

Reflux esophagitis in war-related sulfur mustard lung disease

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Abstract

Background: Sulfur mustard (SM) has acute and chronic effects on skin and mucosal surfaces. The aim of the study was to evaluate the frequency of esophagitis in a historical cohort of veterans who had been exposed to SM in Iran-Iraq war nearly 25 years ago.

Methods: One hundred two veterans with dyspepsia and/or heartburn underwent esophago-gastro-duodenoscopy. Of them, 52 cases had been exposed to SM and had chronic mustard lung disease. Controls included 50 veterans without SM exposure. Esophagitis was defined according to standard criteria.

Results: 81.6% of cases and 70.6% of controls had heart burn and/or regurgitation ($p=0.224$). Esophagitis was seen in 40% of cases and 26.5% of controls ($p=0.155$).

Conclusion: Based on our findings, SM exposure seems not to be associated with increased esophagitis.

Keywords: Sulfur mustard, Esophagitis, Gastroesophageal reflux.

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Introduction

Sulfur mustard (SM) is an alkylating agent that was used as a chemical weapon in wars including World War I and Iran-Iraq War (1980 – 1988). Acute SM exposure causes skin and mucosal injuries. Symptoms include skin blister, rhinorrhea, cough, dyspnea, eye pain and redness, anorexia, nausea and vomiting. In addition, SM causes chronic sequelae in upper and lower respiratory tracts, eyes and hematologic elements among others; the best recognized is bronchiolitis obliterans (BO) of the lung (1-3).

Gastroesophageal reflux disease (GERD)

is defined as troublesome symptoms or complications which develop from reflux of stomach contents to the esophagus. Typical symptoms include heartburn and regurgitation; other symptoms may be chest pain, cough, hoarseness, bitter taste in mouth, etc. Complications of GERD are stricture, Barrett's epithelium and adenocarcinoma of esophagus (4-6).

GERD is among the most common disorders seen by primary care physicians and also by gastroenterologists (4,7,8). Its prevalence is reported between 10-40% and is increasing in recent decades in both developed and developing countries (7-11).

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Presumptive diagnosis of GERD can be done by typical history of heartburn and/or regurgitation. Esophagogastroduodenoscopy (EGD) is only required when alarm symptoms is present or in screening of high risk patients such as older males with chronic GERD symptoms (4, 7, 8).

Association of GERD and pulmonary diseases such as asthma, cystic fibrosis, and idiopathic pulmonary fibrosis has been reported (12-16). Most importantly, GERD has been linked to BO, lung failure and decreased survival in the lung transplant recipients (17).

Ghanei et al. reported increased frequency of esophageal erythema in war-related BO patients (18). This finding is not widely accepted in current classification systems for esophagitis (19, 20). The aim of this study is to assess the frequency of endoscopic esophagitis in SM exposed victims.

Methods

The cases were SM victims from Iran-Iraq war with GERD symptoms and/or dyspepsia, which visited in the Sasan Hospital, a referral center for management of SM casualties in Tehran, from November 2011 to April 2013. All of them had documented exposure to SM nearly 25 years ago in Iraq-Iran War and suffered from chronic mustard lung diseases, mostly BO. Controls were among the same veterans that were not exposed to SM, no history of lung dis-

eases and were referred for EGD for evaluation of their GERD and/or dyspepsia.

Before EGD, demographic data and reflux symptoms were recorded according to the questionnaire used in the only GERD cohort in Iran, Prospective Acid Reflux Study of Iran (PARSI) (9).

Proton pump inhibitors (PPI) and histamine-2 receptor blockers (H2RB) were discontinued for 4 weeks before EGD, if patients took it. Esophagitis was defined according to the Los Angeles classification (Table 1) (19).

The study was approved by the Tehran University of Medical Sciences Ethics committee and informed consent was obtained from the patients.

Statistical methods

Data analysis was done by the SPSS software, version 16.0. Mean and standard deviation (SD) were used for showing the numeric variables and percentages were used for the categorical variables. T-test was used for assessing the relationship between numeric variables with categorical variables. Chi square test was used for assessing the relationships among categorical variables. $p < 0.05$ was considered statistically significant.

