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Review Article

Delayed Complications and Long-term Management of Sulfur Mustard Poisoning: Recent Advances by Iranian Researchers (Part I of II)

CME Article

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Abstract

Chemical warfare agents are the most brutal weapons among the weapons of mass destruction. Sulfur mustard (SM) is a potent toxic alkylating agent known as "the King of the Battle Gases". SM has been the most widely used chemical weapon during the wars. It was widely used in World War I. Thereafter, it was extensively employed by the Iraqi troops against the Iranian military personnel and even civilians in the border cities of Iran and Iraq in the period between 1983 and 1988. Long-term incapacitating properties, significant environmental persistence, lack of an effective antidote, and relative ease of manufacturing have kept SM a potential agent for both terrorist and military uses. Even 3 decades after SM exposure, numerous delayed complications among Iranian victims are still being reported by researchers. The most common delayed complications have been observed in the respiratory tracts of chemically injured Iranian war veterans. Also, skin lesions and eye disorders have been observed in most Iranian SM-exposed war veterans in the delayed phase of SM intoxication. Thus, extensive research has been conducted on Iranian war veterans during the past decades. Nevertheless, major gaps still continue to exist in the SM literature. Part I of this paper will discuss the delayed complications and manifestations of exposure to SM among Iranian victims of the Iran–Iraq conflict. Part II, which will appear in the next issue of Iran J Med Sci, will discuss the long-term management and therapy of SM-exposed patients.

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What's Known

- Sulfur mustard (SM) is the most widely used chemical weapon.
- Eyes, skin, and the respiratory system are 3 major target organs. Since SM affects DNA synthesis, several delayed effects are observed in the body, particularly on the target organs. Delayed respiratory complications are the most prominent and life-threatening ones in SM-exposed patients.

What's New

- Neuropsychiatric, hematologic, and immunologic disorders related to the delayed complications in the 3 target organs have been described based on previous research on SM-exposed patients.
- Atherosclerosis and ectasis of coronary arteries and ophthalmic posterior chamber changes in SM-exposed patients are our new findings.

Introduction and History

Sulfur mustard (SM) is a toxic alkylating chemical warfare agent (CWA) and has been the most effective and widely-used CWA in the past century.[1] Military use of SM during wars dates back to World War I (WWI). Although there are presently more toxic CWAs, SM has remained the chemical weapon of choice in modern tactical warfare, with the sobriquet of "the King of the Battle Gases", as evidenced by its use during the WWI and in the Iran–Iraq conflict between 1983 and 1988.[2]

Injuries caused by SM are usually nonfatal. Mortality from exposure to SM was only 3% during the WWI and 4% in the Iran–Iraq conflict. However, the long-term complications of SM cause significant morbidity.[3,4] SM is a powerful blistering agent, to the extent that a 0.1-mL drop of pure SM contains 20000 times the minimum dose required to blister the skin.[5]

SM is known by different names:

H: Also known as "HS" ("Hun Stuff"): after the inventor of the Levinstein process for SM manufacturing.

Yperite: Ypres was the site of its first military use in Belgium.

LOST: Acronym of the German chemists LOmmel and STeinkopf.

Yellow cross: During the WWI, German shells were marked with a yellow cross that meant "skin damaging agent".

HD: Military code of distilled SM, which is approximately 96% pure, and H is the military code for crude SM.[1,2,6-11]

Acute and long-term incapacitating properties of SM, in combination with the lack of an effective antidote, significant environmental persistence, and relative ease of manufacturing, have kept it a potential agent for both military and terrorist uses.

Historically, SM was prepared at around 1822 by Despretz.[2] In 1886, pure SM was synthesized by Victor Meyer through the reaction of thiodiglycol with phosphorus trichloride.[12] Nonetheless, SM for use in warfare was produced by what is known as the Levinstein process, the reaction of ethylene with sulfur dichloride, by the early 1900s during the WWI.[9]

The first full-scale use of SM began in summer 1917, when German troops launched a chemical attack in Ypres, Belgium, using more than 1 million SM shells against allied troops.[13] Although the use of chemical weapons had been outlawed according to the Hague convention in 1907, during the WWI, many countries utilized CWAs in battlefields. SM was extensively used throughout the WWI by both sides of the war between 1914 and 1918. During the WWI, over 1 200 000 soldiers were intoxicated with SM and about 400 000 of them needed long-term medical care.[14-16] In the U.S. army, out of 36 956 chemically injured soldiers, 27 711 (75%) were intoxicated by SM. According to the Contamination Control Unit of the British army, out of 160 970 chemical warfare victims, 124 752 (77.5%) were due to SM poisoning.[14] In the aggregate, it is estimated that SM caused around 80% of the chemical casualties in the WWI.[17] Thus, it is no wonder that this war is known as "the Chemist's War".[18]

By the time the WWI ended, humanity had learned a lesson about the brutal nature of chemical weapons; still, many military experts believed that future wars would be fought under the new models of CWAs. Sure enough, it did not take long for SM to reappear in other conflicts.

Spain and France used mustard gas bombs to restrain the Berber rebellion in the 1920s.[19] The Italian conflict in Ethiopia was particularly noteworthy: SM was sprayed and dropped from Italian planes and contributed significantly to the Italian victory.[20] There are sparse documents of SM use in 1930s by Poland against Germany and by Japan against China.[21] In the period between the 2 world wars, SM was a key part of defensive planning.

In 1925, the first international accord on the banning of chemical warfare was agreed upon in the Geneva Convention and a widespread campaign was formed to ban CWAs.[22]

During World War II (WWII), the so-called "Unfought Chemical War", there is no evidence of deliberate SM attack. As the only recorded evidence, in December 1943, an Allied ship carrying large scales of SM and other munitions was attacked by German troops and exploded in the harbor of Bary, Italy, which led to more than 600 casualties.[13,21,22]

Since the WWII, accusations of chemical attacks have been common. SM attack by Egyptian forces in Yemen is the most authentic one. Egypt was the first Middle Eastern country to use chemical weapons. It employed phosgene and SM against Yemeni Royalist forces from 1963 to 1967.[23]

During the 20th century, the greatest military use of SM, however, took place between 1980 and 1988 throughout the Iran–Iraq war. In widespread chemical assaults by the Iraqi army, Iran sustained 387 attacks, during which in excess of 100 000 troops and a significant number of civilians were poisoned. There are thousands of Iranian victims who are still suffering from the long-term effects of CWAs, particularly SM.[24] Several features of the Iran–Iraq war render it unique among the conflicts of modern times: the war was the longest warfare attack and one of the bloodiest as well as the most costly of the 20th century.[25]

The Iran–Iraq Chemical War

The Iran-Iraq war broke out on August 22, 1980, when Iraq launched its invasion of Iran. There have been reports of a large-scale use of CWAs, including SM and nerve agents, by Iraqi troops against Iranian troops and civilians (and also against members of the Kurdish population

in Iraq), with the number of chemical attacks amounting to over 30 during the war.[26]

The first use of SM in this war was in November 1980, when Iraqi troops attacked Susangerd (a western Iranian city at the border with Iraq). In defiance of the international conventions on the prohibition of CWAs, Iraqi troops continued to launch extensive chemical attacks, particularly in the period between 1983 and 1988. Some catastrophic chemical attacks were carried out in Majnoon Island in February 1984, Hawizah Marsh in March 1985, Sumar/Mehran in October 1987, and Al-Faw in February 1986 and April 1988, as well as in many western border cities of Iran.[12,26,27]

In March 1988, a chemical attack in Halabja, a Kurdish town in Iraq, caused rapid deaths from exposure to SM and other CWAs, including sarin. It was reported that over 5000 Kurdish civilians were killed in the Iranian-occupied village of Halabja during the chemical attack.

