Int J Clin Exp Pathol 2015;8(8):9629-9637
www.ijcep.com /ISSN:1936-2625/IJCEP0011190

Case Report

Composite primary breast diffuse large B-cell lymphoma and T lymphoblastic leukemia/lymphoma: report of a case and review of literature

Chaoyang Guan*, Jian Li*, Peipei Xu, Jian Ouyang, Bing Chen

*Department of Hematology, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing 210008, P. R. China. *Equal contributors.*

Received June 8, 2015; Accepted July 21, 2015; Epub August 1, 2015; Published August 15, 2015

Abstract: We reported a rare case of composite diffuse large B-cell lymphoma and T lymphoblastic leukemia/lymphoma (T-LBL) in a 46-year-old woman with progressive enlargement of the breast lump. The patient initially sought care at a local hospital with a single left breast lump without any other physical examination findings. Histopathological analysis of which revealed a diffuse infiltration of tumor cells that were rich in cytoplasm with vesicular chromatin and prominent nucleoli. Further analysis of immunohistochemistry showed a cluster of neoplastic cells which express B-cell markers: CD19, CD20 (weak), CD79a, PAX5 and BCL-2, but negative for T-cell markers such as CD2, CD3, CD5 and CD7. PET-CT showed evidence of lymphadenopathy and splenomegaly, which may indicate lymphoma infiltration. Then a biopsy of bone marrow showed typical features of T-LBL. The aberrant terminal deoxynucleotidyl transferase (TDT) and cCD3 positive T-cell population that lack surface CD10 and CD19 were identified by flow cytometric immunophenotyping. Polymerase chain reaction analysis of the T-cell receptor gamma gene and IgH gene revealed a clonal rearrangement and confirming T-cell clonality. Fluorescence in-situ hybridization (FISH) revealed a deletion of the P53 gene in these T-neoplastic cells may indicate a bad outcome of such disease. Neither the large B-cells nor T-cells were positive for Epstein-Barr virus encoded RNA.

Keywords: Composite lymphoma, primary breast diffuse large B-cell lymphoma, T-lyphoblastic leukimia/lymphoma

Introduction

Primary breast lymphoma (PBL) is a unique but distinct extranodal lymphoma sub-type, comprising 0.5% of breast malignancies, around 1% of all non-Hodgkin lymphoma (NHL) and <3% of extranodal lymphomas [1]. The most common histology of PBL is diffuse large B-cell lymphoma (DLBCL). The co-existence of PBL and T-cell lymphoma, however, is a peculiar phenomenon. Like such rare instance, two distinct types of lymphomas are called composite lymphomas (CL). This jargon was initially coined by Custer in 1954 to describe lymphoma occurred in the same anatomical site [2]. In 1977, Kim et al. Defined it as two or more morphologically and immunophenotypically distinct lymphomas that occur in the same organ or tissue site [3]. In recent years, two lymphomas presenting sequentially in a patient are also classified as CL. Most of the types of CL are B-cell lymphoma composite of Hodgkin lymphoma or B-cell lymphoma of different types. T-cell lymphoma/leukemia composite of Non Hodgkin lymphoma (NHL), however, is a kind of more rarely disease. Most of the reported cases of composite B-cell lymphoma and T-cell lymphoma consisted of diffused large B-cell lymphoma/chronic lymphocytic leukemia together with T large granular lymphocytic leukemia/angioimmunoblastic T-cell lymphoma/cutaneous T-cell lymphoma [4-6].

Herein, we reported a unique case and to the best of our knowledge, as yet never reported case of a primary composite lymphoma of PBL and T-LBL.

Case report

The patient was a 46 year Chinese female who presented as a solitary nontender, mobile, palpable mass which located in her left breast for two months. No systemic symptoms were

