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HTLV-I-associated Non-Neoplastic Lymphadenopathy - Atypical Follicular Lesions of Lymph Nodes Found in Anti-Human T-cell Leukemia Virus Type 1 (HTLV-1) Antibodies-positive Subjects without Neoplastic Disorders-

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Introduction

Human T-cell leukemia virus type 1 (HTLV-1) has been reported to tx3 linked to the etiology of adult T-cell leukemiaJqymPhoma (ATLL) [1] and HTLV-1-associated myelopathy [2] etc., although exact pathogenesis of these diseases has not yet been elucidated [3].

As a method to examine whether a patient is infected by HTLV-1 , antibodies to adult T-cell leukemia-associated antigens (ATLA)[4] have been used. But recent studies have been reporting that ATLA is not an enough marker of HTLV-I infection, because a period of immunotolerance to HTLV-1 is shown in some infants after the disappearance of the ATLA transferred from the mother [5]. The ATLA in babies can not always be detected serologically. And from a viewpoint of multi-step carcinogenesis in ATLL and HTLV-1 carriers, an appearance of ATLA was evaluated as one event before ATLL development rather than a sign of HTLV-1 infection [6]. Namely, an appearance of ATLA may indicate a disorder of the immunosystem avoiding to detect HTLV-1-related antigens (a destruction of the immunotolerance) and/or to synthesize ATLA (including a trouble in the immunological memory system to HTLV-1-related antigens), or a dysfunction of the cellular mechanism to suppress activities of HTLV-1 proviral DNA. Then, a new method, polymerase chain reaction VCR) for HTLV-1 [8, 9], is expected to detect HTLV-1 proviral DNA sequence itself even in a HTLV-I carrier who has no ATLA.

It has not yet been enough studied whether an immunodysfunction exists in a natural history of HTLV-1 infection [7]. There is no histopathological concept of non-neoplastic lymphadenopathy in HTLV- 1 in6ection. We experienced unexplained lymph node non-neoplastic lesions examined in the doubt of ATLL in 6 adults and one child in the HTLV-1 endemic area.

Here, we report histopathological findings of these lymph nodes with an investigation of HTLV-1 infection in the formalin-fixed paraffin-embedded tissue by the PCR method [10].

Materials and methods

Main clinicopathological findings of 7 cases examined in this study were listed in Table 1. Serum ATLA was examined by the particle agglutination method. Cases 1 to 4 were positive for ATLA, case 5 was pseudopositive, and case 6 was negative. Case 7 was not examined about serum ATLA, because his swollen mesenteric lymph node was examined in his appendectomy. Case 2 suffered from rheumatoid arthritis and amyloidosis at the same lime. No neoplastic diseases were recognized in these cases. Their clinical course has been followed. No history of blood transfusion was recorded in any of these cases.

Lymph nodes of these cases were examined histologica11y in the stained sections of hematoxylin-eosin, giemsa, periodic acid-schiff reaction and silver, and in paraffin-immunohistochemistry by using several polyclonal and monoclonal antibodies [11].

Polymerase chain reaction (PCR) for HTLV-1 pX Tax region

DNA material for PCR was extracted from paraffin-embedded tissue [10] of the cases 1 , 2, 5 to 7 and from paraffin sections on slide glasses of the cases 3 and 4.

As a pair of primers of PCR for HTLV-1 provirus, SK43 and SK44 primers for pX Taxregion [8] were employed. Fifty-two cycles of PCR were performed, using GeneAmpTM DNA Amplification Reagent Kit (Takara Biomedicals). The denaturing step was carried out at 94℃ for 2 min, the annealing of the primers with DNA was done at 54℃ for 2 min, and the extension of DNA was done at 68℃ for 2 min. An existence of amplified DNA was evaluated in 3% agar-gel electrophoresis.

Table 1. Cases examined in this study.