It is estimated that more than 1800 metric tons of mustard gas were used against Iran during the war. The last SM attack by Iraq was in July 1988 at the south central border of Oshnavieh.

By the end of the war, 398 500 injured individuals as well as 52 000 chemical war victims needed medical and health care follow-up in Iran.[28,29] In the aggregate, more than 100 000 chemical causalities and 25 000 chemical mortalities were recorded in Iran during the war.[30] According to data provided by the Iranian Veterans and Martyrs Affair Foundation (VMAF), even 2 decades after the war, about 40 000 Iranian veterans still have complaints of the delayed effects of SM exposure.[1,2,12,31] The Iraqi attacks demonstrated the deadly and destructive nature of chemicals in modern warfare. An estimated number of Iranian morbidities and mortalities due to chemical exposures during the Iran–Iraq war is presented in table 1.[28,32]

After the Iran-Iraq War

CWA production in Iraq continued even after the Iran–Iraq war and during the Persian Gulf War. After the end of the Gulf War, the U.N. specialists destroyed more than 480 000 liters of Iraq's chemical agents, including SM, as well as 1.8 million liters of its precursor.[23] In summer 2013, more than 1300 metric tons of CWAs were stockpiled in Syria, which were subsequently used in the battles between the Syrian government and the opposition forces. More than 1300 people died and thousands were intoxicated. Although the use of sarin was confirmed by the U.N. mission on the Ghouta area of Damascus (August 21, 2013), the use of blistering agents such as SM remained inconspicuous.[24,33] Military use of SM during conflicts is summarized in table 2.

To date, SM has been used in more than a dozen conflicts, killing and severely injuring millions of military personnel and civilians.[24] At present, Iran is a unique country in the world insofar as it currently hosts tens of thousands of chemically injured war veterans.

Chemical Structure and Properties

SM ($C_4H_8Cl_2S$) (2,2´-dichloroethyl sulfide; HD) is a poorly volatile oily liquid at room temperature with a faint odor of mustard or garlic. SM is clear or straw-colored while pure but dark while crude. It is barely soluble in water (0.07% at 10°C) but highly soluble in organic solvents, lubricants, and fuels.[4,38] SM is heavier than water when it is in the form of liquid and also heavier than air when it is in the form of vapor or gas.[4] It evaporates at 15 °C and in warm temperatures becomes less stable and its vapor form, therefore, increases, and at night it sediments because of the decreased temperature.[39]

SM can easily penetrate into the cell membrane of wood, leather, plastic (plastic breathing masks), rubber, porous cloth, food, and plants, whereas metal, glass, and glazed tiles are resistant against penetration.[40,41] Soil and all objects, including porous materials, foodstuffs, paint, and varnish coatings, may

Table 1: Estimate of the number of Iranian morbidities and mortalities due to chemical attacks during the Iran–Iraq war

Number of Iranians exposed to chemical weapons during the war	1 000 000 people
Number of Iranians who received medical care during their heavy exposures to chemical war gases	100 000 people
Iranians killed by the immediate toxic effects of chemical warfare agents	5500 (3500 people by nerve agents and 2000 people by mustard gas)
Total Iranian mortalities due to poisoning by chemical warfare agents during the war	25 000
Iranians with the chronic effects of chemical warfare agents (not registered and registered)	40 000–70 000 people
Civil Iranians with chronic toxic effects of chemical warfare agents (registered and not registered)	35 000 people

become contaminated by SM for long periods of time, especially in cold and damp climates.[42]

Chemical characteristics of SM such as its low volatility and low solubility in water result in the lengthy persistence of the compound in the field, and this is why it is generally regarded as a "persistent" chemical agent.[2,43] Physicochemical characteristics of SM are shown in table 3.

Toxicodynamics

After absorption, SM undergoes intramolecular cyclization, which leads to the formation of an ethylene episulfonium ion intermediate.[44] The cyclic intermediate reacts with and alkylates a wide variety of electron-rich biological molecules.[21,45] Thus, it can attack and break the DNA at specific nucleotides. The result

Table 2: History of sulfur mustard (SM) military use in conflicts

Year	Event	Ref.
1917-1918	First use in World War I by the German army against the soldiers and civilians in France and Belgium (at Ypres).	(2, 4)
1919	United Kingdom used SM against the Red Army of Russia.	(34, 35)
1921-1927	Spain and France used SM against RIF insurgents in Morocco.	(34, 35)
1930	Italy applied SM against Libya.	(34, 35)
1934	Soviet troops used SM against Xinjiang, China.	(34, 35)
1935-1936	Italy breached the Geneva Protocol treaty and began conquest of Abyssinia (Ethiopia) using SM delivered by aircraft spray.	(4)
1943	A cargo ship carrying a large amount of SM exploded in the harbor of Bari, Italy. The gas was disseminated in the area, injuring more than 600 people.	(2)
1937-1945	Japan invaded china and used chemical weapons (including mustard gas, phosgene, and hydrogen cyanide) against China.	(4, 36)
1963-1967	Egypt used phosgene and SM aerial bombs in support of south Yemen against the Yemeni royalist forces during the Yemeni civil war.	(2, 14)
1983-1988	Iraq extensively used SM and nerve agents against Iran.	(12, 15)
1988	Iraqi army killed 5000 Iraqi civilians in Halabja using SM and the nerve agent sarin.	(12, 15)
1995 and 1997	Sudan applied SM against insurgents in the civil war.	(37)
August 2013	Chemical weapons were stockpiled in Syria, which were subsequently used against the opposition forces.	(24, 33)

Table 3: Physiochemical properties of sulfur mustard

Chemical formulation	$C_4H_8Cl_2S$
Chemical synonyms	Bis (2-chloroethyl) sulfide, 1,1-1thiobis (2-chloroethane); 1-chloro-2-[(2-chloroethyl) thio] ethane; HD, Distilled mustard gas; Yperite, Yellow cross
CAS No.	505–60-2
Color	Colorless, straw color, or pale yellow (pure) to dark brown or black color (impure)
Form	Oily liquid (in room temperature). It transforms into aerosols at 105°C
Odor	Smell of garlic, horseradish, addled egg or fried vegetables or a mustard-type odor
Solubility	Sparingly soluble in water, (water solubility 0.092 g/100 g at 22°C); soluble in organic solvents; lipophilic and highly fat-soluble
Melting point	13–14°C
Boiling point	215–227°C
Volatility	610 mg/m^3 at 20°C
Specific gravity	1.27
Vapor pressure	HD: 0.072 mm Hg at 20°C; 0.11 mm Hg at 25°C
Liquid density	1.274 g/mL
Vapor density	5.4
Solid density	1.37 g/mL
Molecular weight	159.08
Half life	5 min at 37°C
Metabolites	Thiodiglycol, the main metabolite of SM in urine, which can be detected by chromatography with 1ng/mL sensitivity
Excretion	The bulk of SM in the body is excreted through the kidneys after conjugation with amino acid lecithin.
Antitoxin	No specific antitoxin

