Case Report

Open Access Journal of
Biomedical Science
ISSN: 2690-487X

Sequential Development of Primary Cutaneous Anaplastic Large Cell Lymphoma Post Chemotherapy of Follicular Lymphoma

Xiayu Chen[1], Yajiao Liu[1], Ying Zhao[2], Jingfen Zhou[2], Xiaoxing Feng[3], Yeping Sheng[4] and Haiying Hua[2]*

[1]*Wuxi School of Medicine, Jiangnan University, China*

[2]*Department of Hematology, The Affiliated Hospital of Jiangnan University, China*

[3]*Department of Pathology, The Affiliated Hospital of Jiangnan University, China*

[4]*Nantong University, China*

ABSTRACT

We have presented a case of the coexistence of t-cell and b-cell tumors in a different anatomical location in one patient. This study aims to show the sequential development of primary cutaneous anaplastic large cell lymphoma (PC-ALCL) post-chemotherapy of follicular lymphoma (FL) in a case for the first time in the literature. A 38-year-old Chinese male presented to us with complaints of slowly progressing swelling in the inguinal on the left side in 2014. Then the patient revealed a diagnosis of follicular lymphoma for which the patient was treated with 6 cycles of R-CHOP regimen. He had a very good response to chemotherapy. He presented again with a new symptom of multiple nodular protrusions on the left cheek in June of 2015. After a complete work-up, he was diagnosed with primary cutaneous anaplastic large cell lymphoma. He received 6 cycles of CHOP combined with arsenic trioxide, resulting in partial remission. He presented the third time after 3 years with a history of painless progressive swelling in the right side of the neck. Examination revealed cervical lymph nodes. This time, a repeat biopsy and immunohistochemistry were suggestive of follicular lymphoma. He is currently on follow-up.

KEYWORDS: Follicular lymphoma; PC-ALCL; Histologic transformation

ABBREVIATIONS: FL: Follicular lymphoma; PC-ALCL: Primary Cutaneous Anaplastic Large Cell Lymphoma; IHC: Immunohistochemistry; ATO: Arsenic Trioxide; HDS: High-Dose Sequential

INTRODUCTION

Unlike composite lymphoma, which has two or more diverse lymphoma types in a single anatomic site, the situation that different types of lymphomas occurring in different anatomic sites concurrently or sequentially are defined as discordant lymphoma [1]. B-cell lymphoma composite with a T-cell lymphoma is rare, sequential occurrence of Follicular lymphoma (FL) and primary cutaneous anaplastic large cell lymphoma (PC-ALCL) has not previously been reported. Probably due to the low prevalence of the latter in general.

Primary cutaneous anaplastic large-cell lymphoma is part of the spectrum of CD30+ lymphoproliferative cutaneous processes, characterized by single or multifocal nodules that ulcerate, are autoregressive and recurrent. Extracutaneous dissemination may occur, especially in regional lymph nodes. Histology shows a diffuse, non-epidermotropic infiltrate, anaplastic large lymphoid cells of immunohistochemistry CD30+, CD4+, EMA-/+, ALK-, CD15- and TIA1-/+. Prognosis is good and does not depend on the lymphatic invasion. Radiotherapy, removal of the lesion, and/or low-dose methotrexate are the treatments of choice [2]. To the best of our

Quick Response Code:

Address for correspondence: Hai-Ying Hua, Department of Hematology, The Affiliated Hospital of Jiangnan University, China

Received: April 17, 2021 **Published:** May 17, 2021

How to cite this article: Xiayu C, Yajiao L, Ying Z, Jingfen Z, Xiaoxing F, Yeping S, Haiying H. Sequential Development of Primary Cutaneous Anaplastic Large Cell Lymphoma Post Chemotherapy of Follicular Lymphoma. 2021- 3(3) OAJBS.ID.000280. **DOI:** 10.38125/OAJBS.000280

knowledge, it is unusual to see a case report of b-cell lymphoma and t-cell lymphoma occur in one patient. This study aims to show the Sequential development of primary cutaneous anaplastic large cell lymphoma post-chemotherapy of follicular lymphoma in a case for the first time in the literature.

