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REVIEW ARTICLE

Respiratory effects of sulfur mustard exposure, similarities and differences with asthma and COPD

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Abstract

Context: Previous research has found relationships between sulfur mustard (SM) toxicity and its adverse effects.

Objective: SM is highly toxic to the respiratory system, leading to hacking cough, rhinorrheachest tightness, acute pharyngitis and laryngitis, chronic bronchitis and lung fibrosis. In this review, based on the scientific literature, we provide an updated summary of information on SM exposures and their differences with asthma and COPD.

Method: Information of this review was obtained by searching Medline/PubMed, ScienceDirect, Scopus, Google Scholar, ISI Web of Knowledge and Chemical Abstracts.

Results: SM exposure can decrease pulmonary function tests (PFTs) values. In addition, inflammatory cell accumulation in the respiratory tract and increased expression of some pro-inflammatory cytokines including tumor necrosis factor- α (TNF α), IL-1 α , IL-1 β , and reactive oxygen radicals due to SM exposure have been shown. Matrix metalloproteinase (MMP) which degrade extracellular matrix proteins, contributing to inflammatory cell recruitment, tissue injury and fibrosis are also up-regulated in the lung after SM exposure. In the lung, SM exposure also can cause serious pathological changes including airway inflammation, parenchymal tissue destruction and airway obstruction which can lead to asthma or chronic obstructive pulmonary disease (COPD). Following SM poisoning, DNA damage, apoptosis and autophagy are observed in the lung along with the increased expression of activated caspases and DNA repair enzymes.

Conclusion: In the present article, respiratory symptoms, changes in PFTs, lung pathology and lung inflammation due to SM exposure and the similarities and differences between them and those observed in asthma and COPD were reviewed.

Keywords

Asthma, COPD, lung inflammation, lung pathology, pulmonary function tests, respiratory symptoms, sulfur mustard

History

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Introduction

Sulfur mustard (SM), commonly known as mustard gas, is an alkylating agent capable of causing short and long term injury. It is a class of extremely toxic vesicant chemicals that has been used as chemical warfare agents. SM is a cell poison affecting different organs including eyes, skin and airway. It also affects the function of the heart, nervous and digestive systems (Evison et al., 2002; Somani & Babu, 1989). The severity of damage mostly depends on the dose and duration of exposure (Kehe & Szinicz, 2005). In the lung, SM exposure causes various effects including bronchial tissue destruction (Bahadori et al., 1989), inflammation (Emad & Rezaian, 1997) and obstruction of the airways (Emad et al., 1995).

Toxicity of SM is attributed to the alkylate proteins and lipophilic nature which allows it to rapidly penetrate to the

target tissues and reach lipids and nucleic acids resulting in DNA damage and cytotoxicity (Feister, 1991). Acute effects of SM exposure in the respiratory system are hacking cough, rhinorrhea, chest tightness, acute pharyngitis and laryngitis, edema and hyperemia of the airway mucosa, shortness of breath and productive cough. Spirometric studies showed patterns of obstructive lung disease, restrictive lung disease or both (Sohrabpour, 1984). The chronic effects of SM exposure on respiratory system are airway hyper-responsiveness, chronic bronchitis, lung fibrosis, pneumonia (Balali-Mood & Hefazi, 2006; Ghanei et al., 2008) and progressive bronchiolitis (Rowell et al., 2009). Also, pulmonary function tests (PFTs) after exposure to SM also revealed more obstructive patterns than restrictive lung disease (Balali-Mood & Hefazi, 2006).

Regarding acute SM intoxication is often nonspecific and transient, it is reported that 1–3 weeks post-exposure, bronchoscopy reveals inflammation of the trachea with signs of necrosis. At this time, chest X-ray (CXR) findings are normal, indicating that the onset of chronic disease is delayed, and it is recommended to initiate the therapeutic

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interventions at this phase (Kehe et al., 2009b). Based on a 10-year follow-up, exposed individuals have been diagnosed with asthma (11%), bronchitis (59%), bronchiectasis (9%), airway narrowing due to scarring (10%), and lung fibrosis (12%), indicating the induction of chronic obstructive pulmonary disease (COPD) (Emad & Rezaian, 1997). Fifteen years post-SM exposure, 24% of those referred for severe respiratory disorders were reported to have trachea-bronchial stenosis (Ghanei et al., 2004). After 17–19 years, decreased forced expiratory volume in one second (FEV₁) and airway hyper-responsiveness to methacholine were observed, along with the development of reactive airway disease (Mirsadraee et al., 2005). Twenty years after SM exposure, progressive lung deterioration is apparent with bronchiolitis obliterans (BO) being the main pathologic feature in SM-exposed individuals (Rowell et al., 2009). Even 20 years after SM exposure, large cohorts studies on individuals exposed to SM during Iraq–Iran war showed evidence of systemic and pulmonary inflammatory effects including alterations in serum levels of cell adhesion molecules (e.g. selectins), interleukin IL-8 and IL-6 (Pourfarzam et al., 2009; Yaraee et al., 2009b).

Following exposure of rodents or pigs to SM by inhalation for weeks to months, inflammatory cells are observed in the upper and lower respiratory track (Allon et al., 2009; Anderson et al., 2006; Anderson et al., 2009; Calvet et al., 1999; Kumar et al., 2001). Infiltration of neutrophils and macrophages to the lung parenchymal following SM exposure, supports the idea that phagocytic leukocytes and their inflammatory mediators are important in the pathogenic response to inhaled vesicants (Amir et al., 2000). Intra-tracheal inhalation of SM vapors also results in homogeneous lung injury (Weber et al., 2010). In other models of lung injury following SM exposure, inflammatory mediators released by macrophages have been shown to be key elements in the pathogenesis of lung injury (Laskin & Laskin, 2010a) and they may play a major role in the pulmonary response to SM. In humans also, increased numbers of neutrophils and eosinophils are evident in the lung even a decade after exposure (Beheshti et al., 2006; Rowell et al., 2009).

There is evidence of systemic and pulmonary inflammation including alterations in serum levels of IL-8, IL-6 and cell adhesion molecules (e.g. selectins), 20 years after SM exposure (Pourfarzam et al., 2009; Yaraee et al., 2009b). In addition, elevations in serum IL-8 levels in SM-exposed survivors are correlated with incidence and severity of wheezing (Pourfarzam et al., 2009). In patients with COPD due to SM poisoning, increased levels of C-reactive protein (CRP), a nonspecific marker of systemic inflammation, comparable to the severity of disease (Attaran et al., 2009), and augmented serum levels of the pro-apoptotic protein and soluble Fas ligand were observed (Ghazanfari et al., 2009). It was reported that, pulmonary fibrosis following SM exposure is also correlated with increases in inflammatory cytokines and chemokines including tumor necrosis factor (TNF)- α , CCL5, CCL11 and IL-1 α , IL-1 β , IL-5, IL-6, IL-8, IL-12, IL-13 in bronchoalveolar lavage fluid (BALF) (Emad & Emad, 2007; Emad & Emad, 2008). Markers of pulmonary inflammation in individuals exposed to SM confirm the occurrence of oxidative stress, characterized by an accumulation of lipid

peroxidation products such as malondialdehyde (MDA) in the lung and/or BAL, and decreases in antioxidants like superoxide dismutase (SOD) (Shohrati et al., 2008; Shohrati et al., 2010). Recent data also indicate that SM exposure leads to an increased incidence of early-onset lung cancer, which is associated with mutations in the tumor suppressor gene p53 (Hosseini-khalili et al., 2009).

