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Primary Bone Lymphoma: Clinicopathological profile of a rare disease at a tertiary cancer care center in South India

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ABSTRACT

Primary bone lymphoma (PBL) is a rare malignancy. Therefore, the present study aims to study clinicopathological profile at a tertiary cancer care centre in Southern India. The present retrospective study was conducted for two years, from January 2022 to December 2023. Data of all lymphoma patients was reviewed, and patients with PBL were selected. Patient characteristics, pathological features, imaging data, management protocols, and treatment outcomes were subsequently analyzed. 812 patients with lymphoma were registered during the two years, and five cases of PBL were identified. The distinct characteristics of these 5 cases are documented in the present report. The median age at presentation was 50 years (16-65 years). Pain was the most common presenting symptom, whereas the pelvis was the most commonly affected site (3 of 5 cases). The most common histological subtype was diffuse large B cell lymphoma (DLBCL), found in 3 of the five patients. Standard Chemotherapy protocols were started per the histology, and patients were followed. To conclude, since PBL is rare, it is frequently associated with non-specific clinical signs and, therefore, can be missed. Chemotherapy is the preferred treatment of choice. Of all the primary bone malignancies, PBLhas the most optimal outcomes.

Introduction

Primary bone lymphoma (PBL) is an uncommon malignancy. Oberling first described it in 1928 and named it 'reticulum cell sarcoma' (1). It is also referred to as osteolymphoma or malignant lymphoma of the bone. While it is typical for non-Hodgkin's lymphoma (NHL) to affect skeletal and bone structures, primary and exclusive bone involvement is uncommon. In total, <2% of all cases of adult lymphomas and only 5% of all primary bone malignancies are accounted for by PBL (2). According to the World Health Organization Classification of Bone and Soft Tissue Tumors 2020, PBL is classified as patients exhibiting one or more bone lesions without regional lymph node involvement or accompanying visceral disease (3). In addition, only cases with a clear bone origin are classified as PBL, according to a retrospective study performed by the International Extranodal Lymphoma Study group (the IELSG 14 study). Typically, 50 years is the median age upon presentation, whereas diffuse large B cell lymphoma (DLBCL) is the most common histological subtype observed. (4,5). Patients with PBL commonly exhibit localized bulky disease and discomfort (6-8). It is well known that lymphomas are chemosensitive tumors. This has the best prognosis of all the primary malignant bone tumors. It is essential to identify these tumors and treat them promptly.

More current literature on the clinicopathological and treatment characteristics of patients with PBL from India needs to be reviewed. Hence, we conducted this study at a tertiary care center in Karnataka. Eight hundred twelve patients with lymphoma were registered at our institute during the study period of 2 years. The present report documented the unique features of 5 patients with PBL to address the outstanding issues associated with this malignant disease.

Patients and methods

The retrospective study was performed at Kidwai Memorial Institute of Oncology, Bengaluru, a Tertiary Cancer Care Center in South India. The case files of all patients with lymphoma who registered in the two years between January 2022 and December 2023 were reviewed in the hospital database before patients with PBL were selected for the present report. Written informed consent was taken for the study. Patient characteristics, histological features, investigations, treatment strategies administered, and outcomes were assessed for these cases. Staging was performed using PET/CT or contrast-enhanced CT scans, with bone marrow aspiration and biopsy. Patients were staged according to Lugano Staging (9). Biopsies were performed for final diagnosis, and morphological and immunohistochemical analyses were performed. A descriptive study was conducted for the baseline characteristics. Descriptive analysis was done on the patient, disease, and treatment characteristics. Quantitative variables were summarized by mean or median and range.

Results

In the Hospital record search, 812 patients with lymphoma were registered over the two years, with case records of 796 patients available for the present retrospective study. In addition, 0.6% (5/812) of patients were diagnosed with PBL. The clinicopathological characteristics of these 5 cases are shown in Table I.

