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Diffuse large B-cell lymphoma mimicking chronic osteomyelitis of the ankle joint: A case report

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Abstract

Lymphoma is the seventh most common type of malignancy in both males and females. It may develop in any location where lymphomatous tissue exists. Although extranodal presentation in the lower limb and pelvis are uncommon, it could present with diverse manifestations. We report an unusual case of primary extranodal large B-cell lymphoma of the ankle joint initially presumed to be a chronic osteomyelitis. This case report discusses the impact of imaging studies on decision-making and highlights the need to consider malignancy in chronic infections.

Keywords

Osteomyelitis, malignancy, chronic infection, ankle joint

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most commonly occurring lymphoma, estimated to account for 30% of all lymphoma cases globally.[1] However, primary bony lymphoma (PBL) subtype represents approximately 5% of all non-Hodgkin lymphomas (NHLs) and 3%–4% of all bone malignancies.[2] It can involve any part of the musculoskeletal system with the majority of cases reported arising in the lower extremity, particularly the thigh and calf regions.[3] It may present as a single bone lesion with or without an associated soft tissue mass arising from local extension, with or without regional lymphadenopathy or as a multifocal polyostotic disease exclusively involving the skeleton. The median age at diagnosis varies from 45 to 60 years.[4] It has a violent natural history, high morbidity with fatal outcomes and a reduced average survival of <6 months if not treated.[5] Pain and swelling (34%–45%) of the involved site are two of the most common clinical manifestations in most patients with localized disease which is mostly curable.[4,6] Although primary bone lymphoma is not so rare, its presentation as a chronic infection around the ankle joint is very rare. This report presents an unusual case of primary DLBCL in a 42-year-old male with an unknown medical background, who was presumptively diagnosed with chronic osteomyelitis of the ankle joint. Following a comprehensive history, we describe the clinical findings, imaging studies, laboratory results, histopathology features and treatment outcome. The main objective is to highlight the impact of imaging studies, family history and tissue biopsy in reaching diagnosis of PBL.

Case report

A 42-year-old male with unremarkable medical or surgical history presented to our hospital with a 3-month history of progressive left ankle pain and swelling, associated with low grade temperature, sweating and weight loss. There was no history of trauma. Systemically, his vital signs were stable and he was limping but was able to walk with a walking stick. Local examination indicated pronounced swelling and warmth, dark discolorations of the skin with moderate-to-severe tenderness of

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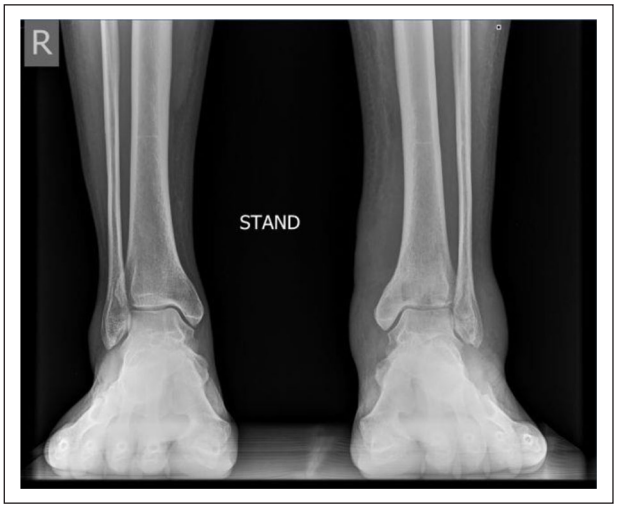

Figure 1. AP right and left ankle radiograph showing soft tissue swelling around the ankle joint with an abnormal bone density.

the ankle and distal third of the leg. No palpable lymph nodes were detected. His ankle range of motion was restricted due to pain and swelling. The blood work revealed normal erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white cell count (WCC), procalcitonin and hemoglobin (Hgb) level. Left ankle radiography showed soft tissue swelling around the joint with an abnormal bone density at the distal end of the left tibia (Figure 1).

