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REVIEW ARTICLE

The systemic nature of mustard lung: Comparison with COPD patients

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ABSTRACT

Sulphur mustard (SM) is a powerful blister-causing alkylating chemical warfare agent used by Iraqi forces against Iran. One of the known complications of mustard gas inhalation is mustard lung which is discussed as a phenotype of chronic obstructive pulmonary disease (COPD). In this complication, there are clinical symptoms close to COPD with common etiologies, such as in smokers. Based on information gradually obtained by conducting the studies on mustard lung patients, systemic symptoms along with pulmonary disorders have attracted the attention of researchers. Changes in serum levels of inflammatory markers, such as C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), nuclear factor κB (NF-κB), matrix metalloproteinases (MMPs), interleukin (IL), chemokines, selectins, immunoglobulins, and signs of imbalance in oxidant-antioxidant system at serum level, present the systemic changes in these patients. In addition to these, reports of extra-pulmonary complications, such as osteoporosis and cardiovascular disease are also presented. In this study, the chance of developing the systemic nature of this lung disease have been followed on using the comparative study of changes in the mentioned markers in mustard lung and COPD patients at stable phases and the mechanisms of pathogenesis and phenomena, such as airway remodeling in these patients.

KEY WORDS: sulphur mustard; mustard lung; COPD; systemic inflammations; chronic respiratory disease

Introduction

The sulphur mustard (SM) or mustard gas is a strong alkylating and vesicant chemical warfare agent that has been deployed by Iraqi troops against Iran (Evison *et al.*, 2002; Paromov *et al.*, 2007; Moin *et al.*, 2009). The former toxicity with this vesicant agent has caused serious disability in more than 34 000 Iranian veterans whose various organs have been affected by this agent (Khateri *et al.*, 2003). The toxicity with SM is followed by short-term and long-term side effects in different tissues (Heidari *et al.*, 2016; Rahmani *et al.*, 2016; Sheikhi & Rahmani, 2016). The humid tissues, such as eye and respiratory system, can be further affected by SM (Ghasemi *et al.*, 2008; Pourfarzam *et al.*, 2009a) and several side effects are involved. Previous studies showed that the respiratory deficiencies are the most prevalent long-term disorders among persons poisoned with SM (Khateri *et al.*, 2003; Pourfarzam *et al.*, 2009a). The victims are complaining from several respiratory symptoms, including coughing, sputum, bloody sputum, and chest pain (Weinberger *et al.*, 2011). The prevalent disorders in the lower part of the respiratory system in SM-exposed patients are as follows: airway obstructive disease, bronchiectasis, and pulmonary fibrosis (Balali-Mood *et al.*, 2011). In humans, inhaling SM causes acute and chronic pulmonary impairment (Emad & Rezaian, 1999; Hefazi *et al.*, 2005; Ghanei *et al.*, 2008; Ekstrand-Hammarstrom *et al.*, 2011). Mustard lung (ML) is a unique form of chronic obstructive pulmonary disease (COPD) that has been proposed as one of the foremost long-term expressions for SM and it is implied that systemic inflammation may involve the pathogenesis of this form of COPD (Lari *et al.*, 2012). Cellular and molecular structural changes in the airway wall under the concept of airway remodeling are one of the major pathological consequences in ML-patients and the clinical picture is similar to what is seen in COPD patients. The remodeling process in ML patients with three signs of bronchial epithelial damage, subepithelial fibrosis, and angiogenesis and thus aberrant repair in airways in response to the damage and inflammation is reported (Figure 1). In chronic conditions, the inflammatory cells are infiltrated and along with epithelial damaged cells of the airways leading to the secretion of different

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inflammatory mediators, including inflammatory, fibrogenic, and angiogenic factors and after remodeling the induction, they present severe inflammatory conditions (Firoozabadi *et al.*, 2017). It has been mentioned in review studies that inflammatory responses and structural changes in the airways may be due to epigenetic changes caused by SM, so that the epigenetic codes to express the pro-inflammatory proteins in the immune and epithelial cells are changed. These changes may include increasing or decreasing methylation of CpG islands, histone modifications, long noncoding RNA expression, and chromosome remodeling (Ghasemi *et al.*, 2008; Imani *et al.*, 2015).

Both cellular and hormonal disorders have been reported following poisoning with mustard gas (Krumbhaar & Krumbhaar, 1919; Dayhimi *et al.*, 1988; Zandieh *et al.*, 1990; Ghotbi & Hassan, 2002). There is also the possibility for the presence of systemic effects caused by mustard gas in ML-patients. Studies of these patients have shown that immunity and inflammatory

