

Cutaneous reactions in nuclear, biological and chemical warfare

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ABSTRACT

Nuclear, biological and chemical warfare have in recent times been responsible for an increasing number of otherwise rare dermatoses. Many nations are now maintaining overt and clandestine stockpiles of such arsenal. With increasing terrorist threats, these agents of mass destruction pose a risk to the civilian population. Nuclear and chemical attacks manifest immediately while biological attacks manifest later. Chemical and biological attacks pose a significant risk to the attending medical personnel. The large scale of anticipated casualties in the event of such an occurrence would need the expertise of all physicians, including dermatologists, both military and civilian. Dermatologists are uniquely qualified in this respect. This article aims at presenting a review of the cutaneous manifestations in nuclear, chemical and biological warfare and their management.

Key Words: Nuclear warfare, Biological warfare, Chemical warfare, Cutaneous manifestations

INTRODUCTION

It is the constant endeavor of warring enemies to use new technologies and means in an attempt to gain advantage.^[1-3] This article aims at increasing awareness among dermatologists of the specific cutaneous manifestations of agents of nuclear, biological and chemical (NBC) warfare (Table 1, 2).^[4] Civilians may encounter these agents during a terrorist or military attack, a riot control operation, or due to accidental exposure during industrial or agricultural use. Military personnel may be exposed during their active use in the battlefield or exposure to areas where the disease may be chronically endemic.

HISTORY

Some weapons not only inflict casualties but manage

Table 1: Agents of chemical warfare

Nerve agents	<ul style="list-style-type: none">• Tabun• Sarin• Soman
Vesicants	<ul style="list-style-type: none">• Mustard• Lewisite• Phosgene oxime
Choking agents	<ul style="list-style-type: none">• Chlorine• Phosgene
Blood agents	<ul style="list-style-type: none">• Hydrogen cyanide
Incapacitants	<ul style="list-style-type: none">• Anticholinergics• Indoles• Cannabinoids
Riot control agents	<ul style="list-style-type: none">• o-chlorobenzylidene malononitrile• 1-chloroacetophenone• Diphenylaminearsine• Dibenz (b,f) -1:4-oxazepine• Bromobenzylcyanide

to strike considerable fear in the enemy. It is the unique blend of real and perceived danger that makes nuclear, biological, and chemical weapons so appealing. Nuclear warfare historically dates back to the bombing of

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Table 2: Biological warfare agents^[4,11]

Agent		Disease
Category A		
Viral	Variola major	Smallpox
	Filoviruses and Arenaviruses	Viralhemorrhagic fevers
	<i>Bacillus anthracis</i>	Anthrax
Bacterial	<i>Yersinia pestis</i>	Plague
	<i>Clostridium botulinum</i>	Botulism
	<i>Francisella tularensis</i>	Tularemia
Category B		
Bacterial	<i>Brucella</i> spp.	Brucellosis
	<i>Burkholderia mallei</i>	Glanders
	<i>Burkholderia pseudomallei</i>	Melioidosis
Viral	Alpha viruses	Encephalitis
Rickettsia	<i>Rickettsia prowazekii</i>	Typhus fever
	<i>Coxiella burnetii</i>	Q fever
Chlamydia	<i>Chlamydia psittaci</i>	Psittacosis
Toxins		Toxic syndromes
Food safety threats		
Water safety threats		
Category C		
Emerging threat agents		<i>Nipah virus</i> , hantavirus

Nagasaki and Hiroshima in 1945. Dr. Michihiko Achiya's diary clearly describes the evolution of radiation symptoms and the constellation of signs associated with radiation poisoning.^[5]

