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Review Article

Clinical Review of Mustard Lung

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Abstract

More than 45,000 of 100,000 exposed patients are suffering from late effects of sulfur mustard (SM) after almost 20 years post-exposure. Respiratory complications of SM exacerbate over time and are the greatest cause of long-term disability in exposed patients. A triad of cough, expectoration and dyspnea has been found to be the main symptoms among patients. Even those who had not developed acute symptoms may suffer from late respiratory complications. Pulmonary function test studies have revealed more obstructive patterns than restriction. High-resolution computed tomography (HRCT) is supposed to be the diagnostic imaging tool of choice in patients with history of SM exposure while chest x-ray may not be helpful. In contrary to earlier reports of interstitial pulmonary fibrosis in these patients, HRCT and pathological studies revealed the diagnosis of bronchiolitis obliterans. Bronchodilators and corticosteroids are widely used to resolve respiratory symptoms of mustard lung. Macrolides and antioxidants may improve respiratory symptoms and pulmonary function. Interferon gamma could improve pulmonary function of SM exposed patients with bronchiolitis.

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Keywords ● Weapon of mass destruction ● chemical weapon ● mustard gas ● respiratory system ● sulfur mustard

Introduction

Mustard gas was the most widely-used vesicant chemical warfare agent in the past century.[1] It was originally employed as a weapon in World War I, and was responsible for more than 80% of all documented chemical casualties.[2,3] It was then, used sporadically until 1983, when the Iraqi army employed it on a large scale against Iranian soldiers during the Iran-Iraq War (1983-8).[4] It is also known as sulfur mustard (SM) [bis-(2-chloroethyl) sulfide], yperite (Ypres was the place of its first military use), Lost (acronym of the German chemists Lommel and Steinkopf who investigated the military use of this chemical), and yellow cross (German shells were marked with a yellow cross which means “skin damaging agent”).[5]

SM is absorbed by inhalation, through the skin, anterior surface of the eyes, or gastrointestinal tract following consumption of contaminated food. The eyes, skin and respiratory system are three major targets of its toxic effects. When absorbed in large amounts, it can damage the rapidly-proliferating cells of bone marrow and may cause leukopenia and severe suppression of the immune system.[6-8] Endocrine and neuro-muscular damages were also reported.[9]

Over 100,000 Iranians were injured by SM. Due to its low mortality rate of 3%–4%, it causes prolonged health problems and more than 45,000 of the exposed patients are currently

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suffering from its late effects after almost 20 years post-exposure.[5,8,10] During the course of the war with Iraq, greater numbers of Iranians sustained exposure to nerve agents than mustards. However, among those who survived, a significantly larger number of mustard agent victims have reported chronic health problems during the years after exposure.[11]

While most studies focused on acute complications of SM exposure, there is scarce knowledge on long-term effects, work-ups and management of patients with history of exposure to SM. There is no definite treatment for acute respiratory complications, however we can manage late respiratory effects to prevent sever disabilities. In this study, based on our experience, we proposed a clinical approach, para-clinical findings and diagnostic and therapeutic studies on patients with SM exposure.

Literature Review

A search of PubMed was performed with different names of SM and search terms including chronic, late and delayed pulmonary (respiratory) complications of SM. Relevant articles were selected from this search. In addition, the reference lists of available articles were reviewed for further relevant articles and books. As we aimed to discuss late respiratory effects, studies on other organs were not included. SM complications in patients within the battle-field (i.e., single) exposure and those with longtime (e.g., occupational) exposure are different. Therefore, we paid special attention to studies on patients with history of exposure to SM in Iran-Iraq war. Case reports were excluded as well as unpublished studies to reach higher level of evidences. Although there was not any high-quality meta-analysis on this topic, all published review articles were fully considered in our review. Human studies were given more priority and concern than animal and *in vitro* studies. During our study, we mostly focused on main clinical controversies, i.e., the underlying disease in mustard lung rather than on SM toxicokinetics and mechanism of action. In this report, hematologic and immune system complications were also reviewed as they might interfere with respiratory complications.

Acute Effects of SM

The first contact to SM is mostly painless and only a garlic or sulfur odor can be noticed. Normally, a symptom-free interval is observed for several hours. The duration of this interval correlates inversely with the absorbed dose of the agent. The maximum intensity of symptoms can be reached after days. The eyes, the nasal mucosa, the throat, the pulmonary tract and the skin are most commonly affected. An exposure to large doses of SM can cause damage to the hematopoietic and the immune system,[5] (table 1).

