# A Patient with Concurrent Lymphomatoid Papulosis Subtypes C and F, Successfully Treated with Methotrexate

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**ABSTRACT:**
Lymphomatoid papulosis (LyP) is a rare subtype of primary cutaneous CD30+ lymphoproliferative disorders, characterized by a chronic, recurrent, asymptomatic, and self-healing papulonodular eruption. LyP is categorized into six major subtypes, composed of A, B, C, D, E, and a subtype with *DUSP22-IRF4* rearrangement. Recently, several authors have postulated the uncommon F (follicular) subtype. Patients with different histologic variants as well as mixed variants have been reported to share similar clinical manifestations, course of the disease, and prognosis. We report the first case of LyP with coexisting subtypes C and F.
A 42-year-old Thai man manifested with asymptomatic, self-healing recurrent skin-colored follicular and non-follicular papulonodules on his head and back. Some lesions developed into ulcers. Multiple skin biopsies showed two different patterns that were consistent with LyP subtypes C and F. Systemic staging workups were negative. He responded well to oral low-dose methotrexate. He had a regular follow-up for more than 5 years without evidence of secondary malignancy.
**Key words:** Lymphomatoid papulosis, Mixed subtypes, CD30+ lymphoproliferative disorders, Primary cutaneous T-cell lymphomas, Methotrexate

## Introduction

Lymphomatoid papulosis (LyP) is a rare subtype of primary cutaneous CD30+ lymphoproliferative disorders (pcCD30+ LPDs) characterized by asymptomatic, chronic, waxing and waning, self-healing erythematous papulonodular eruptions with histology similar to cutaneous lymphoma[1]. It is the second most common primary cutaneous T-cell lymphomas (CTCLs), comprising approximately 12% worldwide; nevertheless, only 1.5% were reported among Thai patients[1,2]. Most experts considered LyP a benign condition with an excellent prognosis and almost 100% 5-year survival rate. However, because of its lymphoma-like microscopic features, it is still categorized as a subtype of CTCLs. The histologic hallmark of LyP is the atypical CD30+ large lymphoid cell infiltrates. Nonetheless, this finding can be seen in other conditions, such as, anaplastic large cell lymphoma (ALCL), mycosis fungoides (MF) with CD30 expression, other lymphomas with CD30+ cells, and also benign inflammatory diseases. Thus, the clinicopathological correlation is crucial for the definitive diagnosis[3-5].

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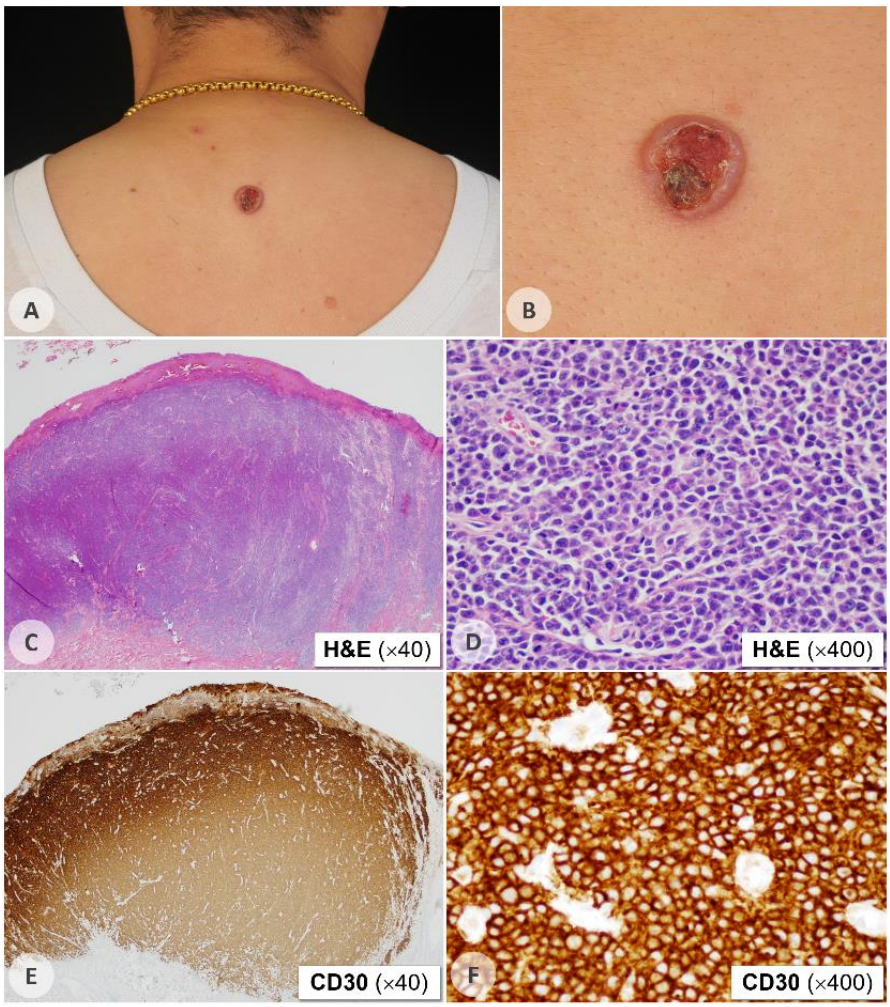


