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Dermatopathic reaction of lymph nodes in HTLV-1 carriers: a spectrum of reactive and neoplastic lesions

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Dermatopathic reaction of lymph nodes in HTLV-1 carriers: a spectrum of reactive and neoplastic lesions

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Dermatopathic reaction of lymph nodes in HTLV-1 carriers: a spectrum of reactive and neoplastic lesions

Aims: Dermatopathic reaction is a histopathological finding of lymph nodes that usually occurs in patients with inflammatory pruritic cutaneous lesions. However, it is sometimes seen in patients with cutaneous T cell lymphoma. Adult T cell leukaemia/lymphoma (ATLL) is a T cell malignancy caused by infection with human T cell leukaemia virus type I (HTLV-1), which is frequently accompanied by cutaneous lesions. However, the detailed clinicopathological characteristics of the dermatopathic reaction of lymph nodes in ATLL patients and HTLV-1 carriers, addressed in this study, remains to be clarified.

Methods and results: We retrospectively analysed 18 nodal lesions with dermatopathic reaction in HTLV-1 carriers. Axillary and inguinal lymph nodes were the primary affected tissues. Three cases with atypical

lymphoid cell infiltration were defined as ATLL with dermatopathic reaction (ATLL-D), showing an abnormal T cell immunophenotype and T cell monoclonality. Two of the three ATLL-D patients died 14 and 7 months after diagnosis (the third case had a very short follow-up). The other 15 patients were indistinguishable from reactive lesions and were defined as HTLV-1-associated lymphadenitis with dermatopathic reaction (HAL-D). They showed an indolent clinical course, with only one case eventually transforming to aggressive disease.

Conclusions: Lymph node lesions accompanied by dermatopathic reaction in HTLV1 carriers represent a spectrum that includes reactive and neoplastic conditions. HAL-D should be distinguished from ATLL-D, especially to avoid overtreatment.

Keywords: adult T cell leukaemia/lymphoma, dermatopathic reaction, human T cell leukaemia virus type 1, immunophenotype, prognosis

Introduction

Dermatopathic reaction is a histopathological finding of the lymph node in which infiltrating Langerhans

cells, interdigitating dendritic cells and pigmented macrophages are observed in the expanded paracortex.¹ It usually occurs in patients with pruritic cutaneous lesions without malignancy. However, nodal lesions in cases with cutaneous T cell lymphoma (CTCL), such as mycosis fungoides, are sometimes accompanied by tumour cell infiltration, which affects prognosis. Distinguishing lymphoma cell involvement from dermatopathic reaction can be challenging, as

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dermatopathic reaction is characterised by polymorphous cellular context, including numerous transformed lymphocytes, activated macrophages and dendritic cells.¹⁻³

Adult T cell leukaemia/lymphoma (ATLL) is a T cell malignancy caused by infection with human T cell leukaemia virus type I (HTLV-1). ATLL exists as four clinical subtypes: smouldering, chronic, lymphoma and acute.^{4,5} The latter two are considered aggressive and generally show a rapid clinical course.⁶ In contrast, indolent ATLL (smouldering and chronic types) usually progresses slowly and does not require cytotoxic chemotherapy.^{7,8} Lymphadenopathy is one of the most frequent manifestations of ATLL. Morphologically, diffuse architectural effacement with proliferation of medium-sized or large pleomorphic cells is usually seen in the aggressive type. Conversely, HTLV-1-associated lymphadenitis (HAL; morphologically reactive lymphadenitis developing in HTLV-1 carriers) has a good prognosis without treatment.⁹ Although the morphological distinction between overt lymphoma and HAL is usually not difficult, some pathological features, such as dermatopathic reaction, make it hard to accurately evaluate lymph node lesions in HTLV-1 carriers.

Although skin is one of the most frequently affected organs in ATLL and may be involved in up to 50% of cases,¹⁰ the detailed clinicopathological findings of ATLL and HAL cases with dermatopathic reaction remain unclear. To address this issue, we carried out a comparative clinicopathological analysis of lymph nodes with dermatopathic reaction in 18 HTLV-1-infected cases with or without ATLL. The majority of these cases were considered to be reactive lesions showing an indolent clinical course, while three cases with definitive involvement by tumour cells showed a relatively poorer prognosis. These findings highlighted the disease spectrum from benign to malignant status in dermatopathic reaction of lymph nodes of HTLV-1 carriers.

Materials and methods

PATIENTS AND SAMPLES

Archival formalin-fixed/paraffin-embedded (FFPE) tissue samples from 15 patients were selected using the search terms 'dermatopathic' and 'lymph node' from the Ryukyuu University Hospital database containing tissue samples of 1134 HTLV-1 carriers diagnosed between 2010 and 2019. A further three cases were identified from the archives of the Okinawa Prefectural Nanbu Medical Center and Children's Medical

Center. All samples were reviewed and confirmed as showing dermatopathic reaction; namely, an expanded paracortex with increased numbers of Langerhans and interdigitating dendritic cells and scattered pigment. Biopsy of a cutaneous lesion was also performed in 15 of the 18 cases.

