Lymphomatoid Papulosis

Reappraisal of Clinicopathologic Presentation and Classification Into Subtypes A, B, and C

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Objectives: To analyze clinicopathologic features of lymphomatoid papulosis and delineate the characteristics of histopathologic variants (types A, B, and C).

Design: Retrospective nonrandomized study.

Setting: University-based dermatologic referral center.

Patients: Eighty-five patients with lymphomatoid papulosis. Clinical data and 1 or more biopsy specimens were available for review in all cases. When possible, immunophenotypic and molecular analyses were carried out.

Results: Of these patients, 78 presented only 1 histopathologic subtype of lymphomatoid papulosis (64 had type A, 3 had type B, and 11 had type C). The last 7 patients presented more than 1 subtype (1 had A and B, 5 had A and C, and 1 had A, B, and C). Two patients had regional lymphomatoid papulosis, an unusual clinical presentation characterized by groups of lesions localized to 1 anatomic region. We observed, we believe for the first time, that some histopathologic patterns, ie, follicular mucinosis (n=1), syringotropic infiltrates (n=1), epidermal vesicle formation (n=2), and syringosquamous metaplasia (n=1), were associated with lymphomatoid papulosis. A distribution along hair follicles, or follicular lymphomatoid papulosis, was observed in 5 biopsy specimens. A bandlike rather than a wedge distribution of the infiltrate was seen in 5 specimens from patients with lymphomatoid papulosis type A. Of 8 patients who had associated lymphoid malignancies, 4 had Hodgkin disease and 4 had mycosis fungoides.

Conclusions: Lymphomatoid papulosis is a cutaneous disorder with multiple clinicopathologic features. Differentiating between mycosis fungoides and anaplastic large cell lymphoma may be very difficult and sometimes impossible. In the spectrum of CD30+ cutaneous lymphoproliferative disorders, boundaries between these 2 entities are not clear-cut.

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The concept of disorders with a benign clinical course but a malignant appearance on histopathologic examination is controversial. Lymphomatoid papulosis (LYP), characterized by spontaneously resolving papules and nodules with strikingly atypical lymphoid cells, belongs to these disorders and has been a mystery since its description by Macaulay in 1968.1 Previously believed to be an inflammatory process, it is now regarded as an indolent cutaneous lymphoma and is listed as such in the current European Organization for Research and Treatment of Cancer and World Health Organization classifications.2-3 Clinical lesions of LYP vary from papules and nodules to—less commonly—vesicles and pustules, and while individual lesions usually resolve within weeks or months, the disease may recur for decades. In a minority of cases, association with other lymphoproliferative disorders such as mycosis fungoides (MF), anaplastic large cell lymphoma (ALCL), and Hodgkin disease (HD) has been reported.4-6 Based on histopathologic findings, 3 types, A, B, and C, differing in cytological and architectural features, have been delineated.7 We present a retrospective study of 85 patients with LYP to redefine the clinicopathologic subtypes and variants of this disease.

Methods

Patients

Eighty-five patients were identified from the database of the Department of Dermatology of the University of Graz as meeting the clinicopathologic criteria of LYP. A review of the clinical data assessed the following parameters: sex, age at diagnosis, morphology and localization of the lesions, disease status, and disease association with other lymphoproliferative disorders.
HISTOPATHOLOGIC STUDIES

Hematoxylin-eosin–stained sections of formalin-fixed, paraffin-embedded tissue from the 85 patients were analyzed. Specimens of second skin biopsies were available for 34 patients. We classified cases into 3 groups according to the following types:

Type A, or histiocytic type, when specimens displayed dense mixed infiltrates characterized by large atypical lymphocytes and neutrophils, eosinophils, histiocytes, and small lymphocytes. The large atypical cells did not form sheets or constitute more than 50% of the infiltrate.

