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

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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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TABLE 1. Reported cases in the literature for primary CNS extraskeletal ES

Study	Age (yrs)/ Gender	Location	Other Spread	Presentation	Hemorrhage	CD99/ t(11:22)	Treatment	Outcome
VandenHeuvel et al., 2015[32]	2/F	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[32]	61/M	Fronto-temporal lobe	None, CSF negative	Slurred speech, lt facial droop, lt hemiparesis	No	+/+	Surgery: STR; no adjuvant chemo or radiation	Lost to follow-up
Weil et al., 2001[14]	21/M	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[12]	60/M	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[13]	34/F	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[10]	35/F	T12–L1, L4–5	Diffuse meningeal 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[33]	14/M	Cauda equina	None	Back pain & lt leg radiculopathy	No	+/+	Surgery: GTR; no adjuvant chemo or radiation	Alive at 3 mos
Uesaka et al., 2003[34]	11/F	C7–T1	None	Progressive paraparesis	No	+/+	Surgery: STR; no adjuvant chemo or radiation documented	Unknown
Harimaya et al., 2003[21]	30/F	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[21]	14/M	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[35]	11/M	C4–T2	None	Progressive quadriparesis	No	+/+	Surgery: STR; chemo: VCR, IFO, ACD, ETP; radiation: none	Unknown
Mobley et al., 2006[22]	32/M	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[18]	26/M	Cauda equina (T11–S2)	Delayed spread to T6–7	Back pain, lower extremity weakness	No	+/?	Surgery: GTR; chemo: VCR, DXR, CPM, IFO, CDDP, ETP; radiation: focal radiation	Alive at 6 mos
Kim & Shin, 2009[36]	32/F	C3–5	None	Progressive upper extremity paresis	No	+/+	Surgery: STR; chemo: ETP, IFO; radiation: focal radiation	Alive at 12 mos

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TABLE 1. Reported cases in the literature for primary CNS extraskeletal ES

Study	Age (yrs)/ Gender	Location	Other Spread	Presentation	Hemorrhage	CD99/ t(11: 22)	Treatment	Outcome
Klimo et al., 2009[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., 2009[38]	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., 2010[9]	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., 2010[6]	38/M	Cauda equina (L2–S2)	None	Back pain, bilat leg radiculopathy	Yes	+/+	Surgery: GTR; chemo: systemic therapy; radiation: none	Unknown
Karikari et al., 2011[39]	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., 2011[23]	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., 2011[40]	8/M	L2–L4	None	Unknown	No	+/?	Surgery: GTR; chemo: systemic therapy; radiation: local radiation	Unknown
Duan et al., 2011[40]	25/M	L2/3	None	Unknown	No	+/?	Surgery: GTR; chemo: systemic therapy; radiation: focal radiation	Unknown
Mateen et al., 2011[12]	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., 2013[7]	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., 2013[7]	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., 2013[5]	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., 2013[15]	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., 2014[41]	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., 2014[42]	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., 2014[43]	26/M	T12–L1	None	Back pain	No	+/+	Surgery: GTR; no adjuvant therapies described	Unknown

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TABLE 1. Reported cases in the literature for primary CNS extraskeletal ES

Study	Age (yrs)/ Gender	Location	Other Spread	Presentation	Hemorrhage	CD99/ t(11:22)	Treatment	Outcome
Mardekian et al., 2014[43]	70/M	T12–L1	None	Back pain	No	+/+	Surgery: STR; no adjuvant therapies described	Unknown
Gong et al., 2015[19]	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[20]	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 & Akatlı, 2016[44]	5/M	T4–7	None	Low back pain & gait disturbance	No	+/?	Surgery: GTR; no adjuvant therapies described	Unknown
Chihak et al., 2016[16]	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[16]	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[17]	31/M	L2–3, sacral lesion	Delayed bone metastasis	Progressive paraparesis	No	+/+	Surgery: GTR of lumbar lesion; chemo: VCR, DXR, CPM, IFO, ETP; radiation: none	Alive at 24 mos
Scantland et al., 2018[8]	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[45]	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[11]	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.

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).

