Journal of Hematopathology (2020) 13:169–177
https://doi.org/10.1007/s12308-020-00400-0

CASE REPORT

Transformation of de novo high-grade B cell lymphoma with *MYC* and *BCL2* rearrangements to double-hit B lymphoblastic leukemia/lymphoma: a case report and review of literature

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Received: 24 March 2020 / Accepted: 19 May 2020 / Published online: 6 June 2020

Abstract

High-grade B cell lymphomas with *MYC* and *BCL2* and/or *BCL6* rearrangements ("double-hit" lymphoma (DHL)/"triple-hit" lymphoma (THL)) are mature B cell neoplasms with highly aggressive clinical behavior and poor response to therapy. Lymphoblastic transformation of mature B cell neoplasms is an uncommon event that is best recognized for follicular lymphoma (FL). To our knowledge, only one case of "B lymphoblastic" transformation of de novo DHL has been reported in the literature. Here, we describe another case of such transformation. The patient was a 57-year-old man who presented with hypercalcemia, high lactate dehydrogenase (LDH), and multiple lytic bone lesions and was diagnosed with high-grade B cell lymphoma with *MYC* and *BCL2* rearrangements. The neoplastic cells were positive for CD45, CD19, CD20, CD79a, PAX5, CD10, BCL6, and BCL2 and negative for CD34, CD99, and terminal deoxynucleotidyl transferase (TdT). The patient received chemotherapy followed by autologous stem cell transplant and achieved complete remission. Nine months after the initial presentation, he developed general weakness and found to have cytopenias and circulating blasts. Bone marrow examination revealed extensive involvement by a high-grade B cell neoplasm co-expressing PAX5, CD10, and BCL2, in addition to precursor markers TdT and CD99. There was loss of CD20, CD79a, and BCL6 expression, and CD34 remained negative. A diagnosis of B lymphoblastic leukemia/lymphoma (B-LBL) was established. Similar *MYC* and *BCL2* rearrangements were identified. *IGH* gene rearrangement studies confirmed clonal relatedness. The patient passed away 3 days after bone marrow examination. This case represents an extremely rare case of DHL transformation to B-LBL.

Keywords High-grade B cell lymphoma · Double-hit lymphoma · B lymphoblastic leukemia/lymphoma · Transformation · *MYC* and *BCL2* rearrangements

Introduction

High-grade B cell lymphomas (HGBCLs) with *MYC* and *BCL2* and/or *BCL6* translocations (DHL/THL) are a group of hematologic malignancies characterized by aggressive behavior, high International Prognostic Index (IPI), and frequent extra-nodal and central nervous system (CNS) involvement [1–3]. The adverse outcome is secondary to the survival advantage of tumor cells resulting from a combination of enhanced proliferation (*MYC* and *BCL6* rearrangements) and decreased apoptosis (*BCL2* rearrangement). These are mature B cell neoplasms arising as de novo disease and do not include secondary cases resulting from the transformation of low-grade B cell neoplasms such as FL [1]. B Lymphoblastic leukemia/lymphomas (B-ALL or B-LBL), on the other hand, are neoplasms of precursor B-cells expressing markers of immaturity including CD34, CD99, and TdT in association with an immunophenotypic profile associated with arrested maturation such as lack of CD20 and surface immunoglobulin light chain expression. Most common cytogenetics and molecular aberrations in B-LBL include t(12;21), t(9;22), *MLL* (11q23)

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rearrangements, hyperdiploidy, hypodiploidy, and *BCR-ABL1*-like genetic profile [1, 4]. Blastic transformation of mature B cell neoplasms has been uncommonly reported. Maybe the best known such transformation is lymphoblastic transformation of FL [1]. This is characterized by blastic morphology, loss of follicular architecture, and acquisition of TdT. Such transformation is often associated with *MYC* rearrangements and highly aggressive course [5–11].

To our knowledge, only one report of lymphoblastic transformation of de novo DHL is present in the literature [12]. Here, we report a novel case of DHL who relapsed with blastic morphology and immunophenotypic evolution associated with the acquisition of several precursor features. A review of the relevant literature with discussion on challenges in immunophenotypic assessment of immaturity is provided.

Clinical history

In June 2018, a 57-year-old man presented to the emergency room with dizziness and was found to have hypercalcemia of 4.78 mmol/L (normal range, 2.10–2.69 mmol/L) and high LDH of 1628 U/L (normal range, 100–235 U/L). Complete blood count (CBC) showed hemoglobin of 163 g/L (normal range, 137–180 g/L), platelet count of 229 × 10^9/L (normal range, 150–400 × 10^9/L), and leukocytosis of 16.7 × 10^9/L (normal range, 4.0–11.0 × 10^9/L) with neutrophilia of 12.1 × 10^9/L (normal range, 2.0–8.0 × 10^9/L). Computed tomography (CT) scan demonstrated a bone lytic lesion in the posterior right sacrum.