The earliest mention of biological warfare is found on an Assyrian tablet dated from 600 BC which refers to a noxious pustule in the ear of grains. Biological warfare attacks took place at the Black Sea port of Kaffa (now Feodosia, Ukraine) in 1346. Other examples are the 'yellow rain' (trichothecene mycotoxins) attacks in Southeast Asia between 1974 and 1981; the weaponization of anthrax, botulinum toxin, and aflatoxin;^[6] and the release of sarin nerve gas in a Japanese subway in 1995 by the Aum Shinrikyo cult.^[3] Other examples include the use of arsenical smoke as early as 1000 BC by the Chinese, mustard gas by Egypt against Yemen, Agent Orange (a defoliant) during the Vietnam War, and more recently, vesicants (blistering agents, e.g. mustard gas) and nerve gas by Iraq.^[7]

NUCLEAR WARFARE

The cutaneous effects of a nuclear explosion are always due to one of three effects: blast injuries (direct and indirect), thermal burns, and radiation injuries. The majority of energy from a nuclear device is blast and thermal energy, the same energy released from a conventional bomb.^[8]

Thermal burns can be caused directly by the initial explosion or by fires that are secondary to it. Ionizing radiation, comprising charged alpha and beta particles, can only penetrate the skin, causing an initial erythema that can progress to superficial and deep ulcers. Conversely, gamma rays, X-rays, and neutrons, all of which have no charge, penetrate deeply into the body and can cause severe damage to vital tissues. Further cutaneous damage depends upon the extent of radiation exposure (Table 3). Individuals exposed to ionizing radiation need long term follow up.^[9]

Skin biopsy reveals keratinocyte damage with pyknotic nuclei, severe dermal edema, and subepidermal vesicle formation. With higher doses, endothelial cell swelling, intravascular thrombi, and fibrosis can be seen. Patient contamination poses little risk to medical personnel and should not hinder appropriate lifesaving measures in an emergency. Management includes decontamination and wound care. For decontamination, soap and water, normal saline or povidone iodine and water can be used. Wound care is similar to that for burns. Sulfhydryl drugs, pentoxifylline and recently topical tazarotene^[10] have beneficial effects.

BIOLOGICAL WARFARE

Biological warfare (BW) is defined as the 'employment

Table 3: Effects of nuclear radiation on the skin

Cutaneous effect	Onset post-exposure
Early	
<ul style="list-style-type: none">• Transitory erythema	Minutes-3 days
<ul style="list-style-type: none">• Deeper erythema	Day 7 - Day 14
<ul style="list-style-type: none">• Scaling, sunburn like reaction and hyperpigmentation	Day 14 - Day 21
<ul style="list-style-type: none">• Epilation	Onset 3 weeks
<ul style="list-style-type: none">• Secondary infections	
Late*	
<ul style="list-style-type: none">• Petechiae	> 3 weeks
<ul style="list-style-type: none">• Dry desquamation	>3 weeks
<ul style="list-style-type: none">• Wet desquamation	> 3 weeks
<ul style="list-style-type: none">• Fixed erythema	Persistent
<ul style="list-style-type: none">• Necrosis	Weeks to months
Sequelae	
<ul style="list-style-type: none">• Fibrosis	
<ul style="list-style-type: none">• Atrophy, keloidal or hypertrophic scarring	
<ul style="list-style-type: none">• Cutaneous malignancies	
Systemic syndromes	
<ul style="list-style-type: none">• Radiation hemopoietic syndrome (100 - 150 rads)	2-3 weeks
<ul style="list-style-type: none">• Gastrointestinal syndrome (400 - 1000 rads)	
<ul style="list-style-type: none">• Central nervous syndrome (1000 - 2000 rads)	

With higher doses at initial exposure changes may appear earlier

of biological agents to produce casualties in man or animals or damage to plants.' These agents are highly virulent, produce severe illness and are usually resistant to common modes of treatment. They are particularly attractive as they can be aerosolized, and reach the lower respiratory tract. A list of such agents and their management are mentioned in Tables 2 and 4.^[11-16]

Anthrax

Anthrax is primarily a zoonotic disease caused by *Bacillus anthracis* that produces a toxin consisting of a protective antigen, edema factor and a lethal factor. The WHO estimates that 50 kg of anthrax spores released upwind in a population center of 500,000 could result in up to 95,000 deaths, with a further 125,000 people incapacitated.^[17]

When the skin is the portal of entry, the earliest finding is that of a pruritic macule that progresses through papular, vesicular, or pustular stages to an ulcer with a blackened, necrotic eschar and surrounding nonpitting, gelatinous, and painless edema on an exposed surface. Satellite vesicles and painful regional lymphadenitis are other features. Systemic features are usually absent, but septic shock and severe edema can occur.

