

Primary Diffuse Large B -Cell Lymphoma of Bone: A Series of 3 Cases and Review of Literature.

Dr. Ranti Ghosh¹, Dr. Somnath Roy¹, Dr. Rajib Bhattacharjee¹

Department of Radiotherapy, I.P.G.M.E &R, India

Abstract: Primary bone lymphoma (PBL) is an uncommon tumor accounting for approximately 4-5% of extra nodal lymphoma and less than 1% of all non-Hodgkin's lymphoma (NHL). Disease may be complicated at presentation by pathological fracture or spinal cord compression. Diffuse large-B cell lymphoma (DLBCL) accounts for the majority of cases of PBL. Owing to its rarity, only a few retrospective series have been published in literature addressing the prognosis and treatment of PBL. We report our experience with three cases of PBL treated with chemotherapy and radiotherapy and review of literature to elucidate the optimal treatment of PBL.

Key words: DLBCL, Primary bone lymphoma, Treatment outcome

I. Introduction:

Malignant lymphoma of bone is a rare clinical entity. It is broadly classified into two groups: primary bone lymphoma (PBL) and secondary bone lymphoma (SBL) according to 2013 WHO Classification of Bone/Soft Tissue Tumors. PBL described as neoplasm of malignant lymphoid cells producing one or more masses within bone, without any supra regional lymph node involvement in absence of other extra nodal lesion.^[1] PBL comprises of only 7% of all malignant bone tumour, 5% of extra nodal lymphoma and less than 1% of NHL; mainly DLBCL subtype.^[2]

According to the 2013 WHO classification, PBL with or without regional nodal involvement, further subdivided into unifocal and multifocal (more than two foci) diseases. It carries good prognosis and usually treated with chemotherapy and radiotherapy. Due to its rarity; only few prospective trials describes the staging, prognosis, and treatment option of PBL cases. There is no consensus guideline to differentiate between PBL and SBL. We report our experience with three cases of PBL treated with chemotherapy and radiotherapy and review of literature to elucidate the optimal treatment of PBL.

II. Case Report:

CASE 1: 58 yrs old female presented with pain and gradually increasing swelling of left leg for last 3 months, difficulty in walking for last 1 month. No history of fever, night sweats and weight loss. On physical examination; a hard tender swelling over left leg was palpable, in absence of any peripheral lymphadenopathy and organomegaly. X-ray of left leg reveal large osteolytic lesion over upper part of left tibia with soft tissue mass along with pathological fracture. Whole body ¹⁸FDG PET-CT scan reveal large osteolytic lesion in upper part of tibia with soft tissue mass (5.1x8.5 cm²) with extensive skeletal lesion involving D4 & L4 vertebra and left femoral head ; standardized uptake value maximum (SUV_{max}) was 27.4. (Fig 1) Biopsy from osteolytic growth shows NHL of DLBCL phenotype, immune-positive for CD 20 & bcl 6 and immune-negative for CD3, CD5 & CD 10. Bone marrow trephine biopsy indicates presence of marrow involvement. She diagnosed as multifocal PBL stage IVE according to 2013 WHO Classification of Bone/Soft Tissue Tumors. She received 6 cycles of Inj Rituximab 375 mg/m² IV D1, Inj Cyclophosphamide 750 mg/m² IV D1, Inj Vincristine 1.4 mg/m² IV D1, Inj Doxorubicin 50mg/m² IV D1 and Prednisolone 100 mg per orally D1-5;(R-CHOP); 21 days interval. After 6 cycles of R-CHOP; end therapy PET CT scan shows complete remission (CR). Since last 13 months, patient was regular follow up without disease recurrence.

CASE 2: 45 yrs female presents with painful swelling over right leg for last 4 months with a hard fixed lymph node (max size 2.5 cm) palpable over right inguinal region. MRI reveals neoplastic mass in mid shaft of right tibia (5.4x6 cm²) with extension in muscular compartment and pathological fracture. (Fig 2) ¹⁸FDG PET-CT showed metabolic uptake over only right tibia (SUV_{max} 37.4). Histopathology confirms NHL of DLBCL phenotype immune positive for CD20, bcl-6 and bcl 2 with presence of marrow infiltration on marrow biopsy. She diagnosed as unifocal PBL Stage IVE. She treated with 6 cycles of R-CHOP followed by consolidate involved field radiotherapy (IFRT) upto total dose of 40 Gy in 20 fractions over 4 weeks to the primary site. Repeat PET scan revealed CR. Patient was regular follow up without disease recurrence since last 11 months.