Method

Information of this review were obtained by searching; Medline/PubMed, ScienceDirect, Scopus, Google Scholar, Embase, ISI Web of Knowledge, Biological Abstracts and Chemical Abstracts using the keywords such as asthma, SM chronic exposure, SM acute exposure, COPD.

Effects of sulfur mustard on respiratory symptoms

After minutes to several hours of SM exposure, chemical war victims (CWVs) experience tracheobronchitis with hoarseness, hacking cough, dyspnea, chest pressure, sore throat due to edema and erythema of the pharynx and bronchial tree (Chan & Allen, 2004; Laohaburanakit et al., 2003). It was shown that, increasing cough, tachypnea and sinus pain are the main objective clinical findings during the next 12 h (Cowan et al., 1997; Ghanei et al., 2005). Four to sixteen hours after exposure, pain and discomfort in the nose or sinuses with increased nasal secretions, sneezing and sore throat were observed (Sidell, 1990; Stepanov & Popov, 1962). Bronchiolar obstruction is probably due to pseudo-membrane formation within the airways, sloughing of epithelium and lower-airway obstruction. In addition, obstructive patterns are more common than restriction lung diseases as shown in spirometric findings (53% versus 2%, respectively) (Chan & Allen, 2004).

Four to seven days after exposure, some symptoms including coughing (92%), sputum (67%), bloody sputum (42%), altered chest (17%) (Kehe et al., 2009b), increased airway resistance (Calvet et al., 1994b; McClintock et al., 2006), irritation, cough and huskiness were observed (Willems, 1989).

After acute phases, respiratory problems are the most important cause of long-term disability among people exposed to mustard gas (Aghanouri et al., 2004). After three years, in more than 80% of Iranian veterans hemoptysis (mainly streaky), chest tightness, chest pain, nocturnal dyspnea, generalized wheezing (the most common sign), crackles, decreased lung sounds, clubbing and cyanosis were observed (Balali-Mood et al., 2005; Eklöw et al., 1984).

Increased respiratory symptoms including night wheeze, morning wheeze, cough, daily wheeze and cough were seen in exposed individuals 18–20 years after exposure to SM (Boskabady & Farhadi, 2008).

Long-term SM-induced lung injuries include chronic bronchitis (59%), tracheobronchial stenosis (24%), asthma (11%), bronchiectasis (9%), airway narrowing due to scarring (10%), rarely honeycomb lung pathology such as fibrosis, and slightly increased incidence of lung cancer after a latency of 20 years were seen (Foroutan, 1997; Hosseini-khalili et al., 2009).

Table 1. Different respiratory symptoms due to SM exposure and their similarities with those of asthma and COPD.

Respiratory symptoms	Time after exposure	Similarities		References
		Asthma	COPD	
Hoarseness, hacking cough, dyspnea, chest pressure, sore throat	Min–several hours	✓	✓	(Chan & Allen, 2004)
Pain and discomfort in the nose or sinuses, increased nasal secretions, sneezing, and sore throat	4–16 h	✓		(Sidell, 1990; Stepanov & Popov, 1962)
Increased cough, tachypnea, sinus pain	12 h	✓		(Cowan et al., 1997; Ghanei et al., 2005)
Coughing (92%), sputum (67%), bloody sputum (42%), altered chest (17%)	4–7 d	✓	✓	(Kehe et al., 2009b)
Irritation, cough and huskiness	42 d	✓		(Willems, 1989)
Cough, expectoration, dyspnea, chest tightness, chest pain, nocturnal dyspnea	3 years	✓	✓	(Afshinniaz & Ghanei, 1995)
Hemoptysis, chest tightness, chest pain, nocturnal dyspnea, generalized wheezing, crackles, decreased lung sounds, clubbing, cyanosis	3 years	✓	✓	(Balali-Mood et al., 2005; Eklöw et al., 1984)
Increased night wheeze, morning wheeze and cough, daily wheeze and cough	18–20 years	✓		(Boskabady & Farhadi, 2008)
Wheezing (66.19%), cough (64.78%), chest tightness (54.4%)	23–25 years	✓		(Boskabady et al., 2012)

SM exposure can also cause acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) (Angelini et al., 2013). Common findings in the upper respiratory tract have been reported to be dysphonia, post-nasal discharge (PND) and mucosal inflammation of larynx (Mood et al., 2010). Chronic respiratory disorders due to SM toxicity can lead to varying degrees of sleep disorders and affect the quality of life (Vahedi et al., 2012).

It was shown that respiratory rate, temperature and heart rate in SM-exposed patients were in the normal ranges but dyspnea (100%), dry cough (66%), hemoptysis (35%) and productive cough (33%) were the most common respiratory problems (Amini & Oghabian, 2013).

A triad of cough, expectoration, and dyspnea has been found to be present in more than 80% of Iranian veterans three years after their initial exposure (Afshinniaz & Ghanei, 1995). Respiratory symptoms and lung disorders due to SM exposure are summarized in Tables 1 and 2, respectively.

In patients who were unprotected during SM exposure, lung symptoms such as coughing (92%), sputum (67%) or even bloody sputum (42%) developed markedly. Blood gases were not altered in 33% of patients but the other 67% had alkalosis (33%), hypoxia (50%) or acidosis (17%) (Kehe et al., 2009b).

Effects of sulfur mustard on pulmonary function tests

Variations in tidal volume, peak inspiratory flow, expiratory pressure and airway hyper-reactivity were observed 24 h after SM exposure (Anderson et al., 2009; van Helden et al., 2004). After 14 d, PFTs changes such as airway hyper reactivity to substance P and histamine (Calvet et al., 1994b; Calvet et al., 1999) were seen. In addition, 5–10 years after SM exposure airway hyper-responsiveness was increased (Bahadori et al., 1989; Emad et al., 1995).

