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Case report

Level of serum IL-33 and emphysema paraseptal in clove cigarette smoker with spontaneous pneumothorax: A case report

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ABSTRACT

A young male clove cigarette smoker experienced spontaneous pneumothorax and later paraseptal emphysema was detected on high-resolution computed tomography (HRCT) scan without respiratory symptoms. Smoking is a known risk factor for emphysema. Paraseptal emphysema is a type of emphysema that rarely causes respiratory symptoms, nevertheless, usually accompanied by spontaneous pneumothorax.

Interleukin 33 (IL-33) is an alarmin cytokine that belongs to the IL-1 family. The effects of IL-33 depend on its structure. In its mature form, it is a cytokine alarmin that binds to ST2 (suppression of tumorigenicity) receptors on the surface of macrophages and innate immune cells to drive Th1/Th2 immune responses, causing oxidative stress, and increased IL-33 production causes polarization of alveolar macrophages to an M2 phenotype.

In this study, long-term exposure to clove cigarette smoke caused an increased serum level of IL-33 (43.72 pg/mL) and paucigranulocytic airway inflammation. In paucigranulocytic inflammation, IL-33 is involved in lung parenchymal damage presumably through oxidative stress, activation of alveolar macrophage and increased MMP12 secretion, resulting in alveolar destruction and airspace enlargement.

1. Introduction

Paraseptal emphysema is characterized by principal involvement of the distal alveoli as well as their ducts and sacs amidst the pleural and interlobular septa surfaces, therefore it is also referred to as distal acinar emphysema [1]. Clinically, paraseptal emphysema is underrecognized because no respiratory manifestation is caused by it. A deeper understanding of the implication of paraseptal emphysema and its effects on pulmonary physiology is still needed. The use of computed tomography (CT) scans, especially high-resolution computed tomography (HRCT) which shows comprehensive evaluation and subtyping, increases the probability of coincidental discovery of paraseptal emphysema [2].

Interleukin (IL)-33 is a cytokine that belongs to the IL-1 superfamily with a dual function. It acts as a cytokine that activates the ST2 receptor and as an intracellular nuclear factor with transcriptional regulation function [3]. IL-33 in its full-length and mature form can bind to the ST2 receptor to produce a pro-inflammatory biological function [4]. The role of IL-33 in inflammation is seen from the intensified recruitment of eosinophils, macrophages, and Th2 lymphocytes. IL-33 also plays a role in worsening of persistent inflammation and respiratory condition with the mediated influx of neutrophils and macrophages. As known before, these cells produce IL-1β, TNFα, and proteases (elastases, metalloproteinases, cathepsins and proteinases), so the effect is IL-33 involvement in the development of emphysema and persistent inflammation of the airways [4].

2. Case presentation

A 29-year-old man was referred from a district hospital with spontaneous pneumothorax. The patient complained of sudden chest pain 1 day before hospitalization, not preceded by coughing, no fever, there was dyspnea on effort. The patient had a history of smoking 16.8 pack-years (filtered clove cigarettes) since 2005. There was no history of asthma and any family history of asthma was also denied. The patient works as a driver in a factory.

From physical examination, the patient was alert with blood pressure 120/75 mmHg, heart rates 84 times/min, respiration rate 22 times/min, axillar temperature 37.2 °C, body weight 55 kg, height 165 cm. Chest examination revealed asymmetrical chest movements, diminished movement in the left side, accompanied by a hyperresonant sound and

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decreased breath sounds. No additional sounds were found on chest examination. Neither edema nor clubbing fingers were found in the extremities.

