



Case Report

Primary bone lymphomas—Clinical cases and review of literature

Anshu Jain ^{*}, Kiran Alam, Veena Maheshwari, Roobina Khan, Hage Nobin, Varsha Narula

Department of Pathology, Jawahar Lal Nehru Medical College, AMU, Aligarh, Uttar Pradesh 202002, India

ARTICLE INFO

Article history:

Received 9 May 2013

Received in revised form

19 July 2013

Accepted 24 July 2013

Available online 1 August 2013

Keywords:

Primary bone lymphoma
 Diffuse large B cell lymphoma
 Non-Hodgkin's lymphoma
 Immunohistochemistry

ABSTRACT

Primary bone lymphoma (PBL) is an uncommon clinical entity and a rare presentation of non-Hodgkin's lymphoma. PBL accounts for less than 5% of malignant bone tumors, 4–5% of extra nodal lymphoma and less than 1% of all non-Hodgkin's lymphoma. Diffuse large-B-cell lymphoma (DLBCL) accounts for the majority of cases of PBL. The incidence of PBL is so rare that many of its aspects remain unknown. A number of studies have been reported from western countries but only a few reports are available from Asia. Out of 20,000 bone lesions received in our department over 5 years, only 5 cases were primary bone lymphoma; all of which were DLBCL. We report our experience on PBLs with main emphasis on two unusual presentations of this rare tumor.

© 2013 Elsevier GmbH. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

According to WHO classification, PBL is defined as a monostotic disease with or without involvement of regional lymph nodes, or as a poly-ostotic disease affecting multiple skeletal sites without visceral- or lymph node involvement [1].

Primary lymphoma of bone is an uncommon clinical entity and accounts for less than 5% of malignant bone tumors, 4–5% of extra nodal lymphoma and less than 1% of all non-Hodgkin's lymphoma. Diffuse large-B-cell lymphoma (DLBCL) accounts for the majority of cases of PBL [2]. The varied clinical and histopathological profiles of PLB are still to be explored entirely.

2. Methods

A 5 year study (2006–2011) of all primary lymphomas of bone were undertaken retrospectively and prospectively in our department. Cases with unusual presentation were studied in detail along with their immunohistochemical profile. In all patients, staging evaluation included hematological and chemical survey, in addition to chest X-rays, abdominal ultrasonography, computed tomography of the chest and abdomen, and bone marrow biopsy. Cases were staged according to the Ann Arbor staging system [3]. Complete data on followup was not available due to either inability of patient to complete followup or referral of patient to

some higher/cancer speciality center. The patients were treated with combined radiochemotherapy. The dose of radiation therapy was between 35 and 45 Gy, and CHOP chemotherapy regimen was employed. Complete Response (CR) was defined as disappearance of all evidence of lymphoma, as documented by a normal physical examination, blood tests, and radiologic imaging. When residual radiographic abnormalities were consistent with normal bone reformation, patients were considered in CR if no other possible signs of disease were present. Partial Response (PR) was defined as > 50% reduction in tumor burden without CR after completion of treatment, and no response as anything else. Local failure was defined as failure in the initial bone site and/or in adjacent lymphnodes. Failure anywhere outside these confines was considered to be distant [4].

3. Observations and results

Out of 20,000 bone lesions received in our department over 5 years from 2006 to 2011, 360 (1.8%) were neoplastic out of which 11 were bone lymphomas. Of the 11 cases of bone lymphomas, 6 cases were secondary involvement by non-Hodgkin's lymphoma and 5 cases were primary bone lymphoma. All the 5 cases of primary bone lymphoma (PBL) were Diffuse large B-cell lymphoma (DLBCL) type, 3 of which presented in pelvis(60%), 1 each in femur (20%) and mandible (20%). 3 cases were of usual and 2 had unusual presentation or morphology. Table 1 summarizes the clinic-pathological characteristics of the patients described in this study.

The first unusual presentation (case 4) was a 65-year-old man who presented with the chief complaints of intermittent fever,

Abbreviations: PBL, Primary bone lymphoma; DLBCL, Diffuse large B cell lymphoma; NHL, Non-Hodgkin's lymphoma.