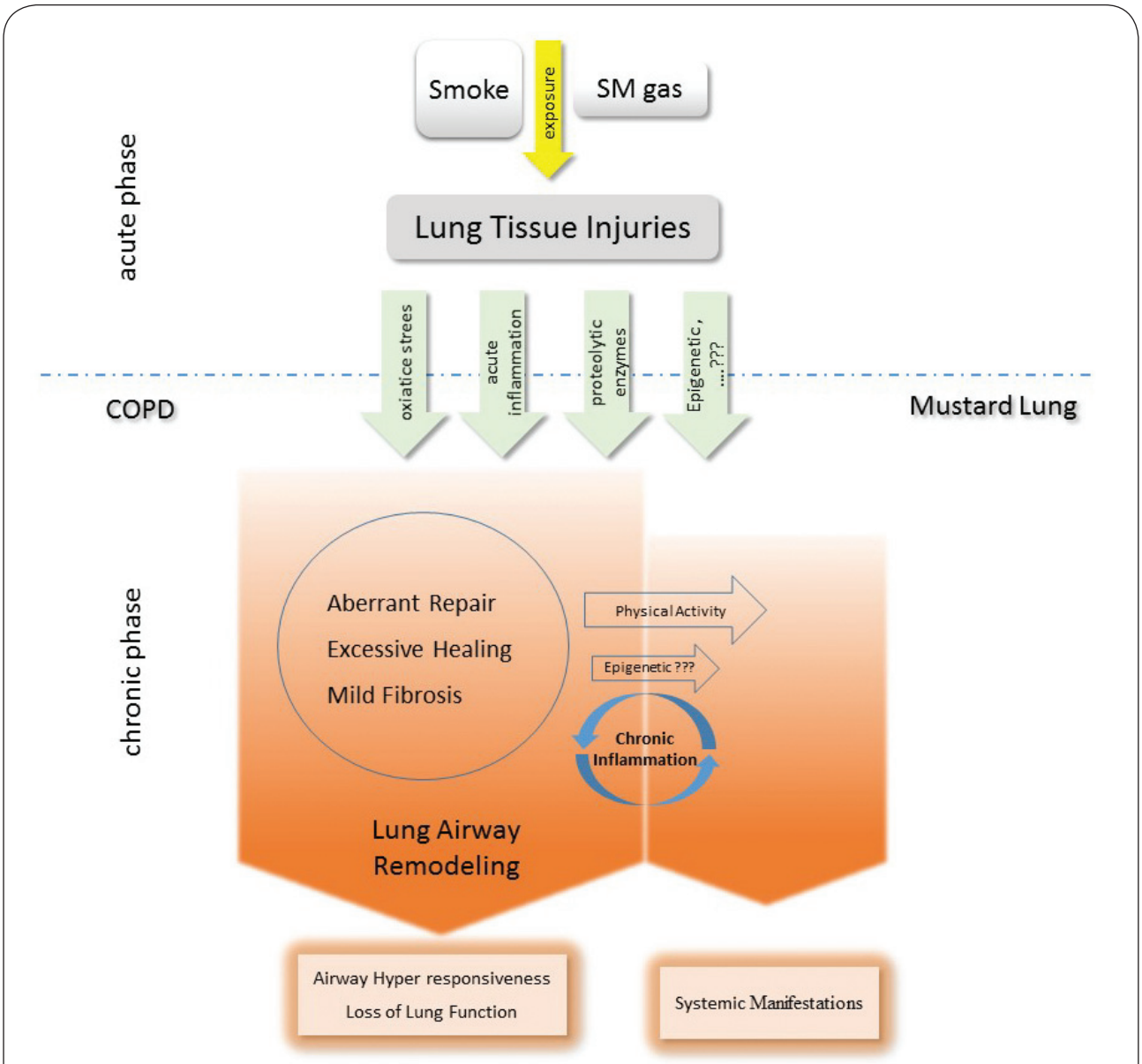

Figure 1. Old SM inhalation in ML patients as exposure to smoking in COPD patients regardless the length of exposure time is followed by acute lung epithelial tissue damage and activates pathogenesis pathways of patients. The prevalence of oxidant, proteolytic, and inflammatory conditions deteriorates the airway and gradually chronic phase conditions develop over the years. However, SM potential in creating epigenetic changes or its other unknown mechanisms can exacerbate this trend. In the course of time, aberrant repair of the airway and the lack of proper repair of epithelial cover, the creation of fibrosis and vascularity with varying degrees form the remodeling phenomenon in the airway of these patients and could also lead to the excessive airway response and the loss of lung function. By making this change, the formed airways and complications are converted into severe chronic inflammation and along with the reduced physical activity in these patients, the area presents systemic responses and extra-pulmonary complications develop.

reactions might have been involved in the morbidity of longterm effects caused by mustard gas at systemic level (Imani *et al.*, 2015). The inflammatory mechanisms form the major part of the pathogenesis of topical processes in pulmonary disorders due to SM (Mahmoudi *et al.*, 2005; Ghanei & Harandi, 2007). At the same time, studies of these patients showed systemic pathogenetc processes, such as rising function of hemocytes (neutrophils, etc.) (Shahriary *et al.*, 2015) and variation at serum level of proinflammatory mediators, including interleukins (ILs), tumor necrosis factor (TNF), chemokines, C-reactive protein (CRP), fibrinogen, etc., as well as other important markers in systemic variations distorting oxidant and antioxidant balance, with this finding visible also in ML-patients (Naghii, 2002). Similarly, emerging extra pulmonary complications (e.g. osteoporosis and cardiovascular diseases), implied in similar chronic pulmonary diseases, such as COPD as systemic effects of disease may be assumed as a further reason for the presence of important systemic variations in ML-patients (Bayat & Aslani, 2010; Karbasi-Afshar *et al.*, 2013). This evidence (Figure 1) draws the attention of researchers to the systemic nature of disease and with respect to similar manifestations in these patients to the pathology of COPD (Ekstrand-Hammarstrom *et al.*, 2011). The multitude of reports about the subject of systemic inflammation and other systemic variations in COPD-patients (Schunemann *et al.*, 2000; Biskobing, 2002; Schols, 2002), are motivating evidence to follow the theory of the presence of systemic manifestation in ML-patients (Shahriary *et al.*, 2017; Shahriary & Rahmani, 2017).

According to the definition proposed by the European Respiration Society (ERS), COPD is a disease that is characterized by restriction of airflow and narrowing of airways and it is an irreversible process (Geddes *et al.*, 2005). Based on the report of the World Health Organization (WHO), there are 80 million patients with (COPD) in the world (Voll-Aanerud *et al.*, 2008). The environmental and genetic factors involved in the morbidity of COPD include smoking and inhalation of the resulting smoke, air pollution, old age, occupational agents, and antitrypsin alpha-1 deficiency (Zakerimoghadam *et al.*, 2011). Patients with COPD suffer from much impairment of which one can refer to asthma, intolerance of physical activity, coughing, sputum, and depression (Mirbagher Ajorpaz & Rezaei, 2009). This disease is a complex inflammatory condition with parenchymal and airway impairment. Emphysema and airway inflammation and impairment, the impairment that leads to enlargement of alveolar airway, fibrosis of pathways, elastic irreversibility, and over-enlargement of smooth muscle, goblet cell hyperplasia and mucus plugging are some of the manifestations and side-effects in these patients (Littner, 2011). The widely conducted studies on COPD patients show noticeable cellular and hormonal variations as well as extreme variations in proinflammatory mediators (ILs, TNF, CRP, fibrinogen, etc.), the presence of wide extra pulmonary complications (cardiovascular and osteoporosis), and variations in oxidant- antioxidant system. Many researchers have not only introduced it as a disease with pulmonary symptoms, but also as a pulmonary disease with extensive systemic manifestation (Agusti & Soriano, 2008; Barnes & Celli, 2009).

