Lymphomatoid papulosis in association with mycosis fungoides: A clinical and histopathologic review of five Taiwanese cases

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ABSTRACT

Background/Objectives: Lymphomatoid papulosis (LyP) is a cutaneous CD30+ lymphoproliferative disorder characterized by recurrent, self-healing lesions with a chronic clinical course. Approximately 10–20% of the patients have lymphomas, including mycosis fungoides (MF). LyP in association with MF is not well documented in Taiwan. We aimed to describe the clinicopathologic characteristics of LyP with MF in a Taiwanese case series of LyP.

Methods: A retrospective clinicopathologic study was performed on cases of LyP with MF diagnosed in our Department during the period 1990–2012. The diagnosis of LyP and MF were based on their characteristic clinical and pathologic features as well as correlation with the clinical course of the specific skin lesions.

Results: A total of 24 cases of LyP (10 males and 14 females, age 18–63 years, mean 40.4 years) were included. Multiple biopsies were often done in individual patients during the clinical course to establish the diagnosis of LyP and MF. LyP was further classified pathologically as type A (n = 16), B (n = 3), C (n = 3), and mixed type with A&B (n = 1) and A&C (n = 1). Five cases (21%) also had MF; two had juvenile-onset LyP and three had juvenile-onset MF (one with hypopigmented MF, one with hyperpigmented MF, two with CD8+ LyP, and two with CD8+ MF). In the case of juvenile-onset hypopigmented CD8+ MF, the patient developed CD8+ LyP 25 years after the onset of MF and died of aggressive epidermotropic CD8+ lymphoma involving the skin and lung.

Conclusion: MF occurred in five of the 24 cases (21%) in the present series of LyP. These five cases had several unusual clinical and pathologic features, including subtle or uncommon skin manifestation of MF and more frequent juvenile-onset and CD8 phenotype of LyP and/or MF lesions. Long-term follow-up and repeated biopsy of selected skin lesions are necessary for correct diagnosis and proper treatment of both diseases.

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INTRODUCTION

Primary cutaneous CD30+ lymphoproliferative disorders (PC-CD30+LPDs) are the second most common group of cutaneous T-cell lymphomas (CTCLs), next to mycosis fungoides (MF), and account for about 30% of CTCLs. The spectrum of PC-CD30+LPDs comprises primary cutaneous anaplastic large cell lymphoma (C-ALCL), lymphomatoid papulosis (LyP), and borderline cases.

LyP is a chronic, recurrent, self-healing papulonodular or papulonecrotic skin disease with infiltration of atypical CD30+ lymphocytes histologically. Clinically, the skin lesions of LyP typically wax and wane with spontaneous resolution in 3–12 weeks. The histologic findings of LyP are variable and three histologic subtypes (types A, B, and C) have been recognized with overlapping features; all three types may be observed in the same patient. Moreover, the age of the individual skin lesion at the time of biopsy also contributes to variability of histopathologic findings.

LyP type A (histiocytic) lesions are characterized by infiltration of scattered or small clusters of large, sometimes multinucleated, or Reed-Sternberg-like CD30+ cells intermingled with numerous inflammatory cells, such as histiocytes, small lymphocytes, neutrophils, and/or eosinophils. LyP type C (ALCL-like) lesions demonstrate a monotonous population or large clusters of large CD30+ T cells with relatively few inflammatory cells. LyP type B...
(MF-like) is uncommon (less than 10%) and is characterized by an epidermotropic infiltrate of small atypical lymphocytes with cerebriform nuclei similar to that seen in MF.

Two new variants of LyP have recently been described. LyP type D is characterized histopathologically by infiltration of medium-sized, CD8+CD30+ pleomorphic, atypical lymphocytes with marked epidermotropism in a pagetoid reticulosis-like pattern, mimicking primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma. LyP type E is characterized by self-healing, oligolesional papulonodules with necrotic eschar clinically, and an angiocentric/angiodestructive infiltrate of small- to medium-sized CD30+, and frequently CD8+, atypical lymphocytes.

