

# Pulmonary Scintiscan Findings in Sulfur Mustard Injured Patients Suspected for Gastroesophageal Reflux; a Descriptive Cross-Sectional Study

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## Abstract

**Background:** Gastroesophageal reflux disease (GERD) prevalence in patients with sulfur mustard (SM)-induced bronchiolitis obliterans (BO) is higher than exposed cases with mild lung injuries. In this study, we aimed to evaluate the prevalence of microaspirations using nuclear scintiscan among BO patients with SM exposure.

**Methods:** This was a prospective cross-sectional study conducted on patients with SM-induced BO and pulmonary symptom exacerbation referred to the Baqiyatallah Hospital, Tehran, Iran during the year 2009. Following the endoscopy-based diagnosis of GERD by a gastroenterologist, anti-reflux medications were withdrawn for 72 hours and then the patients underwent nuclear scintigraphy scan following 12 hour ingestion of fat containing food as radionuclide dinner. High resolution computed tomography (HRCT), spirometry and bronchoscopy were also performed for all patients.

**Results:** In this study, 39 patients (94.9% men) with mean ( $\pm$  SD) age of  $45.1 \pm 6.2$  years were enrolled. The most common clinical complaints of the patients were thick sputum (97.4%) and dyspepsia (94.7%), followed by chest tightness (89.7%), nocturnal cough (82.1%), and nocturnal dyspnea (66.7%). In HRCT, air-trapping was the most common pulmonary finding (92.1%). In spirometry, mean ( $\pm$ SD) FEV1 and FEV1/FVC were  $52.7 \pm 22.4\%$  and  $70.4 \pm 13.9\%$ , respectively. In bronchoscopy, the most common finding was airway remodeling (62.2%), followed by false vocal cord hypertrophy (24.3%). In scintigraphic imaging, only 1 patient had a remarkable finding, in whom, the radionuclide material was seen in the pharynx (proximal GERD), but did not produce marked microaspiration of gastric substances into the airways.

**Conclusion:** Although previous reports demonstrated high prevalence of GERD and microaspiration in patients with SM-induced BO, we did not find remarkable evidence for microaspiration in scintiscan in patients included in this study.

**Keywords:** Bronchiolitis Obliterans; Gastroesophageal Reflux; Mustard Gas; Poisoning; Radionuclide Imaging

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## INTRODUCTION

Micro and macro- aspirations following gastro-esophageal reflux (GER) can trigger airway hyperresponsiveness (AHR) and worsen other pulmonary diseases such as bronchiolitis or chronic obstructive pulmonary disease (COPD) (1,2). Nocturnal microaspiration is a common problem in patients with pulmonary diseases resistant to treatment such as asthma, chronic cough, idiopathic pulmonary fibrosis, and posterior laryngitis. Gastroesophageal reflux disease (GERD) is one of the most common disorders in developing and developed countries. Reflux esophagitis prevalence is up to 80% among the pulmonary patients (3,4). It has been shown that there is a strong association between the incidence of bronchiolitis obliterans (BO) and GER (5). BO is the most challenging respiratory disease in patients with toxic agent exposure and allograft rejection after lung transplant (6). BO

may occur after acute lung injury following sulfur mustard (SM) exposure; however, other lung disorders such as bronchomalacia, bronchitis, or respiratory distress syndrome were also reported in SM-injured patients (7-9).

Previous studies have reported that GER prevalence in patients with SM-induced BO is higher than exposed cases with mild lung injuries (10,11). Furthermore, it has been proven that GER can worsen the severity of BO in the SM-exposed cases (10). Although the traditional GER medications can improve the pulmonary symptoms in SM-injured patients (12), some patients do not show considerable GER symptoms. In this respect, it is well documented that some GER markers are found in bronchoalveolar lavage fluid in undiagnosed cases for GER (13,14). Therefore, it seems that GERD can be a contributing factor for respiratory disorders.

