Lymphomatoid Keratosis

An Epidermotropic Type of Cutaneous Lymphoid Hyperplasia: Clinicopathological, Immunohistochemical, and Molecular Biological Study of 6 Cases

Eiichi Arai, MD; Michio Shimizu, MD; Tetsuya Tsuchida, MD; Seiichi Izaki, MD; Fumihiro Ogawa, MD; Takanori Hirose, MD

Objective: To provide evidence that lymphomatoid keratosis should be categorized as an epidermotropic subtype of cutaneous lymphoid hyperplasia.

Design: Clinicopathological, immunohistochemical, and molecular biological studies of epidermotropic and dermal bandlike infiltrates of lymphocytes without necrotic keratinocytes, Civatte bodies, or Max-Joseph spaces and solar lentigo or seborrheic keratosis adjacent to the lesion, but with epidermal hyperplastic change (clinically scaly plaque) in cases of lymphomatoid keratosis. Conventional histopathologic study as well as immunohistochemical examinations for CD1a, CD3, CD4, CD8, CD20, and CD79a and S100 protein and genotypic examinations were performed.

Setting: University departments comprising 2 sections of dermatology and 1 section of pathology.

Main Outcome Measures: Ratio of T to B cells and of CD4⁺ to CD8⁺ cells, and the phenotype of epidermotropic cells were evaluated. Gene rearrangement of the immunoglobulin heavy chain gene and T-cell receptor (TCR)-β and TCRγ genes was also investigated by the polymerase chain reaction method.

Results: Immunohistochemically, epidermotropic CD20⁺ and/or CD79a⁺ cells were present. In the upper dermal lymphocytic infiltrates, the CD3⁺/CD79a⁺ cell ratio ranged from 5:5 to 8:2. The CD4⁺/CD8⁺ cell ratio was within normal limits. Rearrangements of the TCRγ gene were demonstrated in 2 cases and of the TCRβ gene in 1 case.

Conclusions: Our results indicate that lymphomatoid keratosis is a clinically benign keratotic lesion but histologically malignant, simulating mycosis fungoides. Immunohistochemical findings showed a reaction pattern in all cases, but genotypical examination showed some clonal dermatoses. Therefore, “lymphomatoid” keratosis should be classed as a pseudolymphoma, namely, a subtype of cutaneous lymphoid hyperplasia with epidermotropism.

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The term lymphomatoid keratosis was originally proposed by Kossard and was thought to be a possible variant of benign lichenoid keratosis showing lymphomatoid features. He considered that the case reported by Evans et al as a unilesional mycosis fungoides (MF) should be termed lymphomatoid keratosis. Clinically, the case reported by Evans et al was characterized by an asymptomatic scaly plaque, but the histological features were those seen in MF. Therefore, the most important pathological feature of lymphomatoid keratosis is epidermotropism resembling that seen in MF. Namely, the term lymphomatoid in lymphomatoid keratosis indicates histological simulation of MF. It is noteworthy that the term pseudolymphoma was originally adopted to indicate a lesion clinically or histologically simulating malignant lymphoma. Therefore, the term lymphomatoid is considered to be equivalent to so-called pseudolymphoma.

Epidermotropism is defined as an affinity of tumor cells for the epidermis. Various conditions display lymphocytic infiltrates with tropism for the epidermis. Epidermotropism was not included in the glossary of the fifth edition of Histopathology of the Skin by Lever and Schaumburg-Lever in 1975. However, it appeared in the sixth edition in 1983. In this textbook, epidermotropism was reportedly restricted to MF as follows:

Presence of mononuclear cells in the epidermis without spongiosis occurring in MF. The
cells lie either singly, surrounded by a clear halo, or aggregated as in a Pautrier microabscess. Epidermotropism must be differentiated from exocytosis.

