Pathologic Fractures Secondary to Primary Non-Hodgkin's Lymphoma of Bone: A Report of Two Cases Treated with Surgery

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Abstract

Introduction: Primary lymphoma of bone (PLB) is a rare condition accounting for <2% of lymphomas among adults. Diagnosis is confirmed through clinical features, radiologic findings, and immunohistochemical studies. Treatment consists primarily of chemotherapy and radiotherapy. A lack of consensus remains, however, regarding the role of surgery on prognosis. Interventions with potential to improve quality of life therefore warrant further investigation. The authors report two cases of PLB treated with surgery, with favorable outcomes.

Case Presentation 1: A 21-year-old female presented with the left knee pain unaccompanied by constitutional symptoms. Imaging studies showed an isolated pathologic fracture of the left proximal tibia. Histopathology showed an atypical proliferation of large round cells, which stained diffusely and strongly positive for CD20. 90% of the cells also stained positive for the proliferation marker Ki-67. These findings were consistent with a high-grade B-Cell non-Hodgkin's lymphoma (NHL). The tibial lesion was managed with direct fracture reduction and knee arthrodesis. Six cycles of chemotherapy were completed. Current Musculoskeletal Tumor Society (MSTS) score is 28/30, without evidence of recurrence 3 years post-surgery.

Case Presentation 2: A 69-year-old male sustained a pathologic subtrochanteric fracture after falling on his left hip. Diagnostic imaging revealed no other osseous lesions. Biopsy specimens showed a proliferation of atypical lymphoid cells, and on immunohistochemistry, these were diffusely and strongly positive for lymphocyte common antigen (CD45) and CD20. This was consistent with a high-grade B-Cell NHL. After proximal femoral nailing was performed, no further treatment was given. The patient is currently 2 years post-surgery with MSTS score of 28/30, and no signs of recurrence or metastases.

Conclusion: Current approach to treatment of PLB is multi-modal, but guidelines for surgical intervention are unavailable. Few reports have been made on outcomes after surgery. Pathologic fracture fixation is an option among select patients, affording satisfactory functional outcomes while minimizing morbidity.

Keywords: Knee resection arthrodesis, Non-Hodgkin's lymphoma of bone, pathologic fracture, primary lymphoma of bone.

Introduction

Primary lymphoma of bone (PLB) is rare, with a reported incidence of 5% among all primary bone tumors and <2% of all lymphomas among adults [1, 2, 3]. The incidence of extra-nodal Non-Hodgkin's Lymphoma (NHL) ranges from 24% to 45%. Following a tissue biopsy, the diagnosis is arrived at through a combination of clinical features, imaging, and immunohistochemical studies (IHCs). Patients are confirmed to have PLB if the following features, known as Coley's Criteria, are fulfilled: primary osseous involvement at one or more sites, confirmed histologic diagnosis, and the absence of distant nodal or extra-nodal disease [1, 2, 3. 4].

While treatment of PLB consists primarily of chemotherapy and radiotherapy, a lack of consensus remains regarding the role of surgery on prognosis, as well as surgical indications and recommended margins. These points, combined with the paucity of cases reported in literature, emphasize the need for documentation and further investigation to improve patient outcomes and quality of life.

We sought to describe two rare cases of Primary NHL affecting the proximal tibia in a 21-year-old female and the proximal femur in a 69-year-old male. Both presented with regional pain and swelling secondary to pathologic fractures. Initial symptoms and work-up were non-specific, leading to diagnostic and treatment delays. The approach to management and favorable outcomes for both cases highlight the need for further investigation into treatment options for PLB.

Case Presentation

Case 1

A 21-year-old female sought consult due to intermittent left knee pain of 1 year duration. The patient denied history of trauma or manipulation. Constitutional symptoms and limitations in mobility were not reported. Consult was initially sought with a

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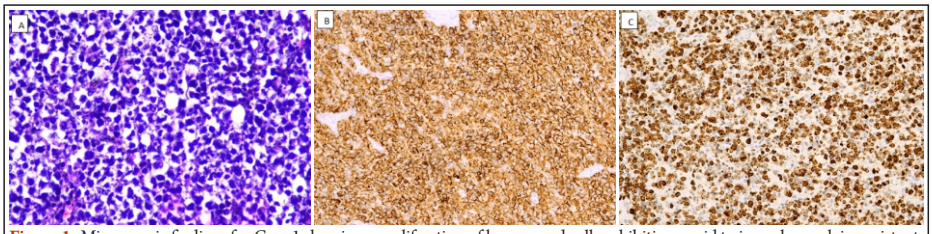

Figure 1: Microscopic findings for Case 1 showing a proliferation of large round cells exhibiting ovoid to irregular nuclei consistent with Primary Lymphoma of Bone. (a) H and E 40×. (b) CD20 immunohistochemistry showing strong and diffuse positivity of tumor cells. (c) Ki-67 staining showed 90% of cells are positive for the marker.