Magnetic resonance imaging (MRI) with and without contrast of the ankle revealed extensive bone marrow and soft tissue edema affecting the distal metadiaphysis of the tibia with a reactive small joint effusion and a subchondral small fluid-like collection ($2.5 \times 2 \times 1.55\,cm^3$) in dimension, indicating an aggressive lesion most likely an inflammatory process/(osteomyelitis) (Figure 2).

Earlier images of a three-phase bone scan showed an increase uptake over the left ankle joint with intense hyper vascular activity which could be related to bone infection (Figure 3).

A gallium scan followed by whole body scan /T/ HYBRID SPECT CT of the knee showed multiple intense gallium uptake drainage lymph nodes in the popliteal and inguinal regions with the possibility of a neoplastic process as a differential diagnosis (Figure 4).

CT of the chest showed two ground glass pulmonary nodules at the left upper lobe and the apical segment of the left lower lobe (Figure 5).

A tissue biopsy was strongly recommended. Patient was taken to the operating room and after preparation, draping under spinal anesthesia, two milliliters (2 mL) of serous fluid was aspirated from the ankle joint with a soft tissue and a bone biopsy taken and sent for histopathology studies. It showed diffuse infiltration of large atypical lymphocytes with frequent mitotic figures and a destructive behavior toward the bone and the surrounding soft tissue consistent with diffuse large B-cell NHL. It is worth mentioning that after the biopsy the patient disclosed that his younger brother was previously diagnosed with the same disease and is currently in complete remission. Neoplastic cells were found to be diffusely positive for CD10, CD20, CD45, CD79a and MUM1, faintly positive for BCL2 and BCL6, while negative for EBER ISH-, CD5-, CD30-, CYCLIN D1-, C-MYC and ALK1. The proliferation fraction on Ki-67 was 80% positive. It was confirmed that the cell of origin is germinal center–type diffuse large B-cell lymphoma (GCB—DLBCL) (Figure 6).

Patient was referred to the Hematology Oncology Center where he had six cycles of immunochemotherapy regimen (R-CHOP) in the form of rituximab, cyclophosphamide, doxorubicin hydrochloride, Vincristine and Prednisone combined with involved-field radiation therapy (IFRT) at a dose of 30 Gy in 15 fractions to his left lower limb and regional lymph nodes with no refractoriness to therapy in between. An end of treatment 18-FDG PET/CT imaging revealed interval regression in FDG activity of previously described left distal tibial lesion at 12 months after combined chemoradiotherapy with no new FDG avid focal bone lesions, lymphadenopathy or lesions elsewhere. At 16 months of follow-up, he showed marked improvement in his symptoms and the 18-FDG PET/CT imaging was consistent with complete metabolic response.

Discussion

NHL is known to have skeletal involvement in up to 25% of cases;[7] however, primary lymphoma of bone is rare and accounts for approximately 3%–4% of all primary bone tumors. The most common site of occurrence is the lower extremity and has the best prognosis compared to all primary bone malignant lesions.[8] The disease shows more male preponderance with a male-to-female ratio ranging from 1.2 to 1.8.[9] The clinical presentation of pain (82%–92%) and swelling (34%–45%) of the involved site are two of the most common clinical manifestations of this disease. It spreads to lymph nodes and bone marrow in about 28% and 35% of cases, respectively.[4] These clinical presentation and prognostic parameters are identical in both young and elderly patients.[10]

Primary bone lymphoma patients whose primary tumor sites were appendicular and craniofacial at presentation had a significant survival advantage over those with axial involvement.[11] DLBCL involving bones as the only site of disease has a favorable prognosis as compared to those with a secondary bone involvement or bone marrow dissemination.[12] However, the prognosis of primary bone DLBCL patients is not only siterelated but is also closely linked to the stage of the disease.