is manifested in the chromatid aberration and inhibition of the DNA, RNA, and protein synthesis.[46] Although SM reacts with RNA, proteins, and phospholipids, the consensus view is that it is a DNA-alkylating agent with an effective role in delayed healing.[46-48] The major alkylating site of the mammalian origin is the nitrogen residue of guanine.[49,50] Cell death from DNA cross-linking is delayed until the DNA replication phase and cell division. However, at higher cellular exposures, other mechanisms become important, causing more rapid cell death. One mechanism that may be involved in the acute damage of SM is nicotinamide adenine dinucleotide depletion. Other potential mechanisms thought to be involved are related to the rapid inactivation of sulfhydryl-containing proteins and peptides such as glutathione. Glutathione and other sulfhydryl compounds are critical in maintaining the appropriate oxidation-reduction state of cellular components as well as in reducing reactive oxygen species in the cell; they can, thus, be preventive in the peroxidation and loss of membrane integrity.[51,52] Glutathione depletion produces reactive oxygen. Acute damage to the mucous membrane and skin, observed following exposure to SM, is probably due to one or more of these mechanisms, leading to necrosis and cell death. In addition to the mentioned mechanisms, SM has some other adverse effects on cells such as mitosis inhibition (effects on the immunologic and hematologic system as well as epithelial and germinal tissues), mutagenesis, carcinogenesis, and cholinomimetic effects.[53]

Kehe et al.[54] (2008) reported that SM in the molecular level induces the releasing of cytokines, prostaglandins, matrix metalloproteinases, and serine proteases. It also increases DNA damage, oxidative stress, and impaired energy metabolism. Consequently, cellular infiltration, apoptosis, and necrosis occur, which is continued by erythema and pain and formation of vesicles, blisters, ulcer, and impaired wound healing.

Toxicokinetics

SM can be absorbed through inhalation and direct contact to the skin via the anterior surface of the eyes or through the gastrointestinal tract following consumption of contaminated food. Injection, as a very rare route of absorption, has not been reported in humans.[31] The skin plays a very important role as a port of entry for the liquid or vapor of SM. Through hydrolysis reaction, it produces half-mustard and thiodiglycol, a major metabolite excreted in urine.[12]

From the total SM amount that penetrates, 80–90% is rapidly transported away from the site of absorption by the circulation and only 10–20% is fixed to macromolecules in the skin.[55-57] In terminally ill patients with cancer, 80–90% of the radioactivity of the injected SM, labeled with ^{14}C, disappears after several minutes from the blood and is excreted mainly in urine within 24 hours.[58] Only limited data are available on the biotransformation of SM in humans. Two studies in rats have revealed that conjugation with glutathione is more important than hydrolysis.[58,59] Other recent investigations have demonstrated that 60% of the dose is excreted in the 24-hour urine.[60]

SM distribution is quick (5.56 min), with a terminal half-life of 3.59 hours. Its volume of distribution at a steady state is 74.4 L.[60] Whole-body autographic studies have shown that elevated radioactivity is detected in the nasal region, followed by the kidneys, liver, and intestines at all times of study following a percutaneous or intravenous administration of ^{35}S-labeled SM.[61] In human beings, unhydrolyzed SM can be present in the brain and fat depots even days after exposure.[62]

Delayed Complications of SM Poisoning among Iranian victims

Distribution of Delayed Complications in Different Organs

According to the effects of SM on body organs, SM complications are divided into acute and chronic/delayed phases. While the term "chronic" is referred to occupational exposure and comes from continuous intakes of the poison over a relatively long period of time, "delayed" or "late" seems to be more suitable for long-term SM effects following battle-field exposure.[12]

Even 3 decades after the Iran–Iraq war in 1980s, the delayed toxic effects of SM poisoning among the surviving victims are still not well-understood. Incidence of organ involvement has been reported differently during the years in various Iranian war veterans with different severities.

In the first Iranian report on the delayed toxic effects of SM poisoning, Balali-Mood[63] (1984) evaluated 236 Iranian SM victims 2–28 months after exposure. The most common complications were found in the respiratory tract (78%), followed by the central nervous system (45%), skin (41%), and eyes (36%). Later on, Balali-Mood and colleagues[64] (1992) reported that most of the SM delayed complications among 1 428 Iranian chemical victims 3–9 years after exposure were in the respiratory tract (90%),

skin (88%), eyes (78%), nervous system (71%), gastrointestinal tract (55%), genitalia (52%), and hematopoietic system (38%).

Khateri et al.[65] (2003) reported findings that were somewhat different from the studies by Balali-Mood. In their study on 34 000 Iranians veterans exposed to SM, the most common complications were observed in the lungs (42.5%), eyes (39.5%), and skin (24.5%). The difference between the studies may be due to the difference in the study population and time after exposure as the patients in the studies by Balali-Mood had severe SM exposure and were evaluated in the first years post exposure, while most of the patients in the investigations by Khateri and colleagues had mild SM exposure and were evaluated 18–23 years following exposure.

Holisaz et al.[66] (2003) in a study on 100 Iranian chemical victims reported dermatologic and ophthalmic complications in 94%, pulmonary complications in 75%, hematologic complications in 10%, and gastrointestinal complications in 5% of the victims.

Balali-Mood and colleagues[67] (2005) described the late toxic effects of SM poisoning in a group of 40 severely intoxicated Iranian war veterans 16–20 years after exposure and reported that the lungs (95%), peripheral nerves (77.5%), skin (75%), and eyes (65%) were the most frequently affected organs.

Namazi et al.[68] (2009) studied 134 patients with the delayed complications of SM poisoning. The most commonly affected organs were the lungs (100%), skin (82.84%), and eyes (77.61%). Distributions of the delayed complications of SM in different body organs according to several studies in Iran are listed in table 4.

Delayed Upper Respiratory Tract Complications

Airway narrowing in the late phase is a sequel of acute damage to the trachea and large airways due to the scarring or granulation tissue formation in the acute phase. Airway stricture usually develops 2 years after exposure.[1,74] Moreover, in the delayed phase, laryngitis is one of the main delayed complications of the upper respiratory tract among Iranian SM-exposed war veterans.[75] Other delayed effects of SM in the upper airways are characterized by the chronic inflammation of the oral cavity, pharynx, and larynx as well as functional aphonia and the inflammation and ulceration of the palate, nasopharynx, and oropharynx.[76]

Expectoration and chronic cough are the main upper respiratory tract symptoms of long-term SM intoxication among patients.[77] The most important causes of chronic cough in the late phase are postnasal drip syndrome, postnasal discharge due to chronic sinusitis, tracheobronchial collapse, gastroesophageal reflux disease, bronchospasm, and bronchiectasis.[78] Ghanei and colleagues[78] (2006) evaluated 39 patients with chronic cough exposed to a high single dose of SM during the Iran–Iraq war. Paranasal sinus mucosal abnormalities were identified in 76.9% of the patients, among whom 20.5% had severe mucosal thickening.

Late laryngeal effects of SM were assessed in 50 victims 20 years following SM exposure by Akhavan and colleagues[76] (2009), who reported chronic laryngitis in 82%, intermittent dysphonia in 74%, hoarseness in 32%, harshness in 14%, laryngeal nodules in 12%, and continuous dysphonia in 4% of the patients. In addition, unilateral vocal cords paralysis was identified in 6% of the patients. Vocal cord paralysis was identified as a long-term neurotoxic effect of SM and vocal cord nodules as a result of laryngeal and bronchial infections. Also, it was concluded that the hypertrophy of the false vocal cords is probably due to the dysfunction of the edematous true vocal cords and dysphonia.