Type B, or lymphocytic type, when specimens displayed a monomorphous infiltrate of small to medium-sized lymphocytes with cerebriform nuclei similar to those observed in MF. This variant has also been referred to in the literature as the MF-like type of LYP.

Type C, when specimens displayed cytologic features similar to those of type A, but the atypical lymphoid cells either formed sheets or large nodules or represented more than 50% of the infiltrate, simulating ALCL. This type has been referred to as borderline LYP-ALCL.

IMMUNOHISTOCHEMISTRY

Immunohistochemical analysis was performed on formalin-fixed, paraffin-embedded tissue sections using the following antibodies: CD4 (Novocastra, Newcastle-upon-Tyne, England; dilution, 1:30); CD8 (Dako Corp, Glostrup, Denmark; dilution, 1:25); CD30 (Dako; undiluted); CD56 (Novocastra; dilution 1:20); and T-cell intracellular antigen 1 (TIA-1) (Immunotech, Marseille, France; dilution, 1:50). Microwave heating with citrate buffer (for CD8, CD30, and TIA-1) or EDTA buffer (for CD4 and CD56) served as antigen unmasking. Positive preparations (of tonsil tissue) and negative preparations (with no primary antibody) were used as controls.

MOLECULAR STUDIES

Genotypic analysis of the T-cell receptor gamma (TCR-γ) chain gene via polymerase chain reaction (PCR) was performed in 18 cases following a method previously described. Two percent to 5% of total template DNA, isolated from formalin-fixed, paraffin-embedded, 5-µm-thick tissue sections, was amplified using consensus primers Vγ11 (250nM), Vy101 (250nM), and Jγ11 (500nM). The DNA was initially denaturated at 94°C for 10 minutes, and then amplified during 40 cycles of 60 seconds at 94°C, 40 cycles of 30 seconds at 50°C, and 40 cycles of 30 seconds at 72°C. The amplified PCR product was then run on a 3.5% Metaphor agarose gel (FMC BioProducts, Rockland, Me), stained with ethidium bromide, and viewed under ultraviolet light. A discrete band, compared with previously identified positive and negative controls, was indicative of rearrangement of the TCR-γ chain gene.

RESULTS

The number of lesions ranged from a few to several hundreds. Although most of them did not exceed 1 cm, in a few cases larger tumors were clinically reminiscent of ALCL. Spontaneous resolution occurred between a few weeks and a few months.

TYPE A

Clinical Findings

Sixty-four patients (75%) (41 men and 23 women; median age, 47 years; range, 4-84 years) showed features of the histiocytic type of LYP (Table 1). Three patients were younger than 19 years, and we observed age peaks in the second and sixth decade of life. A self-limited clinical course of disease was found in 13 (43%) of 30 patients with follow-up data, while 17 (57%) of these 30 patients had protracted disease with relapses of papules and nodules. Thirty-four patients were lost to follow-up. Papulonodular lesions confined to a single anatomic region, typical of regional LYP, were found in 2 patients (Figure 1).

Association With Non-Hodgkin Lymphoma. Two patients had a prior diagnosis of MF, with lesions of LYP developing 9 months and 10 years after diagnosis, re-

Table 1. Clinical Features of 85 Patients With Lymphomatoid Papulosis

<table>
<thead>
<tr>
<th>Type</th>
<th>No. of Patients</th>
<th>Sex, M/F</th>
<th>Median Age, y</th>
<th>Distribution, G/R</th>
<th>Association With Lymphoma, Before/After Onset</th>
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<td>47</td>
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<tr>
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</tr>
<tr>
<td>C</td>
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<td>3/8</td>
<td>38</td>
<td>11/0</td>
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<td>3/4</td>
<td>50</td>
<td>7/0</td>
<td>0/0 1/0 0/0</td>
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</table>

Abbreviations: ALCL, anaplastic large cell lymphoma; G, generalized; HD, Hodgkin disease; MF, mycosis fungoides; R, regional.

