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An Adolescent Case With Ewing Sarcoma of the Kidney

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Ewing sarcoma（ES）is a high-grade malignancy usually identified in children and adolescents. Primary extraskeletal lesions of ES are rarely detected and no established treatments are available for advanced ES. A fifteen-year-old female presented with abdomen discomfort, and had high titer of neuron specific enolase（NSE）, a specific tumor marker for neuroendocrine tumors. Radiological findings showed a large kidney mass with many nodules in bilateral lung and ilium. She was diagnosed as ES after total nephrectomy. She received chemotherapy and autologous peripheral blood stem cell transplantation accompanied with high-dose chemotherapy, but the tumor recurred in lung and bone. Our case suggests that it is necessary to differentiate ES for childhood and adolescent patients of large renal tumor with metastasis having high value of NSE. Developing a new treatment including molecular targeted therapy is warranted for patients with advanced ES.

Keywords: Ewing sarcoma, kidney, extraskeletal, EWS-FLI-1, NSE

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INTRODUCTION

Ewing sarcoma（ES）is a group of rare and biologically-aggressive tumors derived from the neuroectoderm. It is the 2nd most common primary bone tumor in children［1, 2］. The median age of patients with ES is 15 years, and more than 50% of patients are adolescents［1, 2］. Imaging study findings in patients with ES are in general nonspecific. The definite diagnosis of ES is based on the pathologic findings, assisted by immunocytochemistry and/or molecular analysis［1, 2］. ES is treated with multimodal therapy including chemotherapy, surgery, radiotherapy. The patients with metastatic ES receive autologous stem cell rescue with high-dose chemotherapy, and molecular targeted therapy is reported to produce objective responses in metastatic recurrent ES［1, 2］. The presence of metastatic disease is the single most powerful predictor of outcome［2, 3］. Five-year event free survival rates for patients with localized disease are approximately 70%, while that for patients with metastases are less than 30%［2］.

Primary localization of ES is divided into two groups; one is bone and the other is extraskeletal［1, 2］. The frequency of skeletal and extraskeletal mass is 80% and 20%, respectively. In extraskeletal lesions of ES, paravertebral and thoracic soft tissues are mostly affected. Extraskeletal primary ES have been documented in the retroperitoneum, esophagus, pancreas, ileum, kidney, bladder, vagina, uterus, pe-

nis, adrenal gland, lung, breast, spinal cord, orbit, and intracranial tissue [2]. Patients with extraskeletal ES were more likely to be older, female, nonwhite, and have axial primary sites, and were less likely to have pelvic primary sites compared with skeletal ES [4]. Overall survival of patients with extraskeletal ES were superior to those with skeletal origin [5]. However, overall survival in patients with extraskeletal ES with metastases was not different between those with skeletal tumors [4, 5].

Herein, we report an adolescent case with ES of the kidney with lung and bone metastasis.

CASE REPORT

The patient is a 15-year-old female. She felt persistent discomfort in left lower abdomen for 6 months. Her family noticed palpable mass in her lumbar lesion. She was referred to our hospital from the local hospital because of abdominal mass. Her medical history and family history were unremarkable. She had lost 4 kg in weight over a period of 6 months. Her blood pressure was 159/107 mmHg, and palpable mass was touched in the left abdomen. Microhematuria was observed. Complete blood count and biochemical tests were within normal range except for high titer of serum creatinine (0.89 mg/dL). Soluble interleukin-2 receptor (sIL2R) (916 U/mL) and neuron specific enolase (NSE) (329 ng/mL) was elevated, but urinary vanillylmandelic acid (VMA) and homovanillic acid (HVA) were in a normal range. A computed tomography (CT) scan revealed a large left renal mass with a maximum diameter of 20 cm (Fig. 1A) and metastatic lesions in bilateral lungs and ilium (Fig. 1B and C).

