CASE REPORT

Diffuse large B-cell lymphoma, not otherwise specified presenting with bone and bone marrow involvement in the absence of lymphadenopathy

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Abstract A 74-year-old woman visited our hospital because of right chest pain and fatigue. Laboratory examinations revealed pancytopenia and an elevated level of serum lactate dehydrogenase. Although bone lesions were detected by computed tomography, there was no lymphadenopathy. Blastoid cells were evident in the bone marrow. From the patient's medical history and results of immunohistological and chromosomal analysis, she was diagnosed as having diffuse large B-cell lymphoma, not otherwise specified. This form of presentation of diffuse large B-cell lymphoma is very rare, and emphasizes the need for careful evaluation of such cases, including bone marrow biopsy for accurate diagnosis.

Keywords Diffuse large B-cell lymphoma · Not otherwise specified · Bone marrow involvement

Introduction

Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS), is the most common type of aggressive lymphoma, accounting for ~40 % of non-Hodgkin lymphomas (NHLs) [1]. CD5-positive DLBCL is an immunohistochemical subgroup accounting for ~5–10 % of cases of DLBCL, NOS [2]. It is well recognized that CD5-positive B-cell lymphomas such as mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL) sometimes transform into DLBCL during their clinical

course [3]. However, CD5-positive DLBCL initially expresses CD5 in the absence of any history of CLL and MCL. CD5-positive DLBCL differs genetically and immunohistochemically from transformed DLBCL [3]. Accordingly, CD5-positive DLBCL was newly classified as a unique subgroup of DLBCL, NOS in the 2008 revision of the World Health Organization (WHO) classification of hematopoietic and lymphoid tumors [4]. CD5-positive DLBCL is reportedly characterized as being chemotherapy-refractory, with extra-nodal involvement, central nervous system recurrence, and a poor prognosis in comparison with CD5-negative DLBCL [5–7].

Bone marrow involvement has been reported in about 10–25 % of DLBCL cases [8, 9], and is not so rare, especially in refractory DLBCL. However, DLBCL initially presenting with bone marrow involvement without peripheral lymphadenopathy has been reported only rarely. Here, we report a case of CD5-positive DLBCL initially presenting with bone and bone marrow involvement in the absence of lymphadenopathy, and describe the clinicopathological characteristics and impact of this condition with reference to the literature.

Case report

A 74-year-old woman was admitted to our hospital with a two-month history of general fatigue and right chest pain. Physical examination revealed no abnormality, with neither hepatosplenomegaly nor superficial lymphadenopathy. In addition to mild pancytopenia (WBC count 3400/ μ L with 0.5 % blastoid cells, Hb 11.1 g/dL, Plt 7.6×10^4 / μ L), the serum lactate dehydrogenase level was elevated to 826 IU/L. Computed tomography (CT) demonstrated bone lesions in the right rib and thoracic vertebra, but neither

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lymphadenopathy nor hepatosplenomegaly was evident (Fig. 1a, b). Bone marrow aspiration revealed large blastoid cells with basophilic cytoplasm and vacuoles, accounting for 23 % of nucleated cells (Fig. 2). Flow cytometry showed a predominant cell population that was positive for CD5, CD20, and Ig κ and negative for CD3, CD10, CD23, CD34, and Ig λ . MIB-1 was expressed by ~70 % of the abnormal cells. Southern blot analysis of bone marrow showed immunoglobulin heavy chain gene rearrangement, and chromosomal analysis of bone marrow showed complex karyotype abnormalities including t(3;22) (q27;q11.2)/IgL-BCL-6, suggesting a mature B-cell neoplasm (Fig. 3). On the other hand, bone marrow biopsy demonstrated diffuse cell infiltration and slight infiltration of the vascular lumina without significant findings of hemophagocytosis (Fig. 4). These cells were positive for CD5, CD20, BCL-6, and Ig κ and negative for myeloperoxidase, CD3, CD10, CD23, CD34, Ig λ , cyclin D1,

Multiple Myeloma Oncogene 1 (MUM1), and terminal deoxynucleotidyl transferase (TdT), suggesting no evidence of MCL. Moreover, previous laboratory examinations had revealed no history suggestive of CLL. From these results, we finally diagnosed this condition as DLBCL. The patient received 6 courses of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) without any adverse events. The lymphoma cells disappeared from the bone marrow and peripheral blood, and chromosomal analysis showed a normal karyotype after completion of the chemotherapy. In addition, positron emission tomography computed tomography (PET/CT) confirmed complete response (CR), which was maintained for 16 months.

