Clinical and paraclinical guidelines for management of sulfur mustard induced bronchiolitis obliterans; From bench to bedside

Article *in* Inhalation Toxicology · November 2012

DOI: 10.3109/08958378.2012.725783 · Source: PubMed

3 authors, including:

Amin Saburi
Baqiyatallah University of Medical Sciences
156 PUBLICATIONS **735** CITATIONS

SEE PROFILE

Mostafa Ghanei
Baqiyatallah University of Medical Sciences
389 PUBLICATIONS **5,565** CITATIONS

SEE PROFILE

Inhalation Toxicology, 2012; 24(13): 900–906

ISSN 0895-8378 print/ISSN 1091-7691 online
DOI: 10.3109/08958378.2012.725783

informa
healthcare

REVIEW ARTICLE

Clinical and paraclinical guidelines for management of sulfur mustard induced bronchiolitis obliterans; from bench to bedside

Hamid Saber[1], Amin Saburi[2], and Mostafa Ghanei[2]

[1]*Department of Internal Medicine, Mashhad University of Medical Sciences, Mashhad, I.R. Iran and*
[2]*Chemical Injuries Research Center, Baqiyatallah University of Medical Sciences, Tehran, I.R. Iran*

Abstract
It is well documented that inhalation of sulfur mustard (SM) causes injury to the respiratory system. Many Iranian civilians and war veterans are suffering from late respiratory complications of SM exposure. Recent studies have shown that bronchiolitis obliterans (BO) is the major cause of respiratory complications following SM exposure. In this review, we focus on the clinical, pulmonary, radiological, immunological and pathological manifestations in SM-induced BO with intent to provide a practical, clinical and paraclinical guideline for diagnosis and step-wise workup of these patients, which may be used to manage similar lung injuries induced by other similar inhaled toxins.

Keywords: Sulfur mustard, bronchiolitis obliterans, respiratory complications, clinical findings, paraclinical

Introduction

Bronchiolitis obliterans (BO) refers to several conditions of inflammatory lung diseases, particularly those that primarily affect the narrow airways and have varying clinical courses, histological appearances and radiographic findings. Thus, there is limited evidence to support diagnosis of BO; and medical practitioners are unfamiliar with its various clinicopathological and paraclinical findings. The introduction of high-resolution CT (HRCT) scanning has attracted the attention of the healthcare community as a highly useful diagnostic tool especially for BO. Common causes of BO include previous childhood infections (particularly measles, adenovirus and *Mycoplasma*), toxic inhalation, graft-versus-host disease following bone marrow transplantation, chronic rejection following a lung or heart–lung transplant and autoimmune connective tissue disorders such as rheumatoid arthritis treated with penicillamine therapy (Skeens et al., 1989; Müller & Miller, 1995; Heng et al., 1998; Scott et al., 2005). Other conditions have also more recently been linked with BO such as ulcerative colitis (Basseri et al., 2010), hyperplasia and tumoral proliferation of peripheral neuroendocrine cells in the lungs (Myers et al., 2009). It is also a relatively frequent complication of cystic fibrosis following repeated lung infections (Nash et al., 2012). Although unusual, this disease can also be idiopathic, mainly in middle-aged women (Garg et al., 1994). Chemical lung injury via inhaled toxins such as sulfur mustard (SM) can induce BO. Many Iranian war veterans and civilians were exposed to SM during the Iraq–Iran war (1980–1988). SM can induce many respiratory complications; however, the key point in evaluation is the time of exposure. In the short-term post-exposure, contact with SM may lead to alveolar and airway injury and even death due to respiratory distress syndrome; although, it also depends upon the amount and duration of exposure as well. All early pulmonary complications of SM exposure can be explained by cell death; however, late complications vary in nature. Formerly, some studies associated SM exposure with airway hyper-reactivity, chronic bronchitis, bronchiectasis and lung fibrosis (Emad & Rezaian, 1997). Previous multi-centric surveys using imaging, pulmonary function tests (PFTs) and indisputable histopathological studies revealed that BO

Address for Correspondence: Mostafa Ghanei, MD, Chemical Injuries Research Center, Baqiyatallah University of Medical Sciences, Mollasadra St, Vanak Sq, Tehran, I.R. Iran. Tel/Fax: +982188600067. E-mail: mghaneister@gmail.com
(Received 08 June 2012; revised 27 August 2012; accepted 27 August 2012)

is the main respiratory pathology in patients exposed to SM and there is an extensive amount of research supporting this finding (Thomason et al., 2003; Aghanouri et al., 2004; Dompeling et al., 2004; Ghanei et al., 2004a, 2004b; Beheshti et al., 2006; Ghanei et al., 2006a; Ghanei et al., 2008a; Ghanei & Harandi, 2011). Thus, didactic clinical and paraclinical examination of these patients is necessary to further unravel the various characteristics of SM-induced BO (SMBO) and facilitate diagnosis of this disease. There is an abundance of evidence confirming the difference between SMBO and other types of BO. This review focuses on the clinical and paraclinical findings of SMBO based on the related literature at hand as well as our documented experience; we propose a practical set of guidelines by which to diagnose SMBO and its relation to long-term effects of SM exposure.

