Sulfur Mustard-Induced Ocular Surface Disorders

Alireza Baradaran-Rafii, MD,[1] Medi Eslani, MD,[1] and Scheffer C. G. Tseng, MD, PhD[2]

ABSTRACT Sulfur mustard is a vesicant agent with severe irritating effects on living tissues, including skin, mucous membranes, eyes, and respiratory tract. The eyes are the most susceptible tissue to mustard gas effects, and varying degrees of ocular involvement are seen in 75% to 90% of exposed individuals. Most cases resolve uneventfully; however, a minority of exposed patients will have a continuous process, which manifests clinically either as a persistent smoldering inflammation (chronic form) or late-onset lesions appearing many years after a variable "silent" period (delayed form). Distinctive features common to most cases with chronic involvement include chronic blepharitis, meibomian gland dysfunction, dry eye, limbal ischemia, limbal stem cell deficiency, aberrant conjunctival vessels, corneal neovascularization, and secondary degenerative changes, including lipid and amyloid deposition and corneal irregularity, thinning and scarring. Most cases can be managed with conservative measures, eg, preservative-free artificial tears, lubricants, and topical steroids. Punctal plugs or punctal cauterization is helpful in moderate and severe forms of injury. Surgical modalities, including lateral or medial tarsorrhaphies, amniotic membrane transplantation, lamellar or penetrating keratoplasty, and stem cell transplantation have been used.

KEY WORDS chemical warfare agents, corneal burns, corneal transplantation, mustard gas, oxidative stress, sulfur mustard

Accepted for publication May 2011.

From the [1]Ophthalmic Research Center, Department of Ophthalmology, Labbafinejad Medical Center, Shahid Beheshti University of Medical Sciences, and [2]Ocular Surface Center, Ocular Surface Research and Education Foundation, Miami, Florida, USA.

Dr. Tseng and his family are more than 5% shareholders of TissueTech. Inc., which owns US patents 6 152 142 and 6 326 019 on the method of preparation and clinical uses of human amniotic membrane and ProKera™ distributed by Bio-Tissue Inc. Other authors have no proprietary or commercial interests in any concept or product discussed in this article.

Single-copy reprint requests to: Alireza Baradaran-Rafii, MD (address below).

Corresponding author: Alireza Baradaran-Rafii, MD, Labbafinejad Medical Center, Department of Ophthalmology, Boostan 9 St., Pasdaran Ave., Tehran 16666, Iran. Tel-fax: +98-21-22587317. E-mail: alirbr@gmail.com.

I. INTRODUCTION

Mustard gas was first produced by Meyer in 1886. It was used initially as a vesicant agent for chemical warfare in World War I by the German army.[1,2] It is a vesicant agent with severe irritating effects on living tissues, including skin, mucous membranes, eyes, and respiratory tract.[3,4] Because of its use as a weapon in World War I and in over 10 subsequent conflicts, including the Iraq-Iran war (1980-1988), its properties became more widely known in the 20th century.[3,4] Its late-onset, progressively destructive effects were recognized 15-20 years after its use.[5] A minority of exposed patients will develop late destructive ocular complications, which are usually progressive and permanent and can lead to reduction of visual acuity and even corneal blindness.[3,4] The ubiquitous production, simple and cheap chemical synthesis, easy stockpiling, and toxic nature of this agent make it a worldwide threat. Because of its destructive properties, combined with the lack of an effective antidote, some experts have classified mustard gas as one of the most significant chemical warfare agents.[6-8]

II. PHARMACOLOGY

The mustard agent is a straw-colored, oily liquid and has the odor of onion, garlic, or mustard, hence its name.[9] It mainly consists of two chemical forms: sulfur mustard [$S(CH_2\text{-}CH_2\text{-}Cl)_2$ or (2,2'-dichlorethyl sulphide; HD)], and nitrogen mustard [N(CH2-CH2-Cl) or (N-methyl-2,2'-dichlorodiethylamine; HN2)].[2,10] The former is longer acting and more commonly used in chemical warfare, but the latter is more toxic.[2,4,5,11] The popular term "mustard gas" is a misnomer, as this agent actually appears as an aerosol of small oily droplets.[12] The toxicity of sulfur mustard (**SM**) as an incapacitating agent is of much greater importance than its capacity to kill via a lethal dose 50% (**LD50**).[12,13] The LD50 for humans is about 200 mg when the substance is swallowed, 4-5 g when it is applied to the bare skin over a long exposure time, and 1500 mg/min/m^3 when inhaled.[2,14] It is a stable compound in low temperatures, which can persist in clothing or on the ground for months.[3] On contact with human skin, 80% of the liquid evaporates and 20% penetrates; half of this remains in the skin and the other half is absorbed systemically.[2] Additionally, due to free hydrolization by the interface organs, SM causes systemic effects only at very high doses.[15]

