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Commentaries/ letter to editor

The Need to Consider Lymphoma as a Differential Diagnosis in Suspicious Bony Lesions

Vrushab Rao Ruby Hall Clinic, India.
Bhooshan Zade Ruby Hall Clinic, India.

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Lymphoma is a malignancy of the lymphocytes, which are white blood cells that play an important part in the immune system. In addition to lymph nodes and other lymphoid tissues, lymphomas can affect extranodal locations such as bones. An uncommon form of lymphoma known as primary bone lymphoma (PBL) exclusively affects the bone and is generally not disseminated to other lymphoid tissues. Non-Hodgkin lymphoma (NHL) cases from extranodal locations account for about 30% of all NHL cases. PBL is thought to be 3-7% common among primary bone tumors and less than 2% common among all adult lymphomas [1-4]. PBL may appear as a single or several lesions and can affect any bone, however, it most frequently affects long bones including the femur, tibia, and humerus. The spine and pelvic bones are also affected [5].

Depending on the location, size, and stage of the tumor, the clinical presentation of PBL might change. Localized bone pain, swelling, soreness, or a palpable lump can all be symptoms of PBL. In more severe cases, constitutional symptoms such as fever, night sweats, and weight loss may also be present [6]. However, PBL's clinical manifestations can be ambiguous, and a wide range of benign and malignant aetiologies, including infection, trauma, metabolic bone disorders, and other primary bone tumors, are eligible for exclusion from the differential diagnosis of bony lesions. Therefore, lymphoma must be considered as a diagnosis in questionable bone tumors with a high index of suspicion.

The examination of bone lesions requires the use of radiological imaging, which is frequently the initial step in the diagnostic process. To evaluate the location, size, morphology, and extent of bone lesions, conventional imaging methods including plain radiography, computed tomography (CT), and magnetic resonance imaging (MRI) are frequently utilized. The radiological signs of PBL vary greatly and may not be pathognomonic [7]. F-18 FDG PET/CT was a useful imaging tool for the diagnosis and treatment evaluation/restaging of PBL [8].

On regular radiography, CT, or MRI, PBL might show up as lytic, sclerotic, or mixed lytic-sclerotic lesions. In rare circumstances, the presence of a soft tissue mass or periosteal response may also be seen. It might be difficult to distinguish PBL from other aetiologies based only on imaging since these features can overlap with other benign or malignant bone lesions.

For a certain diagnosis of PBL, a biopsy specimen must undergo histopathological analysis. The procedure of core needle biopsy (CNB) or fine-needle aspiration (FNA) [9,10] is frequently performed to collect tissue samples for histopathological analysis. PBL is characterized histologically by the detection of malignant lymphoid cells in the soft tissues, bone marrow, or trabeculae. The physical properties of the lymphoid cells can vary, including their size (small, medium, or large cells), as well as how they may exhibit different immunophenotypic traits. Flow cytometry and molecular genetic testing, along with other supplemental investigations like immunohistochemistry, can help to augment the diagnosis of PBL and provide further information about the subtype of lymphoma.

It can be challenging to make the diagnosis of bony lymphomas since it calls for a high degree of suspicion, a causal relationship between the clinical, radiographic, and histological findings, and the elimination of any other potential causes of bone lesions. To prevent delays in diagnosis and adequate care, it is vital to take lymphoma, particularly PBL, into account when making a differential diagnosis of suspicious bone lesions. We emphasize the need for the inclusion of lymphomas based on our experience in our institution as stated in Table 1.

Site	Signs and Symptoms	Diagnosis	Treatment
Humerus	Pathological fracture	Incidental/biopsy	Chemotherapy+ISRT
Knee Joint	Severe tenderness, loss of mobility, fever	Incidental/multiple surgeries and histopathology	Chemotherapy+ISRT
Iliac bone	Pain on movement	Incidental/biopsy	Chemotherapy+ISRT

Table 1. Extranodal ALCL at Our Centre.

There have been 3 cases diagnosed with extranodal lymphoma in the humerus, knee, and iliac bone respectively in the past 6 months. The diagnosis was initially based on exclusion and clinical symptoms that were indicative of bony infections/tuberculosis and was later followed up by histopathological evaluation which proved the diagnosis as lymphoma in all 3 patients.

The importance of considering lymphoma as a potential diagnosis for bone lesions can be attributed to several factors. First, bone lesions can be caused by primary or secondary lymphoma. Despite its uncommon nature, PBL is a unique entity that demands a more comprehensive diagnosis process and course of care than other primary bone tumors and metastatic bone lesions. To prevent incorrect identification and a delay in detection, lymphoma should be taken into account when making a differential diagnosis of bone lesions.

Second, PBL is a cancer that is highly treatable, and an early diagnosis is essential for the best possible outcome [11]. The prognosis for PBL is typically good, especially if the disease is confined, and it is typically treated with a combination of chemotherapy and local radiation therapy [12]. Yet, a delayed or missing diagnosis of PBL might cause the disease to progress, which can result in worse outcomes and more morbidity. For prompt treatment and a more favorable prognosis, a quick and precise identification of PBL with bone lesions of suspicious etiology in the differential diagnosis is essential.

Third, treating PBL necessitates an integrative approach incorporating pathologists, radiologists, radiation oncologists, and hematologists. Early inclusion of lymphoma in the list of potential diagnoses for bone lesions ensures proper referral, participation, and management of the patient by the required specialists. This guarantees that PBL patients receive the best care and treatment as soon as possible, improving results.

Finally, improvements in molecular diagnostics, particularly next-generation sequencing (NGS), have completely transformed how lymphomas, including PBL, are diagnosed and treated. NGS makes it possible to identify particular genetic mutations, rearrangements, and other genomic abnormalities helping with lymphoma diagnosis, risk stratification, and treatment choice [13]. NGS is beneficial for the diagnosis and management of a variety of lymphomas, including PBL, and it offers crucial prognostic and therapeutic data. The use of NGS and other molecular diagnostic tools may be made easier by incorporating her PBL-containing lymphoma in the differential diagnosis of bone lesions, resulting in more precise and tailored therapy for lymphoma patients.

Apart from PBL, bony lymphomas have also been documented as a complication of surgeries or implants. Implant-associated lymphomas have been documented post-knee replacements. The seeding of the malignancy during the procedure has been postulated to be the cause [14].

In conclusion, it is essential for a quick and correct diagnosis, adequate treatment, and improved

patient outcomes to consider lymphoma, especially PBL, as a potential diagnosis when bone lesions are detected.

Although uncommon, bony lymphomas are an independent disease that necessitates different diagnostic procedures and treatments than other primary bone tumors and metastatic lesions. Lymphoma can manifest as a bone lesion, either primary or metastatic. The timely start of suitable treatment and the inclusion of the required specialists in patient management can be made possible by a quick and accurate diagnosis of PBL that is taken into account in the differential diagnosis of bone diseases. Additionally, improvements in molecular diagnostics, such as NGS, have enhanced the identification and management of lymphomas, including PBL. To achieve the best possible patient care and prognosis, it is crucial to raise knowledge of lymphomas and include them, including PBL, in the differential diagnosis of suspicious bone lesions in clinical practice.

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