

## Primary Lymphoma of Bone Literature Review

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Received Date: June 06, 2017; Accepted Date: June 15, 2017; Published Date: June 22, 2017

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Citation: Elhassadi E. Primary Lymphoma of Bone literature review. Arch Clin Microbiol. 2017, 3: 2.

### Abstract

Primary Lymphoma of Bone (PLB) is a very rare neoplasm presenting most commonly with bone pain and swelling or as an incidental finding on imaging. PLB diagnosis requires tissue biopsy and Non-Hodgkin's lymphoma (NHL) is the commonest sub-type. Disease staging includes thoracic-abdominal-pelvic computed tomography scan (CT), bone marrow biopsy and cerebrospinal fluid cytology. Chemo-immunotherapy with radiotherapy (RT) consolidation is a widely applied treatment strategy for PLB with good outcomes achieved.

### Background

Primary Lymphoma of Bone (PLB) is extremely uncommon, accounting for less than 1% of all lymphoma and around 7% of all primary bone tumours [1]. The median age of diagnosis is 55 years (range 50-60) with a male predominance. PLB is extremely rare in the paediatric and young adult population [2]. The 2013 World Health Organization (WHO) classification of tumours of the soft tissue and bone, defined PLB as a single skeletal lesion with or without the involvement of regional lymph node, and multiple bone lesions without visceral or lymph node involvement [3,4]. The underlying causes of PLB are still to a great extent, obscure.

### Clinical Presentation

The most common presentation is with bone pain and sometimes swelling with a palpable lump at the lesion site, or as an incidental finding on imaging. The femur is preferentially affected, representing 29% of all cases, with other sites affected, including the pelvis, humerus, skull, neck, and tibia, were reported [5]. Forearm involvement has been noted to be extremely rare [6-8]. PLB most frequently presents as a single localised tumour. The clinical presentation and imaging findings are non-diagnostic, with a wide spectrum of differential diagnoses possible including Ewing's sarcoma, osteogenic sarcoma, and chondrosarcoma. Therefore, tissue biopsy is essential to confirm the diagnosis.

### Diagnosis

PLB diagnosis requires clinical examination and appropriate imaging, and is confirmed by histological and immune-histochemical examination on bone/soft tissue biopsy samples. Almost all PLBs are classed as Non-Hodgkin's lymphoma (NHL) with the diffuse large B-cell lymphoma (DLBCL) sub-type accounting for 80% [9]. In a recent report by Chisholm et al, a total of 54 cases of PLB were evaluated in individuals aged 1-21 years, DLBCL was the most frequent sub-type (76%) followed by B-lymphoblastic lymphoma in 15%, anaplastic large cell lymphoma in 6% and low grade lymphoma in 2% [9]. Limited information is available on the molecular features in PLBs, of which partially due to the rarity of this condition and related to degradation of nuclear material occurring during the decalcification process.

### Investigations

PLB workup includes; assessment of patient performance status (PS), an echocardiogram and laboratory investigations including full blood count, hepatic and renal function tests, serum lactate dehydrogenase (LDH) and virology screen. The staging procedures will include thoracic-abdominal-pelvic computed tomography (CT) scan, bone-marrow biopsy and cerebrospinal fluid cytology. The disease stage is determined using the Ann Arbor criteria of which divided into four stages (I-IV) and the majority having extra-nodal stage I or II (IE or IIE) disease [10]. Bulky disease is defined as a lesion exceeding >5 cm [11,12]. Plain X-ray films are non-diagnostic, usually showing either a lytic or sclerotic lesion, or both within the same bone [11]. Magnetic Resonance Imaging (MRI) illustrates the detail and extent of the bony lesions more accurately than CT, though the standard contrast-enhanced CT scan is the primary modality for staging, restaging and follow-up of lymphoma patients.

Positron emission tomography (PET-CT) scan has higher sensitivity and specificity than standard CT [12]. However, limited reports are available on the utility of this imaging modality in PLB. PET scan in PLB has the ability to depict extra-skeletal soft tissue involvement and to identify additional bone lesions on staging [13]. Treatment response can be accurately and reliably assessed by PET-CT scanning with excellent sensitivity and negative predictive value. Whereas, plain X-ray or even MRI may show residual bone abnormalities for longer in absence of active disease. Post-treatment osteonecrosis is a potential cause of false-positive results on restaging PET-CT scans which may lead to concerns [14].

### Prognosis

PLB exhibits a favourable prognosis if treated with chemo-immunotherapy, whether with or without consolidation radiotherapy. Reported 5-year progression free survival (PFS) and overall survival (OS) are 73% and 85% respectively [15]. The conventional international prognostic index (IPI) is not applicable in patients with PLBs [16].

## Treatment

Chemo-immunotherapy (Anthracycline-based chemotherapy with monoclonal antibody therapy) with radiotherapy (RT) consolidation is a widely adapted treatment strategy for primary bone DLBCL [17]. Although the MINT trial and another larger retrospective study suggested that's patients with extra-nodal disease benefited from the addition of Rituximab (anti-CD20 monoclonal antibody), there was limited impact on DLBCL patients with bony involvement [18]. On the contrary, Ramadan et al. reported that in patients with primary bone DLBCL, the addition of Rituximab therapy improved patients three year PFS from 52% to 88% [19]. However, a recent study by Tao et al has questioned this benefit, and speculated that bony DLBCL might perhaps exhibit some Rituximab resistance [20,21].

In general, skeletal involvement, mostly with advanced DLBCL, has been reported to be associated with a high risk of CNS relapse (5%) [20].

Intrathecal chemotherapy or intravenous Methotrexate prophylaxis could reduce this risk [22]. However, CNS prophylaxis in PLB remains controversial, considering such relapse risk rate was halved in DLBCL patient when Rituximab therapy incorporated with chemotherapy [15].

Consolidation radiotherapy to the affected area has been the widely applied approach in patients with PLB, though its role has been subject to debate prior to and during the Rituximab era [17]. Held et al. reported that with-holding radiotherapy consolidation in elderly patient with aggressive lymphoma resulted in an inferior PFS and OS [8]. In contrast, the IELSG-14 study reported no impact of consolidation radiotherapy treatment outcomes with 5 years PFS on chemo-radiotherapy versus chemotherapy alone were 74% and 67% respectively [23].

The radiotherapy dose was further evaluated in this study (IELSG-14) and reported that, in patients with PLB, there were no significant differences in relapse risk, PFS and OS using radiation of 30Gy when compared with standard doses of 40-45Gy [24]. In addition, Tao et al., reported regardless the applied radiotherapy dose (30-35 versus 36 Gy), there was no impact on PFS or OS [25].

The utility of bisphosphonate therapy in PLB has not been formally assessed in clinical trials. However, such an approach has been adapted in clinical practice at some centres based on beneficial impact extrapolated from patients with Multiple Myeloma. Surgery has a limited role in PLB management and has no impact on treatment outcome [26]. Surgical intervention is mainly applied for tissue biopsy sampling or to repair pathological fractures, presence of extensive damage to weight-bearing bones and rarely for decompression of the spinal cord [26].

## Conclusion

PLB is a rare subtype of lymphoma with a favourable prognosis, characterized by localized disease in most cases. Chemo-immunotherapy with or without radiotherapy consolidation is the current standard of care.

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