PFTs results indicated markedly increased residual volume (RV) in all SM-exposed patients 14 years after

exposure. High-resolution computed tomography scan (HRCT) of the chest indicated that none of the cases was in hyperventilation state (Beheshti et al., 2006). FVC, FEV₁ and FEV₁/FVC (FEV₁%) have all been found to be significantly lower in SM-exposed veterans compared to non-exposed healthy subjects as well as survivors who had used a gas mask at the time exposure (Afshinniaz & Ghanei, 1995). The study of Khateri et al. showed that from 34 000 Iranian patients, 42.5% had measurable changes in PFT values (Khateri et al., 2003). Overall, PFT changes show an obstructive pattern such as decreases in the forced vital capacity (FVC), FEV₁ and their ratio. Generally, abnormal PFT values and particularly restrictive patterns tend to worsen over time (Cowan et al., 1997). PFT revealed more obstructive patterns than restriction lung disorders and about half of these obstructive spirometric results are reversible in response to inhaled bronchodilators (Boskabady & Farhadi, 2008).

Airway responsiveness to methacholine was also markedly increased in 15 CWVs compared to control subjects 17–19 years after exposure to SM, and the values for FEV₁ and specific airway conductance (sGaw) were decreased in CWV (Boskabady & Farhadi, 2008).

Some of the PFT parameters including FVC, maximal mid expiratory flow (MMEF) and MEF75 markedly increased due to inhaled salbutamol in SM-exposed individual (20 patients) compared to control group 18–20 years after exposure (Boskabady & Farhadi, 2008).

It was reported that 23–25 years after SM exposure, all the PFT values were markedly decreased in most of CWV ($n=142$) and reduction of FEV₁/FVC was found 25-year follow-up after exposure (Boskabady et al., 2012; Nishimoto et al., 1970).

In addition, increased airway resistance and airway hyper-reactivity which were similar to asthma were observed 14 days post-exposure to SM (Calvet et al., 1994b; van Helden et al., 2004). The effect of SM exposure on PFT changes is shown in Table 3.

Table 2. Various pulmonary disorders due to SM exposure.

Type of pulmonary disorders	Time after exposure	References
Airway narrowing, due to scarring or granulation tissue, as a late sequel of acute injuries to the trachea and large bronchi	2 years	(Aslani, 2000, Ghanei et al., 2004)
Chronic bronchitis (58%), asthma (10%), bronchiectasis (8%), large airway narrowing (9%), pulmonary fibrosis (12%)	10 years	(Black et al., 1997)
Asthma (11%), bronchitis (59%), bronchiectasis (9%), airway narrowing due to scarring (10%) and lung fibrosis (12%)	10 years	(Emad & Rezaian, 1997)
Tracheobronchial stenosis in 24% of those referred for severe respiratory disorders	At 15 years	(Ghanei et al., 2004)

Table 3. The effect of SM exposure on PFT changes and their similarities with those of asthma and COPD.

PFT changes	Time after exposure	Similarities		References
		Asthma	COPD	
Alterations in tidal volume, respiratory frequency, peak inspiratory and expiratory pressure, and airway hyper-reactivity	24 h	✓	✓	(Anderson et al., 2009; van Helden et al., 2004)
Airway hyper-reactivity to substance P and histamine	14 d	✓		(Calvet et al., 1994b, 1999)
Increased airway resistance	14 d	✓	✓	(Calvet et al., 1994a; McClintock et al., 2006)
Airway hyper-responsiveness	5–10 years	✓		(Bahadori et al., 1989; Emad et al., 1995)
Increased residual volume (RV)	14 years		✓	(Beheshti et al., 2006)
Decreased FEV1 and airway hyper-responsiveness to methacholine	17–19 years	✓		(Mirsadraee et al., 2005)
Decreased FEV1 and specific airway conductance (sGaw)	17–19 years	✓	✓	(Boskabady et al., 2008)
Decreased PFT values (FVC, MMEF and MEF 75)	18–20 years	✓	✓	(Boskabady & Farhadi, 2008)
Decreased all PFT values	23–25 years	✓	✓	(Boskabady et al., 2012)
Reduction of FEV1/FVC	25-year follow-up		✓	(Nishimoto et al., 1970)

Effects of sulfur mustard on lung pathology

After minutes to several hours of SM exposure, some pathological changes including increased edema and erythema of the pharynx and bronchial tree were observed in individuals exposed to SM (Chan & Allen, 2004). After 24–48 h, severe SM exposures lead to hemorrhagic pulmonary edema, secondary pneumonia and respiratory failure due to necrosis (Ghanei et al., 2005). Infection of the respiratory tract, resulting in bronchopneumonia observed in the veterans 36–48 h after SM exposure (Hosseini et al., 1989; Keshmiri, 1989; Willems, 1989).

SM exposure can cause several pathological changes of the lung including airway inflammation (Emad & Rezaian, 1997), parenchymal tissue destruction (Evison et al., 2002) and airway obstruction (Emad et al., 1995) which can lead to asthma-like symptoms and/or COPD. The lungs dissected by thoracotomy from Iranian casualties of Iraq–Iran war also demonstrated bronchiectasis and severe chronic inflammation (Emad & Rezaian, 1999; Freitag et al., 1991). Bronchoscopic appearance of airway mucosa showed a combination of erythema, chronic inflammatory changes and mucosal thickening in all SM-exposed patients (Beheshti et al., 2006).

Pulmonary infiltration (83%), pleural thickening (40%) and emphysema (26%) were the most common findings on CXR. According to HRCT scan, pulmonary infiltration (85%), BO

(61%) and pleural thickening (58%) were the most common findings.

SM exposure can also induce airway remodeling (AR) (Ghanei et al., 2004). Fourteen years after exposure, erythema of airway mucosa, chronic inflammatory changes, mucosal thickening (Beheshti et al., 2006) were observed while progressive lung weakening and BO were observed 20 years after exposure in CWV.

Hosseini-khalili et al. showed that in all subjects who had sustained single high-dose SM exposures during Iran–Iraq war, the mean age at the time of diagnosis of lung cancer was 47.4 years (Hosseini-khalili et al., 2009). On average, the time lapse between SM exposure and lung cancer development was 13.1 years. However, lung cancer typically develops after the age of 50 and peaks at approximately 60 years of age (O'Rourke et al., 1987).

SM-induced pathological changes of the lung including increased microvascular permeability in rodents after 5 h (Anderson et al., 2009; van Helden et al., 2004), detachment of tracheal and bronchial epithelial cells, deposition of fibrin containing cellular debris in the airway lumen and edema of the sub-mucosal lining after 6 h in different animal models have been reported (Anderson et al., 1996; Calvet et al., 1994a; van Helden et al., 2004). Lower airway effects including thickening of alveolar walls and perivascular edema are the most important changes seen 14 d post-SM exposure (Calvet et al., 1994a; Malaviya et al., 2010;

Table 4. Lung pathological changes due to SM exposure and their similarities with those of asthma and COPD.