Clinical findings

Typical clinical findings of idiopathic BO include a triad consisting of productive coughs, difficult expectoration and chronic dyspnea in >80% of the patients (Sohrabpour, 1984; Emad & Rezaian, 1997; Ghanei et al., 2004a; Balali-Mood et al., 2005; Ghanei et al., 2005a; Ghanei et al., 2008b; Shohrati et al., 2010). In a previous study, the following symptoms were recorded; coughs with varying degrees of sputum (90%), shortness of breath (98%), chest tightness and difficult breathing (80%; Ghanei et al., 2004b).

Haemoptysis, chest pain and nocturnal dyspnea are also frequently experienced symptoms. The pathology behind hemoptysis in these patients is thought to be a chronic inflammatory process within airway walls; it is reasonable to correlate the hemoptysis in these patients to BO (Mroz et al., 1997; Bijani & Moghadamnia., 2002). Main clinical signs include generalized wheezing (the most common), bilateral early inspiratory crackles, crepitation and decreased peripheral lung sounds (Zarchi et al., 2004).

Although these findings may also be evident in cases of asthma and chronic obstructive pulmonary disease (COPD), it should be noted that hemoptysis is never found 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.

Pulmonary function test

The PFT is a useful diagnostic tool in patients with pulmonary symptoms. Apart from significant respiratory symptoms such as dyspnea, the most common pattern of a pulmonary function test in SMBO is in the expected range of lung function followed by mild obstruction (Ghanei et al., 2004a). The reason may be the branching pattern of the bronchial tree that results in an increasingly large number of small airways in peripheral generations and these airways contribute little to the total pulmonary resistance; thus, a large proportion of small airways may be damaged or obliterated without recognition by any of the conventional pulmonary function tests (Wohl & Chernick, 1978). In a study of 34,000 SMBO patients, it was noted that more than half of the exposed patients (57.5%) developed no significant abnormality on a simple PFT (based on American Thoracic Society Criteria; Khateri et al., 2003). In another study by Khateri et al. on SMBO, 37% had mild, 4.5% had moderate and 1% had severe pulmonary function impairment, while the rest had normal PFT findings (Khateri et al., 2003). Forced vital capacity (FVC), forced expiratory volume in the 1st second (FEV_1), and FEV_1/FVC may be lower in comparison with healthy people. In a cohort study of 407 patients, the pattern of decline in pulmonary function indices was directly proportional to the percentage of each index at the baseline PFT. A continuous decrease in FVC of SM-exposed patients, with a rate less than FEV_1 or peak expiratory flow, can be a consequence of significant air trapping following obstruction; this condition is called pseudo-restriction. The residual volume is markedly increased, and the diffusing capacity of the lung for carbon monoxide (DLCO) rises or remains normal (Beheshti et al., 2006). In addition, arterial blood gas samples of patients do not exhibit hypoxia or hypercapnia except in subjects with severe respiratory failure.

Although the most common feature of PFT impairment is an obstructive pattern, mixed restrictive and obstructive as well as purely restrictive patterns have also been reported (Emad & Rezaian, 1997; Hefazi et al., 2005). Abnormal spirometric findings in general and restrictive patterns, in particular, tend to increase over time. These obstructive PFT findings are reversible in response to inhaled bronchodilators (Ghanei et al., 2005b). Sometimes these patients may have an unexplained resistance to anti-asthma therapy and an irreversible pattern of obstruction (Ghanei & Harandi, 2007). Increases in airway responsiveness have been confirmed by the methacholine challenge test (Mirsadraee et al., 2005). Similar to post-transplant lung injury, it appears that a positive methacholine challenge is associated with the development of BO (Stanbrook & Kesten, 1999; Chan & Allen, 2004). In this way, bronchial hyperactivity can be considered as an early marker of bronchiolitis.

Chest pain, productive cough, hemoptysis and most importantly dyspnea disproportional to PFT or normal PFT findings imply SMBO. While DLCO is reduced in COPD and the methacholine challenge test is reversible in asthma, while reminiscent clinical findings for SMBO with increased DLCO results in patients with an obstructive PFT pattern. An irreversible pattern of obstruction in the methacholine challenge test would be highly suggestive of adult BO, including SMBO, which requires radiological evidence to better identify the pathological process.

Chest x-ray

Increased bronchovascular markings, hyperinflation, bronchiectasis and pneumonic infiltration as well as

pulmonary hypertension have been reported on chest x-rays (CXRs; Ghanei et al., 2005b; Balali-Mood & Hefazi, 2006). Most patients, however, with other symptoms of SMBO have normal or nonspecific changes in their chest x-rays (Bagheri et al., 2003). CXR is not sensitive enough to detect respiratory complications in these patients because the fourth generation segmental bronchi are the smallest units that can be seen with chest radiography; thus, it is considered as an unreliable diagnostic tool for SMBO.