However, there have been descriptions of epidermotropism in other tumors. In 1983, Burg and Braun-Falco (p386) stated that in histiocytosis X, “An important histological feature is epidermotropism of the characteristic cells.” Burkert et al (p464) used the term pseudo-Pautrier abscess for Langerhans cell microgranulomas, and Klein et al (p496) used the term epidermorphic nature to describe porocarcinoma (malignant poroma). Moreover, Murphy and Schwarting (p508) used the term atypical epidermorphic infiltrate for benign conditions such as lymphomatoid drug eruption. Bayer-Garnar et al (p584) reported that CD68+ histiocytes showed epidermotropism in benign lichenoid eruption. Falco (p606) stated that in histiocytosis X, “An important histological feature is epidermotropism of the characteristic cells.”

Therefore, epidermotropism has been used mostly as a descriptor for MF, which is epidermotropism in the narrow sense. All of the cases we have examined have fallen into this category, which shows complete histological similarity to MF. The epidermotropism of MF is a phenomenon whereby lymphocytes infiltrate into the epidermis, slippery with perinuclear halo, and do not attack the basement membrane or keratinocytes. This phenomenon occurs in specific conditions caused by longstanding chronic inflammation in the skin-associated lymphoid tissue of the upper dermis. Kazakov et al (p54) and Massone et al (p519) have described epidermotropism in several of the following conditions: (1) disproportionate epidermotropism (presence of many lymphocytes distributed irregularly), (2) basilar lymphocytes (presence of linear aggregates of small hyperconvoluted lymphocytes located at the dermoepidermal junction), (3) large epidermal lymphocytes (intraepidermal lymphocytes larger than those in the dermis), (4) Pautrier microabscesses (presence of intradermal collection of more than 3 lymphocytes), and (5) haloed lymphocytes (presence of a perinuclear clear space), all of which may be recognized as epidermotropism in the narrow sense.

Based on these facts, we performed clinicopathological, immunohistochemical, and molecular biological studies of 6 cases of clinically benign scaly plaque and epidermotropism histologically similar to that in MF. We investigated whether lymphomatoid keratosis should be classified as an epidermotropic subtype of cutaneous lymphoid hyperplasia.

**METHODS**

A retrospective review of the files of Saitama Medical University Hospital and Saitama Medical Center Hospital, Saitama, Japan, for the period 2000 to 2004 identified 6 cases of lymphomatoid keratosis, which showed solitary scaly plaque clinically, and histologically, typical epidermotropism and bandlike lymphocytic infiltration in the upper dermis without necrotic keratinocytes, Civatte bodies, or Mac-Joseph spaces and solar lentigo or seborrheic keratosis adjacent to the lesion. In the present study, the epidermotropism showed 3 of the following patterns: (1) Pautrier microabscesses, which are intraepidermal collection of more than 3 lymphocytes, (2) disproportionate distribution of haloed lymphocytes in the epidermis, and (3) linear aggregates of haloed lymphocytes at the dermoepidermal junction.

**IMMUNOHISTOCHEMICAL ANALYSIS**

A set of 4-µm-thick tissue sections were prepared from formalin-fixed and paraffin-embedded blocks, deparaffinized in xylene, rehydrated, and microwaved for 10 minutes at 30% power in citrate buffer, pH 9.0 (Dako Japan, Kyoto) for antigen retrieval. Endogenous peroxidase activity was blocked using 0.3% hydrogen peroxide in methanol for 3 minutes. Immunostaining was carried out after antigen retrieval by microwaving in 1 mM EDTA (pH 8.0) 2 times for 5 minutes each time at 900 W. Then the streptavidin-biotin-peroxidase complex method was used for immunostaining with a Ventana OH system immunostainer (Ventana-Biotech, Tucson, Ariz). The primary antibodies against the lymphoid antigens were CD1a (O10; Immunotech, Marseille, France [undiluted]), CD3 (PS-1; Novocastra, Newcastle-upon-Tyne, England [1:100 dilution]), CD4 (1F6; Novocastra [1:40 dilution]), CD8 (CSB/144B; Dakopatts, Glostrup, Denmark [1:100 dilution]), CD20 (L26; Dakopatts [1:100 dilution]), CD68 (PG-M1; Dakopatts [1:200 dilution]), CD79a (JCB117; Dakopatts [1:100 dilution]), kchain (AAB85; Dakopatts [1:100 dilution]), a chain (C4; Immunotech [1:50 dilution]), and S100 protein (Dakopatts [1:300 dilution]). Human tonsillar tissue was used as a normal control. The main features evaluated during immunohistochemical testing were (1) the B to T-cell ratio; (2) the ratio of the CD4+ to CD8+ cells; (3) the phenotype of epidermotropic cells; and (4) the proliferation of CD1a+ and/or S100 protein-positive cells in the epidermis and dermis.

