Spinal intradural extraosseous Ewing’s sarcoma

Farrah J. Mateen,1 Aziza Nassar,2 Aditya Bardia,3 Aminah Jatoi,4 Michael G. Haddock,5 Jan C. Buckner,6 Daniel H. Lachance6

1Department of Neurology, Johns Hopkins Hospital, Baltimore, MD;
2Department of Pathology, Mayo Clinic;
3Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University;
4Department of Oncology, Mayo Clinic;
5Radiation Oncology, Mayo Clinic;
6Department of Neurology, Mayo Clinic, Rochester, MN, USA

Abstract

Extraosseous Ewing’s sarcoma (EES) involving the central nervous system is rare, but can be diagnosed and distinguished from other primitive neuroectodermal tumors (PNET) by identification of the chromosomal translocation (11;22)(q24;q12). We report EES arising from the spinal intradural extradural space, based on imaging, histopathological, and molecular data in two men, ages 50 and 60 years old and a review of the literature using PubMed (1970-2009). Reverse transcriptase polymerase chain reaction (RT-PCR) identified the fusion product FLI1-EWS. Multimodal therapy, including radiation and alternating chemotherapy including vincristine, cyclophosphamide, doxorubicin and ifosfamide and etoposide led to local tumor response. No systemic involvement was seen from the time of diagnosis to the time of last follow-up (26 months) or death (4 years). This report confirms that EES is not confined to the earliest decades of life, and like its rare occurrence as an extra-axial meningeal based mass intracranially, can occasionally present as an intradural mass in the spinal canal without evidence of systemic tumor. Gross total resection followed by multimodal therapy may provide for extended progression free and overall survival.

Introduction

Extraosseous Ewing’s Sarcoma (EES) is a rare tumor of neuroectodermal origin, belonging to the Ewing’s family of tumors. Historically, the characteristic small, round, blue cells with glycogen and a lack of cytoplasmic filaments were diagnostic.1 In 1992, diagnostic accuracy was improved by identification of a tumor specific chimeric gene with the chromosomal translocation (11;22)(q24;q12) occurring in 85% of cases.2 The fusion product that results, most commonly EWS-FLI1, is thought to act as an aberrant transcription factor.3,4

Ewing’s sarcoma limited to the central nervous system is especially rare. In the study of 2792 patients registered in three Intergroup Rhabdomyosarcoma Study clinical trials (1972-1991), 130 patients thought to have rhabdomyosarcoma were found on pathology review to have extraosseous Ewing’s sarcoma and none had Ewing’s sarcoma affecting the spinal canal or its contents.2 The most commonly affected body regions were trunk (32%, including paraspinal, chest and abdominal wall), extremity (26%), head and neck (18%, including orbit). Consequently, nervous system involvement may rarely occur by compression via extension from a primary trunk or head and neck mass. There have been occasional reports where nervous system involvement occurs as a result of compression from a primary spinal epidural lesion, or a dural based mass intracranially. Few cases of spinal intradural EES have been previously reported.5-10 Given the paucity of information available in that literature on treatment and outcomes in this rare circumstance, we report two middle-aged men with molecularly-diagnosed spinal intradural extradural EES and no concurrent or late metastatic involvement outside of the nervous system.

Case 1

A 60-year-old gentleman had lower back pain which radiated to both ankles for two months. There was accompanying numbness in the lateral thigh but no weakness. MRI demonstrated a sausage-shaped, 3.3-cm, inhomogeneous T2-hyperintense, gadolinium-enhancing lesion in the L2-3 interspace.

Meningioma was suspected. There was no prior history of malignancy. Intraoperatively, the tumor appeared to arise from the lumbar nerve root, distinct from the arachnoid mater. It was friable, vascular, and bled easily. Subtotal resection was performed in an attempt to spare the lumbar nerve root.

Histopathologic examination showed a monomorphic population of medium-sized cells in sheets and slightly cohesive nests. The nuclei of neoplastic cells showed fine chromatin and frequent mitotic figures. There was intense membranous immunostaining of the neoplastic cells with CD99 and diffuse cytoplasmic immunopositivity of CD56. Immunohistochemistry further showed positive expression of MIC2, CAM5.2, synaptophysin, and vimentin and was negative for markers of hematolymphoid neoplasm, including CD3, CD43, and CD20. Reverse transcriptase polymerase chain reaction (RT-PCR) identified the fusion product FLI1-EWS, making the diagnosis of extraosseous Ewing’s Sarcoma (Figure 1).

Evaluation by body positron emission tomography (PET) scan did not show tumor elsewhere.

