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ABOUT COVER

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CASE REPORT

Coexistence of diffuse large B-cell lymphoma, acute myeloid leukemia, and untreated lymphoplasmacytic lymphoma/waldenström macroglobulinemia in a same patient: A case report

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Abstract

BACKGROUND

The Coexistence of myeloid and lymphoid malignancies is rare. Myeloid leukemia occurs more frequently as a secondary event in patients receiving chemotherapy agents for lymphoid malignancies. Synchronous diagnoses of diffuse large B-cell lymphoma (DLBCL), acute myeloid leukemia (AML), and untreated lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM) in the same patient have not been reported. Here we report one such case.

CASE SUMMARY

An 89-year-old man had a chest wall mass histopathologically diagnosed as DLBCL. The bone marrow and peripheral blood contained two groups of cells. One group of cells fulfilled the criteria of AML, and the other revealed the features of small B lymphocytic proliferative disorder, which we considered LPL/WM. Multiple chromosomal or genetic changes were detected in bone marrow mononuclear cells, including *ATM* deletion, *CCND1* amplification, mutations of *MYD88* (L265P) and *TP53*, *WT1* overexpression, and fusion gene of *BIRC2-ARAP1*, as well as complex chromosomal abnormalities. The patient refused chemotherapy because of old age and died of pneumonia 1 mo after the final diagnosis.

CONCLUSION

The coexistence of DLBCL, AML, and untreated LPL/WM in the same patient is extremely rare, which probably results from multiple steps of genetic abnor-

malities. Asymptomatic LPL/WM might have occurred first, then myelodysplastic syndrome-related AML developed, and finally aggressive DLBCL arose. Therefore, medical staff should pay attention to this rare phenomenon to avoid misdiagnoses.

Key Words: Diffuse large B-cell lymphoma; Acute myeloid leukemia; Small B lymphocyte proliferative disorder; Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia; Coexistence; Case report

Core Tip: The coexistence of myeloid and lymphoid malignancies is rare. Synchronous diagnosis of diffuse large B-cell lymphoma (DLBCL), acute myeloid leukemia (AML), and untreated lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM) in the same patient has not yet been reported. Herein, we report one such case. We assumed that the three diseases have been occurred in a stepwise manner. Asymptomatic indolent LPL/WM might have occurred earlier, then insidious myelodysplastic syndrome developed into AML, while chest wall DLBCL grew separately.

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) and acute myeloid leukemia (AML) rarely occur concurrently. Only a few cases of DLBCL after AML chemotherapy[1,2] have been reported. Chemotherapy-induced immunosuppression predisposes patients to develop secondary malignancies, particularly virus-related ones[1,2]. Only two cases with a synchronous diagnoses of DLBCL and AML have been reported[3,4]. The coexistence of AML and small B lymphocytic proliferative disorder (LPD) is also rare. Most cases of AML develop after small B LPD (B-LPD), probably due to immunodeficiency over the long course of LPD[5,6] or after treatment[7]. Only a few cases of newly diagnosed synchronous AML and small B-LPD have been reported[8-10]. Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM) is a specific type of B-LPD. To the best of our knowledge, synchronous diagnosis of DLBCL, AML, and untreated LPL/WM in a same patient has not been reported yet. Herein, we report one such case.

CASE PRESENTATION

Chief complaints

An 89-year-old man was admitted to our hospital complaining of cough, expectoration, and shortness of breath for half a month.

History of present illness

The patient complained of cough and expectoration for half a month. His blood test results were abnormal: Leukocyte count, 12.6 (4.0-10.0 × 10^9/L); neutrophil count, 1.44 (2.00-7.50 × 10^9/L); lymphocyte count, 4.21 (0.80-4.00 × 10^9/L); monocyte count, 6.9 (0-0.8 × 10^9/L); hemoglobin level, 73 (120-160g/L); and platelet count 55 (100-300 × 10^9/L). The patient was therefore admitted to the Department of Hematology.

History of past illness

The patient had chronic bronchitis for 10 years, which often deteriorated in winter.

Physical examination

Physical examination revealed skin pallor, enlarged lymph nodes in the armpit, and moist rales in both lungs, but no hepatosplenomegaly.