With view and exploration of various complications caused by mustard gas in ML-patients and on comparing them with what occurs systematically in COPD disease, we attempt to present noticeable documentation on the systemic nature of this disease. In this study, we review the systemic aspects in patients with stable ML, stable COPD, and pay attention to similarities in variation of systemic inflammatory factors for these two chronic pulmonary diseases.

Systemic inflammation and inflammatory factors in pulmonary patients

Many markers are positioned in systemic inflammation among stable COPD-patients and this refers to a remarkable relationship among variations of these markers and complication of the disease in review of various studies (Karadag *et al.*, 2008a). Most of the reports show that inflammatory cytokines play an important role in the pathogenesis of various pulmonary diseases (Vaillant *et al.*, 1996; Chung, 2005; Laskin *et al.*, 2007). Similarly, it has been observed that some of the cytokines may also play a role in primary pulmonary impairments after being exposed to mustard gas, where this important point has been reported *in vitro* and in animal-sample model (Tsuruta *et al.*, 1996; Sabourin *et al.*, 2002). The resulting pulmonary toxicity mechanism from SM is not transparent (Mishra *et al.*, 2012) and typically the precise role of cytokines has not been clearly defined in short-term and long-term effects of mustard gas (Yaraee *et al.*, 2013). Despite the fact that no accurate role of mediators has been properly identified in COPD patients, most of the documentation have shown that systemic inflammation may directly be related to some complications, such as cachexia, disordered function of skeletal muscles, depression, osteoporosis, etc. (Nussbaumer-Ochsner & Rabe, 2011). To examine systemic inflammation in patients with COPD, it is necessary to identify inflammatory factors. Some of these factors have been further noticed in the following, along with expression of variations which are introduced in patients with stable ML and stable COPD (Figure 1, Tables 1 and 2).

CRP

One of the important factors in systemic inflammation studied and assessed in stable COPD patients is CRP. CRP is a plasma protein sensitive to inflammation in humans (Kony *et al.*, 2004) that is included in the group of pentraxin molecules and its gene is located in chromosome No. I (Anderson, 2006). CRP has been used only as an inflammatory marker in infections and inflammatory diseases, but recently it has been identified to be followed with the risk of cardiac infarction, angina pectoris, and

coronary sudden death, and it even plays a role in systemic hypertension (Pinto-Plata *et al.*, 2006; Kraus *et al.*, 2007). One of the foremost characteristics of this protein is, unlike other reactants of the inflammatory phase, that CRP serum level remains high for a long time even in the absence of stimulants (Shrivastava *et al.*, 2015). Many studies have been carried out on CRP serum level in patients with COPD during recent years. They show the relationship between CRP serum level as a marker with functional potential of the patient and respiratory distress (Pinto-Plata *et al.*, 2006; Man *et al.*, 2008) as well as a predictor factor in clinical consequence and primary awareness of COPD (Wu *et al.*, 2005; Dahl *et al.*, 2007; Dahl & Nordestgaard, 2009), along with repeated exacerbation of clinical symptoms (Hurst *et al.*, 2006). Widely conducted studies on COPD patients have reported that CRP serum level is significantly higher in COPD patients and it is related to rale and whizzing sounds as well as to the severity of the disease (Higashimoto *et al.*, 2009). Many researchers including Karadag et al. (Karadag *et al.*, 2008b) have shown that the CRP serum level is increased not only in exacerbated patients but also in patients with stable COPD. The researcher has also analyzed this protein in ML-patients and the results have shown that the serum level of this inflammatory factor has been increased even in stable patients. Purfarzam declared that the CRP serum level is noticeably high in ML-patients and it is significantly related to rale and whizzing sounds. In his investigation, he divided ML-patient into hospitalized and non-hospitalized groups and showed that the CRP level was high in stable patients rather than the hospitalized patients (Pourfarzam *et al.*, 2009b). Similarly, Attaran et al. (Attaran *et al.*, 2009) found a significant difference in high-sensitivity C-reactive protein (HS-CRP) serum level in ML-patients and implied that it is related to exacerbation of the disease in these patients and thus the level of this factor might act as a suitable primary awareness for disease exacerbation. Also in this study the CRP serum level was significantly higher in ML-stable patients than in healthy persons (Attaran *et al.*, 2009). In a new study done by Rahmani et al. (Rahmani *et al.*, 2017), CRP serum level was significantly higher in ML-stable patients than in healthy subjects.

There was only a non-compliant report with the aforementioned studies in a paper by Ghasemi et al. (Ghasemi *et al.*, 2009), since non-hospitalized ML-patients have also been compared separately from healthy controls, but the CRP level had no significant variation in their study. Certainly, sampling details for analysis of samples and sensitivity of kits in this study have not been identical with the above mentioned studies and the authors have not implied any reason to explain the lack of variation in

Table 1. Serum inflammatory markers in COPD patient.

Authors	Year	Marker	Design/population	Method	Outcome
Karadag	2008	CRP	Case: patients with stable COPD Control: age- and sex-matched subjects with normal pulmonary function	Case control	Serum CRP was significantly higher in stable COPD patients than in control
Moermans	2011	TNF-alpha	Case: COPD patients, encompassing the whole severity spectrum of the disease Control: matched subjects with normal pulmonary function	Case Control	TNF-alpha was increased significantly in patients with stable - COPD
Lee	2012	NFkb	Case: patients with stable COPD nonsmoker control smoker control;	Case control	Demonstrated that in patients with stable COPD there is increased activity of NFKB
Aldonyte	2004	MMP	The studied group consisted of 20 controls with PiMM AAT, 10 asymptomatic PiZZ AAT individuals and 20 patients with COPD: 10 PiZZ and 10 PiMM AAT cases.	Case control	Serum level of MMP-9 was increased in stable COPD patients
Montaño	2014	MMP	Case: 1- biomass exposure; 2- tobacco smoking Control: Healthy matched subject	Case control	Indicated rising serum level of MMP-9, MMP-7, and MMP-1 in these patients compared to healthy controls
Moraes	2014	IL	Case: patients with stable COPD Control: with normal lung function and no history of smoking	cross-sectional	Serum levels of IL-8 and IL-6 have been reported higher than in healthy controls
Yanbaeva	2009	IL	Case: COPD patients Control: healthy smokers	Case control	Raised plasma levels of IL-6 were demonstrated in COPD patients.
Hammad	2015	IL-1b	Case: COPD patients Control: healthy subject	Case-control	Serum level in Il-1b was also increased in stable- COPD patients
Pinto-Plata	2007	chemokines	Case: COPD patients Control: matched healthy subject	Case-control	Serum levels of chemokines in these patients are higher than in healthy controls
Spruit,	2003	CXCL8	Case: 1-Hospitalized COPD patients 2-Clinically stable COPD patients Control: Healthy elderly subjects	Case Control	Rather than in exacerbated patients, CXCL8 level was increased in stable patients
Schumacher	2005	PSGL-1	COPD patients Smoking volunteers Non-smoking volunteers	Case Control	Level of P-selectin glycoprotein ligand-1was higher in all COPD stable patients than in healthy controls

