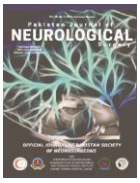

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Review Article

Spinal Extraosseous Extradural Ewing's Sarcoma: A Systematic Review

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ABSTRACT

Objective: The objective of this systematic review was to state and analyze all the case reports published on extraskeletal extradural Ewing's Sarcoma to date.

Material and Methods: We searched PubMed, MEDLINE, EMBASE, and Google Scholar using the following search term, including Boolean operators AND and OR. We only included published case reports and series about Ewing's Sarcoma that were Extra-skeletal and Extradural. We excluded the intradural EWS cases and those that did not have both components, i.e. extraskeletal and extradural. Conference articles, commentaries, and unpublished articles were also not included. A PRISMA flowchart was also formed.

Results: After the first case of EES in 1969, around 40 case reports and series have been reported, which sheds light on the rarity of this disease. Age of presentation varies from as early as two months, with the oldest report being 49 years of age, and most cases presenting in adolescents and young adults. Spinal Epidural extraskeletal Ewing's sarcoma has been more frequently reported in males. The level of occurrence of the tumor also varies among cases, with cervical, thoracic and lumbar regions being more frequently affected than sacral regions.

Conclusion: Extraskeletal extradural ES is an exceedingly rare anomaly. Multicentric collaborative work is the need of the hour for such orphan illnesses, to optimize treatment paradigms as a single-center is exceedingly unlikely to amass cases.

Keywords: Ewing's Sarcoma, Primitive Neuroectodermal Tumor, Spine, Extradural, Extraskeletal.

Abbreviations: ES: Ewing's Sarcoma. PNET: Primitive Neuroectodermal Tumor. WHO: World Health Organization. EES: Extraskeletal Ewing's Sarcoma. PAS: Periodic acid–Schiff. CT: Computerized Tomography. MRI: Resonance Imaging.

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INTRODUCTION

Primary spinal extradural Ewing's sarcoma (ES), also known as primitive neuroectodermal tumor (PNET), is a rare, heterogeneous group of malignant tumors of childhood and early adulthood. According to The World Health Organization (WHO) classification, PNET is an undifferentiated round cell tumor that arises from primitive neuroepithelial cells. Depending on the presentation site, it can be a centrally located or peripheral PNET.[1] Spinal Epidural PNET/peripheral primitive neuroectodermal tumors (pPNET) have an incidence of < 1% of primary spinal tumors.[2] Extraosseous Ewing's sarcoma commonly presents in soft tissues and bones of the lower extremity, paravertebral, and retroperitoneal regions.[3] Tefft et al. in 1969, were the first to describe the extraosseous form of Ewing's sarcoma, and called it 'extraskeletal Ewing's sarcoma (EES).[4]

MATERIALS AND METHODS

Search Strategy

We searched PubMed, MEDLINE, EMBASE, and Google Scholar using the following search term, including Boolean operators AND and OR: (("epidural space"[MeSH Terms]) OR (epidural[All Fields]) OR (extradural[All Fields])) AND ((extraskeletal[All Fields]) OR (extraosseous[All Fields])) AND (("sarcoma, ewing"[MeSH Terms]) OR (Ewing sarcoma[All Fields]) OR ("EWS"[All Fields]) OR (("askin tumor"[Supplementary Concept]) OR (askin tumor[All Fields]) OR ("neuroectodermal tumors, primitive, peripheral"[MeSH Terms]) OR (peripheral primitive neuroectodermal tumors [All Fields]).

Inclusion Criteria

We only included published case reports and series about Ewing's Sarcoma that were extra-skeletal and extradural.

Exclusion Criteria

We excluded the intradural EWS cases and those that did not have both components, i.e. extraskeletal and extradural. Conference articles, commentaries, and unpublished articles were also not included. Study selection criteria are summarized in Table 1.

Table 1: Inclusion and Exclusion Criteria.

Inclusion Criteria	Exclusion Criteria
Published Articles	Unpublished articles
Case Reports	Conference articles and commentaries
Articles related to Extraskeletal and Extradural EWS	Articles related to Intradural EWS

Data Extraction and Analysis

The current results and conclusions presented in the case reports were extracted and tabulated systematically. The PRISMA flowchart for our search strategy is shown in Figure 1.