^{*} Corresponding author. Tel.: +91 9358258737.

E-mail address: vians.jain@gmail.com (A. Jain).

pain and swelling of the jaw for the past 6 months. On examination, multiple draining sinuses were present on right side of jaw. A CT scan of the jaw revealed a breach in the cortex of the mandible on the right side [Fig. 1]. A presumptive diagnosis of tubercular osteomyelitis was made and draining fluid was sent for AFB stain, results came were negative. A biopsy was sent for histopathological examination, which revealed diffuse infiltration of the skin, subcutaneous tissue and muscle with lymphoid cells [Fig. 2]. Immunohistochemistry was positive for LCA, CD20, Ki 67 (50–60%) and negative for CD3 and CD4 [Fig. 3]. Hence a diagnosis of diffuse large B cell lymphoma of the mandible was made and the patient was started on CHOP chemotherapy regimen followed by radiotherapy to which he is responding well. Additional investigations did not show any other bony lesions or lymphnode involvement.

The second peculiar presentation (case 5) was a 54-year-male who complained of pain and swelling of right hip since 5 months with increasing intensity. On examination the patient had restricted movements of left hip joint and a lump could be palpated. X-ray showed soft tissue and bony mass involving the right ileum [Fig. 4]. A presumptive clinicoradiological diagnosis of chondrosarcoma was made and biopsy was performed. Histopathological examination showed small round cell tumor cells in a sclerotic stroma [Fig. 4]. Immunohistochemistry of the lesion showed positivity for LCA, CD 20, CD10, Vimentin, Bcl-2, Bcl-6, PAX-5, MUM1, Ki-67 (70–80%) and

negative for CD 99, Pancytokeratin, Desmin, CD-3, S-100, CD-5, HMB-45 [Fig. 5]. The morphology and immunophenotype was compatible with the diagnosis of diffuse large B cell lymphoma and suggest a follicle center cell origin. So a final diagnosis of diffuse large B cell lymphoma of right ileum was made. No additional bony or lymphnode involvement was found. The patient was advised CHOP chemotherapy followed by radiotherapy.

4. Discussion

Primary lymphoma of bone is a rare disease, first described by Oberling in 1928 and he labeled it as reticulum cell sarcoma of bone because of the presence of characteristic reticulin fibers within the lesion [5]. This work was followed by Parker and Jackson and later by Ivin and Boston who, eventually established the distinct entity of this lesion and labeled it as the malignant lymphoma of bone [6,7]. The use of immunohistochemistry in highlighting the cellular origin of these lymphomas was described by Vassallo in 1987 [8]. Even till today, the diagnosis of these lesions remains challenging and requires the help of immunohistochemical markers along with histopathology to lead to the final diagnosis.

The definition of PLB varies throughout the literature. Generally, this entity is defined as malignant lymphoma arising within the medullary cavity of a single bone without concurrent regional lymph node or visceral involvement [9]. In contrast, Shoji and Miller permitted regional lymph node metastases but stipulated that the interval between the onset of symptoms of the primary focus and the appearance of distant metastases should be greater than 6 months [10]. The vast majority of these lymphomas are non-Hodgkin lymphoma (NHL), the common subtype being diffuse large B cell lymphoma. In addition to DLBCL, other lymphoid malignancies may manifest with primary bone presentation, including

Table 1
Clinico-pathological characteristics of patients described in the study.

Sl. no.	Age	Sex	Site	Diagnosis	Stage	Followup
1	55	M	PELVIS	DLBCL	I E	Referred
2	47	F	PELVIS	DLBCL	II E	Lost
3	59	M	FEMUR	DLBCL	II E	PR
4	65	M	MANDIBLE	DLBCL	I E	CR, no. failure at 1 year
5	54	M	PELVIS	DLBCL	I E	Referred

