Early stage mycosis fungoides with focal CD30-positive large cell transformation

Po-Ju Lai 1,2, Yu-Ping Hsiao 1,3, Jeng-Dong Hsu 4, Shiow-Jiuan Wey 1,*

1 Department of Dermatology, Chung Shan Medical University Hospital, Taichung, Taiwan, ROC
2 Institute of Biochemistry and Biotechnology, Chung Shan Medical University, Taichung, Taiwan, ROC
3 Institute of Medicine, School of Medicine, Chung Shan Medical University, Taichung, Taiwan, ROC
4 Department of Pathology, School of Medicine, Chung Shan Medical University, Taichung, Taiwan, ROC

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A B S T R A C T

Mycosis fungoides (MF) is typically an indolent disease except when large cell transformation (LCT) occurs. The incidence of LCT has been reported to range from 6% to 23% under the criterion of the presence of more than 25% of large cells in a biopsy of typical MF lesions. LCT is more common in advanced-stage MF, but very rarely found in its early stage. Herein, we present a 45-year-old woman with patch stage MF (Stage IB) who developed a papule within one patch, which revealed large cell transformation with expression of CD30 immunostaining on histopathology. The patient then received phototherapy with narrow-band UVB. The skin lesions regressed quickly and no new skin lesions had been noted during the 6-month follow-up. Intense monitoring for recurrence and extracutaneous involvement is still recommended. In this article, we also review the published articles of mycosis fungoides with CD 30-positive large cell transformation and analyze the clinicopathological and prognostic features.

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Introduction

Mycosis fungoides (MF) comprises about 65% of cutaneous T-cell lymphomas. 1 It generally presents with an indolent course and a long evolution, with years to decades elapsing before patches or plaques progress to tumor stage. Large cell transformation (LCT) in MF has been defined by the presence of large cells (at least four times larger than a small lymphocyte) exceeding 25% of the total lymphoid infiltrate or forming microscopic nodules. 2 LCT is often found in advanced-stage disease (≥ Stage IIB) and is very rare in the early stage (< Stage IIA). 3 LCT in MF is associated with an aggressive course and poor prognosis. 3 Large transformed cells may be positive for CD30 or not. 4 Herein, we reported a patient with Stage IB MF, who also showed focal CD30-positive LCT.

Case report

This 45-year-old woman, without major systemic diseases, presented with multiple asymptomatic reddish rashes over the left forearm, left flank, buttocks, and thighs for 10 years. The rash first appeared on the left forearm and slowly extended to the left flank, buttocks, and thighs. She had visited a local practitioner's clinic where she was diagnosed with eczema, but did not respond to treatment. Approximately one year earlier, one reddish papule arose from the reddish patch over her left flank and showed no regression.

Skin examination revealed multiple asymptomatic, scaly, wrinkling, mottled reddish and hypopigmented patches over the left forearm, left flank, both buttocks and thighs (Figure 1A, B and C). About 15% of the total body surface area was involved. Additionally, one reddish papule located within reddish patches over the left flank was also noted (Figure 1B). Review of the patient's history over the previous 10 years indicated absence of fever, chills, or body weight loss. There were no palpable lymph nodes or hepatomegaly. Results of a complete blood count, liver function, and lactate dehydrogenase were within normal limits. The peripheral blood did not show atypical lymphocytes. Chest x-ray revealed no significant findings. Total body positron emission tomography indicated no abnormal uptake in visceral organs.

Histopathology of a biopsy specimen from a reddish patch over the left flank demonstrated mild infiltration of atypical cerebriform lymphocytes at the dermal-epidermal junction with focal epidermotropism (Figure 2A and B). The cells were positively stained with CD3, CD4, and CD8, but negative for CD20 and CD30 (Figure 2C–F). Another skin biopsy was taken from the reddish
papule over the left flank, and the histopathological examination showed diffuse intradermal lymphocytic infiltration with large pleomorphic and hyperchromatic lymphocytes (Figure 3A–C). The cells were positively stained with CD3 and CD4, and focally with CD8 (Figure 3D and E), but negative for CD20. Of all infiltrating atypical lymphocytes, about 60% were large cells. They were strongly positive for CD30 (more than 75% of large cells) (Figure 3F), but negative for anaplastic lymphoma kinase and CD68. Polymerase chain reaction of skin biopsy from the reddish patch over the left flank showed clonality of the T-cell receptor \( \gamma \) gene rearrangement.

Based on the clinical manifestation and histopathological findings, the patient was diagnosed with MF with focal CD30-positive LCT. The staging of disease was T2N0M0, Stage IB. The patient then received topical steroid and narrow-band UVB phototherapy. Her skin lesions regressed quickly and no new lesions were noted at the 6-month follow-up.

Discussion

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphomas. Generally, the clinical manifestation shows three phases—patch, plaque, and tumor stage, and typically runs an indolent course with a long evolution over years to decades. However, with disease progression, a small number of cases develop a morphologic change (large cell transformation), especially more common in the advanced stage of disease. The diagnosis of large cell transformation (LCT) in MF always relies on histologically defined criterion: the presence of large cells exceeding 25% of the total lymphoid infiltrate or forming microscopic nodules. Mycosis fungoides with LCT usually portends an aggressive course and shortened survival. Diamandidou et al reported shorter median survival for patients with LCT in MF (37 months), compared with nontransformed MF (163 months). Arulogun et al also indicated a lower 5-year survival rate for LCT group than nontransformed group of MF patients, 32.5% versus 53.6%. Although the molecular mechanism for LCT has not been fully demonstrated, molecular studies have confirmed that large cells are derived from the original T-cell clone in MF.