This study was approved by the institutional ethics committees of the Graduate School of Medicine and the School of Health Science at the University of the Ryukyus and Okinawa Prefectural Nanbu Medical Center and Children's Medical Center, Japan. The study protocol adhered to the principles of the Declaration of Helsinki.

HISTOLOGICAL AND IMMUNOHISTOCHEMICAL EVALUATION

FFPE samples were used for histological and molecular analyses. Tissue histology was examined by haematoxylin and eosin staining. The diagnosis of HAL-D was made based upon a previous report.⁹ The diagnosis of ATLL-D was defined as a lesion with a significant infiltration of atypical lymphocytes. Immunohistochemistry was performed with the Benchmark ULTRA system (Roche, Tokyo, Japan), according to the manufacturer's protocol, using antibodies against CD3 and CD8 (both from Agilent Technologies, Tokyo, Japan); CD4, CD5, CD25 and CD30 (all from Roche); and CD7 (Abcam, Tokyo, Japan). Case 14 was also analysed by *in-situ* hybridisation for Epstein-Barr virus (EBV)-encoded small RNA (EBER-ISH; Dako, Tokyo, Japan). Immunohistochemistry data provided by cooperating institutions was also included in the analysis.

FLOW CYTOMETRY

Fresh single-cell suspensions were isolated by flow cytometry on a FACSCanto II instrument (BD Biosciences, Tokyo, Japan) using fluorescein isothiocyanate-conjugated CD3 and CD4 antibodies and phycoerythrin-conjugated CD5, CD7, CD25 and CD8 antibodies, all of which were purchased from Beckman Coulter (Tokyo, Japan), apart from anti-CD25 (BD Biosciences, San Jose, CA, USA).

MOLECULAR ANALYSIS

Genomic DNA was extracted from FFPE samples. Clonal rearrangement of the T cell receptor gamma (TCR- γ) gene was analysed by polymerase chain reaction (PCR), according to the BIOMED2 protocol.¹¹ The amplification product was analysed by capillary

Table 1. Clinical characteristics.

Case no.	Diagnosis	Age/sex	Clinical subtype	Proportion of atypical cells in PB	Follow-up period (months)**	Treatment	Progression to aggressive type	Status at the last follow-up	Cause of death
1	HAL-D	69/F	Smouldering (cutaneous) type	Few cells*	7	Topical therapy	-	Alive without transformation	-
2	HAL-D	75/M	Smouldering type	6%	40	Topical therapy + oral VP-16	-	Alive without transformation	-
3	HAL-D	64/M	Smouldering (cutaneous) type	Few cells*	36	Topical therapy	-	Alive without transformation	-
4	HAL-D	90/F	Non-ATLL (HTLV-1 carrier)	Few cells*	21	Topical therapy	-	Alive without transformation	-
5	HAL-D	74/M	Non-ATLL (HTLV-1 carrier)	Few cells*	72	Topical therapy	-	Dead	Unknown
6	HAL-D	86/M	Non-ATLL (HTLV-1 carrier)	Few cells*	2	Topical therapy	-	Alive without transformation	-
7	HAL-D	85/M	Smouldering (cutaneous) type	0%	2	Topical therapy	-	Alive without transformation	-
8	HAL-D	80/F	Smouldering (cutaneous) type	Few cells*	27	Topical therapy	-	Alive without transformation	-
9	HAL-D	81/M	Non-ATLL (HTLV-1 carrier)	2%	4	Topical therapy	-	Alive without transformation	-
10	HAL-D	82/M	Smouldering (cutaneous) type	Few cells*	1	Topical therapy	-	Alive without transformation	-
11	HAL-D	76/F	Smouldering (cutaneous) type	Few cells*	2	Topical therapy	-	Dead	Pneumonia
12	HAL-D	76/M	Non-ATLL (HTLV-1 carrier)	Few cells*	31	Topical therapy	+	Dead	ATLL
13	HAL-D	74/M	Non-ATLL (HTLV-1 carrier)	0%	31	Topical therapy	-	Alive without transformation	-
14	HAL-D	83/M	Smouldering (cutaneous) type	Few cells*	15	Topical therapy	-	Alive without transformation	-
15	HAL-D	68/M	Non-ATLL (HTLV-1 carrier)	Few cells*	2	Topical therapy	-	Alive without transformation	-
16	ATLL-D	74/M	***	Few cells*	14	Oral VP-16	***	Dead	ATLL

Table 1. (Continued)

Case no.	Diagnosis	Age/sex	Clinical subtype	Proportion of atypical cells in PB	Follow-up period (months)**	Treatment	Progression to aggressive type	Status at the last follow-up	Cause of death
17	ATLL-D	79/ M	***	0%	7	VP-16 and anti-CCR4 antibody	***	Dead	ATLL
18	ATLL-D	64/ M	***	41%	3	Topical therapy	***	Alive	-

F, female; M, male; PB, peripheral blood; HAL-D, HTLV-1 associated lymphadenitis with dermatopathic reaction; ATLL-D, overt adult T cell leukaemia/lymphoma with dermatopathic reaction; CCR4, CC chemokine receptor 4.

