Multifocal primary central nervous system Ewing sarcoma presenting with intracranial hemorrhage and leptomeningeal dissemination: illustrative case

Anna L. Huguenard, MD,1 Yuping Derek Li, MD, Nima Sharifai, MD, PhD, Stephanie M. Perkins, MD, Sonika Dahiya, MD,2 and Michael R. Chicoine, MD1

Departments of 1Neurosurgery, 2Pathology and Immunology, and 3Radiation Oncology, Washington University in St. Louis, Missouri

BACKGROUND Ewing sarcoma is a neoplasm within the family of small round blue cell tumors and most frequently arises from skeletal bone. Primary involvement of the central nervous system in these lesions is extremely rare, with an incidence of 1%.

OBSERVATIONS A case is presented of a 34-year-old man who presented with left facial numbness, multiple intracranial lesions, a lumbar intradural lesion, and diffuse spinal leptomeningeal involvement. A lumbar laminectomy and biopsy were performed, which revealed the diagnosis of extraskeletal Ewing sarcoma/primitive neuroectodermal tumor. The patient had a rapidly progressive clinical decline despite total neuroaxis radiation and multiple lines of chemotherapeutic treatments, eventually dying from his disease and its sequelae 6 months after diagnosis.

LESSONS The authors’ review of 40 cases in the literature revealed only 2 patients with isolated intraaxial cranial lesions, 4 patients with cranial and spine involvement, and an additional 34 patients with spine lesions. The unique characteristics of this patient’s case, including his presentation with diffuse disease and pathology that included a rare V600E BRAF mutation, are discussed in the context of the available literature.

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KEYWORDS Ewing sarcoma; oncology; spine; intracranial; BRAF

Ewing sarcoma (ES) is a part of a family of small round blue cell neoplasms that primarily affects patients in the first and second decades of life.1 Approximately 75% of cases arise from bone, whereas the other 25% arise from soft tissue.2 Often, ES can cause neurological symptoms by developing in the bony structures such as the calvaria and spinal column, causing mass effect on adjacent structures. Primary central nervous system (CNS) involvement by ES is rare, with an estimated incidence of 1%.3 The most common origin is the dura, and primary intraparenchymal disease is extremely rare. There are only 2 cases of isolated intraaxial ES and 4 cases of cranial and spine involvement reported in literature (Table 1). In cases with intracranial lesions, patients often present with symptoms of increased intracranial pressure or neurological deficits associated with tumor location. Of note, it is important to distinguish primary CNS ES from CNS embryonal tumors, previously called “central primitive neuroectodermal tumors” (cPNETs), as they differ in underlying genetics, treatment, and prognosis.4 We report a case of multifocal primary CNS ES that presented with intraparenchymal hemorrhage in a 34-year-old man.

Illustrative Case

History and Examination

A 34-year-old man without prior significant history presented with worsening right-sided headache and back pain. He had 3 months of worsening headaches, frequently nocturnal in nature, with interval development of associated nausea and vomiting 3 weeks prior to presentation. Additionally, he was having increasing low back pain that he had been managing with muscle relaxers, oral steroids, and over-the-counter pain medication. In the previous week, he also noted new, intermittent numbness and tingling affecting both his left leg and face.

On neurological examination, he had present but abnormal sensation in all three divisions of the left trigeminal nerve. His ocular and facial movements were all normal. Motor and sensory examinations of his upper and lower extremities were normal.

The computed tomography (CT) scan of the head obtained upon presentation (Fig. 1) was remarkable for a 1.5 × 3.7–cm ovoid, uniformly hyperdense intraaxial lesion in the right frontal medial orbital

ABBREVIATIONS CNS = central nervous system; cPNET = central primitive neuroectodermal tumor; CSF = cerebrospinal fluid; CT = computed tomography; ES = Ewing sarcoma; GFAP = glial fibrillary acidic protein; MRI = magnetic resonance imaging.