High-resolution computerized tomography

Since CXRs and PFTs appear normal in a large number of SMBO patients, high-resolution computerized tomography (HRCT) of the chest should be used for diagnosis of the precise respiratory condition. Recently, the resolution of HRCT has improved, scans are faster and have smaller detectors; multi-detector-row technology has enabled the visualization of airways down to a range of 2 mm in diameter (6th generation; Dirksen, 2008). HRCT has now been identified as a powerful tool to detect both parenchymal and airway abnormalities such as bronchiectasis, air trapping, mosaic parenchymal attenuation (MPA), secondary lobule abnormalities and other pulmonary problems (Webb et al., 1988). Chest HRCT with inspiration and suspended expiration images is a powerful tool for diagnosis of SMBO patients because of its superior ability in delineating details of pulmonary anatomy (Akira et al., 2009). One report regarding a 65-year-old woman with cryptogenic BO stated that the CT scan showed normal findings during full inspiration, but showed multiple, focal, lobule-sized areas of radiolucency consistent with extensive lobular air trapping during a suspended full expiration (Stern & Frank, 1994).

Air trapping on expiratory HRCT scans and MPA are the most frequent and most important abnormal findings in both symptomatic as well as asymptomatic BO patients (Sweatman et al., 1990; Stern & Frank, 1994; Hwang et al., 1997; Essadki & Grenier, 1999; Estenne et al., 2002; Ghanei et al., 2004b). In another study, results from HRCT examinations obtained during deep inspiration and full expiration, with the patient lying in a supine position revealed abnormal findings in (98%) of the cases (Ghanei et al., 2004b). Air trapping was the most frequent finding (76%) among SMBO patients. Other abnormal findings include bronchiectasis, decreased parenchymal attenuation with perfusion redistribution in expiration, dilated irregular trachea and major airways and interlobular septal wall thickening. Significant tracheal and major airway diameter variation (on inspiration and exhalation), irregularity and wall thickness was also observed in two-thirds of these patients; these are not well-known features of BO (Ghanei et al., 2004b). Moreover, several SM-exposed subjects exhibited features of tracheobronchomalacia (TBM), which is again unusual (Ghanei et al., 2006a). We speculate that the same underlying pathologic mechanism that causes BO may also result in a disorder in the large airways such as TBM. Interestingly, both BO and TBM have also been described as possible complications of a lung transplant (Kaditis et al., 2000; Estenne & Hertz, 2002; Egan, 2004). Lesions were more frequent in the left lower lobe; the left middle lobe was the least involved lobe in these patients.

In BO, the mosaic pattern of lung attenuation is caused by hypoventilation of alveoli distal to the bronchiolar obstruction. This leads to secondary vasoconstriction, seen on CT scans as areas of decreased attenuation. Uninvolved segments of a lung show normal or increased perfusion resulting in normal to increased attenuation. Air trapping is seen on chest HRCT scans as the failure of some parts of the lungs to adjust volume or attenuation between inspiratory and expiratory images; these effects are caused by excessive retention of gas in the lungs.

Overall, HRCT can be used as a noninvasive method for SMBO (as a subtype of BO) to differentiate it from COPD and asthma. Any patient with signs and symptoms of intractable asthma who do not respond to treatment should be evaluated with expiratory HRCT. Those with significant air trapping should be considered as adult BO; further assessment is especially important for those with a positive history of contact with a toxic gas to identify the underlying pathologic process (Ghanei et al., 2007a).

Biological markers

It has been suggested that several cellular and molecular markers such as interleukin-8 (IL-8) and IL-6 have primary roles in various chronic pulmonary diseases such as COPD and asthma (Car et al., 1994; Nocker et al., 1996; Danilko et al., 2007; Lee et al., 2008); but there is little evidence regarding underlying mechanisms and serum biomarkers involved in patients with SMBO (Hassan et al., 2006).

In a cross-sectional study of 50 SM-induced BO cases, high sensitive C reactive protein (hs-CRP) serum levels were found to have increased when compared with healthy subjects, which had a direct correlation with disease severity (Attaran et al., 2009). Pourfarzam and colleagues found that serum levels of IL-8 and IL-6 significantly decreased in BO patients compared with the control group (Pourfarzam et al., 2009). In another study, serum levels of IL-8, IL-6, CRP and RF levels were evaluated in 348 adult subjects with chronic SMBO in Sardasht, Iran. The relationship of these inflammatory markers to pulmonary involvement was also studied. Their study demonstrated that both IL-8 and IL-6 were lower in the SM-exposed group in comparison with the control group. However, there was no relationship between serum levels of these cytokines and the severity of pulmonary disorders. Low levels of these cytokines will lead to the absence of an active inflammatory process in these patients that is in favor of the slow progression of the disease in this population (Ghanei et al., 2007b). This suggests that the role of inflammation is less important than that expected; thus, determining and measuring

these markers is not very helpful for diagnosis and or monitoring patients with SMBO.