**Figure 1** The patient presented with solitary painless ulcerated erythematous papule on the back (A) and was 1 cm in size (B) at the first visit. Histologic study demonstrated dense cohesive infiltration in dermis by medium to large atypical pleomorphic lymphocytes with ulceration (C, D). The immunophenotyping revealed atypical lymphocytes with CD30 expression in sheet-like pattern (E, F).

LyP is divided into 5 classical histologic subtypes (A, B, C, D, and E) and a genetic variant with *DUSP22-IRF4* rearrangement. Other rare subtypes are not officially classified[3-5]. The follicular LyP or F subtype was first described in 1980[6]. Kempf et al. revealed that 10% of 113 LyP cases were of the F subtype, and most of them were previously diagnosed as LyP subtype A or C[7]. The histopathologic findings of the F subtype showed follicular involvement, mainly perifollicular infiltrates with or without folliculotropism. Follicular epithelium hyperplasia, hair follicle dilatation and rupture, follicular mucinosis, and intrafollicular pustules were occasionally reported[7-9]. To the best of our knowledge, this is the first case report of a LyP patient with concurrent subtypes C and F.

**Table 1** The histologic study, predominant immunohistochemistry, and differential diagnosis by histology of each LyP subtype[3-5]

| Histologic subtype | Histologic findings | Immuno-phenotypes | Differential diagnosis |
|---|---|---|---|
| **Type A** (~75-80%, most common) | Wedge-shaped infiltration by medium to pleomorphic large, atypical lymphocytes and mixed inflammatory cells | Predominated CD4+ with CD30+ | • Arthropod bite reaction<br>• Transformed MF<br>• PLEVA<br>• Hodgkin's lymphoma |
| **Type B** (<5%) | Epidermotropism with infiltration by small to medium atypical lymphocytes | CD4+ with variable CD30+ or negative | • Classical MF |
| **Type C†** (~10%, second most common) | Nodular cohesive infiltration in sheets by pleomorphic large atypical lymphocytes with small number of inflammatory cells | Predominated CD4+ with CD30+ | • pcALCL or sALCL<br>• Transformed MF<br>• ATLL<br>• HTLV1-associated lymphoma |
| **Type D** (<5%) | Epidermotropism with pagetoid infiltration by small to medium atypical lymphocytes | CD8+ with CD30+ | • pcCD8+ AECTCL<br>• Pagetoid reticulosis |
| **Type E** (<5%) | Angioinvasive infiltration by pleomorphic atypical lymphocytes with variable degree of necrosis and ulceration | CD8+ in most with CD30+ | • ENKTCL, nasal type<br>• pcGDTCL<br>• AITL<br>• PTCL |
| **Chromosome 6p25.3 (*DUSP22-IRF4*) rearrangement** (<5%) | Infiltrations in biphasic growth pattern; epidermotropism with small lymphocytes and large pleomorphic atypical lymphoid cells in the dermis | CD4-CD8- or CD4-CD8+ with CD30+ | • Transformed MF<br>• Pagetoid reticulosis<br>• pcALCL or sALCL |
| **Unofficially type F or follicular subtype†** | Perifollicular infiltration mainly by atypical lymphocytes with neutrophils and eosinophils coexisting with variable degree of follicular destruction and follicular mucinosis | CD4+CD8+ with CD30+ | • Folliculotropic MF<br>• pcALCL or sALCL<br>• Pseudolymphoma |

