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A Clinicopathological Study of Ewing's Sarcoma/PNET experience from a Tertiary Cancer Centre in North East India

Jagannath Dev Sharma[1], Argha Baruah[1], Anupam Sarma[1], Lopa Mudra Kakoti[1], Nizara Baishya[1,2], Shiraj Ahmed[1]

Abstract

Introduction: Ewing sarcoma (ES)/PNET is an aggressive malignant tumor with small round cell morphology affecting mainly children and adolescents. The aim of this study was to study the clinicopathological parameters and immunohistochemical panel of skeletal and extraskeletal ES and to correlate with overall survival.

Case Report: Medical files of 70 patients with ES treated at our center between 2009 and 2015 were retrospectively evaluated. The clinico pathological parameters were extracted and statistically correlated with overall survival(OS). Among 70cases of ES ,41 cases were males and 29 cases were females. Most common age group was 10–20 years. Skeletal involvement was seen in 45 cases(64.2%) and 25cases (35.8%) were extraskeletal. The most common skeletal sites of involvement was lower extremity involving the Femur (24%) and the most common extraskeletal site involved in our study was sinonasal area(5.7%), followed by chestwall, thigh, orbital, calf, gluteal, kidney, and vulva. Two cases showed involvement of the central nervous system(CNS) involving pineal gland and the ventricle. Two cases showed multiple sites of involvement both including chest wall and thigh. Twenty-nine cases(41.4%) showed metastasized disease. The most common site of metastasis was lung followed by bone and brain. Recurrence was seen in 14 cases(20%). Overall 5-year survival was 24%. There was statistically significant correlation found between tumor size (≥8cm) and 5year survival. Furthermore, significant correlation was found between metastasis and 5-year survival.

Conclusion: ES is an aggressive tumor involving skeletal and extraskeletal sites affecting commonly young people, with a poor prognosis for patients with maximum diameter ≥8cm. Metastasisis common in ES and is also a poor prognostic factor.

Keywords: Ewing'sarcoma, skeletal, extraskeletal, survival, metastasis.

Introduction

Ewing's sarcoma(ES) is a highly malignant small round-cell tumor of neuroectodermal origin arising primarily from bone, but occasionally occurs in soft tissue. It is more common in children and adolescents. It is the second most common bone tumor among children and adolescent and is the third most common primary malignant bone tumor in all age groups[1].

It was first described by James Ewing in 1921 as an diffuse endothelioma of bone[2]. ES in soft tissue was reported by Angervall and Enzinger in 1975 [3]. Askin etal. Reported identical tumors in the thoracopulmonary region in 1979 hence the name Askin tumor[4].

ES usually arises from the diaphysis or metadiaphyseal region of long bones, pelvicbones, ribs, skullbones, the vertebra, the scapula, and the small bones of hands and feet. The most common sites of extraskeletal ES are chest wall, paravertebral region, retroperitoneum, gluteal region, and lower extremities. However, few cases have been reported in the kidney, breast, adrenal glands, gastrointestinal tract, prostate, endometrium, brain, and lungs[5].

Material and Methods

It is a retrospective study which includes 70 patients, age range from 1 to 60 years, treated for ES in Dr.B Borooah Cancer Institute from 2009 to 2015. The clinical details such as age, sex, site of involvement, radiological findings, serum lactate dehydrogenase(LDH) value, alkaline phosphatase, soft-tissue extension, metastasis, and recurrence were retrieved. Histopathological slides were reviewed and immunohistochemical(IHC) marker panel of small round cell tumor which included CD99, FLI1, cytokeratin(CK), synaptophysin, chromogranin, desmin, myogenin, and leukocyte common antigen which were also reviewed. Vimentin was also done for all the patients. Overall survival was measured from the date of first diagnosis until the date of death or last follow-up.

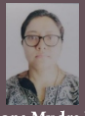
[1]Department of Pathology, Dr.B.Borooah Cancer Institute, Guwahati, Assam, India.
[2]Department of Hospital based Cancer registry, Dr.B. Borooah Cancer Institute, Guwahati, Assam.