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| Study                          | Age (yrs)/Gender | Location                  | Other Spread                  | Presentation                  | Hemorrhage | Hemorrhage Value | CD99/t(11;22) | Treatment                                                                 | Outcome                      |
|-------------------------------|------------------|---------------------------|-------------------------------|-------------------------------|------------|------------------|--------------|---------------------------------------------------------------------------|-------------------------------|
| VandenHeuvel et al., 2015     | 32/2F            | Frontal lobe              | None, CSF negative           | Partial seizures              | No         | +/-              |              | Surgery: GTR; chemo: VCR, CYA, DXR; radiation: focal radiation            | Alive at 6 yrs                |
| VandenHeuvel et al., 2015     | 61/61M           | Frontotemporal lobe       | None, CSF negative           | Slurred speech, Lt facial drop, Lt hemiparesis | No         | +/-              |              | Surgery: STR; no adjuvant chemo or radiation                             | Lost to follow-up             |
| Weil et al., 2001             | 21/21M           | T10–11, L1–2, 2 parietal lesions | CSF negative               | Thoracic back pain, lower extremity weakness/spasticity | No         | +/-              |              | Surgery: STR cranial & spinal lesion; chemo: VCR, DXR, CPM, ETP, IFO; radiation: craniospinal radiation, boost to tumor bed | Alive at 30 mos               |
| Mateen et al., 2011           | 60/60M           | L2–3                      | Delayed diffuse cranial & spine leptomeningeal spread | Back pain, bilat leg radiculopathy | No         | +/-              |              | Surgery: STR; chemo: IFO, ETP, DXR, TMZ; radiation: radiation to L1–4       | Dead at 48 mos                |
| Tan et al., 2019              | 34/34F           | C4–T3                     | Diffuse leptomeningeal disease of spine, rapid intracranial spread | Upper extremity paresthesias, urinary retention | No         | +/-              |              | Surgery: STR; chemo: none; radiation: urgent radiotherapy to craniospinal axis | Dead at 11 mos                |
| Izubuchi et al., 2020         | 35/35F           | T12–L1, L4–5              | Diffuse meningeval spread, multiple intracranial lesions at 10 mos | Radiculopathy & bilat leg paresthesias | No         | +/-              |              | Surgery: STR; chemo: VCR, DXR, CPM, IFO, ETP; radiation: total spinal radiation, later WBRT due to mets | Dead at 16 mos                |
| Hisaoka et al., 1997          | 14/14M           | Cauda equina              | None                          | Back pain & Lt leg radiculopathy | No         | +/-              |              | Surgery: GTR; no adjuvant chemo or radiation                              | Alive at 3 mos                |
| Uesaka et al., 2003           | 11/11F           | C7–T1                     | None                          | Progressive paraparesis      | No         | +/-              |              | Surgery: STR; no adjuvant chemo or radiation documented                  | Unknown                       |
| Harimaya et al., 2003         | 30/30F           | C2–4                      | None                          | Extremity paresthesias, urinary retention | No         | +/-              |              | Surgery: GTR; chemo: VCR, DXR, IFO, ACD; radiation: focal radiotherapy    | Dead at 14 mos                |
| Harimaya et al., 2003         | 14/14M           | Cauda equina (L1–2)       | None                          | Low back pain & lower extremity radiculopathy | No         | +/-              |              | Surgery: GTR; chemo: VCR, DXR, IFO, ACD, CBP, ETP; radiation: none        | Alive at 67 mos               |
| Woestenborghs et al., 2005    | 11/11M           | C4–T2                     | None                          | Progressive quadriaparesis   | No         | +/-              |              | Surgery: STR; chemo: VCR, IFO, ACD, ETP; radiation: none                  | Unknown                       |
| Mobley et al., 2008           | 32/32M           | Cauda equina (L2–4)       | None                          | Back pain, distal lower extremity weakness | No         | +/-              |              | Surgery: GTR; chemo: ACD, VCR, DXR, CPM, ETP, IFO; radiation: regional radiation T12–S3 w/ boost to resection site | Dead at 12 mos                |
| Haresh et al., 2008           | 26/26M           | Cauda equina (T11–S2)     | Delayed spread to T6–7        | Back pain, lower extremity weakness | No         | +/-              |              | Surgery: GTR; chemo: VCR, DXR, CPM, IFO, ETP; radiation: focal radiation  | Alive at 6 mos                |
| Kim & Shin, 2009              | 32/32F           | C3–5                      | None                          | Progressive upper extremity paresis | No         | +/-              |              | Surgery: STR; chemo: ETP, IFO; radiation: focal radiation                | Alive at 12 mos               |