	Lung pathological changes	Time after exposure	Similarities		References
			Asthma	COPD	
Human	Increased edema and erythema of the pharynx and bronchial tree	Min–several hours			(Chan & Allen, 2004)
	Hemorrhagic pulmonary edema, secondary pneumonia	24–48 h			(Ghanei et al., 2005)
	Increased infection of the respiratory tract, resulting in bronchopneumonia	36–48 h		✓	(Hosseini et al., 1989; Keshmiri, 1989; Willems, 1989)
	Erythema of airway mucosa, chronic inflammatory changes and mucosal thickening	14 years	✓		(Beheshti et al., 2006)
	Airway remodeling		✓	✓	(Ghanei et al., 2004; Thomason et al., 2003)
	Progressive lung weakening, bronchiolitis obliterans	20 years	✓		(Rowell et al., 2009)
Animal	Autophagy in the lungs	Immediately		✓	(Chen et al., 2008)
	Increased microvascular permeability in rodents	5 h	✓	✓	(Anderson et al., 2009; van Helden et al., 2004)
	Detachment of tracheal and bronchial epithelial cells, deposition of fibrin in the airway lumen, edema of the submucosal lining	6 h	✓		(Anderson et al., 1996; Calvet et al., 1994a; van Helden et al., 2004)
	Initial DNA damage and apoptosis in bronchial epithelium	6–24 h			(Kehe et al., 2009a; Ray et al., 2008; Ray et al., 2010; Sourdeval et al., 2006)
	Intra-alveolar hemorrhage, edema, intra-alveolar accumulation of macrophages and mononuclear cells, interstitial deposits of fibrin and collagen in the lung, collapse of alveolar structures in rats	24 d	✓		(McClintock et al., 2006)
	Increased epithelial shedding of tracheae and pathological changes in the lungs	14 d	✓		(Gholamnezhad et al., 2015)
	Thickening of alveolar septal walls, perivascular edema	14 d	✓		(Calvet et al., 1994a; Malaviya et al., 2010; McClintock et al., 2006)
	Increase inflammation of the lung	7–21 d	✓		(Kehe et al., 2009b)

McClintock et al., 2006). Autophagy in the lungs of animals shortly after exposure to SM was observed (Malaviya et al., 2010). In addition, SM-treated rats showed a transient increase in the expression of membrane bound LC3B-II, associates with the autophagosome membranes and a significant increase in the number of autophagosomes in endothelial cells in SM-treated animals was observed 6 h post-exposure (Malaviya et al., 2010). Moreover, 24 h to 6 d after exposure to SM, intra-alveolar hemorrhage, edema, intra-alveolar accumulation of macrophages and mononuclear cells, interstitial deposits of fibrin and collagen in the lung and collapse of alveolar structures in rats were observed (McClintock et al., 2006).

Blood congestion in the liver and kidney, cholestasis in the liver and calcification in kidney were the most important pathological changes in these two organs, and epithelial

shedding of tracheae and pathological changes in the lungs increased in guinea pigs 14 d post-exposure to SM (Boskabady et al., 2011b). In addition, thickening of alveolar septal walls and perivascular edema in the lungs increased in guinea pigs 14 d after SM exposure (Malaviya et al., 2010; McClintock et al., 2006).

The pathological changes in different organs following SM exposure could be due to DNA damage (Langenberg et al., 1998) or SM inflammatory and oxidant effects. Initial DNA damage and apoptosis in bronchial epithelium occur 6–24 h after SM exposure (Ray et al., 2008; Ray et al., 2010; Sourdeval et al., 2006).

Langenberg et al. (1998) showed pathological changes in liver, pancreas, thymus and lungs as well as DNA damage in mice exposed to inhaled SM. Anderson et al. (1996) reported pathologic changes in adult male rats following 50-min

intra-tracheal administration of SM. Lung pathological changes due to SM exposure are listed in Table 4.

Effects of sulfur mustard on lung inflammation

Inflammatory cells

Generally, the percentages of inflammatory cell count in BAL fluid were 88, 16, 62 and 0% for neutrophils, lymphocytes, macrophages and eosinophils, respectively in patients 14 years following SM exposure (Beheshti et al., 2006). Inflammatory cell accumulation in the airways and lung which lead to structural and functional alterations in the respiratory tract following exposure of animals to SM was shown (Calvet et al., 1994a; Malaviya et al., 2010). The majority of inflammatory cell are neutrophils and macrophages, supporting the idea that phagocytic leukocytes and inflammatory mediators release are involved in the pathophysiology of the response to inhaled SM (Gao et al., 2010; McClintock et al., 2002).

SM can induce a rapid (30 min to 12 h) immune response in the skin, characterized by infiltration of both CD4+ and CD8+ T-cells (Mishra et al., 2010) which indicates the role of these cells in SM-induced disorders. Bronchoalveolar lavage (BAL) cells increased significantly after exposure of rats to SM (Anderson et al., 1996; Malaviya et al., 2010).

White blood cells (WBCs) count in guinea pigs exposed to SM showed increased percentage of eosinophils and monocytes and lymphocyte decreased 14 d after SM exposure (Boskabady et al., 2011a). Increase in the total WBC and eosinophils counts, as an important indicator of airway inflammation in lung lavage, was also shown in animals exposed to SM (Boskabady et al., 2011c). In addition, WBCs and red blood cells (RBCs) increased in the skin 14 d after SM exposure in mice (Gautam et al., 2005).

Inflammatory mediators

Yaraee et al. showed that serum levels of inflammatory cytokines including TNF, IL-1 α , IL-1 β and IL-1Ra significantly decreased in CWV long after SM exposure (Yaraee et al., 2009a). Serum levels of inflammatory cytokines including IL-1 α , TNF- α , IL-1 β and IL-6 in SM-exposed patients with ocular surface problems, 20 years after exposure to SM were significantly lower than control group (Ghasemi et al., 2009). Serum levels of interleukin IL-8, IL-6 and cell adhesion molecules (e.g. selectins) were also increased in SM-exposed subjects, 20 years after exposure (Pourfarzam et al., 2009; Yaraee et al., 2009b). In addition, an increase in the level of pro-inflammatory cytokines such as interleukin IL-6 and IL-8 was observed in human bronchial epithelial cell culture 6–24 h after exposure to SM (Pohl et al., 2009). In addition, serum levels of IL-4 and IFN- γ were increased in SM-exposed guinea pigs after 14 d (Boskabady et al., 2011a). T-helper 2 (Th2) cells produce interleukin IL-4 and IL-10 while T-helper 1 (Th1) cells produce interleukin 2 (IL-2) and interferon gamma (IFN- γ) which can inhibit Th2 response (Randolph et al., 1999). SM markedly increased the expression of the neutrophil chemokine IL-8 (CXCL-8), inflammatory cytokines TNF- α , interferon (IFN)- γ in the lung, lymph nodes and connective tissue and growth factor was

up-regulated in the skin of SM-exposed animal (Anderson et al., 2009; Mishra et al., 2010; Sunil et al., 2009). Total protein (TP), cytokines IL-1 α and IL-13 markedly increase in lung lavage shortly after exposure (Anderson et al., 2009).

