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# Disseminated Intracranial Ewing's Sarcoma in an Adult: A Rare and Difficult Diagnosis

Emil Lou<sup>a</sup> Ashley L. Sumrall<sup>a</sup> Thomas J. Cummings<sup>a</sup>  
David N. Korones<sup>b</sup> Susan A. Weaver<sup>c</sup>  
Katherine B. Peters<sup>a</sup>

<sup>a</sup>The Preston Robert Tisch Brain Tumor Center at Duke, Duke University Medical Center, Durham, N.C., <sup>b</sup>University of Rochester Medical Center, Rochester, N.Y., and <sup>c</sup>Albany Medical Center, New York, N.Y., USA

## Key Words

Ewing's sarcoma, intracranial · Magnetic resonance imaging · Primitive neuroectodermal tumor

## Abstract

The Ewing sarcoma family of tumors comprises a rare class of cancers of mesenchymal origin. Cases of Ewing's sarcoma in the central nervous system – specifically, intracranial Ewing's – are extremely rare. Almost all reported cases have occurred in children. However, this rare presentation can also occur in the adult population. It is important to distinguish these tumors from primitive neuroectodermal tumors at the time of diagnosis. Testing for EWSR1(22q12) gene rearrangement using fluorescence in situ hybridization is a useful tool for making the distinction between these 2 similar but distinct entities. We present here the case of a middle-aged male patient with intracranial Ewing's sarcoma, and discuss diagnostic challenges and potential new treatment approaches for this rare disease.

## Introduction

Ewing's sarcoma is a rare mesenchymal malignancy which is histologically similar to primitive neuroectodermal tumors (PNETs). The extraosseous/intracranial form of Ewing's sarcoma tumors is particularly rare, and often presents in the pediatric population. Intracranial Ewing's sarcoma is extremely rare in adults. Morphologically, this entity appears similar to PNETs. Particular care must be taken to distinguish the two malignancies in the differential diagnosis, as the treatment approach for each varies. In this report, we present the case of a middle-aged male patient with refractory

intracranial Ewing's sarcoma treated at our institution with vorinostat, etoposide, and bevacizumab.

## Case Report

A 50-year-old man developed severe headache with diplopia, right-sided hearing loss, and tinnitus. MRI of the brain revealed mild hydrocephalus and a cystic mass in the posterior third ventricle. He sought the opinion of 5 independent neurosurgeons, 4 of whom recommended resection or biopsy. The fifth surgeon recommended observation, and the patient opted to follow this recommendation. He continued to have brain MRI performed annually over the next 5 years.

After 5 years, a cystic mass was noted again with some enlargement, and the area of enhancement had decreased in size. Due to his daughter's diagnosis of neuroblastoma and subsequent treatments, he did not pursue further evaluation until 4 years later, when he developed severe right hip and lower back pain. The pain was refractory to standard treatments including chiropractic manipulation and narcotics. Six months later, brain and spinal MRI showed increased size of the pineal mass as well as a 1.5-cm mass located at L5–S1 along the lumbosacral spine, radiologically consistent with leptomeningeal dissemination. He underwent a laminectomy of the right L5–S1 intradural leptomeningeal tumor. Histopathological diagnosis of the tumor at that time was felt to be consistent with PNET, likely pineoblastoma. Per our review of records from that time, cytological analysis of the cerebrospinal fluid (CSF) was not performed peri-operatively. He was subsequently treated with induction chemotherapy with cyclophosphamide, followed by autologous stem cell transplant. The reason for treating with cyclophosphamide as opposed to standard combination chemotherapy was patient preference in light of his underlying hearing loss. He was then treated with radiation to the entire craniospinal axis to a total radiation dose of 3,600 cGy administered over 24 fractions, followed by a boost to the lower spine (T11–S3).