In up to 20% of patients, LyP may be preceded by, associated with, or followed by malignant lymphomas, with MF, Hodgkin’s disease, and CD30+ large cell lymphomas comprising 90% of the associated lymphomas. In patients with LyP associated with MF, including three of 15 cases in the study by Basarab et al, and two cases each by Wood et al and Chott et al, identical clones have been reported in both types of lesions.

Reports of MF in association with LyP from Taiwan are rare. In this study, we aim to describe the clinicopathologic characteristics of cases of LyP with MF affecting Taiwanese.

Materials and methods

Cases of LyP diagnosed during the period 1990–2012 in the Department of Dermatology, National Cheng Kung University Hospital were retrieved from the Department’s Crux database system. In each case, the medical record, clinical photos, and pathology slides were reviewed. Specifically, the morphology (papules, nodules, patches, or plaques), onset and distribution of skin lesions, evolution of individual lesions (waxing and waning versus persistent) as well as the overall clinical course and treatment response were analyzed. Follow-up data were obtained from medical records, the Crux database, and by telephone contact with patients. All skin biopsy specimens were processed for routine histopathologic study. LyP lesions were classified as type A, B, or C based on the features delineated in the literature. Immunohistochemical stainings for CD3 (DakoCytomation Denmark A/S, Denmark), CD4 (BioSB, USA), CD8 (DakoCytomation Denmark A/S, Denmark), CD20 (DakoCytomation Denmark A/S, Denmark), CD30 (DakoCopenhagen Denmark A/S, Denmark), and granzyme B (Fremont, CA, USA) were performed in selected cases.

Results

Clinical presentations, clinical course, histology, and treatment

There were a total of 24 cases of LyP, consisting of 10 males and 14 females with age ranging from 18 years to 63 years (mean 40.4 years). Three patients had juvenile-onset LyP (defined by disease onset before 18 years of age). The LyP lesions were papulonodules, some with crust or necrotic centers. The skin lesions were widespread over the limbs and trunk in 18 patients (75%) and were more limited to the limbs and/or penis in six patients. Most of the LyP lesions waxed and waned, lasting for about 1 week in smaller lesions or up to 1 month in larger lesions. The clinical and pathologic features were summarized in Table 1. Of the 24 cases, LyP was classified as type A in 16 (67%), type B in three (13%), type C in three (13%), and two cases had more than one type: Case 1 with both type A and type B lesions, and Case 5 with both type A and type C lesions. Of these 24 patients, five (21%) also had MF and their LyP was type A in three (60%), type B in one (20%), and mixed type A + B in one (20%). The clinical presentations of these five cases are summarized in Table 2 and briefly described as follows.

Case 1

The patient was an 18-year-old male who had concurrent onset of both LyP and MF at 9 years of age. He first presented to us at the age of 18 years with a 9-year history of recurrent, self-healing
papulonodular lesions on the upper and lower extremities (Figure 1A and B), and persistent patch/plaque lesions on the right calf (Figure 1C). The papulonodular lesions waxed and waned and some nodules would become necrotic with central eschar (Figure 1B). He had six skin biopsies over a course of 28 months. Upon correlating with the clinical course of the lesions, the lesions were classified as LyP type A (1 specimen) (Figure 2A and B), LyP type B (4 specimens, 1 was a resolving lesion) (Figure 3A and B), and MF (1 specimen) (Figure 4A and B). Marked epidermotropism of lymphocytes was observed in all type B lesions. Angioinvasion was noted in a type B lesion and the MF lesion (Figure 4B). The atypical lymphocytes were CD8+ and CD30+ in the type A lesion and CD8+, CD30+, EBER-1+, and CD56– in the type B and MF lesions. Granzyme B was expressed in 10–20% of the CD30+ large atypical cells in the type A lesion. The patient also had some hypopigmented patches of varying sizes on the right upper limb (Figure 1A). Hypopigmented MF was suspected clinically, but was not confirmed pathologically. The LyP lesions in this patient did not respond to ultraviolet B (UVB) 311 phototherapy, but were effectively suppressed by low dose methotrexate (MTX) therapy (7.5 mg per week) with only occasional small papules developed from time to time during the follow-up period of 49 months.