Laboratory examinations

CT-guided puncture of the mass in the chest wall was performed for biopsy. The histopathological examination showed a hyperproliferation of large cells with Ki-67 (70%), CD20 (+++), PAX-5 (++), CD10 (+), MUM-1 (+), BCL-6 (+), c-MYC (< 40%), BCL-2 (< 50%), CD3 (-), CK-pan (-), TTF (-), NapsinA (-), CK7 (-), P40 (-), CK5/6 (-), Syn (-), CgA (-), CD56 (-), and EBER (-), suggesting a diagnosis of DLBCL (Figure 1A-O, Table 1). Blood tests were performed, and many abnormalities were found: Procalcitonin levels, 1.42 (< 0.05 ng/mL); erythrocyte sedimentation rate, 97 (0-20 mm/h); C-reactive protein levels, 370 (0-10 mg/L); lactate dehydrogenase levels, 460 (120-250 U/L); serum albumin levels, 34.3 (40.0-55.0 g/L); serum fibrinogen levels, 7.24 (2.00-4.00 g/L); CA 125, 48.2 (0-35.0 U/mL); pro-B-type natriuretic peptide, 1918 (< 300 pg/mL); serum immunoglobulin (Ig) M levels, 6.55 (0.40-2.30 g/L); urine Kappa light chain, 318 (0-50 mg/L); free triiodothyronine levels, 2.61 (3.10-6.80 pmol/L); and triiodothyronine levels, 0.77 (1.30-3.10 nmol/L). Peripheral blood and bone marrow smears were performed. Surprisingly, no large B lymphocytes were found, but there were 71.6% mature small lymphocytes, along with 23.2% myeloid blasts which were peroxidase (++), periodic acid-Schiff stain (+), and non-specific esterase (-/+, cannot be inhibited by NaF) (Figure 2A-F, Table 1). The patient's peripheral blood had a high percentage of myeloblasts (50%) and a relatively low percentage of B lymphocytes (29%) (Figure 2A-F). Immunohistochemical analysis of the bone marrow biopsy showed mixed expression of myeloblast and mature B lymphocyte markers with CD10 (+), CD20 (+++), CD34 (++), CD43 (+), CD117 (++), PAX-5(+++), myeloperoxidase (MPO) (+), silver staining (++), BCL-6 (-), CD3 (-), and CD5 (-) (Figure 2G-R, Table 1). To identify the features of these mixed cells, flow cytometry was used to gate the two groups of cells from peripheral blood and bone marrow samples. The immunophenotypic results confirmed the morphological findings of the presence of two discrete abnormal cell populations: 49.64% large blasts with dim CD45 expression and 22.21% small lymphocytes with strong CD45 expression. The large blasts population expressed CD34, CD13, and CD117, and partially expressed CD33, HLA-DR, and MPO, but did not express CD3, CD4, CD5, CD7, CD8, CD10, CD11b, CD14, CD15, CD19, CD20, CD36, CD56, CD64, or CD23, compatible with myeloblasts. In contrast, the small lymphocytes expressed CD19, CD20, and Kappa light chain, but did not express CD103, CD25, CD11c, CD34, CD117, CD5, CD10, CD23 or Lambda light chain, which were considered LPD cells (Figure 3, Table 1). Therefore, AML-M2 along with a small B-LPD were suspected. Furthermore, cytogenetic and molecular biology tests were performed on bone marrow mononuclear cells (BMMNCs). Monoclonal IgM Kappa was identified by immunofixation electrophoresis (Figure 4A), which was consistent with the diagnosis of monoclonal B lymphocytosis or plasmacytosis. Fluorescence *in situ* hybridization (FISH) results showed deletion of 11q22 (*ATM*) (83%) and an increased copy number of 11q13 (*CCND1*) (80%) (Figure 4B and C), but no abnormalities of chromosomes or genes in 13q34, 13q14.3, 12, 17p13.1 (*P53*), or 13q14.2 (*RB1*). The IgH rearrangement was confirmed and t(11; 14) was not detected. Chromosomal karyotype analysis was performed and five metaphases were obtained using the routine method, whereas 20 metaphases were obtained after stimulation with CpG-oligodeoxynucleotides. All metaphases showed a complex abnormality with 46, XY, -2, del(5)(q13q31), -8, add(11)(q13), del(13)(q11q32), +mar1, and +mar2 (Figure 4D). A total of 281 genes associated with malignant lymphoid and myeloid diseases were tested by sequencing (Supplementary material). *MYD88* (14.8%) mutation (p.L265P) and 27.3% of *TP53* mutations (p.N29Kfs*14 and p.S215N) were detected (Table 2). Different kinds of copy number variations were found in chromosome 2p25.3p13.3 (2.56 copies), 5q14.3q34 (1.46 copies), 8p23.3p21.2 (4.30 copies), 8q21.3q24.3 (2.55 copies), 11q12.1q14.1 (3.05 copies), 11q14.1q22.1 (1.43 copies), 11q22.3q23.1 (1.44 copies), 11q23.1q25 (4.85 copies), 13q12.3q14.13 (1.43 copies), 13q21.1q22.1 (2.63 copies), and 13q31.1q31.3 (2.49 copies), which were consistent with the karyotype results (Table 2). AML-associated 56 fusion genes were tested using real-time PCR (Supplementary material) and *WT1* overexpression was also detected (Table 2). Newly discovered fusion genes were also tested using RNA sequencing (Supplementary material), and a new fusion gene, *BIRC2(11q22.2)-ARAP1(11q13.4)*, was detected (Table 2). Gene sequencing of the tissue from the chest wall mass was not available because of the inability to obtain sufficient tissue.