*In 42 patients histopathologic specimens showed epidermotropism in the background of a typical type A lesion; similar cases have sometimes been referred to as “overlapping type A/B.” Epidermotropism was found also in 10 patients with histopathologic features of lymphomatoid papulosis type C.
spectively. The first patient presented with a single plaque on the chest characteristic of a solitary variant of MF. This patient was in clinical remission for both diseases at the time of the study. The other one who had conventional MF was lost to follow-up. In 1 patient MF followed LYP after a period of 3 years. The patient was alive and well 9 years after diagnosis of LYP. Two patients with HD subsequently developed typical lesions of LYP. Both were lost to follow-up.

Histopathologic Findings. One hundred four specimens showed the characteristic histopathologic features of LYP type A (Table 2 and Figure 2). The infiltrate was wedge-shaped in 93 specimens. In the remaining specimens 2 different types could be discerned: one showed adnexotropic infiltrates with atypical lymphocytes clustering around hair follicles (n=5) or around eccrine ducts (n=1) (Figure 3), and the other had the cytologic characteristics of LYP type A but featured a bandlike rather than a wedge-shaped infiltrate (n=5) (Figure 4). Epidermal hyperplasia and epidermotropism of atypical lymphocytes were seen in 61 and 55 specimens, respectively. Small to medium-sized atypical lymphoid cells admixed to large pleomorphic lymphocytes were observed in 15 specimens. Multinucleated lymphocytes were found in 41 specimens. The atypical lymphoid infiltrate showed numerous mitotic figures in 41 specimens. The admixed infiltrate contained eosinophils and neutrophils in 70 and 86 specimens, respectively.

Additional Observations. Unusual and as yet unrecognized reaction patterns in LYP included the presence of follicular mucinosis (n=1) (Figure 5), syringotropic infiltrates (n=1), intraepidermal vesicle formation (n=1), and syringosquamous metaplasia (n=1). One patient with eruptive keratoacanthomas and typical

<table>
<thead>
<tr>
<th>Type</th>
<th>No. of Specimens</th>
<th>Sup/Deep</th>
<th>Bandlike</th>
<th>Adnex</th>
<th>Epidermal Changes</th>
<th>Follicular Mucinosis</th>
<th>Pleomorphic Cells</th>
<th>Admixed Infiltration</th>
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<tbody>
<tr>
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<td>93</td>
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<td>6</td>
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<td>55*</td>
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<td>0</td>
<td>16</td>
<td>13*</td>
<td>1</td>
<td>24</td>
</tr>
</tbody>
</table>

*Overlapping features characteristic of so-called composite types A/B and B/C.

Table 2. Histopathologic Features of 85 Patients With Lymphomatoid Papulosis

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Figure 2. Lymphomatoid papulosis type A showing wedge-shaped infiltrate (A) with characteristic large pleomorphic and anaplastic lymphocytes (B).

Figure 3. Syringotropic lymphomatoid papulosis with atypical cells along an eccrine duct with syringotropism of scattered atypical lymphocytes.
lesions of LYP type A developed collision lesions, in which atypical CD30+ lymphocyte–infiltrated keratoacanthomas were observed.

**Phenotype.** All specimens (n=68) tested for CD30 showed this antibody’s characteristically crisp cell membrane staining (Table 3). In 5 of 16 specimens most atypical lymphocytes expressed CD4, and in 6 of these 16 tissue sections atypical lymphoid cells showed predominant reactivity for CD8. Negativity for CD4 and CD8 was observed in 4 of the 16 specimens, and double positivity of these markers in 1 instance. Atypical lymphocytes were stained by CD56 in 9 of 22 specimens and by TIA-1 in 15 of 21 specimens. Clonal rearrangement of the TCR-γ chain gene was detected in 4 of 12 specimens.