*Few atypical cells were observed, but the count was $\leq 1\%$.

**Follow-up period is the time (months) from the lymph node biopsy.

***The clinical subtypes of these cases are discussed in the text.

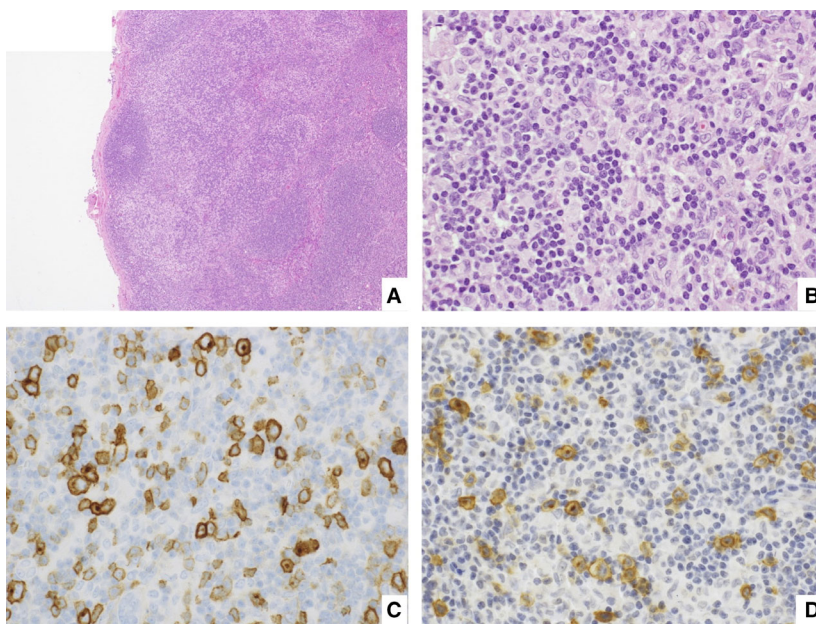
electrophoresis. Southern blot analysis was performed for cases 6 and 17 using genomic DNA from fresh samples. PstI, EcoRI and HTLV-1 probes were used, as previously reported.¹²

Results

CLINICAL CHARACTERISTICS OF PATIENTS

The clinical characteristics of the reported cases are shown in Table 1. The median age was 76 years and 14 of the 18 patients were male. All of the patients were more than 60 years of age, which is older than the cohort in a previous study on lymph nodes with dermatopathic reaction without malignancy.¹³ Erythema was observed in all cases, and one case showed purpura. Most patients had enlargement of axillary or inguinal lymph nodes. One patient (case 2) was diagnosed as smouldering ATLL based on haematological findings in peripheral blood. Seven cases were considered to be a 'cutaneous' variant of the smouldering type based on the pathological findings in skin lesions.¹⁴ Another seven cases did not show clear pathological or molecular evidence of lymphoma cell infiltration in either lymph nodes or skin, and were therefore considered as HTLV-1 carriers. Two patients (cases 16 and 17), classified as ATLL-D, showed a progressive disease course and died 14 and 7 months respectively after diagnosis despite treatment that included mogamulizumab, an antibody therapy against CCR4. Another case of ATLL-D (case 18) showed proliferation of atypical lymphocytes in peripheral blood ($> 40\%$) with a slight increase in serum lactate dehydrogenase (LDH) and decreased serum albumin levels (data not shown), indicating a chronic type with an unfavourable prognosis as the clinical subtype.⁸ The patient with smouldering type (case 2) received oral etoposide (VP-16) treatment, whereas the remaining 14 cases, including patients regarded as HTLV-1 carriers or cutaneous-type ATLL, received topical therapy for their cutaneous lesions. Although a precise comparison of clinical outcome between case 2 and the other HAL-D patients was difficult, because their treatment regimen was different, case 2 showed an indolent clinical course, similar to the other HAL-D cases, with no definitive transformation event. Case 12, initially diagnosed as HAL-D, progressed to aggressive-type ATLL 30 months after lymph node biopsy and died within 1 month. In the pathological review of the lymph node specimen of case 12, Hodgkin-Reed-Sternberg (HRS)-like cells, a