Matrix metalloproteinase (MMP)

The mean level of MMP-9 in serum of mustard-injured patients was significantly increased (Shohrati et al., 2014). Evidence suggests an important role of MMPs in the toxicity of SM in different organs including lung, skin and eye (Shakarjian et al., 2010).

In addition, Seagrave et al. demonstrated that the level of MMP-13 was significantly increased in tracheobronchial epithelial cells, cultured in an air–liquid interface, exposed to SM vapors (Seagrave et al., 2010). MMPs are zinc-dependent endopeptidases that degrade extracellular matrix (ECM) proteins, and contribute to inflammatory cell recruitment, tissue injury, and fibrosis (Chakrabarti & Patel, 2005; Corbel et al., 2002; Lagente et al., 2005). TNF- α is also known to up-regulate the expression of MMPs which degrade ECM components and have been implicated in lung toxicity (Ohbayashi, 2002).

The level of MMPs, including MMP-9 was increased in the respiratory tract within 6–24 h of exposure to SM (Calvet et al., 1999; Malaviya et al., 2010). Some study also demonstrated that SM can cause a dose and time-dependent increase in the expression of MMP-9 in the lung which was mainly localized in bronchiolar epithelium and alveolar macrophages. In addition, MMP-9 protein and gelatinase activity were also up-regulated in BAL following SM administration to rats (Malaviya et al., 2010). A similar expression pattern of MMP-9 has been also described in the respiratory tract after exposure of rodents to 2-chloroethyl ethyl sulfide (CEES) or nitrogen mustard (Sunil et al., 2009). MMP-9 protein and 92 kDa gelatinase activity are also detectable in BAL within 6 h after SM exposure and persist for at least 7 d (Calvet et al., 1999), suggesting that biologically active MMPs are secreted during the pathogenic response to vesicants.

It is possible that MMP-9 plays a role in SM-induced detachment of epithelia and epithelial cell sloughing. This is supported by findings that gelatinase B (MMP-9) is present at epithelial detachment sites, which is directly correlated with SM-induced alveolar epithelial injury, and MMP inhibitors such as doxycycline and ilomastat ameliorate vesicant-induced respiratory lesions (Anderson et al., 2009; Calvet et al., 1999; Guignabert et al., 2005).

Other inflammatory markers

Following SM inhalation, a rapid and transient induction of HO-1 protein was observed in the lung, confirming that SM-induced toxicity is associated with oxidative stress (Korkmaz et al., 2006). A similar biphasic effect on HO-1 has been described after exposure of macrophages to cigarette smoke (Goven et al., 2009). Moreover, studies on serum antibodies levels indicated an initial increase in IgG and IgM levels in SM-exposed subjects during the first week, but their level decreased over the next 6 month of exposure (Hassan & Ebtekar, 2002).

Other studies also indicated an increased serum complement systems C3 and C4 in SM-exposed patients from the first week to the 6th month (Ghannadpour, 1986). Balali-Mood et al. showed increased serum immunoglobulin IgM and complement systems C3 levels in SM poisoning patients 16–20 years after exposure (Balali-Mood et al., 2005). Mehrani et al. identified some proteins including different isoforms of haptoglobin in the plasma of SM-exposed subjects with severe lung disease patients which could provide a novel insight into the pathogenesis of mustard-injured lung (Mehrani et al., 2011). They showed that under experimental conditions, the $\alpha 2$ haptoglobin chain (spots 11, 12, 13) is similarly expressed in the plasma of patients and control subjects, but $\alpha 1$ chain (spots 21, 22, 23) is only expressed in the patients' plasma samples. In addition, haptoglobin isoforms in BAL fluid (BALF) proteomic patterns in SM-exposed patients were significantly higher in patients with moderate and severe lung diseases as compared to mild lung disease and healthy controls (Mehrani et al., 2009). Arredouani et al. also described the role of haptoglobin in the immune system, and showed that haptoglobin directly affects T-cells and suppresses T-helper-cells through down-regulation of cytokine production (Arredouani et al., 2003). Serum amyloid A1 is an acute-phase protein which is induced, like CRP by inflammatory mediators including IL-6, IL-1 β and TNF- α in acute exacerbation of COPD (Sapey & Stockley, 2006). Mehrani et al. found that amyloid A1 isoforms are only detected in the plasma of patients with severe lung diseases and severe acute respiratory syndrome (SARS) patients but not in healthy controls (Mehrani et al., 2011). It has been reported that serum amyloid A1 is increased in SM-exposed patients after 20 years (Mehrani et al., 2011; Sapey & Stockley, 2006). The pathogenesis of SM-induced lung injury via Fas-FasL signaling pathway is important in apoptosis. Fas and FasL levels were significantly higher in BALF cells but caspase-3 activity was not significantly different in patients 20 years after exposure to SM compared with the control group (Pirzad et al., 2011). Moreover, apoptosis occurs in human bronchial epithelium cells 6–24 h after exposure to SM, which is associated with activation of caspase-3, caspase-8 and caspase-9, suggesting the importance of the death receptor pathway in this phenomenon (Ray et al., 2008; Ray et al., 2010).

Increased protein levels after exposure of rats to SM was demonstrated (Anderson et al., 1996; Malaviya et al., 2010). In rats, SM inhalation leads to activation of both caspase-9 and caspase-3 within 6 h of SM exposure and persisted for at least 24 h (Malaviya et al., 2010). Immunohistochemical analysis of tissue sections showed localization of caspases mostly in the bronchial epithelium and increased expression of activated caspases in alveolar macrophages isolated from SM-exposed rats and in bronchial/tracheal and small airway epithelial cells treated with SM *in vitro* (Ray et al., 2008; Ray et al., 2010; Sourdeval et al., 2006).

Following SM exposure, poly-ADP-ribose polymerase-1 (PARP-1) is rapidly inactivated in the lung which suggests potential contribution to tissue injury induced by this vesicant. PARP-1 is a nuclear repair enzyme activated following DNA damage (Debiak et al., 2009). Cleavage of PARP-1 by caspases into 89- and 24-kDa fragments is

considered as a feature of late apoptosis. After SM inhalation, increased expression of both intact and cleaved PARP-1 in the lung were found (Malaviya et al., 2010). These data confirm that SM induces DNA damage 6–24 h after exposure to SM (Kehe et al., 2009b; Ray et al., 2008; Sourdeval et al., 2006), which may be related to apoptosis (Kehe et al., 2009a).

