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Single Case

Large-Cell Transformed Mycosis Fungoides Coexisting with Mycosis Fungoides Bullosa: A Case Report and Review of the Literature

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Keywords
Mycosis fungoides · Mycosis fungoides bullosa · Bullous mycosis fungoides · Transformed mycosis fungoides · $CD30^+$ large cell transformation

Abstract
Mycosis fungoides is the most common form of cutaneous T-cell lymphoma. Both large-cell transformed mycosis fungoides and mycosis fungoides bullosa are rare presentations and predict unfavorable prognosis. We report the case of a 61-year-old woman who presented with generalized erythematous scaly annular plaques, and histopathology confirmed the diagnosis of mycosis fungoides. She was treated with various conventional therapies but only achieved partial response and always relapsed after discontinuation of treatment. Her last treatment was combined chemotherapy (CHOP regimen) followed by romidepsin. However, 1 month after the last cycle of romidepsin, she developed multiple ulcerative masses and nodules. Skin biopsy was compatible with $CD30^+$ large cell transformation, and she was treated with a new combination of chemotherapy (ifosfamide, carboplatin, etoposide). One day after receiving chemotherapy, multiple tense bullae on normal-appearing skin and mycosis fungoid plaques erupted. A histological study demonstrated subepidermal blistering with epidermotropism of atypical lymphocytes. Direct immunofluorescence study was negative. The results confirmed the diagnosis of mycosis

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fungoides bullosa. We present the first reported case of large-cell transformed mycosis fungoides coexisting with mycosis fungoides bullosa.

Case Report

We report on a 61-year-old woman with a 5-year history of mycosis fungoides (MF). She first presented with multiple erythematous scaly annular plaques on her trunk (Fig. 1) and extremities. Skin biopsy showed a dense cellular infiltration of atypical lymphocytes with large hyperchromatic and pleomorphic nuclei throughout the dermis – compatible with MF. Laboratory evaluation revealed normal complete blood count and lactate dehydrogenase level. A computed tomographic scan of her chest and whole abdomen showed no significant abnormalities. MF stage IB was diagnosed. She was treated with PUVA, methotrexate plus acitretin and achieved partial response.

One year after treatment, she noticed a new large plaque on her right tibia. Histopathological analysis revealed tumor stage of MF. MF stage IIB was diagnosed and superficial radiation was started for patch and thin plaques and electron beam for the tumor lesion on her right tibia. All skin lesions were almost cleared, and maintenance therapy with low-dose acitretin (10mg/day) and methotrexate (5 mg/week) was started.

Two years after treatment, her skin lesions relapsed and did not respond to superficial radiation. Hematological consultation was done. Bone marrow biopsy and abdominal computed tomography examination revealed no abnormal findings. Chemotherapy (CHOP regimen) was started, and she responded well.

Two months after the last CHOP cycle, she developed a new ulcerated mass on her left lateral malleolus. Histopathology revealed lymphoma cutis with positive CD30 staining. The differential diagnosis included $CD30^+$ large cell transformation (LCT) of MF and anaplastic large cell lymphoma. A salvage regimen (romidepsin, 6 cycles) was administered, and the lesions disappeared.

One month after the last romidepsin cycle, our patient went on vacation to a hot spring spa. One week later, multiple plaques, nodules, and ulcerative masses erupted on both of her arms, forearms (Fig. 2a), and legs. She had no fever but complained of fatigue. Physical examination revealed multiple erythematous plaques, nodules, and few ulcerative masses affecting all extremities. Her right posterior cervical lymph node, 1×3 cm in diameter, was palpable. She also had both ptosis and upward gaze palsy in her right eye.

Laboratory examination showed a white blood cell count of 5.6×10^{-9} cell/L, a lactate dehydrogenase level of 6,400 U/L (normal range: 125–220 U/L). Magnetic resonance imaging of her brain and orbit revealed lymphomatous involvement of the right temporalis muscle, right upper eyelid muscle, right inferior rectus muscle, left medial rectus muscle, and left inferior rectus muscle. Skin biopsy of the ulcerative plaque showed necrosis of the overlying epidermis and dense diffuse infiltration of atypical mononuclear cells composing 2 types of cells in the dermis and subcutaneous tissue (Fig. 2b): (1) medium-/large-sized atypical lymphocytes with dark hyperconvulated nuclei and scant cytoplasm, and (2) large-sized atypical lymphocytes with large round or oval vesicular nuclei and abundant cytoplasm.

