Eruptive Cherry Angiomas Secondary To Exposure To Sulfur Mustard Gas

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Abstract

During the Iraq-Iran war (1980-1988) many Iranian soldiers had been exposed to mustard gas. We had opportunity to observe the late-onset skin manifestations of these patients. In a prospective study we examined the skin of 2921 patients, were referred to Shiraz Chemical Warfare Victims' Clinic One hundred and seventy-two (5.88%) out of 2921 patients had late-onset skin involvement. Forty-eight (27.9%) of 172 patients had mild mustard dermatosis, 44.8% (77/172) and 27.3% (47/172) had moderate and severe skin involvement, respectively. Cherry angiomas were seen in 62 out of 172 (36%) patients. Twenty-nine out of 62 (46.78%) patients with cherry angiomas had mild mustard dermatosis, 35.48% (22/62) and 17.74% (11/62) had moderate and severe mustard dermatosis, respectively. There were statistically significant correlation between the severity of mustard dermatosis and the incidence of eruptive cherry angiomas (P = 0.00015). The higher of the severity correlates with the less number of cherry angiomas.

INTRODUCTION

Sulfur mustard (SM, dichlorodiethyl sulfide), is a potent alkylating agent that has a long history of use as a chemical warfare agent and has reemerged as a major threat in recent years. The ease of manufacturing SM, even in relatively underdeveloped countries, and the lack of an effective antidote have resulted in a renewed interest in the pathophysiology of the lesions induced by this agent and in development of effective barriers and therapeutic agents for persons at risk of exposure [1, 2].

Although the use of chemical warfare was banned by the Geneva protocol in 1925 [3], research on chemical warfare agents, their mode of delivery, and antidotes continued in the interesting 60 years [4]. The use of chemical war agents by the Iraqi regime against Iranian soldiers was reported and condemned by the United Nations Security Council [5-7], but their use continued, and on March 17, 1988, extensive chemical weapons were delivered to the city of Halabje [8].

In the past SM has been used as a chemotherapeutic agent for malignant tumors, and low concentrations of SM have been used in topical therapy for psoriasis and mycosis fungoides [9-12].

METHODS

In a prospective study, during 1 year, we had opportunity to examine the skin of 2921 patients who had been exposed to sulfur mustard gas during the conflict, and referred to Shiraz Chemical Warfare Victims' Clinic.

The whole of the patients' skin including mucosal membranes and genitalia were examined and the clinical findings recorded in their files. The patients were asked about the intensity of itching according to no itching or mild, moderate, and severe intensity itching that disturb the sleeping.

The data were analyzed with chi-square test.

RESULTS

One hundred and seventy-two (5.88%) of 2921 patients had late-onset skin involvement. The mean age of the patients was 35.48 years (range, 27 to 76 years), and all were male. In the medical history they had extensive skin blistering after contact with SM, which healed in several weeks. The mean time after exposure to SM was 15.4 years. Forty-eight (27.9%) of 172 patients had mild mustard dermatosis consisting of without or mild itching, xerosis and/or mild dyspigmentation. Seventy-seven of 172 patients (44.8%) had moderate degree involvement (moderate itching, xerosis, and

dyspigmentation), and 47 out of 172 patients (27.3%) had severe degree involvement (severe itching, xerosis and dyspigmentation with or without chemical burn scar).

Cherry angiomas, as red papules (confirmed histopathologically) were seen in 62 out of 172 (36%) patients. A mean of 13.4 cherry angiomas (range, 4 to 31) were seen in the patients. Most of the lesions had been developed over the trunk and proximal areas of extremities. Twenty-nine (46.78%) out of 62 patients with cherry angiomas had mild dermatosis. Twenty-two (35.4%) and 11 of 62 (17.74%) patients had moderate and severe mustard dermatosis, respectively.

There were statistically significant correlation between the severity of mustard dermatosis and the incidence of eruptive cherry angiomas ($P = 0.00015$). The higher of the severity correlates with the less number of cherry angiomas.

No other significant dermatological disorders were noticed.

DISCUSSION

Several cutaneous manifestations of mustard gas poisoning have been reported [13, 14]; they include pruritus and burning, erythema, bullae, ulceration, hyperpigmentation and hypo pigmentation, and xerosis.