In respiratory system, the initial or perhaps the only effect is pain and discomfort in the nose or sinuses. This is accompanied by increased nasal secretions, sneezing, and sore throat, which usually develop 4–16 hr after the exposure. Rhinorrhea is often profuse and epistaxis may occur. Larger amounts of SM vapor will cause laryngeal injury (aphonia or hoarseness) and damage to the upper medium-sized airways (tracheobronchitis), which is usually manifested by a non-productive cough.[12,13]

Exposure to large amounts of SM may cause damage to the terminal airways with productive cough, dyspnea, and possibly hemorrhage into the alveoli.[8] Cough may be severe and sputum is often purulent.[8] In severe cases, necrosis of the mucosa with associated inflammation may lead to the formation of a diphtheritic-like membrane. This can occur at any level and may obstruct the airway or break off to obstruct lower airways.[14] Later, as seen in Iranian victims with multi-system organ failure, patients may present the clinical picture of adult respiratory distress syndrome.[8]

Infection of the respiratory tract is a common complication, usually seen 36–48 hr after the exposure. It may result in bronchopneumonia, with death occurring at any time between the second day and the fourth week post-exposure.[15] Although recovery can be rapid, some irritation, cough, and hoarseness may persist for as long as six weeks. Prolonged recovery (1–2 months) can be expected, particularly after secondary infections and necrotic bronchopneumonia. Experience with Iranian casualties shows that the prognosis in those with severe lung complications requiring

Table 1: Acute effects of sulfur mustard on different organ systems

Severity of exposure	**Eye**	**Respiratory tract**	**Skin**	**Systemic toxicity**
Mild	Conjunctivitis, grittiness under the eyelid, tearing	Irritation of nasal mucosa, hoarseness, sneezing, cough	Erythema, itching	Nausea, vomiting, loss of appetite
Moderate	Corneal edema, photophobia, Severe blepharospasm lacrimation,	Rhinorrhoea, loss of smell and taste, hacking cough, tracheobronchitis, pseudomembranes	Severe erythema followed by blister formation	
Severe	Severe corneal damage and ulceration, perforation	Edema in upper and lower airways, ulcerations	Rapid development of erythema and blisters, ulceration of dermal structures	Immune suppression, leukopenia, diarrhea, cachexia, fever

artificial ventilatory support, is very poor, even when sophisticated facilities and intensive care therapy are applied.[15]

Long-term Effects of SM

Evidence on long-term effects of SM comes from studies on exposed soldiers (battle-field exposure) and studies on workers of mustard gas factories (occupational exposure). While long-term effects following battle-field exposure are referred to as ''late'' or ''delayed'' complications, the term ''chronic'' complication seems to be more suitable for the injuries caused by occupational exposure.[8] It must also be emphasized that delayed effects generally occur some months or years after a single or mild exposure and are not the same as chronic poisoning which comes from continuous exposure during a long period of time.[8]

Recent studies on Iranians about 15–20 years after the exposure to SM showed that the most common late complications in descending order of frequency are found in the lungs, eyes, and skin.[10, 16] Respiratory problems are the greatest cause of long-term disability among patients with combat-exposure to SM gas. They exacerbate over time while cutaneous and ocular injuries tend to either alleviate or remain invariable.[8,10,17]

Clinical Presentations

Chronic cough is the most common complaint in these patients. A triad of cough, expectoration and dyspnea were found in more than 80% of Iranian veterans three years after their initial exposure.[8,18] Hemoptysis (mainly streaky), chest tightness, chest pain, and nocturnal dyspnea are also frequent symptoms. The main respiratory signs are generalized wheezing, crackles, decreased respiratory sounds and cyanosis.[8,19,20]

Hypoxemia and hypercapnea are commonly observed in moderate to severe cases of chronic bronchitis, leading to cor-pulmonale and respiratory failure in the final stages of the disease.[8,16] Typical attacks of breathlessness, wheezing and nocturnal cough due to airway hypersensitivity and hyperreactivity, have been reported between four weeks to twenty years after SM inhalation.[21] Direct effects of SM on bronchial wall mucosa and more importantly recurrent respiratory infections following inhalation of SM are known to be responsible for the development of bronchiectasis. Airway narrowing, due to scarring or granulation tissue, is a late sequela of acute injuries to the trachea and large bronchi, usually developing two years after the exposure.[16,18,22-24]