The atypical lymphocytes were $CD3^+$, $CD4^-$, $CD8^+$, $CD20^-$, $CD30^+$, $CD56^-$, ALK^-. From the clinical symptoms and the laboratory findings, large-cell transformed MF stage IVB with eye and lymph node involvement was diagnosed. She received a new combination of chemotherapy (ifosfamide, carboplatin, etoposide) together with systemic antibiotics. One day later, she developed tumor lysis syndrome and multiple tense bullae on normal-appearing skin

and erythematous plaques (Fig. 3a). Chemotherapy was postponed, and skin biopsy of the bullous lesion revealed marked epidermotropism of atypical lymphocytes into the lower portion of the epidermis and subepidermal vesicle (Fig. 3b). There was sparse inflammatory cell infiltration of small lymphocytes, neutrophils, and a few melanophages in the papillary dermis. Direct immunofluorescence, anti-BP180, and anti-BP230 levels were all negative. The patient was diagnosed with MF bullosa, and chemotherapy was restarted at a lower dosage. Her skin and general condition partially improved, but computed tomography of her chest and whole abdomen revealed involvement of multiple axillary and groin nodes with liver metastasis. High-dose methotrexate was started as palliative care. After the 4th cycle, she developed hollow viscus organ perforation, septic shock, and expired.

Discussion

MF is the most common type of cutaneous T-cell lymphoma and accounts for almost 50% of all primary cutaneous lymphoma [1]. MF has an indolent course and typically presents with patch, plaque, and tumor stages. However, many other subtypes have been reported such as hypopigmented MF, folliculotropic MF, pagetoid reticulosis, granulomatous slack skin, and also bullous MF [1, 2].

Bullous MF or MF bullosa is a rare clinical variant of MF. The first case – described as having pemphigus-like lesions – was reported by Kaposi in 1887 [2]. The term "mycosis fungoides bullosa" was first used by Grab and Wise in 1943 [2]. At present, only 23 cases have been reported in the literature [3]. Bullous MF commonly presents in the elderly and has no gender preference [2]. The bullae which can be flaccid or tense may occur before, after, or concurrent with the typical MF lesions [2]. The bullae can arise in classical MF lesions or may also be found on normal-appearing skin [2]. The distribution is local or general, predominantly affecting the trunk and extremities [2].

Histopathologically, the blisters which may be subepidermal or intraepidermal (subcorneal or suprabasal) accompany the apparent histological features of MF (epidermotropism, Pautrier's microabscesses, atypical lymphocytes) [2]. However, because bullous MF is very rare, the diagnosis should only be done after ruling out all other coincidental vesiculobullous diseases such as infection, arthropod bite, burn, allergic contact dermatitis, and autoimmune bullous disease. Therefore, immunofluorescence study plays an important role to exclude a coexisting autoimmune disease. Moreover, several therapeutic modalities for MF have been shown to induce vesicles and blisters including topical mechlorethamine [4], interferon alfa [5], and phototherapy [6].

The diagnosis of bullous MF is sometime inconclusive. Bowman et al. [2] in 2001 proposed 4 criteria for bullous MF: (1) clinically apparent vesiculobullous lesions, with or without typical MF lesions (patches, plaques, tumors); (2) typical histological features of MF (atypical lymphoid cells, epidermotropism, Pautrier's microabscesses) with intraepidermal or subepidermal blisters; (3) negative immunofluorescence (both direct and indirect, if possible) to rule out concomitant autoimmune bullous diseases; and (4) negative evaluation for other possible causes of vesiculobullous lesions (medications, allergy, bacterial or viral infection, porphyria, phototherapy, or photochemotherapy). The appearance of bullous lesions in MF patients often predicts a poor prognosis. In the study by Bowman et al. [2], almost 50% of the patients with bullous MF died within 1 year of the appearance of bullae.