Imaging examinations

Chest and abdominal CT revealed multiple shadows in both lungs, a newborn mass in the left chest wall, and multiple enlarged lymph nodes in the armpits, mediastinum, and hilus pulmonis (Figure 1P-T).

FINAL DIAGNOSIS

The patient was diagnosed with the coexistence of DLBCL, AML, and LPL/WM.

Table 1 Immunophenotype of bone marrow and chest wall tumor

Expression	Molecular marker
The immunophenotype of BMMNCs by flow cytometry	
Group A	49.64%
Expression	CD34, CD13, CD117
Partial expression	CD33, HLA-DR
No expression	CD3, CD4, CD5, CD7, CD8, CD10, CD11b, CD14, CD15, CD19, CD20, CD36, CD56, CD64, CD23
Group B	22.21%
Expression	CD19, CD20, Kappa
Partial expression	
No expression	CD103, CD25, CD11c, CD34, CD117, CD5, CD10, CD23, lambda
The immunohistochemical analysis of bone marrow biopsy	
Expression	CD10, CD20, CD34, CD43, CD117, PAX-5, MPO, silver dyeing
Partial expression	
No expression	BCL-6, CD3, CD5, MPO
The immunohistochemical analysis of chest wall tumor	
Expression	Ki-67 (70%), CD20, PAX-5, CD10, MUM-1, BCL-6, c-MYC (< 40%), BCL-2 (< 50%)
Partial expression	
No expression	CD3, CK-pan, TTF, NapsinA, CK7, P40, CK5/6, Syn, CgA, CD56, EBER

BMMNCs: Bone marrow mononuclear cells; MPO: Myeloperoxidase.

TREATMENT

The patient refused chemotherapy because of old age and performance status.

OUTCOME AND FOLLOW-UP

The patient died of pneumonia 1 mo later. The patient's family refused an autopsy.

DISCUSSION

This patient was admitted to our hospital because of the chest wall mass, which was histopathologically identified as DLBCL (GCB subtype). The cells were large and strongly positive for CD20, PAX-5, BCL-6, and MUM-1, with high Ki-67expression, suggesting an aggressive feature. The positive expression of BCL-2, BCL-6, and c-MYC suggested that DLBCL was a "triple expressor" type. MPO-negative expression of these large cells ruled out the probability of myeloblast infiltration. Blood cell abnormalities were occasionally observed during regular examinations. The two groups of abnormal cells were found in peripheral blood and bone marrow. Morphology and immunohistochemistry suggested a diagnosis of AML and small B-LPD. The two groups of cells were identified by flow cytometry. The cells expressing CD13, CD34, and CD117 were from myeloid blasts, whereas the others expressing CD19, CD20, and Kappa were from B lymphoid mature cells. Based on the morphology and flow cytometry results, the B-cells were found to be small, consistent with a diagnosis of small B-LPD, which is a chronic monoclonal neoplasm, including chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), follicular lymphoma (FL), marginal zone lymphoma (MZL), hairy cell leukemia (HCL), and LPL/WM. Negative expression of CD103, CD25, and CD11b ruled out the diagnosis of HCL or HCLv. The panel of CD5 (-), CD23 (-), and CD10 (-) ruled out the diagnosis of CLL/SLL and FL[11]. Additionally, the lack of t (11;14) ruled out the diagnosis of MCL [11]. Subsequently, LPL/WM and MZL were considered. The patient had monoclonal IgM Kappa and *MYD88 L265P* mutations, and LPL/WM was diagnosed, whereas, MZL with plasmacytoid differentiation could not be completely ruled out. Both LPL/WM and MZL seldom transform to DLBCL,

Table 2 Abnormalities of genes from bone marrow mononuclear cells

Expression	Abnormality
The mutation of genes	
MYD88	p.L265P (14.8%)
TP53	p.N29Kfs*14 (27.3%)
TP53	p.S215N (27.2%)
The fusion of genes or gene expression	
WT1	Positive
BIRC2-ARAP1	Positive
The copy number variations	
chr2p25.3p13.3	2.56
chr5q14.3q34	1.46
chr8p23.3p21.2	4.30
chr8q21.3q24.3	2.55
chr11q12.1q14.1	3.05
chr11q14.1q22.1	1.43
chr11q22.3q23.1	1.44
chr11q23.1q25	4.85
chr13q12.3q14.13	1.43
chr13q21.1q22.1	2.63
chr13q31.1q31.3	2.49

although MZL often infiltrates extranodal tissues, including the lungs. Whether LPL/WM and DLBCL are from the same clone is still unknown since the genes from chest wall masses were not tested because of the limited tissue obtained through CT-guided puncture. Therefore, we considered that in the bone marrow LPL/WM occurred and the chest wall tumor was DLBCL.

