J Med Sci 2010;30(4):161-164
http://jms.ndmctsgh.edu.tw/3004161.pdf

Primary Non-Hodgkin's Lymphoma of Bone Presenting as Thoracic Spinal Compression Fracture: A Case Report and Literature Review

Ying-Tang Wang, Wei-Liang Chen, and Ching-Liang Ho*

Division of Hematology, Department of Medicine,
Tri-Service General Hospital, National Defense Medical Center, Taipei,
Taiwan, Republic of China

Here we report a non-Hodgkin's lymphoma (NHL) with initial manifestation as spinal cord compression fracture. A 23-year-old male presented to our emergency room with refractory lower back pain and deteriorating neurological presentations. An intraspinal tumor of the 12th thoracic vertebral body causing a total compression fracture was confirmed. Result of tissue biopsy and PET scan proved NHL without nodal involvement. Eight courses of anti-CD20 monoclonal antibody combined with chemotherapy, but without radiotherapy which was taken as the standard treatment in primary bone lymphoma, were prescribed. The patient survived for 3 years without tumor recurrence. Anti-CD20 monoclonal antibody, instead of radiotherapy, may provide an alternative treatment of choice for patients with primary bone lymphoma (PBL).

Key words: non-Hodgkin's lymphoma, bone, thoracic spinal compression fracture

INTRODUCTION

Non-Hodgkin's lymphoma (NHL) usually combines nodal and extranodal presentations. Although primary extranodal NHL is not unusual, primary NHL of bone (PBL) is a rare clinicopathologic entity, accounting for 5% of extranodal lymphomas and less than 2% of all lymphomas in adult.[1] The most frequent sites of presentation are the long bones, and pain is the common symptom.[2] NHL might be complicated at presentation by spinal cord fracture, and a retrospective study had reported a 1.3% incidence of bone lymphoma in biopsies obtained during vertebral augmentation procedures for spinal cord compression.[3] We describe a rare case of patient with PBL presenting as spinal cord compression without any nodal involvement.

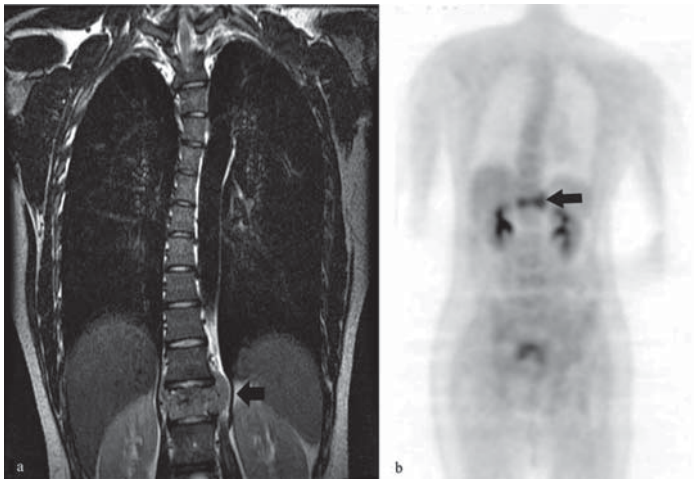

Fig. 1 Radiological appearance of the primary lymphoma of the bone. (a) Magnetic resonance imaging (MRI) of the thoracic spine demonstrates an intra-spinal soft tissue mass originating from the vertebral body of T12 (arrow) causes bony destruction and compression fracture. (b) Positron emission tomography (PET) scan shows a strong FDG uptake over the whole T12 spine (arrow) and no uptake in the nodal region.

CASE REPORT

A 23-year-old male was admitted to our hospital with lower back pain radiating into both lower legs for 2 months. The pain was described as numbing, tingling and sharp. He had worked at an ironworks as an electrician. Muscle sprain-related localized lumbar pain was sus-

Received: October 19, 2009; Revised: March 7, 2010; Accepted: April 12, 2010
*Corresponding author: Ching-Liang Ho, Division of Hematology/Oncology, Department of Medicine, Tri-Service General Hospital, National Defense Medical Center, No. 325, Sec. 2, Cheng-gong Road, Taipei 114, Taiwan, Republic of China. Tel: +886-2-87927208; Fax: +886-2-87927209; E-mail: indown@url.com.tw
Funding: None
Competing interests: None declared