CASE REPORT

A 38-year-old Chinese male was initially diagnosed with "lymphoma" in June 2014 at another hospital. He had an enlargement of bilateral inguinal lymph nodes, while fever, night sweat, or weight loss were not observed. Enhanced CT showed multiple lymph nodes in the bilateral neck, axilla, mediastinum, right diaphragmatic Angle, abdominal cavity, retroperitoneum, pelvic cavity, and bilateral inguinal lymph nodes. A left inguinal lymph node biopsy was performed subsequently. Immunohistochemistry (IHC) performed revealed these cells to be positive for CD20, CD79α, PAX-5, BCL-2, CD10, CD21, CD23, with a partial expression of BCL-6 and KI 67 index of 40%. The cells were negative for CD3, CyclinD1, CD5 (Figure 1). He was eventually diagnosed with follicular lymphoma (FL) and was treated with 6 cycles of frontline R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone. Details of the chemotherapy regimen were not available to us and could not be retrieved. He had a very good response to chemotherapy with a decrease in the size of all lymph nodes mentioned before, but he defaulted and was lost to follow-up.

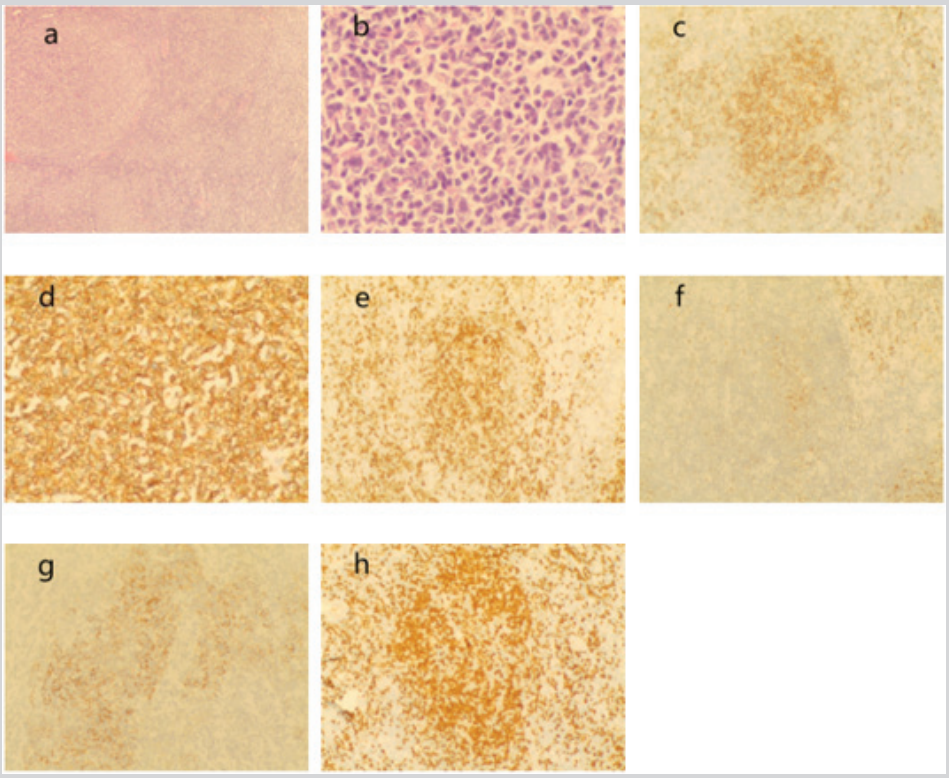

Figure 1: Histopathology Images of Biopsy specimen done in 2014 suggestive of FL.
a. 40× The normal lymph node structure is destroyed and replaced by tightly arranged follicular structures with thinning mantle.
b. 400× The central mother cell with moderate nucleoli is seen here.
c. 100× CD10 positive.
d. 200× CD20 positive.
e. 100× Bcl 2 positive.
f. 100× Bcl 6 positive.
g. 100× CD21 positive.
h. 100× Pax 5 positive.

He had a new symptom of multiple nodular protrusions on the left cheek in June of 2015. Multiple nodules on the left cheek, protruding from the skin surface, partially fused into a piece, dark red, varying in size, with a maximum diameter of 3cm. A new biopsy was then performed. Then he was diagnosed with primary cutaneous anaplastic large cell lymphoma (PC-ALCL) by biopsy in the left neck. Immunohistochemical detection showed that lymphocytes were positive for CD2, CD4, CD30, Vimentin and partial expression of CD7, CD8, TIA-1, CD99, with KI 67 index of 80%. negative for CD20, CD3, CD5, CD79α, CK (pan), EMA, CD56, PAX-5, MUM-1, BCL-2, BCL-6, Perforin, GreB, MPO, S100 and ALK1 (Figure 2). He received 6 cycles of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) chemotherapy combined with arsenic trioxide (ATO), resulting in partial remission finally. CT reexamination in another hospital found that abdominal lymph nodes were swollen, and the recurrence of follicular lymphoma was considered after 3 years, but the details were unknown. He was treated with 8 cycles of chemotherapy regimen (dexamethasone, etoposide, Cyclophosphami, Cisplatin and arsenic trioxide) and had been orally administered with thalidomide to regulate immunity during treatment. He presented to the third time in June 2019 with complaints of chest distress and fever for a duration of half

a month. A bone marrow aspiration and biopsy were done, and it showed significant granulocytic, erythroid, and megakaryocytic hyperplasia, mild morbid changes in granulocytic hyperplasia, and medium and small clusters of platelets (Figure 3).

