ORIGINAL ARTICLE

Late-onset Radiologic Findings of Respiratory System Following Sulfur Mustard Exposure

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Abstract

Background: Sulfur mustard (SM) as a chemical warfare agent, increases permeability of bronchial vessels and damages airway epithelium. SM exposure causes debilitating respiratory complications. This study was designed to evaluate clinical respiratory manifestations, and to compare chest X ray (CXR) and high resolution computed tomography (HRCT) scan of chest in SM exposed patients with respiratory complaints.
Methods: All patients with history of SM exposure who visited Imam Reza Specialized Clinic of Respiratory Diseases from September 2001 to March 2011 were included. Patients with other comorbidities which affect respiratory system were excluded. CXR and chest HRCT scan were performed on the same day and were repeated after 5 years. Clinical and radiologic findings were collected and were compared with each other.
Results: In total, 62 male patients with mean age of 53 (6.9, 41-65) were studied. Dyspnea (61 cases; 100%), dry cough (40 cases; 66%), hemoptysis (21 cases; 35%) and productive cough (20 cases; 33%) were the most common respiratory manifestations. Pulmonary infiltration (51; 83%), pleural thickening (25; 40%) and emphysema (16; 26%) were the most common findings on CXR. According to HRCT scan, pulmonary infiltration (53; 85%), bronchiolitis obliterans (38; 61%) and pleural thickening (36; 58%) were the most common findings (Table 2). Repeated radiologic assessments after 5 years showed a few additional findings in HRCT scan, while in about one fifth of CXRs, new pathologic findings were found.
Conclusion: Patients with SM exposure experience debilitating respiratory disorders in long term. Repeating CXR in patients who present with subjective symptoms may show new findings; however, repeating HRCT scan is probably not necessary.

Keywords: Sulfur mustard; Respiratory disorder; Chemical warfare agents; Poisoning; Radiology

INTRODUCTION

Sulfur mustard (SM) has been used as a chemical weapon for 100 years (1). It was widely used for the same reason in Iraq-Iran war during 1980 to 1988 (2). SM is colorless and odorless when it is pure but when marketed as warfare agents, it has a horseradish odor and yellow-brown color (1). SM poisoning may influence lungs, eyes, gastrointestinal, endocrine and hematopoietic system. It can also induce large blisters on the exposed skin with the same mechanism (3). In addition, SM has been known to be a DNA alkylating agent and considered as a human carcinogen (4). Although most severe complications occur in acute phase of pulmonary involvement, most victims suffer from late-onset chronic respiratory disorders (4).

SM is able to increase permeability of bronchial vessels and damage airway epithelium. This phenomenon leads to accumulation of plasma proteins in peribronchovascular area (5). Subsequently, formation of fibrin-rich casts in the airways causes airway obstruction which ultimately leads to considerable post-exposure morbidity and mortality (5). Pulmonary involvements in acute exposure present as obstructive disorder, while bronchiectasis, emphysema, bronchiolitis obliterans, obstructive lung disease and lung cancer are manifestations of the chronic phase (6,7). SM toxicity can lead to acute lung injury (ALI) as well as acute respiratory distress syndrome (ARDS) (8). Common findings of the upper respiratory tract have been reported to be dysphonia, post-nasal discharge (PND), lower larynx position and mucosal inflammation of larynx (9). Chronic respiratory disorders of SM exposure can cause diverse degrees of sleep disorders and affect quality of life (10).

Chest X ray (CXR) is a primary diagnostic procedure that is used as an initial modality for detecting pathologic conditions or confirming a clinical judgment (9). High Resolution Computed Tomography (HRCT) scan of chest has a worldwide acceptance for the latter as well as a confirmatory diagnostic evaluation to detect patients with suspicious lesions (11).

Although HRCT scan is not indicated for patients with SM exposures, it can show some SM-induced lung injuries. Such findings are the prime reason that some researchers have tried to define standard indications for chest HRCT and if needed to repeat it (11). In this study, we tried to evaluate radiologic examinations in patients with SM exposure.