Age Sex	Symptomes	ATLA in serum	Lymph node examined
Case 1 36 M	Bilateral facical paralysis. Feeling of numbness in extremities.	+	Right inguinal
Case 2 60 F	Bilateral arthropathy. Loss of appetite. Epigastralgia. Diarrhea. Hypoproteinemia. Rheumatoid arthritis and amyloidosis.	+	Right axillar
Case 3 77 M	Fever of unknown origin. Leukocytosis Right inguinal lymph node swelling.	+	Right inguinal
Case 4 67 F	Abdominal pain. Body weight loss. Increase of serum immunoglobulin γ. Bilateral inguinal lymph node swelling.	+	Inguinal
Case 5 14 M	Submandibular lymph node swelling under antibiotics administration.	+/-	Submandibular
Case 6 40 M	General fatigue. Splenic pseudocyst.	-	Left cervical
Case 7 10 M	Acute appendicitis.	n.e.	Mesenteric

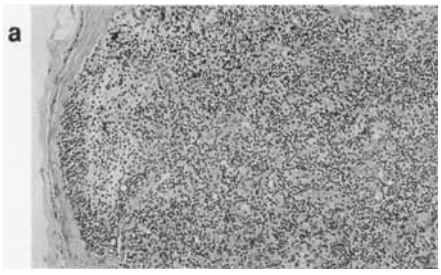
ATLA: Antibodies to adult T-cell leukemia-associated antigens

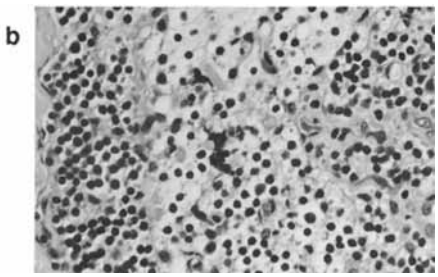
n.e.: Not examined

Results

1, *Histopathological and paraffin-immunohistochemical findings of the lymph nodes*

In case 1, the lymph node showed that the medulla was preserved well and free from any pathological findings. The cortex was not enlarged but showed a loose Cellular area (follicle atrophy in follicle-lysis [12]) near the marginal sinus (Fig.1a and b) and an increase of high endothelial vessels.





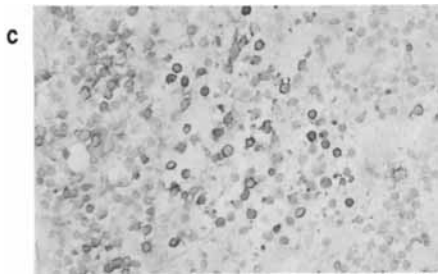
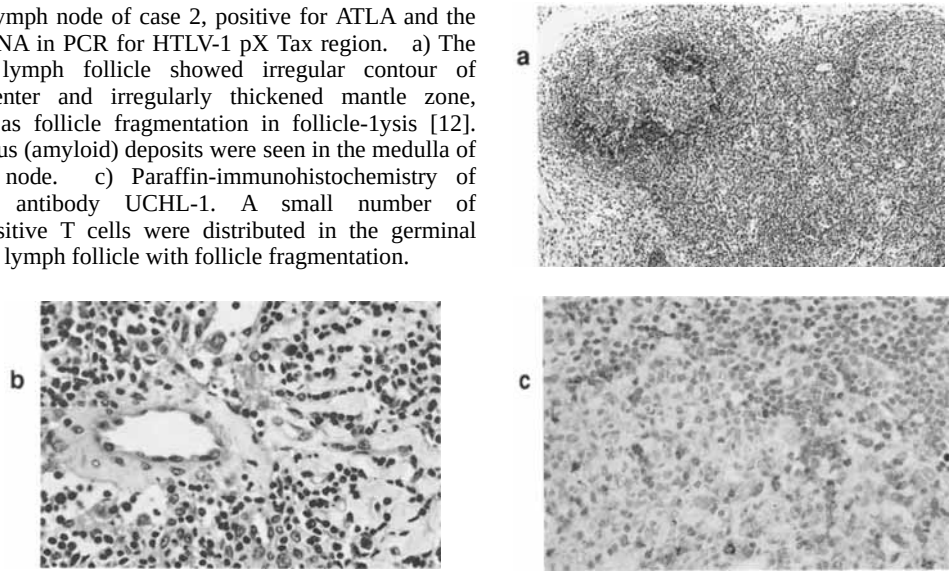