Table 2. Serum inflammatory markers in Mustard Lung Patient.

Study	Year	Marker	Design/population	Method	Outcome
Attaran *et al.*	2009	CRP	Case: Fifty consecutive SM patients with stable COPD Control: Thirty healthy men	Case control	CRP Increased with significant statistical differences
Ghasemi *et al.*	2009	CRP	Hospitalized Group: severity of problems at the exposure time, victims who had moderate to severe problems at exposure time and were hospitalized Not hospitalized Group: patients who had mild and subclinical problems at exposure time Control Group: included men who were matched with the study group by age	Case Control	There was no significant difference in CRP level
Pourfarzam *et al.*	2009	CRP	Hospitalized Group: based on severity of problems at the time of exposure. Not hospitalized Control : based on severity of problems at the time of exposure. Control Control: unexposed	Case control	CRP Increased with significant statistical differences
Shohrati *et al.*	2013	MMP	Case Group: patients exposed to sulfur mustard gas Control Group: healthy participants	Case control	Serum MMPs in chemically injured showed no significant difference from normal people except for the MMP-9.
Kiani *et al.*		MMP	Normal Group: SM exposed but without lung complications Mild Group: SM-exposed with mild lung complications Severe Group: exposed to SM with severe lung complications	Case control	They don't compare not hospitalized patient with healthy people but MMP-9 in Not Hospitalized group was higher than normal range
Pourfarzam *et al.*		MMP	Hospitalized Group: based on severity of problems at the time of exposure. Not hospitalized Control : based on severity of problems at the time of exposure. Control Control: unexposed	Case control	They do not compare not hospitalized patient with healthy people but MMP-9 in Not Hospitalized group was higher than normal range
Attaran *et al.*	2006	IL	Case Control: chemical warfare veterans with stable COPD. All subjects were nonsmoking males who had validated documentation of sulfur mustard gas exposure and experienced symptoms after sulfur mustard poisoning. Control Group: nonsmoking healthy men with no history of pulmonary or inflammatory diseases.	Case control	serum IL-6 is increased in patients with sulfur mustard
Yaraee *et al.*.	2009	IL	Case Control: SM-exposed individuals Control Group: unexposed participants	Case-control	TNF, IL-1α, IL-1β and IL-1Ra levels were significantly lower in the exposed group than in controls
Pourfarzam *et al.*.	2009	IL	Hospitalized Group: based on severity of problems at the time of exposure. Not hospitalized Control : based on severity of problems at the time of exposure. Control Control: unexposed	Case-control	IL-8 and IL-6 significantly decreased in the SM exposed
Shohrati *et al.*	2014	IL	First Group: SM-exposed patients with mild to moderate pulmonary symptoms Second Group: SM-exposed patients with moderate to severe pulmonary symptoms Control: individuals without any history of lung diseases but with matched age and gender	Case Control	IL 6 was significantly higher than the control group's
Ghazanfari *et al.*	2013	IG	Case Group: male participants from Sardasht who were exposed to SM Control Group: unexposed age matched controls from the unexposed town of Rabat	Case Control	IgM and IgG4 were significantly decreased in the peripheral blood
Mahmudi *et al.*	2005	IG	Case Group: All SM-poisoned veterans in the province of Khorasan, Iran, who had severe clinical complications Control Group: 35 healthy age-matched	Case Control	IgM levels were significantly higher in patients
Hassan *et al.*	2002	IG	Review of old report of SM exposed Patient	Comparison SM patient with normal range reference	IgM, IgG and IgE were significantly higher in patients
Ghazanfari *et al.*	2009	Chemokine	Casec: SM exposed Patient Control: non SM exposed Patient	Case Control	Elevated levels ofMCP-1/CCL2, decreased levels of IL-8/CXCL8 and RANTES/CCL5
Yaraee *et al.*	2009	Selectin	Casec Group: exposed Control Group: non exposed	Case Control	sL-selectin and sP Selectin were significantly lower in SM exposed group, sE-selectin was significantly increased
Parvizpour *et al.*.	2011	NFκB	Case: 189 people of Sardasht sulfur mustard victims Control: 32 people of Rabat civil.	Case Control	NFκB expression level in exposure group was upregulated

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CRP level. What was however reported in most of these studies on stable COPD was that stable ML patients showed an increase in this inflammatory factor.

Tumor necrosis factor-α (TNFα)

TNF-α has been proposed as one of the reaction cytokines at acute phase. It is involved in systemic inflammation (Strieter *et al.*, 1993) and it is also important in the study of systemic inflammation in stable COPD patients (Moermans *et al.*, 2011). The active macrophages are the paramount sources for TNF-α and the primary role of TNF-α is the regulation of immunity cells(Rohani *et al.*, 2010). TNF-α activates neutrophils, macrophages, and epithelial cells and releases matrix metalloproteinase (MMP) from macrophages. It further prevents the synthesis of protein in skeletal muscle and thus plays a role in reducing body mass index (BMI) (Reid *et al.*, 2002; Lehmann *et al.*, 2005). The variations at serum level of this factor are important in stable COPD patients. It was found to be increased significantly in comparison with healthy subjects in many studies, such as the study of Moermans et al. (Moermans *et al.*, 2011) who have implied that this factor was significantly increased in patients with stable-COPD. Likewise, Karadag et al. (Karadag *et al.*, 2008b) have also shown a rising serum level of TNF-α in stable-COPD patients. But studies on ML-patients signified noticeable reduction in this factor. This factor was thus noticeably decreased even in stable ML patients compared to healthy subjects in the study of Yaraee et al. (Yaraee *et al.*, 2009a). In the study of Riahi-Zanjani et al. (Riahi-Zanjani *et al.*, 2014), the serum level of this factor was also significantly lower than in the control group. The rising serum level of TNF-α may be logically justified in the trend of occurrence of systemic inflammation in COPD patients since in most of the studies this factor was noticeably increased. It should be mentioned that TNF-α is produced in macrophages and activation of NF-κB transcription factor may induce emerging of the TNF-α gene (Blackwell & Christman, 1997). Thus since variations in NF-κB may show variations in secretion of TNF-α, NF-κB should be explored in these patients.