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METHODS

Study design

This was a prospective study on SM exposed patients with respiratory complaint who visited Imam Reza Specialized Clinic of Respiratory Diseases during September 2001 to March 2011. All ethical approval according to Helsinki declaration was considered. Informed consent was obtained from all participants subsequent to giving an explanation of the aim of the study. The history of SM exposure was confirmed according to governmental documents which were accessible for each patient.

All patients were visited by a pulmonologist (mainly first author). Data including medical history, physical examinations and radiologic findings were entered into a predesigned checklist. Patients with other comorbidities such as autoimmune diseases, chronic obstructive pulmonary disease due to other etiologies, mitral valve disease, pulmonary hypertension, cardiac failure, occupational exposure to industrial fumes, cystic fibrosis and congenital anomalies that can influence pulmonary system were excluded. Such data were confirmed through medical history, physical examination, previous medical visits, electrocardiography and echocardiography. Vital signs (blood pressure, respiratory rate, temperature and heart rate) were documented in the first outpatient visit and then 5 years later. Six-minute walk test was done in both sessions. Pulse oximetry was also done in first outpatient visit.

Radiologic assessments

CXR was performed in posterioranterior and lateral views. A single experienced radiologist reported all radiographs. With the aim of minimizing report interpretation flaws, a second opinion was sought from another radiologist, who was blind to the first reports. Inter-observer variations were validated in the first 15 cases. HRCT was then carried out for all patients to compare with the CXR findings.

Same radiologic examinations (CXR, Chest HRCT scan) were repeated 5 years later.

Statistical analysis

Data analyses were conducted with SPSS for windows version 11.5 (SPSS Inc .Chicago, IL). Analysis of correlations was done using Spearman's correlation coefficient test. Level of significance was considered to be less than 0.05.

RESULTS

Sociodemographic

In total, 62 patients were studied with mean (SD, Min-Max) age of 53 (6.9, 41-65) years. All patients were male and 13 of them were required to be admitted in respiratory disease division of internal medicine department of Imam Reza hospital. The mean time elapsed between exposure and study entry was 20 (2.4, 15-28) years.

Clinical and radiologic findings

In all patients, respiratory rate, temperature and heart rate were within the normal ranges. Dyspnea (61 cases; 100%), dry cough (40 cases; 66%), hemoptysis (21 cases; 35%) and productive cough (20 cases; 33%) were the most common respiratory manifestations of patients (Table 1). Two cases died during the study, one of them due to myocardial infarction and the other due to exacerbation of respiratory problems. No lung cancer was observed during this 5-year period.

Normal CXR was reported for 9 cases (16%) and normal HRCT scan for 8 patients. Pulmonary infiltration (51; 83%), pleural thickening (25; 40%) and emphysema (16; 26%) were the most common findings on CXR (Table 2). According to HRCT scan, pulmonary infiltration (53; 85%), bronchiolitis obliterans (38; 61%) and pleural thickening (36; 58%) were the most common findings (Table 2). Bronchiolitis obliterans could not be identified in CXR.

Table 1. Demographic features and clinical respiratory manifestations of sulfur mustard exposed patients

Feature	Result
Age (year), mean (SD)	53 (6.9)
Disease duration (year), mean (SD)	20 (2.4)
Dyspnea, No. (%)	61 (100)
Dry cough, No. (%)	40 (66)
Hemoptysis, No. (%)	21 (35)
Productive cough, No. (%)	20 (33)
Wheezing, No. (%)	10 (16)
Cyanosis, No. (%)	1 (2)
Respiratory distress, No. (%)	1 (2)

Table 2. Frequency of pulmonary radiologic findings in CXR and HRCT scan

	CXR, No. (%)	HRCT, No. (%)
Normal radiologic study	9 (15)	8 (13)
Findings on abnormal CXRs*		
Pulmonary infiltration	51 (83)	53 (85)
Pleural thickening	25 (40)	36 (58)
Emphysema	16 (26)	25 (40)
Bronchiectasis	9 (15)	14 (23)
Lymphadenopathy	0 (0)	0 (0)
Bronchiolitis obliterans	---	38 (61)

* In some cases more than one pathologic finding were identified.

