A 9-YEAR OLD GIRL WITH METASTATIC EWING’S SARCOMA

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ABSTRACT

Ewing's sarcoma is a common primary malignant bone tumor in childhood. It has usual predilection at the diaphysis of long bone, scapula and pelvic. This case showed unusual multiple site of metastatic Ewing's sarcoma in a 9-years-old girl. We reported a patient diagnosed with Ewing's sarcoma that involved right femur, cruris, pelvic and right frontal bone. Chemotherapy was done with four drug regimen (VACD) and gave significant progress of patient condition.

Keyword: Ewing's sarcoma, unusual metastatic tumor

INTRODUCTION

Ewing’s sarcoma is the second most common primary malignant bone neoplasm in children and adolescent after osteosarcoma. Often occurs in young patients 5-25 years old, Ewing’s sarcoma is more common in males. Its predilection is at the long bones, costae, scapula and pelvis although various other bones may also be involved.1,2,3

Clinical presentation of Ewing’s sarcoma can be either local or systemic manifestations. Local manifestations include: local pain and swelling in the area of the femur or pelvis bone though others may be involved. Systemic manifestations typically include: fever, malaise, and weight loss.1,4,5,6,7 Laboratory results show leukocytosis, anemia, elevated erythrocyte sedimentation rate (ESR) and lactate dehydrogenase (LDH).4,5 Histological finding reveals uniform small round-cells.4,5,6

Roentgenographic appearance of Ewing’s sarcoma shows lesion with ill-defined, permeated or moth eaten-type bone destruction. Also aggressive periosteal reaction and soft tissue mass.1,3,4,6,7 CT scan shows bone destruction and can determine the extent of tumor extension into the medulla and joints. CT scan is very helpful pointing out extra osseous involvement.7,8,9 But MRI is a method of choice for tumor staging. MRI is essential for definite demonstration of the extent of intraosseous and extraosseous involvement by this tumor. In particular, MRI may effectively reveal extension through the epiphyseal plate. T1-weighted images show intermediate to low signal intensity, which become bright on T2 weighted images. Hypocellular region and areas of necrosis are of lesser intensity. Imaging after injection of gadolinium-diethylene triamine pentaacetic acid (Gd-DTPA) reveals signal enhancement of the tumor on T1-weighted sequences. Enhancement occurs only in the cellular areas, allowing differentiation of the tumor for peritumoral edema.4,6

Age and location of the lesion are important factors to exclude the differential diagnosis. Ewing’s sarcoma is often confused with osteomyelitis, osteosarcoma, eosinophilic granuloma, lymphoma and metastatic neuroblastoma.1,4,7

Ewing’s sarcoma treatment protocol begins with 3 to 5 cycles of chemotherapy before radiation. Rosen et al reported that vincristine, actinomycin-D, cyclophosphamide and doxorubicin combination drug regimen (VACD) with radiotherapy could extend long term survival rate.

Prognostic factors in Ewing’s sarcoma are
determined by the presence or absence of distant metastases. The prognosis of Ewing’s sarcoma is likely bad.6

EWING’S SARCOMA

Etiology, incidents, clinical, laboratory and histological findings

Ewing’s sarcoma is a malignant tumor that often occurs in young patients. Its etiology involves genetic exchange between chromosomes that cause cells to become cancerous. Most causes of Ewing’s sarcoma are the result of translocation between chromosomes 11 and 22, which fuses the EWS gene on chromosome 22 to the FLI1 gene on chromosome 11.2,10,11

Ewing’s sarcoma mostly occurs in age 5-25 years (peak incidence 10-15 years old), the majority found in male (55 %) than women (45 %). Predilections of Ewing’s sarcoma are at the diaphysis of long bones, costae, scapula and pelvis. In the pelvis, this tumor usually appears on the iliac bone with a large soft tissue mass.1,4,6 Ewing’s sarcoma less affects the skull, i.e.: maxilla, frontal, parietal, ethmoid, temporal bones. Frontal and parietal convexities are the common site of occurrence.12,13 Peersman et al9 reported that 31.25% case of lesion presented in pelvis, 20.3% in femur, 11% in tibia, 9.4% in humerus, 7.8% in fibula, 6.25% in scapula and 4.7% in costae. When confronted with patients older than 30 years old, the clinician must first eliminate other small round-cell tumors, including such as large-cell lymphoma before making a diagnosis of Ewing’s sarcoma.6