**GENOTYPIC ANALYSIS**

For genotypic studies, DNA was extracted from 10-µm-thick paraffin sections by proteinase K (200 µg/mL) digestion. The supernatant containing DNA was used directly for polymerase chain reaction amplification. The polymerase chain reaction was used to detect rearrangement of the immunoglobulin heavy chain (IgH) gene using 3 Vh primers (FR1c, FR2a, and FR3a) and 2 Jh primers (LJH and VLJH); the T-cell receptor (TCR)β chain gene using the following 5 primer sets: β0, β1 (V + J); β2 (V + J); β3, (D + J); β4, (D + J); and β5, (D + J)14; and the TCRγ chain gene using the following 20 mixed primer sets: mix 1 (V1 V8, V6, V4, J11.1, J11.2, J11.3, J12.1, J12.2, J12.3, J12.4, J12.5) and mix 2 (V5, V10, V31, V12, J11.1, J11.2, J11.3, J12.1, J12.2, J12.3, J12.4, J12.5).

**RESULTS**

The clinical data are demonstrated in Table 1. The patients ranged in age from 36 to 78 years, with a mean age of 59 years, and the male-female ratio was 1:1. The size (largest diameter) of the lesions ranged from 0.6 to 1.6 cm, with a mean of 0.85 cm. All cases revealed solitary scaly plaques (Figure 1). The face was the most common lesion site. Either actinic keratosis or seborrheic keratosis was suspected clinically in 5 of the 6 cases. The period from the patient’s recognition of the lesion until visiting the hospital ranged from 3 months to several years. Follow-up data from the diagnosis were obtained in cases...
1 and 6; neither showed recurrence or cutaneous dissemination in 34 months and 13 months, respectively.

**HISTOPATHOLOGICAL FINDINGS**

All of the cases showed hyperkeratosis, parakeratosis, acanthosis, and bandlike lymphocytic infiltration (*Figure 2*). All of them showed epidermotropism; 3 cases showed Pautrier microabscesses, 3 showed disproportionate lymphocytes, and 2 showed basilar lymphocytes (*Figure 3*). No atypical keratinocytes, basal cells, or atypical lymphocytes were observed. Various degrees of infiltration of plasma cells, eosinophils, and melanophages were noted in all of the lesions.

**IMMUNOHISTOCHEMICAL FINDINGS**

The immunohistochemical data are summarized in Table 2. Dermal infiltrating cells including many CD20* and/or CD79a* cells were intermingled among lymphoid follicles in 2 of the 6 cases. The dermal infiltrating lymphocyte population was composed of various proportions of T and B cells: the CD3*/CD79* cell ratio ranged from 5:5 to 8:2 (Table 2). In all cases epidermotropic CD20* and/or CD79a* cells were present (*Figure 4*). The dermal infiltrating cells comprised normal CD4* and CD8* lymphocytes (*Figure 5*). Cells positive for CD1a and/or S100 protein within the overlying epidermis were increased in number and were also present in the upper dermis. Such cells were also present in the dermal inflammatory infiltrate.

**GENOTYPIC FINDINGS**

The genotypic data are given in Table 2. No rearrangement was observed in the IgH gene. However, using the mix 1 primer set, rearrangements of the TCRγ gene were demonstrated in 2 cases (case 1 [*Figure 6*] and case 6) and of the TCRβ gene in 1 case (case 6).
Lymphomatoid keratosis has been recognized as a variant of lichenoid keratosis, which clinically forms scaly plaques and histologically shows epidermotropism that is a characteristic feature of MF. Al-Hoqail and Crawford reported 15 cases of benign lichenoid keratosis with histological features of MF showing marked overlap with lymphomatoid keratosis. Their cases showed intraepidermal aggregation of 3 or more lymphocytes in 93%, 3 or more lymphocytes aligned along the basal layer without overlying intraspinoous lymphocytes or spongiosis in 93%, and intraepidermal lymphocytes surrounding haloes without spongiosis in 80%. Namely, all of these cases were thought to have epidermotropism in the narrow sense. Clinically, the age of their studied patients ranged from 28 to 83 years, with a mean age of 50 years; the male-female ratio was 3:2; and the lesions ranged in size from 0.2 to 1.8 cm, with a mean of 0.6 cm. The upper trunk was the most commonly affected site in 7 of

