Case report of the successful treatment of lung injury caused by occupational exposure to methyl chloroformate and literature review

Jiayi Zhao, Master candidate[a], Rong Chai, Master candidate[a], Yiping Han, MD[a,*],
Jing Sheng, PhD[b], Chong Bai, MD, PhD[a], Haidong Huang, MD, PhD[a]

Abstract

Background: The treatment of acute lung injuries caused by the inhalation of methyl chloroformate remains a difficult clinical problem, with a poor prognosis and a high mortality.

Case presentation: After inhalation injuries from methyl chloroformate poisoning, bronchoscopy plays an important role in the diagnosis and treatment of patients. A low tidal air volume and earlier application of steroids are also essential for successful treatment. The grading of acute exposure guideline levels (AEGLs) can direct the selection of a therapeutic regimen for patients with methyl chloroformate poisoning.

Conclusions: By analyzing the reported acute methyl chloroformate inhalation poisoning cases in China during 1989 to 2017, this study aims to value occupational protection in production activities, accumulate clinical experiences, and provide guidance for the treatment of such cases in the future.

Abbreviations: AEGL = acute exposure guideline level, CT = computed tomography, i.v. = intravenous, N = neutrophil.

Keywords: bronchoscopy, inhalation lung injury, methyl chloroformate poisoning, occupational exposure

1. Introduction

Methyl chloroformate (ClCOOCH$_3$, methyl chloroformate) is a raw material for pharmaceutical and insecticidal production. It can be used for the preparation of herbicides, fungicides, and Carbendazim, as well as in the manufacture of biochemical weapons.[1] Methyl chloroformate has strong causticity and is an irritant. It reacts with water or vapor, emits heat and releases toxic caustic gases, which can be inhaled via the respiratory tract, ingested through the digestive tract, and absorbed via the skin. Eyes and respiratory mucosa are extremely irritated by these gases, causing mucous membranes or skin burns, severe poisoning, or pulmonary edema.[2] As the supervision of safety production systems has improved, the occupational protection of manufacturing workers has also improved in recent years, and there have only been a few methyl chloroformate inhalation poisoning cases. This article describes the recent and successful treatment of a patient who experienced acute accidental methyl chloroformate inhalation poisoning, as well as the case studies of 6 poisoning patients from 1989 to 2017 in China. The goal of this paper is that the information described here may help improve the clinical understanding of acute methyl chloroformate poisoning.

2. Case report

A 52-year-old female who worked in a chemical plant presented with a chief complaint of an irritating cough after inhaling toxic fumes accidentally, as well as dyspnea with nausea and vomiting for 16 hours. At 6 PM on April 9, 2016, the patient inhaled leaked methyl chloroformate gas following a workplace accident. Then, an irritated cough occurred with a lot of white foam phlegm and systemic discomfort. Once out of the toxic environment, no significant improvement in symptoms, and the cough aggravated, followed by chest tightness, wheezing, dyspnea, nausea, vomiting, and the sensation of pharyngeal infarction. Two hours later, she was sent to the local hospital for emergency observation. She was administered oxygen, antiinflammatory medication, and a cough suppressant, but the symptoms still existed. Because the patient did not have hemoptysis, chest pain, or syncope since onset, she was transferred to our hospital the next day.

2.1. Examinations

Physical examination and investigation included the following findings: T 36.5 °C, blood pressure 133/79 mm Hg, pulse (P) 119/min, respiratory rate (R) 26/min; soft spirit, painful expression, no skin yellowness, mild oral cyanosis, I° tonsil enlargement, no superficial lymph node enlargement, low respiratory sounds, audible phlegm-ringing and wheezing in right lung, no bulge and no abnormal impulse or thrills in the precordial areas, a normal heart border, regular cardiac rhythm, and no pathological murmur at the valve auscultation area. The physical examination of the abdomen, arms and legs, and nervous system showed no abnormalities. Arterial blood gas analysis provided the following findings: pH 7.417, arterial partial pressure of oxygen (PaO_2) 51.5 mm Hg, partial pressure of carbon dioxide (PCO_2) 48.3 mm Hg, HCO_3^- 30.4 mmol/L; white blood cell 12.5×10^9/L, neutrophil (N) 76.1%, red blood test 4.16×10^{12}/L, PLT 252×10^9/L, hemoglobin 127 g/L, creatinine 58 μmol/L, normal liver function test, PCT 0.092 ng/mL, C-reactive protein 2.45 mg/L, D-dimer 0.52 μg/mL, B-type natriuretic peptide 72.9 pg/mL, and troponin 0.012 ng/mL. The computed tomography (CT) showed scattered multiple lobular solid changes with patchy effusion in the lungs, which appeared to be an inhaled lung injury (Fig. 1).