LCT within skin or node biopsies is defined as large cells (≥ 4 times the size of a small lymphocyte) which are $CD30^+$ or $CD30^-$ in ≥25% of the dermal infiltration, and it usually

coincides with the presence of tumors [7, 8]. The incidence of LCT ranges from 8 to 55% [9–11]. LCT has been documented to occur at all stages of cutaneous T-cell lymphoma, but it is more common in patients with advanced disease [10]. It is often advised to obtain biopsy specimens from MF patients who develop new papules, plaques, or tumors in order to rule out LCT and prompt consideration of more aggressive treatment regimen [12]. The prognosis of LCT is reportedly worse than classical MF [7, 8]. Previous studies reported that median survival varied between 2 and 100 months with the most frequent median survival around 2 years [7–10, 13]. Diamandidou et al. [14] found that early transformation (<2 years after diagnosis) and advanced stages (stage IIB or higher) were associated with poor prognosis. Benner et al. [10] collected 100 cases of LCT-MF and reported that CD30 negativity, folliculotropic MF, the extent of skin lesions, and extracutaneous transformation were associated with a reduced disease-specific survival. Another study by Talpur et al. [7] reported poor prognosis in combination with advanced age, LCT at the time of initial diagnosis of MF, high levels of lactate dehydrogenase, and CD30 expression <10%.

Transformed MF is considered to be at least stage IIB, and most patients receive combined chemotherapy and show good response with fast relapse. Recently, brentuximab, a conjugate of an anti-CD30 antibody, has been reported to induce complete remission with subsequent allogeneic stem cell transplant in 1 out of 4 patients with $CD30^+$ large-cell transformed MF [15].

In summary, we report the first case of $CD30^+$ large-cell transformed MF coexisting with a bullous variant. Both large-cell transformed MF and MF bullosa predict poor prognosis. Despite an aggressive management, these conditions are always refractory to available treatment.

Statement of Ethics

Patient consent for publication has been obtained.

Disclosure Statement

The authors declare no conflicts of interest.

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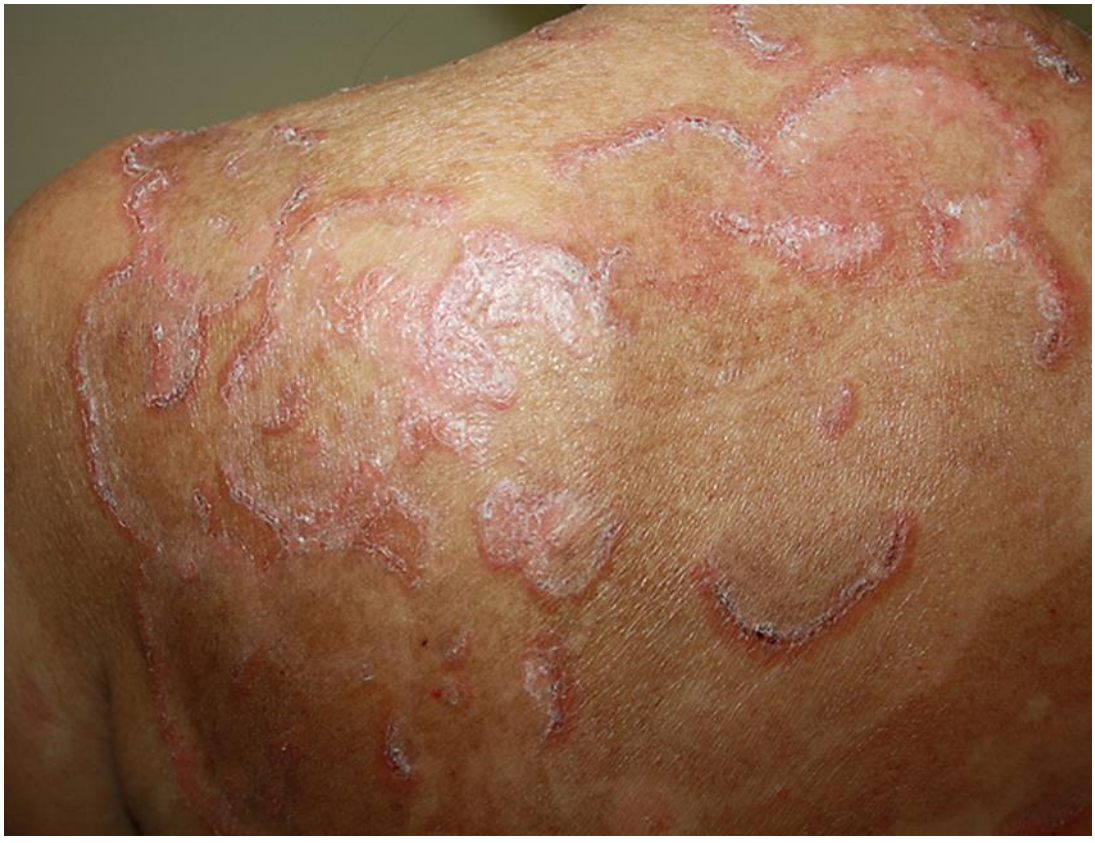

Fig. 1. Multiple erythematous scaly annular plaques on upper back.