Bronchoalveolar lavage

Characterization of proteins secreted into the bronchoalveolar lavage (BAL) fluid facilitates the identification of diagnostic immunologic biomarkers for SMBO (Jafari & Ghanei, 2010). These studies have shown an increased number of inflammatory cells in SMBO in the chronic phase, indicating the presence of an ongoing active alveolar injury (Emad & Rezaian, 1999; Beheshti et al., 2006). Neutrophile count is higher in BAL fluid samples of SMBO patients than in normal individuals; but lymphocyte count, albumin and immunoglobulin (Ig) levels were not significantly increased when compared with healthy subjects. Decreased numbers of macrophages in BAL fluid may also be evident (Beheshti et al., 2006; Emad & Emad, 2007). Levels of transforming growth factor β (TGF-β) tend to increase in BAL fluid (Ghanei et al., 2004c). TGF-β target protein is also reported to be higher in BAL aspirates of SMBO patients (Aghanouri et al., 2004), suggesting an inflammatory process followed by an impaired repair process due to excessive TGF-β production in these patients similar to post-lung transplantation BO (El-Gamel et al., 1999).

Previously, in a first differential proteomic analysis of BAL fluid, we reported an over-expression of vitamin D binding protein, fibrinogen g chain and haptoglobin isoforms, and underexpression of calcyphosine, transthyretin and SPA isoforms in SMBO subjects when compared with healthy controls (Mehrani et al., 2009).

Pro-apoptotic Fas–Fas ligand (FasL) signaling plays a central role in pulmonary inflammation, injury, fibrosis and blockade of Fas–FasL interactions that either prevent or attenuate pulmonary inflammation and fibrosis (Dosreis et al., 2004). In another study, circulating levels of sFasL and nitric oxide (NO) were determined in patients diagnosed with chronic SMBO. Results revealed a positive association between sFasL and pulmonary problems but failed to find any significant relationship between NO and pulmonary problems in these patients, suggesting that pulmonary complications in SMBO may be related to sFasL pathophysiology and may have a role in the regulation of apoptosis in these patients(Ghazanfari et al., 2009). Yaraee et al. (2009) determined serum levels of proinflammatory cytokines including TNF, IL-1α, IL-1β and IL-1Ra in 368 SMBO patients by a sandwich ELISA technique and found that serum proinflammatory cytokine levels were significantly lower in these patients than in controls. Amiri et al. (2009) did not find any significant differences in serum levels of granulocyte-macrophage colony stimulating factor (GM-CSF) in SMBO patients compared with the control group.

In brief, patterns of change in immunological biomarkers in our 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. However, immunological markers do not seem to play a significant role in diagnosis of adult BO.

Pathological markers

Diagnosis of bronchiolitis has caused confusion for pathologists because it comprises a heterogeneous group of diseases with variable etiologies, clinical manifestations and evolution (Colby, 1998; Myers & Colby, 1993). Besides the complexity of these histological findings associated with bronchiolitis, various clinical syndromes that are clinically categorized as bronchiolitis are characterized by overlapping histopathological findings (Ryu et al., 2003). Evidence of bronchiolitis in pathological studies is not sufficient to identify the etiology. The presence of bronchiolitis in a biopsy specimen may represent a primary condition or merely a secondary phenomenon associated with some other primary pathologic disease (e.g. bronchiectasis). Therefore, pathologic diagnosis of BO is of no relevance until and unless it is correlated with the clinical and radiological records. Various wide-spectrum histopathological lesions show inflammatory process in non-cartilaginous airways. Inflammatory derivatives such as cell debris and thick mucus can obscure the airways especially the smaller ones (bronchioles; Visscher & Myers, 2006).

Recently, a form of bronchiolitis, constrictive bronchiolitis also known as BO organizing pneumonia (or simply, organizing pneumonia), was reported among soldiers who came back from Iraq. Constrictive bronchiolitis may occur primarily or following infectious cellular BO with intraluminal polyps, or inhalation injuries. Histopathologically, there are differences between BO and constrictive bronchiolitis, although specific etiology has yet to be identified (Gosink et al., 1973; Kang et al., 2009). There are some histopathological features that provide differences between three mentioned types of bronchiolitis (SMBO, constrictive Bronchiolitis and BO). Active fibroblast proliferation always with pale-staining and immature collagen in microscopic views was seen in BO versus constrictive bronchiolitis, which is characterized by the minimally cellular picture and dense collagen. Collagen deposition in BO was intrinsic (within airspace lumens), whereas the collagen deposition in constrictive bronchiolitis is extrinsic and in SMBO is prebronchial (Ghanei et al., 2004c; Visscher & Myers, 2006; Ghanei & Harandi, 2007; Ghanei & Harandi, 2011). BO is often limited to one lobe and consistently resolves with therapy although constrictive bronchiolitis is diffuse and progressive despite treatment similar to SMBO (Visscher & Myers, 2006). But pathologic findings in SMBO are completely specific in contrast to other types of BO. In an investigation on surgical lung biopsies of these patients, the histopathologic spectrum of changes in 15 patients with SMBO from mild-to-severe gas exposure was examined (Ghanei et al., 2008a). All these cases had partial luminal narrowing by the presence of plaque-like increases in submucosal collagen. In some cases,