Figure 1. Pathological findings of lymph nodes of human T cell leukaemia virus type I (HTLV-1)-associated lymphadenitis with dermatopathic reaction (HAL-D). Expanded paracortex shows clear foci including dendritic cells and Langerhans cells with abundant clear cytoplasm (A, B, case 3). Large lymphoid cells are also scattered and positive for CD25 (C) or CD30 (D) (C,D, case 3).



hallmark finding of incipient ATLL, were not identified. The other HAL-D cases showed no obvious transformation. Case 5 died 6 years after a diagnosis of HAL-D, but the cause of death was unknown and no transformation was confirmed. Case 11, diagnosed as cutaneous type, died from *Pneumocystis carinii* pneumonia 2 months after lymph node biopsy without transformation to aggressive ATLL. Case 14, who exhibited proliferation of EBV-infected atypical large B cells, was aged 83 years. This patient was seronegative for human immunodeficiency virus and no other immunosuppressive status, including immune suppressive therapy, was noted in the history.

PATHOLOGICAL CHARACTERISTICS OF PATIENTS

In cases with HAL-D, lymph node tissue architecture was preserved, and proliferation of transformed large lymphoid cells as well as aggregates of interdigitating dendritic cells, Langerhans cells and macrophages forming mottled clear foci was observed in the paracortex (Figure 1A,B). Transformed large lymphocytes with prominent nucleoli were detected in all cases. Numerous CD25-positive cells distributed in the expanded paracortex were observed in all cases by immunohistochemistry (Figure 1C). The number of CD30-positive cells varied, and there was no clear correlation between the number of positive cells in neoplastic and reactive lesions (Figure 1D and Table 2). No HRS-like cells or CD15-positive large cells were observed in the present series. Although

one patient (case 2) showed T cell monoclonality by PCR for TCR- γ , the definitive atypical tumour cells or phenotypical abnormalities of T cell markers were not identified. No clonal rearrangement was recognised in the other samples (polyclonal pattern in 12 cases and not evaluable in three cases). All lymph node samples of HAL-D showed a normal T cell phenotype by flow cytometry analysis (Figure 3 and Supporting information, Table S1) and/or immunohistochemistry.

Cases 16, 17 and 18, classified as ATLL-D, also showed a polymorphous inflammatory infiltrate admixed with dendritic cells containing abundant clear cytoplasm that were positive for S-100 (Figure 2A-F). Although these findings overlap with HAL-D, a relatively monotonous infiltration of medium-sized lymphoid cells with mild nuclear atypia in the paracortex was observed (Figure 2E). The majority of atypical lymphoid cells exhibited a T cell phenotype lacking CD3 or CD7 expression (Figure 2G,H). Flow cytometry analysis confirmed an abnormal phenotype, consistent with the results obtained by immunohistochemistry (Figure 3).¹⁵ PCR analysis of the TCR rearrangement revealed clonal expansion of T cells in cases 17 and 18 (Table 2).

Skin samples from 10 patients (cases 1, 2, 3, 7, 8, 10, 11, 14, 17 and 18) showed infiltrating lymphoid cells with nuclear atypia in the dermis and/or epidermis (Figure 4A) that occasionally formed Pautrier's microabscesses (Figure 4B). The atypical lymphoid cells were positive for CD4 (Figure 4C) and CD25 (Figure 4D). Yamaguchi *et al.* proposed

Table 2. Pathological characteristics.

Case no.	Diagnosis	Biopsied LN	CD30-positive cells	Flow cytometry	Immunohistochemistry	Clonality (TCR)
1	HAL-D	Axillary	12	No abnormal pattern	CD3 = CD7 = CD5	Polyclonal
2	HAL-D	Axillary	111.75*	ND	CD3 = CD7 = CD5	Monoclonal
3	HAL-D	Inguinal	90	No abnormal pattern	CD3 = CD7, CD5: ND	Polyclonal
4	HAL-D	Axillary	41.75	ND	CD3 = CD7, CD5: ND	Polyclonal
5	HAL-D	Inguinal	73.5	No abnormal pattern	CD3 = CD7, CD5: ND	Polyclonal
6	HAL-D	Axillary	57	No abnormal pattern	CD3 = CD7 = CD5	Polyclonal**
7	HAL-D	Axillary	37.5	ND	CD3 = CD7, CD5: ND	Polyclonal
8	HAL-D	Axillary	28	No abnormal pattern	CD3 = CD7, CD5: ND	Polyclonal
9	HAL-D	Axillary	5.25	No abnormal pattern	CD3 = CD7, CD5: ND	Polyclonal
10	HAL-D	Inguinal	6.5*	No abnormal pattern	CD3 = CD7 = CD5	Polyclonal
11	HAL-D	Inguinal	5.25	No abnormal pattern	CD3 = CD7, CD5: ND	NE
12	HAL-D	Inguinal	64	No abnormal pattern	CD3 = CD7 = CD5	Polyclonal
13	HAL-D	Axillary	8.5	No abnormal pattern	CD3 = CD7, CD5: ND	NE
14	HAL-D	Axillary	90.75	ND	CD3 = CD7 = CD5, EBV(+) cells(+)	Polyclonal
15	HAL-D	Axillary	62.5	ND	CD3 = CD7, CD5: ND	Polyclonal
16	ATLL-D	Inguinal	84.75	CD3 > CD7	CD3>CD7, CD5: ND	NE
17	ATLL-D	Cervical	20	CD3 < CD7	CD3<CD7, CD5: ND	Monoclonal**
18	ATLL-D	Inguinal	82	ND	CD3 = CD5 > CD7	Monoclonal

