Mostafa Ghanei, MD,
Majid Mokhtari, MD, FCCP,
Mohammad Mirmohammad, MD,
Jafar Aslani, MD,
Farshid Alaeddini, MD

High Resolution Computerized Tomography of Chest in Patients Exposed to Sulfur Mustard

Background/Objectives: Pulmonary complications are known to occur in over half of the patients exposed to sulfur mustard (SM). Chemical weapon agents (CWA) including SM were used by Iraq during Iran-Iraq war between 1983 and 1989. We undertook a retrospective analysis of the patients with documented exposure to SM during the war who subsequently developed respiratory symptoms. A review of the chest High Resolution Computed Tomography (HRCT) findings was performed to determine the features of this disease defined by this diagnostic modality.

Materials and Method: Field documents and other medical records of 155 patients exposed to SM during Iran-Iraq war and suffered respiratory complications were studied. The chest HRCTs of these patients were reviewed in order to determine the delayed radiographic patterns in patients with documented exposure to SM.

Results: Fifty chest HRCTs of these patients were evaluated. The most frequent findings were; air trapping 38 (76%), bronchiectasis 37 (74%), mosaic parenchymal attenuation (MPA) 36 (72%), major airway dilatation 33 (66%) and secondary lobule abnormalities 13 (26%) respectively.

Conclusions: Exposure to SM has devastating chronic pulmonary complications potentially disabling those affected severely. Chest HRCT findings of bronchiectasis, air trapping, major airway abnormalities, and EMPA are frequently observed in patients exposed to SM. These findings are highly suggestive of constrictive bronchiolitis obliterans (BO) diagnosis.

Keywords: Chemical Warfare Agents, Mustard Gas, Bronchiolitis, High resolution computerized tomography, Iran

Introduction

Sulfur mustard is an electrophilic DNA alkylating agent with potent mutagenic, carcinogenic, cytotoxic, and vesicant properties.[1,2] SM causes tissue injury to rapidly reproducing cells within minutes of contact with its clinical effect occurring several hours after exposure. Acute clinical manifestations are most evident on the skin, eyes, and the respiratory tract.[3-5].Since SM in vapor form is most readily absorbed through mucous membranes, the respiratory system provides an enormous surface area for entry of the agent and reaction with cellular components. This induces severe inflammation of the tracheobronchial epithelium with heavy leukocyte infiltrate, alveolar hemorrhage with thrombi formation, and vacuolation of lung parenchymal cells. [6] Such injuries are often fatal however survivors of the initial insult develop substantial scarring, often with degradation of pulmonary function and development of chronic bronchitis, bronchiectasis and pulmonary fibrosis. Chronic bronchitis is the most common long term pulmonary consequence occurring in greater than 50% of those exposed to SM and often is associated with marked physical disability.[5] Thousands of Iranians were exposed to SM during Iran-Iraq war as a result of its use by Iraq from 1983 to 1989 as documented by the United Nation's fact finding missions.[7] Some of these victims have suffered chronic respiratory complications and have been followed closely by our institution.

From:
Chemical Warfare Victims Research Center, Baqiyatallah University of Medical Science, Tehran, IRAN.
E-mail:m.ghanei@bmsu.ac.ir

Because HRCT has merged as a powerful tool in detecting both parenchymal and airway abnormalities, we used HRCT for its superiority over plain chest roentgenogram and conventional chest CT in defining finer details of pulmonary structures. To our knowledge HRCT features of chronic pulmonary complications of SM exposure have not been reported in a consistent manner before

Materials and Methods

Study Subjects

We reviewed the chest HRCT of the patients with history of exposure to SM and persistent respiratory complaints of chest discomfort, shortness of breath, cough and exercise intolerance. Data were obtained from the medical records available at a major university hospital that provides tertiary medical care and maintains a large data base of patients exposed to chemical warfare agents during Iran-Iraq war. These files contain the exposure field cards and records of medical management thereafter.

Exposure to SM was determined by documented development of blisters in the exposed areas of skin and transient visual deterioration lasting for several days and associated respiratory symptoms.

The following data were collected: age, gender, history of pre-exposure respiratory illnesses, smoking history before and after exposure, time of exposure, and symptoms at the time of exposure, current respiratory status and the roentgenographic findings.

HRCT

An extensive data base of these patients is kept in a very large and well equipped teaching hospital providing these patients with multispecialty medical care. HRCT is one of the modalities used whenever indicated particularly more so over the last 10 months in this patient population.