Ewing’s sarcoma typically progresses quite rapidly. Skeletal lesion typically progress to large tumors that form in soft tissue within a few weeks. The earliest symptom of Ewing’s sarcoma is pain. At first, the pain can be intermittent and mild, but rapidly progresses to the point at which it becomes so intense as to require the use of analgesic medications. Pain may be present for month and years before patient seek medical attention. When the tumor is vertebral (paraspinal) located or pelvic in origin, the pain may be accompanied by paresthesia.6

Clinical manifestation of Ewing’s sarcoma may be local or systemic. Local manifestations include localized pain and swelling. Soft tissue mass is frequently seen in the area surround the tumor and often palpable and sometimes shows visible fluctuation erythema caused by tumoral bleeding. Systemic manifestations frequently occur, which is typically including fever, fatigue/malaise, anemia and weight loss.1,4,5,6,7

Laboratory results show leukocytosis, anemia, or elevation of ESR and LDH. This condition can be confused with infectious causes such as osteomyelitis and often cause delayed diagnosis of Ewing’s sarcoma.4,5

Histologically, Ewing’s sarcoma is composed of homogeneous population of small round cells with high nuclear to cytoplasmic ratios that are arrayed in sheets. The cells show scant cytoplasm, which is pale, vacuolated and characterized by faded boundaries. Cytogenetic or immunohistochemical studies are often required to differentiate Ewing’s sarcoma from other small round-cell tumors. The t(11;22)(q24;q12) translocation, which is the most common translocation diagnostic for Ewing’s sarcoma, is present in more than 85% of cases.4,5 In contrast to lymphomas which are giving PAS-negative and reticulin-positive staining, Ewing’s sarcoma is often PAS-positive (owing to intracellular glycogen) and reticulin-negative.6

Imaging findings

On plain radiograph, Ewing’s sarcoma appears as an ill-defined, permeative, or focally moth-eaten, destructive intramedullary lesion accompanied by an aggressive periosteal reaction. Several types of periosteal reactions have been observed: (i) ‘onion skin’ or ‘onion-peel appearance’ is a prominent multi-layered periosteal reaction, (ii) ‘sun-burst’ or ‘spiculae’ pattern is a perpendicular periosteal reaction, and (iii) ‘Codman’s triangle’ is a triangular lifting of the periosteum from the bone at the site of detachment. Although the sunburst type of periosteal reaction can be found in Ewing’s sarcoma, it is less common in comparison with its occurrence in osteosarcoma. Large soft tissue mass often accompanies the tumor. Soft tissue
augmentation tend disproportionately compared to the damage/destruction of bone, particularly in the pelvic bone. 1,3,4,6,7

CT scan shows bone destruction and provides more information about attenuation value (Hounsfield Unit) of the lesion, instead of determines of tumor extension into the medulla or joints. CT scan is very helpful pointing out an extra osseous involvement of the tumor. Tumor size can be evaluated using CT Scan with contrast, which is often used for post chemotherapy evaluation. 7,8,9

Magnetic resonance imaging (MRI) is a method of choice for tumor staging. This modality is useful for assessing soft tissue involvement, which the tumor has low intensity signal on T1-weighted (T1WI) compared to normal tissue which has high signal intensity. On T2-weight (T2WI), the tumor appears hyperintense (high signal intensity) compared with muscle. MRI is also can evaluate response to chemotherapy and radiation treatment. 6,7,8

On radioisotope bone scan, Ewing’s sarcoma showed increased uptake technetium-99m methylene diphosphonate (99mTc-MDP). Increased uptake occurred in the area of bone destruction. Whole body scans are used to detect metastatic lesions. Metastases may be present in up to 30% of cases at time of diagnosis. 7,8,9

Differential diagnosis

Age and skeletal location may be important factors in narrowing the differential diagnosis. Ewing’s sarcoma is often confused with osteomyelitis, eosinophilic granuloma (Langerhans Cell Histiocytosis), osteosarcoma, lymphoma and metastatic neuroblastoma.