Biopsy of the sacral lesion showed diffuse infiltrate of intermediate-sized lymphocytes with a round to oval nuclei and dispersed chromatin (Fig. 1a). Immunohistochemical studies showed that the neoplastic cells were positive for CD45, CD20 (subset, variable), CD10, BCL2 (strong), and BCL6 and negative for CD3, CD5, Cyclin-D1, CD30, and MUM-1. Precursor markers CD34 and TdT were negative. Ki-67 showed a proliferation index of more than 90% (Fig. 1b). Flow cytometry identified a markedly expanded population of CD19 (dim) positive B lymphocytes, with moderate CD45 expression, intermediate between lymphocyte, and blast gates, aberrantly co-expressing CD10, with heterogeneous CD20 expression, lacking surface and cytoplasmic immunoglobulin light chain expression (Fig. 1c and data not shown). CD34 and nTdT were negative by flow cytometry. The FISH analysis demonstrated *MYC* rearrangement in association with typical (34.5%) and atypical (56.5%) *IGH/BCL2* rearrangements (Fig. 1d). The diagnosis of high-grade B cell lymphoma with *MYC* and *BCL2* rearrangements was established.

Peripheral blood smear showed the presence of circulating neoplastic cells with round to occasionally irregular nuclei, slightly dispersed chromatin, multiple distinct nucleoli, and small amounts of basophilic cytoplasm (Fig. 2a). Bone marrow examination showed extensive involvement by neoplastic lymphocytes showing mild pleomorphism (Fig. 2b-c) with similar immunophenotype as seen in the sacral lesion (Fig. 2d, positive for CD20 and PAX5, dim variable CD79a expression, negative for CD34, TdT, and CD99). *IGH* gene rearrangement by PCR on the sacral lesion revealed very weak isolated peaks without a polyclonal background and was interpreted as insufficient for the detection of a monoclonal population. PCR analysis on the bone marrow showed a monoclonal gene rearrangement with the size of the clonal product at 331 nt (Fig. 4a).

Imaging studies showed involvement of the liver in addition to bone and bone marrow, consistent with stage IV disease. The patient received 4 cycles of R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) and 2 cycles of high-dose methotrexate for CNS prophylaxis, 4 cycles of R-DICEP (rituximab, dose-intensive cyclophosphamide, etoposide, cisplatin) stem cell mobilization chemotherapy followed by high-dose therapy with busulfan, melphalan, and autologous stem cell transplantation in November 2018. A bone marrow biopsy prior to transplant (September 2018) confirmed morphologic remission status and positron emission tomography/computed tomography (PET/CT, October 2018) showed complete metabolic remission.

In March 2019, the patient presented to the emergency room with general weakness and decreased urine output. CT scan showed an elongated soft tissue mass extending from the right temporal fossa into the infratemporal fossa. The mass caused destruction of the right lateral orbital wall inferiorly with protrusion into the extraconal fat as well as thinning of the right maxillary sinus lateral wall. A smaller intracranial soft tissue mass adjacent to the left sphenoid greater wing was present. New patchy ground-glass opacities of both lungs and small bilateral pleural effusions were evident. The spleen was larger now, measuring 14.2 cm (previously measured 12.5 cm). Recurrence in the left sciatic notch within the pelvis and multifocal soft tissue masses were identified.

CBC showed anemia (hemoglobin of 94 g/L, normal range, 137-180 g/L) and thrombocytopenia (platelet of 47 × 10^9/L, normal range, 150-400 × 10^9/L) with circulating blasts. Blasts were small to intermediate in size with round to slightly irregular nuclear contours, finely dispersed chromatin, inconspicuous nucleoli, and scanty agranular cytoplasm (Fig. 3a). Peripheral blood flow cytometry detected an expanded fraction of circulating dimCD45, CD10, and HLA-Dr positive events (45%) heterogeneously co-expressing TdT. CD19 and CD33 were dim/equivocal. CD34, CD117, CD13, cytoplasmic MPO, cytoplasmic CD3, cytoplasmic CD79a, and cytoplasmic IgM were all negative (not shown).

Bone marrow aspirate and biopsy showed markedly hypercellular marrow (85-90% cellular) with extensive involvement by neoplastic cells with blastoid morphology (> 95% replacement) (Fig. 3b, c). Immunohistochemical studies

