Regression of CD30-positive large cell transformation arising on patch lesion of early mycosis fungoides

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1 | INTRODUCTION

We present the case of a patient with patch-stage mycosis fungoides who developed ulcerative tumors compatible with large cell transformation. Tumor cells were positive for CD30 and CXCR3 and negative for CCR3, and subsequently exhibited spontaneous regression. Thus, large cell transformation in early mycosis fungoides may not indicate poor prognosis.

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma. Although most MF cases show indolent clinical courses, some cases exhibit severe progression. Prior studies have demonstrated that the prognosis for patients with MF depends on several parameters, including age, clinical stage, and specific factors such as large cell transformation (LCT). LCT is diagnosed based on large cells (whether CD30 positive or negative) constituting >25% of the infiltrate or forming microscopic nodules within the MF lesion. LCT of MF (MF-LCT) has been observed in 2.3%-22.6% of MF patients during the course of the disease. Notably, previous studies reported the development of LCT in 21.3%-31.0% of advanced-stage patients, but in only 1.4% of early-stage patients. Thus, MF-LCT usually is associated with an advanced stage of the disease.

CD30 is a cell membrane protein of the tumor necrosis factor receptor family. CD30 is expressed in activated T cells and used as a tumor marker. Neoplastic proliferation of CD30+ lymphocytes in the skin is observed in MF-LCT and CD30+ lymphoproliferative disorders (LPDs) such as lymphomatoid papulosis (LyP) and primary cutaneous anaplastic large cell lymphoma (PC-ALCL). Most LyP cases and about 20% of PC-ALCL cases spontaneously regress with excellent prognoses. However, spontaneous regression of MF-LCT has been reported only rarely. Here, we present a case showing spontaneous regression of MF-LCT in patch-stage MF.

2 | CASE REPORT

A 46-year-old Japanese woman was referred to us with a 2-year history of multiple areas of erythema measuring 1-10 cm in diameter (Figure 1A, B). The patient had been treated using topical steroids and narrow-band ultraviolet B irradiation for 2 years in another clinic. Peripheral blood tests showed a normal hemogram and a normal range of soluble interleukin-2 receptor; the patient was seronegative for anti-human T-cell leukemia virus type-1 antibody.
Histopathological examination revealed that small-sized atypical lymphocyte-like hyperchromatic cells with haloes had infiltrated into the epidermis and upper dermis in a scattered manner (Figure 1C). Tumor cells were primarily positive for CD4 but negative for CD30. The patient was diagnosed with patch-stage MF. Symptoms were well controlled by topical steroids and narrow-band ultraviolet B irradiation therapy.

Two years later, the patient noticed two rapidly growing tumors located on the MF patch lesion in the left chest; the tumors had formed necrotic ulcers measuring 2-4 cm in diameter (Figure 2A). Peripheral blood tests showed a normal hemogram and normal range of soluble interleukin-2 receptor. Imaging examinations revealed no invasion into the viscera. Histopathological examination showed nodular infiltration in the dermis and subcutis with necrotic changes in the epidermis (Figure 2B). Anaplastic large cells (≥4 times the size of a small lymphocyte) had formed nodular nests in the dermis and subcutis (Figure 2C). Small-sized atypical lymphocyte-like cells also had formed nodular nests, primarily in the subcutis (Figure 2D). Most tumor cells were positive for CD3, CD4, and MIB-1 (Ki-67). Anti-CD30 antibodies were reactive to the anaplastic large cells (Figure 2E, F), which comprised ≤75% of the tumor cells, but not to the small-sized atypical lymphocyte-like cells (Figure 2G). The anaplastic large cells were reactive to antibodies against C-X-C motif chemokine receptor 3 (CXCR3) (Figure 2H), but not to antibodies against C-C chemokine receptor type 3 (CCR3) (Figure 2I). Based on these data, a diagnosis of MF-LCT in the patch stage was made. Three months after their original appearance, the tumors spontaneously regressed, leaving scars (Figure 2J). In the year since, no recurrence has been observed.

3 | DISCUSSION

The ulcerative tumors occurring in our patient with MF should not be associated with the tumor stage of typical MF. Typical MF progresses slowly from patch stage to tumor stage through plaque stage over several years, but the tumor lesions in our patient occurred suddenly and grew rapidly. Therefore, the present case is incompatible with the tumor stage of MF.