Osteomyelitis has shorter duration of pain and less aggressive periosteal reaction than Ewing’s sarcoma. Imaging presentation of osteomyelitis reveals predominant reactive changes, including periosteal reaction, sclerosis and edema. Infection is seen in all ages and no typical location. Eosinophilic granuloma is a benign bone tumor, which imaging finding presents as a well-defined lesion with solid periosteal reaction. 1,4,7

Osteosarcoma commonly occurs in long bones of young patients. Instead of osteolytic or bone destruction with typical sunburst or Codman’s triangle, its imaging presentation is sclerotic/osteoblastic lesion in the metaphysis of long bone. Sometimes there are homogeneous, cloud-like osteoid depositions in soft tissues.

To distinguish Ewing’s sarcoma with lymphoma, lymphoma lesions tend to occur in old age. Primary lymphoma of bone also presents with permeative pattern of destruction and often a large soft tissue mass, but usually absence of periosteal reaction. Clinical findings tend to not show severe pain. Last, metastatic neuroblastoma occurs in younger age (the first 3 years), whereas Ewing’s sarcoma is uncommon in the first 5 years. 1,4,7

Staging

Enneking et al created a staging system for both benign and malignant musculoskeletal tumors. The system, based on the histological grade of the tumor, local extent, and the presence or absence of metastasis, integrates the most significant prognostic factors into a set of progressive stages that can help to guide surgical and adjuvant treatments. High-grade lesions, such as Ewing’s sarcomas, are designated as stage II tumors, which can be subdivided according to the extent of local growth. While stage IIA lesions are contained within well-defined anatomical compartments, stage IIB lesions extend beyond their compartment of origin. Stage III includes any lesion that has metastasized, regardless of the size or grade of the primary tumor. Almost all Ewing’s sarcomas fall into stages IIB or III. 6

Clinical staging and histological staging according to the AJCC Cancer Staging 2010 has been applied for all types of bone sarcoma. Clinical staging of Ewing’s sarcoma refers to TNM classification of bone sarcoma. On histological staging, Ewing’s sarcoma is classified as G4. 14
TNM classification of Bone Sarcoma

Primary Tumor (T):
- Tx Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- T1 Tumor less than 8 cm in greatest dimension
- T2 Tumor more than 8 cm in greatest dimension
- T3 Discontinuities tumor in the primary bone site

Regional lymph nodes (N):
- Nx Regional lymph nodes cannot be assessed
- N0 Regional lymph node metastasis
- N1 Regional lymph node metastasis

Distant Metastasis (M):
- M0 No distant metastasis
- M1 Distant metastasis
- M1a Lung
- M1b Other distant site

Histological staging of Bone Sarcoma
- Gx Grade cannot be assessed
- G1 Well differentiated - low grade
- G2 Moderately differentiated - low grade
- G3 Poorly differentiate
- G4 Undifferentiated

Table 1: TNM Classification and histological staging of all types of bone sarcoma according to AJCC Cancer Staging 7th ed, 2010

Management

All patients with Ewing’s sarcoma, despite already had metastases should be treated as well as possible. Successful treatment needs cooperation between the surgeon, chemotherapist and radiotherapist to ensure an effective approach to control the primary lesion and spread of the tumor.15

Ewing’s sarcoma treatment protocol is now often begins with 3 to 5 cycles of chemotherapy before radiation. Currently, most clinical centers performing intensive chemotherapy are reporting long-term survival rates between 60 and 70%, suggesting that Ewing’s sarcoma is sensitive to anti-cancer agents. Current anti-cancer drugs proven effective for the treatment of Ewing’s sarcoma are doxorubicin (DXR), cyclophosphamide (CPA), vincristine(VCR), actinomycin-D (ACT), ifosfamide (IFM), and etoposide (VP16).6

Rosen et al6 reported that the combination of VADC four-drug regimen (vincristine, actinomycin-D, cyclophosphamide and doxorubicin) with radiotherapy led to the long-term survival of 12 patients with Ewing’s sarcoma.

Most Ewing’s sarcoma has well chemotherapy respond to the increased formation of bone sclerosis and soft tissue mass reduction. Percentage change and the size of the soft tissue mass is an important prognostic measures.6,15,16

Initial radiotherapy is considered in patients with vertebral compression and airway obstruction caused by the tumor. Radiation therapy uses high-energy usually to destroy or kill the cancer cells from the tendency to grow and metastasize. This therapy can only be used for specific areas. Radiation cannot be used for areas that are not localized or cancer cells that have spread to parts of the body. There are two ways of radiotherapy routes, external and internal radiotherapy. External radiotherapy defined by sending a high-level of radiation energy coming from the engine directly on the tumor. Internal radiotherapy or brachytherapy, usually done by implanting radioactive material close to cancer. Ewing’s sarcoma is relatively sensitive to radiation. When localized, radiation therapy is the mainstay of therapy but are more effective when combined with chemotherapy.17