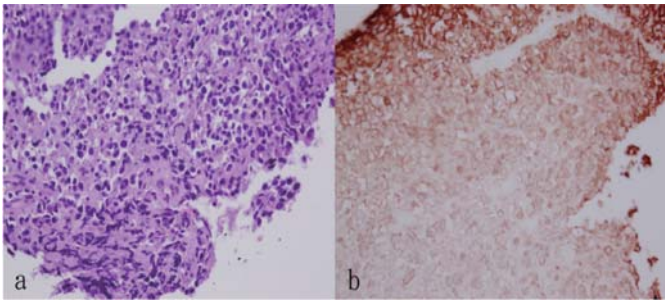

Fig. 2 Histopathological findings in the vertebral body of T12. (a) Diffuse infiltration of atypical lymphocytes with irregularly shaped nuclei (Hematoxylin-Eosin stain, ×400). Mitotic figures are frequent. (b) Immunohistochemical stain with anti-CD20 antibody, a marker of B-lymphoid cells, showing focal positivity within the lymphoid cell (×400).

pected initially. Lower back pain deteriorated after vigorous military training. Intermittent claudication developed afterward. For 1 week prior to admission, the patient had been confined to bed due to severe pain. On admission, the back was tender to percussion. Signs such as weakness with a decrease in muscle power in both legs were noted. X-rays of T-spine revealed a compression fracture of the 12th thoracic vertebral body (T12). Magnetic resonance imaging (MRI) of the thoracic spine showed multiple spinal lesions and an intraspinal tumor originating from the vertebral body of T12, causing impingement of the cord and nerve roots (Fig. 1a). His white blood cell count was 7.80×10^3/uL with 75% of neutrophil, and hemoglobin, 14.8 g/dL. The biochemistry revealed lactic dehydrogenase (LDH), 190 U/L, total calcium, 8.9 mg/dL, albumin, 3.6 g/dL, and total protein, 6.3 g/dL with A/G ration of 1.3. Percutaneous transpedicular biopsy of T12 was performed. Intraoperatively, the compressed vertebral body was reduced and bone cement was injected into the body.

Pathologically, the specimen revealed a picture of malignant lymphoid cell with dyscohesive and bizarre nuclei; positive staining for CD20 and Ki-67, and negative for CD3, CD44, CD138, CD10 and BCL-2. Diffuse large B-cell lymphoma (DLBCL) was confirmed (Fig. 2). The PET/CT scan revealed an increased FDG uptake over the whole T12 spine, with no abnormal FDG uptake throughout the nodal tissues (Fig. 1b). Primary DLBCL of bone, stage IE, IPI score: 1 complicated compression fracture of spinal cord was diagnosed. The patient was started on R-CHOP regimen (rituximab 400mg/m^2 on day 1, adriamycin 50mg/m^2 on day 1, cyclophosphamide 700mg/m^2 on day 1, and vincristine 1.4mg/m^2 (maximum 2mg) on day 1; prednisone 100mg orally on days 1 to 5, every 21 days) for 8 cycles. After 6 months of follow-up, MRI of the T-spine showed regressive lymphoma. The clinical manifestation is also free from tumor recurrence after a 3-year follow-up.

DISCUSSION

PBL was first recognized by Parker and Jackson in 1939 as a distinct entity.[4] In our institution, we could identify only three cases of PBL in 303 cases of NHL in the past decade, leading to an incidence of just 1%. Previous studies emphasized a predominance of long bone involvement, especially the femur.[2] However, Maruyama *et al*. reported that pelvis is the most commonly involved site in a single-institution study in Japan.[5] In a recent British retrospective study, Ramadan *et al*. reported that long bones and spines were the most frequently involved sites.[6] Although the incidence of PBL with involvement of spines varied from study to study (Table 1), the current case showed PBL manifested as vertebral compression fracture because of the peculiar initial clinical presentation. Shindle *et al*. have reported a 1.3% incidence of bone lymphoma in biopsies obtained during vertebral augmentation procedures,[3] while multiple myeloma, the most common cancer developing from vertebral compression fractures in 55-70% of patients, has shown a 2.8% incidence rate.[7] Ramadan *et al*. also demonstrated that half of the 42 patients with bony lymphoma of spine presented with spinal cord compression.[6] In essence, bone pain is the usual presenting symptom. Diffuse large B cell lymphoma (DLBCL) is the main histological subtype. The peak incidence of PBL is the fifth decade of life, with a male/female ratio of 1.8:1.[8]