NE, not evaluable; ND, not done; HAL-D, HTLV-1 associated lymphadenopathy with dermatopathic reaction; ATLL-D, ATLL with dermatopathic reaction; EBV, Epstein–Barr virus; TCR, T cell receptor; LN, lymph node.

*Average of two samples at the same biopsy.

**These cases were evaluated using Southern blot analysis [the results of polymerase chain reaction (PCR) analysis was not evaluable]. PCR analysis was used for the other cases.

three morphological subtypes in cutaneous lesion of ATLL, i.e. perivascular, nodular and diffuse type.¹⁰ All skin lesions analysed in this study were classified as the perivascular type. There was no definite lymphoma cell infiltration in skin samples from five patients (cases 4, 5, 6, 12 and 13) who were regarded as HTLV-1 carriers and from three other patients (cases 9, 15 and 16) who did not undergo skin biopsy.

Case 14 showed a unique histopathological pattern characterised by focal proliferation and aggregation of atypical large lymphoid cells in the lymph node (Figure 5A–E). The cells were uniformly positive for CD20 (Figure 5D), focally positive for CD30 and negative for CD15. These proved to be EBV-infected B cells (Figure 5E). A distinct neoplastic T cell proliferation was not

detected by histological or molecular methods. Based on these findings, Hodgkin-like incipient ATLL was an unlikely diagnosis.

Discussion

This is the first study, to our knowledge, to investigate the clinicopathological characteristics of lymph nodes with dermatopathic reaction in patients infected by HTLV-1. Although HAL-D cases showed an indolent clinical course for the most part, two of the three patients with ATLL-D showed a relatively aggressive clinical course. The third ATLL-D case was accompanied by leukaemic atypical lymphocytes, decreased albumin and elevated LDH, possibly classified as unfavourable chronic type, suggesting a