this increase in collagen was circumferential, while in others it was partial. These airway walls frequently appeared somewhat rigid and lacked normal mucosal convolutions. The process was sometimes accompanied by a mild-to-moderate lymphocytic infiltration. In some cases, other bronchioles in the biopsy were dilated and showed mucus stasis indicating proximal obstruction. The following most common findings were mild-to-moderate chronic bronchiolitis, bronchiolectasis and mucus stasis. In a pathological study the frequency of esophagitis in SMBO patients with a chronic cough was shown to be higher than in the control group (32.3 vs. 14.2%; Ghanei et al., 2006b). In a study of transbronchial lung biopsies of 23 patients with SMBO, myxoid tufts of organizing connective tissue were observed within the alveolar ducts and were incorporated into alveolar walls (Beheshti et al., 2006). Moreover, alveolar wall expansion was observed because of mild mononuclear cell infiltrate, edema and delicate interstitial thickening. Slight intra-alveolar fibrin mixed with mononuclear cells was present in most cases. In post-lung transplant cases, constrictive bronchiolitis lesions were diffused with widespread bronchiolar dilatation (Law et al., 2005). SMBO may be present in symptomatic patients even with a normal chest HRCT and PFTs findings. Thus, open or thoracoscopic lung biopsy plays an important role in the diagnosis of SMBO.

Conclusion

Adult bronchiolitis is considered a rare condition globally, and its diagnostic criteria remain a matter of debate. After the Iraq–Iran war, many investigations have been done on these patients, because of the large number of people exposed to SM in Iran. Recent studies have led to the common consensus that adult BO is the main pathophysiological basis of chronic respiratory lesions evident in these patients (Ghanei & Harandi, 2011). This great body of evidence has provided an opportunity to introduce new guidelines for diagnosis of SMBO that can potentially be useful for other similar kinds of lung injuries from inhaled toxins. It is believed that diagnosis of SMBO requires a team effort to assess a combination of clinical, radiological, immunological and pathological biomarkers. In this review, a comprehensive list of markers has been proposed based on our patients applicable to SMBO diagnosis.

SMBO, as a lung injury by an inhaled toxin, should be considered as a differential diagnosis in a non-smoker patient with cough and hemoptysis and normal CXR in presence of an obstructive lesion in spirometry. SMBO may also be found in non-smoker patients without evidence of emphysema on radiography. Although in this study SMBO in non-smoker patients was mostly discussed, it was previously demonstrated that there are some additive contributions between SM exposure and tobacco use on biological activities of bronchial epithelium at genomics, proteomics and metablolomics aspects among SM-exposed patients who smoke (Ghanei et al., 2007c). Therefore, regarding to probable distorted findings of laboratory tests in SM-exposed smoker patients, the paraclinical findings (especially pathologic findings) should be interpreted more carefully although further studies on the confounding role of smoking in SM-exposed patients are needed.

A discrepancy in clinical findings and spirometry (productive cough with dyspnea+wheezing+air trapping in HRCT) is also suggestive of SMBO in patients with a history of exposure. Therefore, patients with maintained respiratory manifestations or hemoptysis, with dyspnea disproportional to PFT findings, irreversible airway hyper-responsiveness and normal CXR, who show evidence of air trapping in an HRCT scan, should be diagnosed with having BO due to injury from an inhalation.

Acknowledgments

The authors would like to thank Prof. Mohammad Hossein Kalantar-Motamedi for his kindly cooperation in preparing and revising the manuscript.

Declaration of interest

The authors report no conflicts of interest.

References

Aghanouri R, Ghanei M, Aslani J, Keivani-Amine H, Rastegar F, Karkhane A. 2004. Fibrogenic cytokine levels in bronchoalveolar lavage aspirates 15 years after exposure to sulfur mustard. Am J Physiol Lung Cell Mol Physiol 287:L1160–L1164.

Akira M, Toyokawa K, Inoue Y, Arai T. 2009. Quantitative CT in chronic obstructive pulmonary disease: inspiratory and expiratory assessment. AJR Am J Roentgenol 192:267–272.

Amiri S, Ghazanfari T, Yaraee R, Salimi H, Ebtekar M, Shams J, Ghasemi H, Pourfarzam S, Moin A, Sharifnia Z, Soroush MR, Faghihzadeh S, Hassan ZM. 2009. Serum levels of GM-CSF 20 years after sulfur mustard exposure: Sardasht-Iran Cohort Study. Int Immunopharmacol 9:1499–1503.

Attaran D, Lari SM, Khajehdaluee M, Ayatollahi H, Towhidi M, Asnaashari A, Marallu HG, Mazloomi M, Mood MB. 2009. Highly sensitive C-reactive protein levels in Iranian patients with pulmonary complication of sulfur mustard poisoning and its correlation with severity of airway diseases. Hum Exp Toxicol 28:739–745.

Bagheri MH, Hosseini SK, Mostafavi SH, Alavi SA. 2003. High-resolution CT in chronic pulmonary changes after mustard gas exposure. Acta Radiol 44:241–245.

Balali-Mood M, Hefazi M, Mahmoudi M, Jalali E, Attaran D, Maleki M, Razavi ME, Zare G, Tabatabaee A, Jaafari MR. 2005. Long-term complications of sulphur mustard poisoning in severely intoxicated Iranian veterans. Fundam Clin Pharmacol 19:713–721.

