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Case Report

Occurrence of Mycosis Fungoides in an Iranian Chemical Victim of the Iran–Iraq War with a Long-term Follow-Up: A Case Report and Review of Literature

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Abstract

Mycosis fungoides (MF) is the most common form of cutaneous T-cell lymphoma. Persistent antigenic stimulation has been claimed to play a role in the development of this malignancy. We aimed to show the role of sulfur mustard in the pathogenesis of MF. A 45-year-old man with MF is introduced herein. He was a victim of chemical exposure in 1987 during the Iran–Iraq war. He developed skin lesions 3 years after exposure to sulfur mustard gas at the age of 21. Seven years after his exposure to sulfur mustard gas, a biopsy from the posterior distal part of his calf, which was injured and had bulla, revealed MF. Later, he developed more lesions on his extremities, trunk, and abdomen. On his previous admission, his left eyebrow was involved. A punch biopsy specimen was obtained from his eyebrow lesion, which rendered diffuse infiltration of atypical lymphocyte cells with some convoluted nuclei and scant cytoplasm admixed with lymphocytes, histiocytes, and mast cells compatible with the nodular stage of MF. At his last admission, a biopsy was obtained from the plaque lesions on his left thigh, and a *TCR-γ* gene rearrangement of the paraffin block of the plaque lesions revealed positive monoclonality. All the findings supported the MF diagnosis. We concluded that sulfur mustard could be a risk factor for MF development.

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Keywords ● Mycosis fungoides ● Lymphoma, T-cell, cutaneous ● Environmental exposure ● Sulfur mustard

What's Known

- Etiology of mycosis fungoides (MF) has largely remained unknown. Genetic, immunological, and environmental factors all have been proposed. There has been controversy about the relationship between environmental exposure and MF.

What's New

- Clear history of exposure to sulfur mustard gas, progression of inflammatory lesions to MF, and long-term follow-up of the patient (> 20 y) are the novelties of this case report. Additionally, the diagnosis of MF was confirmed by histopathology, immunohistochemistry, and *TCR-γ* gene rearrangement.

Introduction

The etiology of mycosis fungoides (MF) has largely remained unknown. Genetic, immunological, and environmental factors all have been proposed.[1] There has been controversy surrounding the relationship between environmental or industrial exposure and ensuing MF.[2] Regarding the pathophysiology of MF and cutaneous T-cell lymphoma, antigenic stimulation was first proposed more than 20 years ago.[3]

In the following section, a patient with MF in the wake of exposure to sulfur mustard (2,2'-dichloroethyl sulfide) is introduced.

A clear history of exposure to sulfur mustard gas, progression of inflammatory lesions to MF, and long-term follow-up of

the patient (>20 y) are the novelties of the present case report. Additionally, the diagnosis of MF was confirmed by histopathology, immunohistochemistry, and the *TCR-γ* gene rearrangement.

The aim of this study was to highlight sulfur mustard as an environmental risk factor for the development of MF, in support of the antigenic stimulation theory.

Case Report

In September 2015, a 45-year-old man, a known case of MF, was admitted to Razi Hospital, Tehran, Iran, due to the worsening of his skin lesions. He was a victim of chemical weapons in 1987 during the Iran–Iraq war (previously he had been admitted to Razi Hospital several times). He had developed skin lesions 3 years after exposure to sulfur mustard at the age of 21. His skin lesions were on the posterior distal part of his calf, where it was involved with bulla in 1987. The course time between his exposure and diagnosis was 7 years (1994). By that time, he had developed more patches and plaques on his upper and lower extremities, trunk, and abdomen (figure 1a and 1b).

He had undergone 120 sessions of narrow-band UVB in total and had been on acitretin (Neotigason®) capsules (25 mg/d) and topical steroid for the preceding 4 years before this admission.

Moreover, in his previous admission, there was an erythematous plaque with alopecia on his left eyebrow. A punch biopsy specimen was obtained from his eyebrow lesion, which rendered diffuse infiltration of atypical lymphocyte cells with some convoluted nuclei and scant cytoplasm admixed with lymphocytes, histiocytes, and mast cells compatible with the nodular stage of MF. Immunohistochemistry revealed $CD3^+$, $CD4^+$, and $CD7^-$.