The ulcerative tumors that occurred in our patient are compatible with MF-LCT rather than CD30 + LPDs such as PC-ALCL based on the following criteria: (a) LCT develops on pre-existing MF lesions, and (b) LCT consists of CD30 + large cells, which comprise ≤75% of tumor cells, and small-sized atypical lymphocyte-like cells.15,16 Recently, several studies have distinguished between PC-ALCL and LCT as follows: (a) PC-ALCL cells exhibit strong expression of CCR3 and weak expression of CXCR3, while, in contrast, (b) MF cells exhibit strong expression of CXCR3 and weak expression of CCR3.17-19 In our case, more than 25% and less than 75% of the tumor lesions located on patch lesions consisted of small-sized atypical lymphocyte-like cells and CXCR3-positive, CCR3-negative anaplastic large cells, respectively. Based on these findings, the diagnosis of MF-LCT was confirmed.

Our case shows unique features: LCT occurred in early MF and regressed spontaneously. With regard to LCT in
FIGURE 2  Clinical manifestations during the course of the disease. A, Macroscopic findings at two years after the first visit. Two ulcerative tumors are evident on MF patch lesions of the left chest. B, Histopathological findings of the tumor (hematoxylin-eosin stain, loupe image). Nodular infiltration of tumor cells is evident in the dermis and subcutis. C, Histopathological findings of the tumor (hematoxylin-eosin stain, ×400). Some nests consist of anaplastic large cells. D, Histopathological findings of the tumor (hematoxylin-eosin stain, ×400). Small-sized atypical lymphocyte-like hyperchromatic cells have proliferated in the tumor. E, Immunohistochemical examination of the tumor using anti-CD30 antibody (Roche, Basel, Switzerland) (loupe image). Anti-CD30 antibodies are reactive to nearly half of the cells in the tumor. F, Immunohistochemical examination using anti-CD30 antibody (×400). Anti-CD30 antibodies are reactive to anaplastic large cells. G, Immunohistochemical examination using anti-CD30 antibody (×400). Anti-CD30 antibodies are reactive to small atypical cells. H, Immunohistochemical examination using anti-CXCR3 antibody (R&D Systems, Minneapolis, MN) (×100). Anti-CXCR3 antibodies are reactive to anaplastic large cells. I, Immunohistochemical examination using anti-CCR3 antibody (R&D systems) (×100). Anti-CCR3 antibodies are not reactive to anaplastic large cells. J, Macroscopic findings at 3 mo after the initial appearance of the tumors. The tumors regressed spontaneously, leaving scars.
early MF, only two cases (to our knowledge) of CD30 + MF-LCT in the patch stage have been described previously, with both showing favorable prognoses.20,21 These cases, in combination with the case reported here, strongly suggest that CD30 + MF-LCT in early MF does not indicate poor prognosis, although MF-LCT occurring in advanced MF has been reported to relate to poor prognosis.1,6 With regard to spontaneous regression of MF-LCT, there have been only a few case reports22,23; notably, PC-ALCL was not definitely excluded.24,25 Reports of MF-LCT in the patch stage have been described previously, with early MF, only two cases (to our knowledge) of CD30+ MF-LCT, especially in early MF, also may possess the potential for spontaneous regression like that seen for CD30 + LPDs, including LyP and PC-ALCL. The accumulation of additional such unique cases is expected to contribute to deeper understanding of MF-LCT.

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CONFLICT OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS
NK: provided resources. MI: contributed to concentration, validation, and writing. YW: contributed to data curation. YN: performed project administration. AA: provided supervision.

ETHICAL APPROVAL
The case report was approved by the ethics committee of The Jikei University School of Medicine.