Brain MRI repeated 3 months later showed evidence of radiologic improvement. However, after several more months the patient was noted to have weight loss, diminished appetite, and lethargy, which gradually improved. He was started on isotretinoin (Accutane) and continued this medication for 5 months. MRI revealed recurrence of the malignancy in the form of a small residual pineal mass, which was deemed unresectable by surgical consultants. This finding was best visualized on T<sub>1</sub> coronal imaging with gadolinium contrast; enhancement was seen at the pineal gland mass abutting the tectum of the midbrain (fig. 1a, white arrow). Lumbar spine MRI showed multiple areas of linear enhancement best noted on an axial T<sub>1</sub> image with gadolinium contrast and fat saturation, with enhancement seen at the cauda equina (fig. 1b, white arrow). These findings were consistent with progression of disease and new drop metastases. Of note, the patient was symptomatic with worsening lower back pain. There were nodules noted on the lumbar spine and cauda equina. By this time, nearly 11 years had elapsed from the time of initial diagnosis and approximately 5 years from his initial surgery. Additional staging showed no evidence of cancer systemically and CSF cytology was negative.

Recommendations at other institutions included temozolomide in combination with oral etoposide; cisplatin, lomustine (CCNU), and vincristine; or procarbazine with lomustine and vincristine (PCV regimen). He sought further recommendations at our institution.

His medical history was only notable for right-sided hearing loss and tinnitus of undetermined etiology; he had presented with these symptoms shortly before initial diagnosis 11 years prior. Family history was significant for a daughter who died of neuroblastoma at age 9, as well as a sister diagnosed with melanoma at age 41; another sister with breast cancer had been diagnosed in her early forties. His neurologic and physical exams were unremarkable aside from his bilateral hearing loss, for which he required hearing aids.

Upon presentation to our institution, the initial tumor sample from the laminectomy 5 years prior was re-examined by our neuropathology team. Microscopic examination of the biopsy showed a solid proliferation of small, round, blue cells with scant cytoplasm. In light of findings possibly consistent with a rare intracranial form of Ewing's sarcoma rather than PNET, further analysis was performed to revisit the initial diagnosis. By immunohistochemistry there was strong and diffuse CD99 reactivity. Synaptophysin, neurofilament protein, and cytokeratin were also positive. BAF47 was retained in the

tumor nuclei. CD20, GFAP, and PLAP were negative. The Mib-1 index was approximately 15%. Fluorescence in situ hybridization (FISH) testing confirmed rearrangement involving the EWSR1(22q12) gene region as detected by break-apart signals (fig. 2). The diagnosis of a neuroectodermal neoplasm consistent with Ewing's sarcoma was made.

In consideration of the patient's pre-existing bilateral hearing loss and strong desire to avoid any debilitating peripheral neuropathy, we recommended a non-platinum-containing 28-day regimen consisting of the following drugs: etoposide (VP-16) at 100 mg oral for 21 days on/7 days off; vorinostat (Zolinza) 400 mg oral daily on a 7-days-on/7-days-off schedule; and bevacizumab 10 mg/kg IV every 2 weeks. Eight weeks after initiation of this regimen, brain MRI was performed and was consistent with significant radiographic response of his disease at the level of the pineal gland with no evidence of change in the spinal images. Notably, the patient experienced resolution of his lower back pain. MR images 1 year after initiation of treatment demonstrated continued improvement. T<sub>1</sub> coronal MR images of the brain with gadolinium contrast demonstrated reduction in enhancement seen at the pineal gland mass abutting the tectum of the midbrain (fig. 3a, white arrow). A sagittal T<sub>1</sub> MR image of the lumbar spine with gadolinium contrast revealed no significant change in enhancement (fig. 3c, white arrow). The patient continued this treatment regimen for a total of 16 months with no evidence of radiographic or clinical progression. During the treatment course, primary toxicities included diarrhea (grade 1) and fatigue (grade 1). Despite these toxicities, he was able to maintain an active work schedule and good quality of life. At 17 months into his current treatment regimen, the patient was found to have new disease at the right cranial nerves VII and VIII in the right internal acoustic canal along with new disease in the thoracic spinal cord and cauda equina. Salvage therapy was started consisting of metronomic temozolomide 50 mg/m<sup>2</sup> with bevacizumab 10 mg/kg i.v.q. 2 weeks. Unfortunately, the patient developed clinical decline and MRI showed spread of leptomeningeal disease. The decision was made to transition to hospice.

