

Case Report

Double Hit Lymphoma Mimicking B Cell Precursor Phenotype Burkitt Lymphoma/Leukemia in an ElderlyTakashi Miyoshi¹, Fumihiko Kono², Yutaka Shimazu³, Keisuke Shindo¹,
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Academic Editor: Giuseppe Murdaca

Submitted: 3 June 2022 Revised: 21 July 2022 Accepted: 3 August 2022 Published: 12 August 2022

Abstract

Background: The differential diagnosis of Burkitt lymphoma/leukemia (BL) and the double or triple hit lymphomas remains often problematic in terms of immunophenotyping in association with *MYC* gene analysis. In the past, BL-like B-cell malignancy with B-cell precursor phenotype (BCP-ALL) was described. **Case Report:** We report here an 84-year-old male with massive ascites without superficial lymphadenopathy. Abdominal paracentesis revealed chylous (non-bloody) ascites consisting of mostly abnormal BL-like blasts showing CD20-negative BCP phenotype. However, molecular study indicated no *MYC/IGH*, but probable involvements of *MYC/IGL* and *BCL6/IGH* translocations, which were confirmed by FISH studies. The patient was diagnosed as double hit lymphoma mimicking BCP-ALL.

Keywords: double hit lymphoma; burkitt lymphoma; ascites; CD20; terminal deoxynucleotidyl transferase**1. Introduction**

In the 2017 revision of the WHO classification of lymphomas, the term high-grade B-cell lymphoma has been repurposed. Double and/or triple-hit lymphomas with *MYC* and *BCL2* and/or *BCL6* rearrangements are now designated as high-grade B-cell lymphoma [1]. Such high-grade B-cell lymphomas occur in <10% of cases of diffuse large B-cell lymphoma. On the other hand, Burkitt lymphoma/leukemia (BL; consisting of Burkitt lymphoma and/or Burkitt leukemia variant) was once thought to be a highly aggressive B-cell malignancy, but currently BL does not belong to high grade lymphoma because it is a *MYC* only rearranged B-cell malignancy. All types of BL are characterized by dysregulation of the *MYC* gene located at the 8q24 with chromosomal translocations, such as most common t (8;14) (q24;q32), or rare t (2;8) (p12;q24), or t (8;22) (q24;q11) variants [2].

In clinical practice, the differential diagnosis of BL and the double or triple hit lymphomas remains often problematic in terms of immunophenotyping in association with *MYC* gene analysis. In the past, reports were made on BL-like B-cell malignancy with B-cell precursor phenotype [3–5]. In these cases, lymphoblasts had FAB L3-like morphology with *MYC/IGH* or with *MYC/IGL* translocation, and CD20 was largely negative, indicating BCP phenotype [2–4]. In addition, terminal deoxynucleotidyl transferase (TdT)-positive as well as TdT-negative BCP phenotype-BL have also been made [3–5]. On the other hand, in double hit

or triple hit high-grade B-cell lymphomas, immunophenotype shows that TdT expression is absent, CD10 is positive in most cases, CD20 expression is decreased [1,6,7]. From these immunophenotyping alone, differentiation of BCP-phenotype BL and the high-grade B-cell lymphomas are difficult.

When we saw a patient who exhibited FAB L3-like morphology in ascites as well as in bone marrow, we initially thought the diagnosis of rare BL was most likely, also from the karyotype including t (8;22) (q24; q11.2). However, it was necessary to differentiate BL from the high-grade B-cell lymphomas based on atypical immunophenotyping. Eventually, molecular analysis helped us successfully reaching the correct diagnosis.