Multiple chromosomal and gene changes were detected in the BMMNCs (Guangzhou KingMed Diagnostics Group Co., Ltd.). The routine karyotype analysis method, by which more metaphases were from myeloblasts, or CPG-oligodeoxynucleotide stimulating method, by which metaphases were from lymphocytes, detected the homogeneous chromosomal changes of 46, XY, -2, del(5)(q13q31), -8, add(11)(q13), del(13)(q11q32), +mar1, and +mar2. Myeloblasts (49.64%) and lymphocytes (22.21%) shared the same chromosomal abnormalities. Moreover, FISH detected 83% of 11q22 deletions, and 80% of 11q13 multiple copies. Based on this homogeneity, we suspected that myeloblasts and lymphocytes might be derived from the same progenitor, although different clones were not separated for molecular analysis due to the limited specimens.

Often, 5q- is found in AML or myelodysplastic syndrome (MDS), 11q- in small B-LPD, and 13q- in MDS, AML, or CLL. Although the copy number of 11q13 (*CCND1*) increases, no chromosomal change of t (11;14) is found; therefore, MCL should be ruled out. The deletion of 11q22.3 (*ATM*) often causes a defect in apoptosis, similar to deletion or mutation of 17p13 (*TP53*), suggesting a poor prognosis[12,13]. The frameshift mutation of *TP53* (p.N29Kfs*14) leads to a change in amino acid sequence or early termination of protein translation, causing a loss of *TP53* function. Missense mutation of *TP53* (p.S215N) can be found in lymphoid or myeloid malignant diseases, such as CLL, DLBCL, MCL, FL, LPL/WM, AML, and MDS, and are associated with poor prognosis. *WT1* is overexpressed in newly diagnosed or relapsed AML, CML in the accelerated and blastic phases, and high-risk MDS. *BIRC2(11q22.2)-ARAP1(11q13.4)* is a novel fusion gene discovered in this patient. Whether it is related with AML or LPD remains unknown. The patient's complex chromosomal abnormality with 5q- and old age led us to speculate that AML may originate from MDS, although dysplasia in erythroblasts or megakaryocytes was not found.

Multiple theories behind the simultaneous development of several malignancies in an untreated patient have been proposed, including immunosuppression mediated by chronic small B-LPDs[14], a common stem cell defect[15], or just a chance. Therefore, we hypothesized that these diseases occurred in a stepwise manner. Asymptomatic indolent LPL/WM might have occurred earlier, then insidious MDS developed into AML, while chest wall DLBCL grew separately.