## Discussion

The Ewing's sarcoma family of tumors is a rare group of primary tumors of mesenchymal origin which includes axial Ewing's sarcoma as well as PNET. Extraosseous/intracranial Ewing's sarcomas are even rarer, occurring nearly exclusively in the pediatric population. Reported cases of extraskeletal Ewing's sarcoma of the spine in the pediatric [1–3] and adult [1, 4, 5] populations have been documented. There are even fewer case reports of Ewing's sarcoma occurring in the intracranial cavity [4–8], and even then those cases occurred in children. The rarity of this malignancy, in combination with the unusual presentation and location of our adult patient's tumor, contributed to the difficulty in making the histopathological diagnosis. While PNETs are similar in appearance to Ewing's sarcoma cells morphologically, the importance of making a firm distinction between the two is underscored by their varied biologic behavior, responses to different modes of treatment, and clinical prognosis. In this case, the diagnosis of PNET was made following confirmation of CD99 immunostaining and presence of the 11;22 EWS-FLI1 chromosomal translocation.

Extraskeletal Ewing's tumors are composed of malignant small, round cell tumors with chromosomal aberrations involving EWS1 or EWSR1 on chromosome 22q12. The most common result is fusion of EWS with FLI1 – a member of the ETS gene family on chromosome 11q24 which is homologous to murine Friend's leukemia. This fusion results in the characteristic t(11;22)(q24;q12) chromosomal translocation and ETS transcription factor which is present in up to 80% of such cases [9]. The use of immunohistochemical and FISH technologies is necessary to make an accurate diagnosis [10]. The cell surface glycoprotein CD99 (MIC2) is strongly expressed in Ewing's sarcoma and aids in the diagnosis [11], as does positive staining for vimentin.

The absence of glial fibrillary acidic protein and synaptophysin helped to rule out glial tumors and neural tumors, respectively, as the cause of the primary brain malignancy.

Published case series or reports of intracranial or spinal Ewing's sarcomas have documented treatment using a variety of approaches, including combinations of vincristine, doxorubicin, cyclophosphamide, actinomycin-D, followed by either radiation [4], or carboplatin and etoposide leading to autologous stem cell transplant [1]; vincristine, doxorubicin, ifosfamide, and actinomycin-D concurrent with radiation [1]; cyclophosphamide, vincristine, and doxorubicin concurrent with radiation [6]; or vincristine, cisplatin, cyclophosphamide with radiation [5], with generally poor results. At our institution, pediatric patients (<10 years old) have previously been treated with a total of 6 cycles of vincristine, cyclophosphamide, and doxorubicin alternating with ifosfamide and etoposide, as well as either focal or craniospinal irradiation, with more promising results [2]. Alkylating agents have traditionally formed the backbone of treatment for Ewing's sarcomas, while platinum-based chemotherapy is the basis of treatment of PNETs; thus it is important to distinguish between the 2 entities. Furthermore, it has been suggested that the natural history and prognosis for intracranial Ewing's sarcoma may be more favorable than that of central PNETs [4], although the information is limited due to the rarity of this disease.

