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Review

Primary Ewing's sarcoma affecting the central nervous system: a review and proposed prognostic considerations

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ABSTRACT

Ewing's sarcoma (ES) is a part of a larger family of round blue cell tumors, which occasionally manifest as osseous or extraosseous lesions adjacent to or within the central nervous system (CNS). While a large body of literature exists on ES of bone, data are lacking on tumors with cranial or spinal components that affect the CNS. Here, we perform a systematic review of the literature and summarize the best available evidence on diagnosis, treatment and outcomes of ES affecting the CNS with emphasis on the breadth of clinical presentations, diagnostic tools and emerging management options for these rare and challenging lesions. We include a review of known prognostic factors and propose several new considerations for prognostication of ES affecting the CNS.

1. Introduction

Ewing's sarcoma (ES) is the second most common childhood bone tumor after osteosarcoma. ES was first reported by James Ewing who differentiated the former from the latter.[1] The term "Ewing sarcoma family of tumors" is used to describe a heterogeneous group of small blue round cell neoplasms of neuroectodermal origin.[2,3] These include Ewing's sarcoma (ES), Askin tumor and peripheral primitive neuroectodermal tumor (pPNET). These tumors arise in children and young adults and comprise approximately 3% of all pediatric malignancies.

A large body of data exists on ES of bone, which most commonly presents in the long bones or in the pelvis. However, data is lacking on a significant portion of tumors, which have cranial or spinal components affecting the CNS.

A systematic review of the literature revealed that extraosseous ES arising from within the central nervous system as an intra-axial or intramedullary neoplasm is extremely rare (Table 1[4–11]). Moreover, intracranial extraosseous ES arising from the leptomeninges is also extremely uncommon (Table 2[8,12–26]). More commonly, primary ES affects the central nervous system (CNS) by involving bony structures such as the calvarium and spinal column and causing mass effect on neuronal structures.

Improved understanding of the biology of ES, as well as early detection and better multimodality therapy has significantly improved survival for children with ES affecting the CNS. Here, we discuss the unique presentation, management and challenges associated with osseous and extraosseous ES involving the CNS. Current trends as well as future and emerging therapeutic options are presented. We also summarize the best available evidence on patient outcomes and propose new prognostic considerations.

2. Incidence

ES is a rare malignant mesenchymal tumor with approximately 200 new cases diagnosed yearly in the United States.[27] Of these cases 90% occur in the first and second decade of life. Ewing's sarcoma is more common in the Caucasian population, with a slight male predominance.[28] Neoplastic lesions typically arise from bones and most commonly involve diaphyses of long bones (47%), pelvis (29%), ribs and vertebrae (12%).[29] Approximately 25% of cases may also arise from the soft tissues.[30] One quarter of all patients have detectable metastases at the time of diagnosis.[30]

Primary cranial involvement of ES is uncommon with an estimated incidence of 1%.[31] Central nervous system involvement as a result of metastatic disease is much more frequent with a reported range of 10 to 33%.[32] Despite the propensity of ES to metastasize, metastases from primary intracranial sites are rare.

Osseous ES involving the calvarium typically affects the frontal and parietal convexities.[31,33] Less commonly, lesions arise from the squamous and petrous aspects of the temporal bone,[34,35] in addition to the orbit, ethmoid sinus, and skull base.[33] Although lesions may invade surrounding structures including the dura and brain

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Table 1
Reports of primary extraosseous intra-axial and intramedullary peripheral primitive neuroectodermal tumors/Ewing's sarcoma*

Study	Age/gender	Location	CD99/t(11:22)	Treatment	Outcome
Jay et al. (1996)[4]	4/M	Cerebellum	−/+	GTR; VC–Ep; RT then ICEp	Not reported (intracranial and spine recurrence)
Weil et al. (2001)[9]	21/M	Cord at T10–11	+/+	RT; VDC–EI; SSR	Alive at 30 months
Kim et al. (2004)[10]	17/M	Conus medullaris	+/?	RT	Not reported
Mazur et al. (2005)[5]	7/F	Frontal lobe**	+/+	GTR; VDC–EI; RT	Not reported
Bunyaratevej et al. (2005)[7]	17/F	Frontal/parietal lobes	+/?	GTR; RT	Alive at 24 months
Bunyaratevej et al. (2005)[7]	17/M	Temporal lobe	+/?	GTR; RT and chemotherapy	Alive at 12 months
Pekala et al. (2006)[8]	7/F	Frontal lobe**	+/+	Not reported	Not reported
Kazmi et al. (2007)[6]	7/F	Frontal lobe	+/+	GTR; VDC–EI; PBRT	Not reported
Kumar et al. (2007)[11]	18/M	Cervical cord	+/?	RT and chemotherapy	Alive at 6 months

C = cyclophosphamide, D = doxorubicin, E = etoposide, Ep = Epirubicin, GTR = gross total resection, I = Ifosfamide, V = vincristine, PBRT = proton beam radiotherapy, RT = radiation therapy, SSR = stem cell rescue.
* Not including extraosseous dural or leptomeningeal neoplasms.
** Second lesion found elsewhere.