Figure 1. Lymph node of case 1, positive for ATLA and two bands of he amplified DNA in PCR for HTLV-1 pX Tax region. a) prhere is a loose cellular area (follicle atrophy in follicle-1ysis according to Hanaoka [12]) in the submarginal region of the cortex. In the paracortex increase of blood vessels is noted. b) The follicle atrophy. c) Paraffin-immunohistochemistry of monoclonal antibody MT-1 for T cells. There were many MT-1-positive T cells in the follicle atrophy.

Immunohistochemically, the loose cellular area comprised many MT-1-positive T cells (Fig. 1c) and some LN-2-positive B or T cells. No S100 protein-positive dendritic reticulum cells were noted in the cortex area.

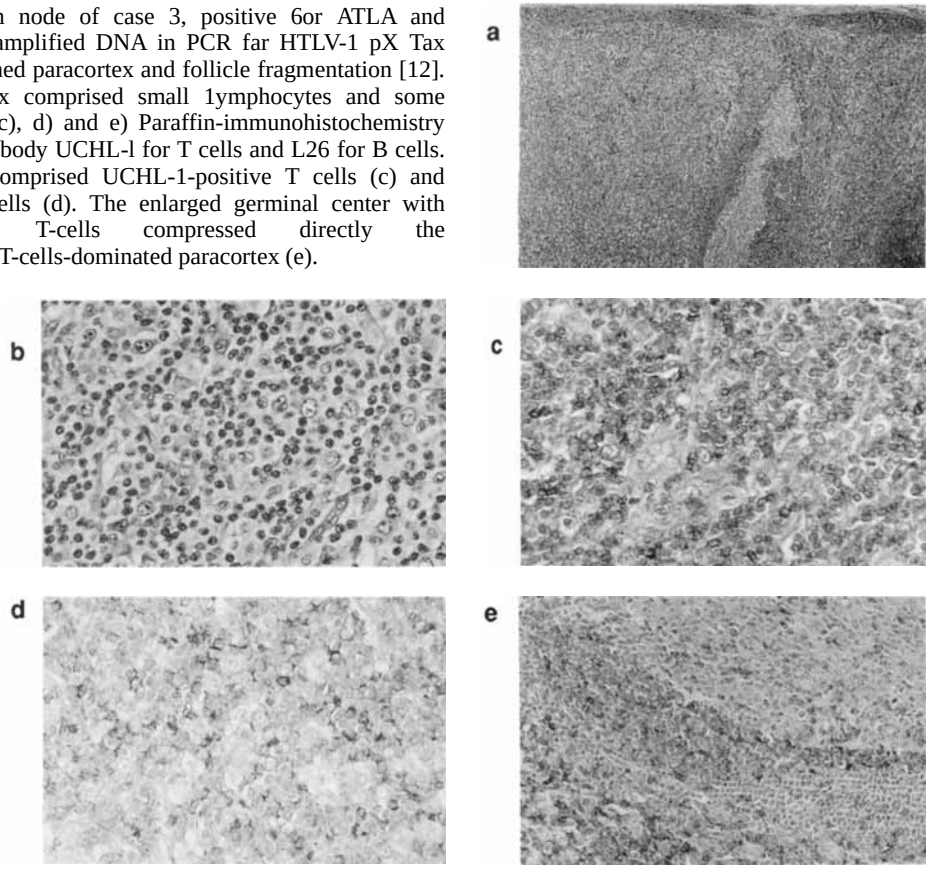
In case 2, several lymph follicles with germinal centers were seen in the cortex (Fig. 2a). Some of germinal centers showed obscure demarcation to mantle zone (Fig. 2a) and a small number of UCHL-1-positive T cells (Fig. 2c), designated as follicle fragmentadon [12]. In the medulla, amyloid deposits were observed (Fig. 2b).