On his last admission, there was no lymphadenopathy or hepatosplenomegaly. The liver function test, complete blood cell, and thyroid function test were normal. The human T-cell lymphotropic virus 1 (HTLV-1) test was negative. Computed tomography scan of the thorax, abdomen, and pelvic was normal. A biopsy was obtained from a plaque lesion, which had appeared recently on his left thigh. Histopathological examination revealed marked epidermotropic haloed lymphocytes linearly aligned along the basal layer with blurred dermoepidermal junction and scant spongiosis (figure 2). High-power images of the epidermis showed medium-sized lymphocytes with cerebriform nuclei arranged in Darier's nests (Pautrier's microabscess) (figure 3a). Within the dermis, a dense infiltration of small-to-medium sized pleomorphic lymphocytes with cerebriform nuclei was seen (figure 3b). An additional finding of these biopsies showed the involvement of the follicles by pilotropic small-sized pleomorphic lymphocytes. No mucin deposition within the follicles (follicular mucinosis) was seen (figure 3c). Also, eccrine gland involvement was seen by the infiltration of lymphocytes arranged predominantly around and within the eccrine glands with syringometaplasia (figure 3d). Histopathological findings were consistent with MF with folliculotropism and eccrinotropism (adnexotropism).

The *TCR-γ* gene rearrangement of the paraffin block of the plaque lesion revealed positive monoclonality. A bone-marrow aspiration was also obtained from the patient. A microscopic examination of the bone marrow specimen revealed no Sézary cell.

The clinical features of the patient, microscopic findings of the lesions, and result of the *TCR-γ* gene rearrangement were supportive of a diagnosis of MF. The dose of acitretin was increased to 50 mg/d at the last admission and psoralen and ultraviolet A (PUVA) therapy

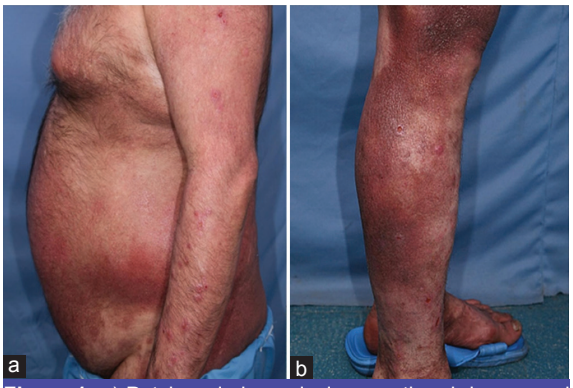

Figure 1: a) Patch and plaque lesions on the abdomen and forearm. b) Patch and plaque lesions on the calf and feet.

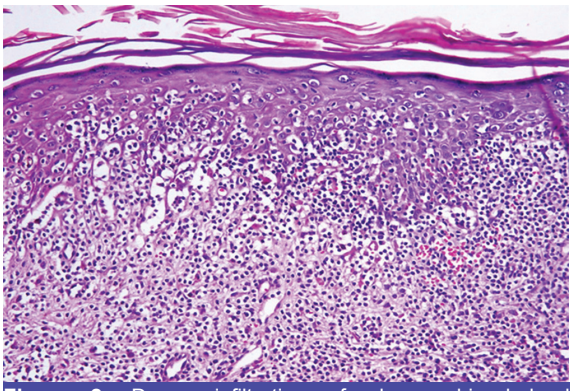

Figure 2: Dense infiltration of pleomorphic haloed lymphocytes with marked epidermotropism linearly arranged along the basal layer and within the epidermis (H&E ×20).