†, as seen in our case; AITL, angioimmunoblastic T-cell lymphoma; ATLL, adult T-cell leukemia/lymphoma; ENKTCL, extranodal natural killer/T-cell lymphoma; HTLV-1, human T-cell lymphotropic virus type 1; MF, mycosis fungoides; pcCD8+ AECTCL, primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma; pcGDTCL, primary cutaneous gamma-delta (γδ) T-cell lymphoma; pcALCL, primary cutaneous anaplastic large cell lymphoma; PLEVA, pityriasis lichenoides et varioliformis acuta; PTCL, peripheral T-cell lymphoma; sALCL, systemic anaplastic large cell lymphoma

## A case report

A 42-year-old Thai man presented with a solitary asymptomatic, skin-colored papule on his back for 2 months. The lesion became centrally eroded and gradually enlarged to approximately 1 cm in size (Figure 1A, B). He had no fever, fatigue, weight loss, or constitutional symptoms. The excisional biopsy demonstrated a dense diffuse infiltrate dominated by medium- to large-sized, atypical lymphocytes in the dermis. The immunohistochemistry (IHC) revealed sheets

of CD30+ALK- atypical lymphocytes with CD3+CD4+CD8-CD20- (Figure 1C-F). The complete blood count and complete metabolic panel, including lactate dehydrogenase, were unremarkable. According to the staging workup, no lymphadenopathy was discovered. A bone marrow biopsy revealed no involvement. These findings suggested a working diagnosis of pcCD30+ LPDs. Remarkably, these lesions spontaneously resolved within 2 months, leaving atrophic scars. The final diagnosis of LyP subtype C was established, according to the self-limiting course. The patient was treated with topical and intralesional corticosteroids, then he was lost to follow-up.

One year later, the patient revisited with recurrent crops of asymptomatic papules on his occipital scalp for 2 months. He was healthy otherwise. Two different morphologies of the cutaneous lesions were observed. Physical examination showed a few ulcerated discrete erythematous papules with central scabs, measuring 0.2-0.5 cm in size, and multiple tiny follicular and non-follicular skin-colored papules on the posterior aspect of the scalp (Figure 2A-C). Two biopsies were performed. An ulcerated erythematous papule (Figure 2B) revealed identical immunohistopathogy to the first biopsy (Figure 2D-G). The section of a tiny follicular skin-colored papule (Figure 2C) demonstrated a folliculocentric infiltration by medium- to large-sized, atypical lymphocytes without epidermotropism. The IHC showed CD30+ALK- with CD3+CD4+CD8-CD20- atypical lymphocytic infiltration (Figure 2H-L). No significant laboratory abnormality was detected.

Finally, he was diagnosed as LyP with dual variants of classical subtype C concurrent with subtype F. The patient was initially on methotrexate 10 mg/week. He became a partial response in a few months. The disease was successfully controlled by oral methotrexate 5-10 mg/week with adjunct topical corticosteroids. However, the lesions tended to recur after stopping methotrexate; varying in time according to disease activity. He has been followed up regularly, and no secondary malignancy has been detected for more than 5 years.