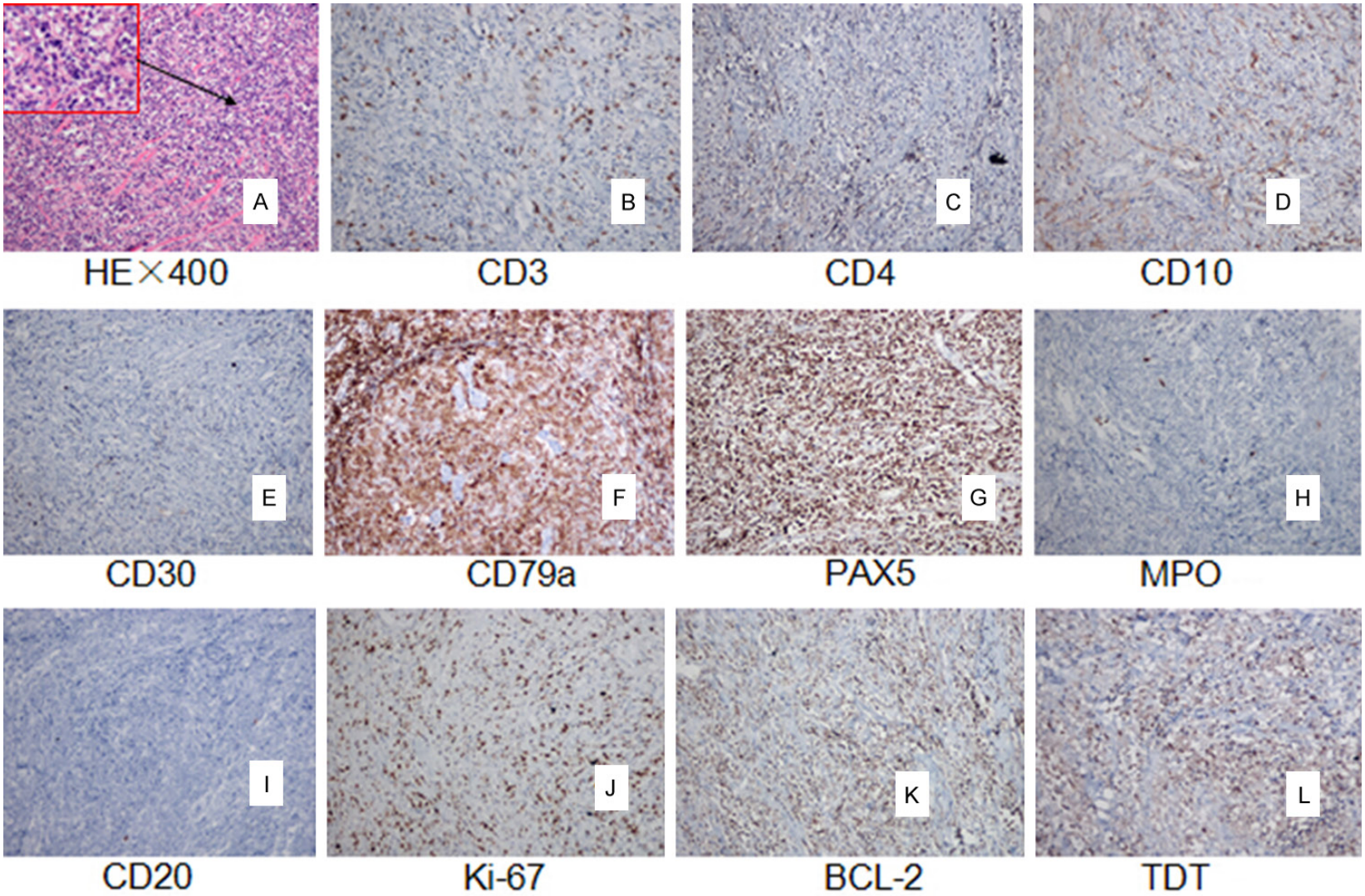

Figure 1. HE staining and immunohistochemistry pictures of the breast mass (×400). HE staining picture revealed a diffuse infiltration of tumor cells that were rich in plasma, and possessed vesicular chromatin accompanied prominent nucleoli (A). The tumor tissue strongly expressed CD79a (F), PAX5 (G), Ki-67 (J), and BCL-2 (K), but was negative for CD3 (B), CD4 (C), CD10 (D), CD30 (E), TDT (L) and MPO (H). Weak expression of CD20 (I) was observed.

Table 1. Results of immunohistochemistry and flow cytometry performed on both components

	Breast diffused large B-cell lymphoma (Immunohistochemistry)	T-lymphoblastic leukemia/ lymphoma (Flow cytometry)
CD2	-	ND
CD3	-	++
CD4	-	ND
CD5	-	ND
CD7	-	ND
CD8	-	ND
CD10	-	ND
CD13	ND	-
CD14	ND	-
CD15	-	ND
CD19	+	ND
CD20	+/-	ND
CD30	-	ND
CD71	ND	+
CD79a	+	-
CD117	-	ND
PAX5	+	ND
MUM-1	-	ND
MPO	-	-
BCL-2	+	ND
BCL-6	-	ND
TDT	-	++
CyclinD1	-	ND
HLA-DR	ND	-
Ki-67	60%	ND
CK	-	ND
S-100	-	ND

+, positive; -, negative; ND, not done.