**TYPE B**

**Clinical Findings**

We identified 3 patients (4%) with LYP type B (all were men; median age, 35 years; range, 29-54 years). Two of them still had waxing and waning lesions of LYP at the time of the study, while 1 patient was lost to follow-up; none of these 3 patients had associated lymphomas.

**Histopathologic Findings.** Eight specimens with characteristic features of LYP type B were available for histopathologic evaluation. The infiltrate was bandlike in 4 specimens. Four tissue sections displayed extension of the infiltrate into the deep reticular dermis, with a wedge-shaped configuration in 1 instance (Figure 6). Epidermal hyperplasia was found in 5 specimens. Epidermotropism of atypical lymphocytes was evident in all specimens (n=8). Atypical lymphocytes were small to medium-sized in all instances (n=8) and mitoses were rarely found. Five tissue sections revealed admixed eosinophils and 3 showed admixed neutrophils.

**Phenotype.** CD30 immunostaining revealed atypical lymphocytes in 3 of 5 tissue sections. Two specimens were tested for CD4 and CD8 (1 tested positive for CD4, and the other tested negative for both markers). Labeling of CD56 was observed in 1 of 2 specimens, and 1 of 1 tissue section tested positive for TIA-1. Genotyping revealed monoclonality of the TCR-γ chain gene in 1 of 4 specimens.

**TYPE C**

**Clinical Findings**

Characteristic findings of LYP type C were observed in 11 patients (13%) (8 women and 3 men; median age, 38 years; range, 7-68 years).

**Association With NHL.** One patient with a prior diagnosis of MF developed lesions of LYP type C after an interval of 10 years (Figure 7). Partial data about this patient were published previously. The patient died of systemic lymphoma 5 years after biopsy-proven LYP. Hodgkin disease was diagnosed 5 years before the occurrence of LYP type C in 1 patient. The current patient’s status is not known.

**Histopathologic Findings.** We reviewed 24 specimens with typical features of LYP type C (Figure 8). The infiltrate was both superficial and deep in 24 tissue sections, of which 9 showed a wedge-shaped configuration. Epidermal hyperplasia was found in 16 tissue sections.
Table 3. Immunohistochemical Features of 85 Patients With Lymphomatoid Papulosis

<table>
<thead>
<tr>
<th>Type</th>
<th>CD4⁺</th>
<th>CD8⁺</th>
<th>CD4⁺/CD8⁻</th>
<th>CD4⁺/CD8⁺</th>
<th>CD30</th>
<th>CD56</th>
<th>TIA-1</th>
<th>M-TCRγγ</th>
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<tbody>
<tr>
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<td>6/16</td>
<td>4/16</td>
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<td>16/16</td>
<td>3/6</td>
<td>4/5</td>
<td>1/2</td>
</tr>
</tbody>
</table>

Abbreviation: M-TCRγγ, monoclonal rearrangement of T-cell receptor γ chain gene.

Figure 6. Lymphomatoid papulosis type B showing wedge-shaped infiltrate (A) with predominance of small- to medium-sized pleomorphic lymphocytes (B). Epidermotropic atypical lymphocytes simulate mycosis fungoides.

Figure 7. Mycosis fungoides associated with lymphomatoid papulosis (type C). Erythematous patches and small plaques of mycosis fungoides on the trunk and upper extremities. Note erythematous papules of lymphomatoid papulosis at both axillae.

sections, and intraepidermal atypical lymphocytes in 13. We observed subepidermal vesicle formation in 1 instance. Small to medium-sized pleomorphic cells admixed to large atypical lymphocytes were found in 5 tissue sections, and multinucleated lymphocytes in 14. Twenty-nine tissue sections showed numerous mitotic figures. Eosinophils and neutrophils were found in 16 and 23 tissue sections, respectively.

**Phenotype.** CD30 stained atypical lymphocytes in all instances (16/16) (Figure 8C). A CD4⁺ phenotype was observed in one third of specimens, a CD8⁺ in one third, and a positivity for both in one third. Atypical lymphocytes were positive for CD56 in 3 of 6 tissue sections, while TIA-1 was detected in 4 of 5. Molecular analysis showed monoclonal rearrangement of the TCR γ-chain gene in 1 of 2 specimens.