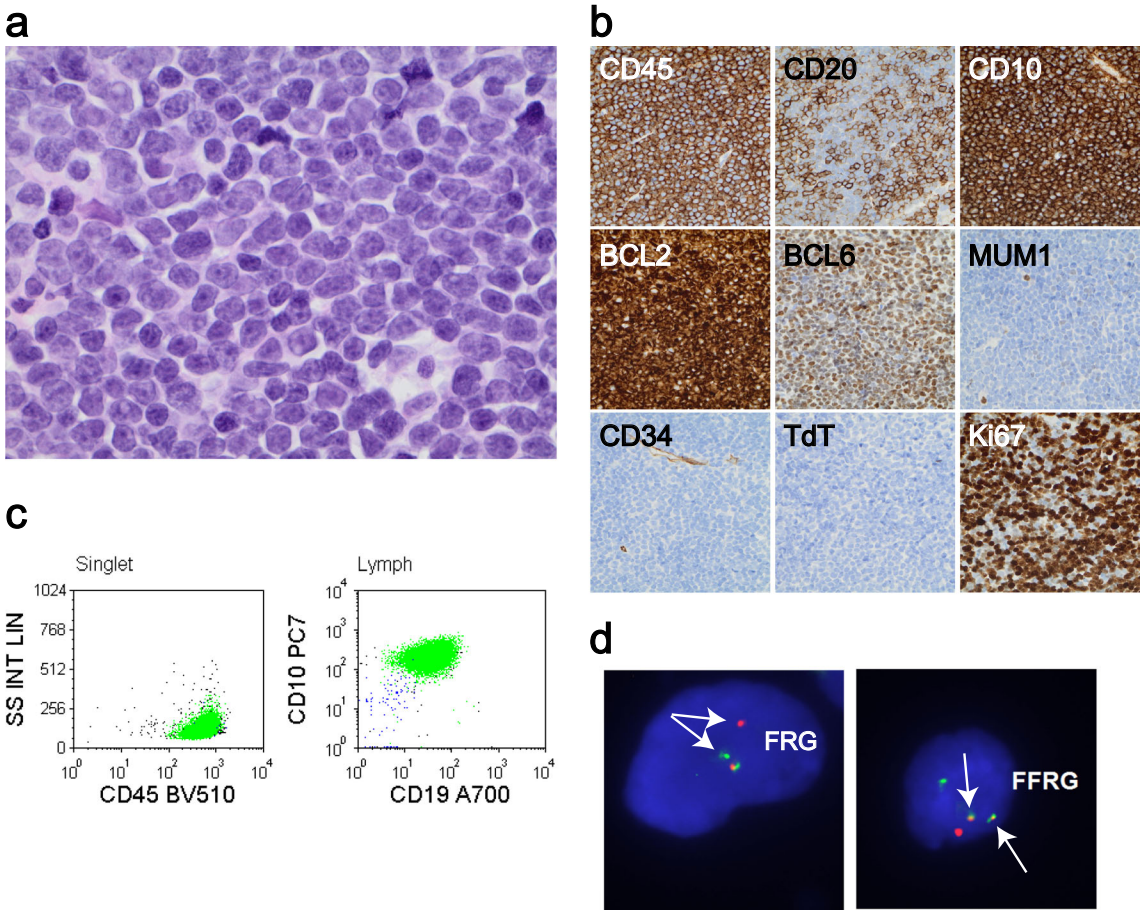

Fig. 1 **a** Biopsy of the sacral lesion showed diffuse proliferation of intermediate-sized lymphoid cells (× 1000). **b** Immunohistochemical studies (× 400) showed that the neoplastic cells are positive for CD45, CD20, CD10, BCL2, and BCL6 and negative for MUM1, CD34, and TdT. Ki-67 showed an increased proliferation index of more than 90%. **c** Flow cytometry identified an expanded population of CD19 (dim)-positive B lymphocytes, with moderate CD45 expression (intermediate between lymphocyte and blast gates) and aberrant co-expression of CD10. **d** FISH studies showed *MYC* rearrangement (left panel, white arrows highlight separation of break-apart *MYC* probes) in association with *IGH/BCL2* rearrangement (right panel, white arrows highlight fusion of *BCL2* (red) and *IGH* (green) probes)

showed that the neoplastic cells were positive for PAX5, CD10 (strong), BCL2 (strong), CD99, and TdT (diffuse and strong) and negative for CD20, CD79a, BCL6, CD3, CD5, Cyclin-D1, MUM-1, and CD34. CD45 was mostly negative and Ki-67 showed a high proliferation index of almost 100% (Fig. 3d). Flow cytometry showed expansion of events (94%) with dimmer CD45 and CD19 expression and brighter CD10 expression compared with the previous specimen (Fig. 3e compared with Fig. 1c). TdT was positive. Surface immunoglobulin light chains, CD34, CD117, CD13, CD33, cytoplasmic MPO, cytoplasmic CD3, cytoplasmic CD79a, and cytoplasmic IgM were all negative by flow cytometry (not shown). Due to the expression of precursor markers (TdT, CD99) and loss of several markers associated with maturity (CD45, CD20, BCL6), a diagnosis of B-LBL was established.

The FISH analysis showed 82% of nuclei with typical rearrangement of *MYC* (FRG) and 8% with atypical rearrangement of *MYC* showing 2 intact and 2 rearranged *MYC* loci (FFRRGG). In addition, there were typical t(14;18) in 22% of nuclei analyzed (FFRG) and atypical t(14;18) with 2 fusion signals in the presence of one copy of *BCL2* and 2 copies of *IGH* in 42.5% of nuclei (FFRGG). Finally, 27% of nuclei had more than two fusion signals and one or more copies of *BCL2* and *IGH*. These were similar abnormal hybridization patterns that were present in the previous specimen (Fig. 3f compared with Fig. 1d). *IGH* gene rearrangement by PCR analysis detected a strong monoclonal peak with the same size of the clonal product as seen previously (331 nt, Fig. 4b).

The patient's condition deteriorated rapidly, and he passed away 3 days after a bone marrow examination.

Material and methods

Histologic and immunohistochemical analysis

Tissue was fixed in buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin (HE).