Fifty HRCT examinations were obtained on one scanner (HiSpeed Advantage; General Electric Medical Systems). Each HRCT examination consisted of five 1.0-mm collimation images obtained during both deep inspiration and full expiration, respectively, with the patient lying in a supine position. Images were obtained at the levels of the aortic arch, midway between the aortic arch and tracheal carina, tracheal carina, midway between the tracheal carina and the right hemi diaphragm, and 1 cm above the right hemi diaphragm. No IV contrast was administered. All images were reconstructed using a high-spatial-resolution algorithm and displayed at standard (level -700, width 1,500) and narrow (level -700, width 1,000) lung window settings.

Inspiratory images were read before expiratory ones and images displayed at standard windows before narrow window settings. The inspiratory images were assessed for the presence of bronchiectasis according to previously established CT criteria.[8-10] The mosaic parenchymal pattern was defined as areas of heterogeneous lung attenuation in a lobular or multilobular distribution in expiratory phase.[11]

The HRCT scans were reviewed by two radiologists and two pulmonologists. A quick read form was developed by the group's consensus for ease of reporting. The only data available to the HRCT reviewers were patient's age, sex and history of exposure to SM. The interobserver agreement for air trapping, bronchiectasis and mosaic parenchymal attenuation were .76 (95% CI: 0.58-0.94), .84 (95% CI: 0.69-0.99) and 68% (95 % CI: 0.48-0.88) respectively.

The expiratory images were also assessed for the presence and lobar distribution of air trapping. The criteria used to diagnose the presence of air trapping were alteration of normal antero - posterior lobar attenuation gradients and/or lack of homogeneous increase in lung attenuation resulting in persistent areas of decreased attenuation.[12] The extent of air trapping was quantified and classified using the same system as defined for hyperlucent regions on inspiratory images, considering that limited air trapping has been reported in normal individuals [12]. Presence of air trapping was considered indicative of BO only if it exceeded 25% of the cross-sectional area of an affected lung on at least one scan level. Expiratory images displayed at standard and narrow window settings were directly compared to determine differences in the conspicuity of air trapping.

To determine the overall frequency of each lesion and prevalent lobar involvement, we analyzed HRCT findings based on type and the number of lesions in total number of lobes in 50 patients. We based total number of lobes in all patients at 250 as we did not have any patient with missing lobe secondary to trauma or surgery. The numbers of each lesion was then counted in lobes involved and a percentage was given in reference to the total number of lobes (involved and uninvolved) in each group of lesions.

Statistical Analysis

Data were analyzed using SPSS software. Analyses were done descriptively and numbers (percentage) were used in text and tables to illustrate the data.

HRCT Finding	No (%)
1- Air Trapping	38 (76%)
2- Bronchiectasis	37 (74%)
3- Mosaic Parenchymal Attenuation (Expiratory)	36 (72%)
4- Dilated Irregular Trachea and Major Airways	33 (66%)
5- Secondary Lobule Abnormalities	13 (26%)

Table 1: Chest HRCT findings in fifty patients fifteen years after documented exposure to sulfur mustard.

HRCT Findings	Lobes number (%)						
	Patient/Lobes	RUL	ML	RLL	LUL	LLL	Total (%) Lesions
Bronchiectasis	37/185	37(100%)	9 (24%)	37 (100%)	35 (95%)	33 (89%)	151 (82%)
Air Trapping	38/190	23 (61%)	6 (16%)	36 (95%)	21 (55%)	38 (100%)	124 (65%)
Mosaic Parenchymal Attenuation	36/180	13 (36%)	3 (8%)	15 (42%)	14 (39%)	36 (100%)	81 (45%)
Secondary Lobule Abnormalities	13/65	13 (100%)	0	7 (54%)	10 (77%)	12 (92%)	42 (65%)
Total lobes	-	86	18	95	80	119	-

Table 2: Distribution of specific lesions in involved lobes of patients fifteen years after exposure to sulfur mustard.