We performed total left nephrectomy including tumor. Tumor thrombosis in inferior vena cava was found at the time of operation. The nephrectomy specimen was 1.6 kg and the maximum tumor size was 20 cm (Fig. 2A). Microscopic examination showed small round cells with high nuclear to cytoplasmic ratio in Hematoxylin and Eosin staining. CD99 was strongly positive on the cells (Fig. 2B). Fluorescence in situ hybridization (FISH) analysis revealed split signal on Ewing sarcoma region 1 (*ESWR1*) (Fig. 3A), resulting in rearrangement

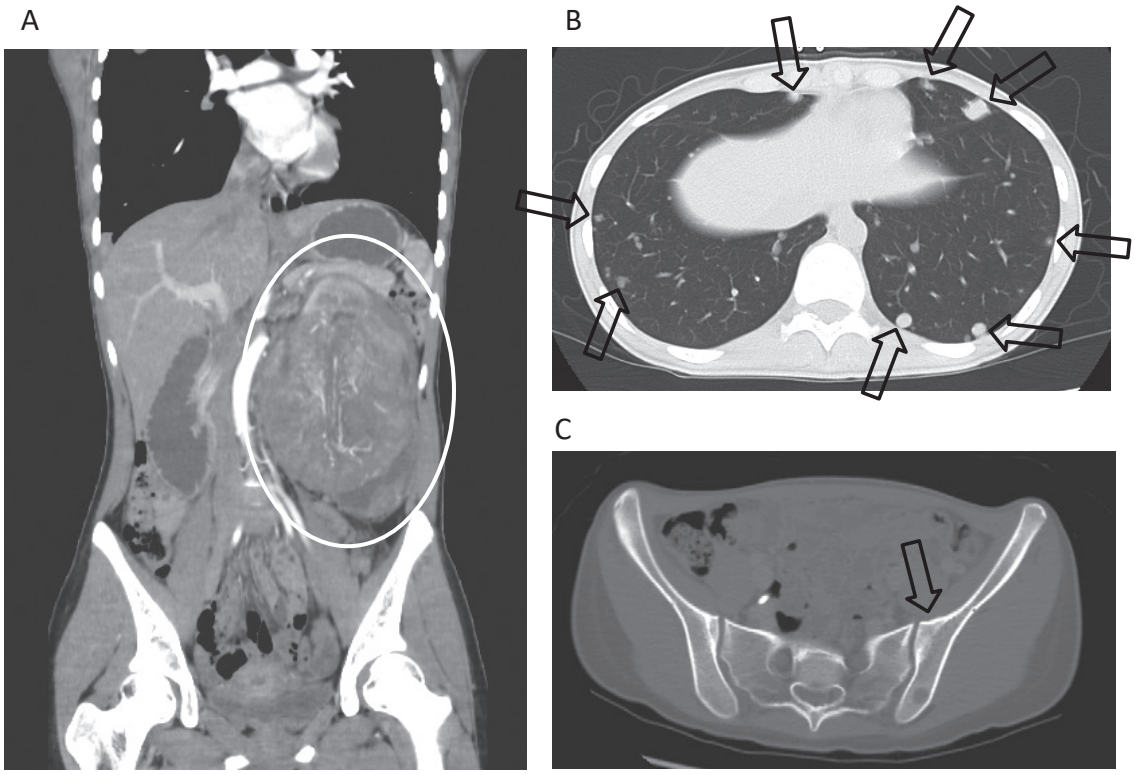

Fig. 1. Image finding of computed tomography scan
A, Coronal section in trunk. Left renal mass indicates within the circle; B, Transverse section in chest. Arrows indicate multiple pulmonary mass; C, Transverse section in pelvis. Arrow indicates bone metastasis in ilium.