Figure 2. Lymph node of case 2, positive for ATLA and the amplified DNA in PCR for HTLV-1 pX Tax region. a) The left upper lymph follicle showed irregular contour of germinal center and irregularly thickened mantle zone, categorized as follicle fragmentation in follicle-1ysis [12]. b) Amorphous (amyloid) deposits were seen in the medulla of the lymph node. c) Paraffin-immunohistochemistry of monoclonal antibody UCHL-1. A small number of UCHL-1-positive T cells were distributed in the germinal center of the lymph follicle with follicle fragmentation.



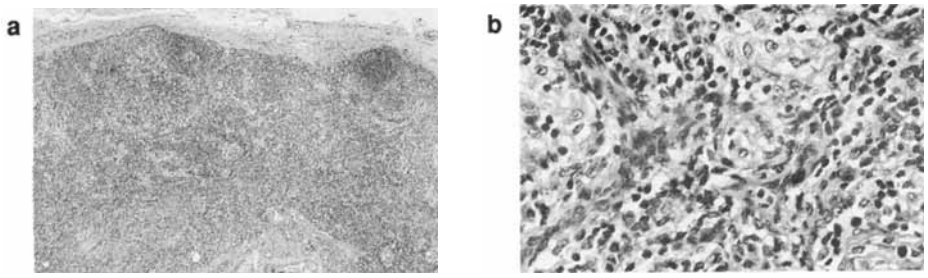
In case 3, atypical enlarged lymph follicles were observed with follicle fragmentation [12] and widened paracortex (Fig. 3a). The paracortex comprised small 1ymphocytes and some immunoblasts (Fig. 3b). Paraffin-immunohistochemically these lymphocytes were MT- 1- and UCHL-1-positive T cells and L26-posidve B cells (Fig. 3c and d). Several S100 protein-positive dendritic cells were found among the lymphocytes. One lymph follicle with an irregularly enlarged germinal center compressed directly the surrounding paracortex Fig. 3e). UCHL-1-positive cells were distributed in the germinal center and in the compressed paracortex Fig. 3e).

Figure 3. Lymph node of case 3, positive 6or ATLA and negative for the amplified DNA in PCR far HTLV-1 pX Tax region. a) Widened paracortex and follicle fragmentation [12]. b) The paracortex comprised small 1ymphocytes and some irrmunoblasts. c), d) and e) Paraffin-immunohistochemistry of monc1onal antibody UCHL-l for T cells and L26 for B cells. The paracortex comprised UCHL-1-positive T cells (c) and L26-positive B cells (d). The enlarged germinal center with UCHL-1-positive T-cells compressed directly the UCHL-1-positive T-cells-dominated paracortex (e).



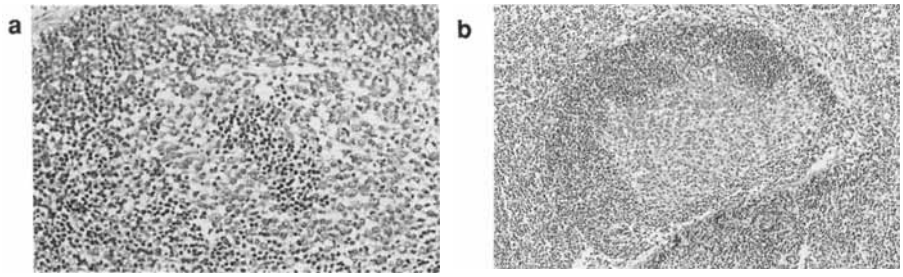
In case 4, only tiny primary follicles were seen in the inguinal lymph node (Fig. 4a). Increased spindle cells in the medulla (Fig. 4b) did not resemble bipolar spindle cells in the lesions of human immunodeficiency virus type 1 (HIV-1) infection [12].

Figure 4. Lymph node of case 4, positive for ATLA and negative for he amplified DNA in PCR for HTLV-1 pX Tax region. a) In die cortex a few any lymph follicles without germinal centers were noted. b) In die medulla there were some hyperplastic spindle-shaped stromal cells.



