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CLINICOPATHOLOGICAL FACTORS AND THEIR PROGNOSTIC IMPORTANCE IN EWING SARCOMA: AN INSTITUTIONAL STUDY

Histopathology

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ABSTRACT

Background: Ewing sarcoma family of tumors are aggressive tumors with small round cell morphology constituting 6% to 8% of primary bone tumors occuring in children and young adults. **Aims:** Study aims to identify the differences in the clinicopathological features and their prognostic importance in patients with skeletal and extraskeletal Ewing sarcoma **Methodology:** A retrospective hospital based study was carried out in the department of pathology from January 2015 to June 2023 after getting approval from institutional committee. Clinic pathological data of Ewing sarcoma cases were collected from hospital records and analyzed. **Results:** our study included 37 cases of Ewings sarcoma. Out of which maximum were skeletal and showed male predominance. Skeletal Ewings were seen more in flat bones and extraskeletal in thigh. Maximum number of tumors were seen in the age group below 20years and were of size more than 5cms. Metastasis was seen in maximum number of extraskeletal ewings, with tumor size larger than 5cms and in patients with age group less than 20 years. **Conclusion:** Extra skeletal Ewing sarcoma, male sex, age less than 20 years, size more than 5cms were associated with worse prognosis.

KEYWORDS

Ewing sarcoma, skeletal, extra skeletal, prognostic factors

INTRODUCTION

Ewing sarcoma is a rare malignant mesenchymal tumor occurring in children and young adults. It is the second most common malignant bone tumor and soft tissue sarcoma. Microscopically tumor is composed of small blue round cells which have glycogen deposition in cytoplasm. On immunohistochemistry (IHC) they express CD99 on cell membrane and nuclear positivity for FLI-1. [1] 85% of these tumors have EWSR1-ETS translocation. [2] James Ewing in 1921 first described Ewing sarcoma as diffuse endothelioma of bone. [3] Currently, Ewing sarcoma is proposed to arise from a progenitor cell derived from mesenchymal or neural crest. Most common sites of involvement are long bones, pelvis and ribs. Extra skeletal involvement is more common in lower extremities and paravertebral region. [4] Patients with metastasis have an unfavorable prognosis. Patients with only lung metastasis have better prognosis when compared to the patients with bone or bone marrow metastasis. [5]

MATERIALS AND METHODS

A retrospective hospital-based study was carried out in the department of pathology from January 2015 to June 2023. Study was conducted after institutional ethical committee approval. Clinico pathological data of Ewing sarcoma cases like age, sex, site, size and presence of metastasis, recurrence were noted with emphasis on skeletal and extra skeletal Ewing's sarcoma from the medical records.

Resected specimens and core biopsies were included in the study. Specimens were fixed in 10% neutral buffered formalin. They were processed and sections were stained by Hematoxylin and Eosin. Morphology was studied and immunohistochemistry was performed with CD99 (Cluster of differentiation 99) and FLI-1 (Friend Leukemia Integration 1) for confirmation of diagnosis. Nuclear staining with FLI-1 and diffuse membrane staining with CD99 is considered positive.

Inclusion Criteria

Cases which were morphologically diagnosed, confirmed by immunohistochemistry and with complete clinical details were included in study.

Exclusion Criteria

Cases which without immunohistochemistry and whose complete clinical details were not available were excluded from study

Statistical Analysis

Collected data was entered in Microsoft excel 2019. Chisquare test was performed between proportions. SPSS 26th version was used for statistical analysis. P value less than 0.05 is considered as statistically significant

RESULTS

The present study included 37 cases of Ewing sarcoma, details of which were taken from hospital records from January 2015 to June 2023. Out of 37 cases, 22 cases (59.5%) were skeletal and 15 cases (40.5%) were extraskeletal. Among 37 cases, 21 (56.8%) cases were seen in males and 16 (43.2%) cases were in females. Both skeletal and extraskeletal Ewing sarcoma showed male predominance. (Table 1)

Table 1: Clinicopathological Features Of Skeletal And Extraskeletal Ewings Sarcoma

	Skeletal (n=22)	Extraskeletal (n=15)
Sex		
Male (n=21)	13 (59%)	8 (53.3%)
Female (n=16)	9 (40.9%)	7 (46.67%)
P value – 0.12		
Site		
Upper limb (n=4)	2 (9.1%)	2 (13.3%)
Lower limb (n=11)	4 (18.2%)	7 (46.7%)
Central (trunk, Head and neck) (n=32)	16 (72.7%)	6 (40%)
P value – 0.12		
Age in years		
10 – 20 (n=18)	10 (45.5%)	8 (53.%)
21 – 30 (n=13)	7 (31.8%)	6 (40%)
31 – 40 (n=2)	1 (4.5%)	1 (6.7%)
41 – 50 (n=2)	2 (9.1%)	-
50 (n=2)	2 (9.1%)	-
P value – 0.54		
Size		
≤ 5 cms (n=10)	8(36.4%)	2(13.3%)
>5 cms (n=27)	14(63.6%)	13(86.7%)
P value – 0.121		