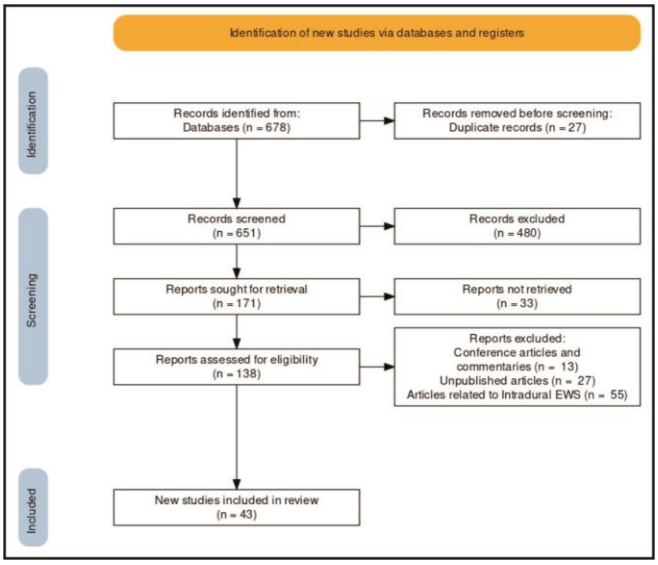

Figure 1: PRISMA Flowchart.

RESULTS

Demography

After the first case of EES in 1969, around 40 case reports and series have been reported, which sheds light on the rarity of this disease. Age of presentation varies from as early as two months, with the oldest case being 49 years of age, with most cases presenting in adolescents and young adults. Spinal Epidural extraskeletal Ewing's sarcoma has been more frequently reported in males.

Location

The level of occurrence of the tumor also varies among cases, with cervical, thoracic and lumbar regions being more frequently affected than sacral regions. Isolated segment involvement is rare, and the tumor is usually seen extending into adjacent segments.

Treatment and Management

The usual treatment regimen consists of partial or complete resection, depending on the tumor's extent, site, and size, along with radiotherapy and chemotherapy. Follow-ups were conducted in all reported cases with outcomes ranging from "no evidence of disease" and "alive with disease" to "dead of disease". Cases not receiving any adjuvant therapy died only a few months after presentation. A complete therapy decreased the chance of local recurrence and metastasis in most cases.

Diagnostic Criteria

Standard diagnostics consist of physical and neurological examinations and radiography. A whole-body bone scan with 99Tc was conducted in some cases to identify any existing metastatic lesions. After the biopsy, light, and electron microscopic examinations were conducted to confirm the diagnosis.

Periodic acid–Schiff (PAS) stain was positive in all reported cases. Immunohistochemistry and genetic testing were also utilized in some cases. Recent cases of extraskeletal Ewing's sarcoma are found to be positive for CD99 (MIC 2). However, the data for cases from before 2000 is not available. Positivity for Vimentin, Synaptophysin, S-100, and other markers varied among the cases and cannot be relied upon as diagnostic. The t(11:22) translocation is also associated with extraskeletal Ewing's sarcoma; however, this was not studied in most of the reported cases. Details of all reported cases are given in Table 2.

Table 2: Reported cases of primary spinal extradural extraskeletal Ewing's sarcoma.

Author (Year of Publication)	Age (Years)	Gender	Level	Resection	Adjuvant Treatment	CD99	t(11:22)	Outcome (Months)
Tefft et al. (1969)[4]	6	F	L4	Complete	RT + CT	N/A	N/A	DOD (48)
	8 Months	M	T11– L2	Partial	RT + CT	N/A	N/A	NED (60)
	2	M	C3	Partial	RT + CT	N/A	N/A	NED (114)
	7	F	C2	Partial	RT + CT	N/A	N/A	DOD (9)
Angervall & Enzinger (1975)[5]	17	M	S1 – S2	Complete	None	N/A	N/A	DOD (1)
	20	M	T2 – T5	Partial	RT + CT	N/A	N/A	DOD (13)
	18	F	L5	Complete	RT + CT	N/A	N/A	DOD (7)
Scheithauer & Egbert (1978) [6]	18	M	L1	Complete	RT + CT	N/A	N/A	NED (16)
	27	F	T4 – T6	Complete	RT + CT	N/A	N/A	NED (120)
Mahoney et al. (1978) [7]	23	M	L5 – S1	Partial	RT + CT	N/A	N/A	DOD (12)