2.2. Diagnosis and treatment

The initial diagnoses at hospitalization were acute methyl chloroformate intoxication, acute chemical inhaled lung injury, and type I respiratory failure.

After admission, the patient was subjected to a liquid diet, electrocardiogram monitoring, an oxygen mask, fluid volume recording, electrolyte and vital sign monitoring, and other general treatments. The following pharmacotherapy interventions were administered: methylprednisolone 120 mg b.i.d. (intravenous [i.v.], 2 times daily) for edema treatment, merlot-sulbactam sodium 3.75 g q8 h (every 8 hours) and moxifloxacin 0.4 g qd (1 time daily, i.v.) for antiinfection treatment, ambroxol 150 mg q8h (i.v.) to eliminate phlegm, lansoprazole 30 mg q12h (every 12 hours, i.v.) to inhibit gastric acid, and sodium bicarbonate 10 mL plus protease 4000 U q6h (every 6 hours, aerosol inhalation). At the 2nd day after
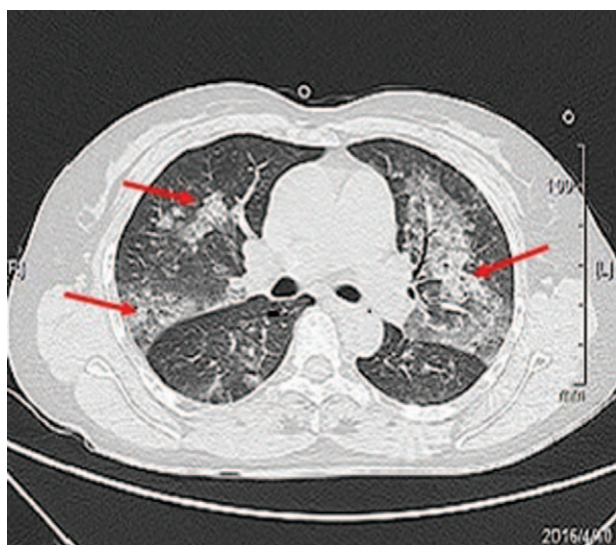

Figure 1. First computed tomography (CT) examination on April 10, 2016 and the red arrows represent the lesion.
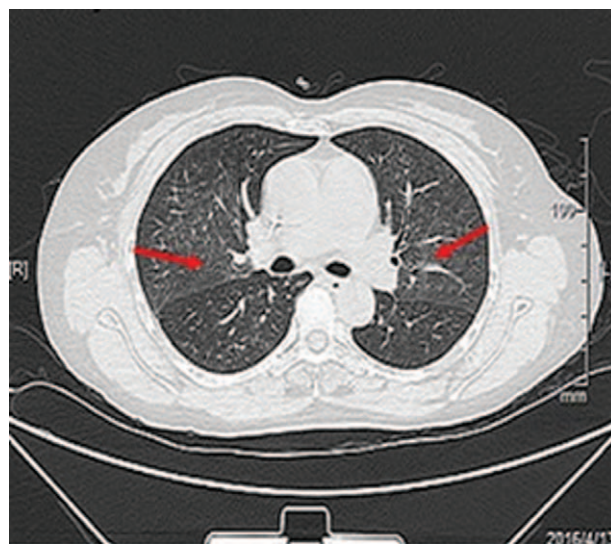

Figure 2. Computed tomography (CT) examination on the 2nd day of hospitalization, on April 13, 2016 and the red arrows represent the lesion.

