

**[ CASE REPORT ]**

## **Acute Eosinophilic Pneumonia Induced by Switching from Conventional Cigarette Smoking to Heated Tobacco Product Smoking**

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**Abstract:**

Acute eosinophilic pneumonia (AEP) is an acute respiratory illness with diffuse pulmonary infiltrates and pulmonary eosinophilia. While the etiology of AEP remains unclear, a relationship between cigarette smoking and AEP onset has been suggested. The use of heated tobacco products (HTPs) has been growing, but the impact of these products on our health is not fully understood. We herein report a case of AEP that developed after switching from conventional cigarette to HTP smoking. The patient's condition improved after the cessation of HTP smoking and corticosteroid treatment initiation. In cases of AEP, physicians should consider HTPs use as a possible cause.

**Key words:** acute eosinophilic pneumonia, heated tobacco products, asthma, corticosteroid, harmful and potentially harmful compounds

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### **Introduction**

Acute eosinophilic pneumonia (AEP) is an acute respiratory illness characterized by diffuse pulmonary infiltrates and pulmonary eosinophilia. The pathogenesis and etiology of AEP remain poorly understood, but there may be some correlation between the AEP onset and prior inhalational exposure, such as to cigarette smoke (1). Symptoms often develop within a few weeks of the patient starting the inhalational exposure, and patients rapidly respond to systemic glucocorticoid therapy. Spontaneous disease improvement without treatment has been reported (2). Only a small subset of AEP patients have a history of asthma or allergic disease (2).

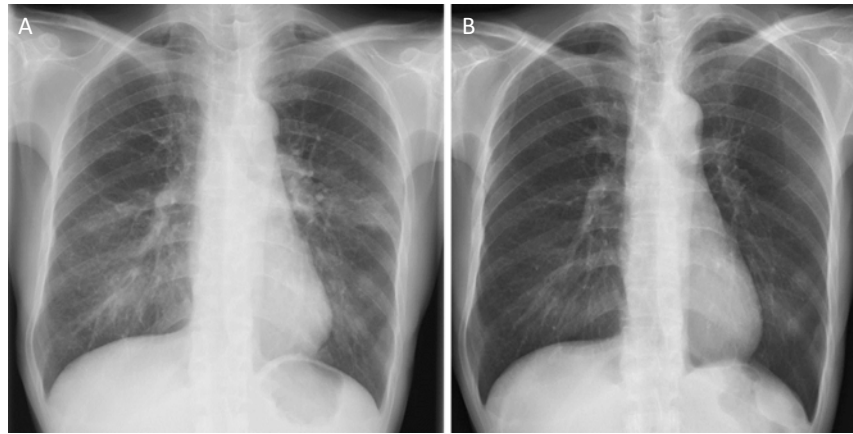
Heated tobacco products (HTPs) are electronic devices that heat processed tobacco to deliver an aerosol with fewer toxicants than those contained in cigarette smoke (3). They were introduced in Japan in 2014 and have gained wide-

spread popularity, while the prevalence of cigarette smoking has declined (4). In a Japanese web-based survey that recruited 8,240 eligible respondents 15–69 years old, the current user rate of HTPs or electronic cigarettes (e-cigarettes) had increased from 1.4% in 2015 to 4.7% in 2017 (4). In a systematic review (5), HTPs are becoming popular among young adults, even in non-smoking groups, despite cultural differences in different continents. While HTPs are categorized as reduced-harm products, the potential impact of HTPs on human health is not yet fully understood (6).

Recently, two case reports suggested an association between AEP onset and HTP smoking (7, 8); however, this number is insufficient to draw any real conclusions. We herein report a case of AEP that developed after switching from conventional cigarette smoking to HTP smoking.

### **Case report**

A 47-year-old woman was referred to the respiratory



**Figure 1.** Chest X-ray on admission showed bilateral infiltrates (A). On day 12 after treatment with oral prednisolone, the bilateral infiltrates had improved (B).



**Figure 2.** Chest CT showed bilateral patchy ground glass opacities with interlobular septal thickening.

clinic of Nagoya City University Hospital because of a cough, low-grade fever, and chest X-ray abnormalities. The patient has been diagnosed with asthma eight months ago in a primary-care clinic. The asthmatic symptoms resolved after treatment was initiated with inhaled corticosteroid (ICS) and a long-acting  $\beta_2$ -agonist (LABA).