Table 2. Immunohistochemical and Genotypical Findings in Lymphomatoid Keratosis

<table>
<thead>
<tr>
<th>Case No.</th>
<th>B-Cell Epidermotropism</th>
<th>Lymphoid Follicles</th>
<th>CD3/CD79a Ratio</th>
<th>TCRβ Rearrangement</th>
<th>TCRγ Rearrangement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PM</td>
<td>+</td>
<td>6.4</td>
<td>−</td>
<td>Mix 1 (+)</td>
</tr>
<tr>
<td>2</td>
<td>PM</td>
<td>+</td>
<td>5.5</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>3</td>
<td>PM</td>
<td>−</td>
<td>6.4</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>4</td>
<td>DE</td>
<td>−</td>
<td>8.2</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>5</td>
<td>DE + BL</td>
<td>−</td>
<td>7.3</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>6</td>
<td>DE + BL</td>
<td>−</td>
<td>7.3</td>
<td>+</td>
<td>Mix 1 (+)</td>
</tr>
</tbody>
</table>

Abbreviations: BL, basilar lymphocytes; DE, disproportionate epidermotropism; PM, Pautrier microabscesses; TCR, T-cell receptor; +, positive findings; −, negative findings.

Figure 3. Epidermotropism in lymphomatoid keratosis. A, Pautrier microabscesses are seen in case 2. B, Lined-up distribution at the dermoepidermal junction is evident in case 6 (hematoxylin-eosin, original magnification ×4 [A] and ×20 [B]).

Figure 4. Epidermotropism of CD3- and CD20-positive cells. Epidermotropic and dermal infiltrative cells in case 4 stained for CD3 (A) and in case 4 stained for CD20 (B) (original magnification ×60 [A and B]).

Figure 5. Immunohistochemical features of lymphomatoid keratosis (case 2). Cells positive for CD20, CD4, and CD8 are intermingled in the upper dermis. Many cells positive for CD20 (and/or CD79a) are present. CD4-positive cells (A) are predominant over CD8-positive cells (B) compared with the normal CD4/CD8 ratio (original magnification ×40 [A and B]).
the 15 cases, followed by the face and extremities in 4 cases. These clinical features were compatible with those seen in our present cases. However, 4 of these 15 cases did not have necrotic keratinocytes and 6 did not have solar lentigo or seborrheic keratosis adjacent to the lesion. Necrotic keratinocytes were adopted as a feature to constitute an entity of popular MF. The presence of solar lentigo or seborrheic keratosis adjacent to the lesion showed that the lesion was in a regressing state from solar lentigo or seborrheic keratosis. Therefore, it is suggested that these cases included some cases having both necrotic keratinocytes and solar lentigo or seborrheic keratosis adjacent to the lesion. These limited cases, which showed the same features as our cases, are in fact thought to be lymphomatoid keratosis. In the cases reported by Al-Hoqail and Crawford, the clinical diagnoses included 10 cases of cutaneous malignancy (basal cell carcinoma, squamous cell carcinoma, and actinic keratosis). In our series, 3 cases of actinic keratosis were noted. Reported cases of benign lichenoid keratosis with histological features of MF and lymphomatoid keratosis have not shown any development of MF.

