Original Article

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Abstract: We report a case of secondary Epstein-Barr virus-associated angioimmunoblastic T-cell lymphoma (AITL) developed after the initial diagnosis of diffuse large B-cell lymphoma (DLBCL). A 59-year-old Chinese male patient was diagnosed as DLBCL based on typical histological and immunohistochemical characteristics in biopsy of the enlarged cervical lymph nodes. The patient received 8 cycles of chemotherapy with R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) and achieved complete remission. Nine months after initial diagnosis of DLBCL, the patient was hospitalized again because of pain in the neck and some enlarged cervical lymph nodes. The lymph node biopsy was performed, but this time the tumor was composed of small to medium-sized lymphoid cells with CD3, CD4, CD10, PD-1 and CXCL13 positive on immunohistochemical staining. The tumor cells were strong positive for EBER by in situ hybridization. The findings of lymph node biopsy were compatible with EBV-associated AITL. DICE chemotherapy (dexamethasone, ifosfamide, cisplatin and etoposide) was then administered, resulting in none response of the disease with pancytopenia and suppression of cellular immunity. To our knowledge, this is the first case of EBV-associated AITL originated from DLBCL. We suggest the patients with lymphoma should perform lymph node biopsy regularly in the course of the disease progression to detect of a secondary lymphoma.

Keywords: Angioimmunoblastic T-cell lymphoma, Epstein-Barr virus, diffuse large B-cell lymphoma, case report

Introduction

Diffuse large B-cell lymphoma (DLBCL) is one of the most common Non-Hodgkin's lymphoma (NHL) in clinical practice, which can be primary and also can be derived from other types of lymphoma. Second lymphoma different from the original lymphoma and the mechanism between the two distinct morphologic types of lymphoma have attracted interests of hematologists. In rare condition, secondary DLBCL may occur in patients with angioimmunoblastic T-cell lymphoma (AITL). However, to our knowledge, so far only one case of DLBCL developed secondary AITL have been described [1]. Herein we report a first case of secondary EBV-associated AITL occurring in a patient with diffuse large B cell lymphoma.

Case presentation

A 59 year-old man without medical history experienced a 6-month history of multiple lymph nodes enlargement in the neck, mandible and inguinal areas, and initially diagnosis and treatment at our hospital in April 2012. Generalized swelling of lymph nodes was found by (18) F-FDG PET-CT. The patient then underwent biopsy of the enlarged cervical lymph nodes. Diagnosis of DLBCL (non-germinal center B cell (non-GCB)) was made by morphological, immunohistochemical and molecular evaluation of lymph node. The nodal architecture was partly effaced by a diffuse proliferation of large sized atypical lymphoid cells (Figure 1). Immunohistochemical staining patterns demonstrated the atypical lymphoid cells expressed
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CD20, Ki-67 and MUM-1, but negative for CD3, CD4, CD10, EBER and bcl-6 (Figure 1). Polymerase chain reaction (PCR) analysis of IgH gene and TCR gene identified no clonal rearrangements (Figure 2). After the diagnosis of DLBCL, the patient received eight cycle of R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). The patient underwent PET/CT after 6 cycles of R-CHOP treatment and achieved complete remission, and followed by two cycles of R-CHOP for consolidation therapy. There was no further complaint from the patient during the follow-up period. In January, 2013, nine months after initial diagnosis, the patient was readmitted to our hospital due to pain in the neck and some enlarged cervical lymph nodes. The patient then underwent biopsy of right cervical lymph node. Under the microscopy, the normal architecture of lymph node was destroyed by polymorphic cellular infiltration composed of diffused small to medium-sized lymphoid cells along with plasma cells and eosinophils (Figure 3). Immunohistochemically, the infiltrated small to medium-sized lymphoid cells were strongly positive for CD3 and CD4, and positive for CD10, CXCL13 and PD-1, but negative for CD20, PAX-5, CD56, MUM-1 and CD30 (Figure 3). The proliferation of follicular dendritic cells highlighted by CD21 and CD23 was prominent throughout node, and entrapped the high-endothelial venules. EBV detection by in situ hybridization for EBER showed diffuse positive reaction (Figure 3). Clonality analysis of lymph node disclosed clonal rearrangement of TCRβ-VJ1, TCRβ-DJ and TCRγ-VJ1 (Figure 2). Based on clinical presentation and histological findings, a histological diagnosis of angioimmunoblastic T-cell lymphoma (AITL) was made according to the criteria of WHO classification.
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After diagnosis, the patient received a cycle of DICE (dexamethasone, ifosfamide, cisplatin and etoposide). Approximately two days after the completion of chemotherapy, the patient returned with enlarging lymph nodes, and fever. Pancytopenia and suppression of cellular immunity were observed. The patient refused further treatment. Eventually, the patient succumbed to his disease three months after the diagnosis of AITL in April 2013.