admission, the chest tightness, shortness of breath, and dyspnea were significantly improved, but there was still a sense of obstruction in the throat. The patient's mental state clearly improved after 1 week of hospitalization without any complaints. The CT scan showed that the 2 lungs held scattered exudate but were significantly improved (Fig. 2). Re-examining the blood gas analysis (nasal tube oxygen 5 L/min) produced the following findings: pH 7.423, PCO_2 45.9 mm Hg, PaO_2 130.7 mm Hg, and HCO_3^- 29.3 mmol/L. Electronic fiberoptic bronchoscopy examination showed pharyngeal follicular hyperplasia, obvious trachea and bronchial mucosa congestion in both lungs, and a little viscous secretion adhered to the surface. The lumen was unobstructed after suction, with no stenosis, bleeding or new organisms, and no congestion edema in the larynx (Fig. 3). Bronchoalveolar lavage was completed on the medial extremity of the right middle lobe. The lavage fluid was colorless and turbid, and the total number of cells was 1100×10^6/L with the following composition (leukocytes 380×10^6/L, Ns 2%, lymphocytes 9%, and macrophages 89%). The bacteria and fungi cultures were negative. The chest CT showed 2 pulmonary scattered exudate areas with dissipation and absorption (Fig. 4). Patient's follow-up at outpatient on March 2017 and CT examination indicated that the heart and lung were in good function without obvious abnormalities (Fig. 5). No abnormality was observed in the electronic bronchoscopy examination (Fig. 6). Patient follow-up was completed in an outpatient setting on October 2017, and the CT examination was then compared to the CT from March 2017 (Fig. 7).

3. Discussion

3.1. Retrieving papers about methyl chloroformate poising

With "methyl chloroformate" as the key word in Wanfang data, the VIP database and Chinese periodical Full-text Data Base (China National Knowledge Infrastructure) were searched to identify papers published before September 30, 2017. In total, 175 papers were retrieved. After reading, 3 papers were identified approximately 6[3–5] methyl chloroformate poisoning cases, plus this one, including 4 males and 3 females (Table 1). With" ([Chinese] OR
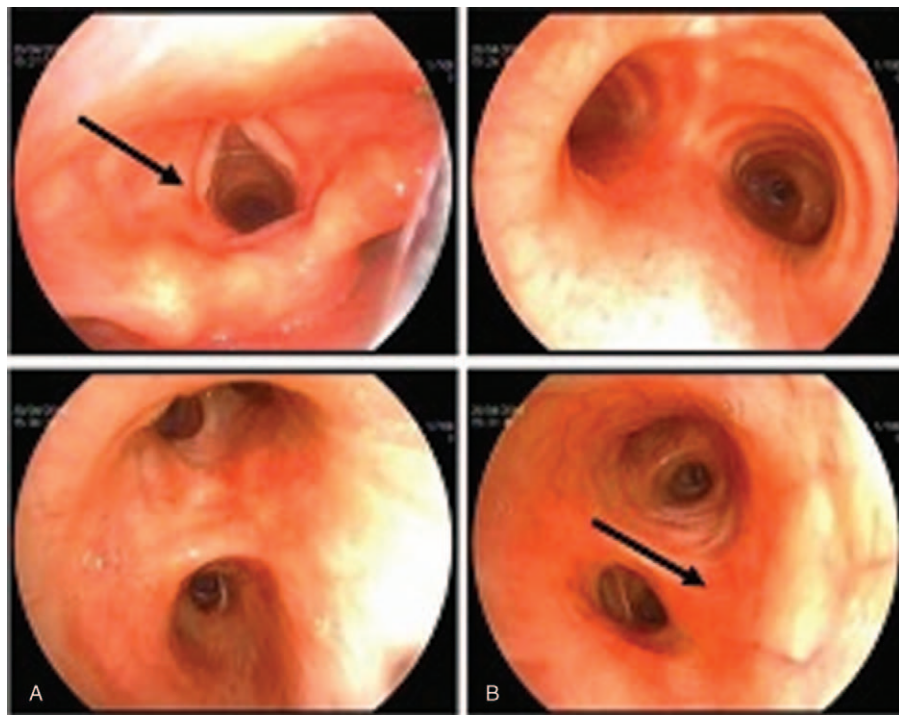
Figure 3. Electronic fiberoptic bronchoscopy examination on April 20, 2016 and the black arrows represent the lesion.

China) AND methyl chloroformate" as the key words in PubMed and Medline, 3 articles were retrieved, but after reading them, none of them truly described cases of methyl chloroformate poising.