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| Study                  | Age (yrs)/ Gender | Location          | Other Spread            | Presentation                | Hemorrhage | CD99/t(11:22) | Treatment                                                                 | Outcome          |
|-----------------------|-------------------|-------------------|-------------------------|-----------------------------|------------|---------------|---------------------------------------------------------------------------|------------------|
| Klimo et al., 2009³⁷  | 37/10 M           | L4–5              | None                    | Rt leg pain & paresthesias | No         | +/-           | Surgery: STR; chemo: VCR, DXR, CPM, ETP, IFO; radiation: radiation to L3–5 | Alive at 12 mos  |
| Theeler et al., 2009³⁸| 28/28 F           | T5–8              | None                    | Lt arm pain, lower extremity paresthesias | No         | +/-           | Surgery: none (CT-guided biopsy); chemo: VCR, CPM, DXR, IFO, ETP; radiation: palliative spinal radiation | Alive at 2 mos   |
| Vincentelli et al., 2010⁹| 40/40 F           | Cauda equina (T11–L4) | None                    | Paraparesis & urinary retention | Yes        | ?/+           | Surgery: STR; chemo: DXR, IFO; radiation: conformational radiotherapy   | Alive at 6 mos   |
| Muzzafar et al., 2010⁶| 38/38 F           | Cauda equina (L2–S2) | None                    | Back pain, bilat leg radiculopathy | Yes        | +/-           | Surgery: GTR; chemo: systemic therapy; radiation: none                   | Unknown          |
| Karikari et al., 2011³⁹| 56/56 F           | L1                | None, CSF negative      | Back pain, leg radiculopathy | No         | +/-           | Surgery: GTR; chemo: VCR, DXR, CPM, IFO, ETP; radiation: local radiation | Unknown          |
| Yan et al., 2011²³   | 10/10 M           | C2–3              | None, CSF negative      | Neck pain, rt hemiparesis   | No         | ?/+           | Surgery: GTR; dead prior to adjuvant therapy                            | Dead at 30 days  |
| Duan et al., 2011⁴⁰   | 8/8 M             | L2–L4             | None                    | Unknown                     | No         | ?/+           | Surgery: GTR; chemo: systemic therapy; radiation: local radiation       | Unknown          |
| Duan et al., 2011⁴⁰   | 25/25 M           | L2/3              | None                    | Unknown                     | No         | ?/+           | Surgery: GTR; chemo: systemic therapy; radiation: focal radiation        | Unknown          |
| Mateen et al., 2011¹² | 50/50 M           | T10–L1            | None                    | Progressive lower extremity paresthesias | No         | +/-           | Surgery: GTR; chemo: VCR, CPM, DXR, IFO, ETP; radiation: focal to thoracolumbar spine | Alive at 26 mos  |
| Pancucci et al., 2013⁷| 55/55 M           | L4–S2             | None, bone marrow biopsy negative | Lower extremity weakness, urinary retention | Yes        | +/-           | Surgery: GTR; chemo: DXR, IFO, ETP; radiation: fractionated external radiotherapy | Alive at 13 mos  |
| Pancucci et al., 2013⁷| 25/25 F           | L2–3              | None, bone marrow biopsy negative | Lower extremity weakness, urinary urgency | No         | +/-           | Surgery: GTR; no adjuvant therapy given patient’s poor performance status | Local relapse at 14 mos |
| Khalatbari et al., 2013⁹| 28/28 F           | L5–S1             | None                    | Back & rt leg pain, acute cauda equina | Yes        | +/-           | Surgery: GTR; chemo: VCR, DXR, CPM, IFO, ETP; radiation: focal radiation | Alive at 72 mos  |
| Bazzocchi et al., 2013¹⁵| 44/44 F           | T6–7, L1–2        | None                    | Sudden-onset paraplegia     | No         | ?/+           | Surgery: GTR of largest lesion; chemo: VCR, CPM, DXR, IFO, ETP; radiation: focal to lumbar spine | Unknown          |
| Lozupone et al., 2014⁴¹| 44/44 F           | Cauda equina (L1–S3) | None                    | Low back pain & radiculopathy | No         | +/-           | Surgery: GTR; chemo: VCR, EPIR, EDX; radiation: focal conformational radiotherapy | Alive at 6 mos   |
| Zhao et al., 2014⁴²   | 14/14 M           | L4–5              | None                    | Rt leg pain & paresthesias | No         | +/-           | Surgery: GTR; chemo: CPM, DXR, IFO; radiation: focal radiation           | Alive at 12 mos  |
| Mardekian et al., 2014⁴³| 26/26 M           | T12–L1            | None                    | Back pain                   | No         | +/-           | Surgery: GTR; no adjuvant therapies described                           | Unknown          |
gyrus. There was surrounding hypodensity, consistent with vasogenic edema. There was local mass effect with an associated adjacent 3-mm right-to-left midline shift.