Table 2
Reports of primary intracranial extraosseous dural-based peripheral primitive neuroectodermal tumors/Ewing's sarcoma

Study	Age/ Gender	Location	CD99/ t(11:22)	Treatment	Outcome
Stechschulte et al. (1994)[12]	25/M	Temporal convexity	+/?	GTR; RT; IMeACtVAd-MArHy	Alive at 19 months
Papotti et al. (1998)[13]	30/F	Anterior fossa	+/+	CAV; RT	Died 10 years from diagnosis
Katayama et al. (1999)[14]	5/M	Tentorium	+/?	GTR; RT; M	Alive after 7 years
Niwa et al. (2001)[15]	5mo/M	Frontal skull base	+/?	Not reported	Died 9 days from surgery
Simmons et al. (2001)[16]	67/F	CPA	+/?	STR; Palliative RT	Death 13 months from diagnosis
Antunes et al. (2001)[17]	6/M	Anterior fossa	+/+	RT and chemotherapy	Not reported
Kalamarides et al. (2001)[18]	34/F	CPA	+/?	STR; RT	Recurrence after 6 weeks
Dedeurwaerdere et al. (2002)[19]	12/M	Anterior fossa	+/?	GTR; MCaVp; RT; CiLV	Alive at 27 months
Dedeurwaedere et al. (2002)[19]	17/M	Anterior fossa	+/+	GTR; Ci–EI; RT	Recurrence after 8 years; alive 12 months after second surgery
Utsunomiya et al. (2004)[20]	7/M	Anterior fossa	+/?	GTR; RT; Ci–EI	Alive at 24 months
D'Antonio et al. (2004)[21]	50/F	Temporal convexity	+/+	Not reported	Alive at 12 months
Mobley et al. (2006)[22]	21/M	Occipital convexity	+/+	STR; AdVDC; RT	Recurrence after 18 months
Pekala et al. (2006)[8]	8/F	Tentorium	+/+	Not reported	Not reported
Attabib et al. (2006)[23]	48/F	Cavernous sinus	+/+	STR; RT; VDC–EI	Stable disease at 14 months
Asano et al. (2007)[24]	2/M	Anterior fossa	+/+	GTR; RT; CV	Alive at 20 years
Navarro et al. (2007)[25]	3/M	Tentorium	+/+	STR; AVC–EI; RT	Alive after 12 months
Furuno et al. (2008)[26]	15/M	Anterior/middle fossa	+/?	GTR; RT; chemotherapy	Alive after 6 months

A = Adriamycin, Ad = Actinomycin D, Ar = arabinase-c, C = cyclophosphamide, Ca = carboplatin, Ci = cisplatin, CPA = cerebellopontine angle, Cy = cytoxan, D = doxorubicin, E = etoposide, Ep = Epirubicin, GTR = gross total resection, Hy = hydrocortisone, I = Ifosfamide, L = lomustine, M = methotrexate, Me = Mesna, RT = radiation therapy, STR = subtotal resection, V = vincristine, Vp = VP16.

parenchyma, the vast majority occupy the epidural space and become symptomatic by way of their mass effect. As summarized in Tables 1 and 2, extraosseous presentation of cranial ES is rare and has been reported to manifest in the anterior, middle and posterior fossas, tentorium, cavernous sinus and cerebellopontine angle.

Osseous ES of the vertebral column is also uncommon affecting 3.5% of patients. ES tend to predominate in the sacrum and hence cases are typically categorized as sacral or non-sacral.[36] Extraosseous presentation of the spinal axis is also well documented. A recent review identified 33 cases of intradural-extramedullary and 21 cases of extradural spinal pPNET/ES confirmed by immunohistochemistry and/or molecular genetics.[37]

3. Clinical presentation

Primary cranial lesions of scalp and calvarium typically present with local swelling and pain attributed to stretching of the periostium and/or innervated scalp tissue.[38] Lesions of the skull rarely breach the dura and therefore can grow to large sizes prior to detection, causing compression of the CNS. As such, patients may present with symptoms related to intracranial hypertension or mass effect. Skull base lesions, such as petroclival ES may cause cerebellar symptoms, obstructive hydrocephalus and lower cranial neuropathies. Dural-based primary ES may present with intracranial hemorrhage in up to 50% of cases.[25]

Osseous involvement of the spinal axis may present with local and/or referred pain. Occasionally, a palpable mass may be appreciated on physical exam. Up to two-thirds of patients with spinal ES present with neurological deficit.[39] Extraosseous epidural lesions may present with isolated back pain, radicular symptoms or myelopathy. Cauda equina syndrome from hemorrhagic primary intradural ES has also been reported.[40]

4. Genetics

The genetic hallmark of ES is a translocation between the EWS gene on chromosome 22 and the ETS protooncogenes, FLI1, ETV1 or ERG, on chromosome 11, 7 and 21, respectively.[2,41] The EWS-FLI1 fusion transcripts are found in about 90% of cases, while the other fusion transcripts are found less commonly. These chimeric proteins promote tumour growth by functioning as an aberrant transcription factor targeting genes involved in cell cycle regulation, metabolism, angiogenesis, intracellular signalling and transcrip-