Balali-Mood M, Hefazi M. 2006. Comparison of early and late toxic effects of sulfur mustard in Iranian veterans. Basic Clin Pharmacol Toxicol 99:273–282.

Basseri B, Enayati P, Marchevsky A, Papadakis KA. 2010. Pulmonary manifestations of inflammatory bowel disease: case presentations and review. J Crohns Colitis 4:390–397.

Beheshti J, Mark EJ, Akbaei HM, Aslani J, Ghanei M. 2006. Mustard lung secrets: long term clinicopathological study following mustard gas exposure. Pathol Res Pract 202:739–744.

Bijani Kh, Moghadamnia AA. 2002. Long-term effects of chemical weapons on respiratory tract in Iraq-Iran war victims living in Babol (North of Iran). Ecotoxicol Environ Saf 53:422–424.

Car BD, Meloni F, Luisetti M, Semenzato G, Gialdroni-Grassi G, Walz A. 1994. Elevated IL-8 and MCP-1 in the bronchoalveolar lavage fluid of patients with idiopathic pulmonary fibrosis and pulmonary sarcoidosis. Am J Respir Crit Care Med 149:655–659.

Chan A, Allen R. 2004. Bronchiolitis obliterans: an update. Curr Opin Pulm Med 10:133–141.

Colby TV. 1998. Bronchiolitis. Pathologic considerations. Am J Clin Pathol 109:101–109.

Danilko KV, Korytina GF, Akhmidishina LZ, Ianbaeva DG, Zagidullin ShZ, Victorova TV. 2007. [Association of cytokines genes (ILL, IL1RN, TNF, LTA, IL6, IL8, IL0) polymorphic markers with chronic obstructive pulmonary disease]. Mol Biol (Mosk) 41:26–36.

Dirksen A. 2008. Is CT a new research tool for COPD? Clin Respir J 2 Suppl 1:76–83.

Dompeling E, Jöbsis Q, Vandevijver NM, Wesseling G, Hendriks H. 2004. Chronic bronchiolitis in a 5-yr-old child after exposure to sulphur mustard gas. Eur Respir J 23:343–346.

Dosreis GA, Borges VM, Zin WA. 2004. The central role of Fas-ligand cell signaling in inflammatory lung diseases. J Cell Mol Med 8:285–293.

Egan JJ. 2004. Obliterative bronchiolitis after lung transplantation: a repetitive multiple injury airway disease. Am J Respir Crit Care Med 170:931–932.

El-Gamel A, Sim E, Hasleton P, Hutchinson J, Yonan N, Egan J, Campbell C, Rahman A, Sheldon S, Deiraniya A, Hutchinson IV. 1999. Transforming growth factor β (TGF-β) and obliterative bronchiolitis following pulmonary transplantation. J Heart Lung Transplant 18:828–837.

Emad A, Emad Y. 2007. Levels of cytokine in bronchoalveolar lavage (BAL) fluid in patients with pulmonary fibrosis due to sulfur mustard gas inhalation. J Interferon Cytokine Res 27:38–43.

Emad A, Rezaian GR. 1997. The diversity of the effects of sulfur mustard gas inhalation on respiratory system 10 years after a single, heavy exposure: analysis of 197 cases. Chest 112:734–738.

Emad A, Rezaian GR. 1999. Immunoglobulins and cellular constituents of the BAL fluid of patients with sulfur mustard gas-induced pulmonary fibrosis. Chest 115:1346–1351.

Essadki O, Grenier P. 1999. [Bronchiolitis: computed tomographic findings]. J Radiol 80:17–24.

Estenne M, Hertz MI. 2002. Bronchiolitis obliterans after human lung transplantation. Am J Respir Crit Care Med 166:440–444.

Estenne M, Maurer JR, Boehler A, Egan JJ, Frost A, Hertz M, Mallory GB, Snell GI, Yousem S. 2002. Bronchiolitis obliterans syndrome 2001: an update of the diagnostic criteria. J Heart Lung Transplant 21:297–310.

Garg K, Lynch DA, Newell JD, King TE Jr. 1994. Proliferative and constrictive bronchiolitis: classification and radiologic features. AJR Am J Roentgenol 162:803–808.

Ghanei M, Akhlaghpoor S, Moahammad MM, Aslani J. 2004a. Tracheobronchial stenosis following sulfur mustard inhalation. Inhal Toxicol 16:845–849.

Ghanei M, Fathi H, Mohammad MM, Aslani J, Nematizadeh F. 2004b. Long-term respiratory disorders of claimers with subclinical exposure to chemical warfare agents. Inhal Toxicol 16:491–495.

Ghanei M, Mokhtari M, Mohammad MM, Aslani J. 2004c. Bronchiolitis obliterans following exposure to sulfur mustard: chest high resolution computed tomography. Eur J Radiol 52:164–169.

Ghanei M, Hosseini AR, Arabbaferani Z, Shahkarami E. 2005a. Evaluation of chronic cough in chemical chronic bronchitis patients. Environ Toxicol Pharmacol 20:6–10.