Laboratory results were hemoglobin 12.8 g/dL, leukocyte 4.55 × 10^3/μL, eosinophil 7.1% (0.30 × 10^3/μL), RBC 4.66 × 10^5/μL, thrombocyte 206 × 10^3/μL, BUN5U/L, serum creatinine 0.68 mg/L, blood glucose 122 mg/dL, anti-HIV (3 methods) non-reactive, AST 27 U/L, ALT 33 U/L, sodium 139 mEq/L, potassium 3.9 mEq/L, chloride 102 mEq/L, HbsAg negative, blood gas analysis with oxygen 6 L per minute (LPM), pH 7.38, $PaCO_2$ 43 mmHg, PaO_2 167 mmHg, HCO_3-25.4 mmol/L, BE 0.3,SaO_2 99%. No parasites were found on fecal examination, total IgE 49.2 IU/mL. Spirometry results were vital capacity (VC) 2370 mL/4320 mL (55%), forced vital capacity (FVC) 2620mL/4320 mL (61%), forced expiratory volume (FEV_1) 2440mL/3700 mL (66%), FEV_1/FVC 2440mL/2620 mL = 93.1%. Serum levels of IL-33 were examined with the Human IL-33 ELISA Kit (Elabscience Biotech Inc. Houston, Texas, USA) and was found to be 43.72 pg/mL. Alpha 1 antitrypsin level: 171 mg/dL (83–199 mg/dL), was examined with the Immunoturbidimetric Assay Quest Diagnostic Nichols Institute method.

Left pneumothorax was seen in chest X-ray (Fig. 1.) and a high-resolution computed tomography (HRCT) taken three days after the chest X-ray revealed paraseptal emphysema in the apical segment of right upper lobe and the apicoposterior segment of the left upper lobe (Fig. 2.)

3. Discussion

In this case, we reported increased levels of serum IL-33 and paucigranulocytic airway inflammation in a patient with spontaneous pneumothorax and paraseptal emphysema who smoke clove cigarettes 16.8 pack-years.

Pulmonary emphysema is defined as a process of chronic obstruction due to changes in the structure of the terminal bronchioles due to dilatation of air space or destruction of the alveoli wall causing loss of lung surface and blood flow, decreased elastic recoil and pulmonary hyperexpansion [5]. Smoking, alpha 1 antitrypsin deficiency, and genetic predisposition are risk factors for emphysema [6]. Morphologically, there are three types of emphysema: centriacinar (centrilobular), pan acinar (panlobular) which is often associated with smoking, and paraseptal (distal acinar) which is usually localized in the anterior and posterior segments of the superior lobe and can be a cause of spontaneous pneumothorax in young patients [6]. The role of smoking in the origin of paraseptal emphysema is not as clear as in the other types of emphysema. However, it has been reported in the literature that paraseptal emphysema cases were found mostly in smokers [2]. We reported a similar finding, in this case, a young man who smoked 16.8 pack-years clove cigarette presented with left spontaneous pneumothorax and an HRCT evaluation revealed paraseptal emphysema of bilateral upper lobes without chronic respiratory symptoms such as shortness of breath.

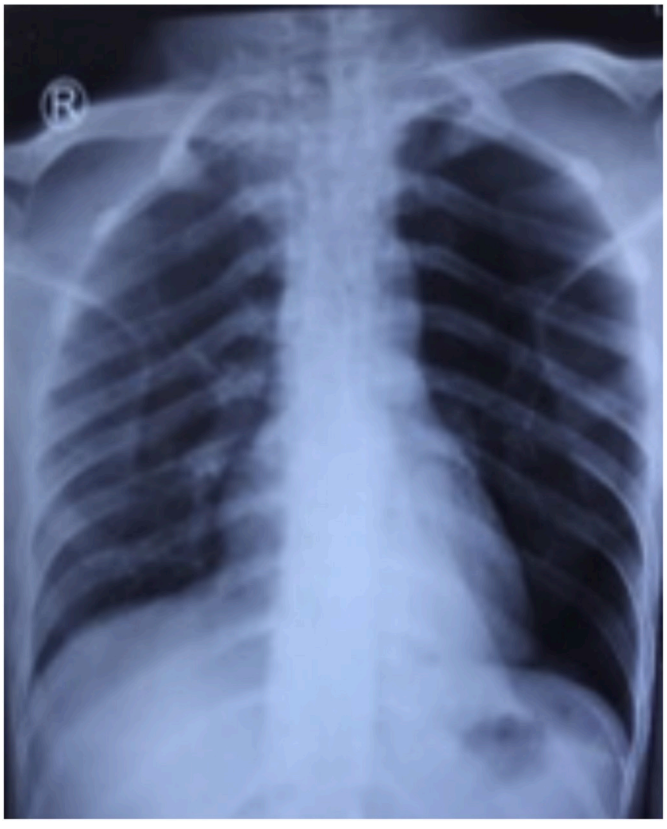

Fig. 1. Left pneumothorax and otherwise normal right lung was seen in chest X-ray.