Histone deacetylase (HDAC) inhibitors have gained favor as a new approach to targeted therapy of various forms of cancer in the past few years. No published clinical trials have yet demonstrated the utility of this class of drug in Ewing's sarcomas, although there is preclinical evidence that HDAC inhibitors inhibit expression of the EWS-FLI1 protein *in vitro* [12]. HDAC inhibitors such as vorinostat have shown similar promise in uterine sarcomas as well [12]. Vorinostat in particular has been considered for use in other intracranial malignancies. Valproate, an anti-epileptic and weak HDAC inhibitor, has been shown to improve survival in patients with glioblastoma undergoing treatment with concurrent temozolomide and radiation [13].

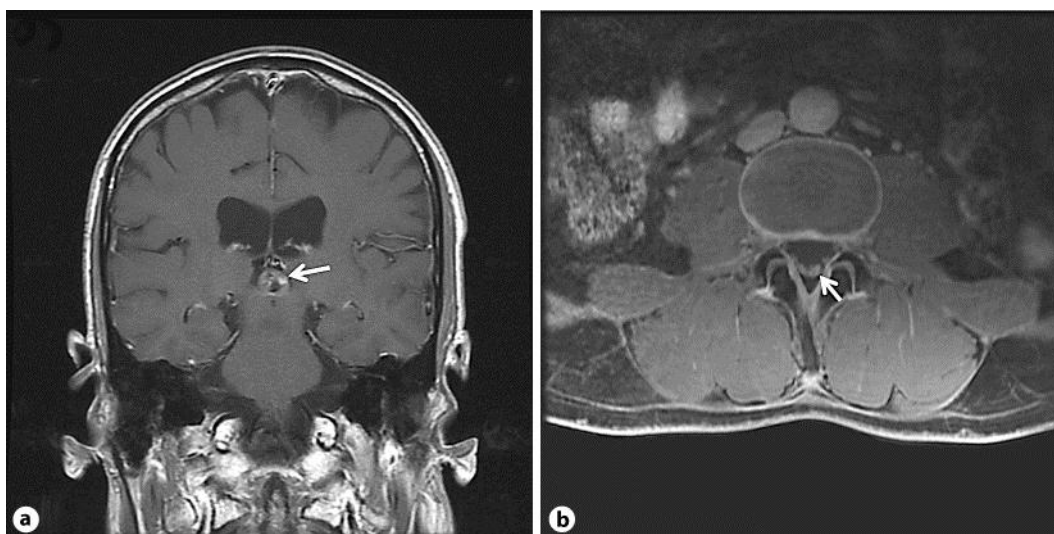
Inhibitors of vascular endothelial growth factor (VEGF) have also been considered as a potential therapy for Ewing's sarcomas. Preclinical models have demonstrated the ability of such inhibitors, including bevacizumab, to significantly delay tumor growth in animal models [14]. Furthermore, higher levels of VEGF in resected specimens from patients correlates with higher 10-year relapse-free and overall survival [15], indicating that the natural course of the disease is at least somewhat favorable independent of treatment. While our patient's disease did eventually recur on this regimen, this combination of vorinostat with oral etoposide and bevacizumab did provide some control of his leptomeningeal disease. This presents a potential alternative approach for pediatric and adult patients with this rare diagnosis.

### Acknowledgements

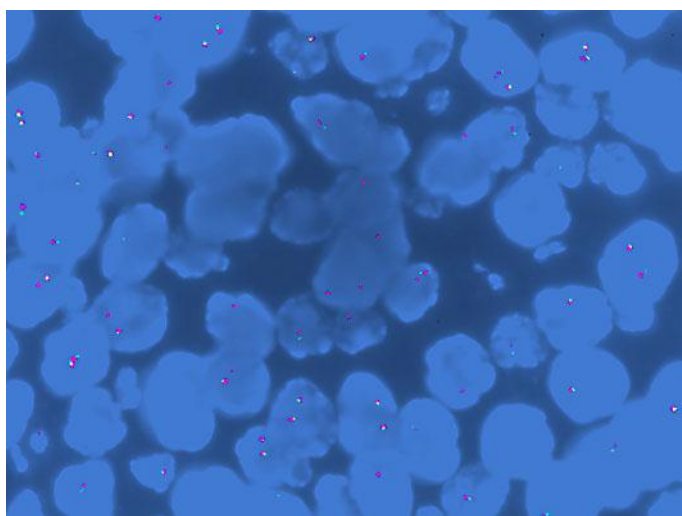
The authors would like to thank the patient for providing consent to publish his case history. We also thank Kelly Seagroves for her excellent assistance with the preparation of the manuscript.