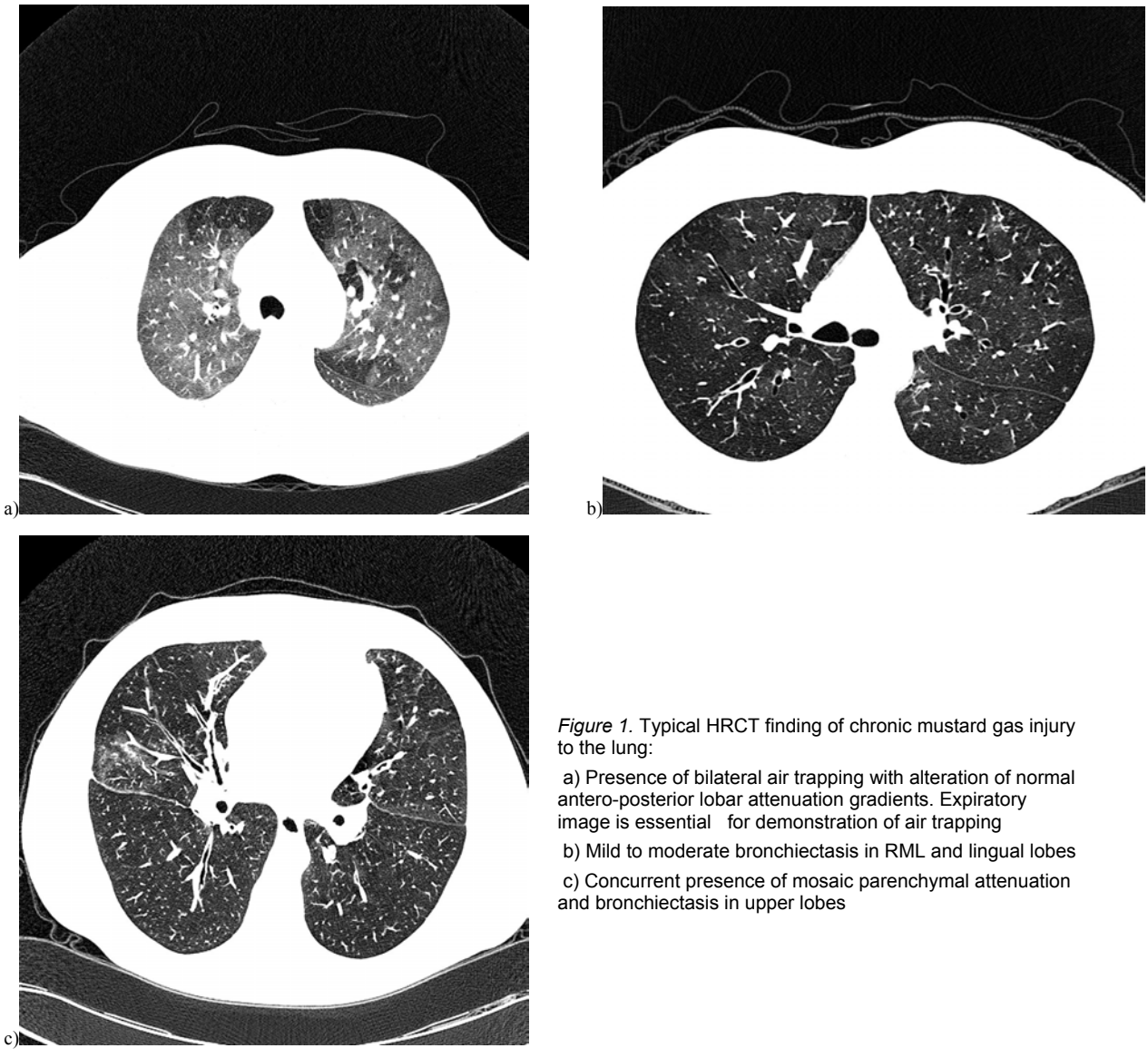

Figure 1. Typical HRCT finding of chronic mustard gas injury to the lung:

a) Presence of bilateral air trapping with alteration of normal antero-posterior lobar attenuation gradients. Expiratory image is essential for demonstration of air trapping

b) Mild to moderate bronchiectasis in RML and lingual lobes

c) Concurrent presence of mosaic parenchymal attenuation and bronchiectasis in upper lobes

Results

Between March 2002 and July 2002, fifty patients with varying levels of SM exposure and respiratory symptoms had one chest HRCT each.

They were predominantly Caucasian males, 45 (90%) with age range and mean of 16-63 and 37.4 years

Respiratory symptoms of varying intensity were present in all patients. Prior to exposure to SM pulmonary problems such as asthma, bronchiectasis, cystic fibrosis or occupational lung diseases were not reported by any of the patients. Twelve (22%) patients had history of smoking three to five pack year. Post exposure majority had to give up smoking secondary to pulmonary symptoms.

Cough with varying degrees of sputum production in 45 (90%), shortness of breath in 49 (98%) and chest tightness and labored breathing in 40 (80%) were the main symptoms reported by the patients.

Postero-anterior and lateral chest roentgenograms were normal in 28 (56%) patients. Increased radiolucency and major airway abnormalities were present in 22 (44%) patients. There was no evidence of hyperinflation or bolus lung disease.