Exposure to cigarette smoke is a risk factor for emphysema/chronic obstructive pulmonary disease (COPD). Airway inflammation occurs as the result of exposure to cigarette smoke and inflammatory response is amplified by the influence of genetic factors, protease-antiprotease/oxidant-antioxidant imbalance, and cell death [7,8]. Exposure to cigarette smoke has direct and indirect effects on alveoli and bronchial epithelial cells. Besides causing changes in epithelial cell sensitivity to changes in the local microenvironment, acute exposure to cigarette smoke also causes damage to epithelial cells. The most important aspect seen in emphysematous damage is oxidative stress or proteolysis and maintains macrophage activation and infiltration of several other immune cells that cause epithelial damage and cell death [8].

Cloves or kretek cigarettes are mostly manufactured in Indonesia. The main ingredients of clove cigarettes are tobacco and cloves, usually with the ratio of 60–80% of tobacco and 20–40% clove and its oil. Other ingredients such as cumin, cinnamon, and nutmeg are sometimes combined. The smoke of clove cigarette consists of eugenol acetate, which is known to have an anesthetic feature [9]. It is previously thought that this feature masks the smoke irritancy and leads to increased inhalation but some studies confront that opinion. Some studies mentioned that clove cigarettes contain higher levels of nicotine, tar, and carbon monoxide than common cigarettes [10]. An Indonesian study reported nicotine levels ranging from 1.10 to 2.17% w/w, tar levels between 0.05 and 0.175% w/w in 9 brands of filtered clove cigarettes [11]. Cigarette smoke contains more than 7000 different chemical compounds, consisting of carcinogens, toxins, oxidants, and particulate matter. These materials are the result of burning cigarettes. The combustion results can be divided into gaseous and particulate components. The most toxic component is in the particulate phase [12]. From several components of cigarette smoke, it is known that the total number of particulate matter (TPM) inhaled greatly influences the extension and nature of the response to cigarette smoke [13]. Another study mentioned that cigarette smoke-induced inflammation is a role of total particulate matter, where low TPM concentrations activate the xenobiotic mechanism and detoxification while high TPM concentrations drive additional inflammatory responses which potentially triggers tissue damage [14].

IL-33 is a member of the IL-1 superfamily that plays an important role in the induction and modulation of the immune response and has been known to be associated with various inflammatory diseases such as asthma, rheumatoid arthritis, etc. The effect of IL-33 depends on its structure [4]. At baseline, full-length IL-33 is expressed in the nucleus of epithelial cells and functions in transcription regulation. After experiencing a physical trauma, stress and cell death, IL-33 is released from the nucleus and quickly becomes mature and is a potential alarmin that binds to ST2 receptors on the surface of macrophages and some other innate immune cells to cause Th1 and Th2 inflammatory responses [4,15]. In this case, IL-33 serum level was 43.72 pg/mL in a patient with paraseptal emphysema and paucigranulocytic airway inflammation without respiratory symptoms. A wide range of serum IL-33 levels has

