

Case report

Primary Non-Hodgkin's Lymphoma of the Bone: A case report

Biomedicine and Surgery

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ABSTRACT

Primary non-Hodgkin's lymphoma of the bone (PLB) is a rare entity. Patients generally present with localized bone pain, soft-tissue swelling or palpable mass. Pathological fracture of the proximal femur and humerus secondary to soft-tissue tumors is well documented in the literature. Lymphomas presenting primarily at these sites with pathological fractures are unusual. A review of the literature shows that the incidence of the skeletal manifestations from non-Hodgkin's lymphoma is less than 5%, and in all these cases, bony involvement was reported many years after the presentation of the primary cancer. Histopathologically, PLB usually represents diffuse large B-cell lymphoma. We report a 56-year-old female patient with primary non-Hodgkin's lymphoma of proximal femur with pathological fracture and management. In January 2014, a 56-year-old woman was diagnosed with stage IV B primary large-cell diffuse primary non-Hodgkin's lymphoma. After one year of initial diagnostic procedures and chemotherapy with rituximab together with cyclophosphamide, vincristine, procarbazine, and prednisolone she achieved a complete response.

KEY WORDS: primary non-Hodgkin's lymphoma of bone; pathological fracture; chemotherapy

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INTRODUCTION

Primary lymphoma of the bone (PLB) is a rare extranodal presentation of non-Hodgkin's lymphoma (NHL) (1). It was first described by Oberling in 1928 (2, 3). It accounts for approximately 3% of the malignant bone neoplasms and is comprised of less than 5% of all extranodal non-Hodgkin's lymphomas. An osseous involvement of a lymphoma is generally seen as a part of a multi-system dissemination. Primary lymphoma of the bone can be defined as a lymphoma which occurs in the bone without any evidence of a distal nodal or an extra-nodal tissue involvement (3, 4). PLB can involve any part of the skeleton, but a trend exists in favor of the bones with persistent bone marrow. The femur is the most common site and it

is affected in 29% of the cases. Other sites include the pelvis, humerus, head and neck, and the tibia (2-5). Clinical presentation depends upon the rate of tumor cell proliferation and initial localization. Patients generally present with localized bone pain and, less frequently, with soft-tissue swelling or a palpable mass. On conventional radiology, PLB has a widely variable imaging manifestations which consist of either „lytic destructive pattern“ or a „blastic sclerotic pattern“ (6). Pathological fractures may be present in approximately one quarter of cases, as seen in our patient.

Diagnostic tests typically include: complete blood cell count (CBC), peripheral blood smear, routine serum chemistries, serum lactate dehydrogenase (LDH) level, bone marrow aspirate

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and biopsy, bone biopsy, chest radiography, plain films, bone scan, computed tomography (CT) scanning and magnetic resonance imaging (MRI). When detectable, primary NHL of the bone can have a heterogeneous appearance with lytic, blastic and mixed lesions (4, 7, 8). Additional imaging features include periosteal reaction, soft-tissue extension, pathologic fractures, and cord compression (4). Radiologic differential diagnosis includes benign (reactive conditions, osteomyelitis) and malignant entities (Hodgkin's lymphoma, sarcoma, neuroblastoma, metastatic disease).

MATERIALS AND METHODS

A 56-year old female patient presented in December 2013 with pain in the chest, thoracic spine, epigastric and right scapular regions for one month duration. Clinically, the patient had a history of 3 kg weight loss and fatigue. On examination, she was found to be hypertensive (160/90 mmHg) and had no palpable hepatosplenomegaly or lymphadenopathy. Patient had a history of arterial hypertension, but took no therapy. In 2009 the patient underwent gastroenterologist's examination: upper GI endoscopy showed a moderate gastroesophageal reflux into the distal esophagus, with hyperemic, vulnerable mucosa, consistent with grade 2 gastroesophageal reflux disease (GERD). Electrocardiogram was unremarkable except for QS in V1-V3.

Antihypertensive and pain therapy was ordered and the difficulties have been reduced. After twenty days the patient was examined by neurologists because of the sudden pain in the thoracic spine that irradiated into the sternal region and in the right leg as well. She started on analgesics, but with no improvement. Neurologically, there were signs of hypoesthesia in the L4 and L5 dermatomes on the right. Lasegue test was terminally positive. The MRI of the thoracic and LS spine was recommended.

Complete blood count and blood chemistry were unremarkable except for slightly elevated C-reactive protein (CRP) that was 14.48 mg/L (reference range 0-5).