Results

Fifty two cases and 50 controls underwent EGD. Mean age for the cases and the

Table 1. Los Angeles endoscopic grading system for esophagitis

Grade A	≥ 1 mucosal breaks confined to folds, ≤ 5 mm
Grade B	≥ 1 mucosal breaks > 5 mm confined to folds but not continuous between tops of mucosal folds
Grade C	Mucosal breaks continuous between tops of two or more mucosal folds but not circumferential
Grade D	Circumferential mucosal break

Table 2. Sulfur mustard (SM) victims and controls data about their gastroesophageal reflux disease

Variable	SM Victims (n=52) percent	Controls (n=50) Percent	p-value
Reflux $\dagger \geq 1$ episode/week	81.6	70.6	0.224
Dysphagia	22	3.9	0.007
Odynophagia	10	17.6	0.007
Vomiting	2	13.7	0.060
PPI use \ddagger	44	24.5	0.113
H2RB use \S	14	22.4	0.113
Smoking	12	33.3	0.01
Esophagitis	40	26.5	0.155

\dagger reflux means heart burn and/or regurgitation, \ddagger PPI means proton pump inhibitor drugs, \S H2RB means histamine 2 receptor blocker drugs

controls were 47.5 ± 5.6 years and 46.8 ± 5 years, respectively. There was no significant difference ($p=0.49$) in age between the two groups. Additionally, educational status was not significantly different between two groups ($p=0.9$).

There was no meaningful difference regarding the frequency of heartburn and regurgitation between the two groups. No difference was also found in the use of PPI and H2RB. Table 2 shows the above mentioned findings in cases and controls.

Forty percent of cases and 26.5% of controls had esophagitis, but this was not statistically significant ($p=0.15$). No significant difference was also detected among the grades of esophagitis (A, B, C, D) ($p=0.276$).

Discussion

Our study didn't show any difference in the frequency of esophagitis between SM victims and controls. Frequency of esophagitis in our cases and controls was also comparable with a previous report of esophagitis in an endoscopy survey in Iran done by Saidi et al. He found a prevalence of 37% for esophagitis compared with 26.5% of our controls and 40% of our cases (21).

Ghanei et al. in a case control study of veterans who had been exposed to SM in Iran-Iraq War showed a prevalence of 70% endoscopic esophagitis as compared to 42.7% of controls without exposure to SM; both cases and controls were veterans with GERD and chronic cough (18). He used a classification that considered erythema or friability as grade 1 of esophagitis and erosion as grade 2.

Currently, only two classification systems are widely accepted worldwide for esophagitis: Savary-Miller and Lose Angeles; both require erosion or mucosal break as the least criteria for esophagitis (19, 20). The difference between cases and controls in Ghanei study was grade 1 patients (62 cases vs. 15 controls); grade 2 or more that requires erosion was not different between the two groups (1 case vs. 2 controls).

As pathological examination of distal esophagus is not useful in diagnosis of GERD and not recommended by current literature, we did not perform it (7, 22).

Conclusion

It appears that SM did not have chronic effect on esophagus and specifically did not increase esophagitis. A larger study is necessary to evaluate the relation of GERD and Mustard lung disease.

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References

1. Kehe K, Szinicz L. Medical aspects of sulphur mustard poisoning. *Toxicology* 2005; 30: 214 (3): 198–209.
2. Ghazanfari T, Faghihzadeh S, Aragizadeh H, Soroush MR, Yaraee R, Mohammad Hassan Z, Foroutan A, Vaez-Mahdavi MR, et al. Sardasht-Iran cohort study of chemical warfare victims: design and methods. *Arch Iran Med.* 2009 Jan; 12(1):5-14.
3. Ghassemi-Broumand M, Aslani J, Emadi SN. Delayed ocular, pulmonary, and cutaneous complications of mustards in patients in the city of Sardasht, Iran. *Cutan Ocul Toxicol.* 2008; 27(4):295-305.
4. Kahrilas PJ. Clinical practice. Gastroesophageal reflux disease. *N Engl J Med.* 2008 Oct 16; 359(16):1700-7.
5. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006; 101: 1900-1920; quiz 1943.
6. Moayyedi P, Talley NJ. Gastro-oesophageal reflux disease. *Lancet* 2006; 367: 2086-2100.
7. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol.* 2013 Mar; 108(3):308-28; quiz 329.
8. Shaheen NJ, Weinberg DS, Denberg TD, Chou R, Qaseem A, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Upper endoscopy for gastroesophageal reflux disease: best practice advice from the clinical guidelines committee of the American College of Physi-