He received two cycles of ifosfamide and etoposide alternating with two cycles of ifosfamide and doxorubicin prior to radiotherapy (5400 cGy in 28 fractions) to L1 through L4. Following radiation, he then received alternating cycles of this same chemotherapy regimen. Seven months following the completion of radiotherapy, there was no visible remaining tumor at the original site upon repeat imaging, but a new T2 hyperintense, gadolinium-enhancing 1.1 cm intradural lesion was seen at the S2-3 level. There was also presumed tumor in lumbar cul de sac, dorsal to the L5 to S2 vertebral bodies (Figure 2a). Fine needle aspiration specimen demonstrated recurrence. He received 5940 cGy in 33 fractions to the lumbosacral spine and adjacent oral temozolomide for 3 months. Imaging performed two months following radiotherapy demonstrated a complete response. Five months later, he developed saddle anesthesia, foot drop, and asymmetric lower extremity numbness. Widespread leptomeningeal metastases were seen at the original L2-3 site, in the cervical and mid thoracic regions, as well as intracranially, predominantly involving the 4th ventricle.

There was no evidence of intraparenchymal involvement or hydrocephalus. Given his previous response to therapy, he received 3500 cGy in 14 fractions to the neuraxis above the prior RT fields, with boosts of 500-1000 cGy in 2-4 fractions to regions with gross disease followed by three cycles of adjuvant vincristine, doxorubicin, and cyclophosphamide. Again, imaging demonstrated a complete response.

He remained symptom and disease free for 8 months until he developed progressive,
symptomatic disease of the cauda equina and received additional radiation, 3000 cGy, in 15 fractions, to the involved region of the lumbar spine. Ten months after reirradiation to the lumbar spine, he again developed symptomatic progression, but with severe deficits including saddle anesthesia, paraplegia, and urinary and fecal incontinence. MRI revealed tumor involving the dura at the level of L2 without evidence of compression of the conus or cauda equina. He received 2500 cGy in 5 fractions using stereotactic technique, followed by oral etoposide, with minor response to etoposide in the non-irradiated sites. However, within two months he developed widespread intracranial and spinal leptomeningeal disease. He died with diffuse disease limited to the nervous system, without evidence of systemic malignancy, 48 months after his initial diagnosis.

Case #2

A 50-year-old man had insidious onset of asymmetric hip and low back pain that radiated into the lower extremities. Within four months, he developed weakness and numbness in the medial thighs and groin. He required a wheelchair, and was no longer able to urinate or defecate. Examination revealed asymmetric, predominantly proximal weakness; increased tendon jerks in the lower extremities; and mute plantar responses. Sensory loss to vibration and proprioception was profound in both lower extremities, with an L1-sensory level to pin-prick and temperature.

A T2-hyperintense, contrast-enhancing mass with areas of cystic degeneration was identified in the T10-L1 extramedullary intradural space on MRI (Figure 3). This was completely resected.

Neoplastic cells were positive for pancytokeratin (AE1/AE3), OSCAR, CAM 5.2, MIC-2, CD56, and synaptophysin and negative for LCA (CD45), S100, chromogranin, and GFAP. Reverse transcriptase polymerase chain reaction (RT-PCR) for the fusion gene EWSR1-FLI1 was positive. The EWSR1-ERG RT-PCR was negative (Figure 4).

Staging evaluation, including whole body FDG-positron emission tomography, was negative for tumor elsewhere.

He received one cycle of VCD followed by IE for two cycles and adjuvant radiation to the thoracolumbar spine (5040Gy, 28f). Twenty six months following diagnosis, he remains stable with no recurrence.

Literature search

An additional search for all cases of intradural extramedullary extra-osseous Ewing’s sarcoma of the spinal cord was performed using PubMed for the timeframe January 1970 to December 2009. Cases were analysed for basic demographic features.
including (age and sex), method of diagnosis (molecular and/or histopathologic), presence of metastasis outside of the central nervous system, and survival time (months) (Table 1).

### Discussion

When EES involves the central nervous system, it usually does so via the epidural space, either as a direct extension of a primary epidural lesion, or more commonly from metastatic bone disease. We are aware of only seven previously reported cases with disease presenting in and limited to the spinal intradural space. Molecular diagnosis, confirming the fusion product (11;22)(q24;q12), was demonstrated in only a subset of these. Reported survival is variable, at 4 to more than 30 months. Notably, our patients were both in late adulthood upon presentation, confirming that EES is not limited to patients in the earliest decades of life, and with aggressive multimodal therapy, one is alive with no evidence of disease at 26 months, and the other, despite subtotal resection initially, lived 48 months.

Pathologically, the differential diagnosis of EES includes all other small round blue cell tumors: lymphoblastic lymphoma, desmoplastic small round cell tumor, rhabdomyosarcoma, neuroblastoma, primary central nervous system primitive neuroectodermal tumors, and small cell carcinoma. While distinguishable clinically as all of these entities in the intradural space would be metastatic and not a primary process, the pathological diagnosis, especially on morphologic grounds, can be difficult. Moreover, both EES and primary central nervous system primitive neuroectodermal tumors are designated PNET and stain for neuroendocrine markers. While vimentin, S100, CD99/MIC2 (in 84% to 100% of cases) as well as neuroendocrine markers including CD56 and synaptophysin may or may not be helpful in distinguishing these entities, the reverse transcriptase polymerase chain reaction (RT-PCR) for the fusion gene EWSR1-FI1 is diagnostic. Additional markers, including those derived from muscle (myogenin, muscle specific actin, MyoD1) and the hematolymphoid system (CD3, CD34, TdT), are strategic in ruling out other small blue cell tumors and ultimately help confirm the diagnosis of EES.