Thoracic spine X-ray showed less calcified body and arches of thoracic spine, with subchondral osteosclerosis surface plate and signs of partial degenerative spondylosis. The height of the bodies of thoracic spine vertebrae was normal. Intervertebral space between Th7 – 8 was slightly reduced. Chest radiograph and abdominal ultrasound were normal.

Gynecological, ophthalmological and dermatological examinations, as well as esophagogastroduodenoscopy (EGD), colonoscopy and MMg, were negative.

The patient was immobilized with Jewett orthosis.

One month after the initial examination by internal medicine specialist and two months of the duration of pain, the patient was reported to our Orthopedics and traumatology department with a pathological fracture of the Th5 and L2 bodies that was confirmed with MRI diagnostics. Serum calcium was 2.39 mmol/L, and Ca-dU was 6.1 mmol/L.

Computerized tomography (CT) scan of the right femur showed small lytic destructions of cortical bone, 10 cm of length in the mid-shaft of the right femur. There were no signs of bone compacta destruction or bone expansion. Pathologic substrate which infiltrated medullary marrow was also presented. According to radiological characteristics, differential diagnosis of the femoral lesion pointed to low-grade chondrosarcoma.

MRI findings revealed a large expandable lytic infiltrative lesion of the medullary canal with very discrete diffuse bone compacta destruction at the level of the mid and distal shaft of the right femur, measuring 16 cm in length (Figure 1). There was absence of bone corticalis lytic lesion (Figure 2). There were no pathological findings of extraosseal soft tissue or periosteal reaction (Figure 3). Radiomorphological characteristic were suggestive of metastasis or an osteogenic tumor.

The first biopsy of the vertebral body showed no signs of tumor tissue. The new intramedullary biopsy of the right femur was performed after seven days: seven samples were positive on vimentine and LCA, negative on pancreatokeratine, S-100 and CD 3. Histological examination showed diffuse large B-cell NHL (high grade). The biopsy report was suggestive of a lymphoproliferative disorder which involved the bone. The tissue was sent for a histopathological examination. The final pathological diagnosis was a primary lymphoma-NHL, diffuse large B-cell type (non-GC subtype) of the shaft of the femur. Immunohistochemically, cells were positive for CD20+, BCL6+, BCL2+, CD10 focal+ (less than 30% of cells), MUM1+, CD5-, CD3-, EBV-LMP1- (clinical stage IVE).

The patient received chemotherapy which consisted of cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP).

Total body scintigraphy was performed with 99m-Tc MBq 740. After 12 months of the diagnosis, there has been no relapse either clinically or radiologically.

Three years after the first symptoms and initial examination the patient still suffered cervical and lumbar spine pain with rare cases of vertigo. She

used cervical collar, Jewett orthosis and analgesics. PET-CT didn't demonstrate any signs of malignant disease or metabolic activity. The conclusion: the remission of disease has been achieved.

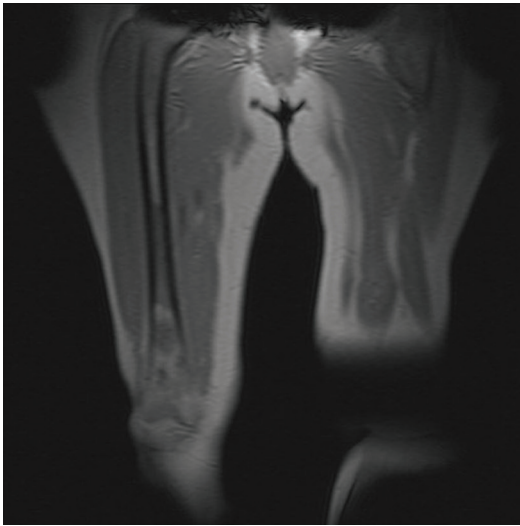


Figure 1. Coronal T1-weighted image reveals few low signal lesions in the marrow of the mid and distal right femoral shaft which contrasts with areas of high signal intensity of normal marrow fat

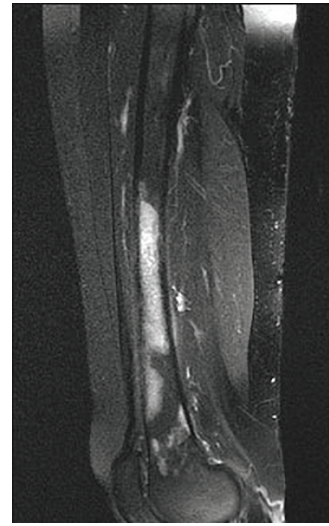


Figure 2. STIR T2-weighted sagittal image shows high signal intensity of the lesions in central and distal part of the right femur

