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The Extracompartmental Tumoral Invasion of Extraskeletal Myxoid Chondrosarcoma Induces Distant Metastasis

YUSUKE MINAMI, SEIICHI MATSUMOTO, KEISUKE AE, TAISUKE TANIZAWA, KEIKO HAYAKAWA, YUKI FUNAUCHI and MASANORI SAITO

Department of Orthopedic Oncology, The Cancer Institute Hospital of The Japanese Foundation for Cancer Research, Tokyo, Japan

Abstract. *Background: Extraskeletal myxoid chondrosarcoma (EMC) is a rare malignant soft-tissue tumor and often shows extracompartmental tumoral invasion. The aim of our study was to investigate the clinical features, especially extra-compartmental tumoral invasion (ETI) of EMC. Patients and Methods: A total of 35 operative patients diagnosed with EMC were enrolled in this study from January 1980 to March 2018 in the Cancer Institute Hospital of The Japanese Foundation for Cancer Research. The operative procedure was principally wide excision. Univariate analysis assessed how clinicopathological factors (e.g. age, gender, tumor site, tumor size, histo-pathological grade, surgical margin, metastasis before operation, barrier invasion, local recurrence, metastasis after operation) influenced patient prognosis. We assessed how clinicopathological factors influenced ETI of EMC. Results: Among 35 patients, 10 patients showed ETI. The average follow-up was 5.57 (range=0.2-20 years). The 5- and 10-year overall survival was 91.3% and 71.2%, respectively. The 5- and 10-year overall survival of patients with M0 disease was 96.1% and 73.2%, respectively, while both were 75.0% for those with M1 disease, respectively. The patients with distant metastasis at first visit tended to have a poor prognosis (p=0.07). It is notable that all of the 10 patients with ETI had distant metastasis after surgery. Conclusion: Patients with distant metastasis at first visit tended to have a poor prognosis. ETI of EMC induced distant metastasis after surgery. Patients with ETI of EMC should, therefore, be carefully monitored over a prolonged period.*

Extraskeletal myxoid chondrosarcoma (EMC) is a rare soft-tissue malignancy characterized by uniform spindle cells arranged in a reticular growth pattern in abundant myxoid stroma (1, 2). The disease generally arises in the deep soft tissues of the proximal extremities and limbs and comprises multiple gelatinous nodules divided by fibrous septa but occurrence in several unusual regions such as the scrotum and finger have been reported (3-5). Considered to be slow-growing, EMC is associated with relatively long survival but has a risk of local recurrence or distant metastasis (1,2, 6, 7).

Histologically, the tumor is classified as a tumor of uncertain differentiation due to its lack of cartilaginous differentiation, although originally believed to be a variant of chondrosarcoma (3). The tumor is distinguished from other sarcomas by its unique histology and characteristic chromosomal translocation, typically t(9;22)(q22;q12.2), fusing Ewing sarcoma breakpoint region 1 (*EWSR1*) to nuclear receptor subfamily 4 group A member 3 (*NR4A3*) (genes formerly known as Ewing sarcoma (*EWS*) and chimerin (*CHN*), translocated in extraskeletal chondrosarcoma (*TEC*) or neuron-derived orphan receptor 1 (*NOR1*), respectively) (8-10). The fusion gene products are responsible for alterations in cellular growth and differentiation (11).

To our knowledge, published reports documenting the clinical features of EMC are limited (12). EMC often exhibits extracompartmental tumoral invasion (ETI) (13). The aim of our study was to investigate the clinical features and ETI of EMC.