Metastatic site		
Lungs (n=6)	4 (66.7%)	2 (33.3%)
Bone +/-lungs (n=5)	1 (20%)	4 (80%)
Other sites (n=6)	3 (50%)	3 (50%)
P -value – 0.298		

When the distribution of Ewing sarcoma was studied, maximum number of skeletal Ewing sarcoma were seen in flat bones (including cranial bones, mandible, vertebra, maxilla, scapula, ribs and pelvis) (72.7%) followed by lower limb and upper limb (Table 2). Most common site in extraskeletal Ewing sarcoma was thigh (46.7%). Other sites were chest wall, forearm, mediastinum, pelvis and spinal cord (Table 3)

Table 2: Distribution Of Skeletal Ewing Sarcoma

Site	No. of cases
Bones of upper limb	2 (9.1%)
Bones of lower limb	4 (18.2%)
Flat bones including cranial bones, mandible, maxilla, vertebra, scapula,ribs and pelvis	16 (72.7%)
Total	22 (100%)

Table 3: Distribution Of Extra Skeletal Ewing Sarcoma

Site	Number of cases
Chest wall	2 (13.3%)
Fore arm	2 (13.3%)
Thigh	7 (46.7%)
Mediastinum	1 (6.7%)
Pelvis	2 (13.3%)
Spinal cord	1 (6.7%)
Total	15 100%)

Skeletal Ewing sarcoma involved more commonly trunk (72.7%) followed by lower limb and upper limb, whereas extra skeletal Ewing more commonly involved lower limb (46.7%) followed by trunk and upper limb. (Table 1)

Both skeletal and extra skeletal Ewing sarcoma were common in age below 20 years (48.6%). In the elderly age group above 40 years only skeletal Ewing sarcoma was noted (Table 1). Mean age of presentation is 26 in skeletal Ewing and 21 in extra skeletal Ewing sarcoma.

Maximum number of skeletal and extra skeletal Ewing sarcoma were larger than 5cms (Table 1).

Tumors with metastasis and recurrence were seen more in males than females (Table 4)

Table 4: Stage Of Tumor With Clinicopathological Features

	Metastasis (n=17)	Recurrence (n=7)	Localized (n=17)
Sex			
Male (n=21)	12 (70.6%)	5 (71.4%)	7 (38.9%)
Female (n=16)	5 (29.4%)	2 (28.6%)	10(61.1%)
P value	0.117	0.384	0.07
Age in years			
10 – 20	9 (52.9%)	2 (28.6%)	8 (47.1%)
21 – 30	6 (35.3%)	3 (42.8%)	6 (35.3%)
31 – 40	2 (11.8%)	2 (28.6%)	-
41 – 50	-	-sss	1 (5.9%)
>50	-	-	2 (11.7%)
Localization			
Skeletal	8 (47.1%)	3 (42.9%)	13 (76.4%)
Extraskeletal	9 (52.9%)	4 (57.1%)	4 (23.5%)
P value	0.156	0.320	0.052
Size of the tumor			
≤ 5cms	1 (29.4%)	1 (42.8%)	9(72.2%)
> 5cms	16(70.6%)	6 (57.2%)	8 (27.8%)
P value	0.008	0.399	0.001

Maximum number of tumors with metastasis were seen below the age of 20 years where as in the elderly age group tumors were localized (Table 4)

Maximum number of skeletal Ewing sarcoma were predominantly localized in comparison to extra skeletal Ewing sarcoma, which were having metastasis (Table 4)

When different sites of metastasis were compared, bone +/- lung metastasis was seen in maximum number of cases of extra skeletal Ewing sarcoma (Table 1)

Maximum number of tumors with size less than 5cms were localized whereas tumors with metastasis were larger than 5 cms (Table 4)

Our study demonstrated 3 cases of Ewing sarcoma with neuroectodermal differentiation which were confirmed by immunohistochemistry with synaptopysin and NSE. All of them were localized. 2 of them were seen in males and were of size >than 5cms

DISCUSSION

Ewing sarcoma family of tumors are aggressive tumors with small round cell morphology. They constitute 6% to 8% of primary bone tumors and are second most common primary bone cancer in children. [6] These tumors show gene fusions involving one member of the FET family of genes (usually EWSR1) and a member of ETS family of transcription factors. 85% of cases have reciprocal translocation t(11;22)(q24;q12) with ES Break point region 1 (EWSR1) fusion to Friend Leukemia virus Integration site 1 (FLI 1). [7] Another 10% of cases show fusion of EWSR1 with ERG {t(21;22)(q11;q12)}. [8] FLI-1 and ERG are members of ETS (Erythroblast transformation-specific) transcription factor family. [9].