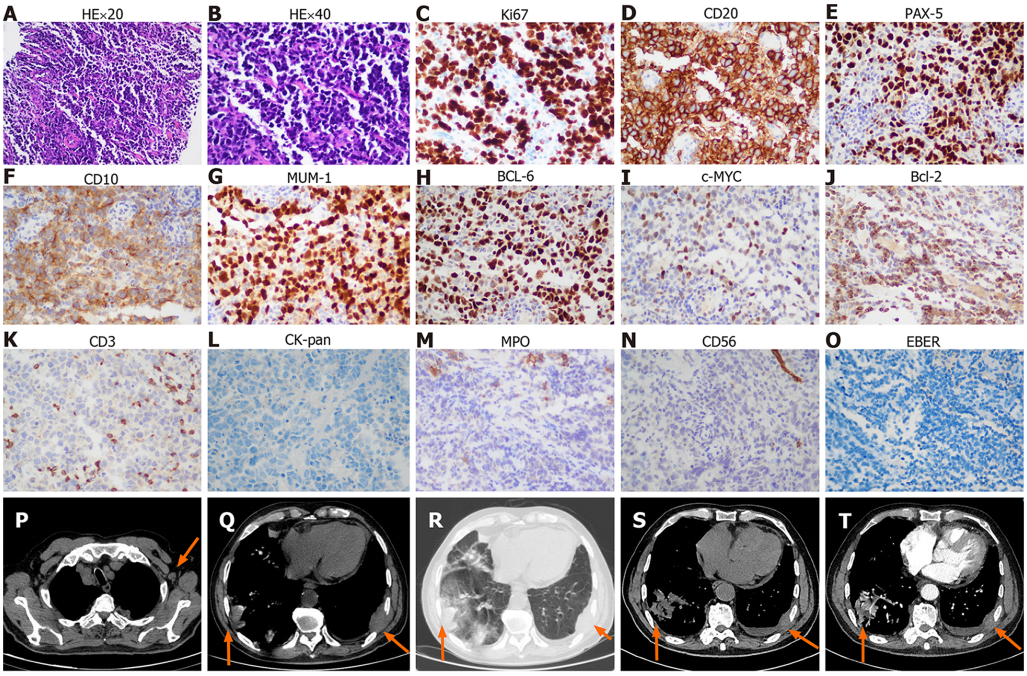

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Figure 1 The biopsy and imaging of chest wall mass. A-O: The HE and immunohistochemistry of chest wall mass; A: Hematoxylin-Eosin (HE) staining × 20 objective; B: HE staining × 40 objective; C-O: The immunohistochemistry shows Ki-67 (++, approximately 70%), CD20 (++), PAX-5 (++), CD10 (+), MUM-1 (++), BCL-6 (++), c-MYC (+, < 40%), BCL-2 (+, < 50%), CD3 (T cells few +), CK-pan (-), myeloperoxidase (MPO) (-), CD 56 (-), and EBER (-). P: Enlarged axillary lymph node (arrow) in the chest computed tomography (CT) scan; Q and R: Infiltration of masses (arrows) to the lung and chest wall on mediastinum window (Q) and lung window (R). S and T: Unenhanced (S) and contrast-enhanced (T) CT images shows the infiltration of masses (arrows) to the lung and chest wall on mediastinal window.

