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Association of Flame-Retardant Clothing With Mycosis Fungoides: A Retrospective Analysis

Katherine E. Park[1], Vignesh Ramachandran[2], Jessica Tran[3], Tejas P. Joshi[4], Naveen Garg[5], Madeleine Duvic[3]

1 Department of Dermatology, University of New Mexico School of Medicine, Albuquerque, New Mexico, USA
2 Department of Dermatology, New York University Grossman School of Medicine, New York, New York, USA
3 Department of Dermatology, University of Texas, MD Anderson Cancer Center, Houston, Texas, USA
4 School of Medicine, Baylor College of Medicine, Houston, Texas, USA
5 Department of Radiology, University of Texas, MD Anderson Cancer Center, Houston, Texas, USA

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Corresponding author: Tejas P. Joshi, BS School of Medicine Baylor College of Medicine, One Baylor Plaza, Houston, TX, USA. E-mail: tejas.joshi@bcm.edu

ABSTRACT

Introduction: Mycosis fungoides (MF), the most prevalent form of cutaneous T-cell lymphoma (CTCL), has been associated with a variety of environmental and occupational exposures. Flame-retardant clothing (FRC), in contrast to flame-resistant clothing, is chemically treated and may constitute a previously unrecognized occupational hazard.

Objectives: To report an association between FRC and MF.

Methods: After encountering several young male patients whose onset of MF coincided with the occupational use of FRC and occupation as fire fighters, we did a retrospective search. Additional biopsy proven MF patients with use of FRC were identified by the EPIC electronic medical record using the search terms "CTCL, mycosis fungoides, flame, and flame-retardant."

Results: Eight MF patients, all males, ranging in age from 31 years to 64 years (median age, 35 years) with exposure to FRC were identified. MF remission was noted in three patients who discontinued FRC use and in one patient who used a cotton undershirt barrier, while disease persistence was noted in one patient who continued to use FRC.

Conclusions: FRC appears to be associated with development of MF through chronic antigen stimulation. Use of FRC is an occupational hazard for fire fighters. Any patient whose MF coincides with use of FRC should avoid further exposure through avoidance or switching to clothing made from inherently flame-resistant fibers.

Introduction

Mycosis fungoides (MF), the most common form of cutaneous T-cell lymphoma (CTCL), is characterized initially by eczematous skin lesions containing clonal epidermotropic memory CD4+ T-cells [1]. Tan et al first suggested that MF is a disease of "chronic antigen stimulation" but the "antigen" is unknown [2]. Our finding of significant HLA-DR5 and DQ-301 associations with MF also supports the possibility of antigen restriction [3] (MF. As in other non-Hodgkin lymphomas, increased rates of MF have also been reported in association with occupational exposures to Agent Orange, aromatic hydrocarbons, and pesticides [4,5]. There have also been several reports of non-random clustering of MF, which further implicate possible environmental or occupational exposure as triggers for MF [6–8]. Moreover, we have demonstrated the presence of geographic hot spots in Texas, a finding consistent with the hypothesis that MF is triggered by particular exposures [9,10].

If occupation-related exposure is associated with increased MF risk, then it may result from chronic antigenic exposure to skin and inherent immune system-altering properties of the compounds [11]. Occupations previously reported to be associated with MF include painters, fire fighters, the military, and oil and chemical plant workers, which require specific workplace attire such as flame-retardant clothing (FRC). Unlike flame-resistant clothing which is made of inherently flame-resistant fibers, FRC is chemically treated and may be worn against the skin. While the specific chemicals used vary by manufacturers, historically these have included compounds such as brominated and chlorinated flame-retardants, as well as formaldehyde-based flame-retardants [12]. Many flame-retardant chemicals have been banned or voluntarily withdrawn from the market; however, they have been replaced with other brominated flame retardants. Previous studies have shown brominated and chlorinated flame retardants to be associated with adverse health effects, including reproductive toxicity, neurologic impairment, hormonal disturbances, and cancer [13–15]. The Epilymph study, a multicenter case-control study, demonstrated a significantly increased risk of mature B-cell lymphomas in patients exposed to brominated flame retardants [16].