Patients and Methods

A total of 35 patients diagnosed with EMC were enrolled in this study from January 1980 to March 2018 at the Cancer Institute Hospital of The Japanese Foundation for Cancer Research. Clinical and pathological data were collected by reviewing medical records at our Institution, with the last follow-up conducted in March 2018. The inclusion criterion confirmed pathological diagnosis by a pathologist at our Institution through histological characteristics of the biopsy specimen, immunohistochemistry and fluorescence *in situ* hybridization; the latter molecular cytogenetic studies for detection of t(9;22)(q22;q12.2) were applied in all cases retrospectively to confirm pathological diagnosis. Patients with no chromosomal translocation were excluded. The histological grade was determined according to French Federation of Cancer Centers Sarcoma Group grading system (14). The tumors were classified at grade 1 to 3, and the histological grade depended on the mitotic rate and the existence

Correspondence to: Yusuke Minami, MD. PhD, 3-8-31 Ariake, Koto-ward, Tokyo 135-8550, Japan. Tel: +81 335200111, Fax: +81 335200141, e-mail: yusuke.m0811@gmail.com

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of necrosis. The following demographic data and treatment factors were examined retrospectively for prognostic importance: Gender, patient age at diagnosis (<60 or ≥60 years), tumor site, tumor size (<5 or ≥5 cm), histological grade, surgical margin (intralesional, marginal or wide margin), barrier invasion, with (M1) or without metastases (M0) at initial visit, local recurrence, and metastasis after operation. The surgical margin was pathologically confirmed through surgical specimens in accordance with the concept of surgical margin (15). Barrier invasion was defined as ETI such as invasion to an adjacent compartment, bone or vessels (red arrows in Figure 1). The operative procedure was principally wide excision.

This research was approved by the Institutional Review Boards of the affiliated institutions. Informed consent was given by patients for use of their medical records and all patient data were anonymized.

Statistical analysis. The data from medical records was collected from the period prior to March 2018 from the Cancer Institute Hospital of The Japanese Foundation for Cancer Research. Comparisons between groups of measurement data with normal distributions were analyzed by the chi-squared test. Survival rates were estimated from the day of surgery with the use of the Kaplan–Meier survival curve and compared with the log-rank test. All statistical tests were bilateral. Univariate analysis was performed on demographic data and treatment factors for prognosis and barrier invasion. Univariate comparisons were performed using log-rank test. The data were analyzed by JMP 14.2 (SAS, Tokyo, Japan). *p*-Values below 0.05 were considered statistically significant.

Results

Baseline information of patients. There were 35 patients with an average age of 54 years (range=34-76 years) in this study. The tumor sites of involvement were a limb in most cases (80.0%). The average size of the tumors was 6.7 (range=0.9-14.2 cm). Twenty patients (57.2%) had tumors larger than 5 cm. Histologically, most patients (74.3%) were diagnosed with high-grade sarcoma (grade 2-3). The surgical margin was evaluated through surgical specimens and was intralesional or marginal in 10 patients (28.6%) and wide in 25 patients (71.4%). Ten patients (28.6%) had ETI and eight patients (22.9%) had distant metastasis at their first visit. Local recurrence after operation was occurred in three patients (9.3%). Distant metastasis occurred in 17 patients (48.5%); all 10 patients who had ETI also had distant metastasis. Baseline information of patients is shown in Table I.

Table I. *Baseline information of patients*.

Characteristic	Patients, n (%)
Total	35 (100%)
Gender	
Male	23 (65.7%)
Female	12 (34.3%)
Age	
<60 Years	25 (71.4%)
≥60 Years	10 (28.6%)
Tumor site	
Limb	28 (80.0%)
Trunk	7 (20.0%)
Tumor size	
<5 cm	15 (42.8%)
≥5 cm	20 (57.2%)
Histological grade	
1	9 (25.7%)
2 or 3	26 (74.3%)
Surgical margin	
Intralesional or marginal	10 (28.6%)
Wide margin	25 (71.4%)
Barrier invasion	
Yes	10 (28.6%)
No	25 (71.4%)
M0 or M1	
M0	27 (77.1%)
M1	8 (22.9%)
Local recurrence	
Yes	3 (9.3%)
No	32 (90.7%)
Metastasis after operation	
Yes	17 (48.5%)
No	18 (51.5%)

Treatment outcome. The average follow-up time was 5.57 years (range=0.2-20 years). At the last follow-up period, 27 (77.2%) patients were still alive and eight patients (22.8%) had died. Among those who died, six patients died due to pulmonary metastasis and the remainder due to other reasons.

