Mycosis fungoides bullosa: An unusual presentation of a rare entity

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INTRODUCTION
Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma with an incidence of 6 cases per million per year.1 Classic MF in adults can present in different stages, including the patch, plaque, and tumor stages.2 While patients with early patch or plaque stage MF usually have an indolent course, patients developing skin tumors require systemic or radiation therapy due to their aggressive course.3 In addition, several clinico-pathologic variants of MF have been described; e.g., poikilodermatous, granulomatous, hypopigmented, folliculotrophic, and vesiculobullous variants.4

Blistering is not usually associated with MF, but when present, it is typically associated with aggressive course and poor prognosis.5 Vesiculobullous MF has only been reported in 35 cases in the literature. Being a less recognized variant, it can easily be missed or confused with other bullous disorders, leading to delayed diagnosis and management.

We present a male patient with generalized vesiculobullous MF. The blisters were arranged in an annular pattern mimicking adult linear IgA bullous dermatosis. The lesions rapidly progressed to tumors necessitating aggressive treatment. The diagnosis of bullous MF was made based on the clinical and histologic findings.

CASE REPORT
A 43-year-old man presented with a 1-year history of progressive, generalized pruritic skin eruption. There was no history of viral infections, contact allergy, systemic illness, or oral drug intake.

Physical examination revealed generalized infiltrated plaques on the trunk and extremities covering most of his body surface area. The plaques were studded with multiple vesicles and bullae (flaccid and tense), arranged in a characteristic annular pattern mimicking adult linear IgA bullous dermatosis. Some of the blisters were ruptured and associated with exudative superficial erosions (Fig 1). There was no mucosal involvement. The patient was well-appearing and denied systemic symptoms.

Skin biopsies were taken from the plaques and bullae. Histologic examination revealed both intraepidermal and subepidermal blisters, along with infiltration of the upper dermis and dermo-epidermal junction by atypical lymphocytes with migration into the epidermis (epidermotropism) (Fig 2, A). With higher magnification, lymphoid cells were observed to be large with convoluted nuclei (Fig 2, B). Immunohistochemical analysis revealed the infiltrate to consist of predominantly T cells, the phenotype of which was CD3+, CD4+, and CD8− (Fig 2, C and D). Direct immunofluorescence for IgG, IgA, immunoglobulin M, and C3 was negative.

Based on these findings, the diagnosis of vesiculobullous MF was made. The patient was lost to follow-up but returned 4 months later with new
skin lesions on the back. Examination revealed a painless, erythematous, eroded 4 × 6-cm tumor on the back (Fig 3, A). The patient had a mobile, non-tender axillary lymph node (1 × 2 cm).

Histologic examination of the nodule showed diffuse atypical lymphoid infiltrate involving the full thickness of the dermis and extending to the subcutaneous tissue (Fig 3, B). By immunohistochemical analysis, the infiltrate was CD3⁺, CD4⁺, and CD8⁻ (Fig 3, C and D). Core biopsies of the axillary lymph node revealed reactive lymphadenopathy. A bone marrow biopsy revealed no involvement. Computed tomography of the neck, chest, abdomen, and pelvis was normal. Clinical and histologic findings were consistent with stage IIB MF (tumor stage). Despite aggressive therapy including cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisolone, the condition rapidly progressed with continuous appearance of new lesions and tumors, resulting in death of the patient less than 1 year after the onset of the bullous lesions.

DISCUSSION

The vesiculobullous variant is a very rare clinical subtype of MF. According to Bowman et al,⁶ the diagnosis is made by the presence of the following: (1) Vesiculobullous lesions ± typical lesions of MF (patches, plaques, tumors); (2) typical histologic features of MF (atypical lymphoid cells, epidermotropism, Pautrier microabscess) with
intraepidermal or subepidermal vesicles; (3) negative immunofluorescence to rule out autoimmune bullous diseases; and (4) negative evaluation for other possible causes of vesiculobullous lesions; eg, drugs, infections, porphyria.