3.2. Physical and chemical properties of methyl chloroformate and the mechanism of methyl chloroformate poisoning

Methyl chloroformate is a colorless liquid with a strong irritant odor. Its molecular formula is $ClCOOCH_3$. It is slightly soluble in water and soluble in benzene, methanol, ether, and other organic solvents.[2] For its chemical properties of ester, hydrolysis, fermentation, ammonia solution reaction and the like can occur. When heated it can be decomposed into ethanol, hydrochloric acid, and carbon dioxide.[6] Its physical and chemical properties are detailed in Table 2. After skin and mucosa contact with methyl chloroformate, the main clinical manifestation is the stimulation of the ocular and respiratory tract. Inhaled poisoning can cause pulmonary edema and death.[4] Its mechanism is currently believed to be associated with the aggregation and activation of Ns in the lungs. When an acidic substance is inhaled, some cytokines such as tumor necrosis factor, interleukin-6, and
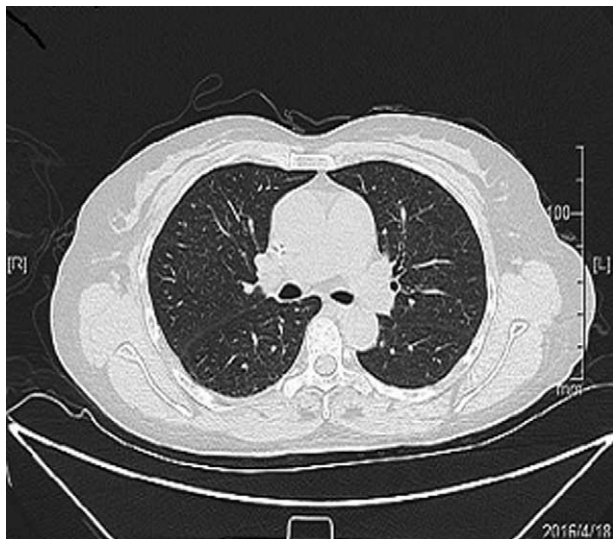

Figure 4. Computed tomography (CT) examination after 1 week of hospitalization, on April 18, 2016.
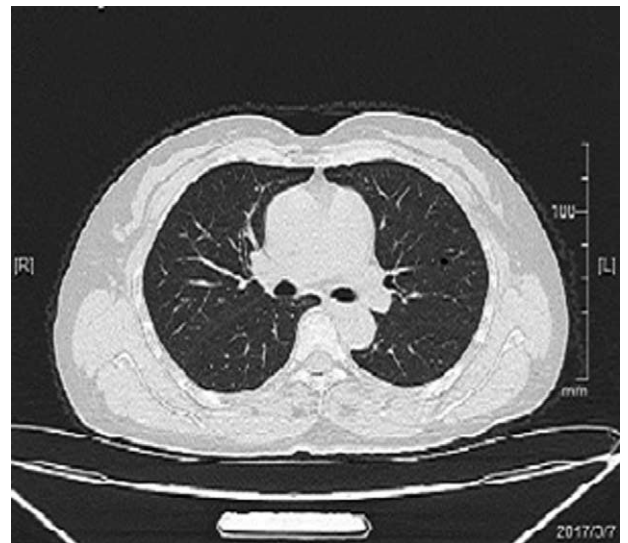

Figure 5. Computed tomography (CT) examination at outpatient on March 7, 2017.

Figure 6. Electronic bronchoscopy examination at outpatient examination on March 7, 2017.

Figure 7. Computed tomography (CT) examination at outpatient examination on September 11, 2017.

interleukin-8 are released.[7,8] These factors trigger the aggregation and activation of Ns in damaged lung tissues, leading to alveolar capillary bleeding and hyperemia, as well as the accumulation of protein infiltrates in the alveoli. These things contribute to pulmonary edema, while edema fluid simultaneously dilutes the endogenous surfactant. As the surfactant is inactivated and its concentration decreases in the alveoli, atelectasis is aggravated.[9]