General characteristics. The median age of presentation was 50 years (16- 55 years). In total, 2 of the five patients were farmers by occupation, and three were from rural communities. The most common presenting symptom was pain, where the most commonly affected site was the pelvis, found in 3 of the five patients. A clinical photograph from one of the patients is seen in Figure 1. The most common histology observed was DLBCL in 3 of the five patients. In contrast, one patient was diagnosed with anaplastic large cell lymphoma (ALCL), and the other was diagnosed with plasmablastic lymphoma. A photograph from the pathological examination is depicted in Figure 2. In addition, four patients were diagnosed with stage II disease, and one patient was diagnosed with Stage I disease. RCHOP, CHOPE, and DAEPOCH regimens were administered to the respective patients (Table II).

Diagnostic data. The pelvis was the most common location in the present series of 5 patients. In particular, soft tissue involvement affects 60% of patients in the present study. The lesions were primarily osteolytic, except for the mixed lytic sclerosis observed in 1 patient. Radiotherapy (RT) was eventually advised in 1 of the patients as she had a Partial Response to chemotherapy. In total, 3 of the five patients received RCHOP. In 1 patient, primary pelvic PBL was diagnosed, where after six cycles of chemotherapy, Complete Metabolic Response (CMR) was achieved, and low-dose RT followed, with continuous follow-up for eight months. Another patient who was diagnosed with pelvic DLBCL, this patient received six cycles of R-CHOP chemotherapy, achieving CMR. This patient continues to be followed up for one year. The third patient was diagnosed with DLBCL in the spine and was administered with RCHOP. Partial Response (PR) was achieved after completing three of the six scheduled chemotherapy cycles but defaulted to reassessment afterward. However, one year later, she complained of tingling and weakness in the bilateral lower limb on telephone follow-up, prompting suspicions of

relapse. She was, therefore, advised to report to the hospital. The fourth patient, who was an adolescent female with ALK + ALCL, achieved CMR after six cycles of the CHOPE regimen and is disease-free at one year of follow-up. The fifth patient, who was diagnosed with plasmablastic lymphoma, achieved stable disease after three cycles of RDAEPOCH but defaulted after that. He was advised to visit the hospital but did not turn up. He succumbed to the disease seven months after initial diagnosis.

Discussion

Oberling first reported the unusual primary bone lymphoma (PBL) condition in 1928 (1). Parker and Jackson (10) then published 'Reticulum Cell Sarcoma of Bone' in 1939, proposing PBL as a separate clinical entity. With male preponderance and a male-to-female ratio of 1.0-1.8:1, the median age of onset is typically 50 years (8,10). The two most common symptoms of PBL are pain (80-90%) and swelling (35-45%) at the affected site (10). If an elderly patient presents with backache, PBL of the spine can be considered possible. One can feel the average time to diagnosis from the symptom onset as eight months (11,12). Pathological fractures and 'B' symptoms, such as fever, weight loss, and nocturnal sweats, are also common. However, B symptoms are less frequent in PBL than in other systemic lymphomas (11,13). Although PBL can affect any part of the skeleton, axial involvement is more common than in appendicular regions, where the pelvis is the most typical site. In addition, the metaphyseal region of the bone tends to be the most common location. (14). In cases of PBL with appendicular bone involvement, the femur is the most common location, accounting for ~33% of all cases (15). In ~28% of cases, bone marrow is involved, while lymph node involvement is observed in ~35%.

Vigilance must be paid for complications such as spinal cord compression, which is seen in ~16% of patients, and hypercalcemia, observed in 5-10% of patients (16). The first diagnostic analysis performed is a plain X-ray, which can reveal the more prevalent osteolytic lesions. However, a mixed osteolytic/blastic or osteoblastic bone transformation can also appear (14). Radiographic observations may resemble other primary types of bone cancers, including chondrosarcoma, osteosarcoma, and Ewing's sarcoma. In lymphoma, because the tumor may overrun the skeletal host response due to rapid growth, despite a significant soft tissue tumor, frequently only minor changes are noted in bone imaging according to MRI. PET/CT is the most sensitive imaging method for lymphoma staging and response evaluation

(17-19). In total, >70% of patients with PBL experience soft-tissue involvement (20). Therefore, the primary indicator of the diagnosis is patients in the 40-50-year age range with a sizable soft-tissue tumor that extends concentrically around the bone and has infiltrated the bone marrow.

