

Primary Bone Lymphoma – Mimicking as Osteomyelitis: An Unusual Presentation

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Abstract

Primary Bone Lymphoma is a rare disorder, even though secondary involvement of bone marrow in systemic Lymphoma is common. Most of Primary Bone Lymphomas are Primary Bone Diffuse Large B-cell Lymphomas. We describe a case of Primary Bone Lymphoma, initially treated as Osteomyelitis of unknown etiology. This case shows the difficulties that can occur while diagnosing this entity. We provide an overview of Clinical, Radiological, Pathological characteristics of these rare tumours along with review of Literature.

Keywords: Primary bone lymphoma; Primary bone diffuse large b-cell lymphoma; Mimickers of osteomyelitis

Introduction

Case Report

The clinical presentation of Primary Bone Lymphoma (PBL), a sub-type of NHL can be a challenging diagnosis. Chronic, intermittent pain of a dull aching nature may be the only presenting complaint. In current case, following detailed history, clinical examination, radiological and laboratory studies, patient was presumptively diagnosed with Osteomyelitis. Considering relative and absolute rarity of PBL, the possibility of such a rare occurrence was considered quite low on the list of differential diagnosis.

Lymphoma commonly occurs in the lymph nodes, and extranodal origin is less frequent. Primary Bone Lymphomas (PBL) is rare, even though secondary involvement of bone marrow in systemic lymphoma is common. Primary Bone Lymphoma was first described by Oberling in 1928 [1]. Parker and Jackson reported a PBL series in 1939 [2] under designation reticulum cell sarcoma of bone, establishing PBL as a distinct entity. The lymphoid and B-cell origin was subsequently proved by Immunohistochemistry [3,4].

Primary Bone Lymphomas account for 7% malignant tumours, 4 to 5% of extra-nodal lymphomas and less than 1% of all malignant lymphomas [5,6]. Most PBLs are Primary Bone Diffuse Large B-cell Lymphomas (PBDLBCL) with a rare occurrence of follicular, marginal zone, anaplastic large cell, Hodgkin and T-cell Lymphoma [5].

Case Report

A 18 yr old man complained of progressive pain in the right hip and low back on and off since January 2015. Had episodes of fever on and off. He was treated at various other hospitals with NSAIDS. This treatment relieved some, but not all, of the symptoms. Six months later, the patient presented to the clinic in our department complaining of pain in right hip and low back on weight bearing activities. He had X-ray images of pelvis that showed lytic radiolucent lesion with motheaten destructive pattern and sclerotic areas, with continuos periosteal reaction, without cortical breach or soft tissue extension in right greater trochanter/ proximal femur (Figure 1). X-ray LS spine showed sclerotic lesion involving body of L5 vertebrae (Figure 2).

The physical examination at this time revealed some pain on palpation of right greater trochanter and L5 vertebrae. Internal rotation of right hip was restricted and without any other signs of inflammation. Significant laboratory studies included: TWBC $10 \times 10^3/\mu$ l (normal 4.5 - $11 \times 10^3/\mu$ l), CRP 2.2 mg/dl (normal 0-1.0 mg/dl), ESR 52/84 mm

(normal 1-13 mm/hr), serum Alkaline phosphatase 94 U/L (normal 60-170 U/L). CT Scan confirmed the X ray findings. MRI Scan was done which showed high intensity signals on T2W images in L5 Vertebral body, (R) Proximal femur, and both Ilium. Due to history, morphology on X-ray, CT scan (Figure 3) and MRI Scan (Figure 4), and Laboratory investigations, Multi-focal Osteomyelitis was suspected. Empirically, patient was started on Antibiotics. No micro-organisms were isolated from cultures of the blood. Patient couldn't get relief from pain with antibiotics and analgesics.

To confirm the diagnosis, Open biopsy of right greater trochanter was done. Grossly, the material consisted of haemorrhagic and highly



Figure 1: X-ray images of pelvis that showed lytic radiolucent lesion with moth-eaten destructive pattern and sclerotic areas, with continuous periosteal reaction, without cortical breach or soft tissue extension in right greater trochanter/ proximal femur.

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Figure 2: X-ray LS spine showed sclerotic lesion involving body of L5 vertebrae.