Subsequent magnetic resonance imaging (MRI) of the brain with and without contrast (Fig. 2) redemonstrated this intraaxial, right-sided, medial orbital gyrus lesion. The lesion demonstrated rim enhancement as well as diffusion restriction. A 5-mm enhancing lesion was seen at the right brachium pontis, and a 1.4 × 2-cm uniformly enhancing lesion was seen expanding Meckel’s cave on the left. Finally, there was evidence of enhancement along cranial nerves V, VII, and VII on the left.

On the 2nd day of admission, the patient developed new weakness of dorsiflexion on his left side, prompting MRI of the total spine (Fig. 3).

| Study                         | Age (yrs)/Gender | Location | Other Spread | Presentation | Hemorrhage | CD99/ t(11:22) | Treatment                                      | Outcome            |
|-------------------------------|------------------|----------|--------------|--------------|------------|----------------|------------------------------------------------|--------------------|
| Mardekian et al., 2014        | 70/M             | T12–L1   | None         | Back pain    | No         | +/+            | Surgery: STR; no adjuvant therapies described | Unknown            |
| Gong et al., 2015             | 39/F             | C4–6     | Delayed development of L4–S1 mass | Progressive Lt arm paresthesias & pain | No | +/+ | Surgery: GTR; chemo: CPM, VCR; radiation: local radiotherapy | Alive at 3 yrs |
| Bostelmann et al., 2016       | 29/M             | C6–T1    | Delayed development of additional spinal metastatic lesions | Rt C7 radiculopathy followed by hemiparesis | No | +/+ | Surgery: GTR, re-resection 4 wks later for recurrence; chemo: VCR, IFO, DXR, ETP, TOPO, CPM; radiation: total spine & local boost | Alive at 18 mos |
| Kartal & Akatl, 2016          | 5/M              | T4–7     | None         | Low back pain & gait disturbance | No | +/? | Surgery: GTR; no adjuvant therapies described | Unknown            |
| Chihak et al., 2016           | 25/M             | C4–7     | None         | Rt hand numbness/tingling | No | +/+ | Surgery: STR; chemo: IFO, ETP, VCR, DXR, CPM; radiation: urgent radiation to tumor bed, total craniospinal radiation, additional boost to tumor area | Alive at 20 mos |
| Chihak et al., 2016           | 34/M             | L4–5, S1–2, S4–5 | None | Cauda equina symptoms | No | +/+ | Surgery: STR; chemo: VCR, DXR, CPM, IFO, ETP; radiation: craniospinal radiation w/ local boost | Alive at 3 mos |
| Paterakis et al., 2017        | 31/M             | L2–3, sacral lesion | Delayed bone metastasis | Progressive paraparesis | No | +/+ | Surgery: GTR of lumbar lesion; chemo: VCR, DXR, CPM, IFO, ETP; radiation: craniospinal radiation w/ local boost | Alive at 24 mos |
| Scantland et al., 2018        | 14/F             | Conus medullaris | None | Progressive back pain | Yes | +/+ | Surgery: STR; chemo: VCR, DXR, CPM, IFO, ETP; radiation: proton beam radiotherapy | Alive at 2 yrs |
| Takami et al., 2018           | 61/M             | L1–3     | None         | Lt leg paresthesias, urinary retention | No | +/+ | Surgery: GTR; chemo: VCR, DXR, CPM, IFO, ETP; radiation: focal to lumbar spine | Alive at 3 mos |
| Khwaja et al., 2019           | 44/F             | C7–T1    | Diffuse leptomeningeal disease of spine | Pain in lower extremities, paraplegia | No | +/+ | Surgery: STR; chemo: CDDP, CCNU, IFO, CBP, ETP; radiation: craniospinal irradiation, focal boost w/ CyberKnife | Alive at 8 yrs |