Accordingly, all patients should have a biopsy-proven diagnosis of lymphoma established by an experienced hematopathologist using the terminology of the current World Health Organisation classification.[9] As the staging procedure improved over time, traditional staging investigations, including history, physical examination, CBC, LDH, CT scan of abdomen and pelvis and the site of presenting bone involvement, and random bone marrow biopsy might be insufficient. The combined use of CT, MRI and now PET is emerging, leading to a higher proportion of patients diagnosed with stage IV disease, which only defined cases with either multiple sites of bone involvement or diffuse involvement of a single large bone according to the Ann Arbor staging system. However, an appropriate definition has not been well established. The majority of studies defined PBL as a malignant lymphoid

Table 1 Previous reports of PBL

First author, Year of publicton (reference number)	Country	No. of patients	Years of enrollment into study	Median age	Percentage of DLBCL (%)	No. of involvement of spine (%)	No. of involvement of T-spine (%)
Ramaden, 2007 (6)	UK	131	1983-2005	63	79	42 (32)	NA
Maruyama, 2007 (5)	Japan	28	1995-2004	47	61	5 (18)	4 (14)
Ford, 2007 (11)	UK	22	1985-2003	50	91	4 (18)	1 (5)
Horsman, 2006 (10)	UK	37	1970-2003	55	73	6 (16)	NA
Beal, 2006 (15)	USA	82	1963-2003	48	80	7 (9)	NA
Stein, 2003 (8)	Israel	11	1979-2000	47	91	2 (18)	2 (18)
Baar, 1994 (16)	Canada	17	1975-1992	36	76	1 (6)	1 (6)
Dubey, 1997 (12)	USA	45	1967-1992	52	91	4 (8)	NA

infiltrate within bone with or without cortical invasion or soft tissue extension and without concurrent involvement of regional lymph nodes or distant viscera.[10,11,12] The WHO classification and previous reports have indicated that a single bone site with/without regional lymph nodes involvement (Group 1) or multiple bony lymphoma without visceral or lymph node involvement (Group 2) should be considered as PBL. Group 3, bone tumor with involvement of other visceral sites or lymph nodes at multiple sites is considered to be systemic lymphoma.[13] Maruyama *et al*. reported no significant difference in the 3-year overall survival rate between Group 1/2 and Group 3 (P = 0.74).[8] A recent Dutch paper showed that the criteria of PBL included dominant bony lesions with a minor degree of nodal involvement.[14] Thus, it could give a complete entity of extranodal NHL instead of systematic nodal NHL with extranodal involvement.

In terms of prognosis, the Ann Arbor staging system, developed for Hodgkin's lymphoma and widely employed for NHL, has been evidenced to be limited in prognostic significance in extranodal DLBCL. International Prognostic Index (IPI) score, once a powerful prognostic index, also fails to provide sufficient information for PBL outcomes.[15] In contrast, younger age at diagnosis had been widely reported as a statistically improved prognostic factor in several studies.[10,15] Horsman *et al*. reported that an age of < 60 years, complete response to treatment, and bony lymphoma rather than other extranodal lymphomas are favorable predictive factors.[10] Beal *et al*. showed that age < 40 years, lack of B symptoms, normal LDH level, and female gender were better prognostic factors.[15] Furthermore, Ramadan *et al*. identified three distinct groups, those of age < 60 years with IPI 1-3, age ≧ 60 with IPI 0-3 and age ≧ 60 with IPI 4-5 showing markedly different 5-year overall survival of 90%, 61% and 25%, respectively.[6] These findings raise the interest in whether an extensive staging workup is of prognostic value. Similarly, the PBL treatment seems to be a formula tailored to the patients' clinical grounds (e.g. age and clinical presentations) regardless of the stage and whether the lesions are primary or metastatic.

The optimal treatment regimen of PBL remains uncertain. Traditionally, the therapeutic strategy of PBL was irradiation or surgery before chemotherapy became available. There has been growing literature and experience in combined chemotherapy and radiotherapy, which is superior to chemotherapy or radiotherapy alone in PBL.[12,16,17] In a randomized clinical trial, Miller *et al*. concluded that the role of radiotherapy in PBL was valuable not only in reducing the number of chemotherapy courses, but also in producing superior overall survival and progression-free survival (PFS).[17] As chemotherapy improves over time accompanied by a remarkable survival benefit, it is reasonable to re-examine the role of radiotherapy.

Rituximab has become the first monoclonal antibody approved by the Food and Drug Administration (FDA) for the treatment of CD20+ NHL since 1997.[18] Several randomized studies in which rituximab was added to various chemotherapy regimens showed not only increased rates of complete response but also prolonged survival as compared with chemotherapy alone.[18] Similarly, Ramadan *et al*. reported a remarkable advantage of rituximab in PFS for patients with primary DLBCL of bone compared with those treated earlier without rituximab (3-year PFS 88% versus 52%).[6] The result is encouraging although the efficacy of rituximab in PBL needs to be proved with longer follow-up, larger sample size and more rigorous trials. Furthermore, rituximab in place of radiotherapy has not been well-evaluated. In the current case, the patient received 8 cycles of R-CHOP without radiotherapy and survived for 3 years. In view of this, the role of radiotherapy in the treatment strategy of PBL needs to be justified in the era of monoclonal antibody combined chemotherapy.