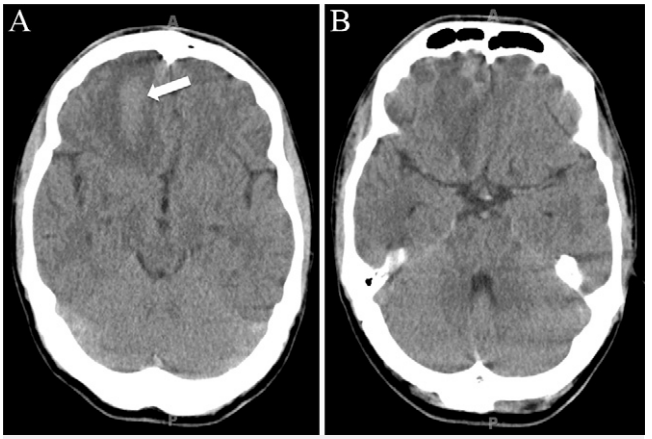

FIG. 1. Non-contrast CT scans of the brain showing a hyperdense intraaxial lesion in the right frontal medial orbital gyrus (**A,** *arrow*), and adjacent cerebral edema (**B**).

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 all 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,

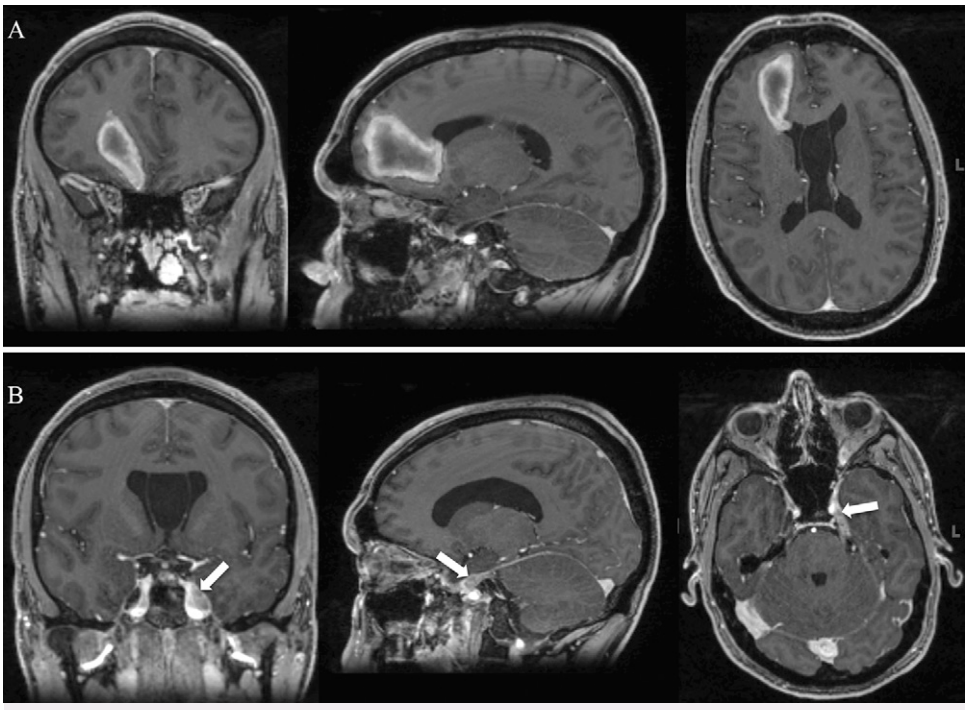

FIG. 2. T1 postcontrast MRI of the brain. **A:** Rim-enhancing right frontal lesion with an associated hemorrhagic component with mild mass effect, shown in coronal, sagittal, and axial planes. **B:** Enhancing lesion within the left Meckel's cave (*arrows*), shown in coronal, sagittal, and axial planes.