+ = mutation present; ? = presence of mutation unknown; ACD = actinomycin D; CBP = carboplatin, CCNU = lomustine; CDDP = cisplatin; chemo = chemotherapy; CPM = cyclophosphamide; CYA = cyclosporine; DXR = doxorubicin (Adriamycin); EDX = epidoxorubicin; EPIR = epirubicin; ETP = etoposide; GTR = gross total resection; IFO = ifosfamide; STR = subtotal resection; t(11;22) = translocation (11;22); TMZ = temozolomide; TOPO = topotecan; VCR = vincristine; WBRT = whole brain radiotherapy.

Includes cranial intraparenchymal lesions, spine lesions, and patients with brain and spine involvement. Note, none of these cases describe a BRAF mutation.
This MRI demonstrated diffuse, nodular, leptomeningeal enhancement, with a significant epidural enhancing soft tissue component in the lumbar spine with mass effect on the adjacent conus and cauda equina. Subsequent whole-body fluorodeoxyglucose–positron emission tomography CT scans of the chest, abdomen, and pelvis and scrotal ultrasound revealed no evidence of tumor outside the CNS.

Operative Details

In light of the relatively accessible nature of the intradural spinal lesions, a left partial L5 hemilaminectomy and biopsy of the intradural lumbar spinal lesion was performed. During the dissection, it was noted that the dura had an abnormal purple-blue hue. Once the dura was incised, there was an immediate return of dark orange fluid, believed to be related to the presence of tumor and blood within the cerebrospinal fluid (CSF). As the dissection continued, abnormal small purplish-tan clumps of tissue were identified adherent to the lumbar nerve roots. Several specimens were collected and sent for frozen and permanent pathology. There were no immediate postoperative complications.

Pathology

Histopathological examination revealed a high-grade malignant neoplasm, partially involving a nerve root, with an overall solid growth pattern. The tumor cells demonstrated minimal to scant pale eosinophilic cytoplasm with indistinct cell borders in a fibrillary appearing background. Nuclei ranged from round to oval to short-spindled, with substantial pleomorphism, hyperchromasia, irregular contours, and inconspicuous nucleoli (Fig. 4). Mitotic figures and karyorrhectic debris were abundant. Focally prominent neutrophilic infiltrates were present in the tumor (Fig. 4).