In addition, a bone biopsy must be conducted to verify any clinical and radiological suspicions of PBL. To lower the risk of pathological fractures, excisional biopsies should be avoided, and the amount of tissue removed should be minimized or avoided altogether. DLBCL is the most common diagnosis in patients with PBL, though Hodgkin's lymphoma, follicular lymphoma, small lymphocytic lymphoma, and marginal zone lymphoma have also been previously observed (21).

The staging criteria for PBL that are the most frequently employed is the Lugano Classification System (22). A single bone lesion or another extranodal site is an example of a disease limited to stage IE. The disease is then categorized as stage IIE if a single skeletal lesion has adjacent lymph node involvement. Stage IV refers to multifocal illness restricted to the skeletal system (23). Previously, RT was the only treatment method available for PBL, which was associated with high recurrence rates. Chemotherapeutic regimens were therefore introduced for treating this cancer [24]. There are, at present, several therapeutic options for PBL, such as surgery, targeted RT, and chemotherapy. However, surgeons are frequently restricted to surgical biopsy, either with or without debulking. Patients who have fractures may require bracing or internal stabilization. Chemotherapy is more efficacious than RT in treating PBLs, with superior 10-year survival rates of 56 vs. 25% respectively. According to a study by Ventre et al. (25), chemotherapy appeared superior to RT in patients with primary bone DLBCL regarding prognosis, irrespective of treatment modality. In addition, compared with either chemotherapy or radiation alone, the overall survival was potentiated further when combined chemoradiation was applied (25). Christie *et al.* (26) previously reported that patients with PBL treated with chemoradiotherapy (with the CHOP regimen for three cycles and field RT) achieved 90% overall survival rates and 70% local control rates after five years. Regimens are typically selected based on the tumor histology. Ramadan *et* al. (27) observed that RCHOP increased the 3-year progression-free survival rate of patients with PBL to 88% with Rituximab and 52% with CHOP.

Some studies on PBL have already been performed globally, but more data on them from India needs to be collected. This study focuses on the clinical characteristics of PBL in

patients from Southern India. Two studies have been published previously on patients from Northern India (28,29). The present study compared the data with those from previous studies from Northern India, as shown in Table III.

According to the comparison, the median age is almost similar. There could be a difference in stage at the presentation. Most patients presented at stages II and IV in the present study. By contrast, the studies from North India revealed that Stages I and IV are the most common, but DLBCL remained the most common histological subtype. There are variations in the use of RT in the management at various centers, though the general outcomes of PBL are primarily favorable. However, patients defaulting during the treatment regimen can compromise the results. Therefore, good communication and patient counseling are recommended to ensure compliance.

Our study has certain limitations, being a single-center study. PBL patients have long-term progression-free and overall survival. Hence, survival analysis and the relation between efficacy and treatment were not feasible as a part of this study, which was carried out with time restraints. This remains another area for improvement of the study.

To conclude, PBL is a rare malignancy. The disease is associated with non-specific clinical signs and can be misdiagnosed. The differential diagnosis list is long and includes all small blue round-cell lesions in bone. Of all the primary malignant bone tumors, PBL has the optimal outcomes. Patient counseling is of utmost importance, similar to other cancers, because patients tend to default to long-term chemotherapy regimens. Since the vast majority of cases are DLBCL, chemotherapy with RCHOP is the standard treatment method recommended. However, there may be similarities and variations in the clinical profile of patients with PBL in Southern India compared with the rest of the world and Northern India.

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Availability of data and materials:

The corresponding author may request the datasets generated and analyzed in the present study.

Authors' Contributions :

AC, SBMC, and AHR contributed to the study's conception. SBMC, AHR, and AC were responsible for the acquisition.AC, LAJ, SBMC, LKN, AHR, LKR, SAB drafted the work. SBMC and LKR substantively revised it. All authors have read and approved the manuscript.

Ethical approval and consent to participate:

Informed consent was taken from all the patients. The study was retrospective, so approval by the Institute Ethics Committee was waived. Confidentiality was maintained as the data did not reveal the identity of any patient. The procedures followed were according to the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964, as revised in 2013.