2. Case Report

We report here an 84-year-old male whose complaints on admission were appetite loss, abdominal distention due to massive ascites retention and renal failure, without superficial lymphadenopathy. Two months earlier he received surgery for choledocholithiasis, when no ascites was present. The patient showed; WBC 9400/ μ L (no abnormal cells), Hb 13.1 g/dL, platelet count 190 K/ μ L, serum CRP 4.76 mg/dL (reference; <0.14), LDH 1674 U/L (124–222), BUN 109 mg/dL (8.0–20.0), creatinine 2.87 mg/dL (0.46–0.79) and uric acid 14.7 mg/dL (2.6–5.5). As one of clinical symptoms, the patient had a large amount of ascites. Abdominal paracentesis revealed chylous (non-bloody) ascites



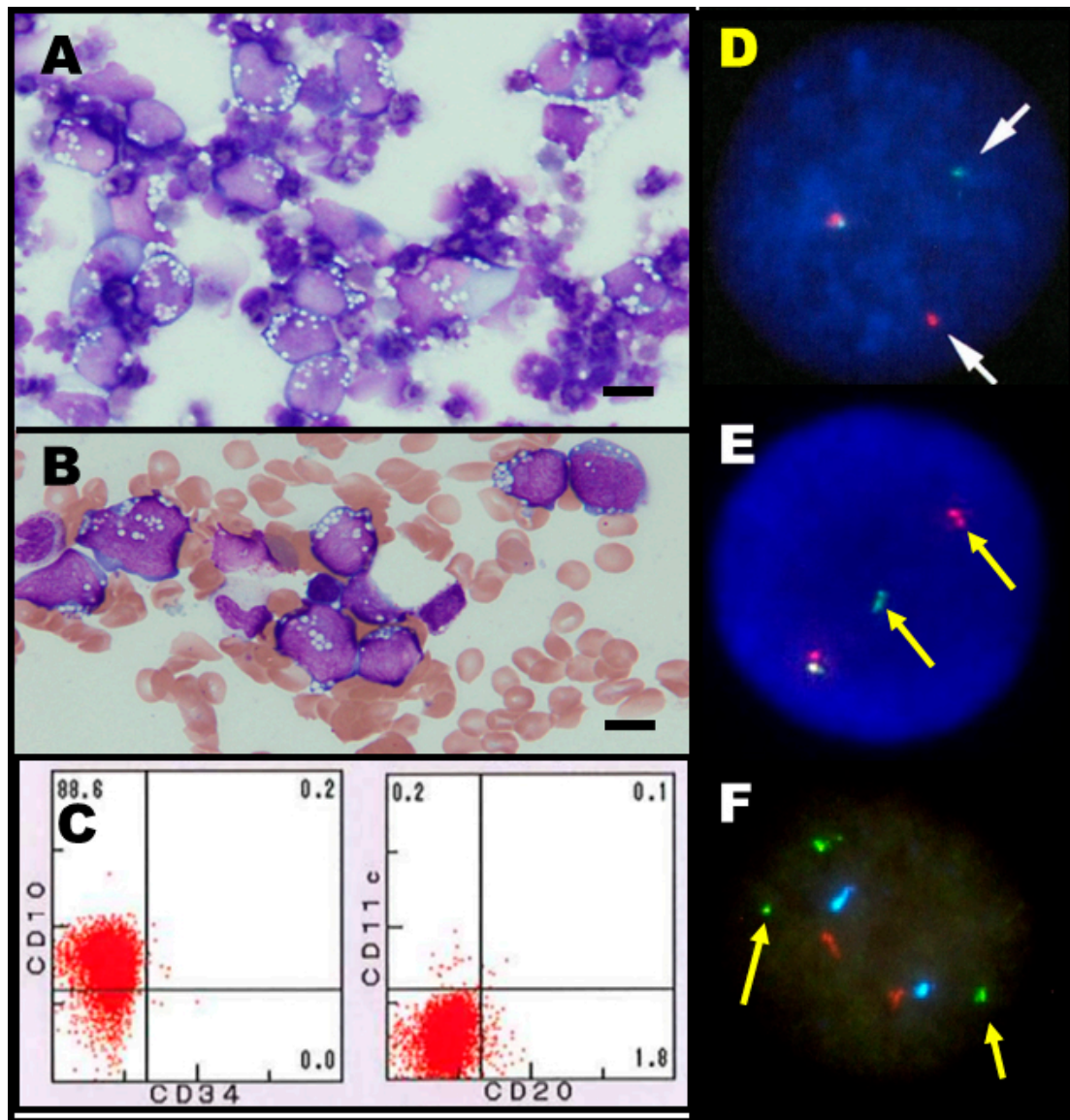


Fig. 1. Cytospin smear of the ascites reveals numerous lymphoblasts with abundant cytoplasmic vacuoles (A; Giemsa stain, original magnification $\times 1000$) and **bone marrow smear** (B; May-Giemsa stain, original magnification $\times 1000$) shows FAB L3 type blasts. In A and B, scale bar indicates $10\ \mu\text{m}$. **Flowcytometry of blast cells in bone marrow** shows CD10-positive and CD20-negative (C). **FISH on interphase nucleus of bone marrow blasts** showed split signals (arrows) of *BCL6* (D), *MYC* (E), and *IGH* (F). Split signals were each detected in 15%; reference $<2\%$. In (F), 3 green spots were *IGH*, 2 red spots were *MYC* and 2 blue spots were *D8Z2*, with use of Vysis™ LSI® *IGH/MYC*, CEP® 8 Tri-color, Dual Fusion Translocation Probe: Abbot Molecular Inc.). These results together with the karyotype indicates probable *MYC/IGL* and *IGH/BCL6* translocations and double-hit lymphoma.