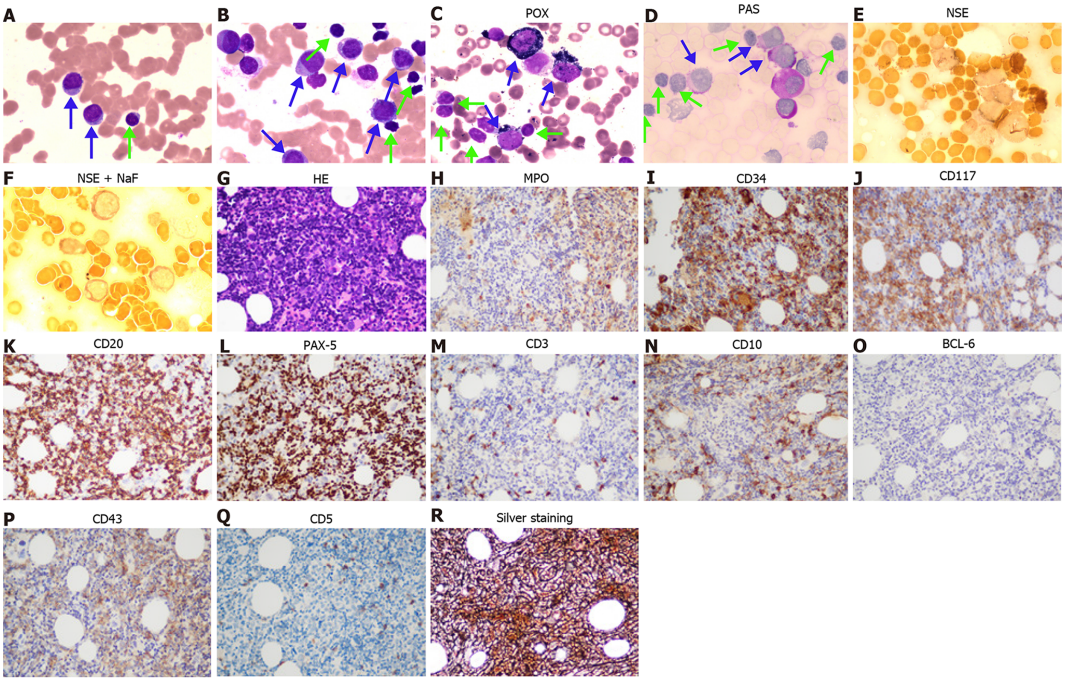

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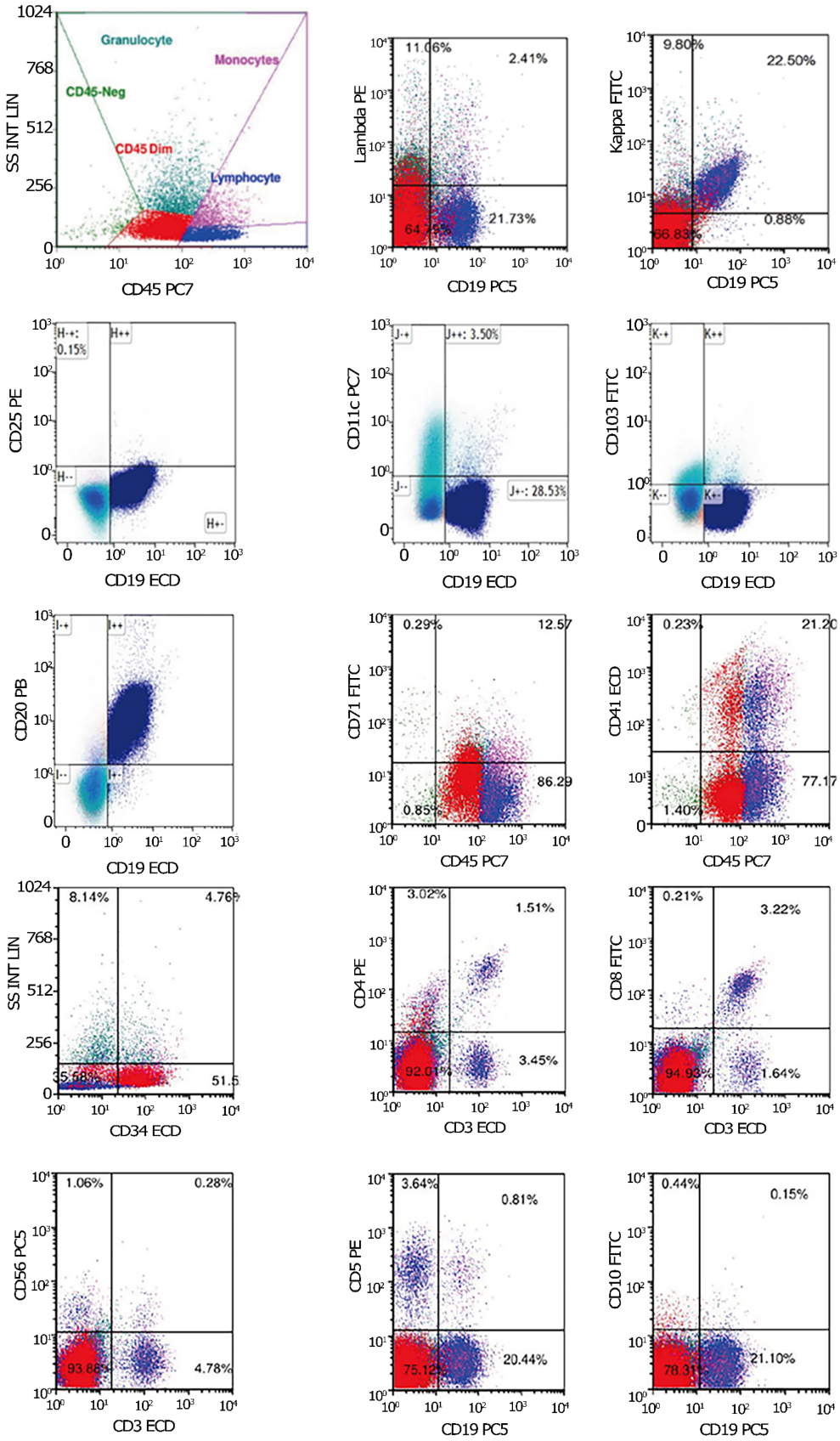
Figure 2 The cytomorphology of peripheral blood and bone marrow. A: Peripheral blood smear (Wright staining, 100 × objective); B: Bone marrow smear (Wright staining, 100 × objective); C-F: Histochemistry staining for bone marrow smear. Peroxidase (52%, 99 points), periodic acid-Schiff stain (86%, 158 points), non-specific esterase (NSE) (32%, 35 points), and NSE + NaF (25%, 26 points) staining for bone marrow smear (Blue arrows direct myeloid blasts, while green arrows direct small lymphocytes); G-R: Bone marrow biopsy (40 × objective); G: Hematoxylin-Eosin staining; H-R: Immunohistochemistry shows myeloperoxidase (myelocytes +), CD34 (myelocytes ++), CD117 (myelocytes +), CD20 (B cells ++), PAX-5 (B cells ++), CD3 (T cells, few +), CD10 (few +), BCL-6(-), CD43(partial +), CD5 (T cells -), and silver staining (+++). POX: Peroxidase; PAS: Periodic acid-Schiff; NSE: Non-specific esterase; MPO: Myeloperoxidase.


