·Clinical Research·

Extraskeletal Ewing's sarcoma: a report of 18 cases andliterature review

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[Abstract] Background and Objective: Extraskeletal Ewing's sarcoma (EES) is a rare, rapidly growing, round-cell, malignant tumor that can develop in the soft tissues at any location. This study was to analyze the clinical features, diagnosis and treatment of EES. **Methods:** Clinical data of 18 patients with EES, treated at between Cancer Center of Sun Yat-sen University between 1995 and 2007, were analyzed. **Results:** Of the 18 patients, 13 were male and 8 were female, aged from 8 months to 60 years. Twelve (66.7%) patients were between 5–25 years of age. Eight (44.4%) patients had tumors originated from low extremities. Sixteen patients had masses at their first visit. Sixteen patients were treated by the combined modality therapy, and 2 patients were treated by the single modality therapy. The 1-, 3- and 5- year actuarial survival rates were 82.4%, 64.2% and 32.1%, respectively. The presence of metastatic disease at the time of diagnosis and the mode of treatment were prognostic factors. **Conclusions:** EES is common in adolescent. It often manifests as a localized mass. The combined modality therapy is recommended for this disease. The presence of metastatic disease at the time of diagnosis and the mode of treatment are prognostic factors.

Key words: Extraosseous Ewing's sarcoma, clinical feature, diagnosis, treatment

Ewing's sarcoma is a highly malignant small round-cell tumor and occurs most often in children and adolescents. In Europe and the United States, its annual incidence rate is 1–3 per a million [1], and it is more rare in Asia and Africa [2]. Extraskeletal Ewing's sarcoma (EES) is the Ewing's sarcoma originating from non-bone tissues, and is constituted by primitive small round cells with piece or lobular distribution. Extraskeletal Ewing's sarcoma is rare and until now the largest case number reported in foreign literatures is 130 [3], while case reports exit mostly in domestic literatures. Now the clinical data of 18 patients with EES treated at Sun Yat-sen University Cancer Center between January 1995 and July 2007 were collected and analyzed, and the clinical features, diagnosis and treatment were discussed with the literature review.

Patients and Methods

General information

Between January 1995 and July 2007, 18 patients with pathologically confirmed EES were treated at Sun Yat-sen University Cancer Center, among whom there were 13 males and 5 females, with a male to female ratio of 2.6:1. Age ranged from 8 months to 60 years, with a median age of 17 years. The age distributions are as follows: four patients were aged ⩽ 10 years, 8 patients were 10–20 years, 2 patients were 20–30 years, 4 patients were > 30 years, and 12 patients (66.7%) were 5–25 years.

Primary sites of tumors and clinical manifestations

Among the 18 patients, 8 (44.4%) patients had tumors originated from lower extremities, 5 patients (27.8%) from paravertebral region, 2 (11.1%) from chest wall, and the remainder originated from upper limb, pelvic and submandibular area each (5.6%). In this group, 16 patients (88.9%) had masses, 5 (27.8%) had local pain, 1 (5.6%) had weight loss, 1 (5.6%) had cough and 1 (5.6%) had physical activity limitation. The minimal diameter of the tumors was 2 cm and the maximum was 15 cm, with a median of 4.5 cm.

Imaging examination

Among 18 patients, 13 patients received CT examination and 5 patients received MR examination. All the imaging examinations showed the soft tissue masses with a less clear-cut boundary, and the adjacent structures shifted by pressure or were invaded (Figure 1). All patients completed chest X-ray or CT examinations, and 1 patient developed lung metastasis; 8 patients completed bone scan, and none had bone metastasis.

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Pathological and immunohistochemical results

All the 18 patients were pathologically confirmed by our hospital or the Medical College of Sun Yat-sen University. Under microscopy it was showed that tumor cells were small, round or oval with little cytoplasm, and nuclei were round or oval with various mitosis; cells were arranged sheet or nest-like, and rosettes could be seen in some patients (Figure 1). Immunohistochemical examinations were performed in all the patients, in which Vim-positive rate was 87.5% (14/16) and CD99-positive rate was 93.3% (14/15) (Table 1).