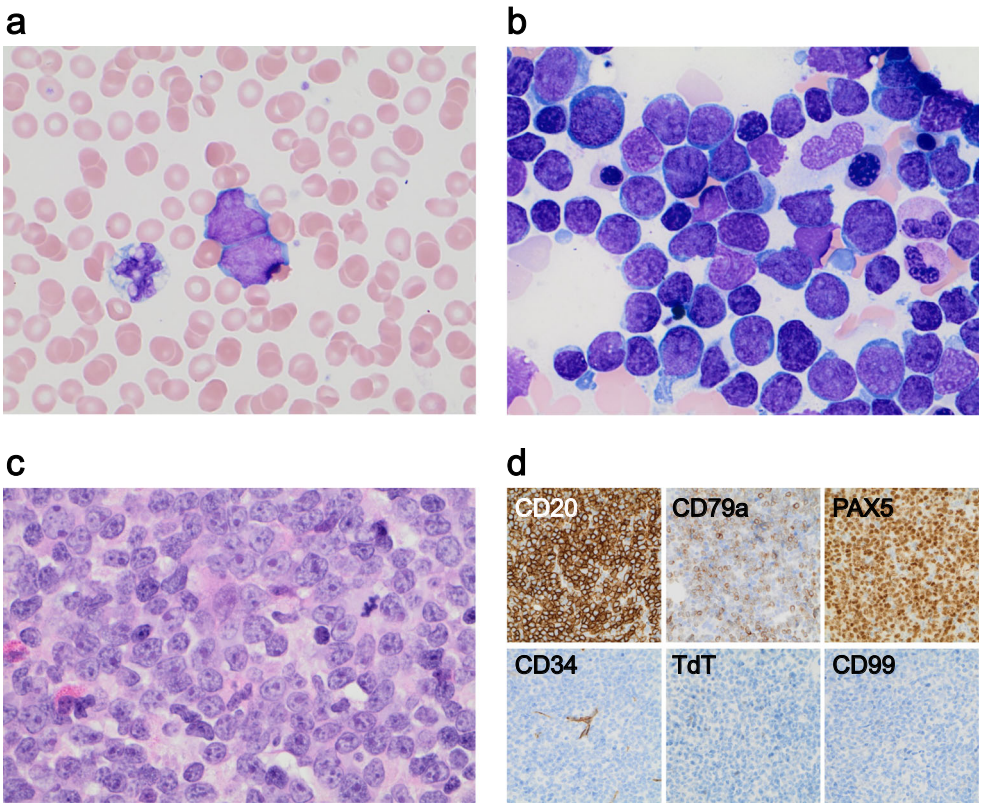

Fig. 2 **a** Peripheral blood smear at presentation showed circulating neoplastic cells with round to irregular nuclei, slightly dispersed chromatin, multiple distinct nucleoli, and small amounts of basophilic cytoplasm (× 1000). **b** Bone marrow aspirate smear (× 1000) and **c** bone marrow biopsy (× 1000) showed extensive involvement by neoplastic cells. **d** Immunostains showed that the neoplastic cells are positive for CD20, CD79a (variable), and PAX5 and negative for CD34, TdT, and CD99

Decalcified bone marrow core biopsies were sectioned and stained with HE. Bone marrow aspirate and peripheral blood smears were stained with Wright-Giemsa. Immunohistochemistry studies for CD45, CD3, CD5, CD20, CD10, BCL2, MUM-1, CD34, TdT, Cyclin-D1, CD30, Ki67 (DAKO, Carpinteria, CA), PAX5, CD79a (Cell Marque, CA), BCL6 (Leica Biosystems, UK), and CD99 (Thermo Scientific, CA) were performed on automated immunostainer (Dako Omnis) using a streptavidin-biotin peroxidase detection system. Antibody dilutions and antigen-retrieval methods were used according to the manufacturer's recommendation.

Flow cytometry

A total of six specimens were studied including initial diagnostic material of sacral lesion, peripheral blood and bone marrow at diagnosis, restaging bone marrow, and peripheral blood and bone marrow at relapse. A 10-color flow cytometry analysis was performed. In summary, aliquots of samples containing 2×10^6 leukocytes were washed 3 times to remove plasma immunoglobulin, followed by the addition of cocktailed antibodies as described below. After a 10-min incubation period, erythrocytes were lysed with ammonium chloride, followed by a wash and finally resuspended in 0.1% formaldehyde for immediate acquisition on a Navios flow cytometer (Beckman Coulter, Miami, FL).