Figure 3: CT Scan showing increased sclerosis of L5 vertebrae and (R) proximal femur.



Figure 4: MRI Scan showing high intensity signals on T2W images in L5 vertebral body, (R) proximal femur, and both ilium.

sclerotic bone specimen. Microscopically, highly concentrated atypical round cell and lymphoid infiltration, areas of necrosis and foci of bone destruction was seen (Figure 5). Immunohistochemical stains were positive for CD45 (Figure 6), CD20 (Figure 7) and negative for CD3 (Figure 8), CD99 and Desmin. Based on these results, the diagnosis of Non-Hogdkins Lymphoma (Diffuse Large B-cell Lymphoma) was made. Ultrasonography of Neck, CT of chest, abdomen and pelvis were done to exclude nodal origin and distant spread, which were negative. Bone marrow aspiration was done and sent for analysis which was Patient was started on chemotherapy with CHOP-R regimen for 8 cycles. Patient had responded well with 4 cycles of chemotherapy and been pain free after that. Total 8 cycles of chemotherapy has been given to the patient. PET scan was done at the end of chemotherapy, for assessing the response and further management. PET scan showed no evidence of significant metabolically active disease in the primary bone lesion site and anywhere else in the body (Figures 9-11). Patient was



Figure 5: Microscopically, highly concentrated atypical round cell and lymphoid infiltration, areas of necrosis and foci of bone destruction.



Figure 6: Immunohistochemical stains were positive for CD45.



Figure 7: Positive for CD20



Figure 8: Negative for CD3.



Figure 9: Total 8 cycles of chemotherapy has been given to the patient.



Figure 10: PET scan was done at the end of chemotherapy, for assessing the response and further management.

given local radiotherapy with a RT dose of 40 Gy for 3 cycles to prevent local recurrence. Patient is on follow-up 4 months post-chemotherapy with 3 more cycles of radiotherapy to undergo. There is no evidence of recurrence to date.

Discussion

The criteria for a diagnosis of Primary Bone Lymphoma was established by Giudici et al. [7] in 1992, (a) on presentation, the patient

demonstrates a primary focus in a single bone; (b) histological proof should be obtained from skeletal focus; and (c) the onset of symptoms of primary skeletal lesion should precede the distant metastasis by atleast six months. In 2005, [8] states that following criteria should be met, (a) solitary bone lesion or multiple skeletal lesion with no prior involvement of lymph nodes or other lymphoid tissue; (b) Histological documentation of Lymphoma in the bone; (c) no lymph node involvement or involvement of regional lymph nodes. All of the above criteria were fulfilled in our case.

There are other case reports in literature where Primary bone lymphoma has been misdiagnosed as infection. [9] Published a case series of three lymphomas masquerading as infection, [10] reported three cases of anaplastic large cell bone lymphoma in children of which two appeared as primary tumour, [11] published three cases of PBL treated as Osteomyelitis.

Due to non-specificity of clinical and radiological features, diagnosing this entity is very difficult, without high level of suspicion, the differential diagnosis include Chronic Osteomyelitis, small round cell tumours, Primary bone tumours, Eosinophilic granuloma. Here we reviewed the clinical features, radiological features, gross and microscopic findings, IHC findings, prognosis and treatment of PBDLBCL.

Clinical features

Most commonly affects the middle aged to elderly population. However, it has been described in paediatric patients as well [10,12]. There is male predominance with Male: Female ratio of 1.5:1. The most common presentation of patients with PBDLBCL is bone pain and less frequently by palpable mass and pathological fracture. Very rarely, neurological symptoms such as paraplegia can occur due to cord compression. Systemic symptoms (B-symptoms) such as weight loss, fever, and night sweats are very rare. Rarely, lethargy, constipation, and somnolence can occur due to hypercalcemia [6].

Anatomic location

According to Beal et al. [13], the frequency of different bone involvement was femur (27%), pelvis (15%), tibia/fibula (13%), humerus (12%), spine (9%), other (5%). According to reference [14], femur (34%), humerus (21%), pelvis (17%) and tibia/fibula (17%). In



Figure 11: PET scan showed no evidence of significant metabolically active disease in the primary bone lesion site and anywhere else in the body.