Diagnosis is based on gram stain, cultures or direct immunofluorescence. Anthrax toxin may be detected in the blood by immunoassays. Organisms can be demonstrated from a full thickness skin biopsy done from periphery of a vesicle or eschar. However, the absence of organisms in the biopsy specimen does not rule out anthrax. Specific management (Table 3)

Table 4: Management of the effects of biological agents adapted from [12-16]

Disease	Incubation period	Diagnostic samples	Diagnostic tests	Initial treatment	Prophylaxis
Anthrax	<i>Bacillus anthracis</i>	1-5 d (up to 6 wk?)	Blood CSF Pleural fluid Skin biopsy	Ciprofloxacin: 10-15 mg/kg (max 400 mg) IV q 12 h, or Doxycycline: 2.2 mg/kg (max 100 mg) IV q 12 h	Ciprofloxacin: 10-15 mg/kg (max 500 mg) PO q 12 h x 60 d, or Doxycycline: 2.5 mg/kg (max 100 mg) PO q 12 h x 60 d
Plague	<i>Yersinia pestis</i>	Blood Sputum Lymph node aspirate	Culture Gram's or Wright-Giemsa stain ELISA	Gentamicin: 2.5 mg/kg IV q 8 h or Doxycycline: 2.2 mg/kg IV (max 100 mg) IV q 12 h, or Ciprofloxacin 15 mg/kg (max 500 mg) IV q 12 h, or Chloramphenicol 25 mg/kg (max 1 g) q 6 h Supportive care	Doxycycline 2.2 mg/kg (max 100 mg) PO q 12 h x 10 d, or Ciprofloxacin 20 mg/kg (max 500 mg) PO q 12 h x 10 d, or Chloramphenicol 25 mg/kg (max 1 g) PO q 6 h x 10 d
Smallpox	Variola virus	Pharyngeal swab Scab material	ELISA, PCR Virus isolation		Vaccination within 4 d (consider vaccinia immunoglobulin: 0.6 mL/kg IM within 3 d of exposure for vaccine complications, immuno-compromised persons)
Tularemia	<i>Francisella tularensis</i>	Blood Sputum Tissue Serum	Culture Serology: agglutination EM	Gentamicin 2.5 mg/kg IV q 8 h, Doxycycline 2.2 mg/kg (max 100 mg) IV q12h or Ciprofloxacin 15 mg/kg (max 500 mg) IV q 12 h, or Chloramphenicol 15 mg/kg (max 1 g) IV q 6 h CDC trivalent antitoxin (serotypes A, B, E), 1 vial (10 mL) IV DOD heptavalent antitoxin (serotypes A-G) (IND) California Dept of Health immunoglobulin (IND) Supportive care	Doxycycline 2.2 mg/kg (max 100 mg) PO q 12 h x 14 d, or Ciprofloxacin 15 mg/kg (max 500 mg) PO q 12 h x 14 d None
Botulism	<i>Clostridium botulinum</i> toxin	Serum	Mouse bioassay	CDC trivalent antitoxin (serotypes A, B, E), 1 vial (10 mL) IV DOD heptavalent antitoxin (serotypes A-G) (IND) California Dept of Health immunoglobulin (IND) Supportive care	None
Viral hemorrhagic fevers	Arenaviridae (e.g. Lassa fever) Filoviridae (Ebola, Marburg)	Serum blood	Viral isolation Ag-ELISA RT-PCR Serology: Ab-ELISA	Ribavirin (arenaviruses) 30 mg/kg IV initially 15 mg/kg IV q 6 h x 4 d 7.5 mg/kg IV q 8 h x 6 d	None

includes ciprofloxacin and doxycycline. In 2001, adsorbed anthrax vaccine was used in the United States in combination with post-exposure prophylaxis (PEP).