Although most of the routine methods are reliable for

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macroaspiration detection, there is no efficient and reliable diagnostic method for microaspiration as an invisible harmful factor in pulmonary patients (15). Assessing the sputum's pepsin, bile, and pH level has been suggested as indices for the diagnosis of microaspiration, but it seems that nuclear scintiscan is more efficient (16-20). In this study, we aimed to evaluate the prevalence of microaspirations using nuclear scintiscan for the first time among SM injured patients with BO.

## METHODS

This was a prospective cross-sectional study conducted on patients with SM-induced BO and pulmonary symptom exacerbation referred to the Baqiyatallah Hospital affiliated to the Baqiyatallah University of Medical Sciences (Tehran, Iran) during the year 2009. Patients with following criteria were included in the study: diagnosis of BO, no history of other pulmonary diseases such as pneumonia (based on a pulmonologist assessment), non-smokers, and previous history of single exposure to SM (patients who had contact with SM in one occasion for a short period based on the documents of the Iranian organization for survivors of chemical warfare exposure). Upper gastrointestinal (GI) endoscopy was done by a gastroenterologist to confirm the GERD diagnosis and to rule out other GI disorders.

All patients gave their written informed consent before starting experiments. Anti-reflux medications were stopped for 72 hours, and then the patients underwent nuclear scintigraphy scan after 12 hours of ingestion of fat-containing food with radionuclide (300 mg fatty soap labeled with 185 MBq  $^{99m}\text{Tc}$  sulfur colloid) at dinner. Scans using nuclear scintigraphy were performed and interpreted by a nuclear medicine specialist. In addition, high resolution computed tomography (HRCT) and bronchoscopy were done in Baqiyatallah University Hospital, for all patients.

Severity of pulmonary disease (dyspnea) was scaled according to American Thoracic Society (ATS) guidelines (21). Spirometric parameters such as forced expiratory volume in the first second (FEV1) and the ratio of FEV1 to forced volume capacity (FVC), that is, FEV1/FVC ratio were measured with a Vmax 20 Spirometer (Chest co., Italy). The best of three maneuvers was selected and expressed as a percentage of the predicted and absolute value.

This study was approved by the Scientific and Ethic Board of Baqiyatallah University of Medical Sciences, Tehran, Iran. The Chemical Injury Research Center, Baqiyatallah University of Medical Sciences, Tehran, supported this research financially and no extra-routine charge was imposed to patients. Data were analyzed using SPSS software. Results are expressed with frequency and percentage for qualitative variables and with mean and standard deviation (SD) for quantitative variables.

## RESULTS

In this study, 39 patients (94.9% men) with mean ( $\pm$  SD) age of  $45.1 \pm 6.2$  years were enrolled.

The most common clinical complaints of the patients were thick sputum (97.4%) and dyspepsia (94.7%), followed by

chest tightness (89.7%), nocturnal cough (82.1%), nocturnal dyspnea (66.7%), and hemoptysis (41%). The severity of dyspnea in patients was mild in 10 patients (25.6%), moderate in 22 patients (56.4%), and severe in 6 patients (15.4%) according to ATS criteria. The baseline spirometric findings are shown in table 1. The mean ( $\pm$ SD) of FEV1 and FEV1/FVC were  $52.7 \pm 22.4\%$  and  $70.4 \pm 13.9\%$ , respectively.

In HRCT, air-trapping was the most common pulmonary finding (92.1%) followed by bronchiectasia (21.1%) and bronchomalacia (13.2%) (Figure 1).