- The most commonly used staging criteria for PBL has been proposed by the Lugano Classification System.[13] The 5-year overall survival (OS) varies from 82% for

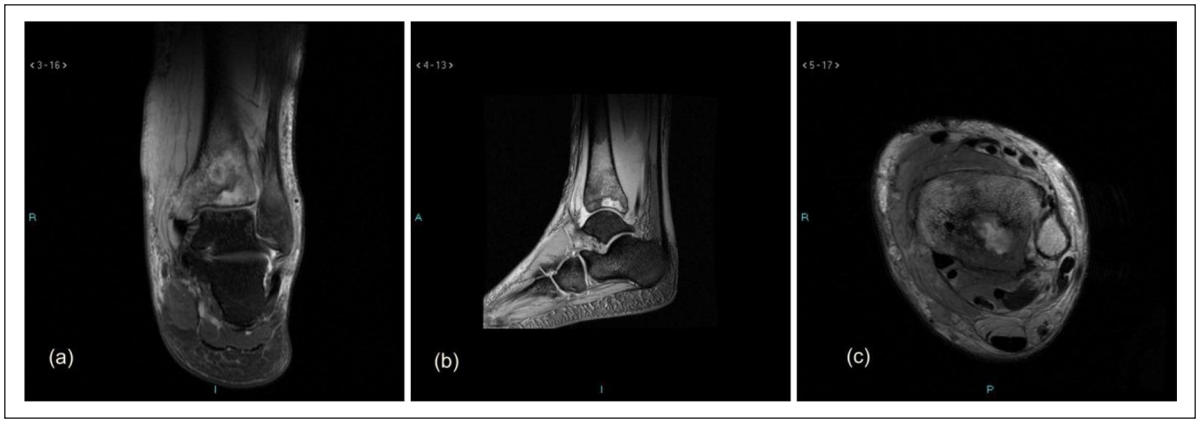

Figure 2. (a) Coronal PD FS, (b) sagittal T1 FS with contrast and (c) axial T2, demonstrating extensive bone marrow edema affecting the distal metadiaphysis of the tibia with significant surrounding soft tissue edema, reactive small joint effusion and subchondral small fluid-like collection ($2.5 \times 2.0 \times 1.5\,cm^3$).

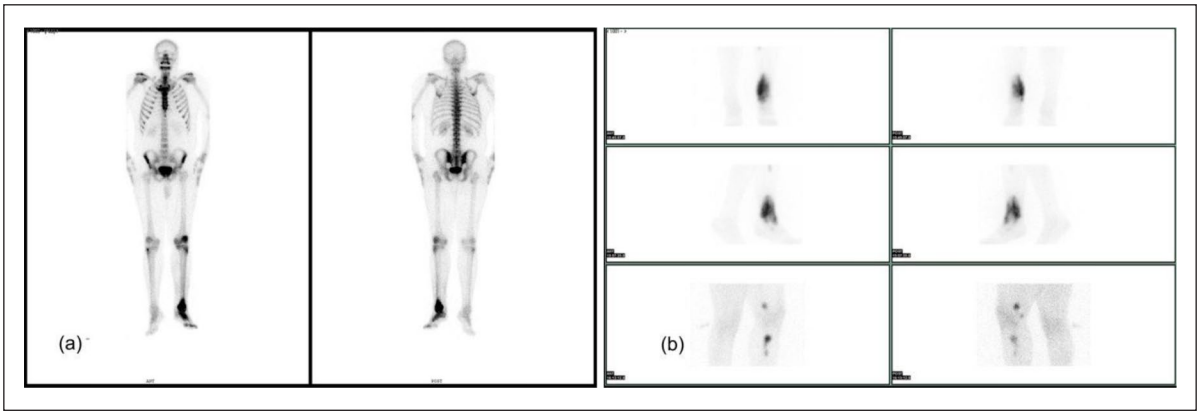

Figure 3. ((a) and (b)) Three phase bone scan showing an increase uptake over the left ankle joint with intense hyper vascular activity at the early images which could be related to bone infection.

