Case report

Follicular T-cell lymphoma mimicking lymphocyte-rich classic Hodgkin lymphoma: a case report of a diagnostic pitfall

Ayako Sakakibara,1) Yuka Suzuki,1) Harumi Kato,2) Kazuhiro Yamamoto,2) Mamiko Sakata-Yanagimoto,3,4) Yuichi Ishikawa,5) Katsuya Furukawa,5) Kazuyuki Shimada,5) Kei Kohno,1,6) Shigeo Nakamura,1) Akira Satou,7) and Seiichi Kato8)

Follicular T-cell lymphoma (FTCL), one of the nodal T-cell lymphomas with T follicular helper (T_{FH}) phenotype, is an uncommon disease. The diagnosis of FTCL is challenging on the distinction from the morphological mimics mostly exemplified by follicular lymphoma. Here, we described a case of FTCL that mimicked lymphocyte-rich classic Hodgkin lymphoma (LRCCHL). A 47-year-old male presented with cervical lymphadenopathy. The biopsy specimen demonstrated nodular lymphoid proliferation, which included scattered CD30+ CD15- CD20- PAX5 weakly+ Hodgkin and Reed-Sternberg (HRS)-like cells and a rich distribution of CD3+ CD4+ PD1+ T-cells. Epstein Barr virus was not detected in HRS-like cells, but it was detected in a small proportion of the scattered lymphocytes. The large cells were also negative for programmed cell death ligand 1, which appeared to be coincidental as described in our previous report of LRCCHL. However, flow cytometry showed a CD3- CD4+ T-cell population that constituted 37.4% of all gated lymphocytes. A PCR analysis showed a clonal T-cell receptor-gamma gene rearrangement, but not a clonal immunoglobulin heavy chain gene rearrangement, and showed \textit{RHOA} G17V mutation. The constellation of these findings led us to revise the diagnosis to FTCL. This result indicated that our case belonged to a relatively indolent subgroup of nodal peripheral T-cell lymphoma of T_{FH} phenotype, which affects patients ≤60 years old, recently proposed by our group. This case report expands our understanding of the morphologic spectrum of FTCL and its clinicopathologic significance.

Keywords: Follicular T-cell lymphoma, lymphocyte-rich classic Hodgkin lymphoma, diagnostic pitfall, programmed cell death protein 1 (PD1), \textit{RHOA} mutation

INTRODUCTION

Follicular T-cell lymphoma (FTCL) is classified as nodal T-cell lymphoma of the follicular helper T-cell (T_{FH}) phenotype, mostly exemplified by angioimmunoblastic T-cell lymphoma (AITL). As far as T-cell lymphoma is concerned, nodal T-cell lymphoma of T_{FH} phenotype is most commonly found in areas that are non-endemic for human T-cell leukemia virus type 1 (HTLV-1), following peripheral T-cell lymphoma, not otherwise specified (PCTL-NOS). Currently, the FTCL incidence is spreading beyond western and eastern countries.\textsuperscript{1} Recognition of the morphologic spectrum of this disease has resulted in a distinction among the three histologic patterns of AITL and an update in the 2017 WHO classification. Indeed, the distinction between FTCL and follicular B-cell lymphoma remains challenging, particularly when B-cell lymphoma is masked with a prominent distribution of T_{FH}-type lymphocytes. Thus, a differential diagnosis requires extensive immunohistologic and molecular studies. Additionally, the English literature has documented the problems involved in performing a differential diagnosis between Epstein Barr virus (EBV)+ classic Hodgkin lymphoma (CHL)
and nodal T-cell lymphoma with T<sub>FH</sub> phenotype with EBV+ non-malignant Hodgkin and Reed-Sternberg (HRS)-like large B cells, due to overlapping histopathological features. We recently showed that the non-malignant HRS-like cells found in nodal T-cell lymphoma with T<sub>FH</sub> phenotype lacked expression of programmed cell death ligand 1 (PD-L1). This finding was highly useful for identifying these cells in our diagnostic approach. Notably, Moroch et al. and subsequently, Alikhan et al. shed light on FTCL cases that strikingly resembled lymphocyte-rich CHL (LRCHL). They emphasized that the differential diagnosis required a careful assessment of the T-cell population in the lesion. Here, we describe a Japanese patient with FTCL that mimicked LRCHL, which complicated a diagnosis based on the routine histopathologic approach of pathologists.

**CLINIQUEAL SUMALLY**

A 47-year-old male was admitted to a local hospital with a left cervical lymphadenopathy without B-symptoms. A lymph node biopsy resulted in a provisional diagnosis of LRCHL. He underwent staging with whole-body magnetic resonance imaging, which revealed swelling in the cervical, mediastinal, and para-aortic retroperitoneal lymph nodes. No detectable lesion was present in the liver or spleen, but bone marrow involvement was detected. Therefore, the lymphoma was considered as stage IVA. The serum level of soluble interleukin-2 receptor (sIL-2R) was 1070 U/mL at diagnosis, and there were no detectable immunoglobulinopathies.