**Discussion**

LyP is a chronic, relapsing, and self-limiting cutaneous eruption without systemic involvement. Despite its undoubtedly excellent prognosis, it is classified as a subtype of pcCD30+ LPDs, under the umbrella of CTCLs. Notably, spontaneous regression is a key characteristic.

As mentioned earlier, LyP is officially divided into 6 subtypes. There are no clinical clues suggested for the diagnosis of certain variants. Each subtype has distinct histologic features and they can mimic various dermatoses (Table 1). Therefore, it is critical to distinguish LyP from such diseases because of the difference in prognosis between LyP and some imitators. LyP subtype A is the most common (75-80%), followed by subtype C (10%). There are no differences in the clinical manifestations, natural course, or prognosis among different LyP subtypes, or even the dual subtypes[3-5]. Understanding and knowledge of the clinicopathological correlation of LyP are essential for making an accurate diagnosis.

Our patient initially presented with a 2-month history of a solitary, asymptomatic papulonecrotic nodule (Figure 1A, B). The skin biopsy revealed a dense and diffuse atypical lymphocytic infiltration with a strong expression of CD30+ T cells in a sheet-like pattern (Figure 1C-F). The differential diagnosis at that time included LyP subtype C, primary cutaneous ALCL (pcALCL), systemic ALCL (sALCL), and MF with large cell transformation (LCT).

Microscopically, LyP, pcALCL, and sALCL can all show the same results. Clinically, the majority of LyP lesions have a diameter of less than 2 cm and often go away completely in a

few weeks to a few months. In our patient, it is challenging to distinguish between LyP and pcALCL based on clinicopathological correlation from the first biopsy and we may not know if it may be self-healing. The diagnosis of "borderline lesions" can be utilized as a working diagnosis for cases that overlap LyP and pcALCL features. Recurrent eruptions and repeat skin biopsies can aid in making a definite diagnosis.