Address of Correspondence
Dr. Argha Baruah,
Department of Pathology, Dr.B.Borooah Cancer Institute,Guwahati-781028, Assam, India.
E-mail:argha20@gmail.com


Dr. Jagannath Dev Sharma


Dr. Argha Baruah


Dr. Anupam Sarma


Dr. Lopa Mudra Kakoti1


Dr. Nizara BaishyaShiraj Ahmed


Dr. Shiraj Ahmed

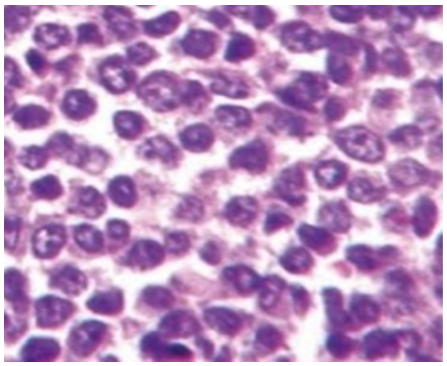


Figure 1: Small round cells with finely dispersed chromatin, and small to prominent nucleoli and scant eosinophilic cytoplasm (H and Estain,×40).

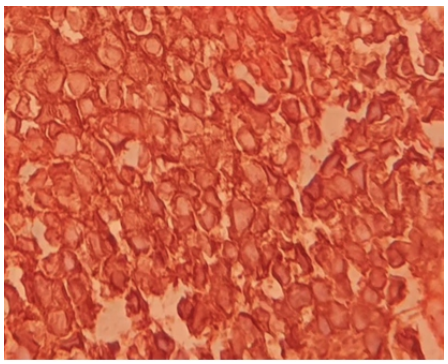


Figure 2: Tumor cells showing CD99 membranous positivity(×40).

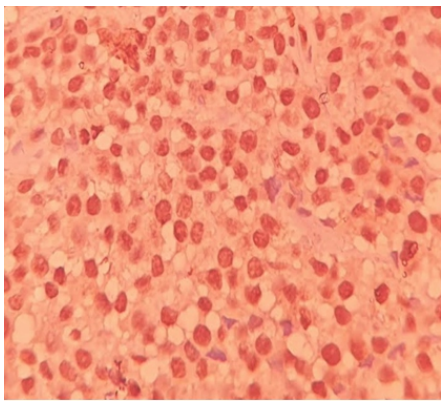


Figure 3: Tumor cells showing FLI1 nuclear positivity(×40).

SPSS 19 version was used for statistical analysis. Kaplan Meir method was used for survival statistics. Comparison between groups was done by log rank test P<0.05 was considered statistically significant at 95% confidence interval.

Results

Clinical data

Seventy cases of Ewing's Sarcoma (ES) were reported in our institute from 2009 to 2015. Forty-one cases were males and 29 cases were females (M:Fratio=1.4:1). The age ranged between 1 and 60 years. Most common age group was 10–20 years. Skeletal involvement was seen in 45cases(64.2%) and 25cases(35.8%) were extraskeletal. The most common skeletal sites of involvement were lower extremity involving the femur(24%), followed by tibia(8.5%), ilium(5.7%),fibula(4.2%),and humerus(4.2%). Other involved skeletal sites were maxilla, mandible, scapula, ribs, clavicle, and sacrococcyx. The most common extraskeletal site involved in our study was sinonasal area(5.7%), followed by chest wall, thigh, orbital, calf, gluteal, kidney and vulva. Two cases showed involvement of CNS involving pineal gland and the ventricle. Two cases showed multiple sites of involvement including chest wall and thigh. Thirty-two cases had size≥8cm.Recurrence was seen in 14cases (20%).Twenty-nine cases(41.4%)showed metastasis. The most common site of metastasis was lung(16cases), followed by bone and brain. Among five cases of sinonasal ES three cases had CNS involvement and two cases had bone metastasis. Among three cases of Askin tumor one case had lung metastasis. One case of orbital ES of a 3-year-old male child had infiltration into bone marrow by acute myeloid leukemia (AML) with monocytic differentiation. Other two cases of orbital ES had CNS metastasis. Vulval ES case had bone metastasis to vertebra and rib. ES involving kidney had metastasis to lung.

Histological and IHC findings

H and E slides showed at lower power a "light" cell and "dark" cell appearance with sheets of small round cells with finely dispersed chromatin, and small to prominent nucleoli and scant eosinophilic or vacuolated cytoplasm (Fig.1). In few cases, tumor cells showed a "peritheliomatous" or a perivascular distribution along with foci of necrosis. ES cells showed membranous expression of CD99/MIC2. Antibody against FLI1 was centered in the nucleus of the tumor cells. Sixty-nine cases showed positivity for both CD99 and FLI1(Fig.2and3,respectively). CD99 was negative in one case. Two cases expressed synaptophysin and chromogranin. Vimentin was positive in seven cases. CK was positive in two cases showing epithelial differentiation.