**PATHOLOGICAL FINDINGS**

The lymph node biopsy specimen revealed a predominantly nodular growth pattern, with some fibrotic bands partially surrounding the lymph node (Fig. 1A, 1B). The nodules were composed of small-to-intermediate-sized lymphoid cells with scattered, large mononuclear cells, or less frequently, binucleate cells, with small distinct nucleoli and abundant basophilic cytoplasm, which resembled HRS cells (Fig. 1C). These HRS-like cells expressed CD30 (Fig. 1D) and showed weakly positive detection of PAX5 (Fig. 1E), OCT2, and BOB1, expressed at variable intensity. These cells did not express CD20, PD-L1 (Fig. 1F), or the EBV-encoded small RNA, although a small number of EBV+ lymphocytes were scattered in the lesion (Fig. 1G). The lymphocytic aggregates, or sheets, that surrounded the HRS-like cells strongly expressed programmed cell death protein 1 (PD1; Fig. 1H). The combination of these findings led us to the initial diagnosis of LRHCL, based on findings in our previous report.

A flow cytometry analysis showed a CD4+ T-cell predominance with a CD4:CD8 ratio of 4.9. We identified an aberrant CD3- CD4+ T-cell population, which constituted 37.4% of all gated lymphocytes (Fig. 2A). We also identified small populations of CD4+/CD10+ cells (6.6%; Fig. 2B) and CD4+/CD8+ cells (8.3%). We did not identify any associated monotypic B-cells. A PCR analysis indicated a clonal T-cell receptor gamma gene rearrangement, but no clonality in the immunoglobulin heavy chain gene (Fig. 2C). The G-banded karyotype was 46, XY, del(6)(q?) [5]/46 XY, add(10)(q22)[2]/49, XY, +3mar[1]/46, XY[7].

Upon re-reviewing the histology of the lymph node section, we noted nodules that comprised slightly atypical lymphoid cells with slightly irregular, small-to-medium-sized nuclei. Their morphologic atypia were initially interpreted as a sign of cellular “activation” of T lymphocytes, as described by Moroch et al. We also noted partial vascular proliferation with atypical lymphoid cells. These “atypical” T cells were largely positive for CD2, CD3, CD4 (Fig. 1G), CD5, PD1 (Fig. 1H), and CXCL13, and they included scattered CD10+ cells. The RHOA mutation (p.Gly17Val) was also identified by direct sequencing (Fig. 2D). Based on these findings, our preferred diagnosis of the case was FTCL that mimicked LRCHL.

**DISCUSSION**

We described a Japanese patient with FTCL that showed LRCHL-like features. The overall pathologic findings were consistent with those previously documented, but only a total of 9 cases has been reported in the literature, including the present case (Table 1). Moroch et al. highlighted the potential diagnostic pitfall of misdiagnosing FTCL that mimicked LRCHL, and showed that the differential diagnosis required careful assessment of the T cells. They also described that their all five cases showed EBV harbored in HRS-like cells. On the other hand, two cases reported by Nicolae et al. were an EBV-negative variant of FTCL that mimicked LRCHL. Alikhan et al. also showed that detecting a high frequency of CD3-/dim CD4+ aberrant T cells was useful in distinguishing FTCL from a morphologic mimic; i.e., LRCHL. The present case provided additional support of those assertions, particularly the assertion by Nicolae et al. that EBV-negative HRS-like B-cells could occur in the background of nodal T-cell lymphoma with T<sub>FH</sub> phenotype. They also showed that HRS-like cells interacted closely with rosettes of PD1+ T cells. That finding suggested that PD1+ T-cell rosettes might play a pathogenic role in this disease. These issues might be underestimated in Japan, because the CHL incidence in the Japanese population is approximately one-third of that in Western countries. The findings of this case study should alert Japanese physicians to the potential pitfalls that can lead to misdiagnosing nodal T-cell lymphoma with T<sub>FH</sub> phenotype as CHL.

In addition, the present case was featured by the absence of PD-L1 expression and the presence of EBV harbored in HRS-like cells; incidentally, this was the same description as that for LRCHL in our previous report. In that study, we indicated that an anti-PD-L1 (clone SP142) immunostain might be helpful for diagnosing HL subtypes, particularly in distinguishing between the nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)/LRCHL and other prototypic CHL cases. NLPHL/LRCHL lacks neoplastic PD-L1 expression on HRS cells; in contrast, other prototypic CHL
Fig. 1. Follicular T-cell lymphoma morphology resembles lymphocyte-rich classic Hodgkin lymphoma, showing (A) capsular fibrosis and (B) a vaguely nodular architecture. (C) Mononucleated Hodgkin-like or popcorn-like large cells (detail in inset) are visible amidst small-to-medium-sized T lymphocytes within the nodule. Large cells strongly express (D) CD30, and are positive for (E) PAX5 at variable intensities, (F) but they do not express PD-L1 (clone SP142). T-lymphocyte clusters are strongly positive for (G) CD4 and (H) PD1, with (I) scattered EBV+ background cells.
shows its positivity on HRS cells. The present case study showed that a differential diagnosis between FTCL and LRCHL cases is still problematic even with immunohistochemical evaluation. This problem has been overlooked in our routine practice, due to the paucity of such cases. In addition, in our case, FTCL was accompanied by scattered, small, EBV+ bystander lymphocytes in the background. Although previous similar studies could not resolve the historical controversy over whether EBV status impacted survival in patients with AITL,6 we recently documented the prognostic impact of EBV status among patients with AITL in different age groups (≤60 and >60 years old).13 We showed that, among younger patients, an EBV-positive status could be associated with an indolent clinical course and a better prognosis, compared to an EBV-negative status. In contrast, EBV-positivity showed no significant impact on survival in