The samples were analyzed using different 10-color antibody cocktails against the following antigens: CD19(J3-119)-APC-AF700, CD20(B9E9)-APC-AF750, CD10(ALB1)-PC7, CD5(BL1a)-PC5.5, CD103(2G5)-APC, CD4(SFCI12T4D11)-FITC, CD8(B9.11)-PE, CD16(3G8)-ECD, nTdT (pool, HT-1, HT-4, HT-8, HT-9)-FITC, CD34(581)-ECD, cMPO (CLB-MPO-1)-PC5.5, CD33(D3HL60.251)-PC7, cCD3(UCHT1)-APC, CD22(SJ10.1H11)-APC, CD13(SJ1D1)-PE, CD117(104D2D1)-PC5.5 (Beckman Coulter, Brea, CA), CD3(UCHT1)-BV421, CD56(B159)-PE-CF594, cCD79a(HM47)-BV421 (BD Biosciences, San Jose, CA), Kappa (F0434)-FITC, Lambda (F0437)-PE (Agilent, Denmark), CD45(HI30)-BV510 (BioLegend Inc., San Diego, CA), and cIgM(R5111)-PE (Dako, Denmark). Up to 99715 events were acquired and analyzed using FCS Express 6 software (De Novo Software, Glendale, CA). The analysis was performed using a hierarchical gating strategy in the search for abnormal populations.

Fluorescence in situ hybridization

Fluorescence in situ hybridization (FISH) was performed on bone marrow specimens at initial diagnosis and at the time of

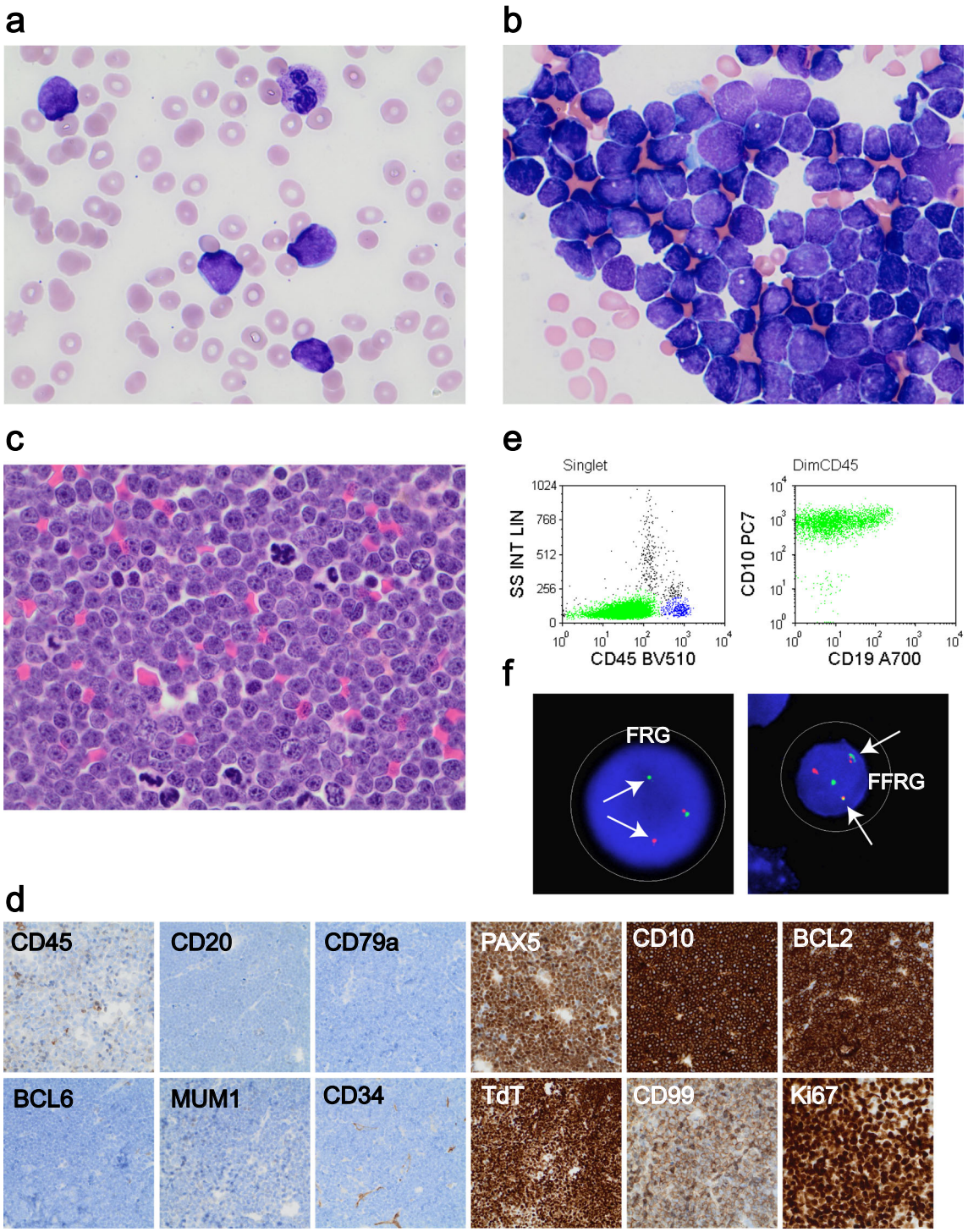

Fig. 3 **a** Peripheral blood smear (× 1000) at relapse showed circulating blasts that were small to intermediate in size with round to slightly irregular nuclear contours, finely dispersed chromatin, inconspicuous nucleoli, and scanty agranular cytoplasm. **b** Bone marrow aspirate smear (× 1000) and **c** bone marrow biopsy (× 1000) showed extensive involvement by neoplastic cells with blastic morphology. **d** Immunostains showed that the neoplastic cells are positive for PAX5, CD10, BCL2, CD99, and TdT and negative for CD45 (most cells), CD20, CD79a, BCL6, CD34, and MUM-1. Ki-67 showed a proliferation index of approximately 100%. **e** Flow cytometry showed the predominance of dimCD45 population with bright CD10 expression and dim to negative CD19 expression. **f** FISH analysis showed rearrangement of *MYC* (left panel, white arrows highlight separation of break-apart *MYC* probes) and t(14;18) (right panel, white arrows highlight fusion of *BCL2* (red) and *IGH* (green) probes)