recorded. She had no medical history of any other diseases. Physical examination found a 1 cm×1 cm mass in her left breast, but without other enlarged superficial lymph nodes being identified. She also had no history of fever, anemia, weight loss, sweats, cough or dyspnea. The blood routine examination and lactate dehydrogenase (LDH) were normal. An excisional lump biopsy was performed in her left breast and revealed a 1 cm×1 cm mass at the local hospital, histopathological analysis revealed a diffuse infiltration of tumor cells that were rich in plasma with vesicular chromatin and prominent nucleoli (**Figure 1**). The tumor cells lacked of expression CD10, CD4, CD3, CD30, MUM1, TDT and bcl-6, but were positive for CD19, CD79a, PAX5 and BCL-2, whereas part of the cells showed expression of CD20 (**Figure 1** and **Table 1**). Positron emission tomography-computed tomography (PET-CT) revealed enlarged hyper-metabolic mass in the patient's left breast mass, bone, and spleen, meanwhile the multiple superficial lymph nodes were found with basically normal metabolism. Thus, the patient was initially diagnosed with "Primary breast large B-cell lymphoma". To further evaluated the classification of the lymphoma, a bone marrow puncture was completed which surprising us to find another cluster of tumor cells. Bone marrow smear revealed a diffuse infiltration of medium-sized tumor cells which have a high nuclear/cytoplasmic ratio, thin nuclear membrane, finely-stippled chromatin and inconspicuous nucleoli (**Figure 2**). Flow cytometric analysis of the neoplastic cell showed high expression of cCD3, CD71, TDT, CD34 and CD33, but negative for B-cell markers CD13, CD79a, CD14, MPO and HLA-DR (**Figure 3**). Both Clonal T-cell receptor Ý chain rearrangement (TCR-Ý) and clonal immunoglobulin heavy chain rearreangement (IgH) were detected by polymerase chain reaction from the patient's bone marrow sample (**Figure 4**). FISH performed on T-lineage differentiation neoplasm cells confirmed the absence of P53 gene, but without t [14, 18] or c-myc and bcl-6 gene splitting (**Figure 5**). Thus, a T-lymphoblastic leukemia/lymphoma was simultaneously diagnosed with PBL in the different organs. Then the patient received a cycle of CHOP-21 (vincristine 1.4 mg/m^2 iv d1; pirarubicin 60 mg/m^2 iv d1; cyclophosphamide 750 mg/m^2 iv d1; and prednisone 50 mg po bid d1-5) regimen and a course of VDP (vincristine, daunorubicin, prednisone) regimen, her symptoms were relieved with CT revealing decreased breast mass but did not receive complete remission in bone marrow (**Figure 2**). The patient died of massive progressive disease two months later after the diagnosis of CL at March 2015.

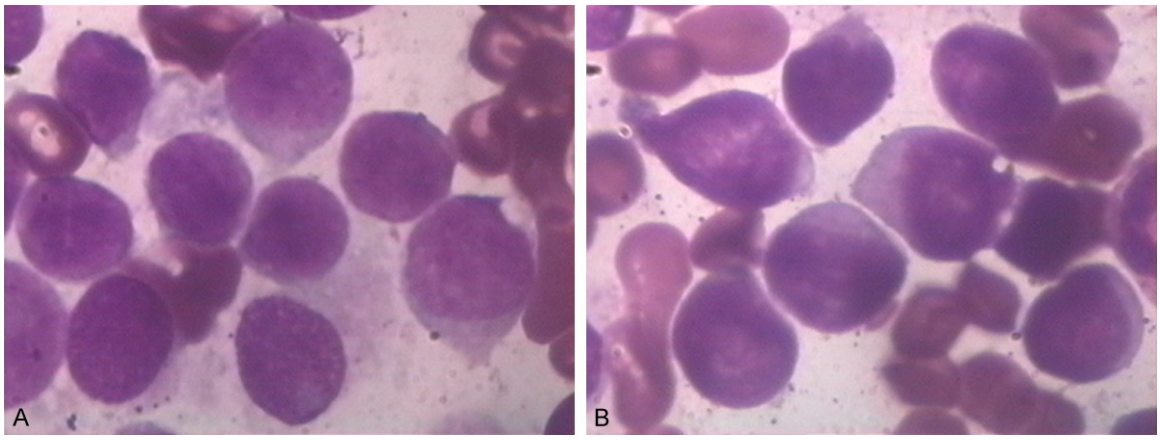

Figure 2. Morphology of the neoplastic cells from bone marrow sample. Picture (A) represent the initial status of the patient; Picture (B) was rechecked after accept the chemotherapy of VDP regimen.