Granulocyte
Monocytes
CD45-Neg
CD45 Dim
Lymphocyte
SS INT LIN
CD45 PC7
Lambda PE
CD19 PC5
11.06%
2.41%
21.73%
Kappa FITC
9.80%
22.50%
0.88%
CD25 PE
CD19 ECD
0.15%
CD11c PC7
3.50%
28.53%
CD103 FITC
CD20 PB
CD71 FITC
0.29%
12.57
86.29
0.85%
CD41 ECD
0.23%
21.20
77.17
1.40%
8.14%
4.76%
51.5
CD34 ECD
CD4 PE
3.02%
1.51%
3.45%
92.01%
CD8 FITC
0.21%
3.22%
94.93%
1.64%
CD3 ECD
CD56 PC5
1.06%
0.28%
93.88%
4.78%
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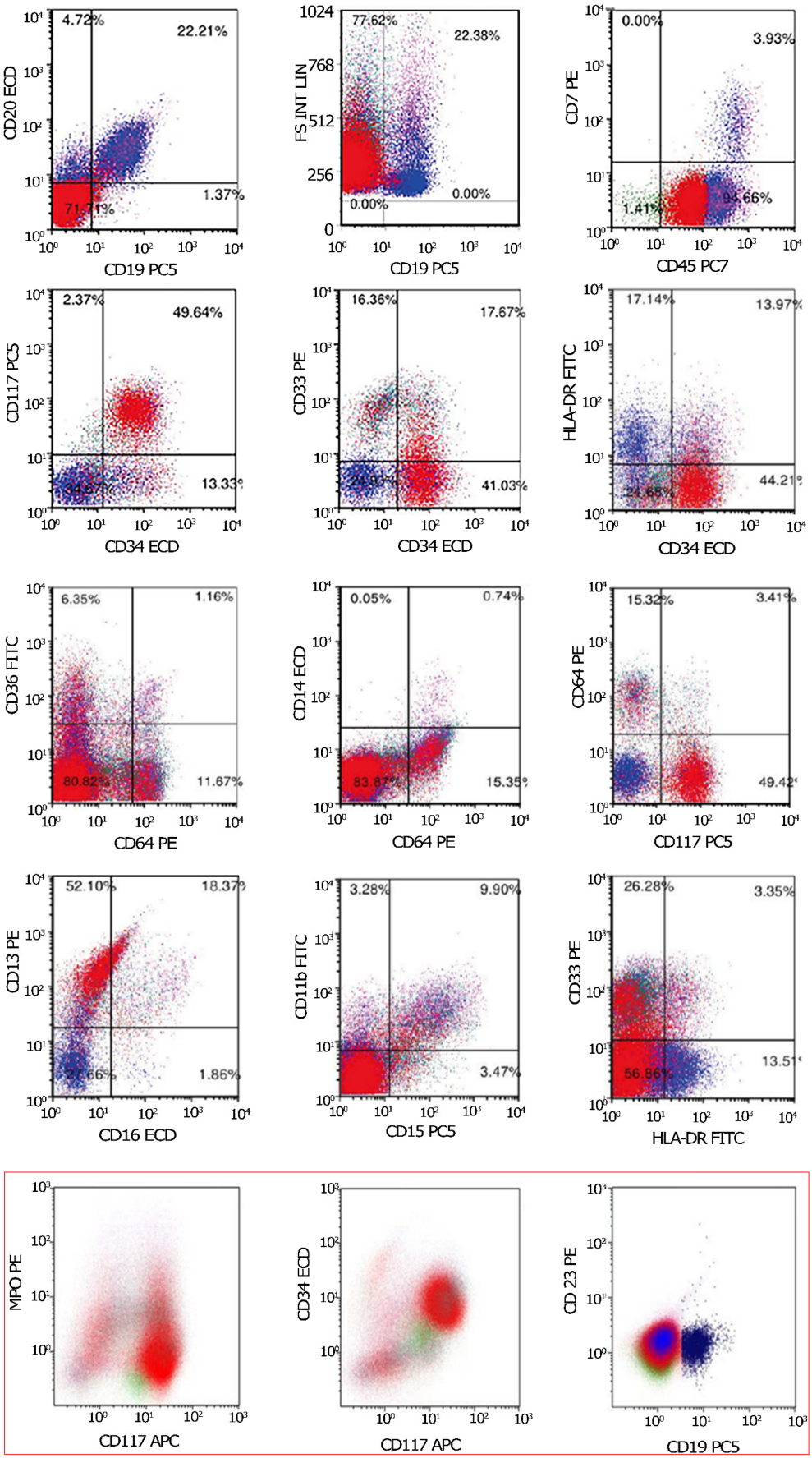

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Figure 3 Immunophenotype of bone marrow mononuclear cells. Cells of group A (red color) are myeloid blasts expressing CD34, CD13, and CD117, and partially expressing CD33, HLA-DR, and myeloperoxidase (MPO). Cells of group B (blue color) are clonal B-lymphocytes expressing CD19, CD20, and Kappa,

but no expressing CD103, CD25, CD11c, CD34, CD117, CD5, CD10, CD23, and Lambda. The results out the red box were from bone marrow sample obtained by bone marrow aspiration. The results in the red box were from peripheral blood gotten by venipuncture since the patient refused frequent bone marrow puncture.