Table1: Comparison of gender, recurrence, metastasis, site and size with 1year,3-year and 5-year survival Added

OVERALL SURVIVAL		FIVE YEAR SURVIVAL IN			SIGNIFICANCE
		1 YEAR	3 YEAR	5 YEAR	
		75.6	40.8	24	
GENDER	MALE	68.3	38.2	27.2	
	FEMALE	86.2	44	25.2	0.51
RECURRENCE	NON RECURRENCE	73.1	55.9	38.5	
	RECURRENCE	85.7	35.7	0	0.223
METASTASIS	NON METASTASIS	95.1	66.2	36.4	
	METASTASIS	47.6	5.3	5.3	P<0.0001
SITE	SKELETAL	79.9	46.8	29.8	
	EXTRASKELETAL	68	30.2	16.1	0.116
SIZE	<8CM	100	90.6	80.5	
	≥8CM	59.1	19.9	0	P<0.0001

Survival

Overall 5-year survival was 24%. There was no statistically significant difference in 5-year survival between males and females (27.2%vs.25.2%). Statistical significant correlation was found between tumor size (≥8cm) and 5-year survival (P<0.0001). Extraskeletal sites of ES had a poor 5-year survival (16.1%) in comparison to skeletal ES (29.8%), but this difference was not statistically significant. Patients with recurrence (14patients) had poor 5-year survival. None of them was alive at the end of 5years. Significant correlation was found between metastasis and 5-year survival (P<0.0001). The comparison between gender, recurrence, metastasis, site, and size with 1year, 3years and 5-year survival is given in Table1.

Extraskeletal ES (EES) had a poor overall survival (16.1%). Five cases of sinonasal ES had and average overall survival of 10 months. Three cases of Askin tumor had an average overall survival of 20 months. Case of orbital ES with bone marrow involvement with AML, the patient expired after 3months of initiating treatment. Other two cases of orbital ES had an average overall survival of 18months. Two cases of CNS ES had an average overall survival of 36 months. Patient with vulval ES had an overall survival of 15 months. One case of ES involving kidney had an overall survival of 9months.

Discussion

This series comprised ES patients diagnosed and treated in a tertiary cancer center in

North East India. Male preponderance was seen. Akhavan et al. in their study evaluated 32 patients with ES and reported 65.2% were male[6].

The age of presentation in our study ranged from 1year to 60years with a mean age of 14years. Biswas et al. reported that the median age was 15years which is not much different from ours[7].Patients with EES usually have a higher mean age[8]. However, the mean age of EES in our study was 16 years. The most common skeletal site of involvement was lower extremity involving the femur(24%), followed by tibia(8.5%), ilium(5.7%), and fibula(4.2%). Other sites of involvement were maxilla, mandible, scapula, ribs, humerus, clavicle, sacrococcyx. In a similar study by Worch etal.most common affected sites are femur (21%ofcases), followed by ilium (12–13%), tibia (8–11%), humerus(10%), fibula (7–9%), ribs(8%), and sacrum(6%)[9]. The most common extraskeletal site involved in our study was sinonasalarea(5.7%), followed by chest wall, thigh, orbital, calf, gluteal, kidney and vulva. Two cases showed involvement of CNS involving pineal gland and the ventricle. According to the literature, EES commonly involves the soft tissues of the trunk and extremities. EES can also involve chest wall, paravertebral region, retroperitoneum, gluteal region, kidney, breast, adrenal glands, gastrointestinal tract, prostate, endometrium, brain and lungs[8].

Initial work up includes plain radiograph and magnetic resonance imaging helps indetermining the extent of disease. Metastatic evaluation includes chest computed tomography scan, bone scan, and bilateral bone marrow aspirate and biopsy. A core biopsy and histopathological examination along with the aid of IHC stains is the best mode of obtaining a diagnosis, but now translocation analyses using reverse transcription-polymerase chain reaction, fluorescence in situ hybridization and chromosomal karyotyping are also being used. Serum LDH is known to reflect tumor burden and its prognostic significance has been demonstrated in few studies. In our study, mean serum LDH was 483units/L and alkaline phosphatase was179IU/L and both could not be correlated as prognostic factor.