3.3. The lung is the main injured target of methyl chloroformate poisoning

The 6 reported cases of previous reports, as in this case, were all cough, sputum, dyspnea, etc. as the first symptom. Five patients died from pulmonary edema showed that lung was the main organ suffered from methyl chloroformate poisoning. Some scholars gave the rats methyl chloroformate by static intoxication and found that the main lesions in the lung included the exfoliation of bronchial epithelial cells, edema in the alveolar interstitial area, swelling of the alveolar wall capillary endothelial cells, an increase of pinocytic vesicles, the formation and breakage of vesicles, and the destruction of type I alveolar cells. Twenty-four hours later, when the endothelial cells are damaged to a certain extent, increases of capillary permeability are seen along with the obstruction of microcirculation, which generates increasing capillary pressure. Liquid then extravasates from the blood vessels to give rise to severe pulmonary edema and fibrin deposition through the destruction of the respiratory membrane.[10] Therefore, alveolar septum interstitial edema is considered to be one of the main characteristics of morphological changes of methyl chloroformate poisoning.

3.4. AEGL grading and treatment advances of methyl chloroformate-inhaled toxicity

An acute toxicity test in mice showed that both the exposure time and the inhalation doses are significantly correlated with the severity of the disease (Table 3). A longer exposure time and higher inhaling concentration are associated with a higher lethal rate, which is consistent with the findings of Hoeschst, etc.[6]

America Acute Exposure Guideline Level Committee (acute exposure guideline levels [AEGLs]) divided methyl chloroformate inhalation poisoning into 3 levels according to the inhaling concentrations in the prescribed exposure time[11]: AEGL-1 is exposed to the concentration that may produce obvious discomfort, including irritating or nonspecific symptoms, which are transient and reversible. In this phase, methyl chloroformate symptoms can be alleviated. AEGL-2 refers to the potential for irreversible or other serious, long-term adverse effects that may occur at a higher exposure concentration. AEGL-3 represents an exposure concentration generating life-threatening effects or even death (Table 4).

AEGL grading is beneficial to determine the severity of disease to improve the prognosis of patients by diverse treatment schemes. Combining the successful treatment of this case, we suggest that:

(1) Poisoned patients should be evacuated from the exposure site immediately, and contaminated clothing should be removed as quickly as possible to reduce poisoning and burn injuries.
(2) Oxygen therapy should be given as early as possible; mask oxygen, mechanical ventilation, and hyperbaric oxygen can all help prevent pulmonary edema. It is worth pointing out that low tidal volume ventilation of mechanical ventilation should be emphasized,[12] as the strong corrosivity of methyl chloroformate can lead to the damage of the alveolar wall and lung tissues, impaired pulmonary compliance, and alveolar elasticity. The pressure of the alveolus will be increased for excessive tidal volume and positive pressure ventilation, which is inclined to cause pneumothorax, barotrauma, and even mediastinal emphysema.
(3) The patients' condition should be evaluated fully. Medical personnel should grasp the occasion and indications of tracheotomy accurately, trying best to avoid tracheal

Table 1

Clinical data of 7 patients with acute chloroformate poisoning.