Forty nine patients (98%) had abnormal chest HRCT findings. Air trapping, bronchiectasis and decreased parenchymal attenuation with perfusion redistribution in expiration were most frequently encountered abnormalities. Findings are summarized in table 2.

Discussion

Visualization of pulmonary lobular anatomy is determined by the size of the structures being imaged and the resolving capacity of the imaging modality. Because the fourth-generation segmental bronchi are the smallest units that can be seen with chest radiography, this modality plays a limited role in the evaluation of small airway diseases. HRCT offers greatly improved resolution over chest radiography and conventional CT, detecting pulmonary lobular structures as small as 0.2 mm. bronchiolar visibility is determined primarily by wall thickness.[13, 14] The normal lobular terminal bronchiole wall measuring approximately 0.1 mm is beyond the resolving capabilities of HRCT.[15, 16] Because the vasculature is not air filled, interlobular arteries measuring 0.2 mm in diameter are routinely seen with HRCT[17]. Peripheral veins measuring 0.5 mm also are usually visible, although the peripheral interlobular septa measuring 0.1 mm in thickness are usually too small to be resolved with HRCT. Although an occasional peripheral septal line is seen on HRCT, the visualization of numerous clearly defined interlobular septa is abnormal. The only structures of the secondary pulmonary lobule that can be seen routinely with HRCT are the central interlobular arteries and peripheral veins.[15, 16]

Chest CT scans obtained during a suspended full expiration are now used to detect bronchiolitis obliterans. In a report on a 65-year-old woman with cryptogenic bronchiolitis obliterans, the CT scan showed normal findings during full inspiration but showed multiple, focal, lobule-sized areas of lucency -findings consistent with extensive lobular air trapping - during a suspended full expiration.[18]

Mosaic perfusion results when perfusion is decreased in areas of bronchiolar obstruction and flow is redistributed to normal areas. Another finding, best observed on CT scans obtained during expiration, is air trapping, which results from partial airway obstruction due to the constrictive bronchiolitis. Many patients with this disorder have only one of these findings.

Bronchiolitis refers to an inflammatory disease primarily involving the terminal and respiratory bronchioles, but in some cases, extending to the adjacent alveolar ducts and alveolar spaces.[19, 20]

The histological appearance of bronchiolitis includes an inflammatory (cellular) bronchiolitis, constrictive bronchiolitis obliterans, or a proliferative bronchiolitis.[21,22] Known causes of bronchiolitis include toxic fume inhalation, tobacco smoke, mineral dust inhalation, penicillamine, collagen vascular diseases, and infections.[23-27] Bone marrow, heart-lung, and lung transplantation have also been associated with this complication.[28,29] Clinically apparent infectious bronchiolitis is generally considered to be a pediatric disease, rarely being recognized in adults.[30]

Thousands of Iranians who were exposed to SM died during the early days of chemical attacks. A very large number of survivors have gradually passed away.

Our study showed that the most frequent complications following SM exposure; are obliterating bronchiolitis (BO) and bronchiectasis and the last complication may be related to long standing bronchiolitis. Based on past history, present medical records and physical examination data the only agent that could be related to outbreak of BO is exposure to chemical warfare agent. Other causes of BO are not compatible with clinical situation of these patients. To our knowledge this study opens a small window in dark area of management of these patients. Although definite determining of disease need further studies such as exact pathologic

definition and molecular aspects of disease but radiological aspects of this disease will provide good clues for further researches.

Prior to deployment to the battle fields Iranian troops had to undergo a brief and intense military training which was preceded by a short medical history and clinical examination. Those with history of respiratory and/or cardiac problems were excluded from the force, although we are aware that the screening criteria at the time of crisis could have been less than perfect. Majority of our study patients were in their mid to late teens at the time of exposure to SM and had no history of pulmonary problems. Smoking did not appear to have played any major role in this population as the average age of patients at the time of exposure (22.5 years) to SM and marked reduction in smoking after exposure have minimized tobacco impact in this disease process.

Exposure to deadly chemical agents both due to industrial accidents or use of such agents as weapon of war, has resulted in tremendous pain and suffering to humanity. Painful death, devastating acute and chronic physical consequences and deep seated psychological impact of lowering humanity and human value to that of a pest, are only a few compelling arguments to make all possible efforts to implement the conventional treaties enforcing a complete ban on production of CWA and destruction of all existing stockpiles of such weapons. As it appears humanity has got a very long way ahead of it to achieve these goals, therefore it is of paramount importance to the medical science to equip itself with knowledge and technology to understand ill effects of these agents on the body to help its victims in the best possible manner.

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