Balali-Mood et al.[79] assessed the delayed toxic effects of SM on the upper respiratory tract in 43 male victims of the Iran–Iraq war 20–25 years after poisoning and reported dysphonia and chronic sinusitis as the most common delayed complications in the upper respiratory tract. Dysphonia was found in 79.1%, postnasal discharge in 41.9%, lower larynx position in 30.2%, vocal cords limitation in 25.6%, and mucosal inflammation of the larynx in 14.8% of the patients. The authors concluded that most of the delayed toxic effects of SM in the upper respiratory tract were inflammatory and infectious complications.

Most of the available evidence regarding mustard-induced cancers of the respiratory tract is related to lung cancer and there is limited evidence about the carcinogenic effects of mustard gas in the upper respiratory tract. Sparse cases of bronchogenic carcinoma have already been reported in Iranian war veterans.[80] Although nasopharyngeal carcinoma and bronchogenic carcinoma have been case reported in Iranian war veterans poisoned by SM,[70,73,81] a study in 1997 on 197 chemically injured veterans of the Iran–Iraq war could not find any more cases of bronchial carcinoma or other lung cancers in the victims 10 years after exposure to SM.[82]

Delayed Lower Respiratory Tract Complications

Respiratory problems are the greatest cause of long-term disability among Iranian veterans with combat exposure to SM gas. Many Iranian

Table 4. Distribution of the delayed complications of sulfur mustard in various organs in several studies in Iran

Author (s)	Publication Year	Population	Case Numbers	Distribution of Complications	Ref. No
Balali-Mood et al.	1984 (2–28 months after exposure)	Veterans	236	Respiratory tract (78%), central nervous system (45%), skin (41%), and eyes (36%)	(63)
Shirazi and Balali-Mood	1987 (2 years after exposure)	Veterans	77	Lungs (58%), eyes (46%), and skin (38%)	(69)
Balali-Mood et al.	1992 (3–9 years after exposure)	Veterans	1428	Lungs (90%), skin (88%), eyes (78%), neural system (71%), gastrointestinal system (55%), and hematopoietic system (38%)	(64)
Khateri et al.	2003 (13–20 years after exposure)	Veterans, civilians	34 000 (mild-to-severe exposure)	Lungs (42.5%), eyes (39%), and skin (24.2%)	(65)
Holisaz et al.	2003 (14–20 years after exposure)	Veterans	100	Skin (94%), eyes (94%), lungs (75%), hematopoietic system (10%), and gastrointestinal system (5%)	(66)
Balali-Mood et al.	2005 (16–20 years after exposure)	Veterans	40	Lungs (95%), peripheral nerves (77.5%), skin (75%), and eyes (65%)	(70)
Etezad-Razavi et al.	2006 (16–20 years after exposure)	Veterans	40	Lungs (95%), skin (90%), and eyes (65%)	(71)
Ghasemi-Boroumand et al.	2008 (19 years after exposure)	Civilians	600	Lungs (45.8%), eyes (37.7%), and skin (31.5%)	(72)
Namazi et al.	2009 (17–22 years after exposure)	Veterans	134	Lungs (100%), skin (82.84%), and eyes (77.61%)	(68)
Zojaji and Balali-Mood et al.	2009 (17–22 years after exposure)	Veterans	43	Lungs (95%), peripheral nerves (77%), skin (73%), and eyes (68%)	(73)

soldiers who experienced SM inhalation during the Iran–Iraq war developed lasting pulmonary injury.

Khateri et al.[65] (2003) conducted a study on 34 000 Iranians exposed to SM and reported that 14 450 (42.5%) of them were afflicted by respiratory problems. As time passes, the respiratory complications of SM exacerbate, while eye lesions do not change significantly and dermal complications tend to decrease.[1,7,31,83] Even victims with no acute symptoms of SM poisoning (subclinical exposure) may suffer from late respiratory complications.[31,84]

In the delayed phase of SM intoxication, chronic cough, expectoration, and dyspnea have been found as the most common respiratory symptoms among Iranian war veterans poisoned by SM.[7,64,77] Hemoptysis (mainly streaky), chest tightness, and nocturnal dyspnea are also frequent. A triad of cough, expectoration, and dyspnea was detected in more than 80% of Iranian war veterans 3 years after SM exposure[85] and in 48.83% of Iranian war veterans 25 years after SM exposure during the Iran–Iraq war.[77]

Namazi et al.[68] (2009) studied the long-term complications of SM intoxication in 134 chemically injured war veterans about 20 years after exposure. In their study, all the patients suffered from dyspnea, 72.38% from coughing, and 52.98% from expectoration.

The most objective findings in the delayed phase of SM respiratory complications are generalized wheezing (the most common sign), crackles, clubbing, decreased lung sounds, and cyanosis.[7,31,64,75]

Spirometry is a valuable diagnostic tool for the evaluation of pulmonary function impairment during the regular follow-ups of SM victims.[80] Pulmonary function testing has revealed more obstructive patterns than restriction, and approximately half of these obstructive spirometric results are reversible in response to inhaled bronchodilators.[1,2,31,64] However, abnormal spirometric findings in general and restrictive patterns in particular tend to increase over time and they have been reported as the dominant patterns of spirometry among SM patients in more recent studies.[31,43,77,82] Emad et al.[82] (1997) in a study on 197 Iranian war

veterans 10 years after a heavy SM exposure reported the diversity of the effects of SM on respiratory patterns according to possible lung fibrosis, based on spirometric findings and lung biopsies.

Increased bronchovascular marking, hyperinflation, and pneumonic infiltration as well as bronchiectasis and radiologic evidence of pulmonary hypertension are the most frequent chest X-ray findings in the delayed phase of SM intoxication.[7,70,86,87] As pulmonary function testing and radiography are not sensitive enough for the detection of the delayed respiratory complications among SM victims, high-resolution computed tomography (HRCT) is the imaging modality of choice in the diagnosis of the SM-induced pulmonary complications.[79,86,88,89] An HRCT study of Iranian war veterans with the delayed complications of SM poisoning revealed a series of delayed destructive pulmonary sequelae such as chronic bronchitis (58%), asthma (10%), bronchiectasis (8%), large airway narrowing (9%), and pulmonary fibrosis (12%).[82]

Hefazi et al.[90] (2005) in a respiratory survey of 40 severely SM-intoxicated Iranian war veterans reported that the main delayed respiratory complications were chronic obstructive pulmonary disease (35%), bronchiectasis (32.5%), asthma (25%), large airway narrowing (15%), pulmonary fibrosis (7.5%), and simple chronic bronchitis (5%). Chest HRCT findings of 23 patients 14 years after exposure to SM revealed 100% bronchial wall thickening, 76% air trapping, 74% bronchiectasis, 35% mosaic parenchymal attenuation, and 26% interlobular septal thickening.[91]

Chronic obstructive pulmonary disease has a significant impact on quality of life in long-term survivors.[92] Late-onset pulmonary fibrosis has been observed in several Iranian war veterans with combat exposure to SM. A histopathological study of transbronchial lung biopsies from SM-exposed Iranian war veterans revealed variegated and diffuse fibrosis in 86% and 4% of the patients, respectively.[82] An electron microscope study of 7 transbronchial lung specimens of SM-poisoned Iranian war veterans conducted by Sohrabpour[93] (1992) revealed abnormal findings, consisting of proliferation, desquamation, and degeneration in the bronchial epithelial cells; interstitial fibrosis; increased type I and type II alveolar epithelial cells; and hyperplasia of the ciliated and goblet cells. The fibrotic process in the lungs may be progressive. Diffusing lung capacity could be used as an objective monitor of the degree of lung fibrosis, as well as a predictor of the prognosis.[74,82,84]

Bronchiectasis usually begins bilaterally in the lower lobes of the lungs and then has cephalic progression. Direct effects of SM on the bronchial wall mucosa and recurrent respiratory infections among SM-exposed war veterans are known to be responsible for the development of bronchiectasis.[31] According to Balali-Mood[67] (2005), both the severity and frequency of bronchiectatic lesions in SM-exposed victims tend to increase over time. Lung HRCT in a patient with diffuse cylindrical bronchiectasis in the lower lobes under the corresponding author's medical care, 25 years post SM exposure, is shown in figure 1.