In the management of Ewing’s sarcoma, complete resection of the primary lesion is associated with superior outcomes. It is noteworthy that the surgical approach toward other diagnostic possibilities for similar appearing intraspinal lesions also requires an attempt at complete resection: meningioma, schwannoma, myxopapillary ependymoma, paraganglioma, hemangioblastoma, and metastasis. Therefore, surgical planning for a gross total resection, where possible, when such lesions are encountered, may improve outcomes for the rare patient who presents with EES involving the intradural extramedullary spinal canal.

Our patients had a favorable therapeutic response to multimodal therapy at treatment initiation, including radiation and alternating...
cycles of Vincristine, Cyclophosphamide, and Doxorubicin (VCD) and Ifosfamide and Etoposide (IE). This is consistent with our unreported institutional experience of molecularly-diagnosed EES in any location, treated with alternating cycles of VCD and IE. In a series of 18 patients at Mayo Clinic with molecularly-diagnosed EES, in any location, alternating cycles of VCD and IE led to a complete tumor response in 83% (15/18) and a partial response in 11% (2/18) with a mean survival of 40 months (personal communication, A. Bardin, unpublished data).

One of our cases demonstrated the propensity for intraspinal EES to recur with leptomeningeal dissemination, suggesting that craniospinal axis radiation may be necessary for long-term disease control. In previously reported cases, only Bouffet et al. provide sufficient follow-up data to determine whether this has been previously encountered.6 In one of the two patients described in that report, metastasis was limited to the intrathecal space. In our patients, there has not been recurrence outside of the central nervous system. However, the second patient reported by Bouffet et al developed metastasis in the lung suggesting that over the long term, patterns of failure in this presentation of EES include locations outside of the nervous system.

Conclusions

EES may occur as late as the 6th decade. Like its rare occurrence as an extra-axial meningeal or dural based mass intracranially, or primary epidural spinal mass, it can occasionally present as an intradural mass in the spinal canal without evidence of systemic involvement. Gross total resection followed by multimodal therapy may provide for extended progression free and overall survival. With subtotal resection, craniospinal axis radiation could be considered to avert diffuse meningeal dissemination, but the use of this approach merits careful assessment of potential toxicities, and should be carefully considered on a patient-by-patient basis.

References

1. Zagar TM, Triche TJ, Kinsella TJ. Extrasosseous Ewing’s sarcoma: 25 years later. J Clin Oncol 2008;26:4230-2.
2. Zucman J, Delattre O, Desmace C, et al. Cloning and characterization of the Ewing’s sarcoma and peripheral neuroepithelioma t(11;22) translocation breakpoints. Genes Chromosomes Cancer 1992;5:271-7.
3. Raney RB, Ashman L, Newton WA Jr, et al. Ewing’s sarcoma of soft tissues in childhood: a report from the Intergroup Rhabdomyosarcoma Study, 1972-1991. J Clin Oncol 1997;15:574-82.
4. Carvajal R, Meyers P. Ewing’s sarcoma and primitive neuroectodermal family of tumors. Hematol Oncol Clin North Am 2005;19:501-25.
5. Uesaka T, Amano T, Inamura T, et al. Intradural, extramedullary spinal Ewing’s sarcoma in childhood. J Clin Neurosci 2003;10:122-5.
6. Bouffet E, Marec-Berard P, Thiesse P, et al. Spinal cord compression by secondary epidermal tumor metastases in childhood. Childs Nerv Syst 1997;13:383-7.
7. Haresh KP, Chinikkati SK, Prabhakar R, et al. A rare case of intradural extramedullary Ewing’s sarcoma with skip metastasis in the spine. Spinal Cord 2008;46:582-4.
8. Weil RJ, Zhuang Z, Pack S, et al. Intramedullary Ewing sarcoma of the spinal cord: consequences of molecular diagnostics. Case report. J Neurosurg 2001;95:270-5.
9. Jia L, Li G, You C, et al. Intramedullary Ewing’s sarcoma of the spinal cord associated with hydrocephalus. Neurol India 2009;57:828-9.
10. Woestenborghs H, Debie-Rychter M, Renard M, et al. Cytokeratin-positive meningeal peripheral PNET/Ewing’s sarcoma of the cervical spinal cord: diagnostic value of genetic analysis. Int J Surg Pathol 2005;13:93-7.
11. National Cancer Institute. U.S. National Institutes of Health. Phase III Randomized Study of Interval-Compressed Versus Standard Chemotherapy in Patients With Newly Diagnosed, Localized Ewing’s Sarcoma or Peripheral Primitive Neuroectodermal Tumor http://www.cancer.gov/ clinicaltrials/COG-AEW5001 Last accessed January 17, 2011.
12. Amukotuw SA, Cook MJ. Spinal disease: neoplastic, degenerative, and infective spinal cord diseases and spinal cord compression in ed. Shapira AH. Neurology and clinical neuroscience. Philadelphia, PA: Mosby, Inc., 2007 pp 530-31.