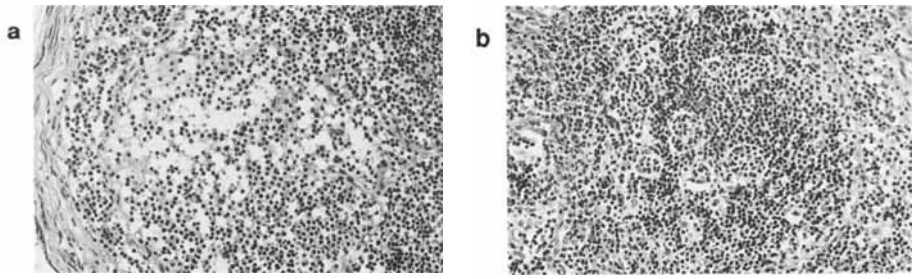
In case 5, pseudoposidve for ATLA, the lymph node showed atypical follicular hyperplasia. Some lymph follicles were “transforming”. (Fig. 5a). Some germinal centers showed irregular contour to mantle-zone Fig. 5b).

Figure 5. Lymph node of case 5, pseudoposidve for ATLA and negative for he amplified DNA in PCR for HTLV-1 pX Tax region. a) Trans6orming germinal center, showing a loose aggregation of small 1ymphocytes. b) Follicle fragmentation [12], showing irregular contour of germinal center and irregularly thickened mantle zone.



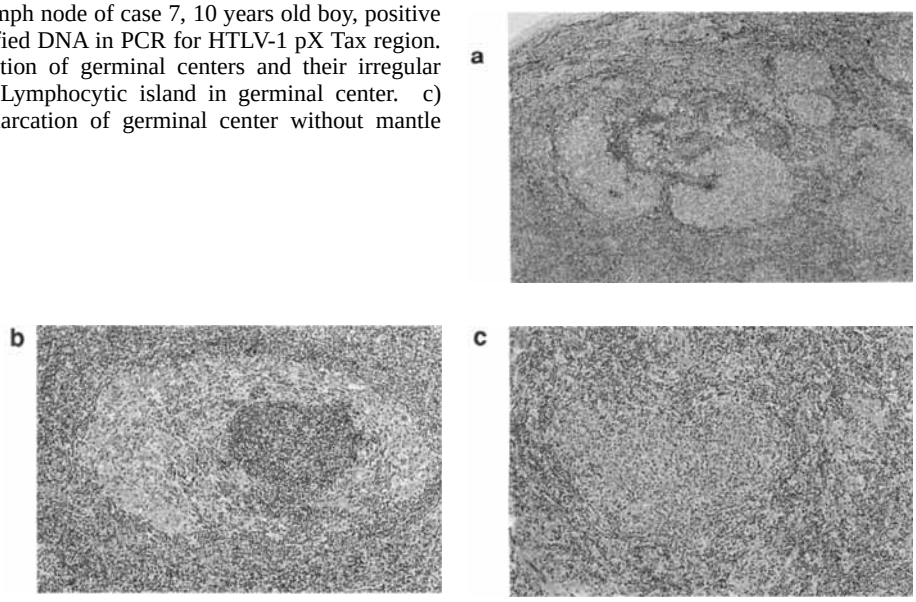
In case 6, negative for ATLA, a loose cellular area was seen (follicle atrophy [12]) near the marginal sinus Pig. 6a). But in a follicle several germinal centers comprising dominantly centrocytes were recognized (Fig. 6b).

Figure 6. Lymph node of case 6, negative for ATLA and for die amplified DNA in PCR for HTLV-1 pX Tax region. a) Follicle atrophy [12]. b) Several germinal centers comprising dominandy centrocytes were found in one follicle.



In case 7, a child case, irregular-sized and fragmented or indented hyperplastic germinal centers were seen with and without small 1ymphocytic island (Fig. 7a, b and c).

Figure 7. Lymph node of case 7, 10 years old boy, positive for the amplified DNA in PCR for HTLV-1 pX Tax region. a) Fragmentation of germinal centers and their irregular contour. b) Lymphocytic island in germinal center. c) Obscure demarcation of germinal center without mantle zone.