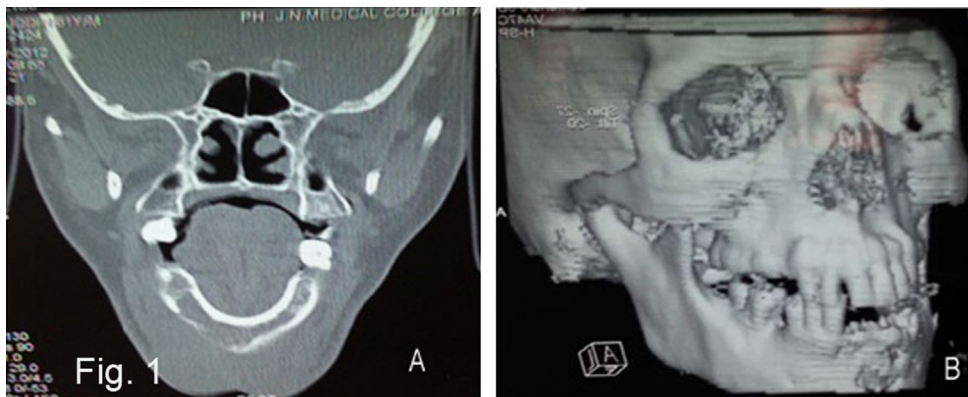


Fig. 1. CT scan revealed breach in mandibular cortex.

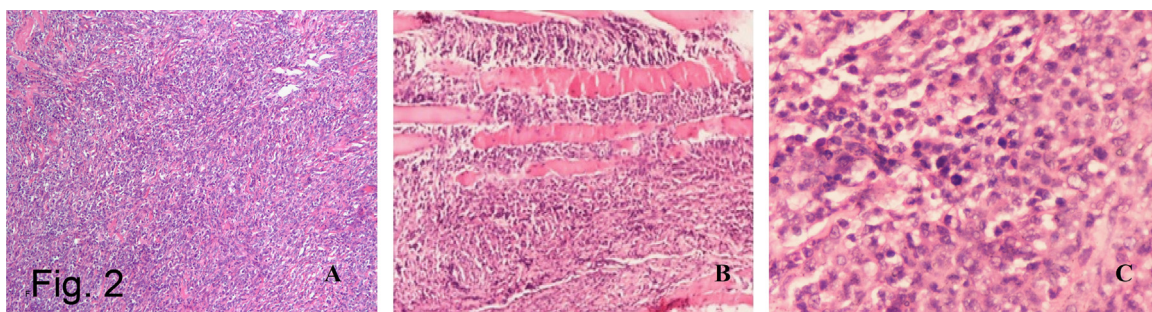


Fig. 2. Diffuse infiltration of large B-cells. (H&E).