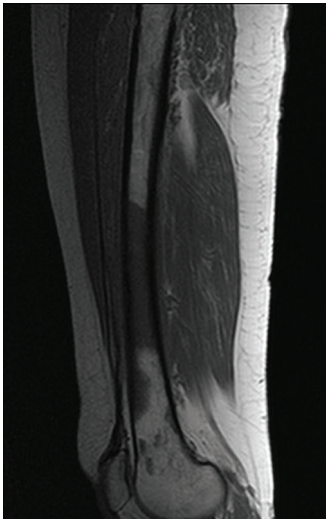


Figure 3. Sagittal T1 – weighted image reveals few low signal lesions in the marrow of the mid and distal femoral shaft without extraosseal soft tissue mass or periosteal reaction

DISCUSSION

Most cases of primary lymphomas of the bone are the NHL type and the most common pathology subtype is diffuse large B-cell lymphoma (DLBCL) (9, 10). Primary NHL of the bone (primary bone lymphoma) is a rare condition, accounting for less than 1-2% of adult NHL, and less than 7-10% of primary bone tumors (11, 12). The majority of cases are limited disease by the Ann-Arbour staging system and occur in adults of age 45-50, with male preponderance with a male to female ratio of 3:2 (2, 6-9, 13, 14).

Primary lymphoma of the bone (PLB) accounts for 3% to 7% of primary neoplasms of the bone and must be distinguished from more common bone tumors in the pediatric population such as osteosarcoma, Ewing sarcoma and other small round blue cell tumors. In this study, pathology databases from 4 institutions were queried for PLB in individuals 1 to 21 years old (15). The femur (29%) is the most common site, followed by the pelvis (19%), humerus (13%), skull (11%) and the tibia (10%) (16). Some studies have found that long bones and flat bones are equally affected (9).

The clinical presentation includes local pain, swelling and a pathological fracture.

The diagnosis is established by biopsy. CT scan of the abdomen and chest to assess the lymph node involvement and serum LDH are done as a part of the staging procedure (10). The most common pattern, the "lytic destructive pattern", described as moth-eaten or focal lyses with well-defined margins, is reported in 70% of the cases (6).

Pathological fractures of long bones, which are secondary to the soft-tissue tumors, are well documented in the literature. However, lymphomas which present primarily at these sites with pathological fractures are unusual.

In a large series of 131 patients with primary bone lymphoma over a 22-year period, one third had lymphoma involvement of long bones with pathological fractures occurring in nine patients (9). In contrast, in a retrospective analysis of 36 patients with primary (n=17) and secondary (n=19) bone lymphoma surgically treated at an orthopedic center over a 15-year period, pathological fracture of the proximal femur or humerus was observed in only three patients (3). Our patient illustrated pathological fracture secondary to lymphoma involving the femur, which is uncommon even in patients with lymphoma involvement of long bones.

In a study of sixteen patients with primary NHL in the spine, who were treated between 1994

and 2006 (17) 5 of them had radicular pain. Our patient had also radicular pain, but no motor signs of neurological deficit.

Overall 5-year survival rate is 49.6%, with a 10-year survival rate of 30.2%. Median overall survival is 4.9 years (95% CI: 3.9 - 6.1). In multivariable analysis, age ($p < 0.0001$), marital status ($p = 0.006$), and appendicular vs. axial tumor location ($p = 0.004$) is found to be independent predictors of survival (1).

Anemia, elevated lactate dehydrogenase (LDH), alkaline phosphatase (ALP), erythrocyte sedimentation rates (ESRs), platelet counts and calcium levels have been reported with primary non-Hodgkin lymphoma of the bone (4, 14).

The treatment for primary NHL of bone includes chemotherapy, and the optimal sequence of treatment is cyclophosphamide, doxorubicin, vincristine, prednisolone, rifuximab regimen (2, 7-9, 14). As necessary, stabilization of a pathological fracture will occur before the initiation of other therapies (4, 9).

Our patient received chemotherapy which consisted cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP). After 12 months from the diagnosis, there has been no relapse either clinically or radiologically. The case presented here agreed with the literature on primary bone lymphoma, in which the diagnostic problem and an excellent prognosis of a malignant tumor have been emphasized (18).

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