Objectives

After encountering 3 young males who presented with early MF lesions in areas where their skin was chronically exposed to FRC, we performed a retrospective search. We report a case series of 8 patients who used FRC prior to developing MF and whose MF improved when FRC was no longer worn.

Methods

A retrospective chart review approved by the MD Anderson Institutional Review Board was performed by Dr. Naveen Garg at the University of Texas MD Anderson Cancer Center (MDACC) to identify and investigate MF patients with a history of exposure to FRC. All patients were seen by a CTCL expert dermatologist (Dr. Duvic) between May 1, 2009 and May 31, 2019. Inclusion criteria for this study were a patient age of 18 years or older, biopsy-proven MF confirmed by expert CTCL dermatopathologists at MDACC, and current/prior exposure to FRC. Patients with use of FRC were identified by searching the EPIC electronic medical record using the Garg Lab search method to create the study population [17]. Search terms included "CTCL, mycosis fungoides, flame, and flame-retardant." Eight patients met the inclusion criteria. Descriptive and demographic data were collected for each patient including demographics (age and sex), stage at presentation, location of skin involvement, treatment history, response to treatment, and length of follow-up.

Results

We identified 8 patients with MF who had worn FRC (Table 1). All patients were men and ranged in age from 31 to 64 years (median, 35 years). We were unable to determine the exact brand of FRC used in 7 patients, although 1 patient (case #2) recalled having used "Bulwark" brand FRC. Three patients were diagnosed with stage IA MF, 3 with stage IB MF, 1 with stage IIB MF, and 1 with stage IIIB MF (erythroderma with blood involvement). Body surface area involvement ranged from 0.25% to 97% (median, 18.95%). In 4 patients, we were able to ascertain the period of FRC use preceding lesion appearance: 2 patients (cases #2 and #8) had worn FRC for 2 years prior to development of MF; the other 2 patients had worn FRC for 3(case #1) and 4 (case #4) years before developing MF. The sequential nature of MF onset after a median of 2.5 years of starting FRC use is suggestive of a causal link between MF and cutaneous exposure to FRC. Unfortunately, we were unable to assess the exact duration of FRC use prior to MF development in any of the remaining four patients.

Three patients (cases #1, 2 and 4) who discontinued use of FRC achieved near complete remission of MF with only minimal adjunctive treatment (natural UVB and topical triamcinolone); 1 patient witnessed partial MF resolution after discontinuing FRC and complete regression following radiation therapy. One patient (case #5), who continued to wear FRC required by his job, had complete remission of his MF by using a cotton undershirt barrier. One patient (case #3) continued to wear FRC without any barrier and has persistent disease. The remission of disease in patients who discontinued FRC, and the persistence of malignancy in the 1

Table 1. Mycosis Fungoides patients with a history of exposure to flame-retardant chemicals