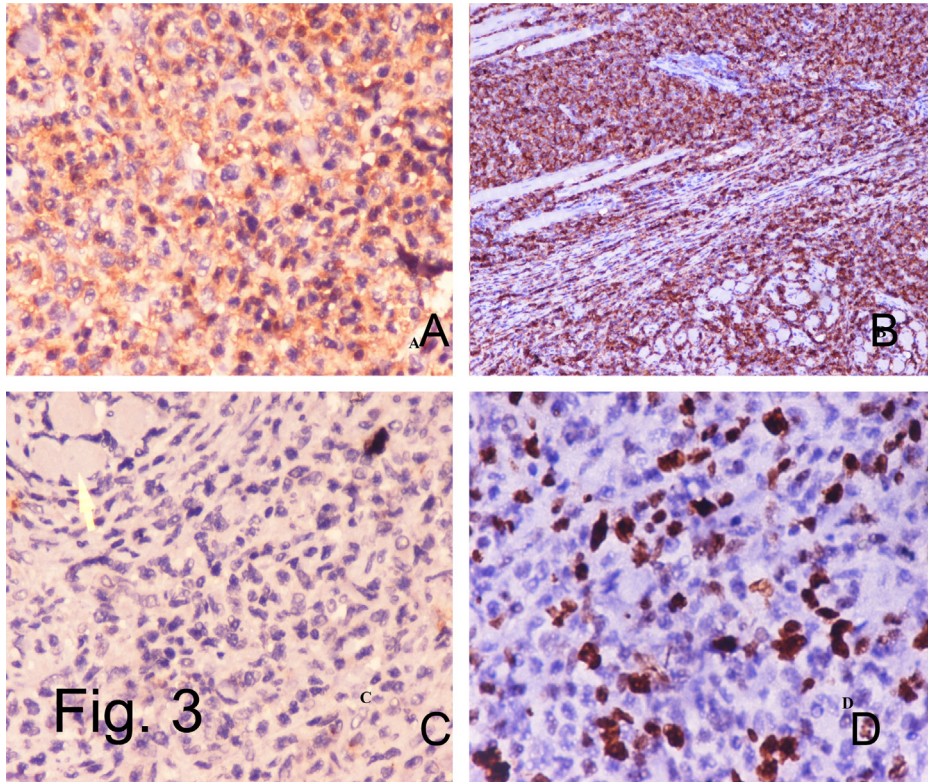


Fig. 3. IHC: POSITIVE: A – CD20, B – LCA, D – Ki67- (50–60%); NEGATIVE: C – CD3.

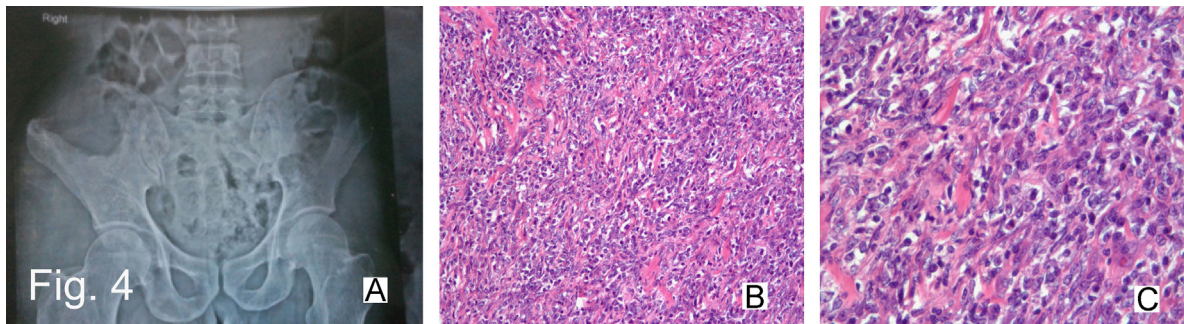


Fig. 4. A: Lytic lesion of right ileum; B and C – small round cells with a sclerotic background (H&E).

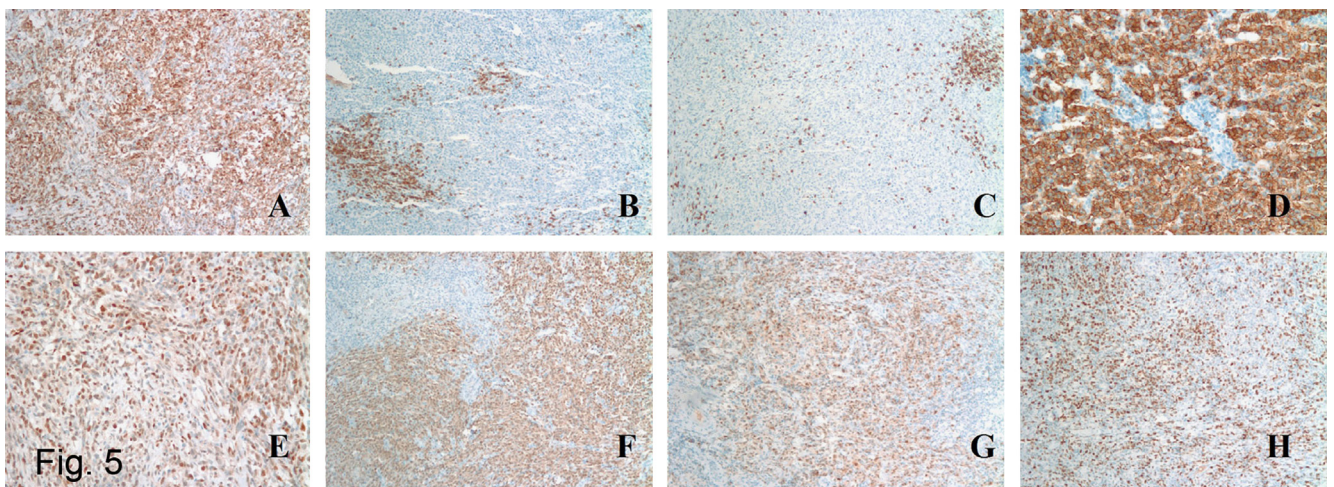


Fig. 5. IHC: POSITIVE: A – BCL2, D – CD20, E – BCL6, F – PAX5, G – MUM-1, H – Ki67; NEGATIVE: B – CD5 C – CD3.