**OVERLAPPING TYPES**

**Clinical Findings**

Seven patients (8%) (3 men and 4 women; median age, 50 years; range, 12-73 years) developed different types of LYP. The most common association was between LYP type A and C (5 cases). One patient had LYP types A and B, and 1 had lesions of histopathologic subtypes A, B, and C.

**Association With NHL.** One patient developed lesions of LYP type C 11 years after the diagnosis of HD and subsequently presented with findings characteristic of LYP type A. The patient was in clinical remission for HD but still had waxing and waning lesions of LYP.

**COMMENT**

We reviewed the clinicopathologic spectrum of LYP, shedding new light on the histopathologic variants and identifying so far unrecognized reaction patterns. In agreement with a previous observation, the median age of patients in our group was 44 years. Only 6% of patients (n = 5) were younger than 19 years. We therefore did not identify as many children as anticipated, which led us to the speculation that in some instances the onset of disease predated diagnosis. The 3 histopathologic subtypes of LYP, namely, A, B, and C, did not differ significantly concerning the age at onset of the disease.

One of the most vexing problems in the classification of LYP is the presence of different patterns—those that have been defined types A, B, and C—and their differentiation from other lymphomas such as MF and ALCL. Patients diagnosed with LYP type A constituted by far the largest group in our study (75%). The wedge-shaped mixed-cell infiltrate with variable numbers of large, atypical lymphocytes is readily recognizable, unless very early or late stages are encountered. Although LYP type B has been defined as “MF-like LYP,” histopathologic appearances over-
lapping with other types of LYP were observed. In fact, a bandlike rather than wedge-shaped infiltrate of atypical lymphoid cells was detected in 5% of type A lesions. Moreover, epidermotropism of pleomorphic lymphoid cells, a cardinal feature of LYP type B, was evident in more than half of type A and C cases. These cases have also been referred to as composite type A/B, or type B/C LYP. Our experience was that LYP type B should not be diagnosed unless a combination of characteristic cytologic as well as architectural features is found. Architectural features on their own do not suffice for a diagnosis of LYP type B. It is crucial to stress that differentiation of LYP type B from MF can only be achieved by clinicopathologic correlation, and that a diagnosis of LYP type B should never be established without complete clinical information. Immunohistochemical analysis with CD30 may not be helpful in distinguishing these disorders, especially if one considers reports of CD30-negative LYP type B. Such cases, however, should be carefully interpreted, because a papular variant of MF shows virtually identical histopathologic features. In our study, in agreement with other reports, we found CD30-positive intraepidermal lymphocytes in more than half of LYP type B cases. Although it might be difficult to accept the concept of a type of LYP devoid of large atypical lymphocytes—the hallmark of the disease described by Macaulay—a parallel with ALCL can be drawn. Even if large, anaplastic lymphoid cells are the rule in ALCL, in some cases the neoplastic infiltrate may harbor a predominance of small to medium lymphocytes, leading to the term “small-cell variant” of ALCL. Thus, it seems likely that the size of the cells alone is not sufficient to classify diseases of CD30+ lymphoproliferative disorders. In this context, it should be mentioned that in 7 patients (8%) we detected different LYP types from different biopsy specimens, underlying once more the overlapping histopathologic features of the subtypes of LYP. Moreover, this percentage may be larger, as not all patients had multiple or repeated skin biopsies.