Discussion

There was a rare phenomenon which first described by Culster in 1954 that two or more distinct lymphoma concurrently occur in one patient and later redefined by Kim and his co-workers. Most of the composite lymphoma concurrently occurred in the same tissue/organ, however, sometimes two lymphomas presenting sequentially or simultaneously happen in different parts in a patient are classified as composite lymphoma either [7]. Like our case, though we first diagnosed it as primary breast diffuse large B-cell lymphoma, but through further examination of bone marrow, other malignant lymphomas (T-LBL) was finally diagnosed. Generally speaking, such composite lymphomas can be composed of a non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL) or of two distinct non-Hodgkin's lymphomas [7]. Two major sub-types of Hodgkin's lymphoma, such as classic and nodular lymphocyte predominant Hodgkin's lymphoma, have also been reported [8]. The occurrence of a B-cell and T-cell NHL, however, is a rare and mysterious phenomenon. A thorough review of the PubMed database shows that various types of B-cell lymphomas, including CLL, NLPHL, DLBCL, MCL, FL and plasma oncogenesis, have been identified combined with different forms of T-cell non-Hodgkin lymphoma, including angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma, peripheral T-cell lymphoma, T-lymphoblastic leukemia/lymphoma, not otherwise specified. In all of these cases, CL which contains T-lymphoblastic leukemia/lymphoma and diffused large B-cell lymphoma, however, has been reported for only once. Herein, we report another similar case. Unlike the previous reported, the two malignant lymphoma happened at distinct anatomical site.

In our patient, the PBL and T-LBL were happened synchronously in a patient from different organs and were detected by using immunohistochemistry, flow cytometry and molecular analysis respectively. The breast mass biopsy specimen showed a B-cell lymphocytes which infiltration of CD19 (+), CD20 (+/-), Ki67 (60%), CD79a (+), PAX5 (+), Bcl2 (+), CD56 (-), CD4 (-), TDT (-), CD30 (-), CD10 (-), MUM1 (-), and cyclinD1-monoclonal large lymphocytes signifies diffuse large B-cell lymphoma (DLBCL), while bone marrow infiltration of CD3 (+), CD33 (+), CD71 (+), TDT (+), monoclonal medium-sized lymphocytes is compatible with T-LBL. Molecular analysis of T-neoplastic cells showed clonal rearrangements of the TCR-Ý gene and the IgH gene. FISH showed a P53 gene deletion.

Current research suggests that there are many kinds of mechanisms which may be responsible for the co-existence of the two lineages in a single patient. One is the patient suffering from a certain lymphoma, but due to the treatment or the transforming of the disease itself, resulting in a second lymphoma appeared. There are many FL which transform to DLBCL are like this [7, 9]. Another is the bi-directional differentiation after malignant transformation at the stem cell or progenitor cell level with capacity to differentiate into a B-cell or T-cell lineage. The biphenotypic acute leukemia is the most clas-