2, *Detection of HTLV-1 pX Tax region by PCR in the eztractcd DNA from the hormalin-fixed lymph node tissue*

Electrophoresis of PCR products of the cases I, 2, 5 to 7 was presented in Fig. 8. In the cases 1, 2 and 7, faint bands of the amplified DNA were recognized at the length a little less than that of the control case of ATLL (159bp). In the case 1 there were 2 bands of the amplified DNA, indicating deletion of pX Tax region of HTLV-1 proviral DNA sequence [13]. In the PCR using the extracted DNA from sections on slide glasses of the cases 3 and 4, no bands of the amplified DNA were found.

Figure 8. Electrophoresis of the products from PCR for HTLV-1 pX Tax region (SK43 and SK44). The left column is molecular weight markers of ϕ x174-Hae III, digest. The right column is a control case of ATLL, revealing one band of the amplified DNA, of which length should be evaluated as 159 bp. In cases 1, 2 and 7, there were faint bands of he amplified DNA at the length a little less than 159 bp and in the case 1 there were the other faint band at the less length.

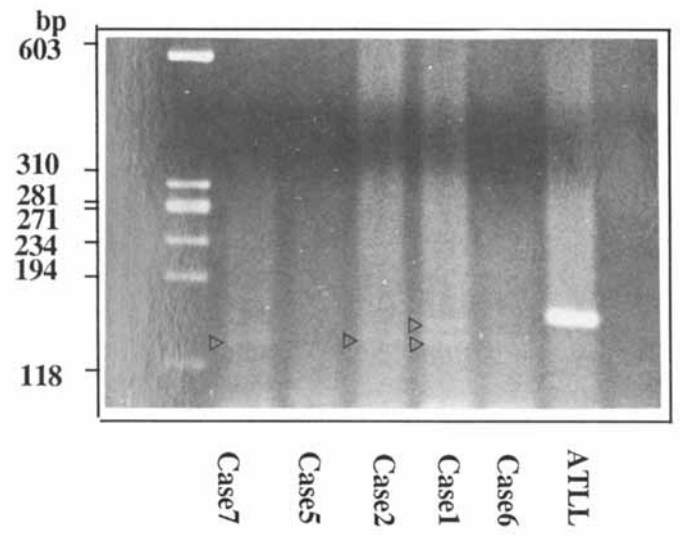


Table 2 shows relationship among ATLA in the serum, follicular lesions of the lymph nodes and the results of PCR for mV-1 pX Tax region. In the follicular lesions of the cases, various configurations of the follicle-lysis were seen according to Hanaoka [12]. In the cases with serum ATLA or the amplified DNA of the PCR, there were no obvious differences in the follicular lesions between the cases with and without die amplified DNA of the PCR. The follicular lesion in case 6 would have no relation to HTLV-1 infection because of no ATLA and no band of the amplified DNA in the PCR.

Table 2. A relationship among a presence of amplified DNA sequence in PCR, serum ATLA and follicular lesions of the lymph nodes

	ATLA	Follicular lesion in lymph nodes	PCR for HTLV-1 pX Tax
Case 1	+	Follicle atrophy in follicle-lysis	Amplified, 2 bands
Case 2	+	Follicle fragmentation in follicle-lysis	Amplified
Case 7	n.e.	Follicle fragmentation in follicle-lysis Small lymphocytic islands in germinal center	Amplified
Case 3	+	Follicle fragmentation in follicle-lysis	Not amplified
Case 4	+	Some primary follicles. (Follicle depletion in follicle-lysis?)	Not amplified
Case 5	+/-	Atypical follicular hyperplasia. (Transforming geminal center etc.)	Not amplified
Case 6	-	Follicle atrophy in follicle-lysis	Not amplified

n.e.: Not examined.

The follicular lesions were categorized according to the criteria of the follicle-lysis in acquired immunodeficiency syndrome (AIDS)-related lymphadenopathy by Hanaoka [12].

Follicle fragmentation: Irregular contour of germinal centers, irregularly thickened mantle zone, infiltration of lymphocytes into germinal centers and increase of blood vessels in germinal centers.

