A Case of Primary Bone Marrow B-Cell Non Hodgkin's Lymphoma with Severe Thrombocytopenia: Case Report and A Review of the Literature

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Received: 30 August 2009 / Accepted: 26 April 2010 / Published online: 6 October 2010
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Abstract A 78-year-old man presented with persistent gingival bleeding. He had low platelet count of $1.0 \times 10^9/L$ without any lymphadenopathy. Bone marrow specimen showed diffusely distributed small-sized lymphocytes. Combined with immunophenotypic analysis, a diagnosis of primary bone marrow B-cell non-Hodgkin's lymphoma was made. Thrombocytopenia was considered to be caused by autoimmune destruction of platelets.

Introduction

Secondary occurrence of non-Hodgkin's lymphoma (NHL) in bone marrow is relatively common [1]. However, primary bone marrow NHL (PBNHL) is rarely seen [2]. Thus far, a total of 32 cases have been reported in the English literature [3–8]. In these cases, bone marrow biopsy revealed infiltration of lymphoma cells with a diffuse or interstitial pattern. Morphologically, mature small lymphocytes or medium-to-large-sized lymphoid cells were seen. Also, based on immunohistochemical stains, most cases were classified as lymphoma of B-cell or T-cell lineage. Among B-cell lymphomas, 7 cases were diagnosed as diffuse large B-cell lymphoma (DLBCL), but the other B-cell lymphoma cases could not be further classified due to lack of specific findings.

Although thrombocytopenia was commonly seen in previously reported cases of PBNHL, it was mostly mild and bone marrow suppression due to infiltration of lymphoma cells was suspected as a cause. Generally, immunologic abnormalities including autoimmune thrombocytopenia have been reported in patients with NHL. Hauswirth et al. reported that the prevalence of autoimmune thrombocytopenia in NHL was 0.72% [9].

Here we report a case of PBNHL associated with severe thrombocytopenia. Further, we review the past literature on primary bone marrow lymphoma and discuss clinical manifestations and diagnostic challenges.

Case Report

A 78-year-old man was admitted for gingival bleeding that had persisted for a week. On physical examination, petechiae were seen diffusely in the trunk and extremities without hepatosplenomegaly or lymphadenopathy. Laboratory findings on admission were as follows: hemoglobin, 7.5 g/dL; platelet, $1.0 \times 10^9/L$; white blood cells, $8.6 \times 10^9/L$ (64.0% neutrophils, 30.0% lymphocytes without any atypical lymphocytes, 6.0% monocytes by manual differential count); serum lactate dehydrogenase, 155 IU/L; immunoglobulin G (IgG), 2953 mg/dL, with IgG- κ type monoclonal protein; and soluble interleukin-2 receptor (sIL-2R), 5610 U/ml. Coagulation profiles were within normal ranges. Platelet-associated IgG (PA-IgG) was elevated to 10^4 ng/ 10^7 cells. Chest and abdominal computed tomography (CT) did not demonstrate either swelling of lymph nodes or hepatosplenomegaly.

Bone marrow aspiration showed hypercellular bone marrow consisting of 74% of small-sized lymphocytes with scant cytoplasm. The number of megakaryocytes was

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Fig. 1 Histologic features of iliac bone marrow. Small-sized lymphoid cells are diffusely proliferated (Hematoxylin and eosin stain, $\times 40$)

increased. Flow cytometric analysis of the bone marrow aspirate revealed that the lymphocyte expressed CD10, CD19, CD20, surface IgG, and κ -light chain. Immunohistochemical staining of the bone marrow biopsy specimen showed diffusely distributed lymphocytes (Fig. 1). The lymphocytes were CD10+ , CD20+ , CD79a+ , bcl-2+ , CD3- , CD5- , CD23- , CD138- , and cyclin D1- . Chromosome analysis of the cells showed normal karyotype. IgH/bcl-2 fusion was not detected in fluorescence in situ hybridization analysis. According to these findings, a diagnosis of PBNHL was made. The morphology and surface marker profile of the lymphoma cells was consistent with that of follicular lymphoma grade 1 in the WHO classification system. Autoimmune etiology was suspected as a cause of thrombocytopenia.