The 5- and 10-year overall survival (OS) rates were 91.3% and 71.2%, respectively (Figure 2A). The corresponding OS rates for those with M0 disease were 96.1% and 73.2%, respectively, and were both 75.0% for those with M1 disease (Figure 2B).

Factors influencing prognosis. The presence of metastases at their initial visit tended to have a negative influence on OS (p=0.07), however, gender, patient age at diagnosis, tumor site, tumor size, histological grade, surgical margin, barrier invasion, local recurrence and metastasis after operation did not influence OS significantly. The analysis of prognostic factors is shown in Table II.

Factors influencing barrier invasion. Univariate analysis was performed to investigate factors influencing barrier invasion. As shown in Table III, all 10 patients with barrier invasion experienced distant metastasis (p=0.0001). The locations of distant metastasis were as follows: lung in eight cases (80.0%), bone in two cases (20.0%).

Discussion

EMC is a rare soft-tissue sarcoma which occurs in those around 50 years of age but also occurs in younger people (1, 2). EMC is distinguished by a biology that is distinct from

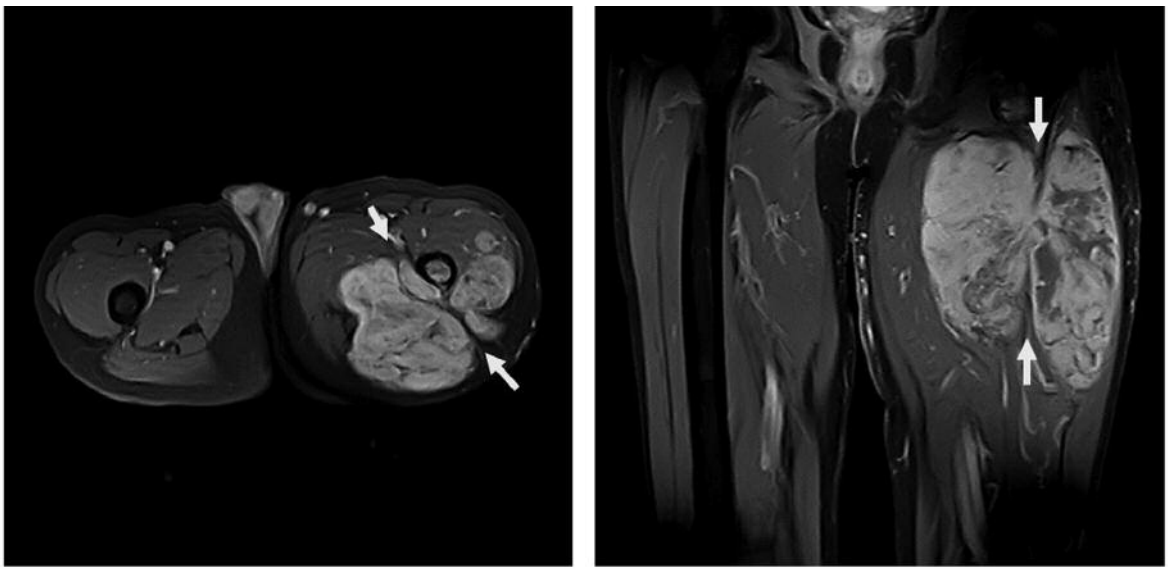

Figure 1. *Magnetic resonance imaging revealed a mass extending into the anterior compartment in the patient's thigh beyond the intermuscular septum (arrows).*