Immunohistochemistry is the most important diagnostic tool for ES. CD99(MIC2) is a cell surface glycoprotein. It is expressed in most cases of ES. CD99 contributes to cell proliferation, migration, and metastasis. In our study, one case of ES of femur showed CD99 negativity. CD99 may be negative in ES. Histomorphology was reviewed and final diagnosis of ES was given. In a study, ES cases were evaluated and IHC was performed in all cases using the CD99 antibody and a positivity of 92.3% was found [10]. CD99 is also positive in other tumors such as lymphoblastic lymphoma, synovial sarcoma, small cell osteosarcoma, mesenchymal chondrosarcoma, desmoplastic small round cell tumors, and atypical fibroxanthoma[11] and hence all these possibilities should be kept in mind while dealing with different clinical and pathological settings.

FLI1 also called Friend leukemia integration-1 is expressed in endothelial cells and hematopoietic cells, including T lymphocytes. It is also positive in vascular tumors, desmoplastic small round cell tumor, lymphoblastic lymphoma, melanoma, and Merkel cell carcinoma. Combination of CD99 and FLI1 immunostaining appears to improve the specificity of these markers for diagnosis of EWS/FLI1 fusion-positive ES[12].

Partial neural differentiation is also seen commonly in ES. In our study, two cases expressed synaptophysin and chromogranin. Epithelial differentiation has also been described in ES. CK,epithelial membrane antigen, and carcinoembryonic antigen are the most widely used antibodies for detecting epithelial differentiation in ES. Two cases were positive for CK in our study. In a study of 43 cases of ES CK was expressed in 17cases (39.5%) infocal, intermediate, or diffuse patterns [13]. Vimentin was positive in seven cases in our study. In a study by Lucasetal .in 17 cases of ES, 88% were vimentin positive[14]. Vimentin in ES highlights the greater amount of filamentous cytoplasmin the cells. Atypical ES has cytologic features dissimilar to the uniformly round classical form. Atypical ES, having unusual alterations at morphological and IHC levels is associated with atypical clinical presentation mimicking sarcomas, carcinomas, and lymphomas.

ES has a wide clinico pathological spectrum and in cases with equivocal IHC results and in tumors occurring at older age group and unusual locations it should be ideally confirmed with molecular testing. ES in 90% of cases is associated with translocationt(11;22)(q24;q12)[15]. There is a balanced chromosomal translocations of a member of the FET gene family which is fused with an ETS transcription factor, the most common fusion being EWSR1–FLI1(ES break point region1 protein and Friend leukemia integration 1 transcription factor). Additional mutations involve STAG2, TP53,and CDKN2A deletions[16].

ES has high recurrence rate and has high propensity of systemic metastasis. Common metastatic sites include lungs, bone and bone marrow. It has a survival of 70–80% for patients with localized disease and~30% for those with metastasis[17]. Advent of multimodality treatment, which includes local control by surgery and radiotherapy and systemic control by chemotherapy, has improved the overall survival. Obata etal. Reported that the 5-year disease-free survival rates in non-metastatic patients with ES were 46.6%[18]. Oksüz et al. Retrospectively evaluated 65patients with non-metastatic ES and reported that the 5- year EFS was 44% [19]. In our study, 5-year survival of ES in non-metastatic patients was 36.4%. In a study by El Weshi et al., in EES 5-year overall survival rates was 47%, respectively [20]. In our study, overall survival of patients with ES was 24%.In a study by Pradhan et al., there was no difference found in the overall survival of patients with skeletal(64%) and extraskeletal ES(61%), and this was also the case when both groups were split by whether they had metastases or not [21].In our study, significant correlation was found between metastasis and overall survival. EES had a poor 5-year survival(16.1%)in comparison to skeletal ES(29.8%)but it was not found to be statistically significant.

In our study, metastasis and maximum diameter of ≥8cm were found to be poor prognostic factors. According to other studies, metastatic status at diagnosis is the strongest bad prognostic factor. Other poor prognostic factors include age at diagnosis>14years, number of bone lesions, primary tumor volume >200mL or maximal diameter ≥8cm, pulmonary metastases, and bone marrow involvement[22].

Conclusion

Our findings suggest that ES is an aggressive tumor involving skeletal and extraskeletal

sites affecting commonly young people, with a poor prognosis for patients with maximum diameter>8cm. Metastasis is common in ES and is also a poor prognostic factor.

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