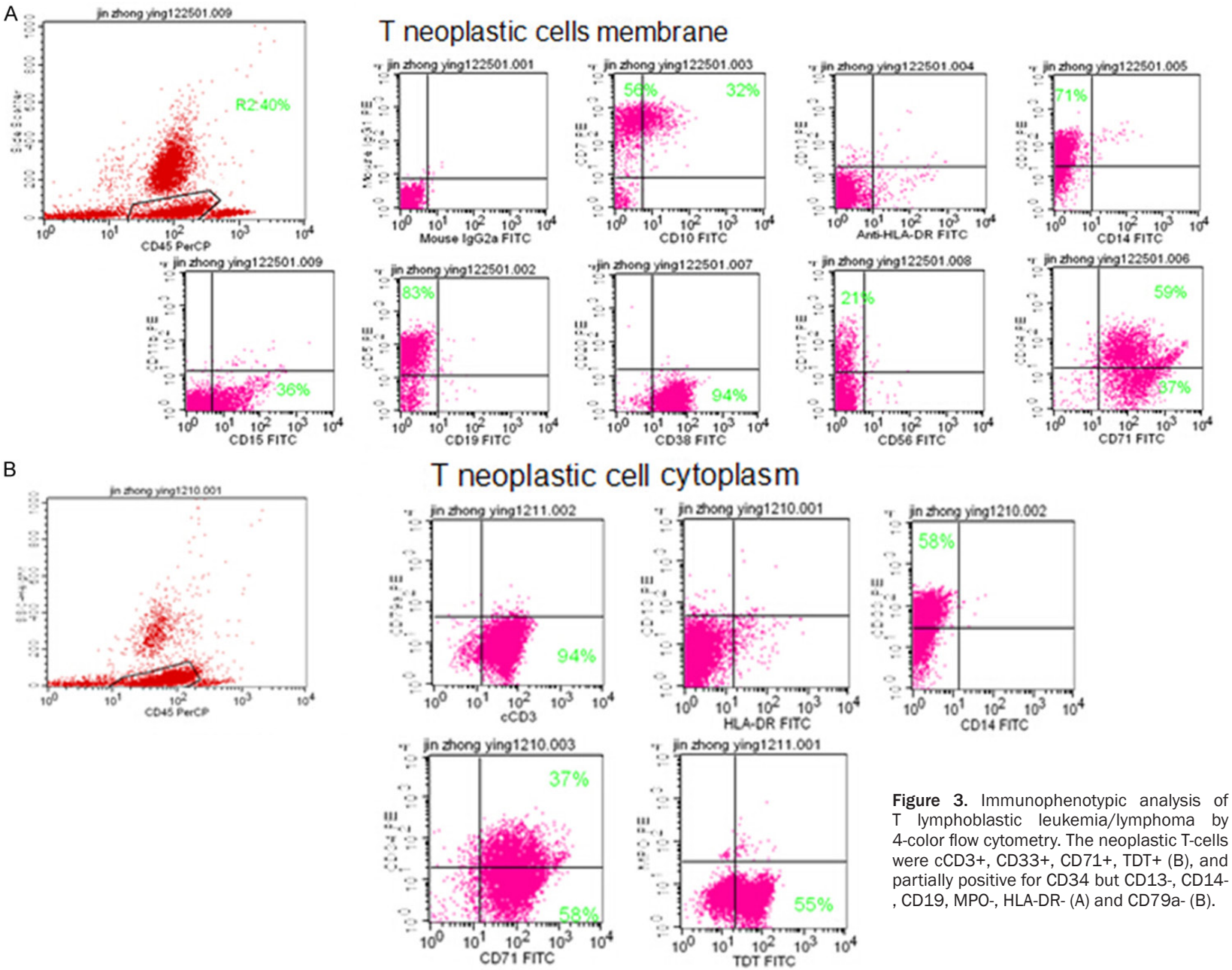

Figure 3. Immunophenotypic analysis of T lymphoblastic leukemia/lymphoma by 4-color flow cytometry. The neoplastic T-cells were cCD3+, CD33+, CD71+, TDT+ (B), and partially positive for CD34 but CD13-, CD14-, CD19, MPO-, HLA-DR- (A) and CD79a- (B).