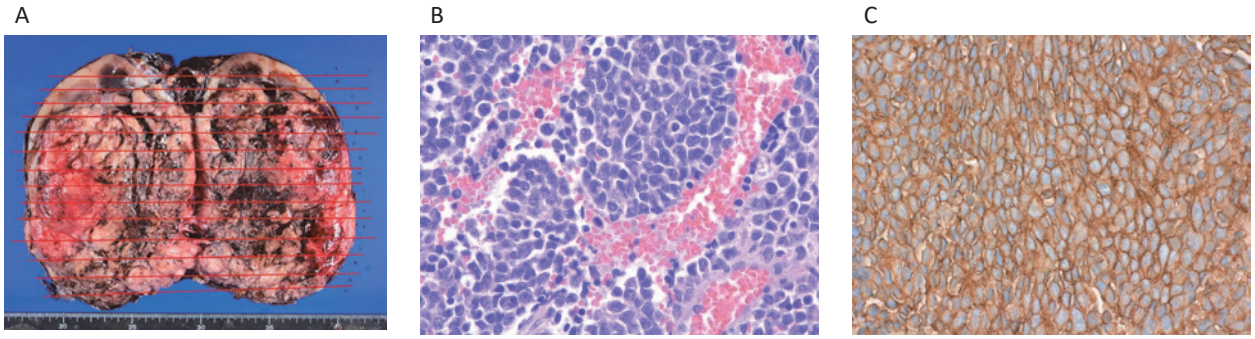

Fig. 2. Pathological finding
A, tumor cut surface; B and C, histological tissue specimen (high magnification). B indicates Hematoxylin and Eosin staining. C indicates CD99 staining.

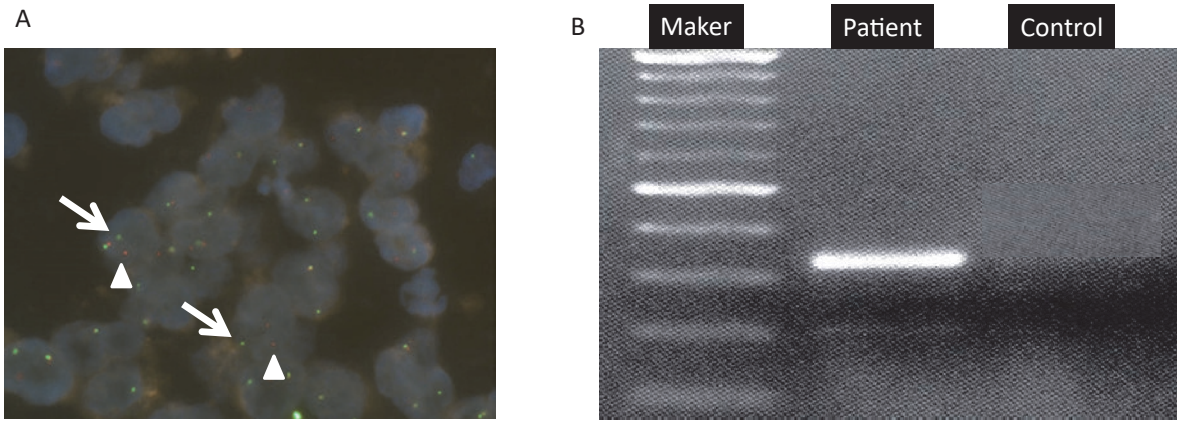

Fig. 3. Molecular genetic analysis
A, Fluorescence in situ hybridization analysis. Green (arrow) and red (arrowhead) signal appears when EWSR1 signal on 22q12 region is splitted; B, RT-PCR analysis for detection of *EWS-FLI1* fusion gene

of the *EWSR1* locus. RT-PCR that identifies fusion partner genes of the *EWS* gene demonstrated presence of *EWS-FLI-1* fusion gene (Fig. 3B). These findings led to the diagnosis of advanced Ewing sarcoma of the kidney with lung and bone metastasis.