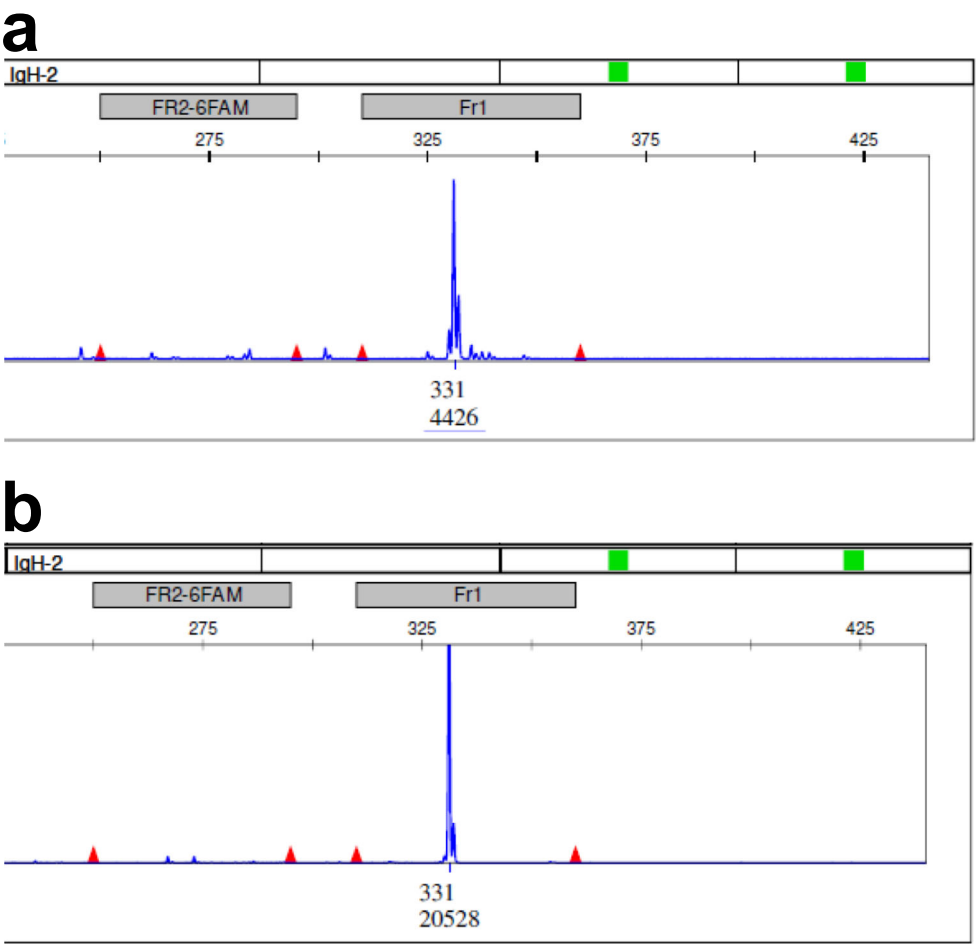

Fig. 4 PCR analysis on bone marrow at presentation (**a**) and on bone marrow specimen at relapse (**b**) showed monoclonal gene rearrangements with the same size of clonal products at 331 nt

relapse. Interphase FISH analysis was performed on formalin-fixed, paraffin-embedded tissue sections according to previously established procedures at our Cytogenomics Laboratory. For the detection of the t(14;18), and *BCL6* or *MYC* gene rearrangements, commercially available LSI dual-color, dual fusion translocation probe for (*IGH*, *BCL2*), LSI break-apart probe for *BCL6*, and LSI break-apart probe *MYC* were used (Vysis, Downers Grove, IL). Images were captured and archived using Leica CytoVision system (Leica Biosystems, ON, CA). For FISH analysis, a total of 200 cells were examined per probe by 2 cytogenetics technologists. The observed signals were considered significant if they were present in greater than cutoff levels previously established for our laboratory. The upper normal cutoff levels in paraffin-embedded tissue samples are 1.5% for t(14;18), 3.1% for *BCL6* rearrangement, and 5.1% for *MYC* rearrangement.

IGH gene management by PCR

DNA was isolated from three specimens (sacral lesion, initial bone marrow sample, and bone marrow at relapse). PCR reactions were performed using InVivoScribe kit (InVivoScribe Inc, San Diego, CA) according to the manufacturer's protocol.