Although lymphomatoid keratosis was first recognized as unilesional MF by Evans et al, Kossard suggested that their case was lymphomatoid keratosis. Therefore, lymphomatoid keratosis should be differentiated from unilesional MF clinicopathologically. Unilesional MF is typified by involvement of less than 5% of the body surface. It is usually found in the same body regions as classic MF, such as the breast, axilla, and buttock. Histopathological findings are identical to those seen in classical MF. Patients with unilesional MF demonstrate an excellent response to topical chemotherapy or irradiation. In other words, unilesional MF appears as a typical clinical cutaneous lesion of MF in spite of its small size. Therefore, clinical information is important to distinguish between these lesions. However, lymphomatoid keratosis clinically mimics basal cell carcinoma, actinic keratosis, or seborrheic keratosis. Unilesional MF usually develops as erythema or plaques, but its boundary is not highly clear. Unilesional MF can also occur in childhood, as Hodak et al and Alsaheh et al have reported.

Kazakov et al have reported that unilesional MF can sometimes recur after surgical excision. However, there have been no reports of extradermal spread, and all reported cases have shown a benign course. Therefore, the cases reported by Yoo et al as “unilesional mycosis fungoides mimicking Bowen's disease” and by Bazza et al as “mycosis fungoides masquerading as seborrheic keratosis” might have been cases of lymphomatoid keratosis. Thus, the diagnosis of lymphomatoid keratosis requires careful clinicopathological examination to make a distinction from unilesional MF.

Hodak et al suggested the possibility of actual T-cell pseudolymphoma in unilesional MFs as well as minimal stage IA MF. We previously demonstrated that cases formerly diagnosed as cutaneous lymphoid hyperplasias (including lymhoicytoma cutis, lymphadenosis benigna cutis, or Spiegler-Fendt–type pseudolymphoma) could be reclassified into cutaneous marginal zone lymphoma, diffuse large B-cell lymphoma, pseudolymphomatous folliculitis, cutaneous lymphoid hyperplasia in the narrow sense, and solitary non-epidermotropic pseudo-T-cell lymphoma. Now we consider it feasible to add not only solitary non-epidermotropic pseudo–T-cell lymphoma but also lymphomatoid keratosis to the cutaneous MF-like T-cell–type “pseudolymphoma” group.

Although lymphomatoid keratosis shows epidermotropism in the narrow sense, its immunological microenvironment is different from that of MF. Our findings from immunohistochemical analysis showed many B cells in the dermal infiltrates and B-cell epidermotropism. Moreover, there were increased numbers of cells positive for CD1a and/or S100 protein within the lesions in the overlying epidermis. In contrast, in MF, S100 protein–positive dendritic cells are increased in the dermis and decreased in the epidermis. Bayer-Garner et al considered the immunopathological change in benign lichenoid keratosis to be “regression.” Cytotoxic T cells might be a final common denominator (key effector cell) of regression. This phenomenon was confirmed by Jang et al. In benign lichenoid keratosis CD3, CD4 T lymphocytes, natural killer cells, macrophages, and Langerhans cells were in-

Figure 6. TCRγ chain gene rearrangement in lymphomatoid keratosis. A, Case 1 of mix 1 shows a positive band; B, case 1 of mix 2 shows a smearlike band at a position different from the control band.
termingled in the dermis. Epidermotropism of cells positive for CD1a, CD68, CD3, and CD8 was also noted. However, no B-cell epidermotropism has been reported in benign lichenoid keratosis. Whereas Smith et al.28 demonstrated no rearrangement of the TCRγ gene by the polymerase chain reaction method in lichenoid keratosis, 2 cases in the present study showed TCRγ clonality and 1 case revealed TCRβ clonality.

There had been an attempt to classify benign lichenoid keratosis into the following 3 groups25: lichen planus–like keratosis, seborrheic keratosis–like lichenoid keratosis, and lupus erythematosus–like lichenoid keratosis. However, Weedon29 claimed that the seborrheic keratosis–like variant should be classified as an irritated seborrheic keratosis. In addition, the lupus erythematosus–like variant is simply a lesion with some basal clefing. Another recent large study of benign lichenoid keratosis, which excluded lichen planus, lichenoid drug eruption, lupus erythematosus, MF, and actinic keratosis, divided the cases into the following 5 groups30: classic, atrophic, early, bullos, and atypical. The pathologic features of the fifth atypical group are scattered atypical lymphocytes and lichenoid infiltrates. In their discussion, the authors described the 15 cases of Al-Hoqail and Crawford31 as follows: “although they noted the presence of significant lymphocytic epidermotropism and formation of Pautrier abscesses, the lymphocytes in this study were not immunophenotyped and there was no mention of a T-cell receptor study or exclusion from cutaneous T-cell lymphoma.”30(p991)