Conventional chemotherapy was initiated two weeks after surgery. Five courses of chemotherapy consisted of vincristine (VCR), doxorubicin (DOX), and cyclophosphamide (CY) (VDC) followed by ifosfamide (IFO) and etoposide (ETP) (IE) at a two-week interval were administered. An episode of clonic convulsion was observed in third cycle of IE [6]. That continued in only 2-3 minutes and brain CT and Magnetic Resonance Imaging (MRI) showed no abnormality. It was suspected the adverse effect of IFO. VDC/IE was continued by using prophylactic use of the anticovulsant drug (levetiracetam) before administering IFO. Lung metastases were almost disappeared after five-cycle chemotherapy, indicating that VDC/IE protocol was effective. High-dose chemotherapy with autologous stem cell rescue was scheduled since she suffered from advanced ES with metastasis and the recurrent ES has been currently incurable [2, 5]. The patient received high-dose chemotherapy using Melphalan (70 mg/kg × 3 days) and Thiotepa (200 mg/kg × 4 days) followed by an autologous peripheral blood stems cell transplantation (auto-PBSCT). While no severe side effects were observed, she complained of pain in her leg 6 months after auto-PBSCT. CT and MRI revealed pulmonary and lumbar recurrence. Salvage chemotherapy (CY and Topotecan × 5 cycles) and whole lung irradiation were given. For the purpose of re-remission, she received CBT from HLA full matched donor after preconditioning regimen (Busulphan (0.8 g/kg × 16 doses) and CY (60 mg/kg ×

2 doses)). A short term of methotrexate and cyclosporine were used for prophylaxis of graft-versus-host disease. CBT was successful, but multiple lung nodules appeared 4 months after CBT. She has been currently under palliative chemotherapy and then, she died of lung metastasis 31 months after diagnosis.

Table 1. Treatment for patients with metastatic Ewing sarcoma

Study		Results	reference
P6 protocol		2-year EFS	15
	CDV+IE	16%	
EICESS-92		3-year EFS	16
	VAIA	52%	
	EVAIA	47%	
CCG-7951		2-year EFS	17
	VDC+IE+ASCT(ME+TBI)	20%	
MetaEICESS		5-year EFS	18
	HyperME+TBI	22%	
	TademME+TBI	29%	
The Société Franç aise des Cancers de l'Enfant		5-year survival	19
	DC+IE+ASCT(BUlMel)	37%	
Euro-EWING 99		3-year EFS	20
	VIDE+VAI+ASCT (BUlMel)	27%	
CCG+COG		8-year EFS	21
	VAdCD	20%	
	VAdCD+IE	32%	
INT-0091		8-year EFS	22
	VAC+IE	28%	
R2Pulm trial		3-year EFS	23
	VIDE+VAI+ASCT (BUlMel)	50.6%	
	VAI+WLI	52.9%	

CDV, cyclophosphamide, doxorubicin, and vincristine; IE, ifosfamide and etoposide;VAIA, vincristine, dactinomycin, ifosfamide, and doxorubicin; EVAIA, epotoside+VAIA; VDC, vincristine , doxorubicin, and cyclophosphamide; VAC, vincristine, Adriamycin, and cyclophosphamide; DC, doxorubicin, and cyclophosphamide; VAdCD, vincristine, dactinomycin, cyclophosphamide, and doxorubicin; VIDE, vincristine, ifosfamide, doxorubicin, and etoposide; VAI, vincristine, dactinomycin, and ifosfamide; WLI, whole-lung irradiation; EFS, event-free survival; ASCT, autologous stem-cell rescue; BUlMel, buslphan, and melphalan; ME, melphalan, and etoposide; TBI, total-body irradiation

Table 2. Treatment for patients with relapse Ewing sarcoma

Drugs	Results	reference
CPT-11 and TMZ	median TTP 8.3 months	24
TOPO and CY	1-year OS 61%	25
GEMDOX	1-year OS 43%	26
With HDTx vs w/o HDTx	2-year EFS 45% vs 10%	27
Pazopanib	PFS 4.6 months	28
IGF-1R monoclonal antibody	median OS 7.6 months	29
Robatumumab	median OS 6.9 months	30
Talazoparib and TMZ	SD 20%	31