SM exposure can lead to up-regulation of inducible nitric oxide synthase (iNOS) and stimulation of the production of reactive nitrogen species in airway epithelial cells (Gao et al., 2008). Oxidative stress in the lung and lung injury can cause rapid generation of the pro-inflammatory cytokine TNF- α , a noticeable macrophage-derived mediator in pulmonary tissues which is implicated in pulmonary pathophysiology (Mukhopadhyay et al., 2006). Although the TNF- α cascade is a major pathway in vesicant-induced lung injury (Chatterjee et al., 2003; Mukhopadhyay et al., 2008), the specific role of TNF- α in mustard-induced toxicity is unknown. TNF- α promoted oxidative metabolism in phagocytic leukocytes and up-regulated a number of other inflammatory cytokines in the lungs of animals following exposure to vesicants (Anderson et al., 2009; Mishra et al., 2010; Sunil et al., 2009).

Pro-inflammatory prostaglandins, reactive oxygen and nitrogen species released by phagocytic leukocytes may also contribute to vesicant-induced toxicity. In addition, following vesicant exposure, iNOS enzyme mediates the production of nitric oxide by macrophages and epithelial cells, and the eicosanoid generating enzyme, cyclooxygenase (COX)-2 are rapidly up-regulated in these cells (Korkmaz et al., 2008; Malaviya et al., 2010; Sunil et al., 2009; Sunil et al., 2011). Moreover, animals lacking iNOS, or treated with an iNOS inhibitor or peroxynitrite scavenger, are protected from vesicant-induced lung injury (Sunil et al., 2011; Yaren et al., 2007).

SM-induced oxidative stress is thought to be a primary event in activation of inflammation process. Early response pro-inflammatory cytokines such as TNF- α are rapidly generated in tissues in response to oxidative stress. It has been suggested that initiation of the free-radical-mediated TNF- α cascade is a major pathway in vesicant-induced lung injury (Chatterjee et al., 2003; Mukhopadhyay et al., 2006).

Inflammatory response to SM exposure in the lower airway is surfactant dysfunctions which have been implicated as causative factors in ARDS (Gregory et al., 1997). Recent studies have also demonstrated that expression of surfactant protein D (SP-D), which possesses anti-inflammatory activity is markedly reduced in rats' lung epithelium following SM exposure (Malaviya et al., 2010; Sunil et al., 2009).

Malaviya et al. showed that SM exposure resulted in a time-dependent decrease in native SP-D expression in bronchiolar epithelial cells which was directly correlated with inflammation and tissue injury (Malaviya et al., 2010). These results are consistent with reports on type II cell damages and alteration of the surface tension of BAL following MS exposure, suggesting a potential mechanism leading to the development of ARDS in SM-exposed individuals (van Helden et al., 2004; Mukhopadhyay et al., 2008; Roy et al., 2005). Interestingly, SP-D staining increased in alveolar macrophages following SM exposure which is likely to be due to uptake of the protein by these phagocytic cells. The effect

Table 5. The effect of SM exposure on lung inflammation and their similarities with those of asthma and COPD.

	Lung inflammation markers	Time after exposure	Similarities		References
			Asthma	COPD	
Human	Rapid and transient induction of HO-1 protein	Immediately			(Korkmaz et al., 2006)
	Rapid immune response in the skin (increased CD4+ and CD8+ T-cells)	30 min–12 h	✓		(Mishra et al., 2010)
	Increased levels of IgG and IgM in first week, but reduction after 6 months	First weeks–6th month	✓	✓	(Hassan & Ebtakar, 2002)
	Increased serum levels of complement systems C3 and C4	Weeks 1–6th month	✓		(Ghannadpour, 1986)
	Increased neutrophils and macrophages cells in BAL fluid	14 years		✓	(Beheshti et al., 2006; McClintock et al., 2002)
	Increased serum immunoglobulin IgM and complement systems C3 levels	16–20 years	✓		(Mahmoudi et al., 2005)
	Increased serum matrix metalloproteinases MMP-9		✓		(Shohrati et al., 2014)
	Decreased serum levels of IL-1 α , IL-1 β and TNF- α	20 years			(Ghasemi et al., 2009)
	Increased serum haptoglobin	20 years	✓		(Mehrani et al., 2011)
	Increased serum amyloid A1	20 years		✓	(Mehrani et al., 2011; Sapey & Stockley, 2006)
	Increased serum levels of IL-8, IL-6 and cell adhesion molecules (e.g. selectins)	20 years	✓	✓	(Pourfarzam et al., 2009; Yaraee et al., 2009b)
	Increased BAL levels of Fas and FasL cells	20 years			(Pirzad et al., 2011)
Animal	Increased BAL caspase-9 and caspase-3	6–24 h			(Malaviya et al., 2010)
	Increased IL-6 and IL-8 and MMPs in cell culture media	6–24 h		✓	(Pohl et al., 2009; Seagrave et al., 2010)
	Increased BAL MMP-9 protein and 92 kDa gelatinase activity	6 h–7 d	✓		(Calvet et al., 1999)
	Total protein, IL-1 α and IL-13	23–24 h	✓		(Anderson et al., 2009)
	Increased neutrophil, IL-8, TNF- α , IFN- γ in the lung, lymph nodes and connective tissue	4 d	✓		(Mishra et al., 2010, Sunil et al., 2009)
	Increased serum IL-4 and IFN- γ	14 d	✓		(Boskabady et al., 2011a)
	Increased WBCs and red blood cells (RBCs) in the skin	14 d	✓	✓	(Gautam et al., 2005)

of SM exposure on lung inflammation is summarized in Table 5.

Comparison of the effect of various doses of SM

Intratracheally instilled SM (0.35 mg SM in 0.1 ml of ethanol) induced pathological changes such as detachment of tracheal and bronchial epithelial cells in the airway lumen and induction of edema in the sub-mucosal lining after 5–6 h in the lung of animals (Anderson et al., 1996; Anderson et al., 2009; Calvet et al., 1994a). In addition, intratracheal administration of SM (0.7–1.4 mg/kg) increased the expression of some proteins such as autophagosome membranes in endothelial cells 6 h post-exposure in rodents (Malaviya et al., 2010).

SM administered by intratracheal instillation also increased the expression of different cytokines and chemokines in the lung, lymph nodes and in the skin of animal and also leads to up-regulation of iNOS and production of reactive nitrogen species in airway epithelial cells (Anderson et al., 2009; Gao et al., 2008; Sunil et al., 2009). Airway resistance was increased 14 d after SM inhalation (400 mg/m³)

(Calvet et al., 1994b, 1999). Intrapulmonary injection of half-mustard gas (HMG) (0–12 mg/kg) induced thickening of alveolar walls and perivascular edema in lower airway 14 d post-SM exposure (McClintock et al., 2002; McClintock et al., 2006). Furthermore, accumulation of macrophages, hemorrhage in alveolar and collapse of alveolar structures in the lung of rats 24 h to 6 d after exposure to intratracheally instilled SM were observed (McClintock et al., 2006).