In table 3, pathologic findings in CXRs were plotted against demographic characteristics and clinical manifestations. Patients who presented with dyspnea were mostly involved with pleural thickening, bronchiectasis and emphysema on CXR. Moreover, pleural thickening and bronchiectasis on CXR were mostly observed in cases with hemoptysis.

Table 4 shows pathologic findings in reported HRCT scans according to demographic characteristics and clinical manifestations. The two most frequent manifestations which were mostly observed and associated with all pathologic findings were dyspnea and productive cough. Bronchiectasis in HRCT scan was mostly associated with dyspnea, productive cough and hemoptysis (Figure 1). Pleural thickening was mostly seen in patients with hemoptysis and productive cough. The six-minute walk results were different according to clinical presentations, however it correlated to new radiologic findings (P<0.001). Patients with emphysema could walk significantly shorter distances (Table 3 and 4).

New pathologic findings in radiologic examinations

Reports by the two radiologists were significantly similar (P<0.001). Pathologic finding could be more identified in HRCT scan compared to CXR. In this regard, pathologic findings on HRCT was identified in 56 patients with dyspnea (90%), while on CXR these pathologies could be found for 49 patients with dyspnea (79%) (Table 5). Repeated radiologic assessments after 5 years showed a few additional findings in HRCT, while in about one fifth of CXRs, new pathologic findings were found. In this regard, 17%, 13%, and 14% of new findings in CXR were found in patients with subjective symptoms including dyspnea, cough and hemoptysis, respectively (Table 5).

DISCUSSION

SM exposure is mostly known for acute dermal and mucosal complications (9). However, in chronic phase, respiratory disorders overcome. In this study, we showed late-onset respiratory manifestations in 62 SM exposed patients during Iran-Iraq war. In this study, we found that dyspnea, dry cough, hemoptysis and productive cough were the most common respiratory manifestations of SM exposed patients. This finding is similar to previous reports of Iranian SM exposed veterans (9).

Table 3. Demographic and clinical respiratory features according to pathologic findings on CXR*

Demographic and clinical features	Radiologic findings				
	Pulmonary Infiltration	Pleural thickening	Emphysema	Bronchiectasis	Normal CXR
Age (year), mean (SD)	52 (3.8)	54 (3.4)	57 (4.1)	56 (3.7)	48 (4.7)
O2 saturation (%), mean (SD)	94 (6.3)	95 (9.4)	94 (8.7)	94 (8.7)	96 (3.7)
Six-minute walk test (m), mean (SD)	268 (56)	328 (73)	210 (44)	217 (54)	350 (23)
Dyspnea, No. (%)	36 (71)	24 (96)	16 (100)	9 (100)	9 (100)
Dry cough, No. (%)	29 (57)	16 (88)	3 (19)	1 (11)	8 (89)
Productive cough, No. (%)	19 (37)	8 (96)	12 (75)	8 (89)	1 (11)
Wheezing, No. (%)	9 (18)	2 (8)	4 (25)	3 (33)	0 (0)
Hemoptysis, No. (%)	19 (38)	24 (96)	4 (25)	5 (100)	0 (0)

* In some cases with abnormal CXR more than one pathologic finding were identified.

Table 4. Demographic and clinical respiratory features according to pathologic findings on HRCT scan*