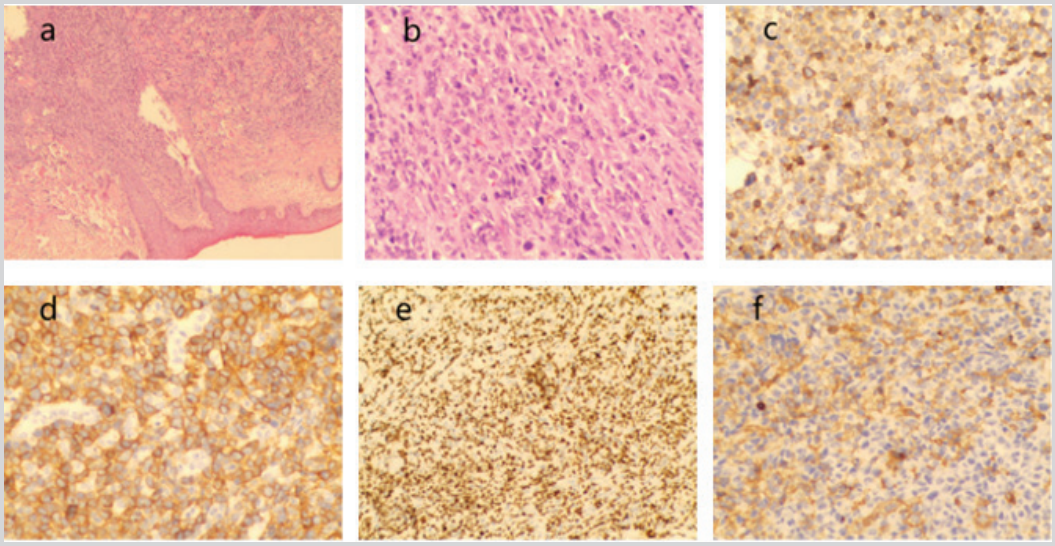

Figure 2: Histopathology Images of Biopsy specimen done in 2015 suggestive of PC-ALCL.
a) 40× and
b) 200× The cells are polymorphic, nucleoli are seen in some cells, and mitosis is common.
c) 200× CD2 positive.
d) 200× CD30 positive.
e) 100× Ki-67 Proliferation Index was 80%.
f) 200× CD4 negative.