Plague

Because of its high mortality (approximately 200 million deaths throughout history), *Yersinia pestis* has attracted attention for development as a possible BW agent. On inoculation 4-10% individuals may develop a pustule at the inoculation site.^[18] Terminal pneumonic and septicemic plague patients would develop livid cyanosis and large ecchymoses on the back. Septicemia could cause petechiae, purpura, ecchymoses, and acral cyanosis and necrosis leading to the infamous description, 'the Black Death.' Cases of ecthyma gangrenosum-like lesions and carbuncles due to plague have been reported.^[19]

Investigations include bubo aspiration for direct microscopy, and culture on blood agar of bubo aspirate, cerebrospinal fluid, blood and sputum. Isolation of patients for a minimum of 72 hours after detection and accompanying the administration of antibiotics (Table 3) is recommended. PEP must be adopted in those exposed but not manifesting the clinical features and the medical personnel involved in the management. An outbreak of endemic plague is heralded by affection of the mammalian reservoirs first while a BW attack would first affect the humans.

Tularemia

Tularemia is a zoonosis caused by *Francisella tularensis*. The commoner forms include the ulceroglandular form, which involves the skin and lymph nodes, and the typhoidal form. A cutaneous ulcer occurs in approximately 60% of patients and is the most common sign of tularemia.^[20] Ulcers are generally single lesions of 0.4 to 3.0 cm in diameter, with heaped-up edges and accompanied with systemic upset. The organism is difficult to culture; hence the diagnosis is usually established by serology.^[21] A live, attenuated vaccine is effective against aerosol infection.^[20]

Melioidosis

Burkholderia (formerly *Pseudomonas*) *pseudomallei* is a gram-negative bacillus. Cutaneous manifestations include severe urticaria,^[22] flushing and cyanosis.

Inhalational melioidosis could lead to pustules or cutaneous abscesses associated with lymphangitis, cellulitis, or regional lymphadenitis, but only after metastatic abscesses to the skin are formed, and this would be likely to take months.^[23]

Viral hemorrhagic fevers

Hemorrhagic fever viruses, with the exception of dengue, are potentially transmitted via aerosol. Cutaneous manifestations are non-specific and include flushing, petechiae, purpura, ecchymoses, and edema.

ELISA to detect specific IgM antibody responses must be done. One should not wait for viral cultures, which consume time, to initiate management (Table 3). Management includes supportive care for prevention of hypotension and shock. Medical personnel need to be protected. Isolation of the patient during active disease and strict barrier nursing must be adopted. Specific treatment may include ribavirin. Only yellow fever has a licensed vaccine.^[24]

Other viral fevers

The viral species important from the warfare context include variola (smallpox), monkeypox, and vaccinia. Smallpox has an incubation period of 7-17 days and a prodrome of 2-4 days. An enanthem on the buccal and pharyngeal mucosa starts on about the second day. An orderly progress of macules to papules, vesicles, pustules (sometimes umbilicated), and crusts distributed in a centrifugal pattern (in distinction to varicella) over a 1-2 week period is typical. Crusts are infective and detach in about 3 weeks leaving depressed, hypopigmented scars. Monkeypox greatly resembles variola, the only distinguishing feature being cervical and inguinal lymphadenopathy.

Trichothecene mycotoxins

Trichothecene mycotoxins ('Yellow rain')^[25] are the only potential BW toxins with cutaneous activity and manifestations. Mycotoxins are a diverse group of small molecular weight compounds produced by the fungi of five fungal genera: *Aspergillus*, *Penicillium*, *Fusarium*, *Alternaria*, and *Claviceps*. 'Yellow rain' was used in Southeast Asia between 1974 and 1981. Most attacks used yellow pigment, but some used red, green, white, or brown smoke or vapor. Vesication often occurred

with 'yellow rain' attacks. At low doses (nanograms), severe skin irritation with erythema, edema, and necrosis is observed.