with cell count of $160,442/\mu\text{L}$ (93.9% mononuclear cells, consisting of mostly abnormal Burkitt-like blasts (Fig. 1A) associated with significantly elevated ascitic LDH 13,045 U/L, suggesting BL in ascites. Bone marrow study also revealed leukemic features with numerous medium-sized blasts (50% of NCC) with Burkitt-like morphology (FAB L3) with deeply basophilic cytoplasm and numerous vacuoles, like those in the ascites (Fig. 1B). Flowcytometry of the blasts in both ascites and bone marrow showed CD10+CD19+ CD20- HLADR+, and without light chain restriction, indicating BCP phenotype (Fig. 1C). At this

point, we suspected BL with BCP-phenotype [3–5]. However, bone marrow karyotype revealed $47, XY, +i(1)(q10), t(3;14)(q27; q32), del(6)(q?), t(8; 22)(q24; q11.2)[12]/46, idem, dup(1)(q21q42), -i(1)[2]/46, idem, +1, der(1;14)(q10; q10), -i(1)[2]$, which suggested no *MYC/IGH*, but probable involvements of *MYC/IGL* and *BCL6/IGH* translocations.

Thereafter, we confirmed that his lymphoma/leukemia was a double hit by identifying split signals of *BCL6*, *MYC*, and of *IGH* separately (because no *IGL* probe available, we were not able to show directly *MYC/IGL* on

FISH) (Fig. 1D–F). In consisting with immunophenotype of the high-grade B-cell lymphoma, immunostaining of blast cells in the bone marrow clot preparation showed; TdT-, CD10+, CD79a+, CD20-, BCL2+/-, BCL6-, MYC+ and Ki67 >90% (Fig. 2). Though it was stated in double hit lymphoma that BCL6 expression can be noted in more than 90% by immunohistochemistry [1], we could not detect BCL6 expression as shown in Fig. 2. In an attempt to find out the cause(s) of lymphomatous ascites, we detected huge pelvic mass on computed tomography (CT), which was further confirmed on ¹⁸F-fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography (PET-CT) as FDG-avid peritoneal involvement as well as mass in the pelvic cavity (Fig. 3), but had no chance to histologically confirm the pathology of masses at the primary site(s). Since the patient was frail and in a condition not tolerable to chemotherapy, he was put on best supportive care. The patient died in 3 weeks after admission.