Demographic and clinical features	Radiologic findings					
	Pulmonary Infiltration	Pleural thickening	Emphysema	Bronchiectasis	Bronchiolitis obliterans	Normal HRCT
Age (year), mean (SD)	52 (4.2)	54 (3.1)	57 (3.6)	56 (2.9)	58 (3.0)	49 (4.4)
O2 saturation (%) mean (SD)	95 (8.7)	95 (9)	94 (7.2)	94 (10.8)	93 (7.0)	96 (3.4)
Six-minute Walk test (m), mean (SD)	288 (53)	339 (69)	218 (30)	237 (46)	325 (58)	350 (39)
Dyspnea, No. (%)	50 (94)	34 (94)	24 (96)	14 (100)	34 (89)	8 (100)
Dry cough, No. (%)	32 (60)	24 (67)	3 (12)	1 (7)	12 (32)	7 (88)
Productive cough, No. (%)	38 (72)	11 (96)	21 (4)	13 (93)	23 (61)	1 (13)
Wheezing, No. (%)	11 (18)	19 (8)	13 (25)	8 (33)	13 (34)	0
Hemoptysis, No. (%)	20 (38)	24 (96)	7 (25)	6 (43)	11 (29)	0

* In some cases with abnormal HRCT scan more than one pathologic finding were identified.

Table 5. Comparison of radiologic findings in patients with sulfur mustard exposure over five years

		Cases, No. (%)	Pathologic findings in 1st CXR, No. (%)	New findings in CXR after 5 years, No. (%)	Pathologic findings in 1st HRCT scan, No. (%)	New findings in HRCT scan after 5 years, No. (%)
Subjective findings	Dyspnea	62 (100)	49 (79)	10 (17)	56 (90)	0 (0)
	Dry cough	58 (94)	49 (84)	8 (13)	57 (98)	1 (2)
	Hemoptysis	23 (37)	16 (70)	9 (14)	21 (91)	2 (5)
Objective findings	Wheezing	29 (47)	17 (57)	0	18 (62)	0 (0)
	O_2 Saturation <94%	11 (18)	11 (100)	0	11 (100)	0 (0)
	Six-minute walk test < 300 meter	42 (68)	41 (98)	1 (2)	42 (100)	1 (2)