**Case 2**

The patient, a 34-year-old female, presented with an 18-year history of generalized hyperpigmented patches (Figure 5A). Biopsy of a patch revealed changes of MF pathologically. With narrow band UVB311 therapy, the MF lesions resolved (Figure 5B) in 1 year. Approximately 1 year into her maintenance UVB therapy, we noticed for the first time a papule on her right lower leg (Figure 5C), which was biopsied and then confirmed to be LyP type B. She recalled that she had similar, but more widespread, erythematous papules since 13 years of age. The lesions would wax and wane with small papules resolving in about 2 weeks spontaneously, while larger lesions would take a longer time. The LyP lesions were not suppressed by UVB311 therapy and new lesions continued to appear from time to time over a 42-month period while she was receiving UVB therapy.

**Case 3**

A 32-year-old male presented with a 1-year history of recurrent, self-healing erythematous papules on the left arm. Biopsy of two papules revealed changes of LyP type A. When the patient returned 1 week after skin biopsy, the popular lesions had mostly resolved.
Close inspection then revealed a persistent hyperpigmented patch in the background skin. Another specimen was obtained from the patch, which showed early changes of MF. He recalled that the pigmented patch had been present for about 3 years. Both types of lesions affected the same circumscribed area of the left upper arm. The papular lesions were suppressed by low dose MTX treatment (7.5 mg per week), but he stopped treatment 2 months later. Since then, new papules would appear episodically in the same area and then resolve in 2–3 weeks. The MF patch remained persistent without obvious change during 3 years of follow-up.

Case 4

This case, except the final outcome, had been reported previously. Briefly, the patient was a 37-year-old male when he first visited us in 1996 for a recurrent, self-healing ulcerative eruption. Examination revealed multiple 0.5–2 cm erythematous papules and nodules with necrosis and ulceration on his trunk and extremities. Biopsies of three separate lesions revealed changes consistent with LyP type A (CD8+). Apart from the LyP lesions, he also had multiple persistent patches and plaques. He recalled that a persistent hypopigmented patch was first noted on his back at grade school. Gradually, red plaques appeared within the white patch over time, and additional plaques and patches developed elsewhere on the trunk and proximal extremities. Biopsy specimens from two persistent red scaly plaques within a large white patch on the right upper extremity revealed changes of MF. The biopsy specimen from the white patch on the back showed changes of the hypopigmented MF with prominent lymphocytic epidermotropism. Immunostaining of these three lesions revealed that the infiltrate consisted of CD4+ and CD8+ lymphocytes, and that over 50% of the lymphocytes in the epidermis and up to 40% in the dermis were CD8+.

He received systemic retinoids [etretinate or acitretin, 10 mg three times a day (tid)] and subcutaneous interferon alpha-2b (3 million units, three times a week) intermittently beginning in 1996. In 1999, about 28 years after onset of MF, erythematous to brownish infiltrating annular plaques began to appear on the extremities; most of these lesions developed central necrosis and then healed in weeks. However, a large infiltrating plaque on the left shin continued to grow and became ulcerated, covered by a large black eschar. Biopsy of an annular plaque in 2005 showed infiltration of atypical lymphocytes that were CD8+ but were negative for CD4, CD30, CD56, and EBER-1. The findings were consistent with CD8+ peripheral T-cell lymphoma. The necrotic

Figure 2 Pathological findings of LyP A Case 1. (A) A biopsy specimen of a LyP type A lesion reveals a superficial and deep, dense perivascular and peri-adnexal lymphocytic infiltrate in the dermis containing numerous medium to large atypical lymphocytes (hematoxylin and eosin; original magnification: 40×). (B) The atypical CD30+ lymphocytes in this infiltrate are highlighted by immunostaining (immunoperoxidase stain for CD30; original magnification: 400×). LyP = lymphomatoid papulosis.