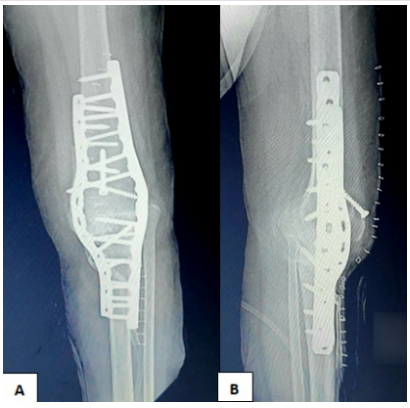

Figure 3: Immediate antero-posterior (a) and lateral (b) post-operative radiographs of the left knee after resection and arthrodesis with dual compression plates.

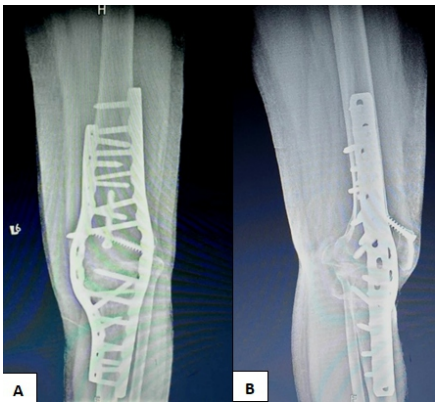

Figure 4: Most recent anteroposterior (a) and lateral (b) radiographs of the left knee, showing stable fixation and no evidence of implant loosening at 3 years post-surgery.

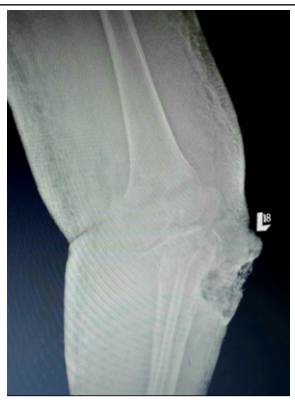

Figure 2: Radiograph of Case 1 showing antero-posterior view of the left knee with pathologic fracture at the medial tibial plateau and collapse of the articular surface, leading to varus deformity. The distal femur is unaffected. Ulceration of the soft tissue can be appreciated (*), which developed before Orthopedic Oncology consult. The wound was healed before definitive surgery.

rheumatologist and oral steroids prescribed. After 3 months, the pain progressed, prompting the patient to discontinue medications and self-administer herbal supplements for 2 months. Persistence of symptoms prompted consult with an internist. Radiographs revealed a permeative lesion at the meta-diaphyseal region of the left tibia. A diagnosis of tuberculous osteomyelitis was made based on laboratory findings, and empiric Anti-Koch's treatment was initiated. Lack of improvement prompted referral to a general orthopedist for biopsy. Biopsy specimens revealed foci of an atypical proliferation of large round cells with round to irregular, hyperchromatic nuclei. These cells were strongly and diffusely positive for CD20, and negative for neuroendocrine markers synaptophysin and chromogranin. Approximately, 90% of the cells showed expression of the proliferation marker Ki-67. This was consistent with a high-grade B-Cell NHL (Fig. 1), prompting transfer of care to Orthopedic Oncology. Repeat radiographs at this point showed a pathologic fracture of the medial tibial plateau, with metaphyseal collapse (Fig. 2). Magnetic resonance imaging (MRI) and computed tomography scans (CT) identified multiple nodular masses located below the diaphragm, confirming regional lymph node involvement. No evidence of other metastases or osseous lesions were seen on bone scan. All findings were consistent with Primary NHL of Bone (NHLB), Ann Arbor Stage IIA. Combination chemotherapy was initiated using the Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP regimen) combined with Rituximab.