REFERENCES

1. Zucca E, Roggero E, Bertoni F, Conconi A, Cavalli F. Primary extranodal non-Hodgkin's lymphomas. Part 2: Head and neck, central nervous system and other less common sites. Ann Oncol 1999;10:1023-1033.
2. Heyning FH, Hogendoorn PC, Kramer MH, Hermans J, Kluin-Nelemans JC, Noordijk EM, Kluin PM. Primary non-Hodgkin's lymphoma of bone: a clinicopathological investigation of 60 cases. Leukemia 1999;13:2094-2098.
3. Shindle MK, Tyler W, Edobor-Osula F, Gardner MJ, Shindle L, Toro J, Lane JM. Unsuspected lymphoma diagnosed with use of biopsy during kyphoplasty. J Bone Joint Surg Am. 2006:88:2721-2724.
4. Parker F, Jackson H. Primary reticulum cell sarcoma of bone. Surg Gynecol Obstet 1939;68:45.
5. Maruyama D, Watanabe T, Beppu Y, Kobayashi Yukio, Kim SW, Tanimoto K, Makimoto A, Kagami Y, Terauchi T, Matsuno Y, Tobinai K. Primary bone lymphoma: a new and detailed characterization of 28 patients in a single-institution study. Jpn J Clin Oncol 2007;37:216-223.
6. Ramadan KM, Shenkier T, Sehn LH, Gascoyne RD, Connors JM. A clinicopathological retrospective study of 131 patients with primary bone lymphoma: a population-based study of successively treated cohorts from the British Columbia Cancer Agency. Ann Oncol 2007;18:129-135.
7. Togawa D, Lieberman IH, Bauer TW. Histological evaluation of biopsies obtained from vertebral compression fractures: unsuspected myeloma and osteomalacia. Spine 2005;30:781-786.
8. Stein ME, Kutan A, Rosenblatt KE, Drumea K, Ben-Shacher M, Zidan J, Haim N, Epelbaum R. Primary lymphoma of bone- a retrospective study. Oncology 2003;64:322-327.
9. Jaffe ES, Harris NL, Stein H, Vardiman JW. World Health Organization Classification of Tumors: Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC 2001.
10. Horsman JM, Thomas J, Hough R, Hancock BW. Primary bone lymphoma: a retrospective analysis. Int J Oncol 2006;28:1571-1575.
11. Ford DR, Wilson D, Sothi S, Grimer R, Spooner D. Primary bone lymphoma – treatment and outcome. Clinic Oncol 2007;19:50-55.
12. Dubey P, Ha CS, Besa PC, Fuller L, Cabanillas F, Murray J, Hess MA, B.B.A., Cox JD. Localized primary malignant lymphoma of bone. Int J Rad Oncol Bio Phys 1997;37:1087-1093
13. Fletcher C, Unni K, Mertens F. Pathology and genetics of Tumours of soft tissue and bone: World Health Organization Classification of Tumours. Lyon, France: International Agency for Research on Cancer; 2002;306-308.
14. Krol AD, le Cessie S, Snijder S, Kluin-Nelemans JC, Kluin PM, Noordijk EM. Primary extranodal non-Hodgkin's lymphoma (NHL): the impact of alternative definitions tested in the Comprehensive Cancer Centre West population-based NHL registry. Ann Oncol 2003;14:131-139.
15. Beal K, Allen L, Yahalom J. Primary bone lymphoma: treatment results and prognostic factors with long-term follow-up of 82 patients. Cancer 2006;106:2652-2656.
16. Baar J, Burkes RL, Bell R, Blackstein ME, Fernandes B, Langer F. Primary non-Hodgkin's lymphoma: a clinicopathologic study. Cancer 1994;73:1194-1199.
17. Miller TP, Dahlberg S, Cassady JR, Adelstein DJ, Spier CM, Grogan TM, LeBlanc M, Carlin S, Chase E, Fisher R. Chemotherpay alone complicated with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med 1998;339:21-26.
18. Cheson BD, Leonard JP. Monoclonal antibody therapy for B-cell non-Hodgkin's lymphoma. N Engl J Med 2008;359:613-626.