Author (Year of Publication)	Age (Years)	Gender	Level	Resection	Adjuvant Treatment	CD99	t(11:22)	Outcome (Months)
Fink & Meriwether (1979) [8]	19	M	L2 – L3	Partial	RT + CT	N/A	N/A	NED (6)
Simonati et al. (1981) [9]	13	M	L3	Complete	RT + CT	N/A	N/A	NED (15)
N'Golet et al. (1982) [10]	30	M	T1 – T3	Complete	RT + CT	N/A	N/A	NED (6)
	47	F	L4	Complete	RT	N/A	N/A	DOD (4)
Demeocq et al. (1983) [11]	16	F	L3 – L4	Partial	CT	N/A	N/A	N/A
Kinsella et al. (1983) [12]	14	F	L4 – L5	Complete	RT + CT	N/A	N/A	NED (48)
Spaziante et al. (1983) [13]	10	M	L4 – S2	Partial	RT + CT	N/A	N/A	DOD (16)
Asorey et al. (1986)*	8	F	N/A	Complete	RT + CT	N/A	N/A	NED (60)
	10	F	N/A	Complete	RT + CT	N/A	N/A	NED (26)
Machin et al. (1986) [14]	4	M	L1	Complete	None	N/A	N/A	DOD (5)
Sharma et al. (1986) [15]	18	M	T11	Partial	RT + CT	N/A	N/A	DOD (42)
Ruelle & Boccardo (1987) [16]	17	M	L3	Partial	RT + CT	N/A	N/A	DOD (8)
Benmeir et al. (1991) [17]	17	F	T8–T10	Complete	RT + CT	N/A	N/A	NED (6)
Kaspers et al. (1981) [18]	7	M	L1 – L2	Partial	CT	N/A	N/A	NED (40)
Allam& Sze (1994) [19]	15	F	T12– L3	N/A	N/A	N/A	N/A	N/A
Christie et al. (1997) [20]	36	F	L2 – L3	Partial	RT + CT	N/A	N/A	DOD (96)
Benesch et al. (1999) [21]	2 months	M	L3 – S1	Partial	RT + CT	N/A	-	DOD
Kennedy et al.(2000) [22]	24	M	C1 – C5	Partial	RT + CT	N/A	N/A	NED (13)
Morandi et al. (2001) [23]	22	M	T4 – T5	Complete	RT + CT	N/A	N/A	NED (66)
	14	M	C3 – C7	Partial	RT + CT	N/A	N/A	DOD (42)
	16	F	C5 – C7	Partial	RT + CT	N/A	N/A	DOD (54)
	25	M	L1 – S2	Partial	CT	N/A	N/A	DOD (7)
Mukhopadhyay et al. (2001)[24]	29	F	C3 – C5	Partial	RT + CT	N/A	N/A	NED (30)
	18	M	T8	Partial	RT + CT	+	N/A	AWD (18)
	22	M	L5 – S1	Partial	RT + CT	+	N/A	NED (15)
	31	M	L3 – L4	Partial	RT + CT	+	N/A	NED (32)
	13	M	C3 – C5	Partial	RT +CT	+	N/A	NED (11)
Shin et al. (2001) [25]	38	M	C5 – C7	Partial	CT	+	N/A	AWD (5)
	22	F	C7 – T1	Partial	CT	+	N/A	NED (48)
Kadri et al. (2002) [26]	15	F	L2 – L3	Partial	RT + CT	+	N/A	NED (7)
Gandhi et al. (2003) [27]	33	M	T5 – T9	Complete	RT + CT	N/A	N/A	NED (3)
Harimaya et al. (2003) [28]	12	F	T1 – T3	Partial	RT + CT + PBSCT	N/A	N/A	DOD (32)
Kogawa et al. (2004) [29]	7	F	C2 – C4	Complete	RT + CT + PBSCT	+	N/A	NED (60)