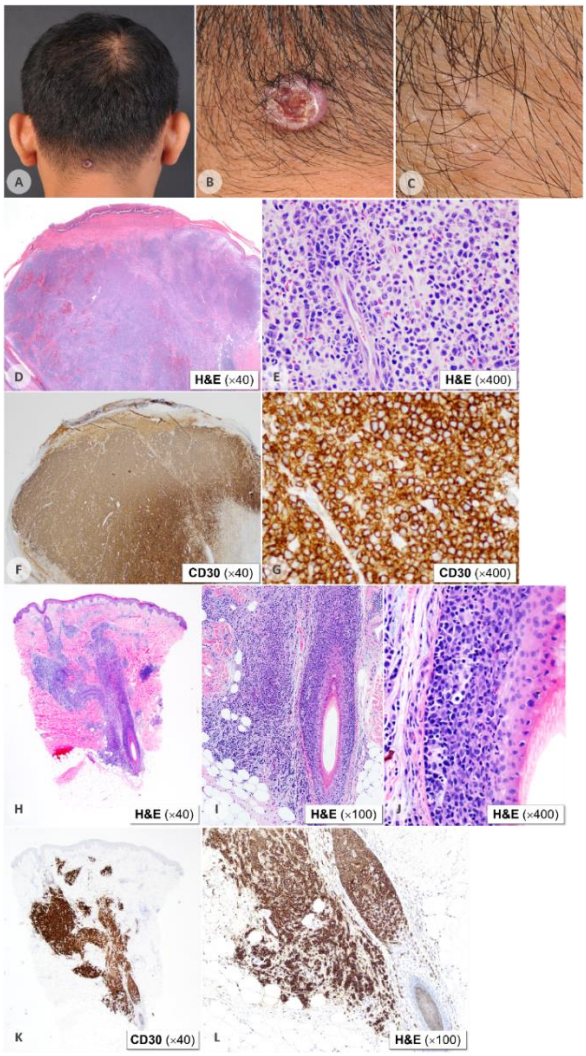


**Figure 2** The patient had lesions with 2 different morphologies for the second episode (A): discrete ulcerated erythematous papules with a central scab (B) and multiple tiny follicular and non-follicular skin-colored papules on the occipital area (C). Histopathology from an ulcerated erythematous papules (B) revealed a dense dermal infiltrates mainly by medium- to large-sized atypical lymphocytes with ulceration (D, E). The immunohistochemistry displayed sheets of CD30+ atypical lymphocytes (F, G). Histology from a tiny follicular skin-colored papules (C) showed a dense perifollicular infiltrate with follicular involvement by medium to large atypical lymphocytes (H-J) with strong CD30 expression (K, L).

The diagnosis of our patient was initially compatible with borderline lesions of LyP and pcALCL. Subsequently, he had recurrent crops of self-healing papulonecrotic lesions, with a skin biopsy confirming the diagnosis of LyP subtype C. According to NCCN guidelines version 1.2023, a complete staging workup is not indicated in classical LyP cases, but it is recommended in atypical LyP cases[10]. Since LyP subtype C and ALCL share similar histopathology, a complete staging workup is necessary to exclude systemic disease in this patient. A negative ALK and a negative systemic staging workup can help to exclude sALCL. Given MF with LCT was on the list of differential diagnoses. MF and LyP can occur concurrently. The absence of prior patches or plaques was helpful to exclude MF with LCT. Despite the fact that CD30 expression levels in MF range from 1 to 50% with no clear cut point, CD30+ T cells in transformed MF rarely reach 75%[11].

The follicular scalp lesions (Figure 2C) as well as the characteristic immunohisto-pathology (Figure 2H-L) supported the diagnosis of LyP subtype F in our patient. The diagnosis of LyP subtype F is challenging and may be underdiagnosed. The skin manifestations are indistinguishable from other classical LyP subtypes, but they tend to affect hair follicles. The differential clinical diagnosis includes simple folliculitis, arthropod bite reactions, folliculotropic MF, and pityriasis lichenoides. The histologic hallmarks of follicular LyP are folliculocentricity and perifollicular infiltrates by atypical CD30+ lymphocytes. Folliculotropism, follicular mucinosis, dilation, hyperplasia, rupture, or neutrophilic infiltrates with pustular collection can be observed[6-9].

Our patient initially had chronic recurrent LyP subtype C, then developed mixed LyP subtypes C and F. To the best of our knowledge, this is the first case report of these two subtypes coexisting. The coexisting LyP variants are extremely rare. There is no distinction between single and mixed subtypes of LyP in terms of clinical manifestation, prognosis, or recommendation of treatment[3-5].

A previous cohort reported that 4.4% (8/180) of the patients had mixed subtypes, with type C (6/8) being the most common co-subtype among variants[12]. Patients with concurrent LyP subtypes may be underreported due to a lower biopsy rate. The risk of having a second cancer in LyP patients has been shown to range from 5% to 52%[3,5,12]. The most common secondary lymphomas are MF, followed by pcALCL. It should be noted that most secondary lymphomas in LyP are also its mimickers. The clinicopathological correlation is crucial, and lifelong follow-up is recommended.

The treatment for LyP may accelerate the healing of the lesions but does not affect the clinical course. In asymptomatic cases, observation is usually advised. Skin-directed therapy is recommended for patients with symptoms or cosmetic concerns. Methotrexate at a low dosage of 10-35 mg weekly is commonly used, with good response and tolerability. However, some patients became methotrexate-dependent[12]. Our patient responded well to oral methotrexate 5-10 mg/week combined with moderate potency topical corticosteroids, but the lesions tended to recur when methotrexate was discontinued.

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