Among Ewing sarcoma family of tumors, skeletal tumors showed predominance, when compared to extra skeletal in our study which did not coincided with the study done by Sudha S Murthy et al (2020) (Table 5). [10]

Table 5: Comparison Of Clinical Features In Our Study And Sudha S Murthy Et Al Study

Ewing's sarcoma	Our study	Sudha S Murthy et al (2020)
Incidence		
Skeletal	59.5%	49.34%
Extraskeletal	40.5%	50.66%
Mean age of presentation		
Skeletal	26	16
Extraskeletal	21	25
Sites of involvement in skeletal Ewings sarcoma		
Upper limb	9.1%	16.11%
Lower limb	18.2%	33.56%
Flat bones	72.7%	50.3%
Sites of involvement in extraskeletal ewings		
Fore arm	13.3%	3.4%
Thigh	46.7%	16.8%
Leg	-	3.4%
Popliteal fossa	-	1.7%
Gluteal region	-	4.2%
Chest wall	13.3%	24.4%
Mediastinal mass	6.7%	4.2%
Paraspinal	6.7%	16.8%
Abdominal and retroperitoneal	13.3%	11.8%
Head and neck	-	13.4%

In our study, skeletal and extra skeletal Ewing sarcoma showed male predominance which correlates with study done by Sudha S Murthy et al (2020) (Table 6) [10]

Table 6: Distribution Of Ewing Sarcoma In Different Sex In Various Studies

Ewing sarcoma	Our study		Sudha S Murthy et al (2020)	
	Male	Female	Male	Female
Skeletal	59%	40.9%	67.8%	32.2%
Extra skeletal	53.3%	46.6%	51.63%	48.37%

In our study mean age of presentation for skeletal Ewing sarcoma is 26 and extraskeletal Ewing's sarcoma is 21 which did not coincide with the study done by Sudha S Murthy et al (2020) which showed higher mean age in extra skeletal Ewing sarcoma (Table 5). [10]

Common site of involvement was flat bones in skeletal Ewing sarcoma which coincided with the study done by Sudha S Murthy et al (2020) (Table 5). [10]

In the present study, common site of involvement for extraskeletal Ewing sarcoma was thigh which did not coincide with the study done by Sudha S Murthy et al (2020) in which common site of involvement was chest wall (Table 5). [10]

In the present study maximum number of cases of both skeletal and extraskeletal tumors were greater than 5cms which coincided with study done by A Pradhan et al (2011) (Table 16). [11]

Table 7: Size And Metastatic Sites Of Skeletal And Extra Skeletal Ewing Sarcoma In Different Studies

Size	Our study		A Pradhan et al (2011)	
	Skeletal	Extra skeletal	Skeletal	Extra skeletal
<5ms	36.4%	13.3%	20%	26%
>5cms	63.6%	86.7%	80%	74%
Metastatic sites				
Lungs	75%	40 %	44%	33.3%
Bones +/-lungs	25%	60%	56%	66.7%

The present study showed that extra skeletal Ewing tumor had more metastasis and recurrence when compared with skeletal Ewing sarcoma which did not coincide with study done by Applebaum MA et al (2011). In their study maximum number of skeletal and extraskeletal were localized (Table 8). [6]

Table 8: Stage Of Disease In Skeletal And Extra Skeletal Ewing Sarcoma In Different Studies

Stage of disease	Our study		Applebaum MA et al study (2011)	
	Skeletal	Extra skeletal	Skeletal	Extra skeletal
Metastasis	36.4%	60%	29.9%	30.1%
Localized	63.6%	40%	70.1%	69.9%

Our study demonstrated that metastasis in lungs and bone were seen more in extra skeletal Ewing sarcoma when compared to skeletal Ewing sarcoma which showed more lung metastasis only. It did not coincide with the study done by A Pradhan et al (2011) which showed both skeletal and extraskeletal Ewing with bone and lung metastasis (Table 7). [11]

Conclusion

Our study showed difference in clinical features and prognosis of skeletal and extra skeletal Ewing sarcoma, though statistical significance could not be demonstrated. Male sex predominance was seen in both skeletal and extra skeletal Ewing sarcoma with mean age of incidence slightly greater in skeletal Ewing sarcoma. Predominance of flat bone location, and localized tumors were seen in skeletal Ewing sarcoma whereas in extra skeletal Ewing sarcoma localization in thigh, and tumors with metastasis were more common. Extra skeletal Ewing sarcoma, male sex, age less than 20 years, size more than 5cms were associated with worse prognosis.

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