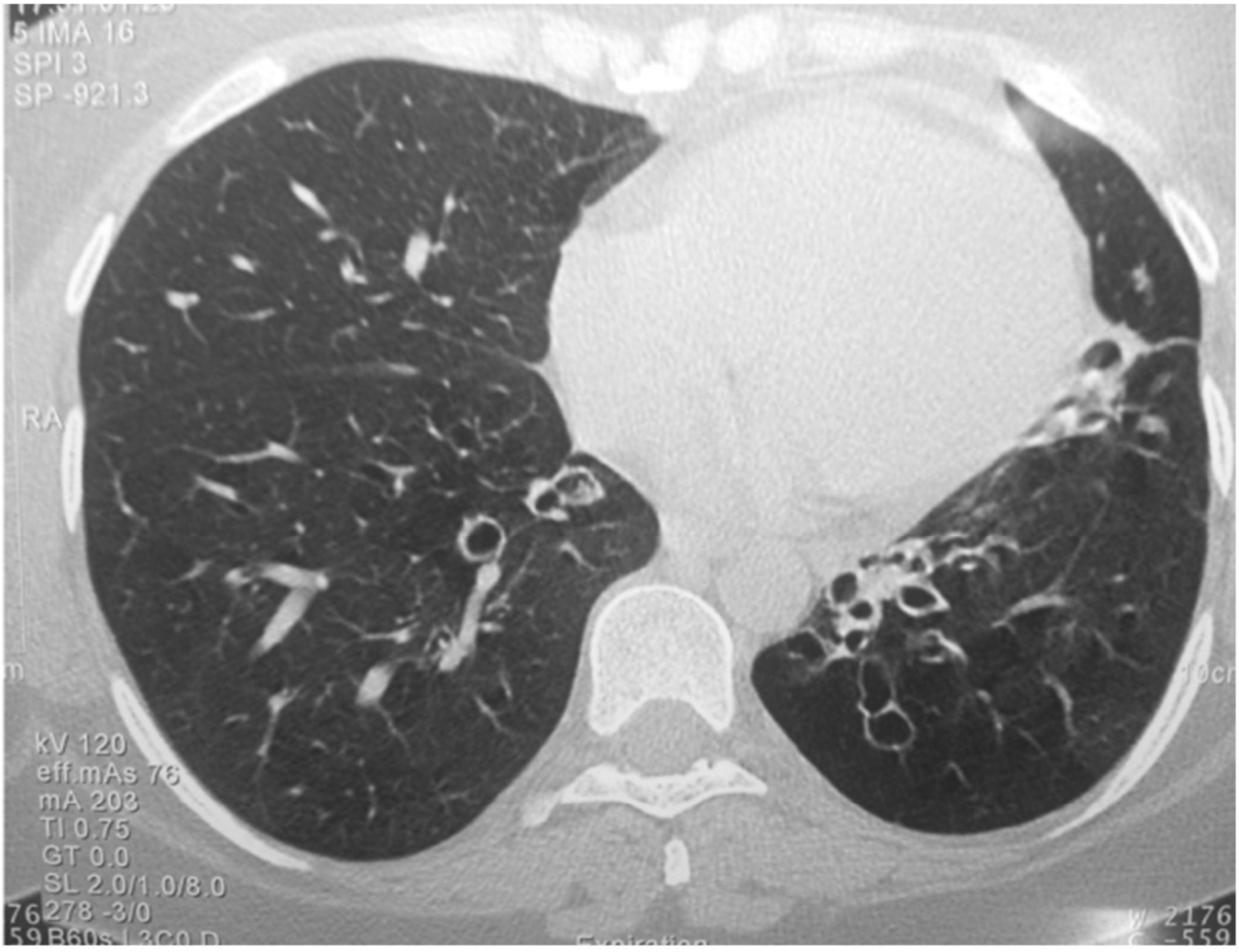

Figure 1. Bronchiectasis following sulfur mustard exposure in HRCT scan

Although a previous study showed bronchiectasis in 44.1% of patients (9), this complication was less frequent in our study (23%). Longer duration of follow up in the aforementioned study compared to this study could explain this discrepancy. Although lung cancer in SM exposure was shown to occur in long term (7), no patient developed this complication in this study. In contrast to study by Taghaddosinejad et al. which showed chronic bronchitis as the most frequent finding in autopsied SM exposed patients (12), this complication was not diagnosed in any of our

patients. This discrepancy emphasizes that chronic bronchitis may be subtle in long term. Despite the previous reports on pulmonary infections and tuberculosis in the survivors of the SM exposure, we did not also observe such problems in our cases (12).

Although the HRCT scan was more sensitive than CXR in showing radiologic abnormalities, this difference was shown to be more significant in case of subjective complaints in comparison with objective clinical findings (13). Similarly, in our study, in patients with dyspnea, HRCT scan showed more pathologic findings than CXR. It can be said accordingly that normal CXR in the presence of subjective manifestations could not exclude any pulmonary abnormality. Hence, for every patient with subjective manifestations and normal CXR performing an HRCT scan is recommended (13). Nevertheless, as it was shown in this study, repeating CXR is probably reasonable for follow up of SM exposed patients while repeating HRCT scan might be unnecessary since it might show only few changes.

LIMITATIONS

Following factors limited the validity of findings of this study. Since the exposure to SM was occurred in the past, dose of exposure, duration of exposure and number of repeated exposures could not be determined. There had been about 45,000 chemical warfare victims during Iraq-Iran war (2), and the small sample in our study could not be representative of the pulmonary findings of whole population. Since MRI is not definitive enough in diagnosis and detection of parenchymal lung disease, we omitted this diagnostic modality from our protocol (14).

It is worthy of mention that we did not exclude smokers because of the small study population. In some studies, it was shown that about 15% of SM exposure victims were smoker (15). Hence, this factor may bias the incidence of aforementioned radiologic findings in the present study.

CONCLUSION

Patients with SM exposure experience debilitating respiratory disorders in long term. Pathologic findings on radiologic examinations are higher in patients with dyspnea and productive cough. Repeating CXR in patients who present with subjective symptoms may show new findings; however, repeating HRCT is probably not necessary.

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Conflict of interest: None to be declared

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