Discussion

Angioimmunoblastic T-cell lymphoma (AITL) is one of the most common subtypes of peripheral T-cell lymphomas, accounting for approximately 15-20% of all cases, or 1-2% of all non-Hodgkin lymphomas [3]. So far, there is only one report of second AITL arising in patients after the initial diagnosis of DLBCL, although a few patients with the initial diagnosis of AITL have been found to develop DLBCL. Clinico-pathological features of patients with DLBCL-developed secondary AITL described in present and previous reports are summarized in Table 1. In our case, not only histological examination of lymph node demonstrated a morphological characteristic of AITL, but also the presence of T cell lineage with aberrant CD4 and CD10 expression identified in neoplastic cells by immunohistochemical staining which also strongly supported a diagnosis of AITL at initial lymph node biopsy.

It is well known that most cases of AITL are frequently complicated with EBV infection. We found indeed that EBV was detected in AITL. In ten cases of second DLBCL after initial diagnosis of AITL with available EBER results, EBV-positive DLBCL was found in all cases [4-8]. The present case is the first report on sequential development of EBV-associated AITL from DLBCL. Although the prognosis is not well known since few cases have been reported, the outcome of the two patients with DLBCL-developed secondary AITL is generally poor. Patients died within 3 months. EBV infections may play a vital role in contributing to the development of a secondary lymphoma. The presence of EBV has been demonstrated and has been suggested to be a possible etiological agent involved in the development of the B-cell lymphoma after an already-existing T-cell lymphoma. EBV-infected lymphocytes have been

![Figure 2. Polymerase chain reaction (PCR) analysis of IgH gene and TCR gene. A. In April 2012, the patient diagnosed with diffuse large B-cell lymphoma without clonal rearrangements of IgH gene and TCR gene. B. Due to the pain and enlarged lymph nodes, the patient was readmitted to hospital and underwent biopsy of right cervical lymph node after achieved complete remission. Then, the patient diagnosed with angioimmunoblastic T-cell lymphoma and different from the initial diagnosis, clonal rearrangement of TCRβ-VJ1 (9), TCRβ-DJ (lane 11) and TCRγ-VJ1 (lane 12) were disclosed. Lane 10, TCRβ-VJ2; Lane 13, TCRγ-VJ2.](image-url)
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Figure 3. Pathology and immunohistochemistry (nine months after initial diagnosis). Follow-up biopsy showing the nodal architecture was composed of diffused small to medium-sized lymphoid cells along with plasma cells and eosinophils (A) and immunohistochemical findings with positivity for CD3 (B), CD4 (C), CXCL13 (E) and PD-1 (F), but negative for CD20 (D). Most of atypical large cells were positive for EBER by in situ hybridization (G). (A, H&E staining, with original magnification ×40; B-G, immunohistochemical staining, with original magnification ×100).

Table 1. Clinicopathological features of patients with DLBCL-developed secondary AITL described in present and previous reports

<table>
<thead>
<tr>
<th>Authors</th>
<th>Age/sex</th>
<th>Tumor site</th>
<th>Interval</th>
<th>EBER</th>
<th>PCR</th>
<th>Treatment</th>
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<td>Yaya</td>
<td>73/M</td>
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Notes: EBER, EBV-encoded RNA; LN, lymph node; +, positive; -, negative; IgH, immunoglobulin heavy chain gene rearrangement; TCR, T-cell receptor gamma-chain rearrangement; R, rituximab; M, months; GEM, Gemcitabine; L-ASP, L-asparaginase; DICE, combination chemotherapy of dexamethasone, ifosfamide, cisplatin and etoposide.

documented in up to 97% of cases of AILT, and authors argue that neoplastic T cells in AILT may be EBV-infected, with the virus possibly having a direct role in lymphomagenesis [9].
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Other studies considered that the presence of EBV seems to be associated with the selective defects of the immune system, rather than with the direct pathogenesis of angioimmunoblastic lymphadenopathy [10]. EBV infection may indicate the deterioration of angioimmunoblastic T-cell lymphoma [11]. Whether or not specific mechanism involved in the sequential development of EBV-associated AITL in DLBCL derived from non-EBV-infected cells should be investigated further.

In conclusion, secondary AITL in DLBCL is rare. Here we report the first case of EBV-associated AITL from DLBCL. Therefore, clinicians should keep in mind that there is a possibility of sequential development of AITL from DLBCL. It is necessary to perform lymph node biopsy regularly in the course of the disease progression to detect of a secondary lymphoma.

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Informed consent was obtained from all individual participants included in the study.

Disclosure of conflict of interest

None.

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References