In many cases, opportunistic infections of the injured respiratory tract result in bronchial pneumonia and even septicemia. Additionally, hemorrhagic inflammation and serious erosions of the tracheobronchial tree are followed by secondary complications such as suppurative bronchitis, chronic infections, and life-threatening stenosis of the entire bronchial tree.[93] Hypoxemia and hypercapnia are observed in severe cases of bronchitis and in bronchiectatic lesions, leading to pulmonary hypertension and core pulmonale in the severe stages of the complications.[67,84,94] Mediastinal emphysema,[95] alveolar microlithiasis,[96] and unilateral lung collapse[97] may rarely occur among SM victims as delayed complications.

Another long-term respiratory effect of SM is bronchiolitis obliterans. Lung HRCT in a patient with air trapping consistent with bronchiolitis obliterans under the corresponding author's medical care, 25 years post SM exposure, is depicted in figure 2.

In an HRCT study of 50 Iranian patients with the delayed respiratory complications of SM, air trapping (76%), bronchiectasis (74%), and mosaic parenchymal attenuation (72%) were reported as the most frequent findings, revealing the diagnosis of bronchiolitis obliterans.[98] This was also proved by subsequent pathologic studies.[91,99] In a cross-sectional study conducted by Beheshti and colleagues[91] (2006), histopathological studies of lung biopsies from 14 SM-exposed war veterans revealed bronchiolitis obliterans organizing pneumonia. Bronchiolitis obliterans seems to be one of the main underlying pulmonary diseases in the delayed phase of SM intoxication and depends on the host's response rather than a dose-response manner.[100]

Bronchoscopic appearance of the airway mucosa is a combination of erythema, chronic inflammatory changes, and mucosal thickening in most SM-exposed patients in the late phase of poisoning.[31]

Bronchoalveolar lavage (BAL) fluid analysis has revealed increased inflammatory cells even more than 2 decades after SM exposure.[101,102]

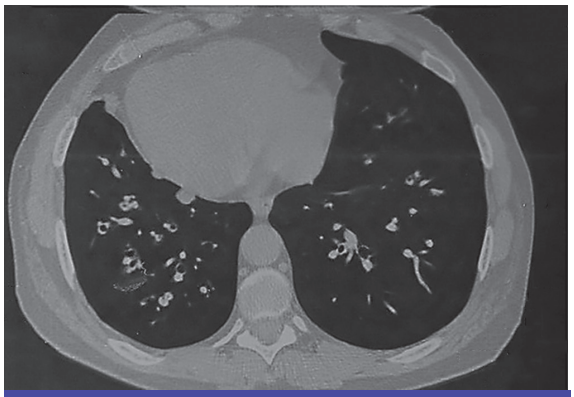

Figure 1: High-resolution computed tomography of the lungs in a mustard gas-exposed case, 25 years post exposure. Diffuse cylindrical bronchiectasis is observed in the lower lobes of both lungs. (from the private collection of the corresponding author)

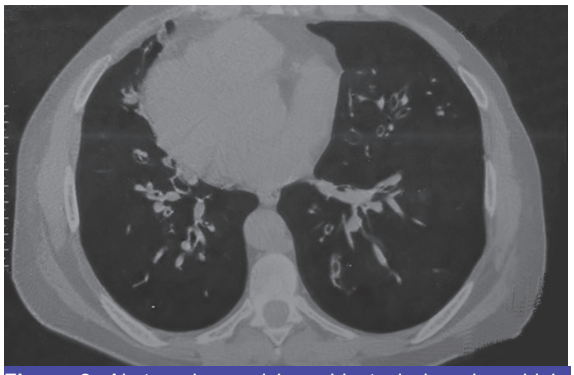

Figure 2: Air trapping and bronchiectasis in a lung high-resolution computed tomography of a mustard gas-exposed case, 25 years post exposure, consistent with bronchiolitis obliterans. (from the private collection of the corresponding author)

Inflammatory patterns of the BAL analysis have been reported to be neutrophil-dominant in previous studies.[103]

Emad and colleagues[82] stated that a BAL fluid analysis of their SM patients illustrated an ongoing local inflammatory process tending toward the development of pulmonary fibrosis, years after initial exposure. The BAL fluid analysis also revealed that pulmonary fibrosis following SM exposure is correlated with increases in inflammatory cytokines and chemokines, including IL-1α, IL-1β, IL-5, IL-6, IL-8, IL-12, IL-13, and tumor necrosis factor-α (TNF-α).[104,105]

Typical SM-exposed patients have normal values of albumin and immunoglobulin in the BAL fluid. Nonetheless, those diagnosed with asthma tend to show an increased immunoglobulin level as well as an increased eosinophil count in the BAL fluid analysis.[91,106]

Reduced levels of lung glutathione have been reported in survivors 20 years post exposure, which is directly linked with altered pulmonary functioning.[107]

Aghanouri et al.[108] reported increased levels of transforming growth factor β1 (TGF-β1) and TGF-β1 receptors in the BAL fluid of SM-exposed Iranian war veterans and concluded that since TGF-β1 can cause bronchiolitis obliterans changes and is substantially increased in the BAL fluid and target tissues of SM patients, the role of bronchiolitis obliterans as the main underlying pathology in mustard lung becomes evident.

SM is termed “the mutagenic alkylating agent”. In vitro studies have shown that mustard is both mutagenic and carcinogenic. Human data from chemical factory workers with prolonged exposure to mustard compounds show an increased risk of pulmonary carcinoma. Nevertheless, figures have failed to make a strong case and there is controversy around a carcinogenic effect after a single low- or high-dose exposure, similar to what happened during the Iran–Iraq war.[109]

Sparse cases of bronchogenic carcinoma have already been reported among Iranian war veterans.[64,80] To date, there have been no substantial reports on Iranian patients regarding this issue. Carcinogenic effects of SM exposure among Iranian victims with mostly single high- or low-dose exposure will become evident only in the longer term. Thus, long-term follow-up is required to discover the incidence of lung carcinogenicity in such patients.

Delayed Ophthalmologic Complications

The eyes are the most sensitive organ to SM, which is attributed to several ocular features. The aqueous-mucous surface of the cornea and conjunctiva and the intense metabolic activity of the corneal epithelial cells and higher turnover rates lead to remarkable sensitivity in the event of SM exposure.[71,68]

In an ophthalmological survey of 40 SM-intoxicated Iranian war veterans conducted by Balali-Mood and colleagues[67] (2005), subjective eye complications were recorded as itching (42.5%), burning sensation (37.5%), photophobia (30%), tearing (27.5%), premature presbyopia with reading difficulties (10%), ocular pain (2.5%), and foreign-body sensation (2.5%). Common objective findings were reported to be comprised of chronic conjunctivitis (17.5%), peri-limbal hyperpigmentation (17.5%), corneal thinning (15%), vascular tortuosity (15%), limbal ischemia (12.5%), corneal opacity (10%), corneal vascularization (7.5%), and corneal epithelial defect (5%).