Although the histological criterion for the diagnosis of LCT in MF has been well defined, making a definite differential diagnosis is still sometimes challenging. MF with focal CD30-positive LCT should be differentiated from other CD30 positive lymphoproliferative disorders, including primary cutaneous anaplastic large cell lymphoma, lymphomatoid papulosis (LyP), and borderline cases. Primary cutaneous CD30+ lymphoproliferative disorders typically have an excellent prognosis with a disease specific 5-year survival of 85% to 100%. However, CD30 positive LCT in MF has worse outcome with a 5-year survival of 28.6% to 44.4%. Meanwhile, the clinical manifestations are obviously different between CD30 positive LCT in MF and primary cutaneous CD30 positive lymphoproliferative disorders. Coexisting MF and LyP is found in 9% of patients with LyP, and represents 3% of MF patients. Many studies show MF with concurrent LyP leads an indolent course and has a favorable prognosis. The clinical course of LyP with concurrent MF is also similar to that of LyP, and the skin lesions tend to regress spontaneously and then recur. By contrast, CD30+ LCT in
MF rarely show spontaneous remission. Besides, LyP could arise from normal skin and/or previous MF lesions, while CD30+ LCT always develops upon pre-existent MF lesions. The coexistence of MF and CD30-positive anaplastic large cell lymphoma (ALCL) has also been reported previously, but, as shown in these cases, the two diseases invariably appear in separate locations and run independent clinical course. The diagnosis of CD30 positive LCT in MF should be made when newly-onset papules or nodules arising from the prior MF lesions are seen clinically, and cerebriform T lymphocytes admixing with <75% of CD30 positive large cells are shown histopathologically. If >75% of large cells have CD30 expression, it is very difficult to distinguish CD30+ LCT in MF from MF associated with CD 30+ lymphoproliferative disorder. In such a situation, Vergier et al indicated the clinical evolution may help us discriminate between these two entities.

Applying this to our patient, we observed one reddish papule developing upon the previous typical MF lesion (clinical evolution), which had not shown spontaneous remission for one year. Dissimilar to LyP, which typically manifests chronic recurrent self-healing papules and nodules that inevitably regress, the clinical course of the reddish papule in our patient showed no spontaneous necrosis or regression. The microscopic examination of a biopsy specimen from the reddish papule in our case revealed infiltration of mononuclear cells mixed with large atypical cells in the upper dermis, and focal epidermotropism of atypical mononuclear cells in the epidermis. There were hardly any neutrophils or eosinophils within the intradermal mononuclear infiltrate. Around 60% of the lymphocytic infiltrates were large pleomorphic and hyperchromatic, with about 90% of those large cells being CD30+. Compared to ALCL, in which the tumor cells commonly extend into the subcutaneous fat or deeper tissues, or LyP, the infiltrate of which often contains large anaplastic cells mixed with neutrophils, eosinophils, plasma cells, lymphocytes and histiocytes, the histopathologic findings of the present case do not match any type of LyP and were not compatible with ALCL. The combination of histological findings and clinical evolution leads to the diagnosis of early stage MF (Stage IB) with focal CD30-positive large cell transformation.

Reviewing the literature, treatments for LCT in MF were heterogeneous and dependent on the clinical stage. For patients with early stage MF, skin-directed therapy including topical corticosteroids, topical nitrogen mustard, light therapy and radiation therapy had been used. One patient presenting with
focal LCT in MF (stage IB) was treated with topical steroid and topical nitrogen mustard, and the lesions almost totally resolved after 2 to 3 months of therapy. Another patient who was diagnosed with LCT in MF (Stage IIB) received electron beam radiation, and no local recurrence or distant metastasis has been noted for 1 year. In our case, the reddish papule was surgically removed first. For residual skin lesions, we suggested PUVA, the first-line treatment for early stage MF, which our patient declined because of its carcinogenic potential. Local radiation was not suitable for multiple skin lesions. Therefore, we administered narrow band UVB phototherapy, which is also effective in management of early stage MF, and her skin lesions regressed quickly with no new skin lesions noted at the 6-month follow-up.

According to the previously published articles, several prognostic factors of large cell transformation in MF have been mentioned. Diamandidou et al reported early transformation (<2 years from the diagnosis of MF) and more advanced disease at transformation (Stage IIB–IV vs. Stage I–IIA) were associated with a poor outcome, while an older age (>60 years) and the presence or extracutaneous spreading (Stage IV) were related with a poor prognosis as indicated by Vergier et al. Although median survival for patients with LCT in MF is markedly shortened, CD30+ large cell

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Table 1
Comparisons of previous studies reporting the incidence of large cell transformation (LCT) in mycosis fungoides (MF).

<table>
<thead>
<tr>
<th></th>
<th>Salhany et al</th>
<th>Greer et al</th>
<th>Diamandidou et al</th>
<th>Vergier et al</th>
<th>Barberio et al</th>
<th>Arulogun et al</th>
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<td>No. of mycosis fungoides</td>
<td>92</td>
<td>113</td>
<td>115</td>
<td>419</td>
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<td>NA</td>
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<td>9</td>
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<tr>
<td>No. of LCTs in early-stage MF</td>
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<td>7</td>
<td>2</td>
<td>7</td>
<td>3</td>
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NA — not available.
diagnosis, we should pay special attention to both clinical and histologic findings. Close observation and systemic surveys are also essential to the evaluation of MF patients. When clinical evolution with changing skin lesion occurs, we need to perform skin biopsy and systemic evaluation to determine the disease status. Thorough explanation to the patient about the disease prognosis and the necessity of regular follow-ups should also be emphasized.

### References


