) High-power (400×) H&E stain showing a perivascular radial array of tumor cell processes. (**E**) Intermediate power (100×) H&E stain from the second tumor at L3 showing microcystic changes characteristic of MPE. (**F**) Intermediate power (100×) H&E stain from the third tumor at S1 showing microcystic changes characteristic of MPE.

form of disseminated disease is more common.

To our knowledge, however, there are only 13 reports of primary seeding in adults (Table 1). Furthermore, in our own series of 6 adults MPEs (5 women, 1 man; age range, 33–73 years; mean, 49 years; mean follow-up, 41 months), this was the only case with primary seeding.

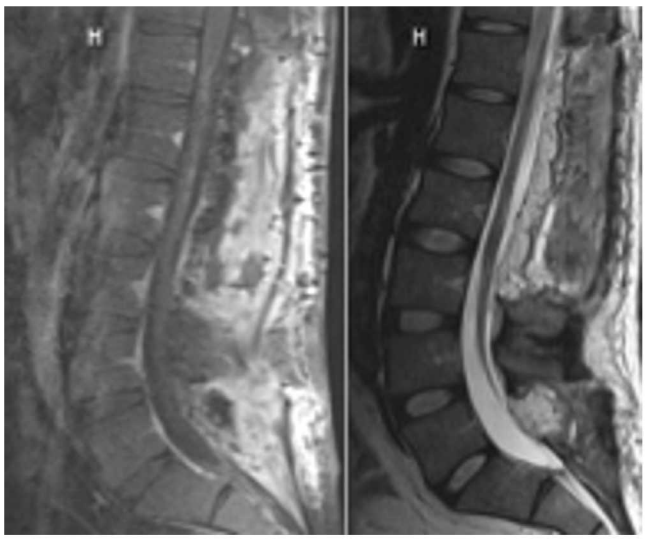

Figure 3. Postoperative magnetic resonance imaging showing T1 with contrast (left) and T2 without contrast (right) verifying gross total resection of 3 separate tumors.

Although MPEs are far more common in adult than pediatric populations, the primary seeding of MPE in the pediatric population is well known and as yet underrecognized in adults. In addition, MPEs in the pediatric population have been reported to have far more aggressive behavior in general than in adults. The reason for this discrepancy remains unclear. The author hypothesizes that there are intrinsic molecular differences and genetic types of MPE that are currently unrecognized. This could represent a spectrum of different grades of MPE, perhaps with the most aggressive tumors presenting earlier in childhood and the indolent tumors remaining clinically occult due to their slow growth and presenting later in adulthood. Also, one can speculate that in the younger pediatric population, tumor cells of the same type have a higher propensity for division.

In pediatric patients with primary seeding, gross total resection is followed by radiation, adjuvant chemotherapy, or both. Because these are subarachnoid metastases, focal radiation targets the lumbar theca and radiation is directed up to midthoracic levels or even applied to the entire craniospinal axis.[28] Because

Table 1. Literature Review Documented Reported Cases of Primary Seeding of Myxopapillary Ependymoma

Author	Year	Age	Sex	Location of Tumor(s)
Woesler et al.[22]	1998	37	Male	1) Suprasellar 2) Multiple spinal tumors
Kittel et al.[15]	2001	N/A	N/A	1) Internal acoustic canal 2) Cauda equina
Andoh et al.[14]	2011	39	Male	1) L2-L3 2) L5-S1
Macedo et al.[17]	2011	33	Male	1) Cerebellum 2) Thoracic and lumbar spinal cord
McLaughlin[18]	2011	28	Male	1) L3-4 2) L5-S2
Shapey[20]	2011	40	Male	1) Cerebellopontine angle 2) T8, conus, filum
Landriel[16]	2012	32/37	Male	1) Multiple locations throughout holospine
Wang et al.[10]	2013	22	Male	1) Third ventricle 2) S2
Straus[21]	2014	63	Male	1) Multiple locations throughout holospine
Khalatbari[27]	2015	N/A	N/A	1) 3 patients with 2 lesions, 1 patient with 3 lesions
Ogul[19]	2015	48	Male	1) Cervical, thoracic, and lumbar
Yener[23]	2016	32	Male	1) L2-3 2) L5-S1
Khan *	2017	32	Male	1) L1-L2 2) L3 3) S1

N/A, not available.
*This study.