NF-κB

NF-κB is a connecting protein to DNA and is proposed as a transcription factor. NF-κB is one of the factors studied in systemic inflammation and it has also been noticed in COPD patients (Imanifooladi *et al.*, 2010). This factor remains non-active in the cytoplasm of cells till they receive the suitable signal for activation. In fact, NF-κB is stimulated and activated in response to cellular stimuli (Fooladi *et al.*, 2012). NF-κB involves various cellular functions and plays an essential role in various biological activities. Among the known functions of NF-κB are regulation of immunity and inflammatory responses, cell division, and apoptosis. It is also necessary in hematopoiesis and in increasing T-, B-, and NK-cells, dendritic cells, macrophages, and neutrophils (Denk *et al.*, 2000; Siebenlist *et al.*, 2005). Similarly, NF-κB plays the role of proinflammatory genes of cytokines, chemokines, immunity receptors, enzymes, and other proinflammatory molecules. Inappropriate function of NF-κB is one of the mechanisms involved in inflammatory diseases (Hayden & Ghosh, 2008; Batra *et al.*, 2011). NF-κB is also important as the basic element in pathologic mechanisms of asthma and other chronic respiratory diseases (Wright & Christman, 2003). NF-κB also induces the production of some of the immunoreceptors, acute phase proteins, Cox-2, INOs, etc. (Blackwell & Christman, 1997). Lee et al. (Lee *et al.*, 2012) demonstrated increased activity of NF-κB in patients with stable COPD. This factor has also been evaluated in ML-patients and in a study that was conducted by Parvizpour et al. (PARVIZPOUR *et al.*, 2011) on SM exposed patients NF-κB was significantly increased. Parvizpour mentioned that the respiratory symptoms caused by SM and variations of spirometry parameters would lead to deficiency in oxygen delivery to tissues and he assumed hypoxia to be one of the reasons for the probable increase of NF-κB. Likewise, there is a positive feedback system between hemocytes and stromal cells, regulated by NF-κB. Since hemocytes are reduced in these patients, this factor may be increased to compensate for shortage of hemocytes (PARVIZPOUR *et al.*, 2011).

Matrix metalloproteinase (MMP)

The studies conducted on stable COPD patients have shown that MMPs might be one of the other important systemic inflammatory mediators in these patients (Aldonyte *et al.*, 2004). MMPs are families of proteolytic enzymes that play a role in digestion of most extracellular matrix compounds and basal membrane tissue and for this reason they are important in physiologic and pathologic processes. MMP-2 and MMP-9 as collagenase enzymes type 4, due to possession of fibronectin triple structure, were able to connect and digest collagen, the most important composition of the basement membrane (Egeblad & Werb, 2002; Visse & Nagase, 2003). The level of MMP-9 is low in normal lungs, but this level has been reported to be high in some diseases, including asthma, idiopathic pulmonary fibrosis, and COPD. MMP-1 is also a type of MMPs that can lead to loss of fibril collagens. In general, the expression of MMP1 is very low under normal conditions, but its cab is overexpressed in alveolar epithelial cells (Fukuda *et al.*, 1998; Foronjy *et al.*, 2003; Kim *et al.*, 2004).

In a study conducted by Aldonyte et al. (Aldonyte *et al.*, 2004) on stable COPD patients, the serum level of MMP-9 was increased. Similarly, the study of Montano (Montano *et al.*, 2014) showed a rising serum level of MMP-9, MMP-7, and MMP-1 in these patients as compared to healthy controls. The conducted researches on ML, such as the study of Shohrati, have shown that the level of MMP-9 was significantly higher in these patients (Shohrati *et*

al., 2014b). Similarly, Kiani reported that serum level of MMP-1 was higher in SM exposed–patients, while the level of activity of MMP-2 was reduced and it was concluded that these variations might play a role in the pathogenesis and viability of pulmonary symptoms in these patients (Kiani *et al.*, 2013). However, these findings are mainly aligned with the recurrence phase of disease and no comparison was done under stable conditions. In another study, Pourfarzam compared hospitalized and non-hospitalized patients and showed that the level of MMP-9 was higher in hospitalized patients (Pourfarzam *et al.*, 2013). In this study, a healthy control group has not been involved for comparison and similarly to the study of Kiani, the severity of the disease (Lung Complications) in exacerbation phase was related to MMP variations.

Regarding the studies of Pourfarzam and Kiani, the mean level of MMP-9 was expressed for stable patients (949 and 1139 ng/ml, respectively) and these values are much higher than the normal range of MMP-9 (Sheu, 2008) (85–332 ng/ml) in healthy persons. These findings comply with the results of studies on COPD patients in such a way that the serum level of MMP-9 in these patients was higher than in other patients under stable conditions.