Prognosis

The most unfavorable prognostic factor in Ewing’s sarcoma is the presence of distant metastasis at diagnosis. The prognosis of Ewing’s sarcoma likely bad. Mortality in the first years after diagnosis is approximately 95%. Lately, combination of radiotherapy, chemotherapy and surgery increased its prognosis. Fever, anemia, elevation of the number and values of WBC, ESR and LDH have been reported to indicate more extensive disease and a poorer prognosis. Long-term follow up in Ewing’s sarcoma patient is important because of toxic effect of doxorubicin such as cardiotoxicity.6 The most dangerous side effect of doxorubicin is heart damage. When the cumulative dose of doxorubicin reaches 550 mg/m², the risks of developing cardiac side effects, including congestive heart failure (CHF), dilated cardiomyopathy and death, dramatically increase.18
Staging attempts to distinguish patients with localized tumors and patient with metastases. Usually metastases occur in the chest, bone and/or bone marrow. Less common site of metastases is in central nervous system and lymph nodes.11

Five-year survival rate for localized tumors was 70%-80% when treated with chemotherapy. Long-term survival for metastatic disease can be less than 10 % but some clinical center declare 25-30 %.6,19

CASE ILLUSTRATION

A 9 years-old female patient who came from Negara – Bali, was admitted to the hospital on February 3, 2012, with main complaint could not walk because of weakness of the knee and leg. She also claimed about intermittent pain on the right hip and knee since 4 months before admission, which required analgesic drug. Sometimes she suffered from fever. She also presented with swelling on the right forehead. There was a history about felt down and her head hit the floor. She had already treated in the State Hospital 1 month before, but her condition got worst. Three weeks before admitted to the hospital, she was complaint about fatigue, stiffness and legs pain, and the swelling on the right forehead became enlarge.

Her general status was within normal limit. Heart, lung and abdomen condition were normal. On physical examination, there were several palpable masses noted: on right forehead with size 8 x 5 cm, on right knee with size 8 x 4 cm, and on the right gluteal with size 2 x 2 cm.

Her laboratory result showed increase of CRP (67.65 mg/dL), LDH (1.129 U/l), LED (LED I: 1 mm; LED II: 30 mm), WBC (11.3 x 10$^3$ /uL), and decrease hemoglobin (9.6 g/ dL). She also performed VMA maker (a neuroblastoma marker) examination that showed normal value (≤ 8 mg/24 hours).

She underwent several radiography examinations on December 6, 2011 at the State Hospital. Radiograph of the right knee revealed cortical bone destruction at the right distal femur and right proximal tibia, presence of periosteal reaction and soft tissue mass that firstly impressed as osteomyelitis of the right distal femur and right proximal tibia.

Repeated radiographs of right and left knee, pelvic, chest and skull were performed on Februari 3, 2012, and showed multiple osteoblastic and osteolytic lesions with periosteal reaction (Fig. 3-5).

She also performed head CT scan examination that revealed osteolytic lesion with bone destruction on the right sphenoid wing, extended up to the right frontal bone, accompanied by sunburst periosteal reaction and surrounding soft tissue mass. There were tumor involvements into the extraocular muscle and into intracranial part. Those findings impressed manifestation of

Figure 1. Soft tissue mass on the right forehead (a), right knee (b) and right gluteal (c).
A 9-YEAR OLD GIRL WITH METASTATIC EWING’S SARCOMA

Figure 2. Right knee radiograph AP/lateral projection showed cortical bone destruction in the right distal femur and right proximal tibia, accompanied by periosteal reaction and soft tissue mass.

Figure 3. Right and left genu radiograph AP and lateral projection showed multiple osteoblastic and osteolytic lesions with permeative type bone destruction in the right and left distal femur, right and left proximal tibia, with the presence of periosteal reactions.

Figure 4. Pelvic roentgenogram (a) showed multiple osteoblastic mixed with osteolytic lesions on right and left ilium, body of the 4th and 5th lumbar spine, and left pubic bone. Skull roentgenogram (b) showed multiple osteoblastic lesions on tabula externa and interna, also wall destruction of the right orbital roof.