Fig. 1 CT scan shows an abnormal soft tissue shadow at the right rib and lytic lesions in the thoracic vertebra (arrows) (a rib; b thoracic vertebra)

Fig. 2 Microscopic features of a bone marrow aspiration specimen. Morphologically, the bone marrow aspirate shows large blastoid cells with basophilic cytoplasm and vacuoles (May-Grünwald-Giemsa staining, ×1000)

Fig. 3 Chromosome analysis of the bone marrow. The karyotype is 45, XX, add (1) (q32), t(1;12) (p32;q24.1), t(3;22) (q27;q11.2), add (6) (q21), t(11;15) (q13;q22), add (17) (p11.2), -21

Fig. 4 Microscopic features of a bone marrow biopsy specimen. Lymphoma cells were demonstrated mainly outside of the lumina and minimally within them. In a small part of the specimen, large atypical cells in bone marrow show diffuse infiltration, slightly within CD34-positive endothelial cells (arrows) (CD34 immunostaining, $\times 400$)

Discussion

Here, we have documented a case of CD5-positive DLBCL in which the initial findings were bone lysis and bone marrow involvement in the absence of lymphadenopathy. DLBCL involving bone marrow is encountered less frequently than indolent lymphomas such as follicular lymphoma, MCL, and CLL [10]. Cases of DLBCL presenting with bone marrow involvement in the absence of lymphadenopathy at onset are reportedly very rare, accounting for only 1–3 % of all DLBCLs [9, 11]. On the other hand, Yamaguchi reported that among 109 cases of CD5-positive DLBCL, 16 showed bone marrow involvement in the absence of lymphadenopathy, suggesting that this feature was more common than in CD5-negative DLBCL [5]. Only 1 of these 109 cases showed bone and bone marrow involvement without lymphadenopathy. Therefore, our present case appears to represent a very rare form of CD5-positive DLBCL.

Diagnosis of CD5-positive DLBCL involving bone marrow without lymphadenopathy is not necessarily easy, because B-cell acute lymphoblastic leukemia/lymphoma (B-ALL/LBL) and other CD5-positive B-cell lymphoproliferative disorders, such as the blastoid variant of MCL, CLL, and other subtypes of DLBCL, must be carefully excluded. In the present case, the blastoid cells were morphologically similar to those of B-ALL/LBL. Although CD5-positive B-ALL/LBL has been reported in 2–4.5 % of B-ALL/LBL cases, it was possible to diagnose the present case as a mature B-cell lymphoproliferative disorder rather than B-ALL/LBL from the negative result of Tdt and presence of *BCL-6* translocation [12]. Also, because this case was immunohistochemically negative for cyclin D1,

t(11;14) (q13;q32)/*IgH-cyclin D1* translocation was not detected, and there was no prior history of CLL and MCL, the latter were excluded.