Ghasemi et al.[110] through an ophthalmological examination of 367 chemical war victims of

Sardasht, Iran, reported photophobia and ocular surface discomfort (burning, itching, and redness) as the most significant symptoms, while bulbar conjunctival abnormalities and limbal tissue changes were the most slit-lamp findings among the victims.

In a study by Namaziet al.[68] (2009), burning sensation, photophobia, red eye, and itching were reported as the most common eye complications among 134 Iranian war veterans with the delayed complications of SM exposure.

Delayed ulcerative keratopathy may develop in the late phase of SM-induced eye complications usually 15–20 years after initial exposure, and it will cause permanent residual effects.[43] Latency periods of as long as 40 years and as short as 1 year have been reported.[71,111] The patients are usually symptom-free for an undetermined number of years before delayed keratitis starts with a sudden onset of photophobia, tearing, decreasing vision, and eventually late-onset blindness.[112] It is characterized by corneal thinning, corneal opacification, neovascularization, and corneal epithelial deficiency.[67,71] The severity of the initial exposure and the duration of the ophthalmic symptoms are directly related to the likelihood of later keratopathy.[113] Incidence rate of 0.5–1% was reported among the SM casualties of the WWI. However, Etezad-Razavi and colleagues[71] (2006) reported that the rate of delayed keratitis was as high as 15% among Iranian SM victims 18 years after initial exposure.

In the initial stages of ulcerative keratitis, the limbal region presents a marbled appearance in which porcelain-like areas of ischemia are surrounded by blood vessels with irregular diameters. Then, vascularized scars of the cornea are covered with crystal and cholesterol deposits, leading to the worsening of opacification, recurrent ulcerations, and sometimes corneal perforation.[7]

Opacification is seen in the lower and central portions of the cornea, while the upper part is almost protected by the eyelids.[114] Lesions are surprisingly recurring even after corneal transplantation.[111]

In a recent cross-sectional study (2013), retinal electrophysiological evaluations, including electroretinography and electrooculography, were performed on 40 severely intoxicated Iranian war veterans with the delayed complications of SM exposure. The study, as the first report on the SM-induced delayed-onset functional retinal changes, showed a general reduction in the function of the retinal photoreceptors in both cone and rod photoreceptors in terms of amplitude and implicit time. It was concluded that SM intoxication also has long-term complications in the neurologic tissues of the eyes such as retina as well as in the anterior chamber of the eyes.[115]

Delayed Dermal Complications

The skin is an appropriate transporting system for SM due to the high affinity of the skin for lipophilic substances and the lipophilic nature of SM. The occurrence and persistence of dermal lesions are specifically related to the duration and severity of the initial SM exposure. Acute SM injury causing erythema and edema without vesicle formation is almost always followed by complete healing. Conversely, necrotic wounds and blistering cause permanent residual effects.[2,12]

Most of the delayed cutaneous skin lesions are on the site of blisters at the acute phase of SM exposure. Previously injured sites on the skin are sensitive to subsequent mechanical injury and show recurrent blistering after mild injury.[116]

Balali-Mood[117] in the first report on the delayed toxic effects of SM poisoning in 236 Iranian veterans 2 years after exposure revealed hyper- and hypopigmentation (34% and 16%, respectively) as well as dermal scarring (8%) as the most common findings (figure 3). The most common skin complaint among these patients was itching, followed by a burning sensation and desquamation. These symptoms are basically caused by dryness of the skin and worsen in dry weather and after physical activity. Even after 2 decades, pruritus was still the most common subjective finding.[67,118]

Fekri[119] compared cutaneous lesions between 500 SM-exposed Iranian war veterans

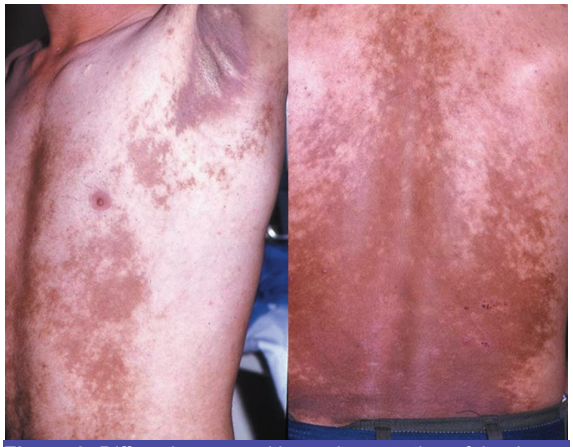

Figure 3: Diffuse hyper- and hypopigmentation of the thorax (left) and the low back (right) in an Iranian war veteran, 16 years after wartime exposure to sulfur mustard. The predilection of sulfur mustard to moist areas is remarkable. (from the private slide collection of the corresponding author, taken with permission of the patient).

and their unexposed counterparts. A significant association was reported between SM poisoning and late skin lesions such as severe dry skin, hyper- and hypopigmentation, eczema, local hair loss, and chronic urticaria. Higher incidence rates of vitiligo, psoriasis, and discoid lupus erythematosus were also reported among the SM-poisoned war veterans. The author concluded that the finding could be attributable to the long-term adverse effects of SM on the immune system.

In a study on the delayed cutaneous complications of SM poisoning 16–20 years after exposure among Iranian war veterans, Hefazi and colleagues[119] (2006) reported that their main objective findings were hyperpigmentation (55%), dry skin (40%), multiple cherry angiomas (37.5%), atrophy (27.5%), and hypopigmentation (25%).

Emadi et al.[120] in a study on 800 war veterans 14–20 years after SM poisoning reported that 93% of their patients showed nonspecific skin disorders, while only 5% developed scars with different patterns, principally at the sites of previous SM-induced skin injuries. Scarring results from connective tissue hypertrophy and dysregulated fibroblast activity during wound repair; it can be incapacitating, especially in the genital area.[121]

In a study on 43 SM-exposed Iranian war veterans conducted by Layegh and colleagues,[122] itching was the main cutaneous complaint (23.30%) among the patients. The most common clinical diagnosis was multiple cherry angiomas (72.1%). Significantly low skin moisture and lipid content in the SM-exposed war veterans was reported compared with the control group. Hence, decreased function of the stratum corneum and lipid production is considered a delayed effect of SM on the skin.

Histopathological studies on skin biopsies have revealed nonspecific pathologies, including keratosis, epidermal atrophy, and basal membrane hyperpigmentation. Nonspecific fibrosis and melanophages have also been observed within the dermis.[67,70,116,119]

Although numerous individuals suffered SM-induced injuries in various chemical attacks during the Iran–Iraq war, the incidence of skin cancer has rarely been reported up to now and no casual connection has been firmly established.[123,124] It can be concluded that cutaneous malignancies appear to be a late uncommon consequence of SM exposure and, thus, may need a longer period of time to occur.