If lymphomatoid keratosis is to be included in a group of lichenoid keratotic reaction, then lichenoid actinic keratosis and benign lichenoid keratosis (including lichen planus–like keratosis) are important differential diagnoses. First, lichenoid actinic keratosis can be differentiated by the presence of atypical cells among basal cells and keratinocytes. Second, benign lichenoid keratosis can be ruled out by the presence of a reaction pattern including necrotic keratinocytes, Civatte bodies, Max-Joseph spaces, and surrounding adjacent solar lentigo or seborrheic keratosis without epidermotropism. To date, in major dermatopathology textbooks, lymphomatoid keratosis has not been considered a variant of benign lichenoid keratosis.29 30

Strictly speaking, in MF, only CD4+ T cells are epidermotropic, whereas in lymphomatoid keratosis, epidermotropic cells as well as infiltrating cells are composed of both T and B cells. The incidence of clonality in lymphomatoid keratosis may not be high, although it did exist in our study cases. In lichenoid keratosis, the essential feature is regression, and no clonality is evident.28 That is, lymphomatoid keratosis and lichenoid keratosis differ in their immunological microenvironment. The most important feature of lymphomatoid keratosis is the mobilization of B cells. The epidermotropism of B cells activates the epidermis, and thereafter scaly plaques may form on the surface of the skin. It has been reported that T-cell clonality, known as clonal dermatitis,31 is present in benign lichenomatoid conditions32: some lymphomatoid keratoses, which is a reactive process that histologically simulates MF, might possess T-cell clonality. Although there may be areas between lymphomatoid keratosis and benign lichenoid keratosis and between lymphomatoid keratosis and unilesional MF where the 2 entities show partial merging, we suggest that lymphomatoid keratosis should be differentiated from lichenoid actinic keratosis, benign lichenoid keratosis, and unilesional MF (Table 3). Our present findings indicate that lymphomatoid keratosis might be a reactive process that histologically simulates MF and that it should be considered a form of cutaneous lymphoid hyperplasia (pseudolymphoma) rather than benign lichenoid keratosis, which is characterized by a regressive process, or unilesional MF, which is characterized by a tumorous process.

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Correspondence: Eiichi Arai, MD, Department of Pathology, Saitama Medical School, 38 Morohongo, Moroyama-machi, Iruma-gun, Saitama 350-0495, Japan (e_arai@saitama-med.ac.jp).

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REFERENCES


Table 3. Comparison of Histological, Phenotypical, and Genotypical Differentiation of Lymphomatoid Keratosis, Lichenoid Actinic Keratosis, Benign Lichenoid Keratosis, and Unilesional Mycosis Fungoides

<table>
<thead>
<tr>
<th>Variable</th>
<th>Epidermotropism</th>
<th>Civatte Bodies and Max-Joseph Spaces</th>
<th>Bandlike Infiltration</th>
<th>Phenotypes of Lymphocytes</th>
<th>TCR Gene Rearrangement</th>
<th>Pathophysiological Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphomatoid keratosis</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>B and T</td>
<td>Partially +</td>
<td>Reaction to stimulus</td>
</tr>
<tr>
<td>Lichenoid actinic keratosis</td>
<td>-</td>
<td>+ (+)</td>
<td>-</td>
<td>Predominantly cytotoxic T</td>
<td>-</td>
<td>Regression</td>
</tr>
<tr>
<td>Benign lichenoid keratosis</td>
<td>- (+)</td>
<td>+ (+)</td>
<td>+</td>
<td>Predominantly cytotoxic T</td>
<td>-</td>
<td>Regression</td>
</tr>
<tr>
<td>Unilesional mycosis fungoides</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Helper T</td>
<td>+</td>
<td>Malignant proliferation</td>
</tr>
</tbody>
</table>

Abbreviations: TCR, T-cell receptor; +, with; −, without; + (−), usually + but sometimes −; − (+), usually − but sometimes +.