Interleukins (ILs)

ILs are also important and measurable markers in systemic inflammation analyzed in various pulmonary diseases, including studies on systemic inflammation; these markers have been noticed in stable COPD patients (de Moraes *et al.*, 2014). Of course, concerning ILs in COPD and ML diseases, most of the studies have been carried out on ILs 1, 6, and 8. ILs are cytokines, which are released from leukocytes and other cells (Ishii *et al.*, 2000). The relationship among ILs-1 with variations has been shown at the beginning of some clinical conditions, chronic inflammatory conditions, and also responses in the acute phase. ILs-1α and β are two relevant structural forms to IL-1 attached to 2 types of existing receptors on target cells. IL-1, often along with other cytokines or other mediators, plays a role in developing disease and normal homeostasis. Although IL-1 and TNF are structurally separated from each other and attach to various receptors, they have some relevant functions (Ishii *et al.*, 2000; Sapey *et al.*, 2009). ILs-6 and 8 are produced from mononucleus phagocytic cells, endothelial cells, and fibroblasts and they act in both innate and adaptive immunity. IL-8 is well known for the induction of lipolysis, suppression of TNFα, and stimulation for producing cortisol (Irwin *et al.*, 2002; Lai *et al.*, 2012). IL-6 has been proposed as a primary main mediator in inflammatory response of the host to infection and its concentration reaches the maximum level immediately after bacteremia. Under such conditions, CRP concentration is increased within a few hours. IL-6 plays an essential role in induction of CRP production in the liver (Procianoy & Silveira, 2004; Barnes *et al.*, 2011). A review on conducted studies in stable-COPD patients shows that serum level of these cytokines is increased; for example, in a study by Moraes et al. (de Moraes *et al.*, 2014), serum levels of IL-8 and IL-6 were reported to be higher than in healthy controls. Hammad et al. (Hammad *et al.*, 2015) have also shown that in Il-1b the serum level was also increased in stable-COPD patients. The review of studies on stable ML patients has shown different variations of levels of these ILs. In a study by Attaran et al. (Attaran *et al.*, 2010), serum level of IL-6 in ML patients was significantly higher than in the control group and it was significantly related to the severity of the disease. Similarly, Shohrati (Shohrati *et al.*, 2014a) reported the serum level of IL-6 to be significantly higher in ML patients and assumed this to be relevant to exacerbation of pulmonary symptoms. Also Yaraee et al. (Yaraee *et al.*, 2009a) found that the serum level of IL-1Ra in ML patients was significantly higher than in the control group and even in stable-ML patients. Of course, serum levels of IL-1α and IL-1β were significantly lower than in the control group in their study (Yaraee *et al.*, 2009a); thus these variations signify systemic variations in these patients. These are unexpected and the reason for their reduction is questionable. Yaraee (Yaraee *et al.*, 2009a) expressed disagreement of his findings with other studies. The difference in the conditions of the patients studied in each of the researches and the exclusive focus of Yaraee (Yaraee *et al.*, 2009a) on the history of exposure to SM, while the focus point of other authors was on the presence of pulmonary symptoms along with exposure history, might be a reason for these variations. Similarly, it should be noted that in the studies conducted by Attaran (Attaran *et al.*, 2010) and Shohrati (Shohrati *et al.*, 2014a), ML patients were not separated in terms of hospitalization or not. Also, Shohrati (Shohrati *et al.*, 2014a) considers the difference between his findings and the study of Pourfarzam (Pourfarzam *et al.*, 2009b) to be in the existing different conditions of patients, including exacerbation and stable state, as well as types of diseases (BO or COPD). Variations of ILs in the study of Pourfarzam et al. (Pourfarzam *et al.*, 2009b) is exposed to the same conflict compared to the studies of Shohrati and Attaran (Attaran *et al.*, 2010) since the findings resulting from their studies have shown that serum level of ILs-6 and -8 were significantly lower than in the control group, even in non-hospitalized patients, yet similar to the study of Yaraee et al. (Yaraee *et al.*, 2009a). In this study, the patients were compared with healthy persons separately based on hospitalization and non-hospitalization. Concerning IL-8, in addition to the study of Pourfarzam (Pourfarzam *et al.*, 2009b), in another study by Riahi-Zanjani (Riahi-Zanjani *et al.*, 2014) reduced serum level was observed where these variations have taken place, unlike what is seen in COPD patients. Finally, a new study done by Rahmani et al. (Rahmani *et al.*, 2017) reported the serum level of IL-6 to be significantly higher in ML patients and they designed this study in valuable inclusion and exclusion criteria to reach better results.

Immunoglobulins

Immunoglobulins also play a role in the pathogenesis of several inflammatory pulmonary diseases, including emphysema, asthma, and bronchitis (Chauhan *et al.*, 1990; O'Keeffe *et al.*, 1991; Groot Kormelink *et al.*, 2011) and are considered to be a biomarker in exacerbation of pulmonary diseases. Shalaby et al. (Samaha *et al.*, 2015) showed that IgE level was higher in stable-COPD patients than in healthy controls. Also, among the types of immunoglobulins, IgE, IgG, and IgM were studied in SM-exposed patients and it has been shown that their levels were significantly increased in these patients. Of course, newer clinical findings signify the reversed variations in some factors within different time intervals after exposure. In the study conducted by Ghazanfari et al. (Ghazanfari *et al.*, 2013), ML patients were studied regardless their stable or exacerbate conditions and it was indicated that the levels of IgM and IgG4 were reduced in these patients. However, it has been reflected in the Ghasemi (Ghasemi *et al.*, 2013) study that IgM was increased in ophthalmic, pulmonary, and/or dermal patients exposed to SM. Also, similarly to Ghazanfari (Ghazanfari *et al.*, 2013), in this investigation the stable and exacerbate patients were not separated. Likewise, in a reviewing research to analyze the effects of mustard gas which Hassan (Hassan *et al.*, 2006) conducted during the first year of exposure, it was shown that immunoglobulin IgE, IgG, and IgM levels were increased significantly in these patients. Of course, only percentage and frequency were mentioned in this study, while statistical and significance tests were not conducted. These variations in stable patients were considered to be a very important clue of systemic variations and this is required in conducting similar studies on ML patients with more reliable documented discussion.