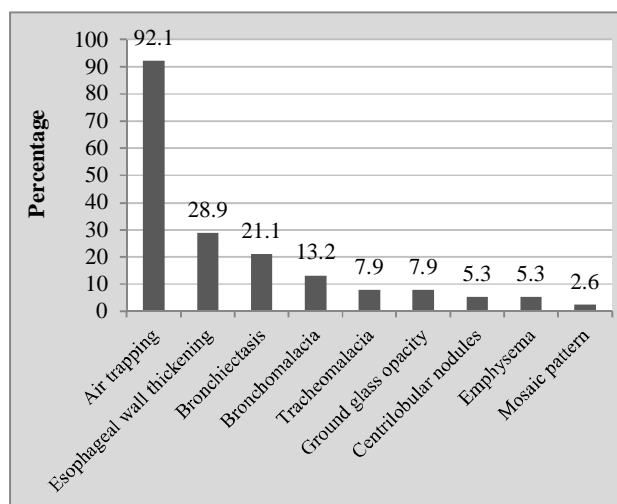
In bronchoscopy, the most common finding was airway remodeling (62.2%), followed by false vocal cord hypertrophy (24.3%) (Figure 2).

The most common endoscopic findings were erosive gastritis (63.2%), followed by reflux esophagitis grade A (50%) and hiatal herniation (31.6%) (Figure 3).

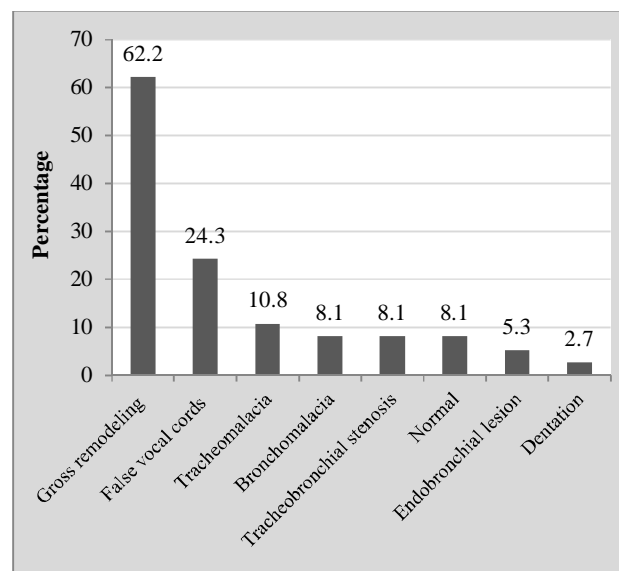
**Table 1.** Spirometric findings of patients with sulfur mustard induced bronchiolitis obliterans (n = 39)

Variable	Mean $\pm$ SD	Max	Min
FEV1	$52.7 \pm 22.4$	118	17
FEV1/FVC	$70.4 \pm 13.9$	92	41
FVC	$59.4 \pm 20.0$	114	29
DLCO	$92.9 \pm 38.1$	213	51
MEF	$39.4 \pm 30.3$	120	7
FRC	$103.1 \pm 36.1$	174	70
IC	$49.6 \pm 18.2$	92	18
RV	$190.8 \pm 93.7$	543	82

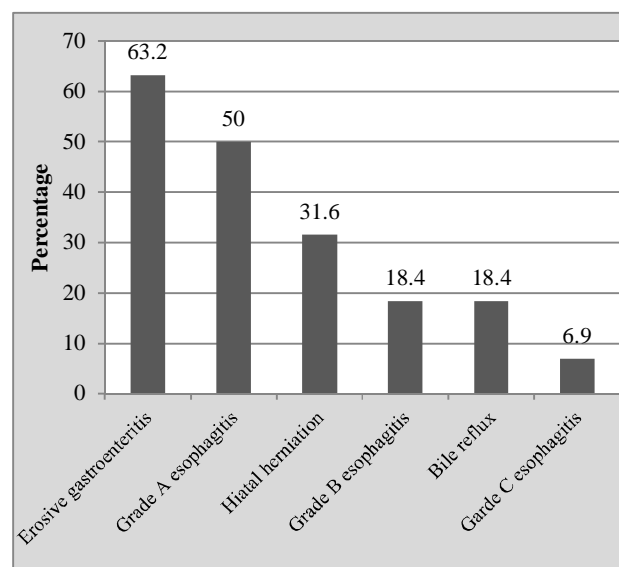
FEV1: Forced expiratory volume in first second, FVC: Forced vital capacity, DLCO: Diffusing capacity of the lungs for carbon monoxide, MEF: Mean expiratory flow, FRC: Functional residual capacity, IC: Inspiratory capacity, RV: Residual volume