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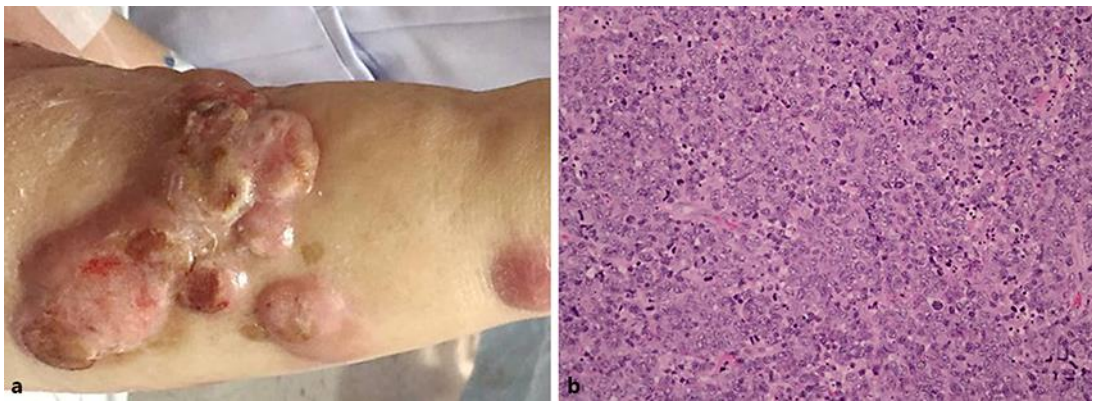

Fig. 2. **a** Multiple erythematous nodules, plaques, and ulcerative masses on right forearm. **b** There are dense diffuse infiltrations of atypical mononuclear cells composed of 2 types of cells: (1) medium/large-sized atypical lymphocytes with dark, hyperconvulated nuclei and scant cytoplasm, and (2) large-sized atypical lymphocytes with large round or oval vesicular nuclei and abundant cytoplasm (H&E, ×400).

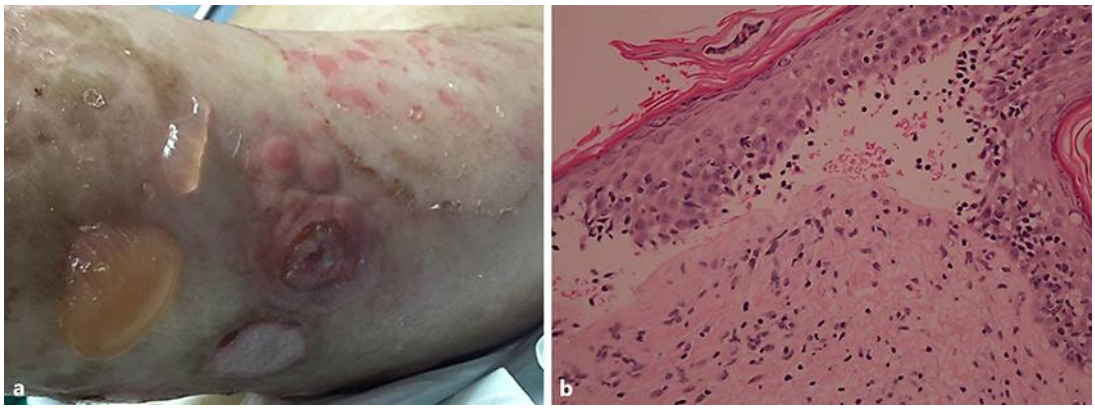

Fig. 3. **a** Tense bullae on left thigh. **b** Subepidermal separation with marked epidermotropism of atypical lymphocytes into the lower portion of the epidermis (H&E, ×400).