Chemokines

Chemokines are a great family related structurally to chemotoxic cytokines and play an important role in the regulation of inflammation and immunity responses (Calderon & Berman, 2005). Some chemokines in COPD and ML patients were noticed in studies on systemic inflammation. Pinto-Plata et al. (Pinto-Plata *et al.*, 2007) showed that serum levels of chemokines in these patients were higher than in healthy controls. Similarly, Spiruit et al. (Spruit *et al.*, 2003) also showed that before exacerbation, CXCL8 level was increased in stable patients. Also the results from studies of Ghazanfari (Ghazanfari *et al.*, 2009) on Iranian veterans and stable ML patients indicated that four chemokines (MCP-1/CCL2, RANTES/CCL5, IL-8/CXCL8, and Fractalkines/CX3CL1) were subjected to variation in serum level in these patients so that the level of MCP-1/CCL2 was significantly increased and levels of IL-8/CXCL8 and RANTES/CCL5 were significantly decreased. Ghazanfari (Ghazanfari *et al.*, 2009) implied that the rising level of MCP-1/CCL2 might be due to anti-inflammatory response and the lower level of IL-8/CXCL8 and RANTES/CCL5 might show differences in pathophysiology and molecular mechanism involved in SM long-term clinical manifestation. In COPD patients, chemokines were lower than other mediators and there were different variations at serum level of the types of chemokines similar to ML patients. Altogether, variations in chemokines show systemic variations; it is thus clear that further research of these factors will open more windows for the researchers of systemic signs and symptoms in pulmonary patients, particularly ML patients.

Soluble L, P and E selectin

Selectins are membrane glycoproteins attached to carbohydrates that are introduced as cell adhesion molecules involved in developing various inflammatory reactions (Ley, 2003). These markers have also been found in COPD and ML. Selectin L, E and P are related to lymphocytes, endothelial and platelets cells, respectively (Yaraee *et al.*, 2009b). The study of Schumacher et al. (Schumacher *et al.*, 2005) reported that the level of P-selectin glycoprotein ligand-1 was higher in all COPD stable patients than in healthy controls. Increased E-selectin was also reported in COPD patients in the study of Aldonyte et al. (Aldonyte *et al.*, 2004). Selectins have been investigated in ML-patients as well. The studies conducted by Yaraee (Yaraee *et al.*, 2009b) reported increased serum levels of E-selectin in patients with SM complications and the level of L&P-selectin was decreased in these patients. Similarly to the variation in other cytokines, selectin expression patterns may show suppression of acute inflammation in SM-exposed patients as compared to healthy controls. This different pattern may play a vital role in regulation of the immunity system in these patients. Of course, these studies were conducted on COPD patients though they should be carried out on ML-patients more widely with more documentation and the involved cells should be identified more accurately.

Oxidant-antioxidant variations in ML and COPD patients

Many studies have shown the relationship among antioxidants, pulmonary function, and progress of COPD (Schwartz & WEISS, 1990,1994) and some other studies have also shown that consuming vitamins and fruits may be accompanied with forced expiratory volume in 1 second (FEV1) and reduced COPD symptoms (Strachan *et al.*, 1991; Miedema *et al.*, 1993; Tabak *et al.*, 1998). A review of conducted studies on COPD patients shows that similar mechanisms involving oxidative stress and pulmonary inflammation may be considered as reasons for many COPD systemic effects (Wouters *et al.*, 2002; Langen *et al.*, 2003).

There is homeostasis between oxidants and antioxidants in healthy persons with normal respiratory system (Sies & Stahl, 1995). Increase in the concentration of

oxidants or reduction in antioxidants may distort this homeostasis and lead to a condition called oxidative stress. It seems that oxidative stress plays an important role in the pathogenesis of pulmonary diseases through direct impairment or involvement of efficient molecular mechanisms in pulmonary inflammation (Adamson & Bowden, 1974). Some of these studies have shown rising oxidant loading that was followed by increase in oxidative stress markers in alveoli, blood, and urine of smokers and patients with pulmonary diseases (Adamson & Bowden, 1974; Sies & Stahl, 1995; MacNee, 2005). The antioxidant system against free radicals may be divided into enzymatic and non-enzymatic parts. Metallo-enzyme of superoxide dismutase is the first natural antioxidant against toxicity of free radicals. There is an extracellular type of superoxide dismutase where the major activity of this enzyme occurs in plasma, lymph, and synovial fluid (Comhair *et al.*, 2000). Some studies reported that extracellular superoxide dismutase enzyme was increased in response to oxidative stresses in various pulmonary diseases (Levitt *et al.*, 2003). Although the pathological basis of acute and chronic effects of mustard gas is still unknown on pulmonary tissue, studies on animals *in vitro* have shown that mechanism of injury by mustard gas, activation of proteases, and production of free radicals may lead to oxidative stress in the given tissues (Kopff *et al.*, 1993; Husain *et al.*, 1996). With respect to these studies, it has been proved that the released free radicals by neutrophils and macrophages are important mediators in injury of lung tissue (Comhair & Erzurum, 2002). In a study carried out by Shohrati et al. (Shohrati *et al.*, 2009), it was implied that a significant difference was observed in catalase enzyme between two control groups and chemically-injured veterans and this enzyme was at a higher level among ML-patients. Of course, no significant difference was observed between the two groups in superoxide dismutase activity. Similarly, Shohrati (Shohrati *et al.*, 2009) reported in his study that the mean value of extracellular superoxide dismutase varied also in the control group, but it was higher in severe ML-patients and this difference was statistically significant. Yet there was no significant difference between the two groups in terms of mean activity of extracellular superoxidase dismutase. With respect to the findings of Shohrati (Shohrati *et al.*, 2009), extracellular superoxide dismutase may play a role in the progress of inflammation and pulmonary impairments caused by mustard gas.