Number	Gender	Occurrence time	Reasons	Poisoning way	Exposure time, min	Cardinal symptoms	Cardinal signs	Imaging manifestation	Laboratory data	Bronchoscopy	Therapeutics	Prognosis	Causes of death
1	Male	January 1983	Unprotected operation	Gas suction	A few minutes	Dyspnea, frothy sputum	Wide-ranging lung rale	–	–	–	General treatment, inhaled oxygen, infusion	Death	Pulmonary edema
2	Female	January 1984	Unprotected operation	Gas suction and skin contamination	–	Cough, cyanosis tachypnea	Lungs rale, especially the left lung	–	ECG: myocardial damage; blood gas analysis: pH 7.29, PaO$_2$ 4.93 kPa, PaCO$_2$ 3.56 kPa, SaO$_2$ 61%	–	Hormone therapy, cardiac, increase BP, inhaled oxygen, symptomatic treatment	Death	Pulmonary edema
3	Male	February 1990	Unprotected operation	Gas suction and skin contamination	5	Shock, obnubilation, tachypnea	Extensive skin burns, moist rale of lungs	–	–	–	Hormone therapy, cardiac, inhaled oxygen, antiinfection, symptomatic treatment	Death	Pulmonary edema
4	Male	December 1990	Unprotected operation	Gas suction	30	Dyspnea, frothy sputum	Coarse breath sounds of lungs	Pulmonary edema	–	–	Hormone, symptomatic treatment	Death	Pulmonary edema
5	Male	June 1995	Unprotected operation, accident	Gas suction	–	–	–	–	–	–	Symptomatic treatment	Death	Pulmonary edema
6	Male	April 2006	Unprotected operation, accident	Gas suction and skin contamination	–	Dyspnea, photophobia, blurred vision	Congestion of right bulbar conjunction and tunica conjunctiva palpebraum	Solid changes of lower lungs, bronchiectasis of lower left bronchus, diffuse hyalinization of lungs	Routine blood test: WBC 18.5 × 10^9/L, N 88.4% RBC 5.57 × 10^{12}/L, Hb 177.8 g/L. Blood gas analysis (oxygen concentration 60%): pH 7.417, PaCO$_2$ 33.5 mmHg, PaO$_2$ 53 mmHg, HCO$_3^-$ 18.8 mmHg/L, SO$_2$ 86%, oxygenation index 88	–	Assisted mechanical ventilation, hormone, anti-infection, symptomatic treatments, CT follow-up	Cure	–
7	Female	April 2016	Unprotected operation	Gas suction	2	Cough, expectoration, dyspnea, nauseated, vomiting	Decreased breath sounds, wheezy phlegm, wheezing sound of right lung	Scattered multiple lobular solid changes with patchy effusion in lungs	Blood gas analysis: pH 7.417, PCO$_2$ 48.3 mmHg, HCO$_3^-$ 30.4 mmol/L; WBC 12.5 × 10^9/L, N 76.1%, RBC 4.16 × 10^{12}/L, PLT 252 × 10^9/L, Hb 127 g/L	Pharyngeal follicular hyperplasia, obvious congestion of trachea and bronchial mucosa in lungs, a little viscous secretion adhered on the surface	Mask oxygen inhalation, hormone, antiinfection, symptomatic treatments, bronchoscopy drainage, CT follow-up	Cure	–

BP = blood pressure, CT = computer tomography, ECG = electrocardiogram, Hb = hemoglobin, N = neutrophil, PaO$_2$ = arterial partial pressure of oxygen, PCO$_2$ = partial pressure of carbon dioxide, PLT = platelet, RBC = red blood cell, SO$_2$ = oxygen saturation, WBC = white blood cell.

Table 2

General chemical and physical properties of chloroformates.

Chloroformate	Molecular weight	Solubility in water	Hydrolysis half-time, min, °C	Hydrolysis products (with CO_2)	Estimated atmospheric half-time	Vapor pressure, mm Hg, °C	Vapor density, g/L (air=1)	Boiling point, °C	Flash point, °C	Flammability limits	
										Lower explosive limit	Upper explosive limit
Methyl chloroformate	93.5	Slightly soluble (hydrolyzes)	20.5 (25)[b]	Methanol, HCL	74 d at 5×10^5 OH, photooxidation	108.5 (25)	3.26	71	12.2	–	6.70%

Table 3

Rat lethal concentration 50% (LC_{50}) values (ppm) for methyl chloroformate and their hydrolysis products.

	1 h		4 h	
	Chloroformate	Alcohol	Chloroformate	Alcohol
Methyl chloroformate	88–123	>145,000	15–52	64,000

Table 4

Standards and guidelines for methyl chloroformate.

Guideline	Exposure duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	4.0 ppm (16 mg/m^3)	2.8 ppm (11 mg/m^3)	2.2 ppm (8.6 mg/m^3)	1.4 ppm (5.5 mg/m^3)	0.70 ppm (2.7 mg/m^3)
AEGL-3	12 ppm (47 mg/m^3)	8.5 ppm (33 mg/m^3)	6.7 ppm (26 mg/m^3)	4.2 ppm (16 mg/m^3)	2.1 ppm (8.2 mg/m^3)

Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects. AEGL = acute exposure guideline level, NR = not recommended.

intubation to prevent aggravating the damage to corrosive airway.