### Disclosure Statement

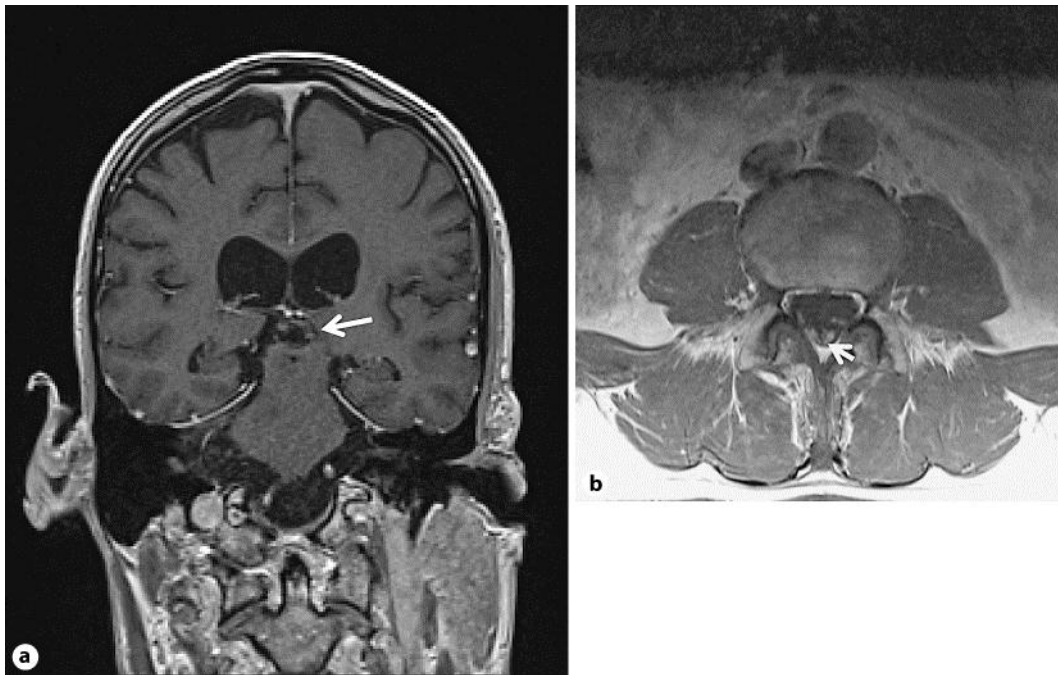
The authors have no competing interests to declare.



**Fig. 1.** MR images at the time of referral to the Duke Brain Tumor Center. **a** Brain MRI, coronal T<sub>1</sub> image with gadolinium contrast, enhancement seen at the pineal gland mass abutting the tectum of the midbrain (white arrow). **b** MRI of the lumbar spine, axial T<sub>1</sub> image with gadolinium contrast and fat saturation, enhancement seen at the cauda equina (white arrow).



**Fig. 2.** Immunofluorescent image of FISH analysis revealing EWS chromosomal rearrangement.



**Fig. 3.** MRI images taken 1 year after the initiation of treatment regimen with etoposide, vorinostat, and bevacizumab. **a** Brain MRI, coronal T<sub>1</sub> image with gadolinium contrast, reduction in enhancement seen at the pineal gland mass abutting the tectum of the midbrain (white arrow). **b** MRI of the lumbar spine, sagittal T<sub>1</sub> image with gadolinium contrast, no significant change in enhancement (white arrow).

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