After 2 neoadjuvant cycles, the medial tibial plateau fracture was managed with direct articular reduction and arthrodesis using dual compression plating (Fig. 3a and b). No attempt was made to resect with wide surgical margins prior to fusion. The post-operative course was unremarkable, and a total of 6 chemotherapy cycles were completed. Adjuvant radiation therapy was recommended in accordance with guidelines for lymphoma management but could not be done due to financial constraints. At present the patient is ambulatory and able to do brisk walking unassisted, without pain on weight-bearing. Current Musculoskeletal Tumor Society (MSTS) score is 28/30, and the patient remains disease-free with stable knee fusion (Fig. 4a and b) and no evidence of recurrence at 3 years post-surgery.

Case 2

A 69-year-old male was brought for emergency consult after falling on his left hip. Radiographs revealed a pathologic subtrochanteric fracture, with no evidence of other osseous lesions on scintigraphy. Biopsy specimens showed an atypical proliferation of lymphoid cells with round to irregular nuclei. Some areas showing associated fibrosis were seen. These cells were diffusely

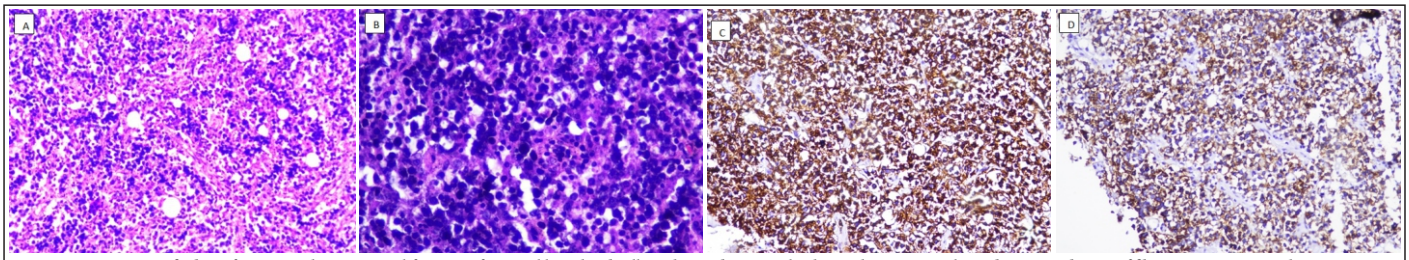

Figure 5: Microscopic findings for Case 2 showing a proliferation of atypical lymphoid cells with ovoid to irregular, hyperchromatic nuclei and associated areas of fibrosis, consistent with Primary Lymphoma of Bone. (a) H and E 20×. showing areas of fibrosis. (b) H and E 40×. showing areas of fibrosis. (c) Lymphocyte common antigen (CD45) immunohistochemistry showing strong and diffuse positivity of tumor cells. (d) CD20 immunohistochemistry showing strong and diffuse positivity of tumor cells.

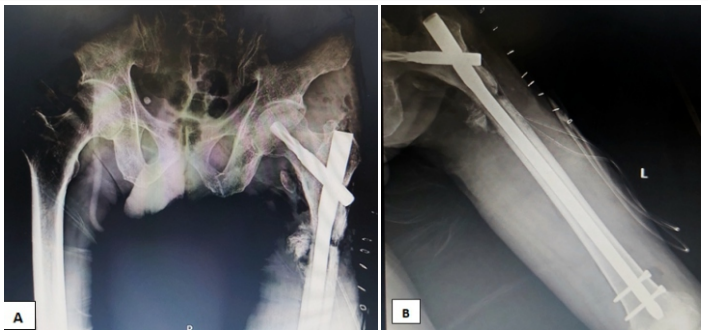

Figure 6: Immediate pelvis (a) and femur antero-posterior (b) post-operative radiographs after proximal femoral nailing.

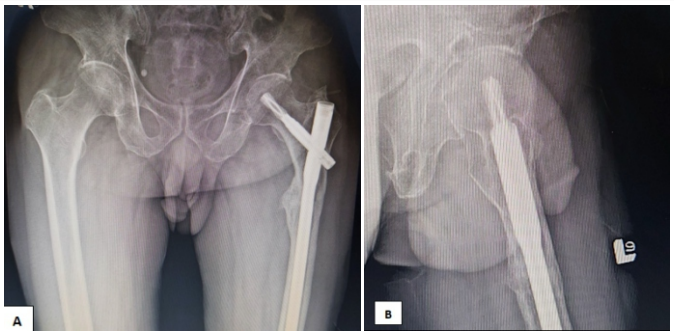

Figure 7: Most recent pelvis antero-posterior (a) and left hip lateral (b) radiographs showing stable fixation and no evidence of implant loosening or local recurrence at 2 years post-surgery.