Follicle atrophy: Disappearance of follicular structure with decrease of B cells.

Follicle deletion: Deletion of lymph follicles.

Discussion

ATLL is a representative and neoplastic lymphadenopathy with a relation to HTLV-1. It had been unknown whether dysplastic and non-neoplastic entities exist in the lymphadenopathy. Some “pre-ATLL” lymph node lesions were reported [14] but it is unknown whether the “pre-ATLL” lesions should be categorized as dysplastic or as an early phase of ATLL. This paper is the first report of the non-neoplastic lymphadenopathy with a relation to HTLV-1.

Integrated proviral DNA sequence of HTLV- 1'has several physiological and probably oncogenic activities [15, 16]. Expression of interleukin 2 receptor on ATLL cells is representative one of the activities [15,17,18]. A quantitative immunohistchemical analysis of S100 protein-positive reticulum cells in T-cell malignant lymphomas (T-ML), including ATLL, showed a possible effect of ATLL cells or the integrated HTLV-1 proviral DNA sequence to induce them among ATLL cells [19]. Under the effects of these activities of HTLV-1 proviral DNA sequence, a peculiar histology of the lymphadenopathy with a relation to frrLV-1 is expected as well as a characteristic histology of low grade malignant T-zone T-ML, including angioimmunoblastic lymphadenopathy with dysproteinemia (AILD)-type T-ML [20]. Authors looked a low number of intermingling B cells and S 100 protein-positive dendritic cells in AILD-type T-ML in patients with ATLA as histopathological modification of T-ML induced by HTLV-1 infection [21]. Especially the decreased S 100 protein-positive dendritic cells in AILD type T-ML with ATLA might be understood as a decrease of follicular dendritic cells (FDC) in HTLV-1 infection, because FDCs were induced in AILD-type T-ML [22] and anti-S100 protein antibody can label some of FDCs. A mixed proliferation of non-neoplastic B-cells, FDCs and neoplastic T cells in AILD-type T-ML [11] may be suppressed under effects of HTLV-1 infection. Therefore, at least, histopathological reflection of HTLV-1 infection would be differemt each other in ATLL, low-grade T-ML with HTLV- 1 infection and probably non-neoplastic lymphadenopathy with HTLV-1 infection.

This study showed various configurations of lymph follicles in lymph nodes of the cases with ATLA and these follicular lesions had a similarity to the AIDS lymphadenopathy. The AIDS lymphoadenopathy is

categorized as hyperplastic, including progressive transforming germinal centers, and atrophic, including follicle lysis. The process of the follicle-lysis is categorized in 3 stages [12]. Follicle fragmentation is the first, showing irregular contour of the germinal center, irregularly thickened mantle zone, infiltration of lymphocytes into the germinal center and increase of blood vessels in the germinal center. Follicle atrophy is the second, showing disappearance of follicular structure with decrease of B cells. Follicle depletion is the third. As shown in Table 2, the follicle fragmentation was found in the cases 2, 3 and 7, the follicle atrophy was found in the case 1 and the follicle depletion corresponded probably to the lymph node cortex of the case 4. It is unknown whether the transforming geminal centers in case 5 correspond to the hyperplastic ones of the AIDS lymphadenopathy. Because a possible damage of FDCs was reported in human immunodeficiency virus type 1 (HIV-1)-related follicle-lysis [23,24] and was discussed as an essential immunological dysfunction in AIDS, the fact that there was follicle-lysis in the cases with ATLA suggests an immunodysfunctional state in HTLV-I carriers, although HIV-1-free follicle-lysis was found [25] beside that in AILD [12].