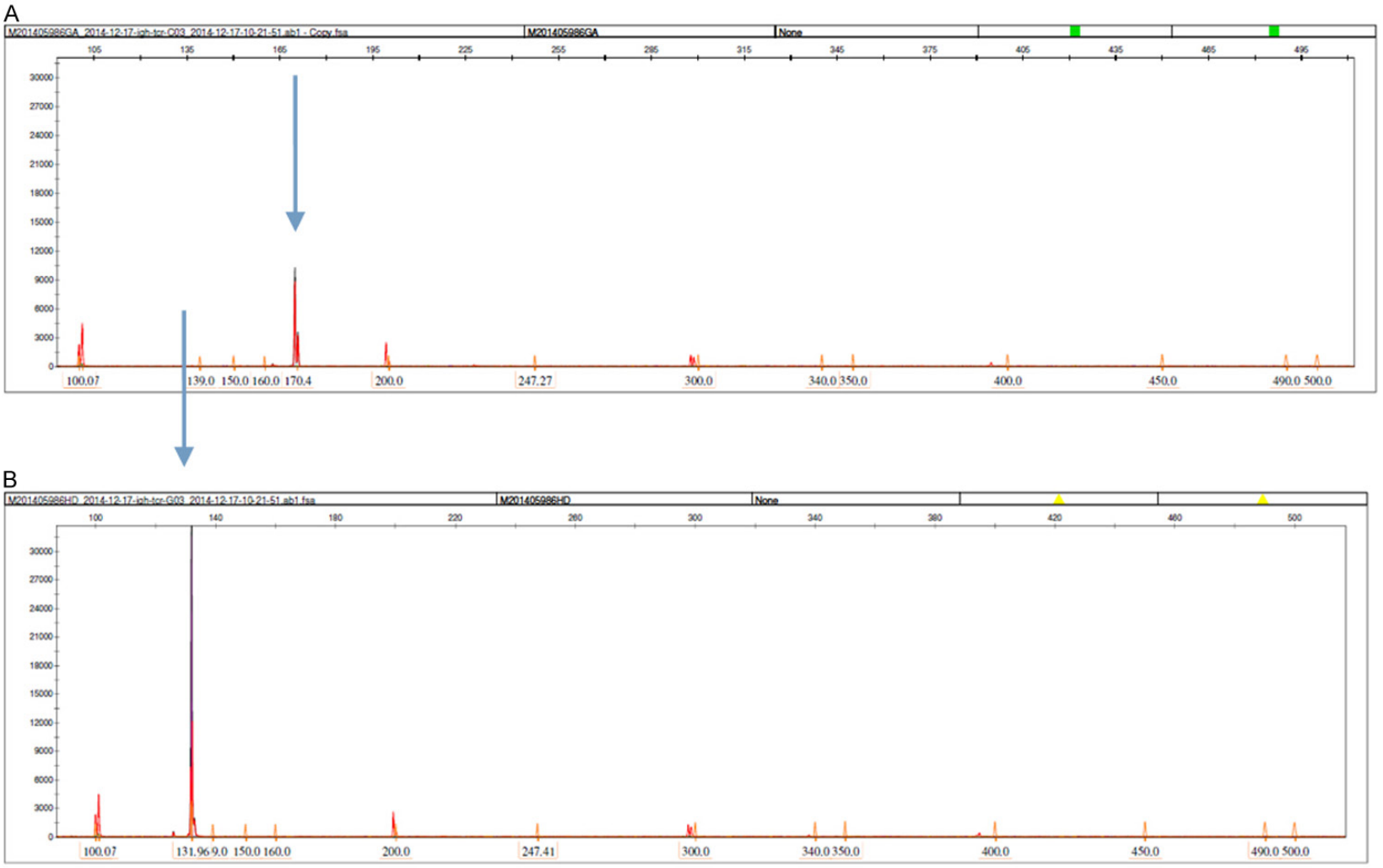

Figure 4. DNA extracted from patient's bone marrow samples and amplified by polymerase chain reaction with primers for the DH region of the immunoglobulin heavy chain (IgH) (A) and the T-cell receptor (TCRÝ) (B). Monoclonal patterns of TCR Ý (131.96 bp, arrow B) and IgH rearrangements (170.4 bp, arrow A) were detected by polymerase chain reaction and electropherogram in the same specimen.

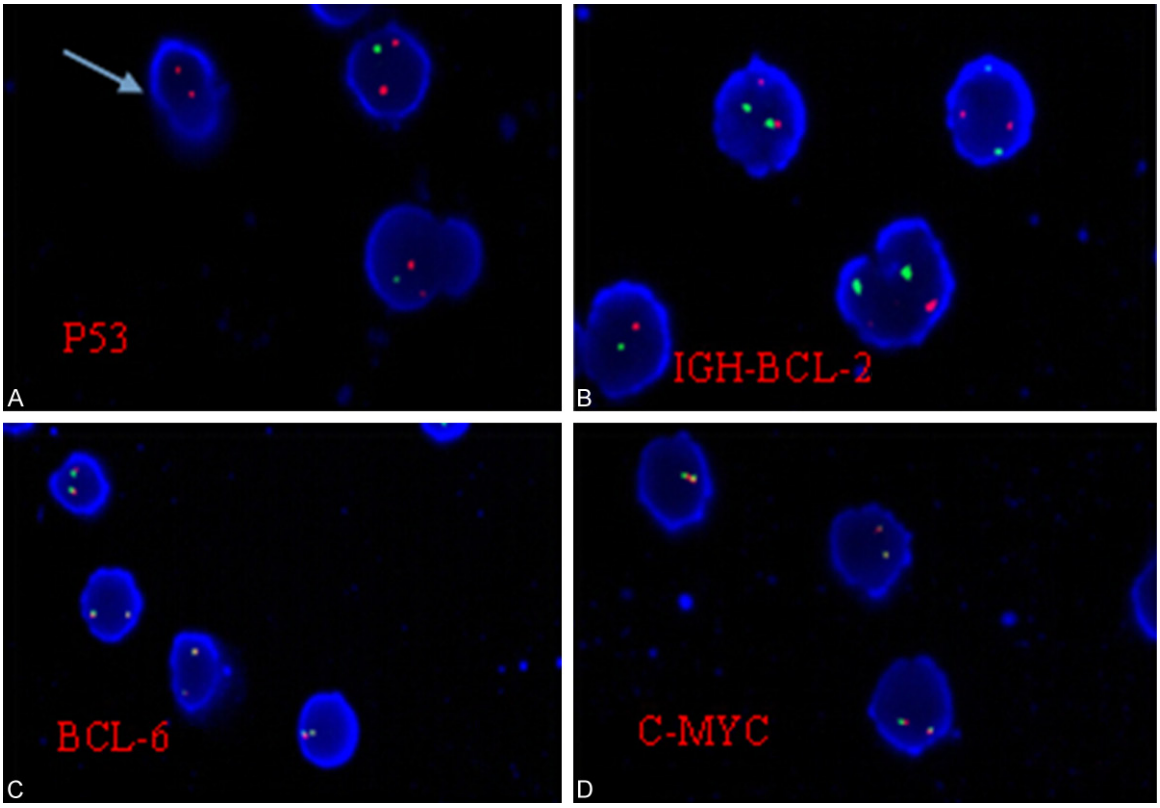

Figure 5. Neoplactic cells in the T-LBL component was detected by Fluorescence in-situ hybridization (FISH) revealed a deletion of P53 gene while in same tumor cells there was no evidence of translocation of the IGH and BCL-2 and expression of BCL-6 and C-MYC gene.