Figure 5: Chest roentgenogram AP/Lateral showed multiple osteolytic lesions on the left proximal humeral, also on the right and left scapula. A well defined opacity also noted on the lower right hemithorax, suspicious of right pleural thickening.
malignant bone tumor on the right sphenoid wing and right frontal bone (Fig. 6).

Pelvic CT Scan revealed permeative-type bone destruction with periosteal reaction (sunray appearance) on several bones (Fig. 7).

On February 20, 2012, she performed FNAB on the right femur, right crus, right forehead head region and the result was similar with small round cell tumor. The differential diagnosis of FNAB finding was PNET (Ewing Sarcoma) and Non-Hodgkin Lymphoma (NHL).

Based on the clinical presentation, imaging findings and FNAB examination, this patient was diagnosed as Ewing’s Sarcoma, and received 3 phase chemotherapy planning according to Ewing’s sarcoma protocol.

Phase I chemotherapy was using intravenous vincristine 1.5 mg/m², cyclophosphamide 500 mg/m², doxorubicin 60 mg/m². Phase II chemotherapy was using intravenous actinomycin-D 0.0015 mg/kg, vincristine 1.5 mg/m², cyclophosphamide 500mg/m², doxorubicin 60 mg/m². Phase III chemotherapy was using intravenous actinomycin-D 0.0015 mg/kg, vincristine 1.5 mg/m², and cyclophosphamide 500mg/m².

After chemotherapy until phase 2a (15 times), there was significant progress of patient condition (Fig. 9)

On June 12, 2012, head CT scan was performed and the result showed visible improvements after 15 times chemotherapy (Fig. 10).

On follow-up on December 26, 2012, the patient’s general condition was excellent. Complaints of pain in the knees and hips are no longer perceived. There was no mass on the right forehead, right knee and right gluteal.

On September 19, 2013, patient underwent chemotherapy in early phase 3a. After chemotherapy she was difficult to breath. She was treated in intensive care unit because of her condition got worst. On September 21, 2013 she died because of cardiac complication. The final result of chest radiograph was pleural effusion and

Figure 6: Head CT Scan axial slices without and with contrast administration showed: (a) Osteolytic lesion with bone destruction on the right sphenoid wing that extended up to the right frontal bone, accompanied by sunburst periosteal reaction (b) and surrounding soft tissue mass. There were also several involvement of the mass into right orbital cavity, lateral rectus muscle, right frontal sinus, sphenoid sinus and intracranial region (c).


**Figure 7**: Pelvic CT Scan revealed permeative-type bone destruction with periosteal reaction (sunray appearance) on the right iliac wing, acetabulum and superior ramus of the right pubic bone with a large soft tissue mass surrounding the lesion. The same lesions also noted on the right one-third distal femur bone and on the left iliac bone.

**Figure 8**: FNAB examination on right femur region (a), right cruris region (b), right frontal region (c) showed small round cell tumor with pseudo rosette picture.
cardiac enlargement.

### Ewing’s Sarcoma Chemotherapy Protocol

<table>
<thead>
<tr>
<th>Phase I (weeks 0-8)</th>
</tr>
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<tbody>
<tr>
<td>Phase II (weeks 9-68)</td>
</tr>
<tr>
<td>Phase 2a (weeks 9-15)</td>
</tr>
<tr>
<td>Phase 2b (weeks 19-25)</td>
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<td>Phase 2c (weeks 29-35)</td>
</tr>
<tr>
<td>Phase 2d (weeks 39-45)</td>
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<td>Phase 2e (weeks 49-55)</td>
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<tr>
<td>Phase 2f (weeks 59-65)</td>
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<tr>
<td>Phase III (weeks 69-98)</td>
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<tr>
<td>Phase 3a (weeks 69-75)</td>
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<td>Phase 3b (weeks 79-85)</td>
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<td>Phase 3c (weeks 89-95)</td>
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**Table 2**: Ewing’s Sarcoma Chemotherapy Protocol

**DISCUSSION**

Our patient was initially treated at the State Hospital, with radiographic impression as osteomyelitis of the right distal femur and right proximal tibia. This condition often find in diagnostic work-up of Ewing’s sarcoma since the symptoms are not specific and similar with osteomyelitis. Our patient complaint was about pain in the knee, with intermittent administration of analgesics, sometimes accompanied with fever, and also had systemic manifestations such as fatigue and anemia, which these conditions can be found in osteomyelitis. The appearance of radiographic finding was also similar with osteomyelitis.