A mask and full-body clothing are protective. The clothing gear and contaminated areas of skin should be washed with soap and water followed by a water rinse. Washing within 4-6 hours of exposure removes 80-98% of the toxin and prevents death and dermal lesions in experimental animals. High doses of systemic steroids decrease toxin injury.

Chemical warfare

A chemical warfare (CW) agent is a chemical substance, gaseous, liquid or solid, which might be employed because of its direct toxic effects on man, animals and plants.

The intention of chemical warfare is to reduce the enemy's numbers by increasing the morbidity. These agents are manmade, volatile, dermally active and act primarily on the skin, eyes and the upper respiratory tract.

The general management in all suspected CW attacks includes decontamination with adequate protection of the attending medical personnel. Skin protection against chemical weapons is provided by special protective clothing which may either be impermeable to liquids or which is permeable to air and moisture but has been treated to prevent chemical weapons agents from getting through. Individual protective equipment, as used by certain armies, includes special clothing, gas masks, and antidotes such as atropine and Fuller's earth (which absorbs the liquid CW agents).

Vesicants

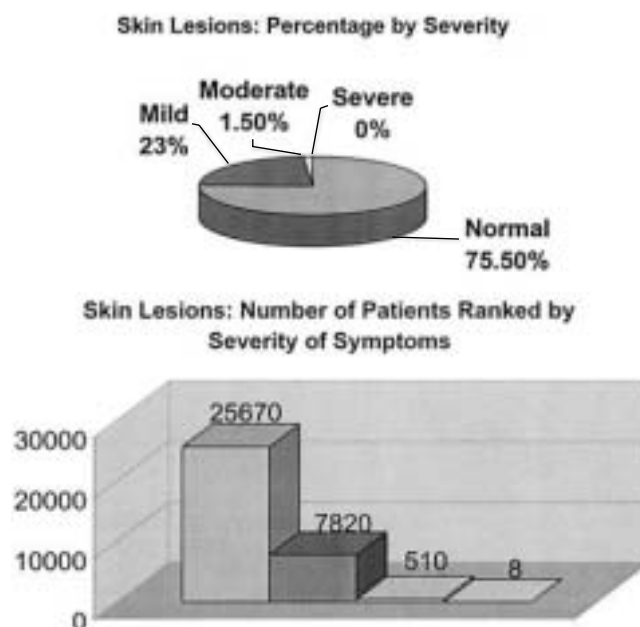
Vesicants were used widely in World War I and have been a dreaded threat in every war fought since then. They include the deadly trio of mustards, arsenicals and phosgene oximes.

Mustards

Mustards derive their name from their color, smell and taste which are similar to mustard. They are highly toxic in low concentrations to all organ systems. Clinical manifestations usually occur after four to six hours. In

a follow up of 34,000 Iranians over a 13-20 year period, Khateri et al noticed skin involvement in 24.5% (Figure 1).^[7] Skin manifestations include tenderness with dusky erythema or painless sunburn and hyperpigmentation involving both exposed and unexposed parts. Parts of the body where the skin is tender and well supplied with sweat glands are more severely affected. Itching and burning may be present. The fully developed bulla is thin walled and yellowish with surrounding erythema. At the end of twenty-four hours the typical appearance includes progressive, painful, virtually blinding conjunctivitis with constant rhinorrhea and a blistered face; the systemic symptoms include intellectual dullness or stupidity, headache, malaise and exhaustion. Cutaneous healing, with or without scarring, takes days to months.