Patient consent for Publication :

Yes, Informed patient consent was taken for publication

Competing Interests:

None of the authors have any competing interests

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Figure 1. Clinical photograph showing a sternal mass

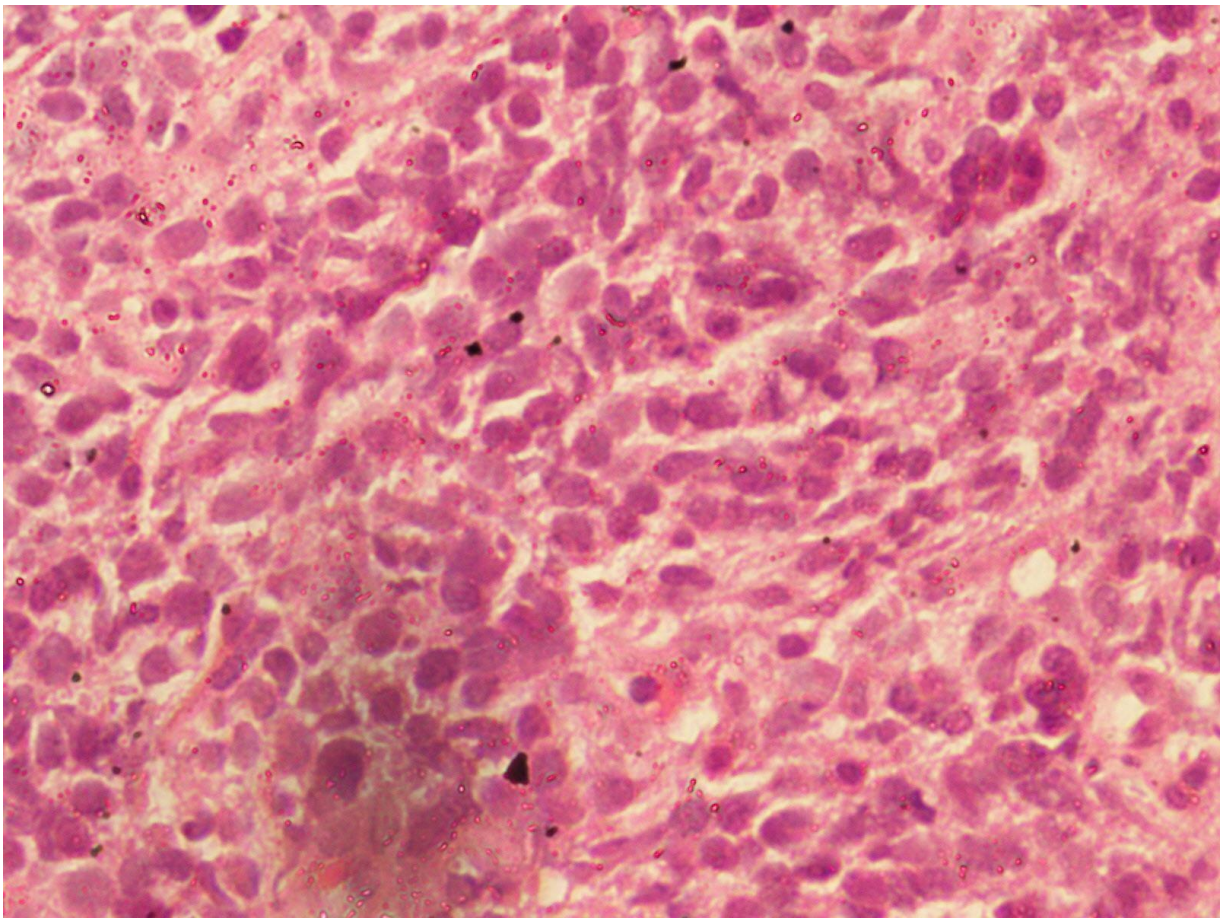

Figure 2. Microscopic view under high power with Hematoxylin and Eosin staining showing Poorly differentiated large malignant cells.