Author (Year of Publication)	Age (Years)	Gender	Level	Resection	Adjuvant Treatment	CD99	t(11:22)	Outcome (Months)
Siami-Namini et al. (2005) [30]	15	F	T3 – T7	Partial	N/A	+	+	N/A
Athanassiadou et al.(2006) [31]	13	M	T9	Partial	RT + CT	+	+	AWD (9)
Isefuku et al. (2006) [32]	20	M	L5 – S1	Complete	CT	+	+	DOD (15)
Bozkurt et al. (2007) [33]	28	M	C3 – C5	Complete	RT + QT	N/A	N/A	NED (18)
Erkutlu et al. (2007) [34]	7	M	C5 – T1	Complete	RT + QT	+	N/A	NED (108)
Lakhdar et al. (2007) [35]	24	F	C6 – T1	Complete	RT + CT	N/A	N/A	NED (12)
Ozturk et al. (2007) [36]	18	M	C6 – T1	Complete	CT	+	N/A	NED (13)
Hsieh et al. (2008) [37]	12	M	T7 – T9	Complete	RT + CT	+	N/A	NED (20)
Dogan et al. (2009) [38]	13	M	T11– L1	Complete	RT + CT	+	N/A	NED (10)
Avcu et al. (2010) [39]	30	M	L5	Complete	RT+ CT	N/A	N/A	N/A
Yasuda et al. (2011) [40]	37	F	T8 – T9	Partial	RT + CT	+	N/A	DOD (22)
Saeedinia et al.(2012) [41]	44	F	S1 – S3	Complete	RT	+	N/A	NED (18)
Garcia Moreno et al.(2014)[2]	45	F	C6 – T3	Partial	RT + CT	+	+	NED (7)
Eloqayli (2017) [42]	49	M	C6 – T2	Partial	RT + CT	+	N/A	NED (12)
Kutty et al. (2017) [43]	12	F	C2 – C4	Complete	RT + CT	+	N/A	NED (16)
Bedoya et al. (2019) [44]	9	F	T2	Complete	RT + CT	+	N/A	DOD (36)

KEY: M: Male; F: Female; C: Cervical; T: Thoracic; L: Lumbar; S: Sacral; RT: Radiotherapy; CT: Chemotherapy; PBSCT: Peripheral Blood Stem Cell Transplantation; DOD: Dead of Disease; NED: No Evidence of Disease; AWD: Alive with Disease; N/A: Not Available; +: Positive Result; -: Negative Result. *: The Complete Original Article Could Not be Found on the Internet; Hence the Data of This Study Was Taken from García-Moreno et al.[2]

DISCUSSION

James Ewing was the first one to describe Ewing's sarcoma (ES) in 1921.[3] He referred to it as diffuse endothelioma, which was later coined to ES by Oberling in 1928. In 1973, Hart and Earle introduced the term primary PNET, meaning a tumor arising from central neuraxis, having a single progenitor cell and containing more than 90 – 95% undifferentiated cells. Ewing's sarcomas that arise from soft tissues are named Extraskeletal Ewing Sarcoma (EES). The first case of EES was reported by Tefft et al. in 1969.[4]

Demography

The peak incidence of EES patients is seen around 20 years of age, with an approximate range from 10 to 30 years. According to Yasuda et al, male predominance is seen in spinal extradural EES, with the male-female ratio turning out to be 1.5:1. He also reviewed 30 EES cases and found out that the mean age of this disease's presentation is 18.8 years, with 73% of all the reported cases being between 10 to 20 years old.[40] This disease is so rare that the frequency in the western part of the world is reported to be 1 – 3 per million.[45]

Location

The most common sites of this tumor are the buttocks, upper and lower extremities, thoracic wall, and retroperitoneal space. However, some cases report these tumors in the larynx, small intestine, kidney, skin, vagina, and paravertebral area.

Clinical Presentation

The most common presenting complaint of the patient is chronic back pain, which occurs due to compression of spinal cord and nerve roots, followed by upper and lower limb muscle weakness.[41] Autonomic dysfunction of the urinary bladder is also a common late presentation. If the mass becomes metastatic, the most commonly involved organ is the lung. In contrast to the spinal EES, the intracranial location of these tumors causes headaches and visual disturbances in the patients. Severe complications may involve intracranial hemorrhages.

Radiological Findings

Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI) is usually employed for diagnosis. It is usually seen as a well-circumscribed, extramedullary, intradural, or extradural mass that may extend through intervertebral foramina and extend into the paraspinal soft tissue.[46] Dumb-bell-shaped tumors with foraminal widening,[47] and scalloping of bones[25] are some additional findings that can be seen. These tumors can also metastasize. CT scan of the thorax is more useful in showing soft tissue mass with or without pleural and rib damage.[48] On a non-enhanced CT scan, a well-defined hypodense mass is seen displacing the thecal sac and contrast-enhancement shows a heterogeneous tumor. EES may present as a biconvex lesion on radiology, resembling an extradural hematoma. Therefore, if a trauma patient arrives at the hospital with minor and multiple lesions, extradural EES should be one of the differential diagnoses. T-1 weighted imaging may show variable isointense and hypointense signals, while T-2 weighted may show isointense and hypertense on unenhanced MRI. Post-contrast MRI usually reveals a heterogeneous color enhancement within the mass suspected of Ewing's Sarcoma.[49]