Delayed Neurological Complications

Studies on the delayed neurological complications of SM are both sparse and focused on peripheral neuropathies and neuromuscular lesions. Balali-Mood et al.[67] in a study on 43 Iranian war veterans with severe late manifestations of SM poisoning who underwent electromyography (EMG) and nerve conduction velocity (NCV) reported 77.5% peripheral neuropathy with more sensory than motor nerve dysfunction. Neuropathies were more prevalent in the lower extremities than in the upper extremities. It was concluded that unlike the late complications of SM on the target organs that are because of its direct toxic effect, neuromuscular complications are probably due to systemic toxicity.

Namazi[68] reported headache (26.86%), epilepsy (16.42%), vertigo (11.94%), and tremor (4.48%) as the most common neurological complications among 134 patients with long-term complications of SM poisoning.

In a recent survey on the delayed neurological complications of SM poisoning, the most common subjective findings were fatigue (93%), paresthesia (88.3%), and headache (83.7%), while hyperesthesia (72.1%) was the most objective finding. The most common clinical neurological complications among the patients were sensory nerve impairments, including paresthesia (88.3%), hyperesthesia (72.1%), and hypoesthesia (11.6%). EMG and NCV findings showed abnormal patterns in 7 out of 12 SM patients (16.3%) with the clinical indication for the experiments. Disruption of NCV patterns were symmetric both in the upper and lower extremities. Three patients had pure sensory polyneuropathy, and 4 patients had sensory-motor distal polyneuropathy in the axonal type. EMG pathologies consisted of chronic polyphasic motor unit action potential in the distal tested muscles. Even after electrophysiological procedures, approximately 50% of the polyneuropathies remain unrevealed.[26]

Delayed Psychiatric Complications

Exposure to CWAs is an extreme traumatic event, with long-lasting adverse consequences on mental health. Psychological events diminish quality of life among SM-exposed victims and may continue for 2 generations.[125] Regardless of chemical intoxication, a strong association has been reported between physical illnesses and psychiatric disorders among CWA survivors. Furthermore, exposure to war, adverse physical health consequences, and also fear of the future CWA exposure represent an additive effect for involved and persistent mental health.[14]

In the first report on SM-induced psychological complications, Balali-Mood[126] found anxiety and post-traumatic stress disorder (PTSD) among

SM-exposed war veterans. Disorders of emotion (98%), memory (80%), behavior (80%), attention (54%), consciousness (27%), and thought process (14%) were also reported as the most common psychological complications.

Tabatabai[127] reported emotional problems (98%), behavioral abnormalities (80%), memory impairment (80%), low concentration (54%), impaired consciousness (27%), and thought processing disturbances (14%) 3–5 years after SM exposure among Iranian war veterans.

Balali-Mood[64] in a survey of 1428 SM-poisoned Iranian war veterans 3–9 years after exposure reported such abnormalities as depression (46%), personality disorders (31%), anxiety (15%), seizure (6%), and psychosis (3%).

Tavallaei[128] assessed mental health among 206 SM victims in the Iranian city of Sardasht by means of a general health questionnaire (GHQ28) and reported that 95.10% of the victims had inappropriate mental health scores.

Vafaee[129] in an assessment of 200 SM Iranian war veterans reported such mental complications as major depression (23%), PTSD (19%), dysthymia (18%), mania (13%), generalized anxiety (4%), panic disorder (4%), schizophrenia (2%), and schizoaffective disorder (1.50%). Vafaee[130] also showed that the frequency of depression in the physically injured victims was twice that the control group and in the SM veterans twice that the physically injured victims.

Hashemian et al.[131] surveyed 153 civilians in 3 northwestern Iranian towns of Oshnavieh (low-intensity conventional weapons), Rabat (high-intensity conventional weapons), and Sardasht (high-intensity conventional and chemical warfare) and reported that those exposed to warfare were at a higher risk for lifetime PTSD, current PTSD, increased anxiety symptoms, and increased depressive symptoms. It was also stated that the occurrence rate of depression and anxiety among the survivors of high-intensity chemical attacks during the Iran–Iraq war was 7.20 and 14.60 times more frequent than that among the individuals exposed to conventional weapons, respectively.

Roshan et al.[132] compared 367 SM-exposed civilians from the Iranian city of Sardasht with a matched control group and reported significantly more somatization, obsessive–compulsive disorder, depression, anxiety, and hostility among the SM-exposed civilians. Significant differences between the 2 groups were also reported based on the global severity index and the positive symptom distress index.

In a recent review of articles (2014), Razavi et al.[133] described the long-term common psychiatric complications of SM exposure. Based on their review of valid published articles, the complications encompassed emotional problems (98%), memory impairment (80%), behavioral abnormalities (80%), social performance disturbances (10.73%), anxiety (18–65%), insomnia (13.63%), low concentration (54%), severe depression (6–46%), personality disorders (31%), thought-processing disturbances (14%), seizure (6%), and psychosis (3%). Lifetime and current PTSDs were reported to have rates of 8–59% and 2–33%, correspondingly.

PTSD is one of the most common and important long-term psychiatric complications among Iranian chemical victims. It is a syndrome that takes place in the face of a push factor causing severe damage. Review of the traumatic event in their thoughts, avoidance of the things that would remind them of the damage, and also slow responses along with arousal state are 3 main diagnostic criteria.[129,133] The frequency rates of PTSD have been reported to be 19%,[64] 41%,[36] and 8–59%,[134] according to different studies on Iranian SM victims.

Clinical features of PTSD in the chemical survivors of the Iran–Iraq war include a wide variety of symptoms such as generalized and long-standing fatigue, muscle tension and contraction, feeling pressure in the head and neck, tremor, excessive sweating, intermittent anorexia, vague abdominal discomfort, mild diarrhea, urinary frequency, palpitations, tachycardia, dyspnea, chest pressure, dizziness, feeling of guilt, depression, sleep disturbances, irritability, difficulty in concentration, and outbursts of anger.[135] There are also high levels of comorbidity between PTSD, depression, and anxiety.[131] PTSD affects not only war veterans but also their families (wives and children). Ahmadi et al.[136] (2010) found that both the frequency and severity of PTSD among the families (termed "secondary PTSD") of the chemically injured war veterans living in the Iranian city of Sardasht were significantly higher than those of the control group.

Delayed Cardiovascular Complications

Knowledge on the long-term cardiotoxic effects of SM reveals a correlation between SM and heart diseases. Ventricular diastolic abnormalities were reported as a late cardiac complication and were much more frequent than ventricular systolic abnormalities.[137-139] Furthermore, lower functional capacity, reduced right ventricular function, and elevated pulmonary artery

pressure have recently been observed in some SM patients.[140]

As the respiratory disorders are the most common long-term SM complication and can lead to the well-known cor pulmonale phenomenon, the role of cardiac performance in the occurrence of this phenomenon remains to be clarified.[82]

Gholamrezanezhad et al.,[137] in a study on 22 war veterans with the late complications of SM exposure during the Iran–Iraq war via scintigraphic myocardial perfusion scan, reported that the patterns of myocardial perfusion in the case group were completely different from those of the control group and resembled to either coronary artery disease or mild cardiomyopathic changes. It was also noted that both dilated right ventricular chamber and ischemia were significantly more prevalent among the SM patients.

In a study conducted by Pishgoo et al.,[138] 60 Iranian veterans with the late complications of SM poisoning underwent cardiac evaluation, including electrocardiography, transthoracic echocardiography (n=58), and conventional coronary angiography (n=7 as clinically indicated) 18 years after initial exposure. Fifty-six (96.5%) subjects showed no significant coronary artery disease. In echocardiographic study, left ventricular diastolic abnormality was reported in 23% of the patients. No considerable valvular or conductive abnormality was reported in the patients. In conventional coronary angiography, 1 patient had nonobstructive coronary artery disease and 1 patient suffered from single-vessel disease.