Table 1 Immunocytochemical results of 18 patents with extraskeletal Ewing's sarcoma (EES)

Item	(+)	(−)	(+/−)	Total
Syn	4 (36.4%)	7 (63.6%)	–	11
NSE	7 (46.7%)	7 (46.7%)	1 (6.7%)	15
Cga	1 (8.3%)	10 (83.3%)	1 (8.3%)	12
Vim	14 (87.5%)	2 (12.5%)	–	16
LCA	1 (10.0%)	9 (90.0%)	–	10
S-100	5 (33.3%)	6 (40.0%)	4 (26.7%)	15
CK	–	12 (92.3%)	1 (7.7%)	13
HHF35	–	13(100.0%)	–	13
Myo	1 (10.0%)	9 (90.0%)	–	10
CD99	14 (93.3%)	–	1 (6.7%)	15

Treatment

Among 18 patients, 16 received comprehensive treatment, including radiotherapy plus chemotherapy in 3 patients, surgery plus chemotherapy in 4 patients, surgery plus radiotherapy plus chemotherapy in 9 patients; 2 patients received non-comprehensive treatment, including chemotherapy and surgery alone in 1 patient each. A total of 13 patients received continuous radiotherapy by ^{60}Co γ ray or X ray, and the radiation dose ranged from 24 to 70 Gy, with a median dose of 54 Gy. In the patients treated with chemotherapy, 9 patients received alternating chemotherapy of CAV (CTX + ADM + VCR) and IE (IFO + VP-16), 4 patients received MAID (ADM + IFO + DTIC) regimen, and the others received combined chemotherapy based on CTX, ADM, DDP, IFO, VP-16 or VCR.

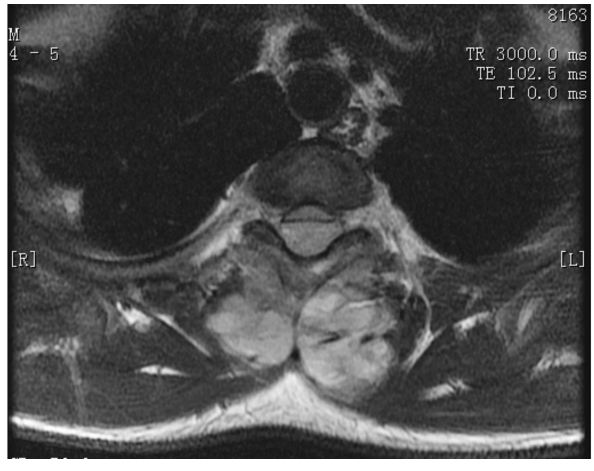

Figure 1 Magnetic resonance (MR) imaging of soft tissue mass of paravertebral region

An ill-defined soft mass in paravertebral region, adjacent tissues are displaced and invaded.

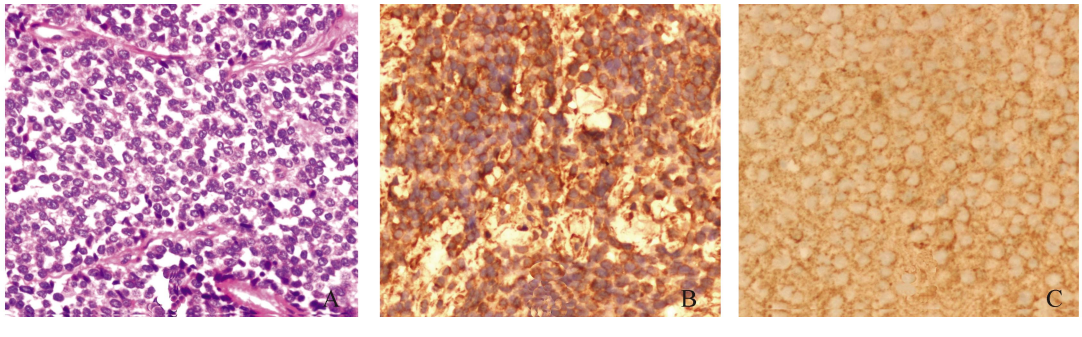

Figure 2 Microscopic features of extraskeletal Ewing's sarcoma (EES)

A, a hematoxylin and eosin stained of the cell block shows clustered groups of small round-to-oval tumor cells with scant cytoplasm. B, Vim immunohistochemistry is positive. C, CD99 immunohistochemistry is positive.