OUTLINE

The measurement of biochemical markers in aqueous humor is a tool for evaluating SM-induced damages even before the onset of clinical signs. The concentration of protein in aqueous humor increases 4-6 hours following exposure; although it decreases after 28 hours, it still remains higher than in non-exposed controls. This increase, together with the presence of cellular lymphocytic infiltration, is indicative of an inflammatory reaction. Aqueous humor glutathione at the very early stages of SM exposure may change in a similar pattern.[16,17]Alkylation products of SM with DNA and proteins (eg, hemoglobin and albumin), as well as its urinary metabolites,[18-22] have proved to be useful targets for diagnosing SM exposure in humans. Urinary markers are readily accessible, although their rapid elimination limits their use for retrospective detection. Adducts with macromolecules such as proteins offer longer lasting (possibly up to several months) biological markers of exposure to SM.[23,24] The DNA adducts can also be detected in urine, processed skin, and blood samples.[25-29]

III. PATHOPHYSIOLOGY

Mustard gas damages viable tissues only, and the exact mechanism for this is not clear. Theories include liberation of intracellular hydrochloric acid, formation of new compounds acting as alkylating agents, and, finally, formation of oxidative derivatives, which collectively can lead to more cellular damage.[9,11,30-34] Mustard gas causes additional injury via skin and eye damage after absorption through the integument and the ocular surface; respiratory damage after inhalation; and systemic toxicity after ingestion or high exposures. As a result, it may further cause gastrointestinal, circulatory, and bone marrow toxicity.[34] Hence, the destructive effects of SM are not localized to the site of application, as remote cells and tissues also become affected.[3] The high sensitivity of the eye to SM is due to the readily accessible aqueous-mucous surface of the cornea and conjunctiva, as well as the high turnover rate and intense metabolic activity of corneal epithelial cells.[35]

SM causes a cross-linking of the 2 complementary strands in the DNA molecule by a monofunctional alkylation of the nitrogenous bases. The major alkylating site of nucleic acids is the nitrogen residue of guanine.[36] The results are manifested in chromatid aberrations; inhibition of DNA, RNA, and protein synthesis; blocking of the cell's cycle in the G2-M phase; and, eventually, cell death.[2,37-40] SM tends to undergo intramolecular cyclization to create a hyperactive compound.[41] Conversion to this derivative is facilitated in an aqueous solution, which accounts for the sensitivity of mucosal tissues (such as in the eye) to its action.[42] The cyclic intermediate reacts with and alkylates electron-rich molecular structures, such as the sulfhydryl (-SH), amino (-NH2), carboxyl, hydroxyl, and primary phosphate groups of proteins and nucleic acids.[12,42-44] Additionally, the alkylated DNA activates poly-ADP-ribose polymerase, which leads to cellular depletion of nicotinamide adenosine dinucleotide (**NAD**), thus inhibiting multiple reactions in the cell.[6,7] The depletion of NAD also leads to upregulation of the hexosemonophosphate shunt, which stimulates protease activity in the cell. These proteases are thought to play a role in blister formation, compounded by the death of multiple keratinocytes.[6,7,43] It also directly inhibits various glycolytic and respiratory enzymes,[36] impairs glucose uptake mechanisms,[45] and generates oxidative stress through the formation of free radicals.[2,46]

Inhibition of cellular respiratory enzymes resulting in the formation of free radicals has been suggested as another pathophysiologic mechanism affecting predominantly proliferative epithelial cells in the ocular surface.[11] Evidence for oxidative stress in tissues exposed to SM or its analogs includes increased formation of reactive oxygen species and the presence of peroxidized lipid products and proteins. Although there is an increase in antioxidant enzymes, eg, superoxide dismutase, catalase, and glutathione-S-transferase, suggesting the presence of cellular defense, further inhibition of antioxidant enzymes, including thioredoxin reductase, by SM disrupts such cellular redox homeostasis.[32] A dramatic increase (30-fold) in copper levels and a decrease in ascorbic acid is observed within the anterior chamber after ocular exposure to mustard compounds, and both of these are indicators of oxidative stress.[17,47]