positive for lymphocyte common antigen (CD45) and CD20, and were negative for CD3 and CD138, confirming a diagnosis of high-grade B-Cell NHL (Fig. 5). Contrast CT scans of the lung and abdomen showed ipsilateral lymph node involvement below the diaphragm, consistent with Ann Arbor Stage IIA. Proximal femoral nailing was performed, which was well-tolerated by the patient (Fig. 6a and b). Post-operative plans for initiation of CHOP regimen followed by radiotherapy were discussed, but the patient opted not to proceed with any other intervention beyond surgery. The patient is currently 2 years post-surgery with MSTS score of 28/30, independently ambulatory without signs of recurrence or metastases (Fig. 7a and b).

Discussion

PLB is a rare disease accounting for <2% of all adult lymphomas, with a reported incidence of 1.7 cases per million adults annually [3, 5, 6]. Rarer still is the incidence of NHLB, ranging from 24% to 45% of cases [3]. This condition typically affects adults within their 2nd to 5th decades, with pain and swelling being the most common presenting symptoms [1, 3, 7].

Radiographic features of NHLB are non-specific and may mimic other conditions. The presence of a solitary lesion with permeative borders affecting the meta-diaphyseal region of a long bone, however, increases the suspicion for NHLB, particular in the setting of a soft tissue mass seen on CT and MRI [2, 3, 7]. While the exact etiology of PLB remains unknown, histologic appearance remains identical to other lymphoid-derived lymphomas and must be present to confirm tissue diagnosis. These include a diffuse pattern of atypical lymphocyte proliferation as well as a combination of various IHC stains, including B-cell-specific CD20 and proliferation-associated protein Ki-67 [6, 7]. The diffuse and strong CD20 expression in both cases is consistent with their B-cell lineage.

The most common histologic subtype seen in primary bone lymphomas is diffuse large B-cell lymphoma (DLBCL), accounting for 70–80% of cases. Other less common subtypes include follicular and marginal zone lymphomas [8, 9]. Primary bone DLBCL can be further subdivided into germinal center B-cell (GCB) type and non-GCB type with immunohistochemistry with BCL6, CD10, and MUM1, since a Non-GCB type of DLBCL suggests a poorer prognosis compared to a GCB type, however a study on a limited population of primary bone DLBCL did not show a difference in overall survival between subtypes [9].

While still controversial, several authors have attempted to define key features that must be fulfilled to confirm a true case of PLB, based on criteria reported by Coley et al. in 1950 [1, 3, 4]. These include the following (Table 1 in Appendix):

1. Primary lesion affecting one or more bones
   - With or without regional node involvement, corresponding to Ann Arbor St. I, II or IV
   - In order of decreasing frequency, osseous sites most frequently involved are the pelvis, humerus, skull and tibia [1, 3, 5]
2. No evidence of distant nodes/ extra-osseous site involvement
3. Histologic findings confirming lymphoproliferative malignancy.

All of the above criteria were fulfilled by our patients during the course of their treatment. Due to the low incidence of PLB, few published studies focused on specific treatment and long-term outcomes are available. Modalities for management at present in use thus remain identical to general protocols for lymphoma. Chemotherapy is the mainstay intervention, consisting of a CHOP-based regimen. Rituximab, a humanized monoclonal antibody which binds exclusively to the CD20 antigen, was introduced in 2001 and has been associated with significant increase in survival rates among lymphoma patients [3, 5]. The role of radiation therapy in improving survival among PLB patients treated, however, has not been established.

In a retrospective study by Jacobs et al. in 2015, no significant difference in 1-, 5-, and 10-year survival rates was noted among PLB

Table 1: Current criteria reported in literature for diagnosis of primary lymphoma of bone

Key Features	RLN[a] Involvement?	Ann Arbor Stage[b]
1. Primary involvement in≥1 bones	Yes or No	St. I, II or IV, A or B
2. Histologic diagnosis confirmed through IHC[c]s	-	-
3. Absence of distant extra-osseous or RLN[a] metastases	Yes or No	No