Statistical methods

SPSS11.0 statistical package was used for statistical analysis of all data, and Kaplan-Meier method was used for survival and univariate analysis.

Results

Survival information

The 18 patients in this group were followed up until December 2008, 1 patient was lost to follow-up, and the follow-up rate was 94.4%. The survival time of 17 patients ranged from 6 to 118 months (Figure 3). Three patients had residual tumor, 2 had recurrence, 2 had pulmonary metastases, and 2 had bone metastases. The 1-, 3- and 5-year survival rates were 82.4%, 64.2% and 32.1%, respectively.

Univariate analysis related to prognosis

The factors related to prognosis (including gender, age, tumor size, tumor location, with or without distant metastasis, with or without anemia, LDH levels, treatment modality, efficacy) were analyzed by univariate analysis, and the result showed that

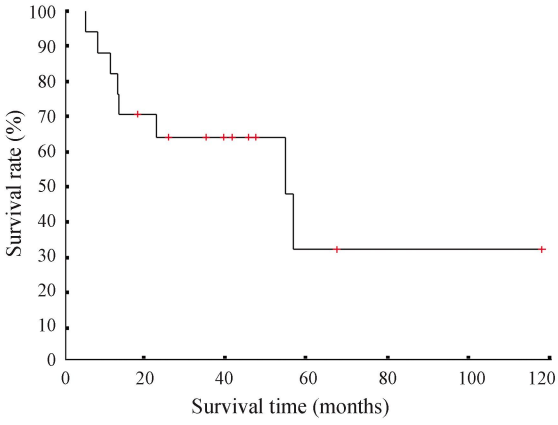

Figure 3 Survival curve of the 18 patients with EES

distant metastasis and treatment modality were relevant to prognosis (Table 2).

Table 2 Univariate analysis of 18 patients with EES

Variable	Patient No.	5-year overall survival rate (%)	*P*
Age (years)			0.53
< 18	9	25.4	
⩾ 18	8	50.0	
Gender			0.36
Male	12	44.8	
Female	5	0.0	
Bulk disease			0.44
⩾ 8 cm	13	0	
< 8 cm	4	34.2	
Metastasis			0.01
Yes	8	33.3	
No	1	0	
Unknown	8	37.5	
Anemia			0.92
Yes	3	66.7	
No	14	31.8	
LDH			0.06
⩽ 260	12	49.4	
> 260	5	0	
Combined modality treatment			0.05
Yes	15	36.4	
No	2	0	

Discussion

Clinical features of EES

EES has a low incidence rate, accounts for 1.1% of malignant soft tissue tumors[4], and most often occurs in young people ranging in age from 15 to 30 years, rarely more than 40 years, and is more common in men [5]. In this group, 66.7% of the patients were aged 5–25 years, with a male to female ratio of 2.6:1, which basically agrees with the reports in the literatures (Table 3).

Table 3 Literature review of EES clinical series

Authors	Year of publication	No. of patients	Age (years)	Male:female	Metastasis at diagnosis	Follow-up	5-year survival rate (%)	Local recurrence
Kinsella *et al.*[6]	1983	11	Average age:19	6 : 5	0/11	42–79 months	–	2/11
Rud *et al.*[7]	1989	42	Average age:22	19 : 23	6/42	>7 years	38.5	16/35
Raney *et al.*[3]	1997	130	Median age:12	70 : 60	16/130	1–10 years	–	9/107
Ahmad *et al.*[8]	1999	24	Average age:15	13 : 11	5/24	64 months	61	1/24
Castex *et al.*[9]	2007	63	Median age:11	35 : 28	0/63	1–9 years	69	5/65
Xie *et al.*	Current study	18	Median age:17	13 : 5	1/18	1–13 years	32.1	2/16

EES occurs mainly at paravertebral region, lower limb and chest wall, and a few occur in the pelvic cavity, retroperitoneal region, upper limb and head and neck[3]. In this group, tumors originated from lower extremities in 8 patients (44.4%), from paravertebral region in 5 patients (27.8%), and from chest wall in 2 patients (11.1%), which was consistent with the reports in the literature. The main clinical symptoms of this disease is the mass deep in the soft tissue, generally without red, swollen, fever and other inflammatory signs in the surface, and local pain may occur in some patients. When the mass grows to a certain degree, it can limit the activity of local muscle and oppress the surrounding tissue. The mass occurring in the spinal canal or near the nerve can cause sensory and movement disorder of the nerve-related limb.