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the long bone, preferred site is meta-diaphyseal region. Rarely, small bones of hand and feet are involved.

Radiological features

On X-rays, primary lymphoma of bone have a variable radiographic appearance and lack specificity [15]. Some are lytic and some are sclerotic lesion. But, most of them are lytic radiolucent lesions with moth-eaten or permeative destructive pattern. This may be associated with sclerotic areas. Cortical erosion and soft tissue extension is frequently seen. Periosteal reaction (continuous or interrupted) can be present. In some cases, tumour may evoke a sclerotic response and present as Osteoblastic lesion, which can be mistaken for Pagets disease or Osteoblastic metastasis [16].

Pathological features

Grossly, Soft fleshy gray-white or haemorrhagic appearance with sclerotic bone specimen [5]. Microscopically, diffuse growth pattern with tumour cells permeating between bony trabeculae and invading haversian canals. There is often a sclerotic stroma and tumour cells can invade in nests, cords or solid sheets. PBDLBCL shows a polymorphous appearance. Tumour cells show marked variation in size and shape with multilobulation, that are accompanied with reactive B and T cells. Occasionally, lymphoma shows immunoblastic morphology with round nuclei, prominent nucleoli and abundant amphophilic crystals [17]. Tumour cells may be crushed during biopsy procedure, which may lead to difficulty in diagnosis. Prolonged decalcification may affect cytological features and Immunohistochemical staining [16].

Immuno-histochemical staining

The tumour cells in PBDLBCL are positive for CD45, CD20, CD79a, PAX5 (B cell markers) and negative for CD3 and CD5 (T cell markers). PBDLBCL can be further divided into germinal centre type and nongerminal centre type by using CD10, BCL6, MUM1 antibodies [18] Germinal centre B-cell type has a better prognosis than non-germinal centre B-cell type, even with addition of rituximab [19].

Treatment

Most PBDLBCL are treated with combined radiotherapy and chemotherapy, with good outcome [20]. The radiotherapy dose ranges from 2000-6150 centigrays (cGy) with a median dose of 4400 cGy. Chemotherapy usually consists of CHOP-R (cyclophosphamide, doxorubicin, vincristine, prednisolone with or without rituximab). According to [21], combined chemotherapy is vital in the treatment of PBL. Chemotherapy followed by Radiotherapy is superior in improving overall survival rate. Although chemotherapy was superior to radiotherapy alone, radiotherapy plays a role in local control. Radiotherapy is better in preventing local recurrence when compared to surgical curettage. An RT dose of >40 Gy for 6 cycles and more than 6 chemotherapy cycles are associated with a good outcome.

Prognosis

A study by Beal et al. [13] in 81 patients, 46 patients (56%) received combined therapy, 24 patients (29%) received chemotherapy and 11 patients (13%) received radiotherapy. The 5 yr overall survival rate was 88%. In a study by Cai et al. [22] 3 yr progression free survival in patients who received CHOP-R was 88% compared with 52% for those who received only CHOP. The 5 yr overall survival ranges between 56% and 61%.

Conclusion

Primary Bone Lymphoma is a very rare entity with

morphological and radiological heterogenecity. The histological and immunohistochemical similarities, ranging from benign conditions such as Osteomyelitis to small round cell tumours, should be borne in mind while assessing these neoplasms to avoid misdiagnosis and inappropriate treatment. Delays in diagnosis can have serious effects on the prognosis of the disease, in which the stage is considered as most important prognostic indicator [23]. Therefore it is essential to diagnose a lesion prior to leukaemic spread or metastasis. Thus in patients with osteomyelitis like symptoms and bone pain refractory to medical treatment, a thorough diagnostic work-up should be undertaken, and unusual neoplasms such as this haematopoetic malignancy should be considered in differential diagnosis [24].

By reviewing our case and other literature, we have come to the same conclusions as [9]: Surgeons should return to the basics of culturing all suspected tumours and obtaining a biopsy specimen of all presumed infections, even in instances of positive cultures or negative biopsy specimens. Significant worsening of symptoms in chronic osteomyelitis requires thorough work up with appropriate imaging studies, and excision of an additional biopsy specimen.

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