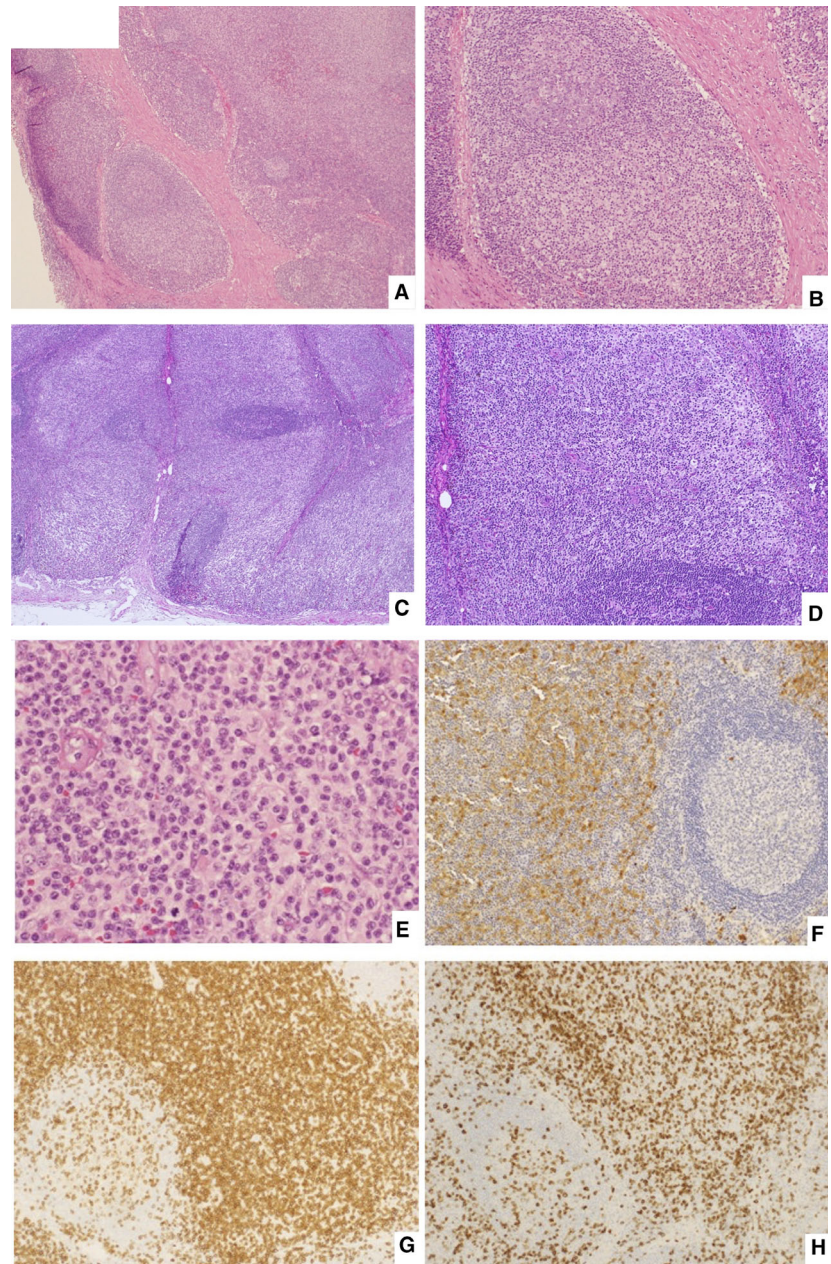


Figure 2. Pathological findings of adult T cell leukaemia/lymphoma (ATLL) with dermatopathic reaction (ATLL-D). The lymph node has an expanded paracortex harbouring proliferating dendritic cells with abundant clear cytoplasm [haematoxylin and eosin (H&E); A,B, case 16; C,D, case 17]. Medium-sized atypical lymphoid cells are admixed with dendritic cells (H&E, E, case 16). Numerous dendritic cells positive for S-100 are detected by immunohistochemistry (F, case 16). Atypical lymphoid cells express CD3 (G, case 16), but show down-regulation of CD7 (H, case 16).

relatively poor prognosis. Our study also showed the usefulness of abnormal T cell immunophenotype to distinguish HAL-D and ATLL-D. This method is also used in the evaluation of other T cell type neoplasms, such as Sézary syndrome.¹⁶ Kobayashi *et al.*¹⁷ established a method for identifying ATLL tumour cells based on flow cytometric detection of CD3 and CD7 expression. With disease progression, ATLL cells gradually change their immunophenotype from CD3⁽⁺⁾/CD7⁽⁺⁾ to CD3⁽⁻⁾/CD7⁽⁻⁾. The abnormal T cell immunophenotype seems not only to

distinguish neoplastic from inflammatory status, but also predicts aggressiveness of the disease. Conversely, CD25-positive transformed lymphoid cells proliferated in all cases. The number of CD30-positive cells varied among cases, but was unrelated to either the distinction of ATLL-D and HAL-D or the clinical course. These cells can be regarded as activated/stimulated lymphocytes. Immunohistochemical analysis of lymph nodes with dermatopathic reaction from two cases without HTLV-1 infection or CTCL revealed that they also harboured proliferating