Discussion

Here, we report a rare case of B lymphoblastic transformation of de novo DHL. To our knowledge, there is only one previous report of such transformation. Glazyrin et al. [12] reported a case of DHL with rearrangements of *MYC*/*IGL* and *BCL2*/*IGH* that transformed into B-LBL with the same chromosomal rearrangements. In that report, the presenting disease was positive for CD45 (bright), CD20, and surface light chain (kappa light chain restricted) and was negative for TdT. The transformed disease showed loss of CD20 and surface light chain expression suggestive of a precursor lesion. However, there were few atypical features for B lymphoblastic classification of the relapsed disease. First, the relapsed disease showed similar large cell morphology resembling the original disease, as per description. Second, the relapsed disease showed only subset/variable expression of TdT, and CD45 remained strong. In contrast, our report shows a clear morphologic

and immunophenotypic transformation from mature DHL to a precursor neoplasm. The presenting disease showed intermediate-sized cells with mild pleomorphism, slightly dispersed chromatin, multiple distinct nucleoli, and small amounts of basophilic cytoplasm (morphology between Burkitt lymphoma and diffuse large B cell lymphoma (DLBCL), previously known as BCL-U), whereas the transformed disease showed finer chromatin, inconspicuous nucleoli, and higher nuclear to cytoplasmic ratio (blastoid morphology). In addition, the transformed disease showed loss of markers associated with maturity, including CD20 and BCL6, both of which were positive at presentation. The transformed disease also showed downregulation of CD45 and strong and homogeneous expression of TdT in all cells further supporting a precursor origin. Interestingly, CD19 and CD79a were both dimly positive in the original disease and were even dimmer or lost in the transformed disease. Surface light chains were not detected at presentation and in the transformed disease. Interestingly, in Glazyrin et al. report the possibility of transformation from FL could not be ruled out, due to the presence of a subset of small cells in bone marrow at relapse. We did not see a small cell component in any of our samples examined. This, however, does not entirely exclude the possibility of a low-grade/indolent component that remained undetected in our patient.

Blastoid cytomorphology is not limited to B-LBL and can be seen in mature B cell neoplasms such as blastoid mantle cell lymphoma and HGBCL. It is known that DHL/THL can present with variable morphologic features ranging from DLBCL to BCL-U and blastoid cytology [13]. In fact, approximately 60% of HGBCLs with blastoid cytology (after exclusion of B-LBL and blastoid mantle cell lymphoma) would classify as DHL/THL [13, 14], with remaining cases falling into HGBCL, NOS category, according to the 2017 World Health Organization (WHO) classification of tumor of hematopoietic and lymphoid tissue [1]. Therefore, although relapsed disease in our case showed blastoid morphology, immunophenotypic evidence of immaturity was essential for its classification as B-LBL.

Transformation of mature B cell neoplasms to B-LBL is a rare event. Among mature B cell neoplasms, lymphoblastic transformation of FL is well documented in the literature [5–11] and is a recognized entity by 2017 WHO [1]. The transformed disease often shows blastoid morphology and loss of follicular architecture, associated with the acquisition of *MYC* rearrangement in almost all cases [5, 6, 8, 10, 11]. Concurrent presentation of FL with *BCL2* rearrangement in lymph node and transformed B-LBL with co-existent *BCL2* and *MYC* rearrangements in bone marrow or lymph node has been reported [5, 6, 8]. Transformed B-LBL in almost all cases showed co-expression of TdT, CD10, and BCL2, and the majority of cases showed dim expression of CD45 and loss of CD20 and BCL6 [5–8, 10]. CD34 has been negative in all cases in which expression was reported [6–8]. Expression of immunoglobulin light chain in transformed disease has been variable, ranging from both surface and cytoplasmic expression to cytoplasmic only or absent light chain expression [5–8, 10, 11]. The median survival of such patients with lymphoblastic transformation of FL has been dismal (less than 1 year in the majority of reports) [5–11] and significantly shorter than de novo B-LBL (excluding rare cases of de novo B-LBL with double-hit rearrangements). These findings are suggestive of a different pathogenesis and have led to proposal of terms such as "lymphoblastic transformation of FL" [6] or "high-grade TdT-positive blastic B cell leukemia/lymphoma [4] instead of B-LBL or B-ALL in such cases.

As mentioned previously, the transformation of de novo DHL to B-LBL has been reported only once. However, TdT-negative DHL has been reported in few studies as an intermediate step during B lymphoblastic transformation of FL (i.e., FL to TdT-negative DHL followed by progression to TdT-positive DHL) [6, 8, 11, 15]. Ok et al. [15] reported several cases of mature B cell neoplasm that co-expressed TdT at presentation or upon relapse. Their cohort included cases of DHL/THL with TdT expression at presentation, FL with transformation to TdT-positive aggressive B cell lymphoma, TdT-negative DHL transformed from FL with subsequent transformation to TdT-positive DHL, and other mature B cell neoplasms (EBV-positive DLBCL and mantle cell lymphoma) that acquired TdT expression at relapse. A common feature among these neoplasms was aggressive clinical course and poor response to chemotherapy. Other groups also reported B lymphoblastic transformation of DLBCL [16] and mantle cell lymphoma [17] in association with *MYC* rearrangement and amplification.