Immunohistochemical stains showed the tumor cells to be strongly and diffusely positive for vimentin and CD99, with nonreactivity for glial fibrillary acidic protein (GFAP), synaptophysin, CD3, CD20, epithelial membrane antigen, CAM5.2, CD56, WT1, and human melanoma black-45. Neurofilament highlighted few remaining axons of the involved nerve root (Fig. 4). INI-1 nuclear expression was retained throughout the tumor. Ki-67 (MIB-1 antibody) was high at around 40% focally.

Fluorescence in situ hybridization using an EWSR1 break-apart probe showed the presence of EWSR1 gene rearrangement. FLI1 immunohistochemistry showed multifocal variable nuclear positivity,
suggesting an EWSR1-FLI1 gene fusion. Altogether, these findings supported a diagnosis of extraskeletal ES/PNET. Follow-up targeted next-generation sequencing showed the presence of mutations in BRAF (V600E), PTCH1 (p.G115 K), EZH2 (p.E249), HIST1H1D (p.K214*), TP53 (p.H179Y), and loss of exons 2–3 in CDKN2A/B.

Postoperative Course

Postoperatively, the patient had progressive worsening of his left leg weakness, followed by progressive weakness of his right leg and eventual bowel and bladder incontinence. He also developed a left corneal abrasion secondary to his V1 numbness. Later, his course was complicated by multiple deep venous thrombi and a pulmonary embolus.

Adjuvant therapy included radiation to a dose of 1260 cGy in 5 fractions to the T12–S1 levels, followed by craniospinal radiation to a dose of 3060 cGy in 180 cGy per fraction. He also received one cycle of chemotherapy with cisplatin, Cytoxan, and vincristine. He also received one cycle of ifosfamide and etoposide. Unfortunately, he continued to have clinical deterioration and progression of his multifocal disease refractory to medical therapy. The patient was transitioned to palliative measures and died 6 months after presentation.

Literature Review

A literature search was performed to better characterize the anatomical distribution, management strategies, and treatment outcomes of primary CNS ES. A search using keywords “primary central nervous system Ewing sarcoma” in PubMed and Ovid-MEDLINE yielded 78 articles. Several of these articles included their own literature reviews, and from these, an additional 44 unique articles were identified for our review. Of these 122 papers, articles referencing peripheral ES with metastatic CNS involvement and those describing cPNETs were excluded. In order to highlight the unique characteristics of our case, we further narrowed our search by excluding 42 papers that described isolated dural-based intracranial tumors.

The remaining 33 papers we included in our study described 40 cases of CNS ES, including patients with isolated intraparenchymal lesions, spinal lesions, and a combination of spine and cranial involvement (Table 1). The average age at diagnosis was 30.9 years, and 60% of the patients were male. All tumors underwent immunohistochemical staining for CD99, genetic analysis (translocation 11:22), or both. None of the cases reported a BRAF mutation from tumor genetic sequencing, as was seen in our case.

The symptoms at the time of presentation for these patients were mainly associated with the location of the lesion. Tumors in the frontal lobe resulted in contralateral hemiparesis or seizures, whereas spinal cord tumors resulted in weakness, radiculopathy, or paresthesias below that level.

In our selected cases, gross-total resection was obtained in 22 cases, with gross-total resection of only the largest lesion in 2 cases, subtotal resection in 15 cases, and CT-guided biopsy alone in 1 case. Hemorrhage at the time of presentation was uncommon and was featured in only 5 cases. However, many authors reported that the tumor was highly vascular in their intraoperative findings.