- cians. *Ann Intern Med.* 2012 Dec 4; 157(11):808-16.
9. Nasser-Moghaddam S, Razjouyan H, Alimohamadi SM, Mamarabadi M, Ghotbi MH, Mostajabi P, Sohrabpour AA, Sotoudeh M, Abedi B, Mofid A, Nouraei M, Tofangchiha S, Malekzadeh R. Prospective Acid Reflux Study of Iran (PARSI): methodology and study design. *BMC Gastroenterol.* 2007 Nov 20; 7:42.
10. Camilleri M, Dubois D, Coulie B, et al. Prevalence and socioeconomic impact of functional gastrointestinal disorders in the United States: results from the US Upper Gastrointestinal Study. *Clin Gastroenterol Hepatol.* 2005; 3:543-52.
11. Festi D, Scafoli E, Baldi F, Vestito A, Pasqui F, Di Biase AR, Colecchia A. Body weight, lifestyle, dietary habits and gastroesophageal reflux disease. *World J Gastroenterol.* 2009 Apr 14; 15(14):1690-701.
12. Belcher JR. The pulmonary complications of dysphagia. *Thorax.* 1949; 4:44.
13. Davis MV. Evolving concepts regarding hiatal hernia and gastroesophageal reflux. *Ann Thorac Surg.* 1969; 7:120.
14. Pearson JE, Wilson RS. Diffuse pulmonary fibrosis and hiatus hernia. *Thorax.* 1971; 26:300.
15. Mays EE, Dubois JJ, Hamilton GB. Pulmonary fibrosis associated with tracheobronchial aspiration. A study of the frequency of hiatal hernia and gastroesophageal reflux in interstitial pulmonary fibrosis of obscure etiology. *Chest.* 1976; 69:512.
16. Tobin RW, Pope CE 2nd, Pellegrini CA, Emond MJ, Sillery J, Raghu G. Increased prevalence of gastroesophageal reflux in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med.* 1998; 158:1804.
17. Davis CS, Gagermeier J, Dilling D, Alex C, Lowery E, Kovacs EJ, Love RB, Fisichella PM. A review of the potential applications and controversies of non-invasive testing for biomarkers of aspiration in the lung transplant population. *Clin Transplant.* 2010 May-Jun; 24(3):E54-61.
18. Ghanei M, Khedmat H, Mardi F, Hosseini A. Distal esophagitis in patients with mustard-gas induced chronic cough. *Dis Esophagus.* 2006; 19(4):285-8.
19. Lundell LR, Dent J, Bennett JR et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999; 45: 172 – 80.
20. Ollyo JB, Lang F, Fontollet C, Monnier P: Savary-Miller's new endoscopic grading of reflux-oesophagitis: A simple, reproducible, logical, complete and useful classification. *Gastroenterology.* 1990; 98: A100.
21. Saidi F, Malekzadeh R, Sotoudeh M, Derakhshan MH, Farahvash MJ, Yazdanbod A, Merat S, Mikaeli J, R Sotoudehmanesh, Nasser-Moghadam S, Majidpour A, Arshi S, Abedi-Ardakani B, Yoonessi A, Sadr F, Sepehr A, Fleischer D, Fahimi S. Endoscopic esophageal cancer survey in the western part of the Caspian Littoral. *Dis Esophagus.* 2002; 15(3):214-8.
22. Takubo K, Honma N, Aryal G et al. Is there a set of histologic changes that are invariably reflux associated? *Arch Pathol Lab Med* 2005; 129: 159-63.