In a retrospective case–control study conducted by Rohani and colleagues,[139] 50 Iranian SM-exposed war veterans underwent the exercise stress test and echocardiography. Two patients were reported to have a positive exercise stress test. Left ventricular diastolic abnormality was detected in 23% of the patients.

Shabestari et al.[141] in a study on 40 SM-poisoned patients reported coronary artery ectasia as a pathologic finding of conventional angiography with a prevalence of 22.5%, as opposed to 2.2% in the control group. The most involved artery in the war veterans was the left anterior descending artery. The authors concluded that coronary ectasia, as a delayed cardiovascular complication of SM poisoning, was approximately 11 times more frequent in the SM-poisoned veterans. It was the first report on coronary artery ectasia as a late effect of SM poisoning.

Karbasi-Afshar and colleagues[142] compared conventional angiography findings between SM-poisoned Iranian war veterans and their unexposed counterparts and reported a significantly higher incidence rate of atherosclerotic lesions among the SM patients.

Since cardiovascular diseases are the main cause of death among CWA patients[143] and given the dearth of data on this topic in the literature, more investigations will assist physicians in better cardiac management of SM patients. More detailed studies on cardiac complications are now being undertaken by the authors of the current review article and the results will be published soon.

Delayed Urogenital and Reproductive Complications

Only a few studies are available regarding the urogenital complications of SM poisoning. Hence, data on this issue are both lacking and contradictory and the studies are exclusively on males. According to a self-reported history of urologic conditions among 289 Iranian war veterans 19–26 years after high-dose SM exposure, history of urinary calculi in 17.3%, recurrent urinary tract infections in 8.7%, benign prostatic hyperplasia in 1.7%, and kidney failure in 0.7% of the patients constituted the common findings.[144]

Taghaddosinejad and colleagues[145] defined the renal pathology of SM based on autopsy. Simple renal cysts and membranoproliferative glomerulonephritis (MPGN) were the most pathological findings of the kidneys. As MPGN is immune-mediated glomerulonephritis presenting in young adulthood, the presentation of MPGN in the victims older than 40 years old might be attributed to SM exposure.

Data addressing the long-term reproductive toxicity of SM in human models are both lacking and contradictory. In the delayed phase of SM intoxication, the main target of the gonadal effect injury is spermatogenesis.[146] Balali-Mood[64] reported a significantly diminished sperm count among SM-exposed war veterans in comparison to their unexposed counterparts, 3–9 years post exposure. Azizi[147] reported a sperm count of below 3 million cells/mL and increased follicle-stimulating hormone levels among SM-exposed victims. In contrast, the results of another study by Ghanei et al.[148] failed to demonstrate an association between long-term infertility and SM exposure in the residents of Sardasht, Iran.

Three years after SM exposure during the Iran–Iraq war, infertile victims showed almost total atrophy of the seminiferous epithelium and intact interstitial cells. In addition, the infertile azoospermia in the SM victims appeared to have

a Sertoli cell-only pattern in the testicular biopsy.[149] Several years later (2009), these findings were confirmed by Amirzargar and colleagues.[150]

Although increased levels of follicle-stimulating hormone and luteinizing hormone as well as decreased testosterone and dehydroepiandrosterone levels were reported in the first months of SM exposure,[147] the serum levels of the reproductive hormones were reported within the normal range in SM-poisoned men several years post exposure by more recent studies.[150]

Ahmadi et al.[151] reported the prevalence of sexual dysfunction in Iranian SM-poisoned war veterans to be 65.9%, as opposed to 33.0% in nonchemically injured war veterans. The most domain of dysfunction in both groups was erectile dysfunction.

Carcinogenicity

SM is considered a suspected carcinogenic CWA due to its ability to cause chromatid aberration and inhibit DNA, RNA, and protein synthesis and is, thus, classified as a carcinogen agent. SM is known by the International Agency for Research on Cancer (IARC) as a human carcinogen.[43]

Behravan and colleagues[152] investigated DNA breaks using the single-cell microgel electrophoresis technique under alkaline conditions (Comet assay) among Iranian war veterans 25 years post SM exposure. Significantly high levels of lymphocyte DNA damage were reported among the SM-exposed patients compared with a matched control group. Moreover, point mutations of p53 consistent with SM-induced DNA damage have been observed in some Iranian victims with lung cancer.

Hosseini-Khalili et al.[107] assessed p53 and Kirsten rat sarcoma mutations in 18 SM victims with lung cancer. They found 8-point mutations in p53 but no mutation in Kirsten rat sarcoma.

For all the reports on the excessive occurrence of malignancies after the WWI and in high-dose occupational exposures, there are sparse studies reporting higher occurrence of malignancies among the chemical victims of the Iran–Iraq war. Bronchogenic carcinoma, nasopharyngeal carcinoma, gastric adenocarcinoma, thyroid cancer, and acute myeloblastic and lymphoblastic leukemia have been case reported in Iranian war veterans poisoned by SM.[70,73,81,153]

Gilasi et al.[154] investigated a group of 500 Iranian SM-exposed patients and compared them with 500 unexposed soldiers 18 years post exposure and reported only 3 cases with malignancies among the exposed veterans, while no such cases were found in the unexposed group. There was no significant correlation between cancer occurrence and SM exposure. Another study in Iran, performed on 43 chemically injured war veterans 20–25 years after exposure to SM, found no malignancy in the upper or lower respiratory tract as well as in the lungs.[79]

In contrast, Zafarghandi et al.,[155] through a 25-year follow-up study, described the incidence of cancer in 7570 Iranian SM-exposed war veterans compared to 7595 unexposed subjects. During the follow-up period, 84 cases of cancer were identified in the exposed group, while 49 cases were detected in unexposed group. It was claimed that cancer incidence was significantly increased with exposure to SM; however, no increased risk of site-specific cancer was found. The crude incidence rate for cancer was 1.81 (95% CI: 1.15 to 2.34) and its hazard ratio was 2.02 (95% CI: 1.41 to 2.88) in their study group. Another study on Iranian SM-exposed war veterans during the Iran–Iraq conflict at levels sufficient to cause severe signs of toxicity indicated a potential increased incidence of chronic myelocytic leukemia.[24]

Overall, as quantitative risk assessment cannot be developed from the available data, long-term follow-up is required to discover the incidence of carcinogenicity among Iranian SM victims. It must be stated that all the mentioned delayed effects are due to a single-dose exposure to SM and differ from those caused by chronic occupational exposure.

Conclusion

CWAs were frequently used by Iraqi troops during the Iran–Iraq war and caused hundreds of thousands of morbidities and mortalities, millions of displacement cases, and billions of dollars in cost. Iran was subjected to several chemical attacks with SM during the imposed war. Even 3 decades after the war, around 40 000 Iranian war veterans still complain of the delayed effects of SM poisoning. SM distributes systematically and, thus, affects several body organs. The most common delayed complications have been observed in the respiratory tract, skin, and eyes. There are other potential effects of SM exposure which will become evident only in the longer term. These effects, which are currently under investigation, include the development of cancer, immunological and neuropsychiatric changes, and reproductive effects. Accordingly, the literature should be made in Iran. It is vital that Iranian scientists and clinicians investigate more possible delayed and long-term effects

of SM.

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