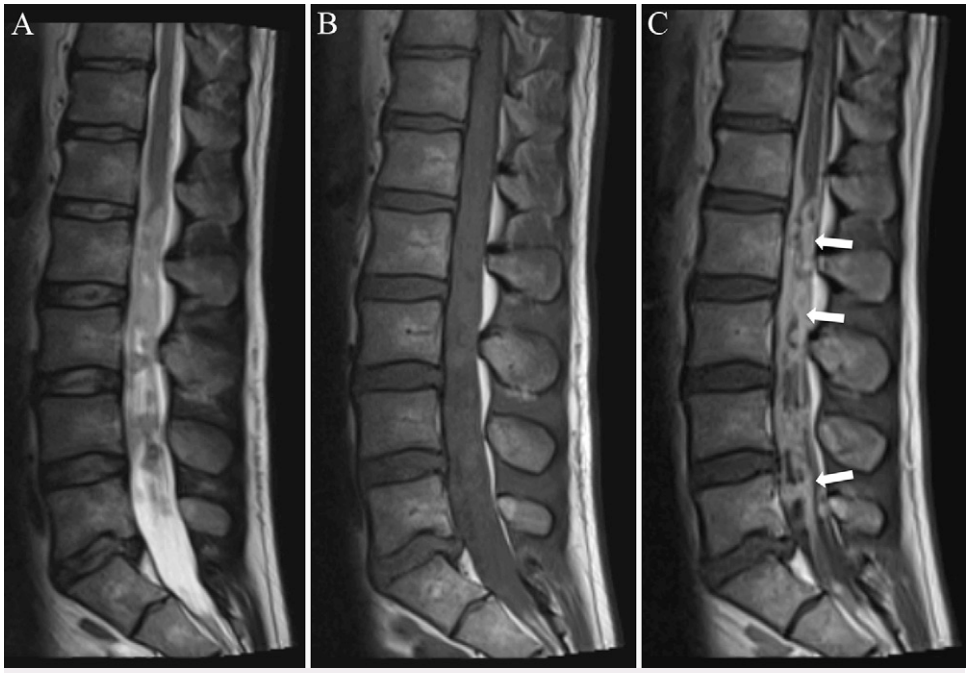

FIG. 3. Sagittal slices from MRI of the lumbar spine, with sequences of T2 (**A**), T1 without contrast (**B**), and T1 with contrast (**C**). There is a contrast-enhancing soft tissue epidural mass filling the thecal sac and compressing the adjacent conus medullaris (*arrows*) and, below that, the nerve roots of the cauda equina.

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 was then transitioned to high doses 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.[5–9] 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,[10–13] 5 patients were found to have multiple lesions on initial presentation,[10,14–17] and an additional 4 patients developed new discrete lesions later in the course of the disease.[17–20]

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

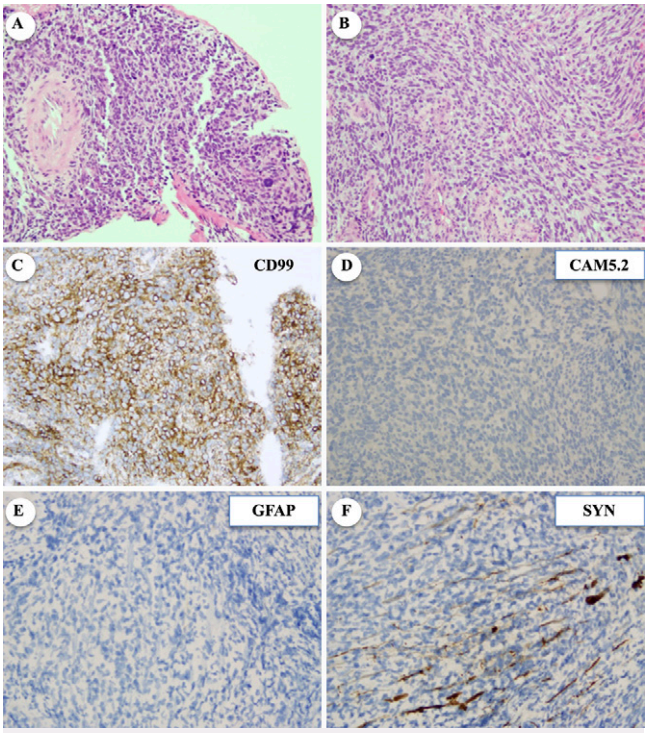

FIG. 4. Histopathological characteristics of resected lumbar intradural tumor—extraskeletal ES/PNET. Original magnifications ×400. Hematoxylin and eosin–stained images (**A** and **B**) show a small blue cell tumor, with variably round to spindle-shaped nuclei, karyorrhexis, brisk mitotic activity, and a patchy neutrophilic infiltrate. Immunohistochemical stains were performed, and the tumor cells show membranous expression of CD99 (**C**) and nonreactivity for CAM5.2 (**D**), GFAP (**E**), and synaptophysin (SYN) (**F**). SYN highlights entrapped axons within the involved nerve root.

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 cytoreduction 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 ES/PNET, 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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Conception and design: Huguenard, Li, Dahiya, Chicoine. Acquisition of data: Huguenard, Li, Dahiya, Chicoine. Analysis and interpretation of data: Huguenard, Li, Perkins, Dahiya, Chicoine. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Huguenard. Study supervision: Chicoine.

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