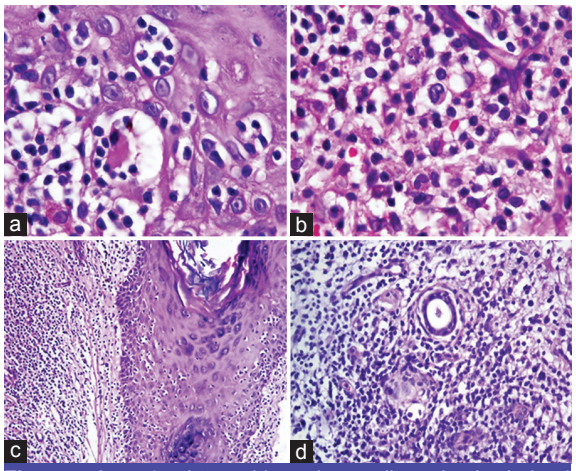

Figure 3: a) Intraepidermal medium-sized haloed lymphocytes, forming Darier's nest (Pautrier's microabscess) with accompanied disproportionate spongiosis (H&E ×40). b) Dense infiltration of small-to-medium sized lymphocytes in the dermis with large cerebriform (convoluted) nuclei (H&E ×40). c) Folliculotropism in mycosis fungoides characterized by the infiltration of small-sized lymphocytes written the follicle. Note pilotropic lymphocytes without deposition of mucin (H&E ×20). D) Eccrinotropism characterized by the infiltration of small-sized lymphocytes within and around the eccrine glands accompanied with syringometaplasia (H&E ×20).

was started. We obtained the patients' written consent to report the case.

Discussion

We herein introduced a patient with an established diagnosis of MF. He had a history of exposure to sulfur mustard 3 years prior to the diagnosis of MF. Sulfur mustard is a powerful vesicant chemical warfare agent.[4,5] The toxic effects of sulfur mustard, as an alkylating agent, are exerted through several mechanisms, including DNA alkylation, NAD depletion, and inactivation of glutathione.[5] The 3 major targets of the toxic effects of sulfur mustard are the skin, eye, and respiratory system.[5] The carcinogenicity of sulfur mustard has been verified, and an increased incidence of the upper respiratory tract and cutaneous malignancies following occupational exposure to sulfur mustard has been reported.[6]

The most common type of cutaneous T-cell lymphoma is MF, which accounts for half of all primary cutaneous lymphomas. The incidence of MF is about 0.4 in 100,000 per year in the United States.[1] Men are affected twice as often as women. The mean age of the affected patients at the time of diagnosis is between 55 and 60 years.[1]

The etiology of MF has largely remained unknown. Genetic, immunological, and environmental factors all have been proposed.[1] There has been controversy surrounding the relationship between environmental or industrial exposure and ensuing MF.[2] In 1979, Fischman and colleagues[7] studied the history of exposure to chemical, biological, and physical agents in patients with cutaneous T-cell lymphoma, including MF and the Sézary syndrome. The authors showed that a high percentage of their patients had a history of chemical exposure. Researchers have also demonstrated that exposure to aromatic and/or halogenated hydrocarbons could be associated with MF and hypothesized that job exposure could be an etiological factor for the appearance of MF.[8] In a recent publication, the development of the Sézary syndrome, namely the erythrodermic stage of MF, in a victim of chemical weapons during the Iran–Iraq was reported.[4] MF has an indolent course with a protracted progression from patch stage to plaque, tumor, and visceral involvement. It may take many years or sometimes even decades before a definite diagnosis.[9] The immunophenotype of neoplastic cells in MF shows CD3+, CD4+, CD45RO+, and CD8-.[7] A minority of the patients exhibit CD3+, CD4-, and CD8+ without any clinical and prognostic differences.[10]

According to the antigenic stimulation theory, long-term stimulation of lymphocytes could lead to the transformation of lymphocytes to T-cell lymphoma with low-grade malignancy.[3] In addition, Burg and colleagues[11] showed that chronic inflammation through long-term antigenic stimulation could give rise to neoplasia. A case-control study as well as mutation gene analysis showed that sun exposure, as an environmental factor, could be a contributing factor in the development of MF.[8,12] In the case presented herein, sulfur mustard may have led to the inflammation of skin and eczematous lesions. Subsequently, the chronic inflammation of the skin may have resulted in chronic antigenic stimulation. Finally, the above-mentioned process may have resulted in the development of MF.

Conclusion

The progression of inflammatory lesions to MF, a type of cutaneous T-cell lymphoma, showed that chronic inflammation and consequently, chronic antigenic stimulation could lead to neoplasia. At least, sulfur mustard could be a risk factor for the development of MF, presumably through antigenic stimulation.

Conflict of Interest: None declared.

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