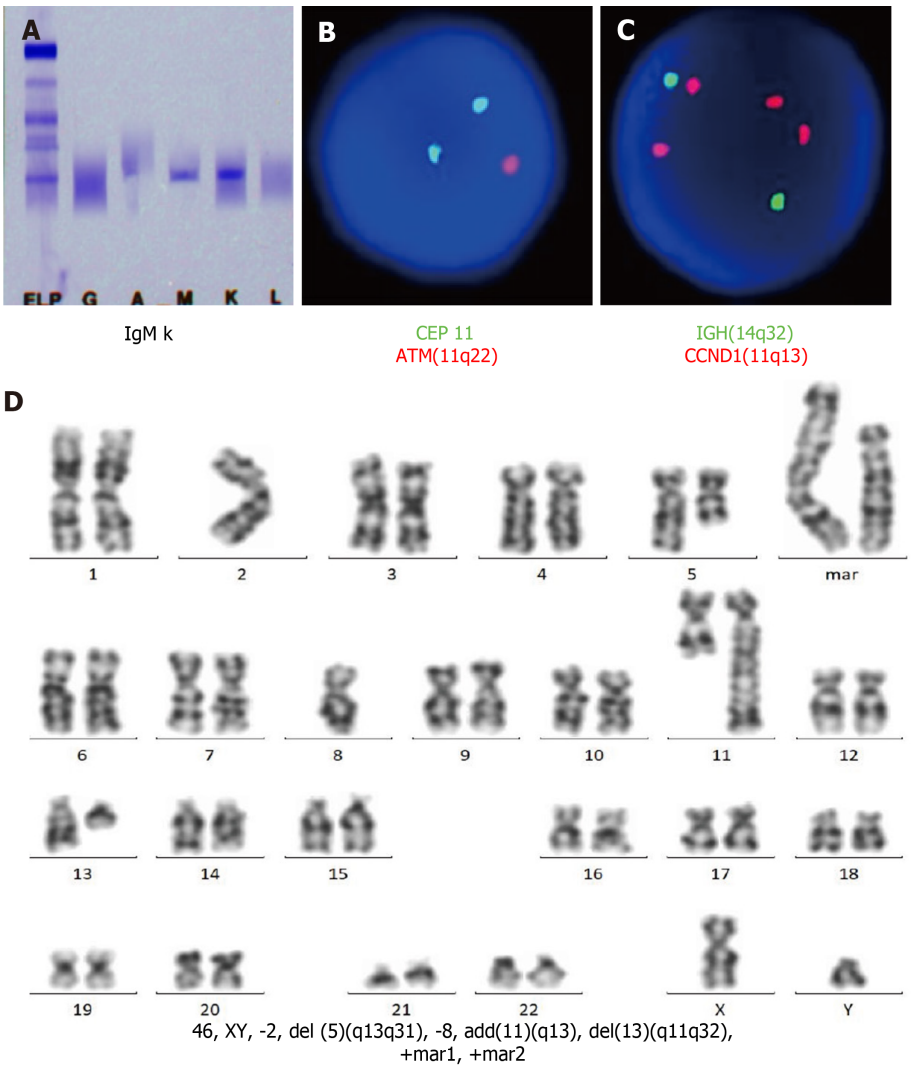

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Figure 4 The immunofixation electrophoresis of serum and cytogenetic analysis of bone marrow mononuclear cells. A: The monoclonal IgM Kappa is found by serum immunofixation electrophoresis; B and C: Fluorescence *in situ* hybridization of bone marrow mononuclear cells (BMMNCs) shows a deletion of ATM gene at 11q22 (2G1R 80%, 2G2R 17%, 1G1R 3%) and 4 copies of CCND1 gene at 11q13 (80%); D: The karyotype analysis of BMMNCs detects 46, XY, -2, del(5)(q13q31), -8, add(11)(q13), del(13)(q11q32), +mar1, +mar2 [5] or 46, XY, -2, del(5)(q13q31), -8, add(11)(q13), del(13)(q11q32), +mar1, +mar2 [20] under the stimulation of CpG-oligodeoxynucleotide.

CONCLUSION

The coexistence of DLBCL, AML, and untreated LPL/WM in a same patient is extremely rare. Herein, we reported one such case that might have resulted from multiple steps of gene mutations. In the bone marrow, asymptomatic indolent LPL/WM might have occurred earlier, then insidious MDS developed into AML. Finally, aggressive DLBCL in the chest wall grew. Hematologists should pay close attention to this extremely rare case to avoid misdiagnoses. However, this report has some limitations. Ideally, different clones from BMMNCs should have been separated for molecular analysis, genes from chest wall masses should have been tested, and an autopsy should have been performed.

FOOTNOTES

Author contributions: Zhang LB collected the sample and analyzed the clinical data; Zhang L analyzed the morphology of bone marrow; Xin HL collected the sample and performed gene sequencing; Wang Y analyzed the

histopathology of tissue; Bao HY, Meng QQ, Jiang SY, Han X, and Chen WR analyzed the clinical data; Wang JN and Shi XF provided the conception, analyzed the data, and wrote the manuscript.

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