Case No.	Age, Sex	HPI	Rash Location	Initial Stage/ BSA	Topical steroid	Other Interventions	Cessation of FRC	Follow-up
1	31, M	3 yr history of pink to light brown patches beginning after starting work at an oil refinery where he used FRC	Popliteal fossa, hips, flanks, and groin	IB/18.95%	Y	NS	Y	6 mo
2	48, M	2 yr history of hypopigmented patches starting 2 yrs after beginning to wear Bulwark FRC	Arms, lower abdomen, thighs	IA/4.5%	Y	NB-UVB	Y	1 yr
3	35, M	Hyper- and hypopigmented patches with atrophy and telangiectasias of unknown duration recently diagnosed as MF; current FRC use	Axilla, hips, thighs, buttocks	IB/15%	Y	NS	N	1.5 yrs
4	31, M	4 yr history of erythematous scaly patch located where flame-retardant harness rubbed	Thigh	IA/0.25%	Y	UV-B	Y	2 yr
5	47, M	10 yr history of "psoriasis," 4 yr history of exposure to flame retardant clothing; wears cotton undershirt after previous urticarial reaction to FRC	Scalp, arms, trunk, legs	IB/54%	Y	PUVA, topical nitrogen mustard	Cotton undershirt barrier	13 yrs
6	35, M	History of flame-retardant exposure since age 18 with erythematous patches diagnosed as MF at OSH; presented with unrelated rash	Dorsal feet	IA/% unknown	Unknown	PUVA	Unknown	6 mos at OSH
7	64, M	4 yr history of erythematous patches with desquamation initially on lower legs with previous exposure to FRC	Generalized	IIIB/97%	Y	ECP, Bexarotene 225 mg	Unknown	5 mo
8	35, M	10 yr history of erythematous patches, plaques, and tumors that began 2 yrs after starting job with exposure to FRC and gamma-radiation	Head, trunk, and extremities	IIB/48%	Y	TSEB; bexarotene 300 mg	Y	3 mo

BSA = body surface area; FRC = Flame-retardant clothing; M = male; N = no; No = number; NS = natural sunlight; ECP = Extracorporeal photopheresis; TSEB = total skin electron beam; PUVA = psoralen + ultraviolet A; NB-UVB = narrow band ultraviolet B; OSH = outside hospital; Y = yes; yr = year.

patient who continued FRC use, further implicate FRC as the trigger for MF induction.

While we are unable to exclude the possibility that other factors (eg environmental and occupational exposures independent of FRC use) could have also initiated MF in our patients, the distribution of lesions in sun shielded areas in most of our patients is also consistent with FRC use (although it should be noted that presentation of MF lesions in sun shielded areas is also common in MF not associated with FRC). Seven of the 8 patients (cases #1-5, 7-8) we report had MF lesions in skin regions that directly contacted FRC, suggesting that FRC exposure to the skin may have induced malignancy of skin resident T-cells. Notably, patient #4 reported a history of an erythematous scaly patch on the thigh at the exact location where the FRC harness rubbed, further strengthening the association between FRC and MF. Altogether, considering the temporal and spatial nature of the association between MF and FRC, we suggest that FRC could be the offending agent in the development of MF in our patients. Of note, treatment with topical steroids and UVB therapy was successful in producing remissions in early-stage IA or IB patients; MF did not recur following removal of the clothing and topical therapy.

Conclusions

Although the precise mechanism(s) through which FRC could have induced MF in our patients is unclear, we speculate that chemicals in FRC may have been absorbed in exposed skin causing mutations in T-cells or acting as antigens driving T-cell proliferation. Indeed, dermal absorption of flame retardants has been demonstrated in both *in vitro* and human studies [18,19]. Additionally, there have been other reports of undefined skin rashes associated with FRC which could have been undiagnosed MF [13,14,20]. Moreover, our proposed explanation of MF induction is consistent with the paradigm of MF pathogenesis first suggested by Tan et al, who first hypothesized that MF results from persistent antigen stimulation [2]. Although we did not have the means to conduct a patch test for FRC components, we note that a positive patch test would have lent further support to our hypothesis of antigen stimulation. Patch testing for evaluation of future MF patients with history of exposure to FRC may be suggested to further elucidate the mechanism of MF induction by FRC.

FRC use appears to be associated with MF and may be an unrecognized occupational hazard for firefighters or other chronically exposed individuals. Patients who develop suspicious rashes in areas of contact with FRC should have skin biopsies for diagnosis. Patients with MF coinciding with FRC use should limit further exposure through avoidance or switching to clothing made from inherently flame-resistant fibers. Newer inherently flame-resistant clothing alternatives use next-generation polymers and fibers rather than chemical flame-retardants. Additionally, unlike FRC, clothing from inherently flame-resistant fibers does not lose efficacy with repeated washes [21], and therefore represents both a safer and more economical option compared to FRC.

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