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REFERENCES
1. Agar NS, Wedgeworth E, Crichton S et al Survival outcomes and prognostic factors in mycosis fungoides/Sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas-European Organisation for Research and Treatment of Cancer staging proposal. J Clin Oncol. 2010;28:4730–4739.
2. Lebowitz E, Geller S, Flores E et al Survival, disease progression and prognostic factors in elderly patients with mycosis fungoides and Sezary syndrome: a retrospective analysis of 174 patients. J Eur Acad Dermatol Venereol. 2019;33:108–114.
3. Diamandidou E, Colome-Grimmer M, Fayad L et al Transformation of mycosis fungoides/Sezary syndrome: clinical characteristics and prognosis. Blood. 1998;92:1150–1159.
4. Greer JP, Salhany KE, Cousar JB et al Clinical features associated with transformation of cerebriform T-cell lymphoma to a large cell process. Hematol Oncol. 1990;8:215–227.
5. Barberio E, Thomas L, Skowron F et al Transformed mycosis fungoides: clinicopathological features and outcome. Br J Dermatol. 2007;157:284–289.
6. Scarisbrick JJ, Prince HM, Vermeer MH et al Cutaneous lymphoma international consortium study of outcome in advanced stages of mycosis fungoides and Sezary syndrome: effect of specific prognostic markers on survival and development of a prognostic model. J Clin Oncol. 2015;33:3766–3773.
7. Arulogun SO, Prince HM, Ng J et al Long-term outcomes of patients with advanced-stage cutaneous T-cell lymphoma and large cell transformation. Blood. 2008;112:3082–3087.
8. Salhany KE, Cousar JB, Greer JP et al Transformation of cutaneous T cell lymphoma to large cell lymphoma. A clinicopathologic and immunologic study. Am J Pathol. 1988;132:265–277.
9. Vergier B, de Muret A, Beylot-Barry M et al Transformation of mycosis fungoides: clinicopathological and prognostic features of 45 cases. French Study Group of Cutaneous Lymphomas. Blood. 2000;95:2212–2218.
10. Vural S, Akay BN, Botsali A et al Transformation of mycosis fungoides/Sezary syndrome: clinical characteristics and prognosis. Turk J Haematol. 2018;35:35–41.
11. Talpur R, Sui D, Gangar P et al Retrospective analysis of prognostic factors in 187 cases of transformed mycosis fungoides. Clin Lymphoma Myeloma Leuk. 2016;16:49–56.
12. Bekkenk MW, Geelen FA, van Voorst Vader PC et al Primary and secondary cutaneous CD30+ lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. Blood. 2000;95:3653–3661.
13. Kempf W, Pfaltz K, Vermeer MH et al EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Blood. 2011;118:4024–4035.
14. Benner MF, Willemze R. Applicability and prognostic value of the new TNM classification system in 135 patients with primary cutaneous anaplastic large cell lymphoma. Arch Dermatol. 2009;145:1399–1404.
15. Kadin ME, Hughey LC, Wood GS. Large-cell transformation of mycosis fungoides-differential diagnosis with implications for clinical management: a consensus statement of the US Cutaneous Lymphoma Consortium. J Am Acad Dermatol. 2014;70:374–376.
16. Willemze R, Kadin ME, Kempf W, Pauli M. Primary cutaneous CD30+ T-cell lymphoproliferative disorders. In: Elder DE, Massi D, Scolyer RA, Willemze R, eds. WHO Classification of Skin Tumours (4th edn). Lyon, France: International Agency for Research on Cancer; 2018: 236–239.
17. Suga H, Sugaya M, Sato S. C-C chemokine receptor type 3 expression in lymphomatoid papulosis, but not in mycosis fungoides lesions from the same patient. Clin Exp Dermatol. 2012;37:75–77.
18. Suga H, Sugaya M, Miyagaki T et al Differential patterns of CXCR3, CCR3, and CCR10 expression in mycosis fungoides, Sezary syndrome and CD30(+) lymphoproliferative disorders: immunohistochemical study of 43 samples. J Dermatol Sci. 2011;64:142–144.
19. Yamaguchi T, Ohshima K, Karube K et al Expression of chemokines and chemokine receptors in cutaneous CD30+ lymphoproliferative disorders. Br J Dermatol. 2006;154:904–909.
20. Lai Po-Ju, Hsiao Yu-Ping, Hsu Jeng-Dong, Wey Shiow-Jiuan. Early stage mycosis fungoides with focal CD30-positive large cell transformation. Dermatol Sin. 2013;31(2):73–77.
21. Ohtani T, Kikuchi K, Koizumi H et al. A case of CD30+ large-cell transformation in a patient with unilesional patch-stage mycosis fungoides. *Int J Dermatol*. 2009;48:623–626.

22. Watchorn RE, Pawade J, Wachsmuth RC. Unilesional CD30+ mycosis fungoides with large cell transformation and spontaneous regression, masquerading as verruca vulgaris. *Clin Exp Dermatol*. 2018;43:633–635.

23. Besch-Stokes JG, Costello CM, Bhullar PK et al. Regression of mycosis fungoides with large-cell transformation following skin biopsy. *J Eur Acad Dermatol Venereol*. 2020;34:e82–e84.

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