(4) Early, adequate, and short-range glucocorticoids should be used to block the inflammatory reaction effectively and prevent pulmonary edema, as described in Pusa et al.[13]

(5) Early examination of electronic bronchoscopy, when necessary, and alveolar lavage will help evaluate the pathogenetic condition in a timely manner to adopt an individualized comprehensive treatment. Bai et al[14] suggested that bronchoalveolar lavage is beneficial to clear the harmful substances away and improve the ventilatory function of patients. In this case, the patient underwent bronchoscopy examination in a stable condition. On the one hand, the examination helps to identify the degree of damage of the airway mucosa, strengthening the drainage of secretions. On the other hand, alveolar lavage was used for the bacteria assessment, fungal cultures, and drug susceptibility tests to select effective antibiotics to control pulmonary infection. In addition, regular follow-up of bronchoscopy examination is favorable to reduce the incidence of airway scar stenosis caused by long-termed chemical damage.

(6) Chest CTs should be carried out regularly to master the dynamical changes of pulmonary lesions.

4. Conclusions

There is no special antidote for methyl chloroformate poisoning. The basic handling methods include general treatment and symptomatic support. It should be dealt with as early as possible with comprehensive treatment, such as oxygen therapy, glucocorticoid treatment, antibiotics, and the like to control the development of illness.

All 7 cases were exposed to the poison by not taking protective measures during occupational work or not wearing protective tools at the accident scene. It is essential to strengthen the awareness of occupational protection for workers and to provide protective equipment in the manufacturing process (such as goggles, gas masks, latex gloves, protective clothing, etc.). It is also critical to enhance the consciousness of self-protection and the adaptability of contingencies.

Author contributions

All authors contributed to this study.

Treatment of the patient and analyzed the clinical data: Jiayi Zhao, Rong Chai, and Yiping Han.

Provided the pictures of bronchoscopy: Haidong Huang, Chong Bai.

Provided the images of the chest CT: Jing Sheng.

Data curation: Jiayi Zhao, Rong Chai, Yiping Han, Jing Sheng, Chong Bai, Haidong Huang.

Writing – original draft: Jiayi Zhao, Rong Chai.

Conceptualization: Yiping Han.

Funding acquisition: Yiping Han.

Writing – review & editing: Yiping Han.

References

[1] Xie K, Li Z. Methanol and Its Ramification. Beijing: Chemical Industry Press; 2002; 392.

[2] Ren B, Gao R, Zhu LB. Identification and Prevention of Common Occupational Hazard Factors. Qingdao: China Ocean University Press; 2007; 263–264.

[3] Wu J, Su Y, Wu Y. A successful rescue of acute respiratory distress syndrome caused by methyl chloroformate inhalation: a case report. Chin J Emerg Med 2007;16:722.

[4] Zhang YR. Analysis of death causes of 4 cases of acute methyl chloroformate poisoning. Chin J Ind Med 1993;6:28–9.

[5] Sun Z, Yin Y, Yue Z. A death report for methyl chloroformate poisoning. Chin J Forensic Med 1997;12:50.

[6] Levels, C. O. A. E., et al. Acute Exposure Guideline Levels for Selected Airborne Chemicals[M]. Washington (DC): National Academies Press (US), 2016, 20:14-15, 20-38.

[7] Venkatesha SH, Astry B, Nanjundaiah SM, et al. Suppression of autoimmune arthritis by Celastrus-derived Celastrol through modulation of pro-inflammatory chemokines. Bioorg Med Chem 2012;20: 5229–34.

[8] Williams AE, Chambers RC. The mercurial nature of neutrophils: still an enigma in ARDS? Am J Physiol Lung Cell Mol Physiol 2014;306: 217–30.

[9] Feng S, Jia C, Liu Z, et al. Advances in pathogenesis and treatment of severe smoke inhalation injury. Chin J Burns 2016;32:122–5.

[10] Sun Y, Qiu X, Wu G, et al. The effects of porcine pulmonary surfactant on smoke inhalation injury. J Surg Res 2015;198:200–7.

[11] AIHAMethyl Chloroformate Emergency Response Planning Guidelines. Fairfax, VA: American Industrial Hygiene Association, 2006; CAS Reg. No. 79-22-1.

[12] Guo G. Respiratory support and treatment of severe inhalation injury. Chin J Burns 2013;29:134–8.

[13] Pusa T, Sokoowski R, Targowski T, et al. Damage of the lungs after exposure to obscurant smoke-case report. Pol Merkur Lekarski 2015;39:146–8.

[14] Bai C, Huang HD, Yao X, et al. Application of flexible bronchoscopy in inhalation lung injury. Diagn Pathol 2013;8:174.