



Case report

Diffuse alveolar damage and e-cigarettes: Case report and review of literature

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A B S T R A C T

The prevalence of e-cigarette usage has increased in non-smokers and those who are planning to quit smoking since introduced in 2003. Although the potential long term adverse effects have not been studied in humans, there have been studies showing that e-cigarette vapor causes release of proinflammatory cytokines leading to cytotoxic damage to alveolar epithelial cells, increase in the release of fibroblast growth factor (FGF) in the alveolar epithelial cells which leads to fibroblastic proliferation, and increased risk of staphylococcus aureus and viral infections which are implicated in the pathogenesis of diffuse alveolar damage. We describe a case of a 47-year-old woman who was diagnosed with histologically confirmed diffuse alveolar damage (DAD). She had no significant medical history and she had been smoking e-cigarettes for 3 years prior to presentation. This case report describes the potential association between e-cigarettes and diffuse alveolar damage while making reference to relevant associated studies.

1. Introduction

E-cigarette was developed in 2003 and has been used increasingly by smokers planning to quit, non-smokers, and most concerning is its tremendous increase in consumption by teenagers [1]. The main contents of E-cigarettes include propylene glycol or glycerol and flavoring. The Food and Drug Administration found that E-cigarette vapor contains toxic compounds similar to those found in tobacco cigarettes [2], yet they have not been regulated in any way [3]. Previous studies have documented the cytotoxic effects of e-cigarettes on alveolar epithelial cells, increased risk of respiratory infection by staphylococcus aureus, decreased antimicrobial activities of macrophages, and increased release of proinflammatory cytokines, all of which eventually lead to alveolar damage [4–6]. A recent case report published by Agustin et al. found a 33-year old male who was diagnosed with diffuse alveolar hemorrhage induced by vaping [7]. (see Figs. 1–3)

Diffuse Alveolar Damage (DAD) is a histopathological diagnosis that is associated with diffuse alveolar hemorrhage [8] and also commonly found in patients with acute respiratory distress syndrome (ARDS). It can be caused by inhalational injuries, respiratory infections, connective tissue disorders, and medications [9].

2. Case report

We present a case of a 47-year-old woman with a past medical history of actinic keratosis, seborrheic dermatosis, anxiety, deep vein thrombosis, and depression, who presented with a 4-day history of progressively worsening shortness of breath, nasal congestion, fevers, chills, cough, lower extremity swelling, and generalized body aches. There was no history of sick contacts, TB exposure, or recent travel. She was on the following medications: alprazolam, amlodipine, buspirone, clonazepam, dicyclomine, losartan, ondansetron, warfarin, escitalopram oxalate, ibuprofen, methadone, and topical tretinoin.

While in the emergency room, she was unable to maintain adequate oxygenation and required endotracheal intubation. Bilateral crackles and rhonchi were heard on chest examination. Patient was treated empirically with multiple antibiotics. After no significant improvement, she was placed on steroids as well as azathioprine and managed with supportive care. CBC with differential showed a WBC count of 9.97, hemoglobin 9.9, hematocrit 35.8, and platelet count of 266. Blood culture showed no growth. Influenza A and B Antigen and cryptococcal antigen were negative. Bronchoalveolar lavage culture showed no growth and gram stain was negative. Serology for rheumatoid factor was normal and histoplasma antigen was not detected. Electrolytes, blood urea nitrogen, and creatinine were normal. Echocardiogram revealed elevated right ventricular systolic pressure (81–90 mmHg) with

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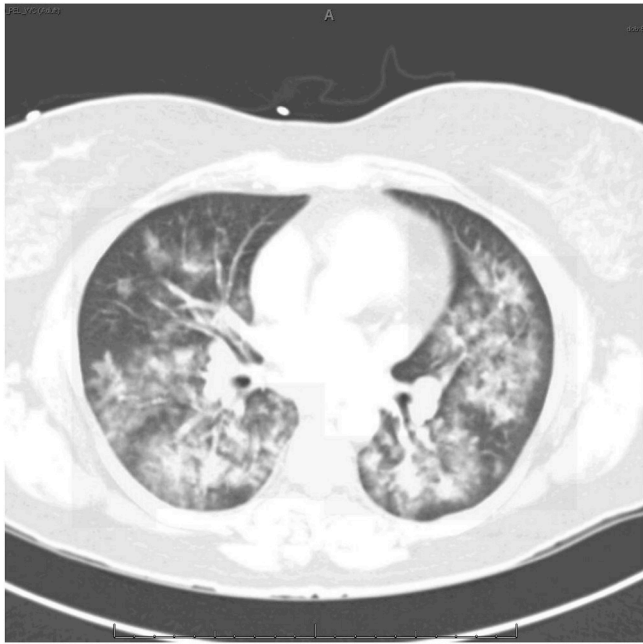