Of the cases we reviewed, 4 patients presented with or developed diffuse leptomeningeal disease, 5 patients were found to have multiple lesions on initial presentation, and an additional 4 patients developed new discrete lesions later in the course of the disease. Duration of follow-up in our reviewed cases was variable, with no documented case outcome in 11 patients. Of those with documented outcomes, 5 patients died within 2 years of diagnosis. Of
these patients, all initially presented with spine lesions. Two developed delayed diffuse leptomeningeal disease, including intracranial spread.10,13 Two patients underwent gross-total resection with adjuvant chemotherapy and focal radiation.21,22 One patient underwent gross-total resection but died from their disease before adjuvant therapy could be given.23

Discussion

Observations

In this report, we discuss the case of a 34-year-old man who was diagnosed with, and eventually died from, an extraskeletal, primary multifocal CNS ES. This is a rare clinical entity, with limited literature available to guide appropriate management or predict prognosis. Unique to our case, the patient’s largest lesion was a hemorrhagic intraparenchymal lesion. There was also extensive CNS dissemination at the time of presentation, with numerous intracranial and spine lesions and diffuse leptomeningeal disease.

Lessons

For both CNS ES and non–CNS ES, resection is a mainstay of treatment, although the recommendations for timing often differ. For ES involving the extremities or pelvis, treatment conventionally begins with induction chemotherapy prior to subsequent resection,24 which allows for cyto reduction and increased ability to perform a complete resection. However, in cases of ES involving the CNS, patients often present with progressive neurological deficits or increased intracranial pressure requiring urgent surgical intervention. This can present a challenge to the surgeon, as complete resection becomes more difficult to accomplish. In cases such as that of our patient, diffuse disease prevents more definitive surgical resection.

Radiation and chemotherapy are important adjuvant therapies in the treatment of CNS ES.25 The common chemotherapy regimens utilized include cyclophosphamide, doxorubicin, etoposide, ifosfamide, and vincristine. It is important to note that, although chemotherapy is effective for ESPNET, it comes with significant side effects, including cardiac toxicity, particularly with doxorubicin.25

With regard to prognosis, predictors of a poor outcome for any patient with ES include the size of the lesion, the presence of metastatic disease, a pelvic location, a high serum lactate dehydrogenase, and an age greater than 17 years.26–28 The average time of survival for a patient with ES involving the CNS is believed to be between 6 months and 3 years.25,29 Ibrahim et al. proposed a set of prognostic indicators for CNS ES that include age greater than 17 years, surgically inaccessible location, incomplete resection, multifocal disease, and unfavorable tumor biology (e.g., poor histological response to initial chemotherapy, non–type 1 EWS-FLI1 fusions, P53 and P16 mutations, and lower levels of vascular endothelial growth factor expression).29 However, these prognostic characteristics have not been confirmed through large cohort studies.

Based on the available literature, our patient had several factors that portended a poor clinical course, including his age, his widely metastatic disease, and his inability to undergo complete resection given the locations and diffusivity of his lesions. His disease progressed rapidly over the course of 6 months despite neuroaxis radiation and multiple chemotherapeutic agents.

Another distinct finding in our patient was the presence of a V600E BRAF mutation, which was not identified in any of the other cases we reviewed. Ahmed et al. previously used their tumor bank of 68 ES tumors to perform immunohistochemistry and evaluate for mutations that may inform pathway-specific therapies in ES.30 Although high expression of Akt-1 and nuclear factor-kappa beta was common, high expression of BRAF was seen in only 3% of cases. Furthermore, they found no significant correlation between BRAF expression and prognosis in these patients.30

Work performed by Gouravan et al. targeted V600E BRAF mutations in sarcomas using vemurafenib.31 Vemurafenib has previously been used to target melanoma with V600E BRAF mutations with a good response rate and prolonged progression-free survival, though similar results were not seen in colorectal cancer patients with the same mutation owing to rapid resistance. In this preclinical trial using four sarcoma lines, one of which was an ES, there was evidence of poor response to vemurafenib, suggesting that it may be an ineffective candidate for clinical application in sarcomas.31 Future studies may reveal a more effective agent for targeting this specific mutation in sarcomas.

Given the rarity of this disease, it is important that clinicians continue to amass the clinical, pathological, and radiological characteristics of these patients to better guide clinical management and prognostic discussions with patients and their families.
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Correspondence
Anna L. Huguenard: Washington University in St. Louis, MO. ahuguenard@wustl.edu.