Histopathological Findings

On light microscopy, poorly differentiated, small round cells are seen, which have mitotic figures, a high nucleus to cytoplasm ratio, and scanty cytoplasm. The typical arrangement may be in the form of nests, sheets, lobules, or occasionally rosettes. EES are hence classed as small round cell tumors and can be misdiagnosed as lymphoma or a small cell carcinoma of the lung. However, most of the lymphomas are LCA positive too. On Electron microscopy, scanty cytoplasmic organelles are seen, accompanied by growth cones suggestive of glial cell differentiation.[48]

Immunohistochemistry

Immunohistochemical analysis is needed for further classification and definitive diagnosis of EES. About 95% of the EES cases show CD99 (MIC2) positivity. Although a very suggestive marker, it is not specific.[50] In addition; synovial sarcomas also show CD99 positivity in some cases. Therefore, during lab analysis, in addition to CD-99, other tumor markers that are usually ordered include CD-34, CD-20, CD-10, Tdt, and others, to rule out other potential causes of tumors.

FISH Analysis

The t(11;22) (q24;q12) translocation is a chromosomal aberration seen in 90% of cases of ES and is used for confirmation.[51] It results in the formation of the EWS-FLI1 fusion gene.[52] ERG, ETV1, EIAF, and FEV variant translocations are also observed in a few cases. The fusion protein EWS-FLI1 possesses oncogenic properties. Lab studies performed on immunocompromised mice show that its expression can hasten tumorigenesis of murine NIH 3T3 cells.[53] Repression of this fusion gene using antisense constructs has shown to

decrease cell growth in-vitro as well as tumor growth in-vivo in human cell lines.[54] However, the function of the EWS-FLI-1 fusion protein is highly dependent on the cell in context. Identifying the genes involved in the initiating phase of Ewing's Sarcoma development may evade approaches using established heterologous cell lines and cells derived from late-stage Ewing's Sarcomas. To have a clear understanding of the pathogenesis of this disease, the mechanism of initiation of the fusion protein and involvement of the type of target cell should be determined.[55]

Treatment and Management

Surgery is the mainstay of treatment if long-term survival is intended. Depending on the adherence and accessibility of the tumor, biopsy, near-complete resection, or complete resection can be performed.[56] Laminectomy is generally advocated. Radiotherapy and chemotherapy are the proposed adjuvant therapies. Frequently used chemotherapeutic drugs include Vincristine, Cyclophosphamide, Cisplatin, and Ifosfamide. The 5-year survival rate of EES even after the adjuvant therapy ranges from 38%[57] to 67%.[58]

Prognosis

Primary intraspinal EES/pPNET is an aggressive malignant tumor that leads to mortality within two years of diagnosis in almost half of the patients. Age is an important determinant of the prognosis of the tumor. At both extremes, that means the mortality rate increases as the age group gets younger and as the age group gets older. However, no specific pattern can be seen when it comes to the gender of the patient. Surgical resection, whether subtotal or total, combined with adjuvant therapies including chemotherapy and radiotherapy significantly improves the outcome of the patients.

CONCLUSION

Extraskeletal Ewing's Sarcoma is an exceedingly rare anmaly. Gross total resection and adjuvant therapy are very important for the long-term survival of such patients. Proper education and techniques should be utilized to ensure early detection and treatment. Metacentric collaborative work is the need of the hour for such orphan illnesses, to optimize treatment paradigms as a single-center is exceedingly unlikely to amass cases.

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AUTHORS CONTRIBUTIONS

Sr.#	Author's Full Name	Intellectual Contribution to Paper in Terms of:
1.	Kashif Ali Sultan	Study design and methodology.
2.	Biah Mustafa	Analysis of data, paper writing, referencing.
3.	Mohammad Ashraf	Data collection and calculations.
4.	Minaam Farooq	Analysis of data and paper writing.
5.	Naveed Ashraf	Analysis of data and interpretation of results.
6.	Mukarram Farooq	Literature review.
7.	Musa Ali Rizvi	Literature review.
8.	Waaiz Ali Wajid	Literature review.