Patients who had not developed acute symptoms may suffer from late respiratory complications. Symptomatic patients who were in contaminated areas and had no acute signs and symptoms at the time of exposure (subclinical exposure), experience delayed respiratory complications such as bronchiectasis and Bronchiolitis Obliterans (BO).[18] We have previously shown that 38% of these patients had shown significant air trapping in chest high-resolution computed tomography (HRCT); 24% had at least air trapping added to other defects. Septal wall thickening and bronchiectasis were also reported.[18] Thus, the late respiratory complications of SM and mustard lung should be taken into account when a patient with suspicious exposure to SM develops respiratory signs and symptoms.

Diagnostic Evaluation

Spirometery

Pulmonary function test (PFT) is a common diagnostic tool in SM-exposed patients as respiratory problems are the greatest cause of long-term disability among them. PFT studies have revealed more obstructive patterns than restriction. Forced vital capacity (FVC), forced expiratory volume in the 1st second (FEV_1), and FEV_1/FVC ($FEV_{1\%}$) may be lower in comparison to healthy non-exposed people as well as to those chemical warfare survivors who used a gas mask at the time of attack.[8] FEV_1 appeared to decrease at a rate of 50 mL/year.[25] The residual volume (RV) is markedly increased while Diffusing Capacity of the Lung for Carbon Monoxide (DLCO) remains normal.[26] It was shown that more than half of the exposed patients developed no PFT impairment.[10] Others with impaired PFT usually show more obstructive patterns than restriction[8,27] while mixed restrictive and obstructive, and pure restrictive patterns are seen less frequently[20-22,28]. In a study by Khateri, et al, 37% of patients suffering from respiratory problems had mild, 4.5% had moderate and 1% had severe pulmonary function impairment while others had normal PFT results.[10]

Obstructive spirometric results may be reversible in response to inhaled bronchodilators.[8] However, we may encounter some patients who have unexplained resistance to anti-asthma therapy, irreversible pattern of obstruction and/or with a discrepancy among disease symptoms and signs, PFT and radiological findings.[27]

Typical findings are seen in patients with sever exposure and acute symptoms while patients with mild exposure who developed delayed respiratory complications usually had normal PFT or mild obstructive involvement.[18] Abnormal spirometric findings, in general, and

restrictive patterns, in particular, tend to increase over time.[18]

High Resolution Computed Tomography of the Chest

Chest HRCT is supposed to be the diagnostic imaging tool of choice in patients with history of SM exposure.[28] Taking chest HRCT in both supine and prone positions and deep expiration phase along with inspiration phase is necessary to show small airway changes.[27] Air trapping and mosaic parenchymal attenuation are the most frequent abnormal findings in both symptomatic as well as asymptomatic patients. Bronchiectases (74%), irregular and dilated major airways (66%), bronchial wall thickening (90%), and interlobular septal wall thickening (26%) are other common abnormal findings in chest HRCT.[28-30]

The reports of Interstitial Lung Disease (ILD), Interstitial Pulmonary Fibrosis (IPF) or emphysema in chest HRCT,[22,29] were not supported by other studies using revised diagnostic criteria and new tools for work-up and definition.[27] In a study on chest HRCT of 155 symptomatic patients exposed to SM during Iran-Iraq war, bronchiectasis, air trapping in expiration, and mosaic parenchymal attenuation revealed the diagnosis of bronchiolitis obliterans.[30] This was also proved by later pathologic studies.[26]

Chest X-Ray

Chest x-ray is not a reliable diagnostic tool in patients with mustard lung. The majority of symptomatic patients have normal or nonspecific changes in their chest x-rays.[29-31] Although increased bronchovascular markings, hyperinflation, bronchiectasis, pneumonic infiltration and radiologic evidence of pulmonary hypertension have been reported on chest roentgenogram,[16,30] chest x-ray is not sensitive enough for detection of respiratory complications in these patients and chest HRCT may be required to made the final diagnosis.[29] Chest x-ray should not be considered as a leading tool to detect new cases of chemical inhalation injury with mild respiratory complaints.[27]