Inhaled SM (40 mg/m³) induced pathological changes, including blood congestion in the liver and kidney, cholestasis in the liver and calcification in kidney in different organs of guinea pigs and also epithelial shedding in tracheae 14 d post exposure (Boskabady et al., 2011b). A rapid immune response in the skin (infiltration of both CD4+ and CD8+ T-cells) occurred after SM (400 mg/m³) exposure (Mishra et al., 2010).

Expression of caspases in bronchial epithelium and alveolar macrophages were increased following SM exposure *in vitro* and *in vivo* (Ray et al., 2008; Ray et al., 2010; Sourdeval et al., 2006). DNA damage and apoptosis in bronchial epithelium and an increase in the inflammatory cytokines, MMP-9 protein and 92 kDa gelatinase activity in

Table 6. Various doses of SM used in different studies.

Models of study		Methods of administration		SM doses	References
<i>In vivo</i>	Rat	Instillation	Intratracheal	1.4 mg/kg	(Anderson et al., 2009)
				0.14 mg/kg	(Anderson et al., 1996)
				0.7–1.4 mg/kg	(Malaviya et al., 2010)
				0–24 mg/kg	(Mcclintock et al., 2002)
				0–24 mg/kg	(Mcclintock et al., 2006)
	Mice Guinea pig Guinea pig	Inhalation	Aerosol exposed	3 or 6 mg/kg	(Sunil et al., 2009)
				0.3 mg/kg	(Calvet et al., 1994a)
				40 mg/m ³	(Boskabady et al., 2011a)
				100 mg/m ³	(Boskabady et al., 2011b)
				10 000 mgmin m ³	(Langenberg et al., 1998)
<i>In vitro</i>	AEC HBEC, (SAEC) HBEC HBEOC HSAEC	Exposure	Exposed cells to SM	2400 mgmin m ³	(Langenberg et al., 1998)
				400 mg/m ³	(Mishra et al., 2010)
				0.1–0.5 mM	(Sourdeval et al., 2006)
				0, 50, 100 and 300 µM	(Ray et al., 2008)
				0, 50, 100 and 300 µM	(Ray et al., 2010)
				30, 100, 300 and 500 µM	(Pohl et al., 2009)
				100 µM	(Gao et al., 2008)

Airway epithelial cell (AEC), human bronchial epithelial cells (HBEC), small airway epithelial cells (SAEC), human bronchial epithelial explant-outgrowth cells (HBEOC), human small airway epithelial cells (HSAEC).

BAL occur 6–24 h after SM exposure (Pohl et al., 2009; Ray et al., 2008; Ray et al., 2010). Various doses of SM used in different studies are shown in Table 6.

Similarities and differences between various adverse effects of SM exposure, asthma and COPD

Symptoms and PFT

CWV mostly complained of cough, dyspnea and wheezing that are very similar to the asthma symptoms. These subjects were healthy for a period of time after exposure. Their disease shows some difference from asthma such as a steady state course, resistance to treatment and the severity of the respiratory disease. One study reported that 75% of CWV showed airway hyper-responsiveness which is more similar to asthma (Brent, 2005). Hemoptysis, chest pain and nocturnal dyspnea are also frequently experienced by SM-exposed patients who are similar to asthma and COPD.

Functional changes in the lung following exposure of animals to vesicants have also been described. Within 5 h of administration of SM to rodents, respiratory system resistance and microvascular permeability are markedly increased, and by 24 h, alterations in tidal volume, respiratory frequency, peak inspiratory and expiratory pressure, and airway hyper-reactivity are observed (Anderson et al., 2009; van Helden et al., 2004). After 14 d, airway hyper-reactivity to substance P and histamine is noted which are consistent with asthma-like changes (Calvet et al., 1994b, 1999). Similar alterations in pulmonary mechanics have been described in rodent models of 2-CEES – or nitrogen mustard-induced pulmonary intoxication (Sunil et al., 2011; Wigenstam et al., 2009). CEES induces desensitization of beta-2 adrenergic receptors in the lung, possibly contributing to bronchospasm (Kabir et al., 2009). Chest pain, productive cough, hemoptysis and most importantly dyspnea disproportional to PFT or normal PFT findings imply SM-induced BO (SMBO). Although these findings may also be evident in cases of asthma and COPD, it should be noted that hemoptysis is never seen in asthma. COPD can be ruled out in patients with a negative history of smoking. Thus, excluding these two common respiratory

disorders (asthma and COPD), SM patients with any of the above-mentioned clinical conditions should be further evaluated for SMBO.

Smoking cessation improves the accelerated decline in FEV1 in COPD which is another difference between the pathogenesis of COPD and that of mustard lung (Willemse et al., 2004). According to the differences between the pathogenesis of COPD and mustard lung, different therapeutic approaches have been considered for these conditions (Aghanouri et al., 2004). However, there is no cure for mustard lung injury, the main strategy of treatment is to prevent injuries by an effective protection and if occurred, prevention of disease progression is of higher priority than curing or treating the symptoms.

The concentration–response curves for salbutamol in CWV as reported by Boskabady et al. (2008) compared to normal subjects were different from those of smokers (Boskabady & Farhadi, 2008) but were similar to the asthmatic patients (Boskabady & Saadatnejad, 2003).

Pathology

The pathology behind hemoptysis in patients exposed to SM is thought to be a chronic inflammatory process within airway walls. It is reasonable to correlate the hemoptysis in these patients to BO (Bijani & Moghadamnia, 2002; Mroz et al., 1997).

It has been reported that 36–48 h after SM exposure some pathological changes like infection of the respiratory tract resulting in bronchopneumonia occurred, which is similar to COPD (Hosseini et al., 1989; Willems, 1989). Autophagy observed in lungs of animals shortly after exposure to SM suggests that this cytotoxic mechanism may be important in the pathogenesis of chronic lung diseases in exposed individuals. This is supported by findings that exposure to cigarette smoke, which is also a causative agent for COPD induces autophagy in lung epithelial cells (Chen et al., 2008).

AR is reported in complex diseases such as asthma, COPD and mustard lung as the main respiratory pathological change. In addition, progressive dyspnea and airflow limitations,

mucostasis and mucosal inflammatory reaction are usually associated with AR (Ghanei et al., 2004; Thomason et al., 2003). Mustard lung has an irreversible pattern of airway obstruction like COPD without any evidence of emphysema (Ghanei & Harandi, 2007).

AR is a pathophysiologic process which also exists in obstructive airway diseases. CXCL17 is a chemokine which induces the production of pro-angiogenic factors such as vascular endothelial growth factor (VEGFa) involved in tumor angiogenesis and is an anti-inflammatory factor which is over-expressed in mustard lung (Najafi et al., 2014). Also, CXCL17 is expressed in some aggressive types of gastrointestinal, lung and breast cancer cells (Matsui et al., 2012).