**Figure 1.** HRCT findings of patients with sulfur mustard induced bronchiolitis obliterans (n = 39)



**Figure 2.** Bronchoscopic findings of patients with sulfur mustard induced bronchiolitis obliterans (n = 39)



**Figure 3.** Endoscopic findings of patients with sulfur mustard induced bronchiolitis obliterans (n = 39)

In scintigraphic imaging, only 1 patient had a remarkable finding. In this patient, the radionuclide material was seen in the pharynx (proximal GERD), but did not produce marked microaspiration of gastric substances into the airways.

## DISCUSSION

In this descriptive cross-sectional study on SM-exposed patients, we found that thick sputum was the most common clinical finding followed by dyspepsia and chest tightness. The mean of FEV1 and FEV1/FVC were lower than normal

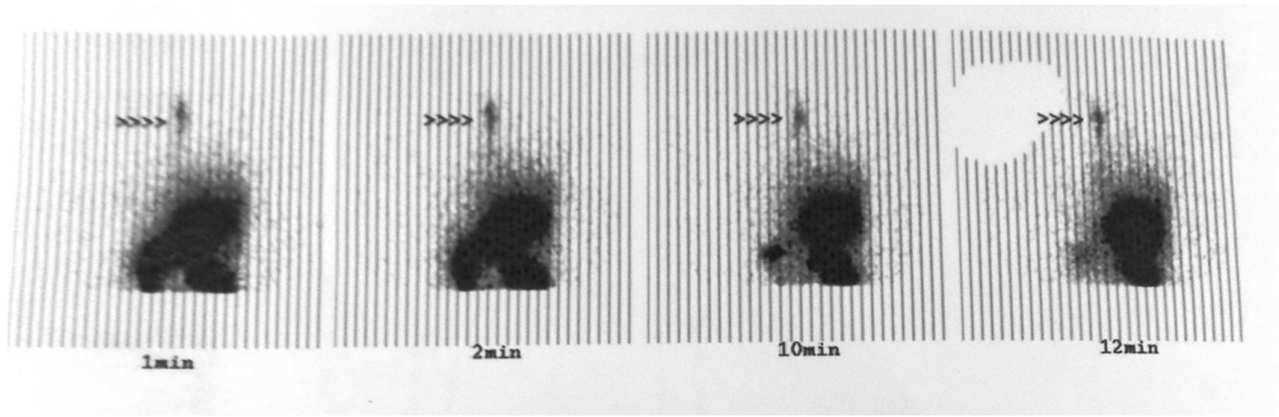
levels. In HRCT scan, air-trapping was the most common finding. Only 1 patient had remarkable finding in scintiscan, which could not provide enough evidence for analysis between positive and negative groups in terms of clinical variables. This study extended our knowledge about the GERD in patients with SM exposure. In a study by Aliannejad et al (14), bile acids in bronchoalveolar lavage (BAL) fluid as a marker for microaspiration among SM-injured patients were found in 84% of them, though pepsin and trypsin (other microaspiration biomarkers) were detected in BAL fluid of all patients. They finally concluded that in addition to the high prevalence of GER in BO patients after exposure to SM, GER *per se* might be an aggregating factor for BO exacerbation.