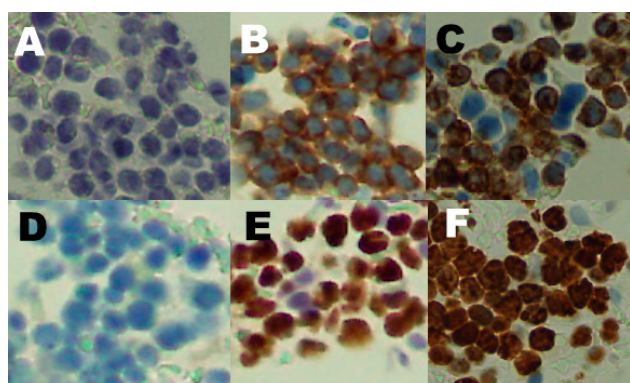


Fig. 2. Immunostaining of bone marrow blasts. TdT-negative (A), CD10-positive (B), CD79a-positive (C), BCL-6-negative (D), MYC-positive (E) and Ki-67-positive (>90%) (F) (original magnification; $\times 200$).

3. Discussion

Our case, although we first suspected BL, was in fact a double-hit lymphoma confirmed by a combination of bone marrow karyotype and FISH analysis (split signals of *BCL6*, *MYC* and *IGH* indicating probable *MYC/IGL* and *IGH/BCL6* translocations) (see Fig. 1D–F) with compatible immunophenotype such as no TdT expression, positive CD10 as well as lack of CD20 [1,6,7]. Clinically, our case behaved like BL; first manifested as lymphomatous lesion in the ascites, as that BL often occurs as a primary lymphomatous effusion in ascites [8,9]. As a cause of diffuse lymphomatous ascites development in our case, we could not determine the pathology of masses at the primary site(s), though we could detect huge pelvic mass as well as peritoneal lesions on abdominal CT and PET-CT images as shown in Fig. 3. These images of rapidly progressed lymphomatous lesions may be comparable with those in double

hit lymphoma.

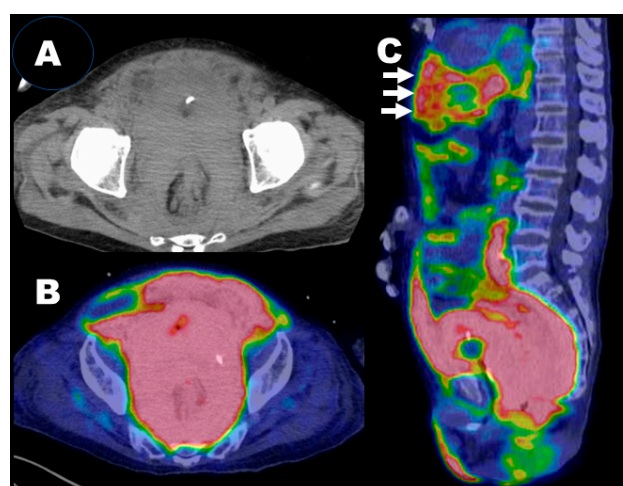


Fig. 3. Computed tomography (CT; A; axial view) and PET-CT (B; axial and C; sagittal views) show irregularly shaped and FDG-avid (SUVmax; 12.79) huge pelvic mass, which might be extended towards the center from the retroperitoneum or pelvic wall. In the upper abdomen (C), FDG accumulation (SUVmax; 6.77) in the peritoneum (arrows) was detectable, indicating probable lymphomatous peritonitis.

Treatment regimens differ between BL and double or triple hit lymphomas [1]. BL and its variants are generally treatable with more intensive chemoimmunotherapy than R-CHOP with central nervous system management [10]. On the other hand, double-hit lymphomas show a poor prognosis when treated with such chemoimmunotherapy, thus are required new regimens incorporating targeted agents based on future clinical trials [11]. Unfortunately, because our patient was frail and not in a condition tolerable to chemotherapy, he was on best supportive care and died.

In summary, when patients show B-cell type leukemia/lymphoma with BL-like morphology but with BCP-like immunophenotype, detailed analysis of cytogenetic as well as molecular studies are required to differentiate BL and double or triple hit lymphomas because the differentiation is often difficult from the flowcytometric and histochemical data alone.

Author Contributions

TM and KS took care of the patient. FK performed pathological diagnosis. YS and SI analyzed karyotypic and FISH data. TM and SI wrote manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

The work was carried out in accordance with the Declaration of Helsinki. Written informed consent to publish was obtained from the patient.

Acknowledgment

The authors acknowledge all staffs taking care of the patient.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflicts of interest.

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