Transforming growth factor beta1 (TGF-beta1) is involved in ECM regulation, leading to AR in chronic airway diseases. Willems-Widyastuti et al. (2011) proved that TGF-beta1 which acts through ECM regulation could also play a critical role in bronchial angiogenesis and vascular remodeling via VEGF pathway in asthma.

AR usually refers to epithelial layer injury followed by structural changes in the airways and lung construction (Tschumperlin & Drazen, 2001). The cellular and molecular processes in SM-exposed individuals depend on the individual, type and state of the disease. The respiratory disorder due to SM exposure is resistant to anti-asthma therapy and an irreversible pattern of obstruction existed in these patients. Based on these similarities between asthma and COPD, mustard lung can also be a good model for the evaluation of AR. Epithelium layer damage plays an important role in driving AR which exists in asthma. AR is the major cause of long-term disability among patients with war-exposure to SM gas (Ghanei et al., 2008; Mishra et al., 2012).

Inflammation

Inflammatory cell increase in the respiratory tract is a prominent histologic feature of mustard gas-induced pulmonary injury. The role of inflammatory cells in the pathogenesis of lung diseases such as bronchitis, asthma and COPD is well documented, which are also long-term consequences of SM poisoning. *In vitro*, macrolide antibiotics (e.g. erythromycin, azithromycin, roxithromycin) suppress vesicant-induced expression of pro-inflammatory cytokines and nitric oxide synthase in human airway epithelial cells and monocytes (Gao et al., 2008; Gao et al., 2010).

In asthma, eosinophils, mast cells and T lymphocytes represent the predominant cell types in the inflammatory process (Sutherland & Martin, 2003) which is similar to SM-exposed individual 30 min to 12 h after exposure (increased CD4+ and CD8+ T-cells) in the skin (Mishra et al., 2010). In addition, COPD and bronchiectasis demonstrate a greater number of neutrophils, macrophages and CD8+ T lymphocytes which are also similar to SM-exposed patients 14 years after exposure (increased neutrophils and macrophages cells in BALF) (Beheshti et al., 2006; McClintock et al., 2002).

It has been shown that levels of IL-8 and IL-6 in BALF of patients with mustard gas-induced pulmonary fibrosis were significantly increased (Emad & Emad, 2007). IL-8 and IL-6 have a primary role in various chronic pulmonary diseases such as COPD and asthma, and are suggested as biomarkers

for the diagnosis and disease activity (Car et al., 1994; Lee et al., 2008).

An increase in the number of neutrophils in the BALF or in the sputum of smokers has been reported. One study reported a higher concentration of IL-8 in induced sputum of normal smokers than normal nonsmokers (Keatings et al., 1996).

Inflammatory markers, such as CRP, IL-6 and TNF- α , are also important in the pathogenesis of COPD, and raised levels of these factors have been found in stable COPD patients (Sin & Man, 2008; Yanbaeva et al., 2009). Serum levels of highly sensitive CRP (hs-CRP), as an inflammatory marker, are elevated in patients with SM poisoning, correlated inversely with FEV₁, FEV1 percent predicted, and increased in SM patients with COPD (Attaran et al., 2009).

MMPs, including MMP-9, increase in the respiratory tract within 6–24 h of exposure to SM (Calvet et al., 1999; Malaviya et al., 2010). Some studies approved the role of MMPs in the pathology of asthma. MMP-9 (gelatinase B) is highly expressed in bronchial biopsies from asthmatic patients (Ohno et al., 1997). Other studies have demonstrated increased levels of MMP-9 in BALF and alveolar macrophage supernatant in untreated asthmatics (Mautino et al., 1997). Increased MMP-9 activity measured by zymography in BALF of asthmatic patients after allergen challenge was also reported (Warner et al., 1997). Furthermore, Vignola et al. (1998) showed increased sputum levels of both MMP-9 and TIMP-1, but a decreased MMP-9/TIMP-1 ratio, in both asthmatic and chronic bronchitic patients. Mattos et al. (2002) demonstrated that in patients with mild, stable asthma, there is a higher concentration of TIMP-1 in BALF than healthy, nonsmoking subjects, despite similar levels of MMP-9.

Defective secretion of pulmonary surfactant by alveolar type II cells and surfactant dysfunction have been implicated as causative factors in ARDS, which is an inflammatory outcome of SM exposure in the lower airway (Calvet et al., 1994b; Gregory et al., 1997). CEES administration to guinea pigs significantly decreases expression of cholinephosphotransferase, a key enzyme involved in surfactant biosynthesis, and finally increased levels of ceramides, which are thought to contribute to apoptosis and surfactant dysfunction (Chatterjee et al., 2003; Roy et al., 2005).

Saber et al. (2012) showed that the patterns of change in immunological biomarkers in SMBO subjects comply neither with asthma nor COPD. These findings showed that alteration in IL-8 and IL-17 levels is unique for this disorder.

Taravati et al. (2012) showed low paraoxonase 1 (PON1) activities in SM-exposed veterans in comparison with the control group. It was observed that patients with asthma, pulmonary tuberculosis and COPD showed a lower paraoxonase activity (Selek et al., 2008; Tekes et al., 2010). The role of PON1 in protection of airways against tobacco smoke has already been studied (Seo et al., 2008). The association between PON1 polymorphisms and the lung function of smokers, in which 192 R allele was introduced as a novel risk factor for airway injury, has previously been examined (Takayuki et al., 2007).

The similarities and differences in respiratory symptoms, pulmonary disorders, PFT values, lung pathology and lung inflammation in SM-exposed patients with those of asthma and COPD are listed in Tables 1–5.

Conclusion

Shortly after SM exposure, patients experience some symptoms and disorders including tracheobronchitis with hoarseness, hacking cough, dyspnea, chest pressure, sore throat, erythema of the pharynx and bronchial tree. Increasing cough, tachypnea, sinus pain were the main objective clinical findings in the steady state course. Regarding resistance to treatment and severity, SM exposure was different from asthma. However, chest pain and nocturnal dyspnea are also frequently experienced symptoms that are similar to asthma and COPD.

After SM exposure, some pathological changes such as increase in the infection of the respiratory tract, resulting in bronchopneumonia and autophagy similar to COPD were seen. AR is also observed in complex diseases such as asthma, COPD and mustard lung.

Eosinophils, mast cells and T lymphocytes were the predominant cell types in asthma and the number of neutrophils, macrophages and CD8+ T lymphocytes in COPD was higher which were similar to SM-exposed patients. CRP, IL-6, IL-8 and TNF- α , are also important in the pathogenesis of COPD, asthma and mustard lung.

Declaration of interest

Authors do not have conflicts of interest

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