CASE 3: 55 yr. male with painful swelling over lower part of right forearm followed by spontaneous fracture over last 5 months. X-Ray wrist joint showed expansile osteolytic lesion associated with soft tissue thickening and cortical destruction over lower metaphysis and diaphysis of right radius. (Fig 3) ¹⁸FDG PET-CT revealed

extremely intense metabolic uptake over only lower end of right radius .Histopathology confirm NHL of DLBCL phenotype; immune positive for CD20, bcl-6 and bcl 2 with absence of marrow infiltration on marrow biopsy. He diagnosed as unifocal PBL Stage IE. He received 4 cycles R-CHOP followed by consolidate IFRT upto total dose of 40 Gy in 20 fractions over 4 wks to the primary site. Post treatment PET-CT scan showed no significant uptake; achieving CR. Patient was regular follow up without disease recurrence since last 7 months.

III. Discussion:

PBL is a separate clinico-pathological entity, but remain controversial issue in literature particularly in case of regional nodal involvement or stage IV disease, at initial presentation. PBL mainly involve 45-50 years age group with male preponderance.^[3] It preferably involves femur, tibia, pelvis and less commonly spine, ribs, scapula, mandible, terminal phalanxes of hand and feet. Patients usually present with localized bone pain, soft tissue mass, pathological fracture, rarely B symptoms particularly in stage IVE disease.^[4]

Majority PBL are of NHL type, among them 54-92% are of DLBCL phenotype, but T cell NHL and primary Hodgkin variety was also reported.^[5] *Heyning et al* classified 46% stage I, 16% stage II and 16% stage IV disease of PBL cases at presentation and 20% with an unknown stage.^[6] Stage IV disease was exclusively caused by the presence of multiple bone lesions⁶. Approximately half of the primary DLBCL cases demonstrated a germinal center B-cell phenotype by immuno-histochemistry, with high Bcl-2 and or Bcl-6 expression and relatively low MUM-1 expression.^[7] Unifocal primary DLBCL carries good prognosis where as multifocal primary DLBCL carries poor prognosis, similar to SBL. Here lies the controversy, is there any necessity to distinguish multifocal PBL from SBL clinically. For comprehensive staging of PBL conventional X-Ray, MRI, USG whole abdomen, CT scan , bone marrow biopsy, ¹⁸FDG PET scan necessary. Radio logically PBL appears as solitary osteolytic lesion with moth-eaten margin in diaphysis of long bone with periosteal reaction, minimal cortical break and soft tissue extension. MRI was reported as the most sensitive imaging technique in the diagnosis of PBL.^[8] PET CT scan helps in proper staging, response assessment and detection of recurrence during follow up.^[9]

No standard guideline for PBL cases is there; conventionally unifocal primary DLBCL treated with combined chemotherapy and radiotherapy with 5 yr survival rate approximately 70-78%; whereas multifocal primary DLBCL treated with chemotherapy alone. PLB is sensitive to anthracycline based regimens and addition of IFRT where indicated; achieving excellent long term disease free survival (DFS). Progression free survival (PFS) and overall survival (OS) times in patients with CD20 positive cases have been markedly improved by adding rituximab to CHOP chemotherapy.^[10] Patient with age less than 60 yrs, localized or unifocal disease, absence of marrow involvement, low lactate dehydrogenase level, good international prognostic index (IPI) score carries superior outcome.

IV. Figure

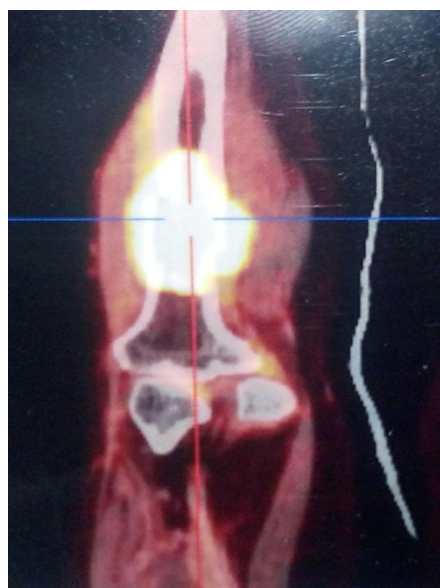


fig 1



fig 2



fig 3

Legends of figure 1:

Whole body ¹⁸FDG PET-CT scan reveal large osteolytic lesion in upper part of tibia with soft tissue mass (5.1x8.5 cm²).

Legends of figure 2:

MRI reveals neoplastic mass in mid shaft of right tibia (5.4x6 cm²) with extension in muscular compartment.

Legends of figure 3:

X-Ray wrist joint showed expansile osteolytic lesion associated with soft tissue thickening and cortical destruction over lower metaphysis and diaphysis of right radius.

V. Conclusion:

We here sharing our experience of three cases of PBL, fully evaluated, properly treated with chemotherapy and IFRT where indicated, indicating PBL has good prognosis as like other extra nodal primary lymphoma. But more prospective studies are necessary for proper staging, understanding behavior of PBL and optimum treatment guidelines.

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