![Diagram](image-url)
older patients. Those findings suggested that younger patients with EBV-positive status formed a distinct group of patients with AITL. In the present study, our patient might have belonged to this unique subgroup of indolent clinical course, beyond the morphologic boundaries of either of AITL or FTCL in the category of nodal T-cell lymphoma with T\(\text{\textsc{in}}\) type. The recognition of such indolent subgroup may further influence the therapeutic approach to him for avoiding overtreatment.

It is too soon to draw any definite conclusions, based on our findings, due to the paucity of available data. Future studies should aim to clarify whether FTCL with LRCHL-mimic morphology might have any clinical distinctively.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

A. Sakakibara and Y. S. reviewed the slides and wrote the paper. H. K., K. Y., Y. I., K. F., and K. S. provided the clinical information. K. K. and S. N. made the original diagnosis and reviewed the slides. M. SY. identified RHOA mutation by direct sequencing. S. N., A. Satou, and S. K. supervised the project.

REFERENCES

1 Chihara D, Ito H, Matsuda T, et al. Differences in incidence and trends of haematological malignancies in Japan and the United States. Br J Haematol. 2014; 164 : 536-545.
2 Banks PM. The distinction of Hodgkin’s disease from T cell lymphoma. Semin Diagn Pathol. 1992; 9 : 279-283.
3 Quintanilla-Martinez L, Fend F, Moguel LR, et al. Peripheral T-cell lymphoma with Reed-Sternberg-like cells of B-cell phenotype and genotype associated with Epstein-Barr virus infection. Am J Surg Pathol. 1999; 23 : 1233-1240.
4 Nicolae A, Pittaluga S, Venkataraman G, et al. Peripheral T-cell lymphomas of follicular T-helper cell derivation with Hodgkin/Reed-Sternberg cells of B-cell lineage: both EBV-positive and EBV-negative variants exist. Am J Surg Pathol. 2013 ; 37 : 816-826.
5 de Leval L, Gisselbrecht C, Gaulard P. Advances in the understanding and management of angioimmunoblastic T-cell lymphoma. Br J Haematol. 2010 ; 148 : 673-689.
6 Eladl AE, Satou A, Elsayed AA, et al. Clinicopathological Study of 30 Cases of Peripheral T-cell Lymphoma with Hodgkin and Reed-Sternberg-like B-cells from Japan. Am J Surg Pathol. 2017; 41 : 506-516.
7 Sakakibara A, Kohno K, Eladl AE, et al. Immunohistochemical assessment of the diagnostic utility of PD-L1: a preliminary analysis of anti-PD-L1 antibody (SP142) for lymphoproliferative diseases with tumour and non-malignant Hodgkin-Reed-Sternberg (HRS)-like cells. Histopathology. 2018 ; 72 : 1156-1163.
8 Moroch J, Copie-Bergman C, de Leval L, et al. Follicular peripheral T-cell lymphoma expands the spectrum of classical Hodgkin lymphoma mimics. Am J Surg Pathol. 2012 ; 36 : 1636-1646.
9 Alikhan M, Song JY, Sohani AR, et al. Peripheral T-cell lymphomas of follicular helper T-cell type frequently display an aberrant CD3 (-/dim) CD4 (+) population by flow cytometry: an important clue to the diagnosis of a Hodgkin lymphoma mimic. Mod Pathol. 2016; 29 : 1173-1182.
10 Fujisawa M, Chiba S, Sakata-Yanagimoto M. Recent Progress in the Understanding of Angioimmunoblastic T-cell Lymphoma. J Clin Exp Hematop. 2017; 57 : 109-119.
11 Miyoshi H, Sakata-Yanagimoto M, Shimono J, et al. RHOA mutation in follicular T-cell lymphomas: Clinicopathological analysis of 16 cases. Pathol Int. 2020; 70 : 653-660.
12 Lymphoma Study Group of Japanese Pathologists. The World Health Organization classification of malignant lymphomas in Japan: Incidence of recently recognized entities. Pathol Int. 2000 ; 50 : 696-702.
13 Eladl AE, Shimada K, Suzuki Y, et al. EBV status has prognostic implication among young patients with angioimmunoblastic T-cell lymphoma. Cancer Med. 2020 ; 9 : 678-688.