Ghanei M, Khalili AR, Arab MJ, Mojtahedzadeh M, Aslani J, Lessan-Pezeshki M, Panahi Y, Alaeddini F. 2005b. Diagnostic and therapeutic value of short-term corticosteroid therapy in exacerbation of mustard gas-induced chronic bronchitis. Basic Clin Pharmacol Toxicol 97:302–305.

Ghanei M, Akbari Moqadam F, Mohammad MM, Aslani J. 2006a. Tracheobronchomalacia and air trapping after mustard gas exposure. Am J Respir Crit Care Med 173:304–309.

Ghanei M, Khedmat H, Mardi F, Hosseini A. 2006b. Distal esophagitis in patients with mustard-gas induced chronic cough. Dis Esophagus 19:285–288.

Ghanei M, Amiri S, Akbari H, Kosari F, Khalili AR, Alaeddini F, Aslani J, Giardina C, Haines DD. 2007a. Correlation of sulfur mustard exposure and tobacco use with expression (immunoreactivity) of p53 protein in bronchial epithelium of Iranian "mustard lung" patients. Mil Med 172:70–74.

Ghanei M, Harandi AA. 2007b. Long term consequences from exposure to sulfur mustard: a review. Inhal Toxicol 19:451–456.

Ghanei M, Tazelaar HD, Harandi A, Peyman M, Hoseini Akbari HM, Aslani J. 2007c. Clinical differentiation between resistant asthma and chronic bronchiolitis: testing a practical approach. Iran J Allergy Asthma Immunol 6:207–214.

Ghanei M, Tazelaar HD, Chilosi M, Harandi AA, Peyman M, Akbari HM, Shamsaei H, Bahadori M, Aslani J, Mohammadi A. 2008. An international collaborative pathologic study of surgical lung biopsies from mustard gas-exposed patients. Respir Med 102:825–830.

Ghanei M, Harandi AA. 2011. Molecular and cellular mechanism of lung injuries due to exposure to sulfur mustard: a review. Inhal Toxicol 23:363–371.

Ghazanfari T, Sharifnia Z, Yaraee R, Pourfarzam S, Kariminia A, Mahlojirad M, Faghihzadeh S, Jalali-Nodoushan MR, Ardestani SK, Soroush MR, Amiri S, Hassan ZM, Ghavami S, Ghanei M. 2009. Serum soluble Fas ligand and nitric oxide in long-term pulmonary complications induced by sulfur mustard: Sardasht-Iran Cohort Study. Int Immunopharmacol 9:1489–1493.

Gosink BB, Friedman PJ, Liebow AA. 1973. Bronchiolitis obliterans. Roentgenologic-pathologic correlation. Am J Roentgenol Radium Ther Nucl Med 117:816–832.

Hassan ZM, Ebtekar M, Ghanei M, Taghikhani M, Noori Daloii MR, Ghazanfari T. 2006. Immunobiological consequences of sulfur mustard contamination. Iran J Allergy Asthma Immunol 5:101–108.

Hefazi M, Attaran D, Mahmoudi M, Balali-Mood M. 2005. Late respiratory complications of mustard gas poisoning in Iranian veterans. Inhal Toxicol 17:587–592.

Heng D, Sharples LD, McNeil K, Stewart S, Wreghitt T, Wallwork J. 1998. Bronchiolitis obliterans syndrome: incidence, natural history, prognosis, and risk factors. J Heart Lung Transplant 17:1255–1263.

Hwang JH, Kim TS, Lee KS, Choi YH, Han J, Chung MP, Kwon OJ, Rhee CH. 1997. Bronchiolitis in adults: pathology and imaging. J Comput Assist Tomogr 21:913–919.

Jafari M, Ghanei M. 2010. Evaluation of plasma, erythrocytes, and bronchoalveolar lavage fluid antioxidant defense system in sulfur mustard-injured patients. Clin Toxicol (Phila) 48:184–192.

Kaditis AG, Gondor M, Nixon PA, Webber S, Keenan RJ, Kaye R, Kurland G. 2000. Airway complications following pediatric lung and heart-lung transplantation. Am J Respir Crit Care Med 162:301–309.

Kang EY, Woo OH, Shin BK, Yong HS, Oh YW, Kim HK. 2009. Bronchiolitis: classification, computed tomographic and histopathologic features, and radiologic approach. J Comput Assist Tomogr 33:32–41.

Khateri S, Ghanei M, Keshavarz S, Soroush M, Haines D. 2003. Incidence of lung, eye, and skin lesions as late complications in 34,000 Iranians with wartime exposure to mustard agent. J Occup Environ Med 45:1136–1143.

Law L, Zheng L, Orsida B, Levvey B, Oto T, Kotsimbos AT, Snell GI, Williams TJ. 2005. Early changes in basement membrane thickness in airway walls post-lung transplantation. J Heart Lung Transplant 24:1571–1576.

Lee TM, Lin MS, Chang NC. 2008. Usefulness of C-reactive protein and interleukin-6 as predictors of outcomes in patients with chronic obstructive pulmonary disease receiving pravastatin. Am J Cardiol 101:530–535.