The underlying mechanism of lymphoblastic transformation of DHL in our case is not clear. Few mechanisms have been suggested for lymphoblastic transformation of FL. One model proposes the presence of an immature common precursor cell with t(14;18) in the bone marrow that gives rise to FL and B-LBL in parallel [5, 18]. Another model is supportive of secondary genetic events in pre-existing mature FL leading to reactivation of precursor immunophenotype and de-differentiation into lymphoblastic lymphoma [4, 10, 11]. Although *MYC* rearrangement is always present during B lymphoblastic transformation of FL, it is unlikely to be the sole driver of lymphoblastic transformation, as similar rearrangements occur in approximately 8% of FL cases transforming to DLBCL with no acquisition of lymphoblastic phenotype [19]. As mentioned previously, we did not identify a low-grade FL component in any of our specimens. Our PCR study was consistent with clonal relatedness of the DHL and transformed disease. Obviously, other hits/somatic mutations (in addition to *MYC* rearrangement) are required for the de-differentiation of DHL to B-LBL in our case, although no further studies were performed.

Immunophenotypic aberrancies used to define transformation to precursor B cell neoplasm include downregulation of CD45, bright CD10 expression, loss of CD20 and surface light chain expression, and co-expression of precursor markers CD34, CD99, and TdT. Of note, some of these features are commonly seen in mature high-grade B cell neoplasms. For example, immunophenotypic features of DHL/THL include positivity for CD10, variably decreased expression of CD20 and/or CD19, increased expression of CD38, variable expression of CD45, and dim-restricted or loss of surface light chain expression [20–23]. In DHL/THL, absent surface light chain expression can be attributed to the translocation of several immunoglobulin loci. In addition, CD99 expression has been reported in up to 60% of DLBCL cases [24]. The relatively common finding of these immunophenotypic features of "immaturity" in mature high-grade B cell neoplasms, including DHL/THL, argues against their application, in isolation, to define B lymphoblastic transformation.

Terminal deoxynucleotidyl transferase (TdT) is a nuclear DNA polymerase that functions during VDJ recombination to increase the diversity of immunoglobulins or T cell receptors in developing B or T lymphocytes, respectively. Therefore, its normal expression is limited to primary lymphoid organs of bone marrow and thymus [25], although low percentage expression has been reported in benign lymph nodes of pediatric patients [26]. While it is widely expressed in B and T lymphoblastic leukemia/lymphoma [27, 28], its specificity is limited due to expression in other immature hematologic malignancies such as acute myeloid leukemia (especially M0 and M1 subtypes) [28, 29] and blastic plasmacytoid dendritic cell neoplasm [30], as well as non-hematolymphoid neoplasms such as Merkel cell carcinoma, medulloblastoma, and rare cases of small cell lung carcinoma, rhabdomyosarcoma, and Ewing sarcoma [31, 32]. In the context of a high-grade B cell neoplasm with blastoid morphology, TdT expression is a key factor in differential diagnosis. Based on 2017 WHO, positivity for TdT is the main factor used to define B-LBL in a case otherwise positive for *MYC* and *BCL2* and/or *BCL6* rearrangements [1]. Several groups, however, challenged this notion, given that disease course and prognosis of such patients are vastly different from de novo B-LBL [4, 6, 15]. Extra caution should be applied when TdT is used to diagnose B-LBL especially when features that are atypical for B-LBL are present. These features may include an unusual clinical presentation (e.g., extensive lymphadenopathy with limited bone marrow involvement, lack of leukemic presentation) and atypical morphologic (e.g., mature or non-blastoid morphology) or immunophenotypic (e.g., surface light chain expression, bright CD38 expression, positivity for BCL6) findings [33]. Therefore, an appropriate diagnosis of B-LBL requires consideration of different clinical, morphologic, and immunophenotypic aspects of disease, as observed in our case. Regardless of classification, however, we believe that in cases like our patient, genetic findings outweigh morphologic and immunophenotypic classification for the purpose of prognostication and predicting response to therapy.

Rare cases of de novo B-LBL with rearrangements of both *MYC* and *BCL2* genes are reported [2, 4, 7, 34–37]. Similar to lymphoblastic transformation of FL, these patients have a highly aggressive disease with poor response to therapy and very short survival. In addition, immunophenotype of the blast population in such cases resembles that of lymphoblastic transformation of FL (TdT+ CD34- CD38+). Consequently, some authors suggested that de novo B-LBL with double-hit rearrangements and lymphoblastic transformation of FL are closely related and likely represent an entity with pathogenesis that is distinct from other genetic subclasses of de novo B-LBL [4]. Our case shares many features with the abovementioned two groups and adds to the existing literature of B lymphoblastic neoplasms with double-hit rearrangements that arise as de novo or transformed diseases. Large multi-center studies are required to understand the pathogenesis of this unique entity and to develop appropriate diagnostic and therapeutic guidelines for this group of extremely rare but highly aggressive neoplasms.

Compliance with ethical standards

Conflict of Interest The authors declare that they have no conflicts of interest.

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