There is a growing concern about relationship between GERD and pulmonary diseases. Nowadays, it has been approved that micro and macro gastroesophageal reflux can induce chronic lung diseases such as asthma, COPD, and even pulmonary fibrosis, but there are some doubts and controversies about this relationship (2). It is known that aspiration of gastroesophageal fluids; either micro or macroaspiration, is notorious for pathogenesis of reactive airway diseases. It was demonstrated that gastroesophageal microaspiration into the airways, which is generally associated with limited or no GI symptoms, has a significant role on producing chronic cough (2). However, microaspiration is often neglected in patients with pulmonary symptoms. Macroaspiration, on the other hand, raises more remarkable GI symptoms and patients with such problem seek for treatment for it. Hence, macroaspiration may be less effective in progression of GER-induced pulmonary diseases due to the fact it is treated at earlier stages.

It should be determined which component of the GI juice such as bile acids, pepsin, gastric acid, etc. is more dangerous for lungs. The low effectiveness of current acid suppressive therapies, even powerful proton pump inhibitors (PPIs), on extra-esophageal symptoms of GERD may suggest that non-acid reflux can exert symptoms through mechanisms beyond excessive acid production (2,22). In this respect, Tutuian et al demonstrated that in GER patients treated with anti-acid suppressive medications such as PPIs, non-acid reflux could induce a lot of symptoms such as cough (23).

It is a matter of debate whether GERD induces lung diseases or it only accelerates progression of these disorders. There are so many trials to respond to this question. It has been reported that adding PPIs even in high doses, compared with placebo, improves neither symptoms nor lung function of patients with asthma, but was associated with more adverse events such as higher incidence of respiratory infections (24,25). However, it has been shown that using a PPI, omeprazole, in addition to a dopamine antagonist, domperidone, for asthmatic adults with GER is beneficial by reducing asthma symptoms, and improving pulmonary function (26). In general, because of low adverse effects of PPIs or anti-acid medications, it is better to use them in patients with refractory symptoms of pulmonary diseases.

There is still no concrete agreement over the best method for GERD diagnosis in patients with pulmonary diseases. Sputum or salivary pepsinogen and pepsin levels can be



**Figure 4.** Pulmonary scintigraphic imaging of the index case (Pointer shows reflux of the tracer to the pharynx from the stomach)

measured for this purpose (27,28). In addition, substance P and neurokinin A are increased in response to inflammatory process at the respiratory epithelium (29). Although scintigraphy has been recommended for GER detection in patients who are presented with chronic cough and pulmonary diseases (28), in this study, we found discouraging evidence over the utility of this diagnostic method for GER. In this regard, in our study on SM-injured patients with BO, although GER was detected with endoscopic findings in the majority of cases, only one patient had remarkable findings in scintigraphy. These results can be attributed to shorter duration between nucleotide food ingestion and performing scintiscan (30). It seems that using other methods (such as pH metry) would be helpful to achieve more accurate diagnosis of GER due to non acid components such as bile and pepsin components (2).

Finally, many scientists argued over the causative role of GERD for pulmonary disorders. There has been evidence approving the similarity of both airway and esophagus innervations (2,31). Hence, as reflux may stimulate vagal reflex arc, cough and/or bronchospasm consequently might occur (32-34). In contrast, patients with constrictive pulmonary diseases are susceptible to GERD because of the treatments they receive, i.e. muscle relaxant effect of beta blockers or corticosteroids on lower esophageal sphincter.

#### LIMITATIONS

One of the limitations of this study was lack of a control group, though it was a cross-sectional and descriptive study on sulfur mustard induced BO patients, and further studies are better to be conducted in case control design. In addition, we need studies which evaluate microaspiration treatment efficacy on GERD extra-pulmonary manifestations to confirm the role of any degree of reflux in GERD pathogenesis in lung tissue. In addition, there are no methods for following up treatment efficacy and it can be proposed for future studies" (2).

#### CONCLUSION

Although previous reports demonstrated high prevalence

of GERD and microaspiration (using measurement of pepsin) in patients with SM-induced BO, we did not find remarkable evidence for microaspiration in scintiscan in patients included in this study.

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