Mehrani H, Ghanei M, Aslani J, Golmanesh L. 2009. Bronchoalveolar lavage fluid proteomic patterns of sulfur mustard-exposed patients. Proteomics Clin Appl 3:1191–1200.

Mirsadraee M, Attaran D, Boskabady MH, Towhidi M. 2005. Airway hyperresponsiveness to methacholine in chemical warfare victims. Respiration 72:523–528.

Mroz BJ, Sexauer WP, Meade A, Balsara G. 1997. Hemoptysis as the presenting symptom in bronchiolitis obliterans organizing pneumonia. Chest 111:1775–1778.

Müller NL, Miller RR. 1995. Diseases of the bronchioles: CT and histopathologic findings. Radiology 196:3–12.

Myers JL, Colby TV. 1993. Pathologic manifestations of bronchiolitis, constrictive bronchiolitis, cryptogenic organizing pneumonia, and diffuse panbronchiolitis. Clin Chest Med 14:611–622.

Myers PO, Gasche-Soccal PM, Robert JH, Pache JC, Bongiovanni M. 2009. Neuroendocrine proliferation after lung transplantation. J Heart Lung Transplant 28:406–408.

Nash EF, Volling C, Gutierrez CA, Tullis E, Coonar A, McRae K, Keshavjee S, Singer LG, Durie PR, Chaparro C. 2012. Outcomes of patients with cystic fibrosis undergoing lung transplantation with and without cystic fibrosis-associated liver cirrhosis. Clin Transplant 26:34–41.

Nocker RE, Schoonbrood DF, van de Graaf EA, Hack CE, Lutter R, Jansen HM, Out TA. 1996. Interleukin-8 in airway inflammation in patients with asthma and chronic obstructive pulmonary disease. Int Arch Allergy Immunol 109:183–191.

Pourfarzam S, Ghazanfari T, Yaraee R, Ghasemi H, Hassan ZM, Faghihzadeh S, Ardestani SK, Kariminia A, Fallahi F, Soroush MR, Merasizadeh J, Mahlojirad M, Naghizadeh MM, Ghanei M. 2009. Serum levels of IL-8 and IL-6 in the long term pulmonary complications induced by sulfur mustard: Sardasht-Iran Cohort Study. Int Immunopharmacol 9:1482–1488.

Ryu JH, Myers JL, Swensen SJ. 2003. Bronchiolar disorders. Am J Respir Crit Care Med 168:1277–1292.

Scott AI, Sharples LD, Stewart S. 2005. Bronchiolitis obliterans syndrome: risk factors and therapeutic strategies. Drugs 65:761–771.

Shohrati M, Shamspour N, Babaei F, Harandi AA, Mohsenifar A, Aslani J, Ghanei M. 2010. Evaluation of activity and phenotype of α1-antitrypsin in a civil population with respiratory complications following exposure to sulfur mustard 20 years ago. Biomarkers 15:47–51.

Skeens JL, Fuhrman CR, Yousem SA. 1989. Bronchiolitis obliterans in heart-lung transplantation patients: radiologic findings in 11 patients. AJR Am J Roentgenol 153:253–256.

Sohrabpour H. 1984. Clinical manifestations of chemical agents on Iranian combatants during Iran-Iraq conflict. Arch Belg Suppl:291–297.

Stanbrook MB, Kesten S. 1999. Bronchial hyperreactivity after lung transplantation predicts early bronchiolitis obliterans. Am J Respir Crit Care Med 160:2034–2039.

Stern EJ, Frank MS. 1994. Small-airway diseases of the lungs: findings at expiratory CT. AJR Am J Roentgenol 163:37–41.

Sweatman MC, Millar AB, Strickland B, Turner-Warwick M. 1990. Computed tomography in adult obliterative bronchiolitis. Clin Radiol 41:116–119.

Thomason JW, Rice TW, Milstone AP. 2003. Bronchiolitis obliterans in a survivor of a chemical weapons attack. JAMA 290:598–599.

Visscher DW, Myers JL. 2006. Bronchiolitis: the pathologist's perspective. Proc Am Thorac Soc 3:41–47.

Webb WR, Stein MG, Finkbeiner WE, Im JG, Lynch D, Gamsu G. 1988. Normal and diseased isolated lungs: high-resolution CT. Radiology 166:81–87.

Wohl ME, Chernick V. 1978. State of the art: bronchiolitis. Am Rev Respir Dis 118:759–781.

Yaraee R, Ghazanfari T, Ebtekar M, Ardestani SK, Rezaei A, Kariminia A, Faghihzadeh S, Mostafaie A, Vaez-Mahdavi MR, Mahmoudi M, Naghizadeh MM, Soroush MR, Hassan ZM. 2009. Alterations in serum levels of inflammatory cytokines (TNF, IL-1α, IL-1β and IL-1Ra) 20 years after sulfur mustard exposure: Sardasht-Iran cohort study. Int Immunopharmacol 9:1466–1470.

Zarchi K, Akbar A, Naieni KH. 2004. Long-term pulmonary complications in combatants exposed to mustard gas: a historical cohort study. Int J Epidemiol 33:579–581.