[a]RLN: Regional Lymph Node involvement.[b]Stage I: Single lymph node or lymphoid organ involvement, Stage II: Involvement of 2 or more lymph node regions on same side of diaphragm. Stage IV: Involvement of extra-nodal site beyond that designated in E, limited to marrow extension in same bone; A: no "B symptoms" (Fever of 38°C, night sweats, and weight loss defined as 10% of body weight over 6 months), B: with "B symptoms"; E: Involvement of single extra-nodal site contiguous OR proximal to known nodal site.[c]immuno-histochemical staining

patients who underwent combined chemotherapy and radiation versus those who underwent chemotherapy alone. Far less is known, however, about the role of surgery on prognosis. Recommendations are varied with regard to indication and timing, which range from no surgical intervention at all, to excision with wide margins. A lack of consensus remains with regard to surgical guidelines for PLB [1, 2, 3, 5, 10].

Few authors have explored the possible relationship between surgery and long-term survival specifically for PLB, with just one by Scoccianti et al. focused on evaluating the role of surgical intervention for PLB in a series of 21 patients [1, 5]. In their report, 6 patients presented with or developed a pathologic fracture during the course of the study, with 4 who eventually underwent surgery: two to address severe back pain with myelopathic symptoms, and two with long bone fractures. All patients underwent chemotherapy, and 3 were subjected to post-operative radiotherapy. No attempt beyond an intralesional margin was made. All 4 patients were alive at the end of the study, with no evidence of disease at 6–9 years following completion of treatment modalities. For both of our patients, the course of diagnosis and management was similar: pain and pathologic fractures prompted consult, and surgical intervention was carried out with intended intralesional margins. However, while the first patient was able to complete 6 cycles of chemotherapy, the second patient refused to continue with systemic treatment and radiotherapy. Both patients are currently alive without evidence of disease.

Conclusion

PLB is a rare condition, and diagnosis is confirmed through combined clinical, radiologic, and histopathologic features. Pathologic fractures secondary to PLB are debilitating and increase the risk of complications, impair the ability to perform activities of daily living, and decrease overall quality of life. In the setting of improved survival rates and a high disease incidence during the productive years of adult life, the favorable outcomes seen in our patient highlight the need for further investigation into the role of surgery in PLB. The scarcity of available literature outside of single-center retrospective studies emphasizes the need for accurate case documentation, to investigate interventions with the potential to improve quality of life and long-term survival in these patients.

References

1. Scoccianti G, Rigacci L, Puccini B, Campanacci DA, Simontacchi G, Bosi A, et al. Primary lymphoma of bone: outcome and role of surgery. Int Orthop 2013;37:2437-42.

2. Tsoucalas G, Papaioannou TG, Mainta I, Thomaidis V, Fiska A. A rare case of a non-Hodgkin's lymphoma presented as a single bone lesion. Biomed J Sci Tech Res 2018;3:1-3.

3. Singh T, Satheesh CT, Lakshmaiah KC, Suresh TM, Babu GK, Lokanatha D, et al. Primary bone lymphoma: A report of two cases and review of the literature. J Can Res Ther 2010;6:296-8.

4. Coley BL, Higginbotham NL, Groesbeck HP. Primary reticulum cell sarcoma of bone; summary of 37 cases. Radiology 1950;55:641-58.

5. Jacobs AJ, Michels R, Stein J, Levin AS. Socioeconomic and demographic factors contributing to outcomes in patients with primary lymphoma of bone. J Bone Oncol 2015;4:32-6.

6. Jawad MU. Primary lymphoma of bone in adult patients. Cancer 2010;116:871-9.

7. Kitsoulis P, Vlychou M, Papoudou-Bai A, Karatzias G, Charchanti A, Agnantis NJ, et al. Primary lymphomas of bone. Anticancer Res 2006;26:325-38.

8. Mavrogenis AF, Angelini A, Pala E, Zinzani P, Ruggieri P. The role of surgery for haematologic neoplasms of bone. Acta Orthop Belg 2012;78:382-92.

9. Messina C, Christie D, Zucca E, Gospodarowicz M, Ferreri AJ. Primary and secondary bone lymphomas. Cancer Treatment Rev 2015;41:235-46.

10. Bhagavathi S, Fu K. Primary lymphoma of bone: A review. Semin Diagn Pathol 2014;31:48-52.

11. Bhagavathi S, Micale MA, Les K, Wilson JD, Wiggins ML, Fu K. Primary bone diffuse large B-cell lymphoma. Am J Surg Pathol 2009;33:1463-9.

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