



Periorbital Involvement in Early Stage Mycosis Fungoides

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Mycosis fungoides (MF) is the most common form of cutaneous T-cell lymphomas (CTCL) and accounts for approximately 50% of all CTCL (1, 2). Classically, it presents with erythematous patches on sun-protected areas 2–10 years before confirmed on skin biopsy (3). Approximately 10% of patients initially presenting with patches will subsequently progress to advanced stages of disease (4). Since its first description, MF continues to evolve with discovering of new variants (2).

Periorbital involvement is a rare finding in MF and is usually associated with advanced stages of disease. In 1892, Besnier & Hallopeau reported the first patient with periorbital involvement, and extensive and ultimately, fatal disease (5). While the majority of cases describe patients with advanced stages, to date only few reports of isolated periorbital involvement, in early stage MF have been published (6–11).

Herein, we report the clinical, epidemiological and histopathological presentation of 7 patients with biopsy proven early stage MF and periorbital lesions.

PATIENTS AND METHODS

We conducted a retrospective study of patients seen with periorbital MF lesions, at the CTCL clinic at the MD Anderson Cancer Center, Houston Texas. The study protocol was approved by the institutional review board (#PA16-0091). Additional informed consent was obtained from all individual participants for whom identifying information is included in this article. Electronic medical records and paper-based flow charts were screened for patients with periorbital involvement in MF. Clinical and histopathological data were re-evaluated. Diagnosis and staging of MF were made by a CTCL expert (M.D), according to the modified International Society of Cutaneous Lymphomas/European Organization for Research and Treatment of Cancer revisions of the TNMB Classification of MF and Sézary syndrome (1).

All analyses were conducted using SPSS version 22.0 (IBM Corporation, Armonk, NY, USA). Continuous data are expressed as mean \pm standard deviation (SD) and median (range), as appropriate. Basic summary statistics were used to describe demographic data, treatment modalities, and response.

RESULTS

A total of 7 patients were evaluated, and their clinical characteristics are summarized in Table S1¹. The mean \pm SD age at diagnosis of MF was 62.9 \pm 8.3 years and the mean age of periorbital involvement was 66.4 \pm 7.6 years. The majority of subjects were women ($n=6$, 85.7%) and Caucasian ($n=5$, 71.4%).

The mean \pm SD duration of disease, from the initial diagnosis to death or last follow-up was 7.8 \pm 4.6 years. A total of 4 (57.1%) patients were stage IIB, two (28.6%) were stage IA and one (14.3%) was stage IB, at diagnosis of periorbital involvement. The mean percentage of the modified severity-weighted assessment tool (mSWAT) involved at diagnosis of periorbital MF was 10.24 \pm 8.30. Lactate dehydrogenase levels were within normal ranges in all patients (517 \pm 63 U/l).

Periorbital findings included: eyelid thickening and the presence of erythematous patches in 7 patients (100%) and plaques in 6 cases (85.7%). No subject had tumors. Ectropion was documented in 3 cases (42.9%). Blepharitis was diagnosed in 4 patients (57.1%), with positive skin cultures revealing: methicillin-resistant staphylococcus aureus ($n=2$), staphylococcus aureus ($n=1$) and enterococcus ($n=1$). Two patients had lost their eyebrows (Patients 1 and 4) and one (Patient 6) had lost her eyelashes, due to the periorbital involvement. Examples of clinical pictures are shown in Fig. 1 and Fig. S1¹.

The clinical diagnosis of MF was confirmed by skin biopsies in all 7 patients. Folliculotropism was identified in 5 cases (71.4%). Three of these patients had large cell transformation (LCT) and CD30⁺ aberrant T cells in addition to their diagnosis of folliculotropic MF (FMF) (Patients 2, 3, 7). Altogether LCT was noted in 5 patients (71.4%), with two subjects not showing features of folliculotropism (Patients 1 and 6).

The median number of medications used, at the time of diagnosis of periorbital MF was 3 (range 2–6). Three subjects (Patients 4–6) continued to have progression with topical tacrolimus ointment applied to facial lesions. A total of 5 (71.4%) cases developed periorbital lesions while being treated with phototherapy (Patients 1 and 6 received narrowband UVB, Patients 2, 4, and 5 received PUVA). The most efficient treatment modality was localized low dose radiation to treat the involved periorbital areas (Patients 1, 4, 5, and 7; see Fig. S1¹ for an example).

Two out of the 7 patients died during the follow-up period (93.3 \pm 55.3 months): one died from disease progression to CNS lymphoma; for the other case the cause of death is unknown.

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DISCUSSION

Eyelid involvement in MF is more prevalent in late disease stages. Stenson & Ramsay (6) prospectively followed 30 advanced staged MF patients over a 5-year period and found that 11 (37%) developed periorbital lesions during the course of disease. However, the low number of studied patients and the focus on advanced stages may have over-estimated the real prevalence of periorbital involvement in MF. A more precise frequency of occurrence is reflected by a retrospective study conducted over a 15-year period by Cook et al. (7), who reported that 42 out of 2,155 patients (1.95%) with CTCL developed ophthalmological findings.

With such a low prevalence of periorbital involvement in MF, it is important to consider other conditions, such as contact dermatitis, eczema, atopic dermatitis, seborrheic dermatitis, discoid lupus, or atypical blepharitis as a differential diagnosis. All of these entities may mimic MF of the eyelid (8–10). Four patients of our cohort had a concomitant diagnosis of blepharitis with positive skin cultures, indicating that both conditions can occur in the same patient, which might delay a correct diagnosis.

If in doubt, an additional biopsy of the periorbital region should be obtained.

FMF is a distinct variant of MF, both histologically and clinically (12). The histological hallmark of FMF, are atypical T cells invading the hair follicle (folliculotropism) (12). FMF commonly affects hair dense areas, including the head and neck. It is interesting that 5 out of our 7 patients with periorbital lesions had biopsy proven FMF. Furthermore, the two patients (patients 1, 6) with biopsies failing to show classical features of FMF exhibited clinical features. The first reported case of FMF affecting the periorbital area was a 68-year-old woman, diagnosed after blepharoplasty (13). Patients suffering from FMF also tend to have a worse prognosis than patients with classical MF. This might also explain the progressive disease course in some of our patients (12).

Treatment options for MF, include skin directed therapies, biologic response modifiers, or combination therapies (14). Treatment modalities used in our cohort (either prescribed by a referring physician or by one

of the authors (MD)) included: phototherapy, topical steroids, topical tacrolimus, and low dose radiation (Table S1¹). Five patients on phototherapy experienced progression of their skin lesions. Tacrolimus applied to the face caused an exaggeration of periorbital lesions in 3 patients and is therefore not recommended. Periorbital MF may be refractory to most skin targeted therapies; this can be partially explained by the high prevalence of FMF in our cohort (12).

The most effective therapeutic approach in this cohort was low dose electron beam radiation (Table S1¹). This is an important finding that also demonstrates that low dose radiation is equivalent to high doses in terms of response but with the benefit of reduced long-term side effects. This highly effective treatment modality will need further discussion by expert panels to be included into future treatment guidelines.

The authors declare no conflicts of interest.

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Fig. 1. Patients nos. 2, 3 and 5 with periorbital involvement of mycosis fungoides. Written permissions from the patients are given.

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