CPT-11, irinotecan; TMZ, temozolomide; TOPO, topotecan; CY, cyclophosphamide; GEMDOX, gemcitabine and docetaxel; IGF-1R, type 1 insulin-like growth factor 1 receptor; TTP, time to progression OS, overall survival; EFS, event-free survival; RFS, progression-free survival; SD, stable disease

DISCUSSION

Renal tumor is observed in 7% pediatric malignancies and the most common one is Wilms tumors [7-9]. On the other hand, renal cell carcinoma is more frequent in teenagers [9]. The other renal tumors are medullary carcinoma, angiomyolipoma accompanied with tuberous sclerosis complex, metanephric adenoma/fibroadenoma, and lymphoma [8]. One of the rare renal tumors is ES, representing only 1% of childhood renal cancer [9, 10].

It is difficult to make preoperative diagnosis for ES because few serum tumor markers are available [7]. NSE is a specific tumor marker for neuroendocrine tumors (NETs) [11]. Patients with neuroblastoma, the most common pediatric NETs tumors, have high titer of NSE [11]. ES is also considered to be a NETs-family tumor [1]. Little is known that serum NSE, not immunohistochemical NSE, is a biomarker for ES. Only one paper reported that elevated NSE prior to therapy was found in 44% of patients with localized ES and in 80% with metastatic ES [12]. Our case had an elevated NSE and metastatic lesions at the time of onset. These suggested that it is necessary to differentiate ES when adolescent patients have a metastatic renal tumor with high value of serum NSE.

Two reports summarized clinical features of patients with ES of the kidney [13, 14]. Median onset age was approximately 30 years old (range, 8-78 years). Only 3 patients was under 18 years of age. Male patients were more predominant than female. The most common initial symptoms were flank pain and hematuria. Other non-specific symptoms include fever, weight loss, night sweats, nausea and vomiting. The median largest tumor dimension was greater than 10 cm (range, 2-35 cm). Metastasis at diagnosis was frequently found (more than 40%). The most common metastatic site was lung, subsequently bone. The definitive diagnosis of ES of the kidney was based on immunostaining and molecular genetic analysis. Our patient was an adolescent (15-year-old) girl having abdominal discomfort. Tumors were found at diagnosis in kidney besides lung and bone. The maximum tumor size was 20 cm. Compared with previous reports of ES in the kidney, clinical features in our case were similar except for young onset age. These suggested that it is important to differentiate ES for childhood patients of large renal tumor with metastasis.

Regardless of metastasis, most patients undergo nephrectomy and chemotherapy including VDC/IE, VCR + Adriamycin +CY (VAC), and VAC + dactinomycin (VACD) [2, 5, 13, 14]. The chemotherapeutic agents were not different between skeletal and extraskeletal ES such as renal ES. Radiotherapy was performed for patients whose tumors could not be completely removed. Patients with localized ES of the kidney have shown excellent survival with an overall survival rate of more than 5 years [13, 14]. On the other hand, the prognosis of patients with metastases was poor with survival of only about 15 to 17 months. Our patient took multimodal therapy including nephrectomy, chemotherapy (VDC/IE) and high-dose chemotherapy with auto-PBSCT. However, it had recurred in lung and bone 6 months after auto-PBSCT and then recurrent tumor had been chemotherapy-resistant. There is no standardized treatment strategy for patients with metastasis and relapse [2, 5, 15-31] (Table 1, 2). Therefore, it is important to develop new treatment for patients with advanced ES. Some translational researches and clinical trials are currently underway for patients with refractory ES [32]. These include ganitumab, mTOR inhibitor, Anti-GD2 antibody, eribulin, multi-targeted tyrosine kinase inhibitor, cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors, and poly-ADP-ribose polymerase (PARP) inhibitors. It is necessary to build a platform to clarify the effectiveness of new therapeutic agents for a small number of patients such as advanced ES.

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