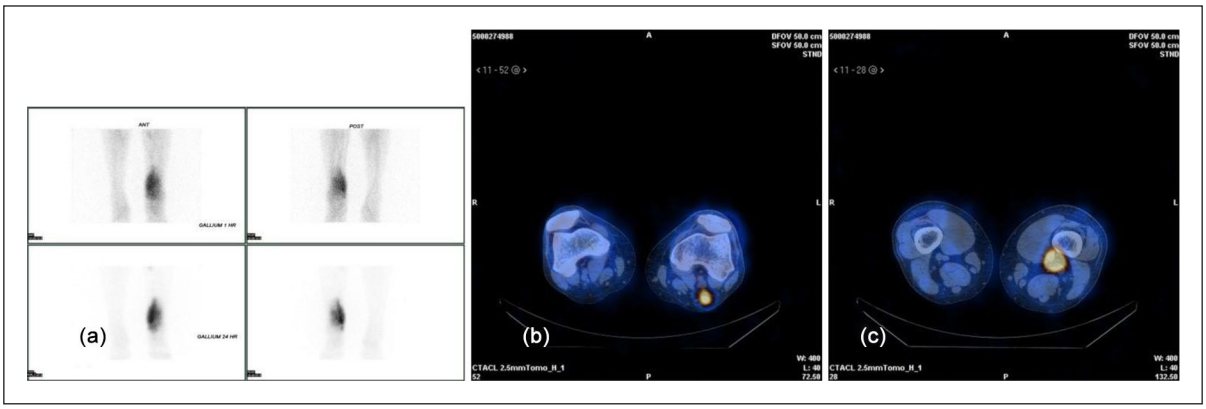

Figure 4. (a)–(c) Gallium scan followed by whole body scan /T/ HYBRID SPECT CT showing multiple intense gallium uptake drainage lymph nodes in the popliteal and inguinal regions.

patients with stage IE disease to 38% for cases of disseminated DLBCL with skeletal involvement.[14] Furthermore, the GC phenotype with certain molecular features (i.e. CD10 expression, BCL-6 mutations, and translocations involving 3q27) is associated with favorable outcomes in primary bone DLBCL.[15] A

family history of a specific subtype is most strongly associated with the risk for that subtype, supporting subtype-specific genetic factors.[16] The incidence of CNS relapse following R-CHOP is very low (1.9%) confirming the reduced incidence in the rituximab era.[17] The risk of CNS relapse was low (2.5%) in a series of 161 patients with stage I/II primary bone DLBCL from the International Extranodal Lymphoma Study Group (IELSG) who predated the use of PET or rituximab, despite only six patients receiving prophylaxis.[12] MD Anderson researchers reported 102 primary bone DLBCL patients (56% of them in stage I/II) demonstrating a 5-year progression-free survival of 80% after R-CHOP chemotherapy with documented improvement after consolidated radiation therapy (RT) in stage I/II disease.[18] Several studies have demonstrated improved OS rates of 90% and 5-years local control rates of 72% when using combined chemoradiation.[19] Therefore, it is currently recommended that patients with PBL receive treatment with combined chemoradiotherapy to achieve best survival outcomes. The main differential diagnostic considerations, depending on the age of the patient and the clinical presentation, include osteosarcoma, Ewing's tumor, secondary metastases as well as chronic osteomyelitis or myositis.[20] In the literature, a broad range of presentations involving the musculoskeletal system, such as chronic leg ulcer,[21] long-standing chronic suppuration[22] and pain in the subtalar and talonavicular joints without bony involvement on the top of rheumatoid arthritis,[23] are reported. McCammon et al.[10] reported a large B-cell lymphoma mimicking iliopsoas abscess following the open revision of an infected non-union proximal femur. A 27-year-old female with DLBCL of the right distal femur, recognized after a three-year history of chronic osteomyelitis, was documented by Alfredo et al.[24] However, it is difficult to make a conclusive diagnosis of musculoskeletal lymphoma using imaging criteria alone.[20] This is further emphasized in our case report which re-affirms the importance of physical examination, family history, imaging and careful histopathological examination in reaching an important diagnosis of primary bone DLBCL.