of the effectiveness of surgery and radiation in the pediatric population, chemotherapy is reserved for patients with tumors that are refractory to radiotherapy and is generally considered less effective.[3]

In adults with primary seeding and after a gross total resection, however, the issue of adjuvant therapy is not established, probably because primary seeding of MPEs is not a recognized phenomenon. Only follow-up with craniospinal MRI studies after gross total resection—or "prophylactic" postoperative irradiation and chemotherapy after gross total or subtotal resection—may be considered.[3]

Despite the benign histology and slow-growing nature of most MPE tumors, some MPEs behave in an aggressive manner. Signs of aggressive behavior that appear postoperatively, after either subtotal or gross total resection, are local recurrence and aggressive growth. Another sign of aggressive behavior is secondary seeding (metastasis) of an MPE to distant craniospinal sites or local spinal sites after surgery. Primary seeding of an MPE is extremely rare, with our case being one of the few reported in an adult population. We hypothesize that this phenomenon could be another sign of more aggressive behavior—one that could potentially be recognized before surgical intervention and point to an MPE in the differential diagnosis of intradural extramedullary spinal tumors in the filum terminale area. It is unclear whether this is a form of "drop metastasis" or retrograde dissemination given that there are often locations located both above and below the usual location of the filum terminale region.

In one of the largest series on this topic, MPEs have also been reported to be more aggressive in the pediatric population, with local rates and recurrence of 64% compared with 32% in adults.[29] Furthermore, the fact is that primary MPE seeding is well recognized in pediatric patients and underrecognized in adults, despite the fact that MPEs are far more common in adult population. These differences lead us to hypothesize that there may be a more aggressive variant of MPE that occurs predominately in younger populations. EGFR protein expression has been shown to predict a worse clinical correlate for patients with intracranial MPEs.[30] A recent study evaluating the role of EGFR in MPE tumors found that EGFR was present in all recurrent tumors but not in tumors that did not recur.[31] This finding leads us to hypothesize that there may be an EGFR variant that is more apt to disseminate throughout the cerebrospinal axis. The receptor tyrosine kinase cMET has been linked to brain malignancies, including ependymoma. cMET activation in brain malignancy enhances cell proliferation, migration, and invasion and inhibits cell death. On the basis of widespread involvement of cMET in central nervous system malignancies, several cMET pathway inhibitors are being currently developed.[32] One may speculate that a positive cMET gene mutation in our case and the known fact that cMET enhances proliferation, migration, invasion, and inhibits cell growth may indicate that cMET may have a role in more invasive behavior of MPE. Further studies of cMET focusing on MPE are needed to evaluate this relationship. A recent study by Gu et al[33] identified HOXB13 as a molecular signature for MPE and hypothesized that further research could lead to using these genes as a therapeutic target. In this study, it was noted that HOXB13 is more specific for MPE while HOXA9 is more specific for ependymoma. HOXB13 was expressed equally in pediatric and adult patients with MPE. HOXB13 and cMET need to be included in histologic and molecular analysis research of MPE. Different genetic variants could be more prevalent in the pediatric population with a few rare outliers appearing in adults. Signs of more aggressive MPE behavior should prompt us to carry out close craniospinal imaging (i.e., MRI)

preoperatively and during postoperative follow-up. One may consider diagnostic lumbar puncture at the time of diagnosis and before resection—or at a time of recurrence—to assess dissemination. Postoperative treatment, such as irradiation and chemotherapy, could be considered. A study by Nakamura et al[34] in 2009 evaluated long-term outcomes for MPE of the cauda equina. This study evaluated 25 patients and concluded that, if a complete resection was performed, the patient should be followed conservatively; however, if the capsule was violated or there was a subtotal resection, craniospinal irradiation should be performed to prevent cerebrospinal fluid (CSF) dissemination.[34] The authors' current opinion of primary MPE seeding is to treat it as having "aggressive" behavior and as a malignant tumor, if capsular violation is found. Therefore our institution practices craniospinal irradiation, following total resection of primary multifocal MPE, if there is a capsular violation. Chemotherapy is typically withheld for patients who are refractory to radiation, following surgical management. Long-term or even lifelong MRI follow-up for these patients should be considered. Neurosurgeons should be aware of the possibility of primary seeding and drop metastasis of an MPE and should consider complete craniospinal imaging as part of both the preoperative work-up and postoperative follow-up and surveillance. Genetic MPE tumor studies, such as cMET and HOXB13, should be routinely performed and studied in the future.

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