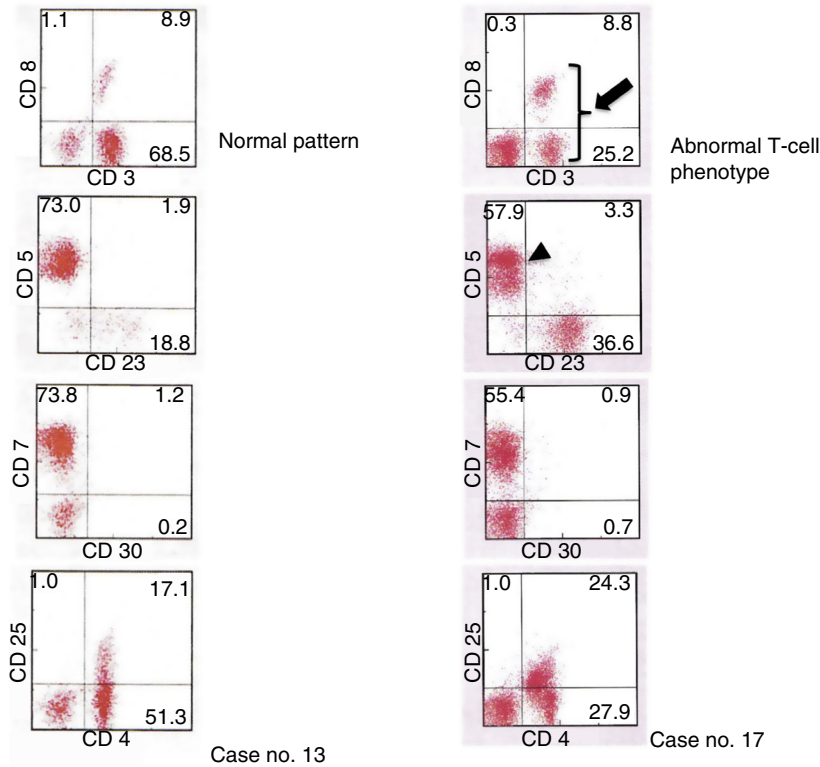


Figure 3. Flow cytometry analysis of cases with human T cell leukaemia virus type I-associated lymphadenitis with dermatopathic reaction (HAL-D) (case 13, left side) and adult T cell leukaemia/lymphoma dermatopathic reaction (ATLL-D) (case 17, right side). In HAL-D, the proportion of CD3-positive cells is 77.4%, which is similar to those of CD5 (74.9%) and CD7 (75.0%). Conversely, the proportion of CD3-positive cells in case 13 is 34.0% (arrow), which is much lower than those of CD5 (61.2%) and CD7 (56.3%). Abnormal cells with low CD5 expression were faintly distinguishable from a highly immunopositive population (arrowhead).

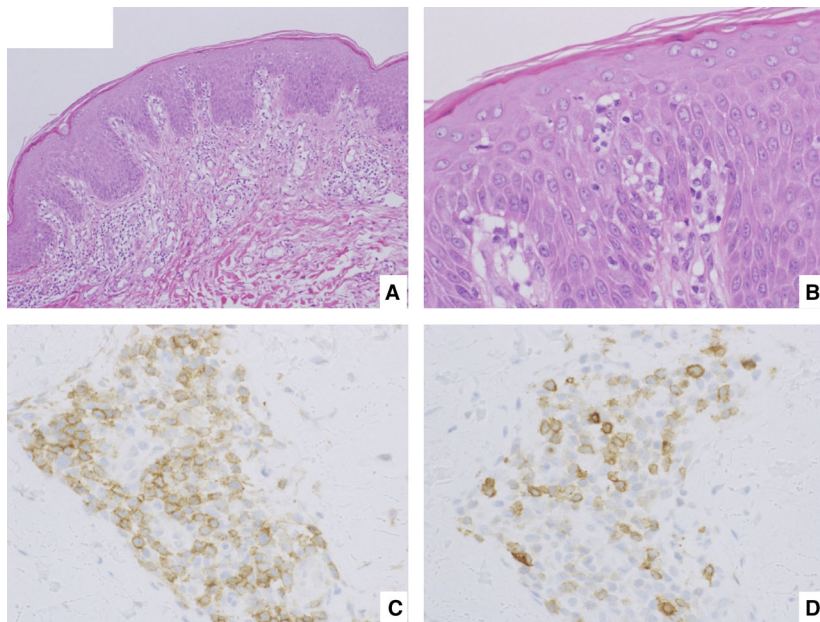


Figure 4. Skin lesion diagnosed as smouldering adult T cell leukaemia/lymphoma (ATLL) (cutaneous variant, case 3). Small- to medium-sized lymphoid cells mainly infiltrate the upper dermis (haematoxylin and eosin, A). Although nuclear atypia is not evident, infiltrating lymphoid cells form a Pautrier's microabscess (B) positive for CD4 (C) and CD25 (D).

CD25- and CD30-positive cells, suggesting that this is not specific to HTLV-1-associated lesions (Supporting information, Supplemental Figure 1). This could complicate diagnosis in cases where infiltration of lymphoid malignancy is suspected, including ATLL.

In case 14, there was focal proliferation of EBV-infected large B cells, whereas definitive clonal T cell proliferation or abnormal T cell immunophenotype was not observed. This finding has been described in several lymphomas, including angioimmunoblastic T cell lymphoma, and reflects an immunodeficient local