The pathologic mechanism underlying blister formation in MF has not been elucidated. One explanation is the confluence of Pautrier microabscesses in MF lesions, which may lead to intraepidermal bulla formation.7 Alternatively, the proliferation of neoplastic lymphocytes and/or the release of lymphokines by malignant T cells may result in a loss of cohesion between keratinocytes and the basal lamina.8,9

The main differential diagnosis is autoimmune bullous disease, that has been reported to occur concurrently with classic MF.10,11 In our patient, the blisters were arranged in an annular pattern similar to adult linear IgA bullous dermatosis; however, immunofluorescence testing was negative.12 Annular MF has been previously described both in the absence of bullae13 and associated with vesicles and bullae, similarly to our case.12,14 Bullae in MF may also be seen in the setting of eczema herpeticum.15 Bullous drug eruption and bullous impetigo should also be considered as a differential diagnosis. In our case, this was excluded by the absence of history of drug intake and the absence of characteristic histologic findings; eg, necrotic keratinocytes and eosinophils.

The diagnosis of this rare entity is challenging, and the suspicion can only be raised by the presence of typical lesions of MF along with vesiculobullous lesions. Our patient had generalized MF plaques of prolonged duration with severe itching that developed into tumors in a short period of time.

This presentation highlights the aggressive nature of this variant. The treatment of bullous MF follows...
the usual treatment of MF according to the clinical stage. Phototherapy, methotrexate, interferon, bexacotene, radiotherapy, and histone deacetylase inhibitors are established treatments used in other variants of MF and have also been shown to improve bullous MF lesions.\(^{16,17}\)

Epidemiologic, clinical, and histologic aspects of previously reported cases of bullous MF are presented in Table I. Review of previously reported cases revealed that bullous MF has a predilection for male patients with a mean age of 61.5 ± 15 years. The bullous lesions may arise *de novo* or on top of typical MF lesions. Bullous MF may present with flaccid or tense bullae, may have negative or positive Nikolsky sign, and may be generalized or localized, without specific predilection site. Regarding the histopathology of bullous MF, the line of cleavage may be intraepidermal, at different levels, or subepidermal; however, the majority of the patients displayed the CD4\(^+\) MF phenotype.

The case is usually treated as plaque or tumor stage MF, taking into consideration that the appearance of bullous lesions in a patient with MF appears to carry a poor prognosis; almost half the reported patients died within 1 year of the appearance of bullae, despite aggressive therapy.\(^6\)

To conclude, we present a case of vesiculobullous MF with a distinguished presentation and a rapidly progressive course. Dermatologists should keep in mind the diverse presentations of MF to avoid misdiagnosis and delayed management.

**Conflicts of interest**

None disclosed.
### Table I. Summary of the reported cases of bullous mycosis fungoides