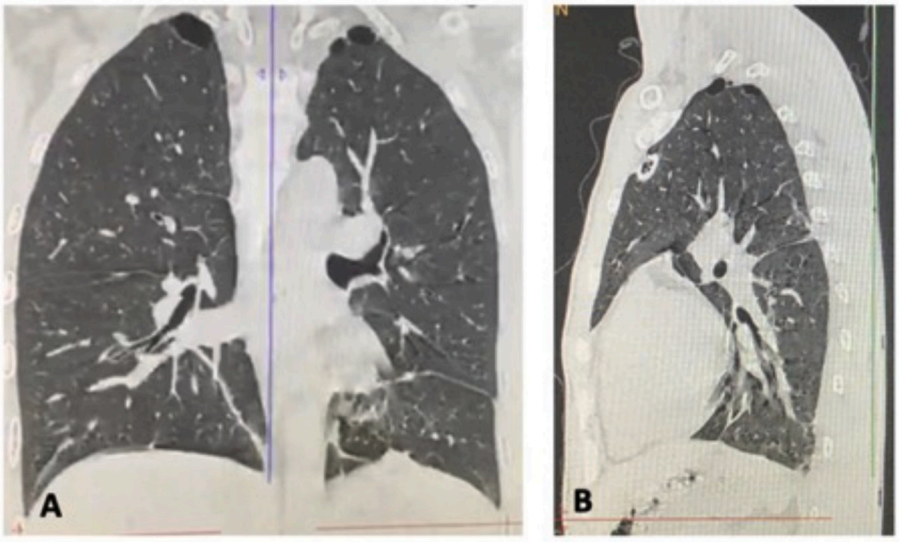

Fig. 2. A. A high-resolution computed tomography (HRCT) taken three days after the chest X-ray (Fig. 1.) revealed paraseptal emphysema in the apical segment of the right upper lobe and the apicoposterior segment of the left upper lobe. B. These abnormalities are shown in the axial plane.

been reported. The median value of serum IL-33 of 11.9 pg/mL was reported by Kim et al. in stable COPD patients, Tworek et al. reported a mean serum IL-33 concentration of 32.86 ± 1.74 pg/mL in COPD patients, and Xia et al. reported a mean serum IL-33 level of 319.24 ± 77.47 pg/mL in COPD patients [16–18]. The serum IL-33 concentration in COPD patients was significantly higher than healthy non-smokers and non-COPD smokers [18].

Paucigranulocytic airway inflammation is an inflammation characterized by normal numbers of eosinophils and neutrophils [19], similar to the characteristics seen in this case. Long-term cigarette smoke exposure leading to oxidative stress as free radical exposure exceeds antioxidant defense capacity. Several methods were used in evaluating the existence of oxidative stress in COPD. Exhaled breath condensate (EBC) is a practical approach for evaluating the output of oxidative stress identified in the lungs [20]. One study has reported that H_2O_2 was markedly increased in EBC of COPD patients compared to healthy controls [21]. The presence of arachidonic acid can be determined at EBC and was found to be heightened at COPD [22]. A Higher level of malondialdehyde (MDA) in the EBC was also seen to be significantly higher in COPD patients compared to normal controls, asthma and bronchiectasis patients [23]. Immunohistological staining can show some oxidative stress products in the cellular units of the lung, for instance, 4-hydroxy-2-nonenal (4HNE), an end product of lipid peroxidation. Indicators of derivational oxidative stress nitrogen such as nitrotyrosine and inducible nitric oxide synthase (iNOS) are known to increase in COPD [24]. IL-33 study with COPD model mice with cigarette smoke exposure by Zou et al. shows IL-33 exacerbates lung injury in COPD mice with increased inflammatory response and oxidative stress [25]. In patients who smoke clove cigarettes with increased IL-33, oxidative stress is thought to play a role in causing lung parenchymal damage.

Macrophages have a very important role in the pathophysiology of COPD [26]. The number of macrophages in the lung tissue and alveolar space of emphysema patients is twenty-five times that in smokers with preserved lung function [27]. Cigarette smoke and other irritants stimulate macrophages to produce inflammatory mediators. Alveolar macrophages also produce elastolytic enzymes (proteases) such as matrix metalloproteinase (MMP)-2, MMP-9, MMP12, cathepsin K, L and S as a result of irritation and infection, and all of these products of macrophages cause lung parenchymal destruction [28]. Increased IL-33 production causes polarization of alveolar macrophages to an M2 phenotype and increased expression of MMP 12 will cause changes in the lungs including inflammation and alveolar airspace enlargement as reported by John et al. in studies with mice [29].

The limitation of this study is the lack of ST2 receptor and MMP 12 (matrix metalloproteinase-12) examination.

4. Conclusion

A patient with a history of clove cigarette smoking was found to have paraseptal emphysema without respiratory complaints after a spontaneous pneumothorax episode. Smoking stimulates airway epithelial cells to secrete IL-33. In paucigranulocytic airway inflammation as in this case, an increase in IL-33 might cause oxidative stress and activation of alveolar macrophages which may result in alveoli destruction and airspace dilation.

Author contributions

All authors made contributions to all of the following [1]: the conception of the case report, acquisition and analysis of data [2], drafting the article or revising it critically for important intellectual content [3], final approval of the version to be submitted.

Declaration of competing interest

There was no conflict of interest in this study. No funding was received for this study. Written informed consent was obtained for publication of this case report.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.rmcr.2020.101133.

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