sic example of this possibility [10]. The third possibility is that there may be only a chance or linked to a underling genetic predisposition for lymphoma generation ,or an environmental risk factor could be involved [11, 12]. Moreover, an immunological factor may be involved, including chronic viral infections or got other immunodeficiency disorders [13, 14]. The lymphoma cell can make cytokines or other factors that chronically stimulate other lymphocytes, or an immunosuppressive environment in a lymphoma could promote the unrestricted expansion of other lymphocytes, thus increasing the risk of a second lymphoma developing in parallel to the initial malignant clone. Our patient had not the history of autoimmune disease and previous malignancy, nor was our case associated with EBV, which may reflect immune system. Furthermore, she got the composite lymphoma in different tissues. Thus, we hypothesize that there may be just one chance to occur in the present case.

Both of the PBL and T-LBL are following an aggressive clinical course and have poor outcome. The use of surgical restriction in the management of primary breast lymphoma has declined since 1990 [15]. There are many evidence suggest that surgical restriction has no benefit to these patients. Multiagent anthracycline-based chemotherapy with rituximab, sometimes with radiation, is considered to be the optimal treatment regimen for patients with aggressive B-cell lymphoma. According to the latest NCCN guidelines, the optimal treatment regimen of T-LBL is to choose the similar regimen of other types of T-cell acute lymphoblastic leukemia (T-ALL), especially when bone marrow got infiltration [16]. The prognosis of T-LBL, as with other lymphomas, depends on the age of patients, stage and LDH levels [17]. Nevertheless, because of the lowest incidence of such composite lymphoma, there are no suggestions of frequently-used or standard treatment regimen. We still pose a great challenge, especially if findings from imaging studies reveal disease manifestations at different locations, thus exact stage of each part of the lymphoma can often not be identified. On account of the effect of stage on the type and

intensity of therapy, all manifestations can't be ambiguously attributed to a component of the disease but should be ascribed to the lymphoma with the less favourable prognosis [7]. Lots of reported literatures propose that if a T-cell lymphoma accompanies a treatment-requiring B-cell lymphoma, an anti-CD20 containing regimen should be selected [18, 19]. Not unexpectedly, the outcome is largely determined by the T-cell component [19, 21]. For example, Daisuke Niino has reported a similar case of who received eight cycles of R-CHOP therapy and achieved completed remission [20]. For our case, the patient underwent one cycle of chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), though the breast mass seemed regression, however, remission was not achieved in bone marrow. It may indicate that the outcome of such CL is largely determined by the T-cell component and a T-cell leukemia/lymphoma chemotherapy protocol may be preferred. Therefore, she was subsequently treated with another course of the chemotherapy regimen VDP (vincristine, daunorubicin, prednisone), which was usually seemed to be the appropriate treatments for T-ALL. Followed this course of chemotherapy she got a secondary neutropenic infection but got better after using antibiotics and colony-stimulating factor. Then we recheck the bone marrow show that precursor T-cells accounted for 81.5% of the bone marrow of the patient. She has not got any anesis yet. The patient denies accepting further treatment and died of disease progression one month later.

In summary, we reported a composite lymphoma of PBL and T-LBL. Because of the low incidence of PBL and T-LBL simultaneously in the same patient, and especially both of which undergoing a highly aggressive characteristics, there is a lack of recommendation on the treatment so far. Different treatment plans may be required when the two components of the composite lymphoma have entirely different natural histories.

Acknowledgements

We gratefully acknowledge the pathologists in our hospital for their expertise and generous provision of data.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Bing Chen, Department of Hematology, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Zhongshan Road 321, Nanjing 210008, China. Tel: +86 25 83304616-61441; E-mail: chenbing2004@126.com

References

[1] Validire P, Capovilla M, Asselain B, Kirova Y, Goudefroye R, Plancher C, Fourquet A, Zanni M, Gaulard P, Vincent-Salomon A, Decaudin D. Primary breast non-Hodgkin's lymphoma: a large single center study of initial characteristics, natural history, and prognostic factors. Am J Hematol 2009; 84: 133-139.

[2] In: Custer R. Pitfalls in the diagnosis of lymphoma and leukemia from the pathologist's point of view. New York: Second National Cancer Conference; 1954. pp. 554-557.

[3] Kim H, Hendrickson R, Dorfman RF. Composite lymphoma. Cancer 1977; 40: 959-976.