Bronchoscopy

Direct toxic effects of SM can lead to tracheobronchial stenosis with different degrees of involvement ranging from diffuse tracheal stenosis to isolated stenosis of the left main bronchus or stenosis of glottic and subglottic areas.[22] The broncoscopic appearance of airway mucosa is that of a combination of erythema, chronic inflammatory changes, and mucosal thickening in all of the patients.[26]

Inflammatory cells are usually increased in the Broncho-Alveolar Lavage (BAL) of patients, even more than ten years of the exposure.[20,26,32] Neutrophil counts (especially in chronic bronchitis) are significantly higher than normal while lymphocyte counts remain normal. Patients have increased eosinophil counts which is more common in asthmatic respiratory conditions. Decreased number of macrophages in BAL fluid may also be seen.[19,26] Typical SM-exposed patients have normal values of albumin and immunoglobulin (Ig) in the BAL fluid. On the other hand, those who are suspicious to have asthma show an increased IgG level.[19,26]

Level of transforming growth factor β_1 (TGF-β_1) tends to increase in BAL fluid.[24,33] Furthermore, TGF-β_1 receptors are considerably increased in target tissues of SM-exposed patients, compared with non-exposed individuals.[27,34] TGF-β in macrophages, mesenchymal, and mesoendothelial cells can cause BO changes.[35-37] Progression of bronchiole inflammation in pulmonary tissue of the chemical warfare injured exposed to mustard agent is not an exception. Since TGF-β target protein is substantially increased in BAL aspirates and target tissues in these cases, the role of BO as the main underlying pathology in mustard lung becomes evident.[34]

Hematologic Findings

Early investigations on SM casualties during the Iran-Iraq War showed decreased immunoresponsiveness, expressed as leukopenia, lymphopenia, and neutropenia, as well as hypoplasia and atrophy of the bone marrow.[38] Decrease in both cell-mediated and humoral immunity may occur several years after the exposure to SM.[39-42] Due to the hypoxemic status of the patients as a result of their chronic respiratory problems, the total red cell (RBC) count and hematocrit (Hct) is higher than expected while hemoglobin (Hb) level remains normal. Increased White Blood Cell (WBC) count is usually seen which is probably attributed to the high frequency of acute respiratory infections in these patients rather than the direct toxic effects of SM on the bone marrow.[38] There was no significant differences in platelet count between SM-exposed patients and normal population.[38]

Years following exposure to SM, the immune system is still impaired which might be due to their present health problems as recurrent respiratory infections. Sixteen to twenty years after exposure to SM, the percentages of monocytes and CD3+ lymphocytes were significantly higher and the percentage of natural killer (NK; $CD16^+/56^+$) cells was lower than non-exposed individuals.[42-43] However, the activity of

NK cells ($CD56^+/CD25^+$) was noticeably higher than the control group.[42] C_3 levels are considerably higher than normal while serum IgA, IgE, and C_4 remain normal. IgM and IgG might increase slightly but this was not supported by controlled studies. These changes make the patient susceptible to respiratory disease and may be the predisposing factors for development of chronic bronchiectasis and bronchitis exacerbations which are very common among SM-exposed patients.[22,14]

Differential Diagnosis and Clinical Management

There is no explicit treatment for mustard lung. However, some general and specific treatments have been suggested to improve the patients' quality of life and to manage some specific symptoms. Physiotherapy, oxygen and assisted ventilation are the mainstays of treatment.[8] Nonetheless, there is not enough evidence supporting administration of humid air.[8]

Late respiratory effects of SM may frequently disable patients with sever exposure. Since there is not a distinct treatment for the main underlying pathology, which is likely to be BO, the plan of management should be selected according to each probable complication. The most frequent diagnoses were reported as chronic bronchitis (59%), asthma (11%), pulmonary fibrosis (12%), and bronchial stenosis (10%).[32] However, recent studies showed that pulmonary fibrosis is not the main underlying pathology while bronchiolitis obliterans seems to be the main disease.[27,30] In contrary to the first reports of emphysema, evidence did not support the correlation between emphysema and exposure to SM.[30] Emphysema is not caused by exposure to SM and if occurs, other confounding factors (e.g., smoking) should be considered.[18,30]