Biopsy shows hydropic degeneration of basal cells and a split at the level of lamina lucida. No specific antidote



Mild: Dry skin, hypo- or hyperpigmentation or both; or depigmentation less than 18% of body surface; or in covered area, alopecia areata totalis, or universalis, generalized vitiligo, psoriasis (less than 20% of body surface), lichen simplex and limited prurigo, limited and mild eczema, limited scars in area of lesional involvement, single keloid without limitation in range of motion and in covered area, severe acne vulgaris and nodulocystic or suppurative hydradenitis, chronic hives or angioedema, vesicular lesions (localized), recurrent superficial fungal disease (chronic resistant dermatophytosis).
Moderate: Severe and diffuse eczema, generalized prurigo, diffuse scarring in uncovered areas, keloid with limitation in range of motion and in area outside of lesional involvement, generalized recurrent vesicular lesions, generalized and chronic itching with clinical lesions, psoriasis (more than 20% of body surface), basal cell carcinoma (BCC)
Severe: Skin or mucosal cancer (except BCC)
 (Reproduced with permission from Khateri et al^[7])

Figure 1: Follow up of 34,000 Iranians (exposed to mustard agent) over a 13-20 year period by Khateri et al^[7]

exists for mustard. Management includes personal protection, decontamination of the patient, and burns after care. Topical preparations to ameliorate the effects are albumin, collagen, powdered milk, gel or collagen dressings, activated charcoal slurry (for inactivation), ice bags (to cool the skin), trichloroacetic acid crystal application,^[26] vitamin E and niacin.

Arsenical vesicants

Chlorovinyldichloroarsine, or Lewisite, is an arsenical vesicant. Lewisite acts like mustard but does not cause immunosuppression. Other differences include earlier onset of pain (within seconds to minutes of exposure), a decreased incidence of skin infection, and a shorter healing time (2-3 weeks). Topical application of British anti-Lewisite (BAL) ointment within 5 minutes of exposure and an intramuscular injection of the same may decrease some of the epidermal and systemic toxicity of Lewisite.

Halogenated oximes

Phosgene oxime (CX) belongs to a class of chemical agents called urticants or nettle gases. It penetrates rubber and garments much more easily. Phosgene oxime is not a true vesicant, but it is extremely irritating to the epidermal and mucosal tissues. Immediate irritation and burning similar to stinging nettle is followed by urticaria like edema, and blistering after 24 hours. The skin can become necrotic, and healing may take 3 months or even longer. Specific treatment consists of immediate decontamination with water and sodium bicarbonate solution.

Nerve agents and cyanides

Five organophosphorous compounds are generally regarded as nerve agents (Table 1).

Nerve agents inhibit cholinesterase which then cannot hydrolyze acetyl choline. They differ from common organophosphorous agents by being much more toxic. The cutaneous effects of nerve agents are mostly limited to the areas of exposure. Increased sweating and goose bumps and fasciculations secondary to the muscarinic-like effect of the agents on eccrine sweat gland innervation and arrector pili are evident. Tabun and sarin cause cyanotic redness and edema of the skin respectively. Treatment of nerve agents consists of the

administration of atropine followed by pralidoxime chloride to reactivate acetylcholinesterase.

The cyanides (blood agents) act by inactivating cytochrome oxidase, preventing cellular oxygen utilization. The blood remains oxygenated and the mucosal membranes and skin of an affected individual appear dark red. The only effective therapy is amyl nitrite inhalation followed by sodium thiosulfate.

Riot control agents

Agents used in riot control (Table 1) are primarily lacrimators, sternutators and vomiting agents. Cutaneous reactions are secondary and not the primary intentional event. After an initial burning sensation, erythema develops and persists for an hour or so. However continual or large exposure results in intense erythema and vesiculation. Initial exposure may later be followed by an allergic contact dermatitis.^[27] Dermatological management is as for any dermatitis. Sodium hypochlorite (household bleach) is useful in the management.

The threat of chemical warfare is ever real and all dermatologists must be prepared to treat a large number of affected individuals if such an event occurs. The fact that medical personnel need to adopt adequate protection, follow strict decontamination procedures and triage during administration of treatment is what differentiates these casualties from ordinary accidents involving these chemicals.

CONCLUSION

The primary threat from chemical and biological agents today is from terrorists. Civilians in densely populated regions are the likely targets. Therefore, both civilian and military dermatologists need to be aware of how a biological, chemical or nuclear attack would present, to minimize its effects. Dermatologists can play a role in recognizing the early markers of an attack and in its management.

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