The imaging of EES is different from that of bone Ewing's sarcoma since they originate from different sites. EES has very few direct violation to bone, and its imaging showed soft tissue mass with unclear boundary and changes of hemorrhage, cystic change and necrosis, but without significant calcification[4,10]. X-ray film shows soft tissue mass with muscle tissue density, the peripheral soft tissue swelling, pressured and displaced, or invaded, but without calcification and onion skin-like radiation characteristics which is specific to bone Ewing's sarcoma. Unenhanced CT imaging shows mass with hypodensity or uneven density and unclear edges due to the hemorrhagic necrosis, and the surrounding tissues show pressured shift and

invaded changes; enhanced scan shows that the mass is heterogeneously enhanced. Unenhanced T1-weighted MRI shows mass with low signal or equal signal and tumor hemorrhage with high signal; T2-weighted MRI shows mass with slightly higher signal, and enhanced scan shows heterogeneously enhanced mass. The patients in this group all showed soft tissue masses with unclear boundary, and the surrounding tissue showed pressured shift and invaded changes, which was consistent with those reported in the literature.

Since this disease has a high rate of distant metastasis, and the most common sites of metastases are lung and bone, it is suggested that chest X-ray or CT and bone scan should be done before treatment to exclude distant metastasis and make a clear stage. With the clinical application of PET/CT, we believe that it is more timely and accurate than traditional imaging methods, and it has significant value in staging before treatment and finding tumor recurrence and metastasis after treatment.

Diagnosis of EES

EES has no specific clinical manifestation, so timely pathological biopsy is the principal means to clarify a diagnosis. Under ordinary optical microscope this disease usually presents poorly differentiated small round cells, so it should be differentiated with small round cell tumor occurring in soft tissues, such as metastatic neuroblastoma, alveolar rhabdomyosarcoma, metastatic small cell carcinoma, PNET and malignant lymphoma. Ewing's sarcoma and PNET have similar characteristics in morphology, cytogenetics, tumor gene expression in the original agreement, cell culture, immunohistochemical and ultrastructural structure, so they are difficult to be differentiated by light microscopy. In general, under ordinary optical microscope, Ewing's sarcoma shows small round cells with tight piece or lobular distribution, and among the interlobules is the fibrous connective tissue with various width intervals; nuclear shape is regular, round or oval, with clear nuclear membrane and various mitoses, and cytoplasm is sparse or shows irregular-shaped small vacuoles, with some rosettes structures[11]. Immunohistochemistry shows positive PSA, CD99, Vimentin, various expressions of NSE, SYP, Leu-7, and negative S-100, NF. Electron microscopy shows sparse organelles, undeveloped Golgi apparatus, and glycogen granules can be seen in cytoplasm. Relatively speaking, the nucleus of PNET tumor cell has more cohesion and deep dyeing chromatin with small nucleolus, and the cytoplasm is sparse or unclear. Furthermore, in some tumors, two-phase morphology can be seen, which is compounded by cells with less volume, deep-dyed nuclear, scarce cytoplasm, morphologically similar to small lymphocytes, and medium-large cells with larger volume, vacuole-like nuclear chromatin, relatively abundant and pale staining cytoplasm, morphologically similar to the epithelial cells. In addition to tablets or lobular distribution, sometimes the tumor cells show beam-like or fascicular arrangement similar to small cell carcinoma or carcinoid tumors and with H-W rosettes arrangement. Immunohistochemistry shows the expression of at least two kinds of different neural markers. The electron microscopy confirms that the cells contain neuroendocrine granules.