Cytogenetic abnormalities are also important for differential diagnosis. In this case, the lymphoma cells carried *BCL-6* translocation, which is one of the most common genetic abnormalities in B-cell lymphoma, especially DLBCL [13]. Although pre-B cells at a specific stage of development have been reported to exceptionally express BCL-6, BCL-6 is necessary for germinal center formation and is usually selectively expressed at a high level in germinal centers [13, 14]. *BCL-6* translocation is detected in 5–15 % of follicular lymphomas, Burkitt lymphomas, and in 20–40 % of DLBCLs, but is not usually detected in B-ALL/LBL, CLL, lymphoplasmacytic lymphoma, MCL, or marginal zone B-cell lymphoma [13]. Kramer has reported that *BCL-6* translocation is detected more frequently in DLBCL patients with extranodal disease than in those with nodal disease, although there is no significant correlation between *BCL-6* translocation and the sites of presentation including bone and bone marrow [15]. On the other hand, in one study, *BCL-6* translocation was reportedly observed in 6 of 66 CD5-positive DLBCL patients [6]. However, few reports have described whether *BCL-6* translocation correlates with the clinical features or prognosis of CD5-positive DLBCL, and the clinical significance of *BCL-6* translocation in this neoplasm is still unclear.

On the other hand, Kajiura has reported that 10 of 37 cases of DLBCL manifesting bone marrow involvement were CD5-positive [16]. These 10 cases included subtypes of DLBCL known as CD5-positive DLBCL and IVLBCL. IVLBCL is characterized by selective growth of large cells only in the lumina of small vessels of various organs [17]. However, some reports have indicated that CD5-positive DLBCL with partial intravascular proliferation accounted for 19–38 % of cases [5, 18]. Although there was no significant difference in survival between CD5-positive and CD5-negative IVLBCL, both CD5-positive IVLBCL and de novo CD5-positive DLBCL with partial intravascular proliferation showed poorer prognosis than CD5-positive DLBCL without intravascular proliferation [18]. These findings indicate that because intravascular proliferation of lymphoma cells is associated with an adverse prognosis of DLBCL regardless of CD5 expression, it is essential to evaluate intravascular proliferation precisely in bone marrow biopsy specimens. However, intravascular proliferation of lymphoma cells is not associated with lack of lymphadenopathy because CD5-positive DLBCL with and without vascular infiltration shows significantly more frequent lymphadenopathy than IVLBCL [18]. Although the mechanisms responsible for this distinction between IVLBCL and CD5-positive DLBCL have not yet been fully reported, the clinical features of the present case appear to overlap those of CD5-positive DLBCL and IVLBCL.

Some previous reports have documented that peripheral blood and bone marrow involvement significantly worsened the overall survival of DLBCL patients, irrespective of the International Prognostic Index score, whereas bone involvement did not [19, 20]. However, according to Miyazaki's report, which analyzed 329 cases of CD5-positive DLBCL, 81 cases (24 %) with bone marrow and/or peripheral blood invasion did not have an increased incidence of central nerve recurrence that would have strongly affected survival [7]. This suggests that CD5 expression is more important than bone marrow involvement and peripheral blood involvement as an adverse prognostic factor of DLBCL. In fact, the addition of rituximab to chemotherapy improves the survival of patients with CD5-positive DLBCL patients but does not decrease the CNS relapse rate even in rituximab era [7]. This suggests that a new treatment strategy is necessary for these lymphoma patients to overcome the limitation of rituximab combined chemotherapy. This also suggests although our case demonstrates a favorable short-term clinical course, maybe we should have considered additional prophylaxis of CNS relapse. On the other hand, some reports have documented that patients with CD5-positive DLBCL with bone marrow invasion in the absence of lymphadenopathy suffered rapid disease progression and died, regardless of intravascular infiltration [11, 16]. These problems make it difficult to clarify the clinicopathological features of CD5-positive DLBCL. However, there may be clinically and molecularly distinct subgroups among CD5-positive DLBCLs which initially show bone marrow involvement without lymphadenopathy.

In conclusion, we have described a very rare case of DLBCL, NOS presenting with bone and bone marrow involvement without lymphadenopathy. This condition showed some unusual histopathological features suggesting that careful evaluation of intravascular proliferation in bone marrow biopsy specimens is necessary for accurate diagnosis. Further studies will be needed to clarify the clinicopathological characteristics and prognostic impact of this condition.

Compliance with ethical standards

Conflict of interest None of the authors have any conflicts of interest to declare.

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