Figure 3 Pathological findings of LyP B in Case 1. (A) A biopsy specimen of a type B lesion is characterized by prominent lymphocytic epidermotropism with infiltration of atypical lymphocytes at all levels of the epidermis, especially in the lower half (hematoxylin and eosin; original magnification: 100×). (B) Most of the intraepidermal lymphocytes are CD8+ (immunoperoxidase stain for CD8+; original magnification: 200×). LyP = lymphomatoid papulosis.
tumor on the shin was shown to be an ulcerated cutaneous CD8+ lymphoma with fusariosis, and then systemic chemotherapy after lung involvement by CD8+ lymphoma with fusariosis, and then systemic chemotherapy after lung involvement by CD8+ lymphoma with fusariosis. She had eight biopsies between 1997 and 2007. The eruption had been waxing and waning for 4 years. The patient was a 31-year-old female who first presented in 1997. The first two biopsies from two nodules revealed changes consistent with LyP type A. Two more biopsy specimens were obtained from persistent reticulated brownish lesions on both forearms in 2002 and showed changes of MF. Four additional skin biopsies were performed and revealed changes of LyP type A (2 specimens), type C (1 specimen), and early or late lesion of LyP (1 specimen). No evidence of extracutaneous lesions was detected by positron emission tomography. The patient had been treated over a 15-year period, starting with a low dose of MTX for about 4 months. Because the effect was not satisfactory, she was then treated effectively with psoralen ultraviolet A (PUVA) therapy for the following years except for a 2-year period of acitretin therapy. With PUVA therapy, only small numbers of new small papules would appear from time to time.

**Discussion**

In this report, we described 24 Taiwanese cases of LyP. Five (21%) of them also had MF, a rate comparable to the 10–20% reported in the literature. Of the five patients with LyP and MF, the LyP lesions were type A&B, B, A, A, and A&C, respectively. The MF in three of these patients had either subtle or unusual features clinically. One manifested as a single persistent patch where LyP lesions colocalized, one as hyperpigmented variant and one as hypopigmented variant. The onset of LyP and MF was concurrent in Case 1, and was LyP or MF first in the remaining four cases (Table 2). In Case 4, the patient with hypopigmented CD8+ MF, the CD8+ LyP and aggressive epidermotropic CD8+ lymphoma were fatal with pulmonary involvement. Although the aggressive CD8+ lymphoma in this patient could have been the result of malignant transformation of his longstanding MF, the atypical cells in the CD8+ lymphoma did not have the characteristics of MF with large cell transformation, specifically, the atypical cells were not of large cell type and were not CD30+ as commonly seen in lesions of MF with large cell transformation. Moreover, the MF lesions on the trunk and proximal extremities changed little over decades, while the infiltrative annular plaques on the lower extremities showed obvious progression in a few years. Therefore, based on the pathological findings, the clinical features and clinical course of the lesions, the aggressive CD8+ lymphoma in this patient was more likely to be a separate lymphoma from the longstanding MF.

Reports of LyP associated with MF in Taiwan are limited. In a recent series of 34 cases of LyP, the authors observed associated lymphoma in two cases (6%), both with ALCL. There was no mention of MF. In comparison, our series had a much higher rate of MF. However, it should be pointed out that the MF lesions were relatively subtle or of unusual presentation in our patients, and such lesions could easily be overlooked or misdiagnosed clinically and/or pathologically. Nonetheless, our effort in close monitoring of skin lesions clinically combined with repeated skin biopsy had allowed us to make the diagnosis of MF in addition to LyP.

