Journal of Hematopathology (2019) 12:41–45
https://doi.org/10.1007/s12308-019-00342-2

CASE REPORT

Leukemic presentation of high-grade B cell lymphoma with MYC and BCL2 rearrangement—a series of two cases and review of literature

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Received: 13 November 2018 / Accepted: 14 January 2019 / Published online: 31 January 2019

Abstract

High-grade B cell lymphoma (HGBL) is a recently introduced category of aggressive mature B cell lymphoma which is clinically and biologically distinct from diffuse large B cell lymphoma (DLBCL), NOS, and Burkitt Lymphoma. HGBL consists of two categories; the first category includes HGBL with *MYC* and *BCL2* and/or *BCL6* rearrangement which is so-called double or triple hit lymphoma. The second category includes HGBL, NOS which lacks genetic double or triple hit; however, its morphology is intermediate between DLBCL and Burkitt lymphoma or appear blastoid. Clinically, patients present with advanced disease, bone marrow involvement, elevated lactate dehydrogenase (LDH), extranodal disease which includes CNS involvement and a high international prognostic index (IPI). Leukemic presentation has been described in various types of B and T cell non-Hodgkin lymphoma; however, peripheral blood involvement as an initial presentation is seldom described in the literature for HGBL with *MYC* and *BCL2* rearrangement. Here, we report two cases of HGBL whose initial presentation was leukocytosis with peripheral blood involvement mimicking acute leukemia.

Keywords High-grade B cell lymphoma · Leukemic presentation · *MYC* and *BCL2* rearrangement

Introduction

High-grade B cell lymphoma (HGBL) is a recently introduced category of aggressive, mature B cell lymphomas which is clinically and biologically distinct from diffuse large B cell lymphoma (DLBCL), NOS, and Burkitt Lymphoma (BL) [1]. Clinically, patients with HGBL present with advanced disease, bone marrow involvement, elevated lactate dehydrogenase, extranodal disease, and a high international prognostic index [2]. Leukemic presentation has been described in various types of B and T cell non-Hodgkin lymphoma [3]; however, peripheral blood involvement as an initial presentation is seldom described in the literature for high-grade B cell lymphoma with *MYC* and *BCL2* rearrangements. Here, we report two cases of B cell lymphoma whose initial presentation included leukocytosis with peripheral blood involvement, mimicking acute leukemia. Both cases had rearrangements of *MYC* and *BCL2*; however, the second case most closely resembled circulating follicular lymphoma at initial evaluation.

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Clinical history

Case 1

The patient is a 64-year-old male without any significant past medical history who presented to the emergency department with severe back pain, fever, night sweats, fatigue, and weight loss. His physical examination was unremarkable on admission. Complete blood count revealed a hemoglobin level of 11.7 g/dL, a total leukocyte count of 21,700/mL with 38% blast-like cells, and a platelet count of 71,000/mL. A provisional diagnosis of acute leukemia was made on the peripheral blood smear which revealed medium-sized blast-like cells with dispersed nuclear chromatin, prominent nucleoli and scant, slightly basophilic cytoplasm and a bone marrow biopsy was recommended. However, the final diagnosis was HGBL with *MYC* and *BCL2* rearrangement based on flow

cytometry, cytogenetics, and FISH analysis. The patient underwent two cycles of high-dose hyper-CVAD (fractionated cyclophosphamide, vincristine, adriamycin, and dexamethasone) and experienced a significant response. Follow-up blood film review showed a total leukocyte count of 400/mL with no blast-like cells. Due to insurance issues, the patient transferred to another hospital for follow-up and no further details are available.

Case 2

A 55-year-old man with a past medical history significant for hypertension presented to the emergency department with a clinical concern for acute leukemia. He initially presented to a local hospital for a 1-week history of fatigue, malaise, and dyspnea. He also recently noticed bilateral axillary and inguinal lymphadenopathy. The complete blood count at our institution revealed a hemoglobin level of 7.2 g/dL, total leukocyte count of > 400,000/mL, and a platelet count of 62,000/mL. Bone marrow biopsy was performed and a final diagnosis of HGBL with *MYC* and *BCL2* rearrangement was made based on flow cytometry, cytogenetics, and FISH analysis. The patient was scheduled to receive 6 cycles of chemotherapy which consisted of one cycle of R-EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) and five cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). He will be maintained on rituximab for 2 years. After one cycle of R-EPOCH, the patient demonstrated a marked response with reduction in total leukocytes from > 400,000/mL to 200/mL and repeat CT showed stable anterior mediastinal mass and axillary and inguinal lymphadenopathy.