| Reference | Clinical | Pathology | Associations |
|-----------|----------|-----------|--------------|
| Kaposi, 1887 | Pemphigus-like lesions | Intraepidermal and subepidermal bullae |  |
| Lortat-Jacob and Legrain, 1926 | Few bullae with typical MF plaques | Subepidermal bullae |  |
| Goeckerman and Montgomery, 1931 | Generalized bullae with crusts |  |  |
| O’Leary et al, 1935 | Few bullae on the abdomen | Intraepidermal and subepidermal bullae | Blisters mostly in the summer |
| Garb and Wise, 1943 | Blisters on the scalp, face, neck, and back |  |  |
| Lortat-Jacob and Legrain, 1926 | Few bullae with typical MF plaques | Atypical lymphocytes and lymphoblasts |  |
| Goeckerman and Montgomery, 1931 | Generalized bullae with crusts | Large intraepidermal, subcorneal bullae with acantholytic cells | Alopecia mucinosa |
| O’Leary et al, 1935 | Generalized bullous eruption |  | Pemphigus foliaceus |
| Garb and Wise, 1943 | Generalized vesicles and bullae |  |  |
| Konrad, 1982 | Nikolsky sign present |  |  |
| Maeda et al, 1987 | Bullae on normal and involved skin | Subepidermal bullae |  |
| Cawley et al, 1951 | Bullae within MF plaques | Subcorneal bulla, numerous leukocytes, and large atypical lymphocytes |  |
| Kint et al, 1972 | Bullae on both normal and affected legs | Intraepidermal and subepidermal bullae |  |
| Van Velde, 1974 | Several bullous eruptions |  | Follicular mucinosis |
| Maeda et al, 1987 | Generalized bullous eruption | Atypical lymphoid cells | Leonine facies |
| Kartsonis et al, 1990 | Pruritic rash and blisters + MF plaques and tumor | Subepidermal bullae |  |
| Turner et al, 1994 | Bullae on both normal and affected legs | Atypical lymphoid cells |  |
| Franken and Haneke, 1995 | Bullae on hands, legs, feet, and sole | Subepidermal vesicle with infiltrate | Alopecia mucinosa |
| Aranha et al, 1997 | MF patches and plaques + vesicles and bullae |  | Lymphadenopathy |
| McBride et al, 1998 | Extensive exudative lesions showing early blister formation | Dense lympho-histiocytic infiltrate in the dermis | CD3⁺, CD4⁻, weakly CD8⁺ |
| Ho et al, 2000 | Painful and large malodorous mass with bulla + intact bullae on chest and abdomen | Intraepidermal (foot) and subepidermal (abdominal wall) bulla formation |  |
| Ono et al, 2004 | Bullae on the back and extremities | Subepidermal blistering + atypical lymphocytes in the dermis | Inguinal lymphadenopathy |
| Gantcheva et al, 2005 | Nikolsky sign | Increased CD4/CD8 ratio | CD3⁺, CD4⁻, CD8⁻ |
| Layegh et al, 2007 | Plaque and tumors on head, trunk, and limb + vesicles and erosions | Intraepidermal blistering + epidermotropism | Sézary cells |
| Pearce et al, 2007 | Multiple bullous plaques | Intraepidermal vesiculation with epidermotropism | Adenocarcinoma of the lung, colorectal carcinoma, and bladder carcinoma |
| Balighi et al, 2007 | Multiple bullous plaques | Intratypial lymphocytes |  |
| Liu et al, 2008 | Flaccid acral bullae on erythematous MF plaque and normal skin | Intraepidermal bulla | CD4⁺ |
| | Vesicles on the lesion of the abdomen | Subepidermal bullae |  |
| Authors            | Year | Clinical presentation                                                                 | Pathological findings                                                                 | Other findings                                                                 |
|--------------------|------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Kamran et al, 2008 | 2008 | Large bullae on the limbs and trunk. Plaques with poikilodermic features               | Subepidermal clef with several atypical lymphocytes                                      | Axillary lymphadenopathy CD3⁺ |
| Kneitz et al, 2010  | 2010 | Two erythematous plaques on thigh Intact bullae within plaques                           | Subcorneal and intraepidermal bullae                                                    | Leukemoid reaction CD4⁺, CD8⁺, CD30⁻ |
| Sato et al, 2011    | 2011 | Plaques and tumors Acute bullous eruption                                               | Subepidermal bullae                                                                      | Inguinal and axillary lymphadenopathy Hepatosplenomegaly CD4⁺, CD8⁺, CD30⁻ |
| Xu et al, 2013      | 2013 | MF patches and plaques, flaccid vesicles, bullae, and pustules                           | Intraepidermal and subepidermal blisters                                                | IgG⁻ and IgM⁺ for Herpes simplex virus -1 |
| Korekawa et al, 2015| 2015 | Bullae and erythematous macules on trunk and extremities                                | Subepidermal bullae accompanied by extensive infiltrates of atypical lymphocytes        | Bullous pemphigoid BP180 NC16A⁺ |
| Porntharukcharoen et al, 2017 | 2017 | Multiple tense bullae                                                                   | Marked epidermotropism and subepidermal vesicle                                        | Large-cell transformed MF stage IV-B with lymphadenopathy CD4⁺, CD8⁺, CD30⁺ |
| Ilhame et al, 2017  | 2017 | Bullous erosions of the trunk and limbs Nikolsky sign negative                           | Epidermal cleavage + atypical lymphocytes                                              | Inguinal lymphadenopathy CD4⁺, CD8⁺, CD30⁻ |
| Juzot et al, 2020   | 2020 | Blisters on the trunk and lower limbs Flaccid bullae and erosions on the scalp, neck, trunk, and extremities | Subepidermal bullae                                                                      | Sézary syndrome CD4⁺,CD8⁺, CD30⁻ |
| Wu et al, 2020      | 2020 |                                                                                         | Intraepidermal and subepidermal bulla formation                                          | CD4⁺, CD8⁻ |
| Nofal et al, 2021   | 2021 | Erythematous annular plaques of MF Vesicles and erosions within infiltrated plaques     | Subepidermal and intraepidermal blistering                                              | CD4⁺, CD8⁻ |

*MF, Mycosis fungoides.*