On repeated radiographs (right and left left knee, pelvic, chest, skull AP, as well as pelvic and head CT scan), increased the suspiciousness of bone malignancy. Based on the patient condition, as a young patient (9 years old), who presented permissive-type cortical destruction on diaphysis of the long bones (tibia, femur), pelvic, scapula and accompanied by aggressive periosteal reaction (Codman’s triangle and sunburst appearance), the diagnosis was lead to Ewing’s sarcoma.

Ewing’s Sarcoma can affect all bones, but is slightly more common in tubular bones. The flat bones that most often involved are iliac, ischium and scapula. More than 50% patients have soft tissue component. Our patient presented tubular bone (tibia and femur) and flat bone (pelvic bone) involvement, with surrounding soft tissue mass. Pelvic CT scan with contrast showed permissive-type bone destruction with sunray periosteal reactions on the right iliac wing, acetabulum and superior ramus of the right pubic bone with large soft tissue masses around the lesion. The same lesions also appeared on the right one-third distal femur bone and left iliac bone.

Ewing’s sarcoma that affects the skull accounts for only 1 to 6% of total case and usually develops in patients younger than 20 years old. Primary Ewing’s sarcoma of the skull typically respects dural planes and often presents as an expansive mass causing symptoms of increased intracranial pressure. Within the skull, Ewing’s sarcoma affects the frontal and parietal bone. Our patient had an expansive mass on the right forehead with proptosis of the right ocular bulb. Her head CT scan showed osteolytic lesion with bone destruction on the right sphenoid wing, extended up to right frontal bone, accompanied by sunburst periosteal reaction and surrounding soft tissue mass that infiltrated into the right lateral rectus muscle and pushed right ocular bulb to the anterior and medial.

Affirmation against Ewing’s sarcoma strengthened after FNAB examination in the right femur region, right cruris region, right frontal region, which showed similar appearance with small round cell tumor. Literature overview of histopathology finding of Ewing’s sarcoma is uniform small round cell tumor. However, some other tumor have similar histologic finding, such as lymphoma. But, radiologic finding of our patient was more tend to Ewing’s sarcoma than lymphoma.

Based on this diagnosis, patients underwent chemotherapy using vincristine, actinomycin-D, cyclophosphamide, and doxorubicin (VACD). According to Rosen et al, four-drug combination
A 9-YEAR OLD GIRL WITH METASTATIC EWING’S SARCOMA

Figure 9: After underwent 15 times chemotherapy (late phase 2a), no visible soft tissue mass in the right forehead (a) and diminished soft tissue mass on the right knee (b).

Figure 10: Head CT Scan after underwent 15 times chemotherapy. There was no longer visible soft tissue mass in the forehead (a), only hyperostosis was noted on the right frontal bone (b).

Figure 11: Patient on December 26, 2012. After underwent 30 times chemotherapy (early phase 2c).

regimen VACD can increase long term survival rate. Most of Ewing’s sarcoma has a good response as an increase formation of bone sclerosis and soft tissue mass reduction. It was proven in this patient whose repeated head CT scan after received 15 times chemotherapy showed significant improvement, as no longer visible soft tissue mass in the right frontal region instead of a hyperostosis on right frontal bone. Physical examination after underwent 15 times chemotherapy (late phase 2a) revealed diminish soft tissue mass on the right knee. After received 30 times chemotherapy (early phase 2c), there were no visible soft tissue mass on the right forehead, right knee and right gluteal.

Although response of chemotherapy so far seems good, there is also increase awareness due to cardiotoxicity effect of some chemotherapy agent, especially doxorubicin. Patient can die because of cardiac complication. While the cumulative dose of doxorubicin reaches 550 mg/m², the risks of developing cardiac side effects including CHF, dilated cardiomyopathy and death are also increasing. Our patient has received chemotherapy until early phase 3a, with accumulative doxorubicin dose more than 550 mg/m², and she died because of cardiac complication.

SUMMARY

This case report showed about unusual multiple site of metastatic Ewing’s sarcoma, which gave manifestation as multiple osteolytic and osteoblastic processes with periosteal reaction and soft tissue mass in several bones. Although prognostic of metastatic Ewing’s sarcoma is likely bad, chemotherapy with four drug regimen (VACD) of this patient apparently showed significant progress of patient condition.

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