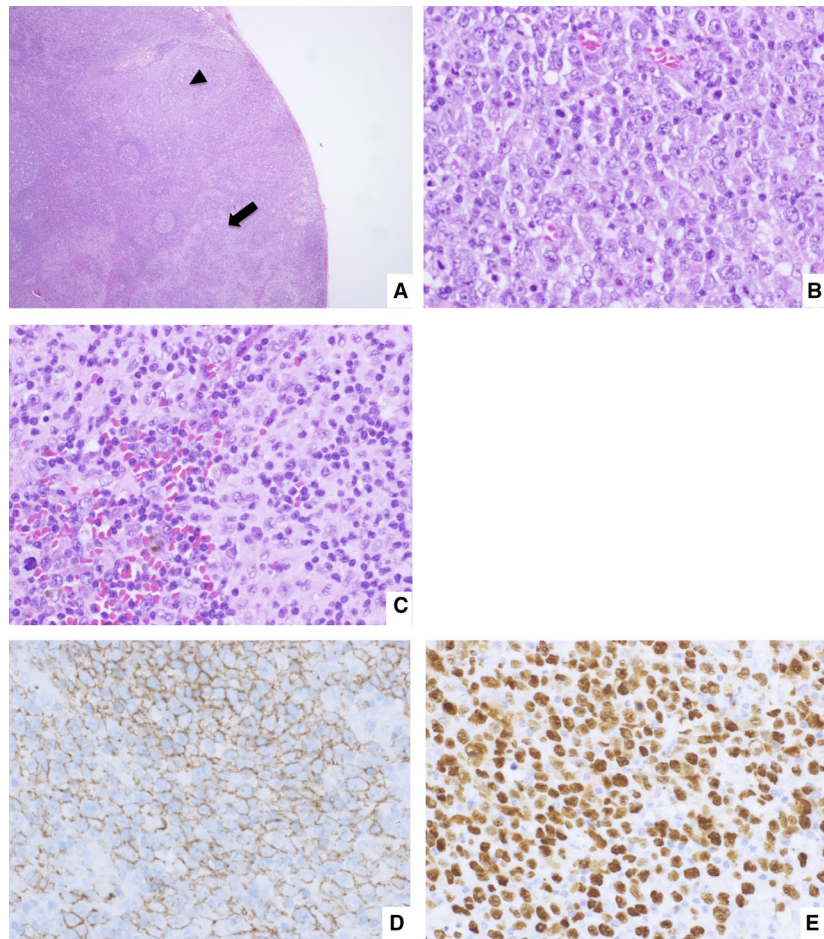


Figure 5. Human T cell leukaemia virus type I (HTLV-1)-associated lymphadenopathy with dermatopathic reaction, with focal proliferation of Epstein–Barr virus (EBV)-positive transformed B cells (case 14). This lymph node shows an expanded paracortex with increased dendritic cells and pigment deposition (haematoxylin and eosin, arrow in A and C) and monotonous proliferation of atypical large lymphoid cells (arrowheads in A and B). Transformed large lymphoid cells were positive for CD20 (D) and EBV-encoded small RNA *in-situ* hybridisation (E).

environment created by tumour cells.¹⁸ This case was distinguished from the Hodgkin lymphoma-like variant accompanied by incipient ATLL because the proliferating cells were uniformly positive for CD20 (Figure 5D), focally positive for CD30 and negative for CD15.¹⁹ EBV-positive B cell lymphoproliferative disorders, associated with age-related immune deficiency and comprising a wide disease spectrum from benign to malignant status, is one possibility.^{20,21} However, an immunosuppressive status induced by HTLV-1 infection could also contribute to the proliferation of EBV-infected cells, as previously reported.^{22,23} ATLL tumour cells and HTLV-1-infected cells often exhibit the phenotype of regulatory T cells, including expression of CD4, CD25 and forkhead box P3.²⁴ EBV-positive cell proliferation combined with dermatopathic reaction mimicking lymphoma-type ATLL can be a potential pitfall in routine diagnosis.

Although ATLL-D is a form of neoplastic status of ATLL, it is unclear whether these cases should be treated as lymphoma type, which usually have a very

aggressive clinical course and dismal prognosis⁸. Ohshima *et al.* described a Hodgkin-like type as an incipient ATLL.¹⁹ Even though the morphological findings of ATLL-D are different from Hodgkin-like type, ATLL-D could be regarded as another variant of incipient ATLL. In fact, one ATLL-D patient (case 18) was classified clinically as chronic type. However, assessment of the clinicopathological findings in other similar cases is needed to verify this.

In conclusion, the present study highlighted a spectrum of nodal lesions accompanied by dermatopathic reaction in HTLV-1 carriers. While HAL-D and ATLL-D share several features, careful observation for the detection of atypical lymphoid cell infiltration and abnormal T cell immunophenotype and clonality rearrangement may support the distinction between reactive and neoplastic conditions. Once the possibility of overt lymphoma is excluded, an indolent clinical course can be expected. Cases of HAL-D should be treated with topical therapy, and overtreatment with cytotoxic chemotherapy should be avoided.

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Conflicts of interest

The authors declare no potential conflicts of interest.

Authorship contributions

Conception and design: K. Karube, S. Chinen, T. Miyagi, K. Takahashi. Development of methodology: M. Takatori, S. Sakihama. Acquisition of data: S. Chinen, Y. Murakami, I. Nakazato, Y. Kariya, S. Yamaguchi, K. Karube.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Pathological findings of lymph nodes of reactive lymphadenitis with dermatopathic reaction in a HTLV-1 uninfected patient.

Table S1. Flowcytometric analysis of lymph nodes.