Materials and methods

Peripheral blood and bone marrow aspirate smears were stained with Wright-Giemsa. The bone marrow clot and core biopsy specimens were fixed in formalin, sectioned after decalcification of the core biopsy, and stained with hematoxylin and eosin by standard protocol. Immunostaining was performed following the standard protocol on a Dako Immunostainer (Dako, Carpinteria, CA). The following antibodies were performed: CD3, CD20, PAX5, BCL2, BCL6, CD10, MUM1, Ki67, C-MYC, and Cyclin D1. In addition, an EBV stain for early RNA transcripts EBER-1 and EBER-2 by chromogenic in situ hybridization was also performed. Six-color flow cytometry was performed on a FACSCanto cytometer using FACSDiva software (Becton-Dickinson, San Jose, CA) using standard protocols. The following antibody panels were used: IgK/Dako, IgL/Dako, CD38, CD19, CD45, CD5, CD23, CD10, CD20, CD11c, CD4, CD8, CD3, CD7, CD45RA, CD57, CD34, C-KIT, CD56, CD71, CD123, CD15, CD33, HLA-DR, CD11b, CD16, CD13, CD41, CD14, CD64, CD138, CD37, CD44, CD79b, cyto MPO, and TdT. Conventional cytogenetic was performed on bone marrow aspirate sample which was harvested and cultured following 24 and 48 h of incubation periods in *Chang Marrow* medium (Irvine Scientific). Chromosome spreads were G-banded by standard trypsin-Giemsa banding (GTG) technique and a total of 20 metaphase cells were microscopically analyzed. FISH analysis for *MYC*, *BCL6*, and *BCL2* was performed using the LSI *MYC* or *BCL6* dual-color break apart and LSI *IGH@BCL2* dual-color, dual fusion probes (Abbott Laboratories, Des Plaines, IL, USA).

Result

Case 1

Peripheral blood smears revealed medium- to large-sized blast-like cells with dispersed nuclear chromatin, prominent nucleoli and scant, slightly basophilic cytoplasm (Fig. 1). Flow cytometric analysis detected a lambda restricted clonal B cell population expressing CD45, CD19, CD20, CD22, and CD10 without TdT, MPO, or CD34. Bone marrow aspirate and trephine biopsy revealed a hypercellular bone marrow (> 90% cellularity) replaced by medium- to large-sized neoplastic lymphoid cells which were positive for CD10, BLC2, and BCL6 with a high Ki67 proliferation index (over 90%) (Fig. 2a and d). FISH analysis demonstrated *MYC*/*BCL2* gene rearrangement (Fig. 2b and c). which was confirmed by karyotyping as t(8;22)(q24.1;q11.2) and t(14;18)(q32;q21.3). Secondary cytogenetic abnormalities were also detected which included add (9)(p22) and del(16)(q22). The distinct cytogenetic abnormalities with rearrangement of *MYC* and *BCL2* genes were consistent with a diagnosis of HGBL with *MYC* and *BCL2* rearrangement.

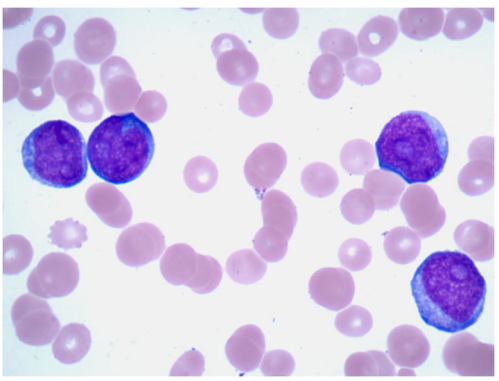

Fig. 1 Peripheral blood smear with medium- to large-sized blast-like cells with dispersed chromatin, prominent nucleoli, and scant basophilic cytoplasm (Giemsa, × 1000)

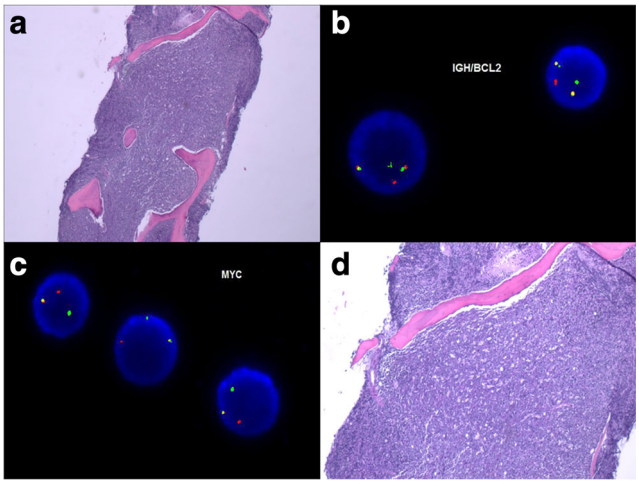

Fig. 2 **a** Hypercellular bone marrow with diffuse involvement by atypical lymphoid cells (H&E, ×40). **b** Dual color fusion probe for *IgH* gene and *BCL2* gene shows juxtaposed signal consistent with *IgH/BCL2* rearrangement. **c** *MYC* break apart probe shows separate red and green signals, consistent with *MYC* translocation. **d** Hypercellular bone marrow with diffuse involvement by atypical lymphoid cells replacing normal marrow elements (H&E, × 100)