In a natural history of HTLV- 1 infection in a perinatal period, follicle-lysis may correspond to destruction of immunotolerance to HTLV-1, because ATLA would appear first in HTLV-1 carriers after destruction of immunotolerance to HTLV-1. A fluctuating serum level of immunoglobulin μ type ATLA [26] suggests a disorder in the immunological system of antigen-recognition, antibody-production and memory cells, induced by HTLV- 1 infection. An existence of HTLV-1 proviral DNA sequence recognized by PCR in the cases 1, 2 and 7 suggested that HTLV-1 might have a relation to the outcome of these follicle-lysis, while no existence in the cases 3, 4 and 5 suggests that these follicle-1ysis would occur in lymph nodes under an immunodysfunctional state in HTLV- 1 carriers, as well as those in AILD and others [12,25]. The follicle-lysis in the case 6 is an example of such follicle-lysis, because the case 6 was negative for ATLA and for amplified DNA in PCR and multiple formation of germinal centers occurred in one lymph follicle (Fig. 6b). A pathogenesis of these follicle-lysis in HTL-1 infection must be studied further by using in situ detection methods for HTLV- 1 proviral DNA sequence and its activation.

This study examined a presence of HTLV-1 proviral DNA sequence by PCR employing the primers for HTLV-1 pX Tax region, because products of HTLV-1 pX Tax region have several physiological activities and HTLV-1 pX Tax region itself was reported to be most frequently recognized by PCR method in the tissue with ATLL cells' infiltration [27] and in HTLV-1 carriers [9]. On the other hand, the PCR protocol in this study was designed, comparing the Shibata's PCR protocol [27]. And under the strict experiment condition of the annealing at 54°C for 2 min in this study showed two bands of the amplified DNA in the case 1, indicating deletion in HTLV-1 pX Tax region [13], because an expected length of the amplified DNA sequence of pX Tax region of HTLV-1 by PCR using SK 43 and SK 44 was 159 bp [8]. The bands of the amplified DNA in the cases 2 and 7 positioned at the length a little less than that of ATLL (corresponding to 159 bp) in Fig. 8, suggesting also a possibility of deletion of HTLV-1 pX Tax region. Although it was suggested that different variants of HTLV-1 would induce ATLL and HTLV-1-associated myelopathy, it is unknown whether the deletion of HTLV-1 pX Tax region had a relation to the lymph follicle-lysis in HTLV-1 carriers.

Since there is a report of co-infection of HTLV-1 and II in Fukuoka prefecture in Japan [28], HTLV-II may induce immunodeficiency state, and further, the PCR employing SK43 and SK44 primers can not differentiate the Tax region of HTLV-1 proviral DNA sequence from that of HTLV-II, these lymph node lesions must be studied further with an attention to the co-infection of HTLV-I and II.

Summary

Histological findings of unexplained lymph node lesions found in 6 cases of human T-cell leukemia virus type 1 (HTLV-1) carriers and one HTLV-1 non-carrier were reported with an investigation of HTLV-1 pX Tax region by means of polymerase chain reaction (PCR) employing a pair of primers SK43 and SK 44 in the DNA extracted from formalin-fixed and paraffin-embedded tissue. Follicular lesions of these lymph nodes were various but had a similarity to the acquired immunodeficiency syndrome (AIDS)-lymphadenopathy, categorized as follicle-lysis. The amplified DNA was recognized as a faint band at the length a little less than the expected length of DNA sequence in 3 cases of the HTLV- 1 carriers, suggesting a possibility of a deletion of HTLV-1 pX Tax region. Further, in one of them the other faint band of the amplified DNA was found, indicating also deletion in HTLV-1 pX Tax region. It

suggested direct and indirect effects of HTLV-1 on these lymph nodes with follicle-lysis that amplified DNA was found in 3 out of the 6 lymph nodes. It was unknown whether the deletion of HTLV-1 pX Tax region had a relation to the outcome of the follicle-lysis in HTLV-1 carriers. In a natural history of HTLV- 1 infection the follicle-lysis might correspond to the destruction of an immunotolerance to HTLV-1, reported in a prospective study of HTLV-1 infection in newborns and infants, or to the lymph node lesions in the HTLV-I carriers having fluctuating serum level of immunoglobulin μ type antibodies to HTLV-I-related antigens. Since follicle-lysis was observed in human immunodeficiency virus type 1 infection and angioimmunoblastic lymphadenopathy with dysproteinemia, an existence of the follicle-lysis in the HTLV-1 carriers' lymph nodes may indicate their immunodysfunction.

Acknowlegment

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