As it was mentioned earlier, the main controversy in clinical management of SM-exposed patients, arises from whether we believe that the main underlying disease is IPF or BO. Recent pathologic studies revealed bronchiolitis as a late respiratory disorder in SM-exposed patients.[44,34] In these studies, BO-organizing pneumonia was confirmed in pathologic examinations of many patients with previously-diagnosed IPF who underwent open lung biopsy.[26] The reports of IPF in earlier pathologic studies were based on histopathologic investigation using only trans-bronchial lung biopsy (TBLB).[22] Thus, they failed to disclose the exact nature of pathology because of usual interstitial pneumonia (UIP)-like pattern that can mimic interstitial fibrosis which can lead to misdiagnosis.[45] Previous studies have questioned the diagnostic reliability of TBLB compared with open lung biopsy in diagnosis of fibrosis. They have shown that diagnosis by TBLB is unreliable and often entirely misleading.[46,47] However, there is a consensus regarding the chronic bronchiectasis and bronchitis in SM-exposed patients.[14,22]

As mentioned before, chronic cough is the most common symptom in these patients. Chronic bronchitis and bronchospasm should be considered as the first causes of cough. Gastro-esophageal reflux disease and post-nasal discharge syndrome seem to be other causes.[19] Awareness of the fact that chronic cough can be due to more than one condition is important for accurate diagnosis and successful treatment of cough. Accordingly, more than 90% of SM-exposed patients have combination of causes of chronic cough.[19] Esophagitis can also be associated with chronic cough in patients with SM exposure. The BO, along with other lung disorders, can be considered as a potential contributor to the pathogenesis of esophagitis in these patients.[48]

Treatments should address different clinical features which are discussed above. Bronchodilators have been shown to be helpful in patients with increased airway hyper-reactivity and especially in those with moderate to severe pulmonary obstruction.[8,49] Combination of a β-agonist (e.g., salbutamol) and an anticholinergic (e.g., ipratropium bromide) has been found to be more effective than any of other bronchodilators used alone.[50]

Corticosteroids are widely used to resolve respiratory symptoms of mustard lung. Despite some different pathological features causing air flow obstruction in asthma and chronic bronchitis, some studies have shown that corticosteroids are as effective in some patients with exacerbated chronic bronchitis as they are in most asthmatic patients.[27]

Inhaled corticosteroids and long-acting β_2-agonists are effective in treatment of patients with chronic bronchiolitis following exposure to SM. However, a medium dose of fluticasone/salmeterol has the same clinical effect on the airways reversibility as the high dose of beclomethasone with short acting β-agonist.[51]

According to the concurrent pulmonary disorders, such as asthma[22] and BO,[30,45] patients may show different responses to corticosteroids. Complete response (13.8%) was seen in patients with asthmatic bronchitis,[51,52] while those with airway hyper-responsiveness and bronchospasm (30.8%) showed partial response[52]. Others with no response to oral or intravenous corticosteroids (50%) seemed to have BO, along with chronic bronchitis.[52] Since oral corticosteroid is as beneficial as intravenous pulse therapy, it is recommended as the

method of choice for administration so that the side effects of pulse corticosteroid would not occur.[52] A short-term bolus steroid therapy can categorize patients into responders and non-responders for subsequent treatment with corticosteroids. Previous studies have shown the presence of chronic bronchitis in the majority of patients exposed to mustard gas.[22,31] Short-term intravenous pulse or oral corticosteroid therapy can improve FEV_1, FVC and PEF of patients with mustard gas-induced chronic bronchitis if exacerbation occurs.[52] However, improvement in spirometry indices did not differ between oral and intravenous administrations.[52]

Administration of antibiotic is recommended in view of the risk of secondary infections.[8]

Future Directions

Macrolides and antioxidants may improve respiratory symptoms and pulmonary function in patients with SM-induced BO due to their anti-inflammatory effects.[27] In an open-labeled clinical trial, clarithromycin and acetylcysteine were administrated concomitantly for six months to SM-exposed patients with chronic bronchitis and BO who had not responded to conventional treatments. Improvement was observed in cough and sputum production in all patients. The FEV_1 and FVC were noticeably improved with no significant change in FEV_1/FVC ratio.[53] However, there is not enough evidence supporting long-term use of macrolides in patients with mustard lung.

IFN-γ can negatively regulate the transcription of selected TGF-β genes,[54] which is known as an important contributor to the pathophysiological factor of lung fibrosis and bronchiolitis. Recently, it was shown that six-month treatment with IFN-γ_{1b} plus a low-dose prednisolone could improve pulmonary function of SM-exposed patients with bronchiolitis.[55]

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