[4] Boyer DF, Lindeman NI, Harris NL, Ferry JA. Peripheral T-cell lymphomas with cytotoxic phenotype in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma. Am J Surg Pathol 2014; 38: 279-288.

[5] Inokuchi T, Shincho M, Moriwaki Y, Ka T, Takahashi S, Tsutsumi Z, Lin Y, Hirota S, Yamamoto T. Coexistent B-cell lymphoma and cutaneous T-cell lymphoma. Intern Med 2006; 45: 641-647.

[6] Suefuji N, Niino D, Arakawa F, Karube K, Kimura Y, Kiyasu J, Takeuchi M, Miyoshi H, Yoshida M, Ichikawa A, Sugita Y, Ohshima K. Clinic pathological analysis of a composite lymphoma containing both T- and B-cell lymphomas. Pathol Int 2012; 62: 690-698.

[7] Küppers R, Dührsen U, Hansmann ML. Pathogenesis, diagnosis, and treatment of composite lymphomas. Lancet Oncol 2014; 15: 435-446.

[8] Szczepanowski M, Masqué-Soler N, Oschlies I, Schmidt W, Lück A, Klapper W. Composite lymphoma of nodular lymphocyte-predominant and classical Hodgkin lymphoma-Epstein-Barr virus association suggests divergent pathogenesis despite clonal relatedness. Hum Pathol 2013; 44: 1434-1439.

[9] Miyata-Takata T, Takata K, Sato Y, Taniguchi K, Takahashi Y, Ohara N, Yoshino T. A case of diffuse large B-cell lymphoma transformed from primary duodenal follicular lymphoma. Pathol Int 2014; 64: 527-532.

[10] Batinić D, Dubravcić K, Rajić L, Mikulić M, Labar B. Biphenotypic and bilineal acute leukemias. Acta Med Croatica 2008; 62: 387-390.

[11] Krikorian JG, Burke JS, Rosenberg SA, Kaplan HS. Occurrence of non-Hodgkin's lymphoma

after therapy for Hodgkin's disease. N Engl J Med 1979; 300: 452-458.
[12] Toner GC, Sinclair A, Sutherland RC, Schwartz MA. Composite lymphoma. Am J Clin Pathol 1986; 86: 375-378.
[13] Ho JW, Ho FC, Chan AC, Liang RH, Srivastava G. Frequent detection of Epstein-Barr virus-infected B cells in peripheral T-cell lymphomas. J Pathol 1998; 185: 79-85.
[14] Holm LE, Blomgren H, Lowhagen T. Cancer risks in patients with chronic lymphocytic thyroiditis. N Engl J Med 1985; 312: 601-604.
[15] Neri A, Caruso S, Cerullo G, Lenoci MP, Marrelli D, Roviello F. Primary non-Hodgkin's breast lymphoma: surgical approach. Cases J 2008; 1: 311.
[16] In: Swerdlow SH, Campo E, Harris NL, editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th edition. Lyon, France: IARC Press; 2008. PP. 178.
[17] Morel P, Lepage E, Brice P, Dupriez B, D'Agay MF, Fenaux P, Gosselin B, Bauters F, Gisselbrecht C. Prognosis and treatment of lymphoblastic lymphoma in adults: a report on 80 patients. J Clin Oncol 1992; 10: 1078-85.
[18] Suefuji N, Niino D, Arakawa F, Karube K, Kimura Y, Kiyasu J, Takeuchi M, Miyoshi H, Yoshida M, Ichikawa A, Sugita Y, Ohshima K. Clinicopathological analysis of a composite lymphoma containing both T- and B-cell lymphomas. Pathol Int 2012; 62: 690-698.
[19] Balague O, Martinez A, Colomo L, Roselló E, Garcia A, Martínez-Bernal M, Palacín A, Fu K, Weisenburger D, Colomer D, Burke JS, Warnke RA, Campo E. Epstein-Barr virus negative clonal plasma cell proliferations and lymphomas in peripheral T-cell lymphomas: a phenomenon with distinctive clinicopathologic features. Am J Surg Pathol 2007; 31: 1310-1322.
[20] Niino D, Ohsaki K, Arakawa F, Watanabe J, Kimura Y, Kiyasu J, Takeuchi M, Miyoshi H, Yoshida M, Sugita Y, Ohshima K, Okamura T. Composite T lymphoblastic leukemia/lymphoma and diffuse large B-cell lymphoma: case report. Pathol Int 2011; 61: 363-368.
[21] Du Z, Chen J, Zhou X, Zhang T, Chen B, Tang F. Composite lymphoma with relapse of enteropathy-type T-cell lymphoma. Leuk Lymphoma 2009; 50: 749-756.