The clinical diagnosis of EES is difficult. According to our cases and those reported in the literature, we think the main reasons are as follows: (1) the incidence rate is low and doctors have low vigilance; (2) it has no specific characteristics in symptoms, signs and imaging; and (3) it has no typical histological features and it is easy to make pathological misdiagnosis. The exact diagnosis of EES relies mainly on pathology, but it has no typical characteristics of pathological manifestations under ordinary optical microscope. So for some young patients with poorly differentiated or undifferentiated tumor cells, which are difficult to be differentiated with other tumors, immunohistochemical examination should be performed to determine the source tissue and make a clear diagnosis. Furthermore, since 90%–95% of Ewing's sarcoma has a characteristic t(11; 22) (q24; q12) chromosomal translocation, which results in the fusion of FIL-1 gene on 11q24 with EWS gene on 22q12, and generate EWS -FLI-1 fusion gene[12-14], we can specifically detect and diagnose Ewing's sarcoma by detecting EWS-FLI-1 and t(11; 22) with RT-PCR and FISH.

Treatment of EES

EES has the same chromosomal translocation with bone Ewing's sarcoma, and at present it is considered that the standard treatment used in the bone Ewing's sarcoma can achieve a good therapeutic effect in EES[14,15]. The main treatment for EES is chemotherapy, surgery and radiotherapy-based comprehensive treatment. This study showed that the treatment modality which patients accepted had a significant effect on the prognosis, and the prognosis of comprehensive treatment group was significantly better than that of non-comprehensive treatment group (P = 0.05). Rud *et al*[7]. retrospectively analyzed 42 cases of EES , and the results showed that comprehensive treatment could improve the survival rate, and adjuvant radiotherapy could improve the local control rate in margin positive patients; and adjuvant chemotherapy could eliminate micro-metastases in all patients. The treatment recommended by 2009 NCCN bone tumor guideline is chemotherapy plus local treatment (surgery and / or radiotherapy) plus chemotherapy. Multi-drug combination chemotherapy is recommended, and recommended drugs include cyclophosphamide, ifosfamide, etoposide, doxorubicin and vincristine. In this group, CAV / IE alternating chemotherapy was mostly used. It has been confirmed that CAVD (CTX + ADM + VCR + DACT) / IE alternating chemotherapy can improve the metastasis-free survival rate of bone Ewing's sarcoma and primitive neuroectodermal tumor when compared with CAVD alone, but there is no significant statistical difference for the patients with metastasis[16]. In addition, doxorubicin also has an important status in the treatment. Castex *et al.*[9] compared the treatment programs of EES by the International Pediatric Oncology Society (SIOP) and the French Pediatric Oncology Society (SFOP) (SIOP used malignant stromal tumor treatment program, and SFOP used bone Ewing's sarcoma treatment program), and the results showed that the 5-year overall survival rates were 59% and 83%, respectively, and treatment program adopted turned out to be the only factor affecting the survival rate. After comparing the two treatment programs, the authors considered that the use of anthracycline drug resulted in

improved survival rate of EES. The main local treatments of EES are surgery and radiotherapy. The current view is that surgical resection should be performed if the tumor can be completely resected. Multi-drug chemotherapy should be given for 12–24 weeks before surgery. A local wide resection is the recommended operation[7,8,17], with the goal of a complete resection of tumor lesions and negative surgical margin, and the extent should include a 2–3 cm normal tissue surrounding the tumor if possible. If the surgical margin is positive or insufficient, or the tumor locates at a special site or is bulky with wide invasion and hard to be resected, radiotherapy may be practicable. Both the dose and scope of radiotherapy can refer to bone Ewing's sarcoma. Since adequate clinical evidence is deficient to confirm the difference of surgery and radiotherapy in tumor control rate, individualized treatment program should be chosen according to patient's specific circumstances.

Most authors believe that EES has a better prognosis, with a 5-year survival rate above 60%, and prognostic factors are age, tumor location, tumor size, with or without distant metastasis, genetic mutation type and treatment programs[7-9,14]. This study shows that the main factors influencing the prognosis are distant metastasis and treatment modality. We think that early diagnosis, clear stage and active individualized comprehensive treatment are the keys to improving the therapeutic efficacy for EES.

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