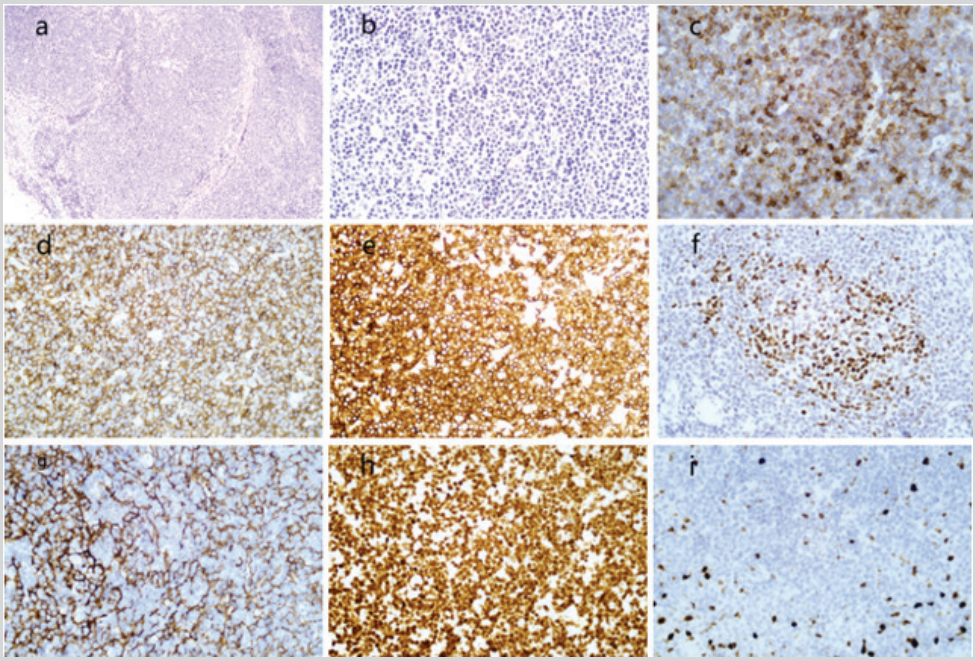

Figure 3: Histopathology Images of Biopsy specimen done in 2019 suggestive of FL.
a- 40× and
b- 200× Structure destruction, lymphatic follicular proliferation, follicular cell morphology tends to be consistent, mainly the center cells.
c- 200× CD10 positive.
d- 200× CD20 positive.
e- 100× Bcl 2 positive.
f- 200×Bcl 6positive.
g- 200× CD21 positive.
h- 100× Pax 5 positive.
i- 100× Ki-67 Proliferation Index was 20%.

A biopsy of the left cervical lymph node was performed, then he was diagnosed with follicular lymphoma with pathological grade 1-2. Immunohistochemistry (IHC) performed revealed these large cells to be positive for BCL-2, CD10, CD20, PAX-5, and BCL-6 with a KI 67 index of 20%.FDC meshwork was highlighted by CD21. Negative for CD5, CD3, Cyclin D1.

TCR gene rearrangements were detected by PCR, meanwhile, rearrangements of IGH, IGK, IGL were found. Pleural fluid lymphoma immunophenotyping: visible abnormal B lymphocytes, 3.08%, small FSC, germinal center origin, consistent with CD5-CD10+small B cell lymphoma phenotype, more common in FL. Immunophenotyping of lymphoma of bone marrow: abnormal B lymphocytes, 20.77%, small FSC, of germinal center origin, consistent with CD5-CD10+ small B cell lymphoma phenotype, more common in FL. A PET-CT scan showed there were multiple enlarged lymph nodes, splenomegaly, and systemic bone marrow lesions with varying degrees of increased FDG metabolism, it is considered that lymphoma tumor has active lesions with multiple infiltrates.

Then the patient had received six cycles of R-CHOP regimen and achieved a stable disease so far. The reexamination of bone marrow aspiration and biopsy revealed an active high level of proliferation significantly, mild pathological changes of granulocyte proliferation and small and single scattered platelets.

On March 31st, 2020, a reexamination of PET-CT showed: after chemotherapy for lymphoma recurrence, compared with the previous PRT-CT, the lymph nodes in the left inguinal region were smaller than before, the metabolism of FDG was higher than before, most of the remaining systemic multiple lymph nodes disappeared or significantly shrank as shown in the previous film, and the spleen was smaller than before, without abnormally high FDG generation. On May 3rd, 2020, the patient was given Rituximab 600mg. Since then, the patient was maintained on monthly and achieved a stable disease so far.

DISCUSSION

The histologic diagnosis of discordant lymphoma is challenging as the geographic distribution of each lymphomatous component is often uneven due to space competition between the two clonal processes. Often one component with a growth advantage may dominate over the other, causing the latter to be overlooked. In our experience, some pathologists may stop pursuing secondary suspicious findings once they have identified one major neoplasm [3,4].

Some hypotheses about the coexistence of t-cell and b-cell tumors in a single anatomical location have been proposed: a theory attributes the simultaneous transformation of t-cell and b-cell components to certain viral infections, such as EBV. It has been thought that EBV antigens expressed in neoplastic B-cells might stimulate T-cell proliferation and, through clonal selection, eventually induce neoplastic transformation [5].

However, we didn't detect EBV infection in either of two biopsies by using in situ hybridization, nor any evidence of immune dysfunction complications. Rheumatoid factor and autoimmune disease-related antibodies, including antinuclear antibodies, anti-Sm antibody and antistreptolysin O, were normal.

Results of bone marrow aspiration were normal. So, we consider this case as a sequential discordant lymphoma, which may be caused by the chemotherapy of follicular lymphoma. Some researchers hypothesized that immunodeficiency and hypogammaglobulinemia caused by R-CHOP therapy led to the development of such a phenomenon [6]. Multivariate analysis demonstrated that three factors had an independent association with secondary solid tumor occurrence: advanced age, rituximab addition to high-dose sequential (HDS) program, and radiotherapy after HDS [7]. Due to the negative effect on the immune system, rituximab combined with chemotherapy has the potential possibility to induce a secondary lymphoma. Additionally, the underlying mechanism for developing discordant lymphoma remains unclear despite cumulative evidence attained from the growing number of published case studies.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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