Extrapulmonary complications in ML and COPD patients

Osteoporosis

Osteoporosis is characterized with decreased density in bone mass and increase in risk of fractures. The main signs of osteoporosis include reduced construction of minerals and bone matrix that contains collagen and non-collagen proteins, while the matrix-mineral ratio remains fixed (Kelley *et al.*, 1997). The relative risk of osteoporosis in patients with COPD is higher than in the general population (Iqbal *et al.*, 1999) and this issue is proposed as an important problem in COPD. In patients with progressive COPD, osteoporosis is prevalent with some symptoms, such as pain, rising dependency, and it is also followed by increase in mortality. The etiology of osteoporosis varies in these patients, including smoking, vitamin D deficiency, and lower body mass index (BMI), hypogonadism sedentary lifestyle, and glucocorticoid drug use (Biskobing, 2002). Some studies have shown that low bone mineral (BMD) in COPD-patients is highly prevalent even in milder stages (Jorgensen & Schwarz, 2008). Likewise, a wide investigation in which 6000 patients with COPD were studied reported that more than half of the patients suffered from osteopenia and/or osteoporosis (Calverley *et al.*, 2007). Similarly, vertebral compression fractures are relatively prevalent in COPD patients and furthermore kyphosis is also observed in these patients, in relation to reduced pulmonary function (Carter *et al.*, 2008). The probability of morbidity of these impairments is very high in COPD patients since it includes many similar backgrounds with etiology of osteoporosis in COPD patients, such as sedentary lifestyle and intake of glucocorticoids. Few studies have been conducted on osteoporosis in these patients. The report presented by Agin et al. (Agin, 2004) shows that osteoporosis in SM-exposed patients cause severe disability in which significant difference was observed in two ML and the control group (with osteoporosis and osteopenia ranges) and most variations (65%) were seen in spine vertebrae. The intensity of involvement was higher in the hipbone (5%) in the ML group. Further studies with reliance on a wider population in stable patients may contribute further to perception of variations in ML patients at systemic level in the morbidity of osteoporosis. Yet despite wide studies in COPD patients, this finding has not come to a single result in systemic mechanisms in these patients. A review of studies has shown that morbidity of this impairment keeps still increasing in COPD patients (Graat-Verboom *et al.*, 2009).

Cardiovascular signs and symptoms

Based on epidemiologic findings, reducing FEV1 is solely important as one of the morbidity and mortality markers in cardiovascular diseases (Sin & Man, 2005). It should also be noted that the relevant cardiac failure secondary to coronary vessel athrosclerosis is seen in 20% of COPD patients (Rutten *et al.*, 2005). Similarly, Lahousse et al. (Lahousse *et al.*, 2013) have shown that the main causes of mortality in their COPD patients studied was cardiovascular impairment and heart failure, stroke, sudden (cardiac) death, cardiac arrest, acute myocardial infarction, and chronic ischemic heart disease as mortality causes for 38.3% of their patients. Although the conducted studies on ML-patients have been focused mainly on intrapulmonary complications and also sometimes on some cellular and hormonal factors, based on a few reports about extrapulmonary impairments, cardiovascular complications are considered a noticeable factor

in deterioration of the status of ML patients and of their rising morbidities and even mortalities (Rohani *et al.*, 2010). In a control case study, Rohani et al. (Rohani *et al.*, 2010) reported that exercise stress test has been positively significant in SM-patients since the group of patients were categorized in coronary arteries diseases. Similarly, there was left ventricular (VV) diastolic abnormality in 23% of patients and generally the conclusion resulting from the study signifies that cardiovascular complications are assumed to be one of the other long-term impairments in SM-patients (Rohani *et al.*, 2010). Likewise, in a study that was carried out on ML patients as candidates for coronary artery bypass graft (CABG) surgery by Fakhraddin et al. (Fakhraddin *et al.*, 1999), it was implied that physical activity was significantly lower in ML-patients and hypercholesterolemia and sedentary lifestyle were followed by coronary vessel complications in ML-patients. Similarly, Rezaian (Rezaian *et al.*, 2008) also expressed in a study on ML-patients that SM caused exercise capacity constraint in these patients. Karbasi and Afshar (Karbasi-Afshar *et al.*, 2013) also expressed that angiographic variations and cardiovascular diseases are exacerbated in these patients. As mentioned, such studies in COPD patients may also signify the presence of cardiovascular impairment in these patients; this refers to the reduced exercise capacity and ability of patients as well as to increase in cardiovascular diseases within a wider range.

Conclusion

The presented study was carried out to explore the systemic expressions in chemically-injured and pulmonary veterans exposed to mustard gas with inhaling toxicity by single dosage of mustard gas for several years and their comparison with systemic manifestation in COPD patients. As implied in the introduction and other sections of this article, the main objective was systemic variations in stable-phase in these patients where these goals caused many studies to be excluded from the range of this paper since many studies relating to systemic factors have been examined in exacerbate-phase and studies that dealt with these patients at stable-phase play a lesser role among the published articles. Similarly, variations of inflammatory factors have been explored at serum level in this essay, while most of the studies have reviewed these factors and explored the level of these variables in pulmonary fluid. As it has been reviewed in various parts of this article, it was witnessed in stable ML-patients that CRP increases, TNFα decreases, NF-κB raises, MMP-9 and MMP-1 increase, MMP-2 decreases, serum level reduces in IL-1α, and IL-1β, while IL-6 usually increases and IL-8 decreases, IgE, IgG, and IgM increase (and reduction was also seen in IgM and IgG4), MCP-1/CCL2 increases and IL-8/CXCL8 and RANTES/CCL5 reduce, E-selectin increases, and L&P-selectin decreases and deactivation of extracellular superoxidase dismutase enzyme occurs. Exacerbation of disability and skeletal failure along with cardiovascular complications are observed. Systemic variations of these factors have a regular and routine trend in stable COPD patients in various studies where CRP was increased, TNFα increased, NF-κB increased, MMP-1, MMP-7, and MMP-9 increased, IL-6 and Il-6 increased, and IgE IL-1b increased. An increase is seen in chemokines including CXCL8 and selectins, including P-selectin glycoprotein ligand-1. Similarly, increased rates of cardiovascular diseases and osteoporosis were also seen in these patients. In general, all the aforementioned factors presented noticeable variations in this group; however, these variations were accompanied with a more regular and routine trend in COPD patients than in ML-patients, where according to the viewpoint of researchers, such a difference may show different pathophysiology and molecular mechanism involving SM-long term clinical expressions and/or it might be due to different conditions of patients and type of disease (BO or COPD) and/or the fact that variations in factors tend to compensate less the number of hemocytes since it has been reduced with exposure to mustard gas. This difference in results may be due to the difference in samplings and methods.

Conclusively, it is to be noted that with respect to the review of various studies in this article and observation of results regarding various extrapulmonary complications in ML-patients, it seems that the resulting complications from SM gas may create a wider range of disorders in which the involvement of various systems signifies the presence of systemic effects in ML-patients. Considering the fact that the volume of information on the subject is small, more studies should be designed and if the findings of this article are confirmed, then they show the start of a new phase of SM-gas side-effects in ML patients. This phase makes it necessary to apply wider and multifactor therapeutic strategies in these patients. It is therefore suggested to give more transparent answers to systemic ambiguities in ML-patients by conducting extensive studies on the factors reviewed in this investigation.

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