Case 2

A peripheral blood smear showed marked lymphocytosis consisting of small- to intermediate-sized cells with irregular/convoluted nuclei, mature chromatin, and scant to moderate cytoplasm. (Fig. 3). Peripheral blood flow cytometric analysis detected lambda surface light chain restricted clonal B cells expressing CD45, CD19, bright CD20, bright CD38, dim CD5, dim CD10, CD37, and CD79a without TdT, MPO, CD23, CD11c, CD3, and CD44. The neoplastic B cells had a low S-phase fraction (< 1%). The bone marrow biopsy was hypercellular (> 90% cellularity) and replaced by medium-sized neoplastic lymphoid cells (Fig. 4a and d). By immunohistochemical studies, the neoplastic cells were positive for CD20, PAX5, BCL2, and MYC with minimal reactivity for BCL6 and CD10 with a low Ki67 proliferation index (~ 35%) (Fig. 4b and c). They were negative for MUM1, cyclin D1, SOX11, EBV, and HHV8. Fluorescence in situ hybridization analysis was positive for *MYC* and *BCL2* gene locus rearrangement in 96% and 95.3% of cells, respectively. The karyotype was complex, 47-49,XY,+add(X)(q22),t(1;9)(p21;p24),add(3)(p25),+7,der(8)t(8;14)(q24.2;q32.3),der(9)t(9;12)(p22;q13),-12,del(13)(q12q14),der(14)t(8;14)(q24.2;q32.3),add(8)(q24.3),-add(14)(q32.3), add(17)(p11.2),der(18)t(14;18)(q32.3;q21.3),+der(?)(?::14q32.3::18q21.3 18qpter),mar13[cp15]. Prior to FISH and karyotyping, the diagnosis of circulating follicular lymphoma was entertained. Ultimately, the patient was diagnosed with "double hit" B cell lymphoma with rearrangement of *MYC* and *BCL2* genes.

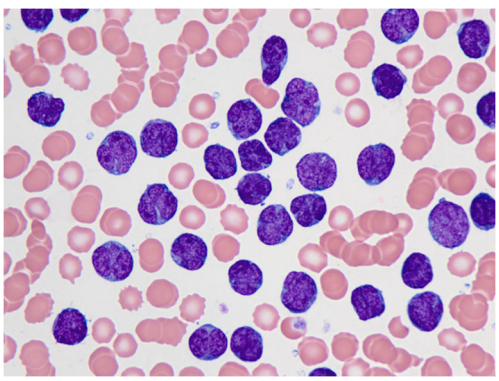

Fig. 3 Peripheral blood smear with marked leukocytosis with small- to intermediate-sized atypical lymphoid cells with irregular/convoluted nucleus, slightly mature chromatin, and scant to moderate cytoplasm (Giemsa, × 1000)

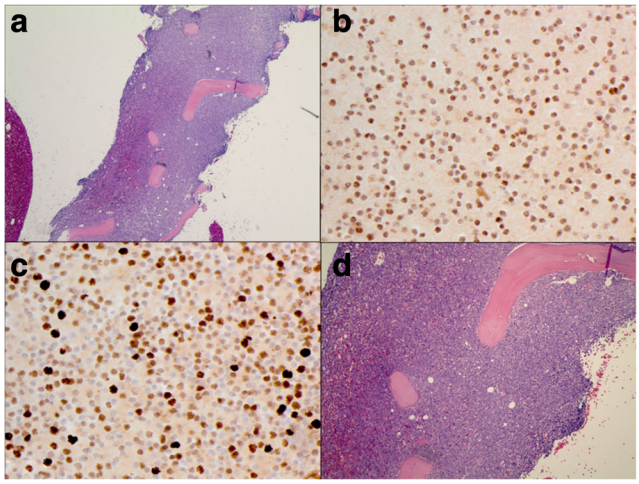

Fig. 4 **a** Hypercellular bone marrow with diffuse involvement by atypical lymphoid cells (H&E, ×40). **b** The Ki67 proliferation index done on a peripheral blood cell clot was relative low (35%)(Ki67 IHC,×200). **c** Neoplastic cells were positive for MYC (> 50%) (MYC IHC, × 200). **d** Hypercellular bone marrow with diffuse involvement by atypical lymphoid cells replacing normal marrow elements (H&E, × 100)