Fig. 1. Computed Tomography (CT) of the chest showing diffuse opacities.

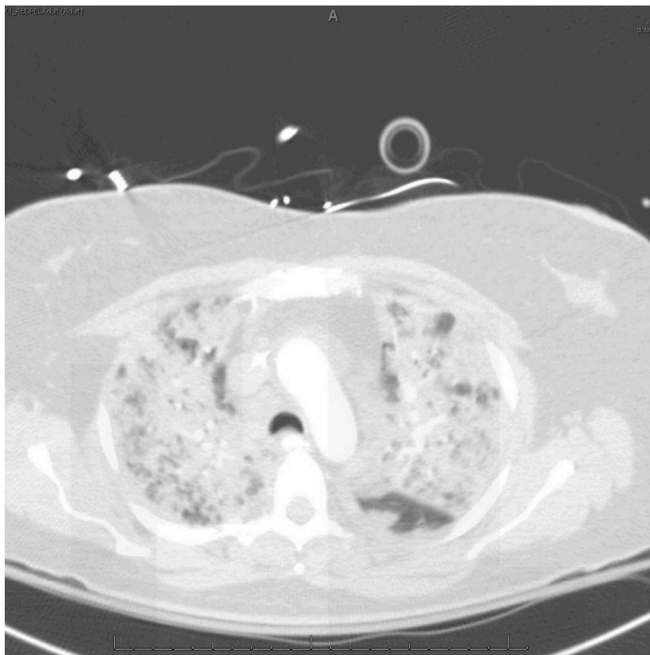


Fig. 2. Computed Tomography (CT) of the chest showing worse features.

subsequent right heart catheterization confirming pulmonary hypertension. Chest CT with contrast revealed bilateral diffuse predominant ground glass attenuation with scattered alveolar opacities of the lungs. Due to clinical deterioration, a repeat chest CT without contrast done 9 days after showed multifocal consolidation in bilateral lungs which had worsened when compared to previous CT. Small trace pleural effusions were present but no pneumothorax.

CT Angiogram pulmonary embolism protocol with contrast was done 5 days after the second chest CT and it showed no filling defect within the pulmonary arterial system to indicate any significant pulmonary embolus but revealed small partial occlusive filling defect in the right internal jugular vein. The heart and pericardium were unremarkable.

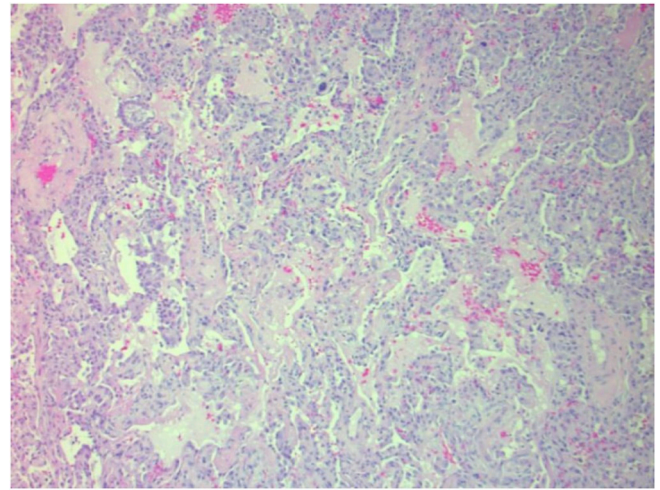


Fig. 3. Histopathologic film showing features of DAD.

Extensive multifocal airspace opacities were seen in the bilateral lungs which worsened compared to the prior exam. These were greater in the bilateral upper lobes.