Concerning LYP type C, the diagnosis is not always straightforward because of its close histopathologic resemblance to ALCL. The differential diagnosis between LYP and primary cutaneous ALCL, even from a clinical standpoint, may be extremely difficult, if not impossible. Primary cutaneous ALCL usually presents with a single nodule or tumor, but satellites in the vicinity of a larger nodule are occasionally found and may simulate the clinical picture of localized LYP. In addition, patients with ALCL may present with a widespread papular eruption rather than with a solitary lesion. Just as in LYP, lesions of primary cutaneous ALCL have the capacity to spontaneously regress, a phenomenon that accounted for the term regressing atypical histiocytosis in the earlier literature. Results from a large study on CD30+ lymphoproliferative disorders indicate that even the biological differences between LYP and ALCL limited to skin cells is less pronounced than expected, because in cases treated with chemotherapy relapses of skin lesions can occur regardless of the original classification. Taken together, LYP and ALCL only represent 2 ends of a spectrum, and it has to be recognized that there is a small group of patients who do not fit neatly in either of these categories. It seems likely that the spectrum of CD30+ cutaneous lymphoproliferative disorders, including LYP and ALCL, does not present clear-cut boundaries between these 2 entities.

Beside ALCL, there is a well-documented association of LYP with other lymphoproliferative disorders, especially MF and HD. In concurrence with other observations, 9% of patients in our study had associated lymphoproliferative neoplasms. However, the percentage may be higher because long-term follow-up was not always available. It is important to differentiate associated lymphomas preceding or following LYP, especially if one deals with MF. If there is a history of MF before the development of CD30+ cutaneous lymphoid infiltrates, transformation of MF to a CD30+ large cell lymphoma has to be considered. Unlike the favorable prognosis of LYP and primary cutaneous ALCL, transformed MF is usually associated with an aggressive clinical course. Differentiation of transformed MF from MF-associated LYP therefore carries profound clinical implications. Lesions with a LYP-like morphology following MF, therefore, should be interpreted with caution, as in some instances they may represent a transformation of MF. This might be true also for 1 of the patients in our study, who had MF and subsequently developed LYP type C, and who eventually died of systemic lymphoma. Unfortunately, data on molecular analysis of the MF and LYP lesions in this patient were not available, and we could not search for an identical clone, as has been described in the literature.

An unusual clinical presentation in our study was the observation of clusters of lesions localized to a single anatomic region in 2 patients. These cases of regional LYP are more often found in children than in adults. During the course of the disease dissemination of lesions to other body sites may occur, a feature that was not observed in our patients. We would also like to underline some unusual and yet never reported histopathologic features, including the presence of a syringotrophic—rather than pilotrophic—infiltrate, which was reminiscent of reaction patterns found

Figure 8. Lymphomatoid papulosis, type C. A and B, Sheets of large anaplastic lymphocytes evocative of the histopathologic appearance of anaplastic large cell lymphoma. C, Staining for CD30 shows positive atypical cells in sheets.
in cutaneous T-cell lymphomas such as MF. It is intriguing that we observed 3 additional reaction patterns well documented in MF, such as follicular mucinosis, intraepidermal and subepidermal vesicle formation, and syringosquamous metaplasia, probably reflecting the close relationship between these 2 lymphoproliferative disorders. From an immunohistochemical standpoint, results with CD56, being controversial in the literature, were interesting.

We observed positivity in almost half of the lesions irrespective of the histopathologic subtype. The frequency of CD56 expression differs also significantly in various publications on ALCL and some of the difference might be attributable to the use of different antibodies. Expression of TIA-1, similar to previous observations, ranged between 70% (type A) to 80% (type C). Clinically, cases with and without a cytotoxic phenotype did not behave differently. Although CD4 and CD8 expression was almost equally positive in lesions irrespective of the histopathologic subtype. The frequency of CD56 expression differs also significantly in various publications on ALCL and some of the difference might be attributable to the use of different antibodies. Expression of TIA-1, similar to previous observations, ranged between 70% (type A) to 80% (type C). Clinically, cases with and without a cytotoxic phenotype did not behave differently. Although CD4 and CD8 expression was almost equally positive in lesions irrespective of the histopathologic subtype.

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