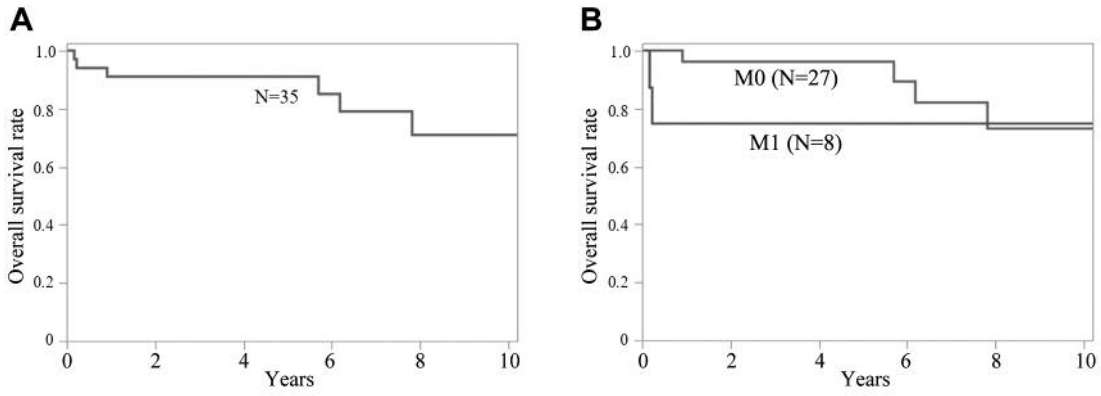

Figure 2. *A: Kaplan-Meier plot showing overall survival of the 35 patients with extraskeletal myxoid chondrosarcoma. B: Kaplan–Meier plots showing overall survival of the 27 patients without metastasis (M0) and eight patients with metastatic (M1) extraskeletal myxoid chondrosarcoma.*

the genetic heterogeneity observed in other forms of chondrosarcoma (7). The majority of cases of this disease are characterized by translocations that lead to abnormal gene products. The most common of the translocations is t(9;22)(q22;q11), resulting in the juxtaposition of the genes *EWSR1* on chromosome 22 and *NR4A3* on chromosome 9 (16-18). To our knowledge, there are very few published reports documenting the clinical features of EMC. Moreover, EMC is known to exhibit ETI often (13).

In the previous study of EMC, the 5- and 10-year overall survival rates were 91% and 84%, respectively (12). In our study, the rates were 91.3% and 71.2%. These and the rates for those with and without metastatic disease were consistent with those of the previous study.

Tumor size and metastasis at first visit are one of the important factors influencing prognosis in EMC (12). In our study, patients with metastasis at first visit tended to have a worse prognosis (p=0.07).

Of 35 patients in our study, 10 patients showed barrier invasion (ETI). It is notable that all 10 patients with barrier invasion also developed distant metastases. Suspecting hematogenous metastasis in these patients, we investigated vascular invasion through their surgical specimens histologically. Vascular invasion was partially noted though the surgical specimens, however, there were few vascular invasions in the mass. It was considered that tumor cells extended to these vulnerable vessels, which induced distant metastasis hematogenously. The findings in our study are