Due to lack of clinical improvement, a video assisted thoracoscopic surgery (VATS) with biopsy of the right middle and lower lung lobes was performed which revealed a diffuse alveolar septal thickening, due to combination of fibroblastic proliferation and alveolar lining cell hyperplasia. Scattered eosinophilic hyaline membranes were also present and these findings were supportive of diffuse alveolar damage. Several fibrinous thrombi were also noted in the small arteries. No viral inclusions were identified and biopsy cultures showed no growth.

Patient had significant improvement with continued supportive treatment and was discharged 20 days after admission to a long-term care center, advised to stop e-cigarette smoking, and to follow up with the pulmonologist and the primary care physician in the clinic on outpatient basis. Patient adhered to lifestyle modification and clinic visits and a repeat chest CT scan done about 3 months following discharge showed significant improvement in the previously seen infiltrates with complete resolution in the upper lung zones.

3. Discussion

E-cigarette use has tremendously increased over the years in adult smokers and non-smokers with an increase from 1.8% to 13% among ever users of e-cigarette and 0.3%–6.8% among current users from 2010 to 2013 [10]. To date, no longitudinal study has been done on humans to show the toxicity of e-cigarette vapor on the human lung. However, studies have shown different mechanisms by which the compounds in e-cigarette vapor lead to the destruction of alveolar epithelial cells in-vitro. The major component of e-cigarette vapor, propylene glycol, has been shown by in-vitro studies to be 50–70% cytotoxic to A549 alveolar type II epithelial cells [4] which are in vitro model for the human type II alveolar epithelial cells. Another component of e-cigarette is glycerol with a nicotine mixture, this was found to be 99% cytotoxic in a dose-dependent pattern [4]. Moreover, lactate dehydrogenase, a common byproduct of cell death [11], was found elevated in A549 cells exposed to e-cigarette vapor when compared to A549 cell controls exposed to clean air [6], suggestive of cell death.

Interleukin-6 (IL-6), a proinflammatory cytokine that has stimulatory effects on T-cells and B-cells [12], was found to be elevated in a dose dependent pattern after young healthy non-smokers hTBE cells (human tracheobronchial epithelial cells) were exposed to e-cigarette fluid [5]. Furthermore, there was an increase in fibroblast growth factor (FGF) in A549 alveolar epithelial cells, which was also part of the pathogenesis of DAD [6].

E-cigarettes were also found to promote Human Respiratory Viral (HRV) infections by inhibiting innate immunity (SPLUNC1 mRNA expression) in cultured human airway epithelial cells [5]. The results of the study done by Parambil et al. showed that the microbiological analysis of bronchoalveolar lavage (BAL) done on patients histopathologically diagnosed with DAD yielded HRV (respiratory syncytial virus, influenza A and influenza B) in 14% of the patients, and HRV was listed as one of the possible associated risk factors of DAD [9]. Exposure to e-cigarettes also led to a reduction in antibacterial activity of alveolar macrophages, epithelial cells, and neutrophils against staphylococcus aureus [4].

In this patient, the biopsied tissue from the lung showed alveolar septal thickening due to fibroblastic proliferation and alveolar lining hyperplasia. This may be explained by e-cigarette induced FGF stimulation and increase, as observed in the in-vitro studies discussed above. Review of patient's previous medications revealed that none are associated with DAD. She also had no history of connective tissue disorders, nor were any other significant hematologic or rheumatologic disorders found on investigation. Her chest CT resolution after cessation of e-cigarette use at three months after discharge tells a lot about e-cigarette being a possible etiology of the DAD.

4. Conclusion

Diffuse alveolar damage does not occur commonly, but it is a life-threatening condition with a high mortality rate of 43–50% [13]. Given the patient's history of chronic e-cigarette use and the evidence of associated adverse effects as demonstrated by the in-vitro studies described above, there may be an association between e-cigarette use and diffuse alveolar damage. Tobacco smoking was not regarded as harmful when it was first introduced, but studies were able to reveal the causal relationships between tobacco smoking and many diseases. This case report suggests a new avenue of investigation for studies to assess

the long-term effects of e-cigarettes on humans.

Conflicts of interest

We have no conflict of interest to declare.

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