LyP had been reported only rarely in children. The clinical picture and histopathology were similar to those in adults, but no malignant transformation has been documented in childhood-onset LyP, even if the disease carries on into adulthood. Of our five cases with LyP and MF, Case 1 and Case 2 had juvenile onset of LyP, and neither developed malignant transformation to ALCL. 13 years and 25 years, respectively, after onset of LyP.

Another feature worth noting is that three of our patients with LyP and MF (Cases 1, 2, and 4) had juvenile-onset MF, and two of the MF (Cases 1 and 4) was CD8+, including a case of hypopigmented MF (Case 4). Interestingly, the LyP was also CD30+ in the type B lesion in Case 1 and in the type A lesion in Case 4. CD8+ is an uncommon phenotype in MF with a reported rate of less than 5%. However, this phenotype is more common in juvenile-onset MF, up to 38% in a study of 34 cases with juvenile-onset MF. Notably, 71% of the CD8+ MF cases in that series manifested hypopigmented lesions. The over-representation of a cytotoxic phenotype in children with MF had also been reported by others.

Additional unusual features in the present study were the findings of prominent epidermotropism and angioinvasion in Case 1. Prominent epidermotropism was observed in all of his biopsy specimens of LyP type B and MF lesions, and angioinvasion was noted in a type B lesion and the MF lesion. There are two newly defined variants for LyP, namely, type D and E. The type D variant is characterized by CD30+, CD8+ with marked epidermotropism and the type E variant is characterized by CD30+ with...
angioinvasion/angiodestruction. Although there was prominent lymphocytic epidermotropism as well as angioinvasion in LyP lesions in Case 1, the infiltrating lymphocytes were CD8-positive, CD30-negative. Therefore, these lesions could not be classified as type D or E of LyP.

The optimal treatment for LyP has not been established and there is no evidence to suggest that the treatment can alter the natural course or malignant transformation. Because LyP lesions usually resolve spontaneously in 2–12 weeks, active treatment is optional and is generally reserved for symptomatic relief and cosmetic reasons. However, systemic agents or skin-directed treatments may be warranted in generalized disease. Topical treatment with carmustine, nitrogen mustard, MTX, imiquimod cream, intralesional interferon, low-dose cyclophosphamide, chlorambucil, medium-dose UVA-1 therapy, excimer laser therapy, photodynamic therapy, and dapsone have been reported to be helpful in disease suppression. Low-dose oral methotrexate (5–20 mg/week) is the most effective therapy to suppress the development of new skin lesions of LyP, but the disease often relapsed within months in most series, and treatment of LyP did not necessarily decrease the risk of development of a second hematological malignancy.

For patients with concurrent MF and LyP, the patients can be treated with a single agent therapy that is effective for both diseases, including topical steroids, topical nitrogen mustard ointment, oral weekly MTX, PUVA photochemotherapy, low dose interferon alpha, oral bexarotene, and electron beam radiation therapy. MF and LyP typically responded to therapy within 2–6 months. Topical steroids and nitrogen mustards are often only modestly helpful for LyP, mostly for newly emerged lesions. PUVA and systemic medications can suppress the formation of new lesions. For follow-up, some institutes recommended annual physical examination or sooner, including palpation of lymph nodes, liver, spleen, and laboratory tests for relapsed/progressive disease.

Patients with recurrent disease can undergo repeated courses of PUVA phototherapy before moving onto an oncologic approach. Most of our patients with LyP and MF were treated with UVB, PUVA, UVB311, MTX or topical steroids effectively, except one patient (Case 4) who did not receive regular treatment. He unfortunately developed fatal epidermotropic CD8+ lymphoma of the skin with pulmonary involvement years later.

Conclusion

MF was diagnosed in five cases (21%) among 24 cases of LyP affecting Taiwanese. These five cases had several unusual clinical and pathologic features, including subtle or uncommon skin manifestation of MF, and more frequent juvenile onset and CD8 phenotype of LyP and/or MF. Long-term follow-up and repeated biopsy of selected skin lesions are necessary for correct diagnosis and proper treatment of both diseases.

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