Table II. *Analysis of prognostic factors.*

Factor	Patients, n (%)	Survival 5-Year	Survival 10-Year	*p*-Value*
Gender				
Male	23 (65.7%)	86.9%	63.4%	0.16
Female	12 (34.3%)	100%	85.7%	
Age				
<60 Years	25 (71.4%)	96.0%	71.0%	0.28
≥60 Years	10 (28.6%)	80.0%	80.0%	
Tumor site				
Limb	28 (80.0%)	100%	75%	0.55
Trunk	7 (20.0%)	89.2%	71.0%	
Tumor size				
<5 cm	15 (42.8%)	100%	85.7%	0.15
≥5 cm	20 (57.2%)	84.7%	61.7%	
Histological grade				
1	9 (25.7%)	100%	85.7%	0.23
2 or 3	26 (74.3%)	88.2%	64.3%	
Surgical margin				
Intralesional or marginal	10 (28.6%)	80%	80%	0.41
Wide margin	25 (71.4%)	95.8%	61.3%	
Barrier invasion				
Yes	10 (28.6%)	90.0%	64.2%	0.80
No	25 (71.4%)	91.8%	80.3%	
M0 or M1				
M0	27 (77.1%)	96.1%	73.2%	0.07
M1	8 (22.9%)	75.0%	75.0%	
Local recurrence				
Yes	3 (8.5%)	100%	33.0%	0.63
No	32 (91.5%)	90.5%	82.9%	
Metastasis after operation				
Yes	17 (48.5%)	88.2%	58.8%	0.29
No	18 (51.5%)	94.4%	94.4%	

*Univariate.

Table III. *Factors Influencing barrier invasion.*

Factor	Barrier invasion, n (%) Yes	Barrier invasion, n (%) No	*p*-Value*
Gender			
Male	7 (20.0%)	16 (45.7%)	0.73
Female	3 (8.5%)	9 (25.7%)	
Age			
<60 Years	6 (17.1%)	19 (54.2%)	0.34
≥60 Years	4 (11.4%)	6 (17.1%)	
Tumor site			
Limb	9 (25.7%)	19 (54.2%)	0.34
Trunk	1 (2.8%)	6 (17.1%)	
Tumor size			
<5 cm	2 (5.7%)	13 (37.1%)	0.08
≥5 cm	8 (22.8%)	12 (34.2%)	
Histological grade			
1	2 (%)	7 (20.0%)	0.62
2 or 3	8 (%)	8 (51.4%)	
Surgical margin			
Intralesional or marginal	3 (8.5%)	7 (20.0%)	0.90
Wide margin	7 (20.0%)	18 (51.4%)	
M0 or M1			
M0	8 (22.8%)	19 (54.2%)	0.79
M1	2 (5.7%)	6 (17.1%)	
Local recurrence			
Yes	2 (5.7%)	1 (2.8%)	0.12
No	8 (22.8%)	24 (68.5%)	
Metastasis after operation			
Yes	10 (28.6%)	7 (20.0%)	0.0001
No	0 (0%)	18 (51.4%)	

*Univariate.

significant because distant metastasis directly led to poorer prognosis in the patients with EMC.

Heyse *et al*. documented metastasis in chondrosarcoma (19). They reported that overexpression of CD44s correlated significantly with metastatic potential and with poorer survival. However, their study includes only two cases of extraskeletal chondrosarcoma, and ultrastructural studies of EMC have also uncovered evidence of markers of neuroendocrine differentiation (20, 21), such as class III β-tubulin and microtubule-associated protein-2 (22). These reports argue against a chondrocytic or pre-chondrocytic origin of EMC, and further distinguish EMC as unique among sarcoma types.

Limitations of our study include the fact that patients underwent multimodality treatment including surgery, radiotherapy, and chemotherapy, depending on the clinical stage of each tumor, which might have influenced OS or distant metastasis. Moreover, the small number of patients also needs to be considered. Because this was a single-center study, there could be consistency in treatment and management of the patients. We believe that our conclusion has great clinical significance for understanding the prognosis of this rare tumor.

In conclusion, our experience with the present series in EMC has shown that the patients with distant metastasis at first visit tended to have a poor prognosis. Patients with barrier invasion (ETI) of EMC experienced distant metastasis after surgery. Patients with barrier invasion of EMC should therefore be carefully monitored over a prolonged period.

Conflicts of Interest

None declared.

Authors' Contributions

Yusuke Minami designed the study, and wrote the initial draft of the article. Yusuke Minami also contributed to analysis and interpretation of data, and assisted in the preparation of the article. All other Authors have contributed to data collection and interpretation, and critically reviewed the article. All Authors approved the final version of the

article, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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