atypical Burkitt's lymphomas, follicular lymphoma, small B-cell lymphomas, B-cell lymphoplasmacytic lymphomas, anaplastic large cell lymphomas, peripheral T-cell lymphomas, HL and precursor B-cell lymphoblastic lymphomas [11]. Primary Hodgkin lymphoma (HL) of bone is extremely rare, and the majority of patients have concurrent nodal involvement at presentation [12].

Clinically, the most commonly affected age group is 20–50 years with a male preponderance (male: female=3:2). Femur (29%) is the most common site affected followed by pelvis (19%), humerus (13%), skull (11%) and tibia (10%) [13]. Heyning FH [10] reported femur to be the most common site of involvement whereas Susnerwala et al. [14] found pelvis to be the most common site which is consistent with our study. Three out of five cases had involvement of pelvis. Median age of diagnosis was 37 years with male:female ratio 4.9:1 in study by Susnerwala et al. [14] whereas median age of diagnosis was 56 years with male:female ratio of 4:1 in our study.

Local pain and swelling are usually the most common presenting complaints [15] but multiple discharging sinuses has rarely been seen as a feature as was seen in one of our cases which was misleading towards an infectious etiology. Radiologically, there exists a wide spectrum of findings ranging from a normal appearing bone to an extensive, destructive or infiltrative lesion. The destructive lesions are patchy, radiolucent, mottled, moth eaten and occasionally exhibit complete loss of the outline. This may be accompanied by cortical bone thickening and destruction in 25% of cases and occasionally large soft-tissue extension [9].

Apart from histopathology, which still remains the mainstay of diagnosis, numerous investigations which aid in diagnosis are skeletal survey, bone scan, bone marrow biopsy, CT scan of whole abdomen and chest to assess lymph node involvement and serum LDH estimation done as part of the staging procedure. With the combined use of CT, MRI and now PET scan, a higher proportion of patients are diagnosed with stage IV disease [10]. The differential diagnosis of PBL are metastatic carcinoma, Ewing's sarcoma, osteosarcoma, eosinophilic granuloma (skeletal) and chronic osteomyelitis [11] and needs to be differentiated from them. The present study emphasizes that it is the wide range of immunohistochemical markers that offers the final rescue in cases with atypical morphology.

PBL was defined as a separate disease entity in the realm of lymphoma on the notion of a comparably favorable outcome. This tumor has a significantly different clinical course and a much better prognosis than Non-Hodgkin's Lymphoma (NHL), secondarily affecting bone. Radiotherapy is an effective modality for good local control due to its radio-responsiveness, but distant failures occur in approximately 50% of initially localized bone tumors. Thus employment of adjuvant systemic chemotherapy in a multimodal approach is warranted for improvement of results [14].

In contrast to adults, PBL in children is regarded as a clinical entity that is distinct from its adult counterpart. Like many other pediatric malignancies, PBL is considered a systemic disease in children. In small retrospective studies, PBL in children is characterized by rapid progression, a higher incidence of micrometastasis, and a propensity for spread to the central nervous system, yet children have a better prognosis [16].

In a multivariate analysis, adult patients who had local disease and who were younger had a significant survival advantage. Similarly, there was a significant association between young age and a histological classification of "NHL-Large B-cell diffuse". A survival analysis of patients with localized disease revealed that radiation therapy was associated with improved survival, whereas surgery did not prove to be of survival benefit [16]. A current study [16] supports sub-classification of group of patient with PBL who have localized disease because there is a difference in their prognosis and outcome compared with patients who have other, more extensive disease.

In this paper, we promulgate our experience of PBL with emphasis on their unusual presentations, one of which had abnormal clinical presentation and the other had abnormal morphology of the cells and emphasize that DLBCL is to be kept in mind while dealing with any bony lesions.