After 2 courses of rituximab and THP-COP (pirarubicin, cyclophosphamide, vincristine, and prednisolone), platelet counts elevated gradually to about $100 \times 10^9/L$ although bone marrow aspiration did not show any significant change in the distribution of lymphoma cells.

Discussion

Primary involvement of lymphoma in bone marrow is quite rare. In the 1980s, two reports of primary bone marrow lymphoma were done [3, 4]. However, in both reports, the diagnosis was made based only on physical examination and chest X-ray without CT scan. Therefore, there is a possibility of any lymphadenopathy not detected by those examinations. Ponzoni et al. reported four cases of lymphoma confined to bone marrow in 1994 [5]. Immunophenotyping revealed three cases of T-cell and one case of B-cell NHL. Detailed investigations of surface markers of

lymphoma cells were not performed in those cases. Chachashvili et al. also reported two cases of PBNHL [6]. In both cases, bone marrow was infiltrated by small lymphoid cells, which were derived from B-cell origin according to the analysis of immunophenotypes. Further subtype classification could not be done. Moreover, there have been two reports of primary bone marrow diffuse large B-cell lymphoma [7, 8]. In both reports, diagnosis was based on findings of diffuse infiltration of large lymphoid cells and immunophenotypic analysis.

At present, classification of NHL subtypes consists of a combination of morphologic, immunophenotypic and genetic characteristics. In case of PBNHL, analysis of lymphoma cells in bone marrow is required for subtype diagnosis without lymph node specimens. In this patient, the morphology of lymphoma cells was characterized by small, relatively mature lymphocytes with scant cytoplasm and diffuse infiltration pattern was observed. The pattern of bone marrow involvement in lymphomas is divided into 5 major patterns; focal nonparatrabeular, focal paratrabeular, intrasinusoidal, diffuse interstitial, and diffuse solid [10]. Combinations of these patterns are frequent. Analysis of the pattern is useful for classification, but each pattern is not specific for a particular type of lymphoma [11]. Moreover, the presence of follicular structures is mostly associated with follicular lymphoma and might be useful for diagnosis if detected. However, follicular pattern is not frequently seen and Torlakovic et al. reported that the pattern was identified in only 12 of 260 cases of bone marrow infiltration by follicular lymphoma [12]. Therefore, in most cases including follicular lymphoma, it is difficult to diagnosis only based on the involvement patterns.

In this case, morphology of the lymphoma cells is typical of chronic lymphocytic leukemia (CLL), and makes DLBCL or Burkitt lymphoma unlikely. However, surface markers were negative for CD5 or CD23, and peripheral lymphocyte count was not increased. These findings do not match features of CLL. Also, the lymphoma cells were positive for surface membrane IgG, which does not meet the possibility of acute lymphoblastic leukemia. Considering surface marker pattern and morphology, follicular lymphoma was suspected. In this case, t(14; 18) chromosomal translocation, which is often seen in follicular lymphoma, was not detected. However, bcl-2 gene rearrangement is less frequently seen in Japanese cases and Amakawa et al. reported that it was detected in only 30% of follicular lymphoma cases in Japan [13].

The vast majority of the previous cases of primary bone marrow lymphoma had pancytopenia or bicytopenia at diagnosis [3–8]. The cause of cytopenia was estimated to be associated with infiltration of lymphoma cells and thrombocytopenia was not severe in most cases. In our

case, bone marrow aspiration revealed increased megakaryocytes. Moreover, the platelet count decreased quickly after platelet transfusion. In addition, platelet count recovered after two courses of chemotherapy although bone marrow aspiration showed little change in infiltration of lymphoma cells. Therefore, it seems that thrombocytopenia is due to autoimmune destruction rather than bone marrow suppression associated with infiltration of lymphoma cells. Indeed, autoimmune thrombocytopenia is reported in some cases of NHL [9].

In the treatment of autoimmune thrombocytopenia in NHL patients, prednisolone alone is often ineffective, and chemotherapy for the lymphoma is recommended [9]. In this case, the patient is considered to have recovered from thrombocytopenia due to the administration of THP-COP and rituximab.

In conclusion, we have reported PBNHL complicated with severe thrombocytopenia. It is sometimes difficult to diagnose subtypes of PBNHL since the criteria for diagnosis are not well established. In addition to analysis of morphology and infiltration pattern, detailed investigation of immunophenotypic features is useful for narrowing down the diagnosis.

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