Table I. Clinicopathological characteristics and outcomes

	Histology	Stage	Presenting complaints	Site	Chemotherapy regimen	Outcome
42 years /Female	DLBCL Ki 67 55 to 60%	II	1.Left thigh pain x 3 months 2. Swelling left lower Limb x 1 month	Left iliac bone, acetabulum, head, and neck of femur	RCHOP regimen	6# RCHOP → CMR→ RT. Disease-free at eight months post-treatment
35 years /Female	DLBCL Ki 67 67 to 80%	II	1. Left hip pain x 2.5 months	Left iliac bone, left femur, Right SI joint	RCHOP regimen	6# RCHOP → CMR. Disease-free at 12 months post-treatment
65 years /Female	DLBCL Ki 67 >70%	II	1.Bilateral lower limb weakness x 15 days 2. Backache x 1 year	T1 vertebra, 6th, 7th 10th rib on Right side	RCHOP regimen	3# RCHOP →PR, further 3# RCHOP→ Defaulted for reassessment. Presently, 12 months posttreatment, suspected recurrence

16 years /Female	ALK+ ALCL	II	1. Left hip pain x 3 months	Left iliac bone, acetabulum, head, and neck of femur	CHOPE regimen	6# CHOPE→ CMR . Disease-free at 12 months post-treatment
50 years /male	Plasmablastic Lymphoma	I	Sternal swelling x 1.5 months	Sternum	DAEPOCH regimen	3# DAEPOCH→ SD→ Defaulted Expired

DLBCL, diffuse large B cell lymphoma; ALCL, anaplastic large cell lymphoma; CMR, complete metabolic response; PR, partial response; SD, stable disease.

Table II. Chemotherapy regimens.

Day	Drug	Dose	Frequency
RCHOP			
D1	RITUXIMAB	75 mg/m2	q 21 days
	DOXORUBICIN	50 mg/m2 IV bolus	
	VINCRISTINE	1.4 mg/m2 (maximum 2 mg*)	
	CYCLOPHOSPHAMIDE	750 mg/m2	
D1 to D5	PREDNISOLONE	40 mg/m2 PO daily	

From D6	G-CSF primary prophylaxis	for five days.	
CHOPE			
D1	RITUXIMAB	75 mg/m2	q 21 days
	DOXORUBICIN	50 mg/m2 IV bolus	
	VINCRISTINE	1.4 mg/m2 (maximum 2 mg*)	
	CYCLOPHOSPHAMIDE	750 mg/m2	
D1-D3	ETOPOSIDE	100 mg/m^2 IV	
D1 to D5	PREDNISOLONE	40 mg/m2 PO daily	
From D6	G-CSF primary prophylaxis	for five days.	
DA EPOCH			
	ETOPOSIDE	50 mg/m 2 /day IV	q 21days, adjust dose levels of cyclophosphamide, Doxorubicin, and Etoposide as indicated
	DOXORUBICIN	10 mg/m 2 /day IV	
	VINCRISTINE	0.4 mg/m 2 /day IV	
	PREDNISOLONE	60 mg/m2 OD PO	
	CYCLOPHOSPHAMIDE	750 mg/m 2 /day IV bolus	
From D6	G-CSF primary prophylaxis	Till ANC more than 1000 for two	

		consecutive readings	

PO, per oral; IV, intravenous.

Table III. A comparison of the present study with other Indian studies.

	Present study	Mahajan et al. [28]	Sharma et al. [29]
Year of publication	-	2021	2020
Institute Location	South India	North India	North India
Years of study	2	8	13
Number of patients	5	22	35
Median age	50 years	44 years	52 years
Most common stage	Stage II (40%) and stage IV (40%)	Stage I (59.1%)	Stage IV (63.2%)
Most common location	Pelvis 60%.	Spine 54.5%.	Spine 25%.
Most Common Histology	DLBCL 60%	DLBCL 36.4%.	DLBCL 94.8%
Radiotherapy administered	20%	86..1%.	37.1%.
Complete response	60%	68.1%.	80%.
Partial Response.	20%	18.2%.	8.8%.