5. Conclusion

PBL in itself is a rare tumor with a comparably favorable outcome and only few studies having been done on it. Therefore, its varied clinical and histopathological profiles are still to be explored entirely.

We report our experience on PBLs and highlight two unusual presentations along with emphasizing the fact that although PBL is a rare entity, still it should be kept in mind while dealing with bone lesions especially in the setting of an unusual presentation. A final diagnosis should be made only after proper clinical, radiological, ancillary studies, histopathological and immunohistochemical correlation.

The locally limited PBL should be differentiated from potentially systemic variant because they have different characteristics with regard to clinical outcome. There is a need to further analyze the local and systemic PBL separately.

Submission declaration

We declare that the work described has not been published previously and that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere including electronically in the same form, in English or in any other language, without the written consent of the copyright-holder.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Funding source

None.

Acknowledgments

We are very thankful to Prof. Ashraf Khan, MD, Anatomic Pathology, University of Massachusetts Medical School, USA; for his help in detailed immunohistochemical profiling and diagnosis of the second unusual case involving right ilium.

References

- [1] Unni KK, Hogendoorn PCW. World health organization classification of tumors. Pathology and genetics of tumors of soft tissue and bone. Lyon: IARC Press; 2002.
- [2] Lakshmaiah, et al. Primary non-Hodgkin's lymphoma of bone: poly-ostotic versus mono-ostotic subtypes. *ecancer* 2013;7:330.
- [3] Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the committee on Hodgkin's disease staging classification. *Cancer Research* 1971;31:1860–1.
- [4] Zinzani, et al. Primary bone Lymphoma: experience with 52 patients. *Journal of Hematology* 2003;88:03.
- [5] Oberling C. Les reticulosarcomes et les reticuloendotheliosarcomes de la moelle osseuse (sarcoma d'Ewing). *Bulletin de l'Association Française pour l'Étude du Cancer* 1928;17:259–96.
- [6] Parker F, Jackson H. Primary reticulum cell sarcoma of bone. *Surgery, Gynecology and Obstetrics* 1939;68:45–53.

- [7] Ivins JC, Dahlin DC. Malignant lymphoma (reticulum cell sarcoma) of bone. *Mayo Clinic Proceedings* 1963;38:375–85.
- [8] Vassallo, et al. Malignant lymphomas with primary bone manifestation. *Pathology—Research and Practice* 1987;182(3):381–9.
- [9] Mulligan ME, McRae GA, Murphey MD. Imaging features of primary lymphoma of bone *AJR. American Journal of Roentgenology* 1999;173:1691–7.
- [10] Heyning, Hogendoorn, et al. Primary non-Hodgkin's lymphoma of bone: a clinicopathological investigation of 60 cases. *Leukemia* 1999;13:2094–8.
- [11] Fidas P, Spiro I, Sobczak ML, Nielsen GP, Ruffolo EF, Mankin H, et al. Long-term results of combined modality therapy in primary bone lymphomas. *International Journal of Radiation Oncology Biology Physics* 1999;45:1213–8.
- [12] Coley BL, Higginbotham NL, Groesbeck HP. Primary reticulum cell sarcoma of the bone; a summary of 37 cases. *Radiology* 1950;55:641–58.
- [13] Salter M, Sollaccio RJ, Bernreuter WK, Weppelmann B. Primary lymphoma of bone: the use of MRI in pretreatment evaluation. *American Journal of Clinical Oncology* 1989;12:101–5.
- [14] Susnerwala, et al. Primary lymphoma of bone: experience of 39 cases at the Tata memorial hospital. *Indian Journal of Surgical Oncology* 1990;44:229–33.
- [15] Yasir Salam Siddiqui, et al. Pathological Fractures in primary non-Hodgkin's lymphoma of the bone: a case series with review of the literature. *Journal of Clinical and Diagnostic Research* 2013;7(3):513–7.
- [16] Jawad MU, Schneiderbauer MM, Min ES, Cheung MC, Koniaris LG, Scully SP. Primary lymphoma of bone in adult patients. *Cancer* 2010:871–9.