Discussion

The 2016 revision of the World Health Organization classification of lymphoid neoplasms eliminated the category of B cell lymphoma, unclassifiable, with features intermediate between diffuse large B cell lymphoma and Burkitt lymphoma and introduced HGBL as a separate entity; emphasizing the importance of the *MYC*, *BCL2*, and *BCL6* oncogenes. This category includes the so-called double and triple hit lymphomas which have an aggressive clinical course and poor outcome [4]. Approximately, 80% of the cases in the "double hit lymphoma" category harbor concurrent *MYC* and BCL2 translocations and the remaining 20% harbor *MYC* and *BCL6* translocations [4].

These HGBLs typically express CD19, CD20, CD79a, and PAX5 and lack TdT. CD10 and BCL6 expression is found in majority of these lymphomas (75–90%) and IRF4/MUM1 is

expressed in approximately 20% of cases [1]. Almost all cases with *BCL2* translocation have strong cytoplasmic expression of the BCL2 protein by immunohistochemical study. The Ki67 proliferation index and MYC protein expression can be highly variable and cannot be used to screen cases toward MYC fluorescence in situ hybridization studies. HGBL can be indistinguishable from DLBCL; hence, double hit status should be investigated in all DLBCL cases using cytogenetic or molecular studies [1]. CD18, CD43, CD44, and CD54 are adhesion molecules which have been reported to be overexpressed or underexpressed in Burkitt lymphoma relative to other non-Hodgkin lymphoma subtypes particularly diffuse large B cell lymphoma [5]. CD44 has role in lymphoma dissemination and is associated with worse prognosis and the majority of Burkitt lymphoma lack expression of CD44 [5]. Our second case lacked CD44 raising possibility of Burkitt lymphoma which was ruled out by FISH and cytogenetic studies.

Clinically, a majority of patients present with advance disease including multiple extranodal sites of involvement. Bone marrow and central nervous system are among the most common extranodal sites. Most patients have elevated lactate dehydrogenase levels with a high international prognostic index [6].

Leukemic presentation with extensive bone marrow and peripheral blood involvement, as in our two cases, has been described in various B and T cell non-Hodgkin lymphomas. The likelihood of leukemic dissemination depends on the lymphoma subtype [3]. Matutes et al. [7] have described leukemic presentation of mantle cell lymphoma in 58 patients. Sarkozy et al. [8] have described 37 cases of follicular lymphoma with leukemic phase at diagnosis which was associated with poor prognosis. Similarly, authors have described cases of DLBCL [9, 10], angioimmunoblastic T cell lymphoma [3] and anaplastic large cell lymphoma [11] with an unusual overt leukemic phase at diagnosis. Peripheral blood lymphocytosis at initial presentation is seldom described in high-grade B cell lymphoma with *MYC* and *BCL2* rearrangement [12]. Extensive literature review found only one case of "triple hit lymphoma" with a leukemic presentation [13].

B cell lymphomas with *MYC* and *BCL2* rearrangements can have diverse pathologic features. Some cases of follicular lymphoma may have a "double hit" genotype [1]. In the absence of cytogenetic information, our second case would have been classified as follicular lymphoma in leukemic phase given the morphologic features, low Ki67 proliferation index, and low S-phase fraction. Beltran et al. have described 7 patients with the pathologic diagnosis of follicular lymphoma who presented with leukemia [14]. These cases followed an aggressive clinical course. Most described cases had t(14;18), but *MYC* gene status was not discussed. This, as with HGBL, highlights the discordancy between Ki67 immunohistochemical proliferation index and disease biology. The use of Ki67 to screen cases for further *MYC*, *BCL2*, and *BCL6* studies is not recommended.

The optimal treatment regimen for HGBL has not yet been established. In selected patients, therapy intensification, such as R-EPOCH or Hyper-CVAD, has led to superior progression free survival [6, 15]. However, many HGBL patients have poor functional status and are thus poor candidates for high-dose chemotherapy [4]. With R-CHOP, the complete response rate is relatively low and overall survival is poor with a median survival of 4.5–18.5 months [1]. Intensified chemotherapy may be more appropriate in younger, healthier patients [4].

In summary, the initial presentation of HGBL can mimic leukemia, including follicular lymphoma in a leukemic phase, and a high level of suspicion must be maintained to arrive at the correct diagnosis.

Compliance with ethical standards

Conflict of interest None.

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