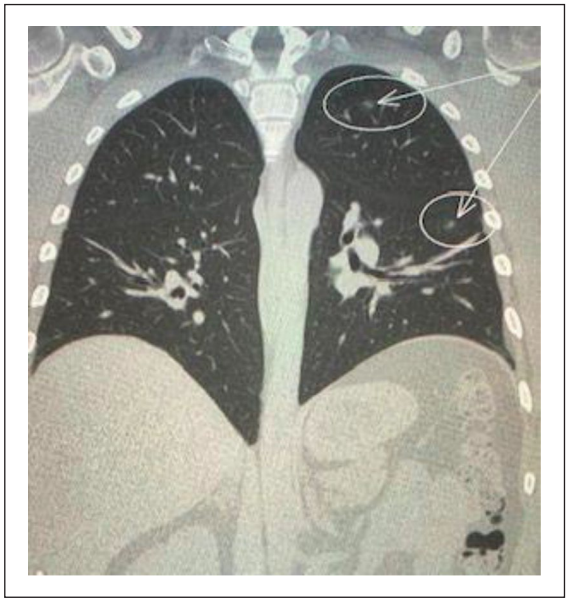

Figure 5. CT chest demonstrating two ground glass pulmonary nodules at the left upper lobe and the apical segment of the left lower lobe.

Conclusion

This case underlines the importance of family history in considering the possibility of malignancy in chronic inflammation. Lymphoma should be considered in patients with bone

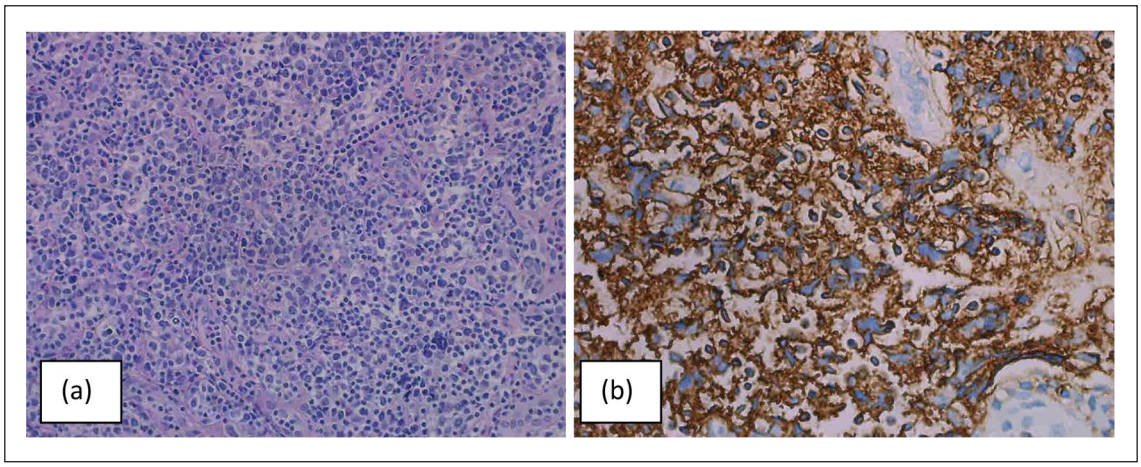

Figure 6. (a) Hematoxylin and eosin stain revealing atypical large diffuse lymphocytic infiltration and (b) CD20 showing strong membranous immunoreactivity.

and joint pain not responding to analgesic and antibiotics. While MRI imaging can be useful in the diagnosis and staging of lymphoma, it has its limitations. In the diagnosis and prognostication of DLBCL, histopathology, molecular and cytogenetic analysis are essential features.

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