In the first report of the sudden eruption of several cherry angiomas [15], 38 patients for 18 months after their contact with SM gas had been assessed. In all, 10% of the patients had several cherry angiomas over the skin, but in our study it was 36%.

Sulfur mustard is an oily liquid that vaporizes slowly at temperate climates and may be aerosolized with spraying or explosive blasts. Although SM may be lethal, it is more likely to cause extensive incapacitating injuries to the eyes, respiratory tract, and skin of advancing forces. Alkylation reactions of SM with tissue are rapid and irreversible, and may go undetected because the agent can be difficult to smell in the battlefield and because cutaneous lesions do not become apparent for 1 to several hours [11, 16]. Persistence of SM within the environment long after release adds to its potential for injury [16].

About 20% of the SM that contacts the skin is absorbed [16]. Because SM is lipophilic, it penetrates the skin rapidly with more penetration down hair follicles than in sweat glands. SM can also diffuse across cellular membranes [16]. It has been estimated that 12% to 50% of the absorbed SM reacts with skin components, and 70% of this SM remains within the epidermis and 30% within the dermis [17].

Although the aqueous nature of sweat ducts may limit the absorption of lipophilic SM, sweat contains significant levels of iron and copper ions that are catalytic for free-radical reactions [18, 19]. This and possible secretion of systemically absorbed hydrolyzed SM intermediates in sweat may help explain the more severe clinical lesions seen in intertriginous areas.

Besides dose, other factors also affect the severity of acute skin lesions. Higher temperatures and increased moisture potentiate SM-induced effects. In addition, some anatomic locations appear more sensitive. The skin folds and areas with a thin epidermis and/or a loose dermal component are more sensitive. Light skin pigmentation, youth, and female gender may also predispose to more severe SM skin injury [16].

Dyspigmentation and more diffuse cutaneous hyperpigmentation are clinical features commonly seen with resolution of acute SM-induced cutaneous lesions [16, 20, and 21]. Post inflammatory hyperpigmentation is a common feature seen after a number of inflammatory dermatoses. It has been proposed to results from melanocytic stimulation by several locally cytokines and inflammatory mediators [22]. This has also been reported after systemic administration of nitrogen mustard (NH2) and after chemotherapeutic drugs that produce DNA damage and/or increase generation of reactive oxygen species. Enhance DNA repair enzymes, which are up-regulated after exposure to DNA damaging agents; have also been shown to enhance melanogenesis [23]. Dyspigmentation may result from agents that increase reactive species, because melanocytes which contain relatively less catalase, peroxidase and superoxide dismutase than do many other cells, including keratinocytes, are more susceptible to reactive oxygen species [22].

In addition, the loss of cellular adhesion seen histopathologically with reepithelialization and effects on keratinocytes including variable effects on keratinocytes within the basal cell layer, may be related to direct and/or indirect effects of SM on dermal-epidermal interactions including effects on the basement membrane and/or effects on protease, and more pronounced toxic effects on the epidermal stem cell population [16, 28, and 29]. The footprints of protease and degradation of basement membrane protein and inflammatory factors is common with angiogenesis.

Angiogenesis is the process by which new blood vessels are formed. The exact sequence of events that results in formation of new blood vessels is not fully understood, but it appears to be regulated by a complex interplay of soluble growth, inflammatory and chemotactic factors and the influence of the extra-cellular matrix. The formation of mature vascular system within the developing embryo and the formation of blood vessels within the adult share many common mechanisms. For new blood vessel formation in adults from preexisting blood vessels, increase in vascular permeability and vasodilatation often result in signals that induce angiogenesis. Subsequently, endothelial cells enlarge, form pseudo pods and producing a variety of proteases capable of degrading basement membrane proteins, they can migrate, and form vascular sprouts [30-32].

Although SM is recognized as a carcinogen and a mutagen [33], most studies on an association with the development of cancer have been retrospective and have been failed to control for exposures to other carcinogenic agents [34-39]. Short-term SM exposure has shown no association with the development of either pulmonary or skin tumors except in cutaneous scars. However long-term exposure to SM has been associated with an increase of airway and cutaneous malignancies [34-36].

The last, erupted cherry angiomas are a common, late-onset skin manifestation in the chemical warfare victims. Severity of mustard dermatosis had reverse correlation with incidence of eruptive cherry angiomas.

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