Four months before the referral, the patient, who had been a smoker for 27 years, had switched from conventional cigarette smoking to HTP smoking. The patient developed a non-productive cough shortly after starting HTP smoking. Nevertheless, the patient continued smoking HTPs. The cough worsened despite further asthma treatment. The patient then developed a fever and general malaise. Two months before the referral, the patient was found to have an abnormal chest X-ray shadow at a medical checkup. The patient did not undergo a detailed medical examination and chest X-rays were also not taken. As a result, the abnormality was therefore not identified in a timely manner. Two weeks before the referral, chest computed tomography (CT) at the primary-care clinic revealed lung abnormalities, and the patient was referred to our clinic. The patient was not taking any supplements or medications except for an ICS-LABA combination and a leukotriene receptor antagonist.

At presentation, the patient's vital signs were as follows:

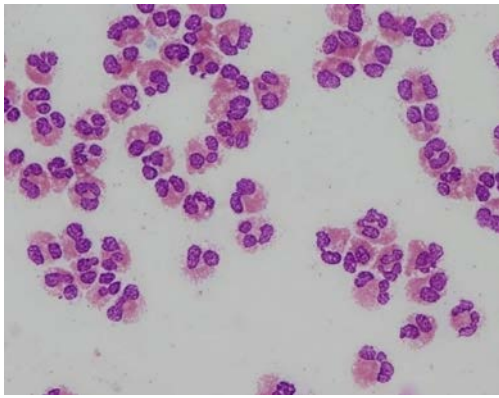
body temperature, 37.3 °C; respiratory rate, 19 breaths/min; oxygen saturation on room air, 96%; and heart rate, 87 beats/min. Expiratory wheezes were heard on lung auscultation. An arterial blood gas analysis on room air revealed a pH of 7.408,  $\text{PaO}_2$  of 76.0 Torr, and  $\text{PaCO}_2$  of 39.5 Torr. The white blood cell count was 7,000/ $\mu\text{L}$ , with 48.5% eosinophils, 23.0% neutrophils, and 22.2% lymphocytes. The C-reactive protein level was slightly elevated to 0.44 mg/dL. The serum immunoglobulin E (IgE) level was 201 IU/mL. Serum specific IgE against aspergillus, anti-parasitic antibody, and anti-myeloperoxidase antibody findings were negative. The exhaled nitric oxide levels were 210 ppb. Spirometry showed a vital capacity of 1.94 L (55.3% predicted), forced expiratory volume in one second ( $\text{FEV}_1$ ) of 1.41 L (50.9% predicted), and an  $\text{FEV}_1/\text{forced vital capacity}$  ratio of 73.1%. Chest X-ray revealed bilateral infiltrates (Fig. 1A), and chest CT showed bilateral patchy ground-glass opacities with interlobular septal thickening (Fig. 2).

Bronchoalveolar lavage (BAL) was performed to establish an accurate diagnosis. In total,  $11.0 \times 10^5/\text{mL}$  cells comprising 72% eosinophils, 22% macrophages, 4% lymphocytes, and 2% neutrophils, were recovered from the BAL fluid (Fig. 3). BAL cultures were negative for cytomegaloviral, fungal, and bacterial pathogens. Based on the modified Phil-lit criteria (9), the patient was diagnosed with AEP. Her respiratory symptoms, chest radiographic abnormalities (Fig. 1B), and vital capacity (60.1% of predicted value) improved after treatment with oral prednisolone 25 mg daily was initiated. No relapse was observed after the cessation of HTP smoking and the initiation of oral corticosteroid treatment.

## Discussion

To our knowledge, this is the first report of AEP potentially induced by switching from conventional cigarette smoking to HTP smoking.

AEP is an acute respiratory illness of varying severity that



**Figure 3.** Bronchoalveolar lavage fluid showed the aggregation of eosinophils.

is characterized by febrile illness, diffuse pulmonary infiltrates, and pulmonary eosinophilia (1). At present, the modified Philit criteria (9) are used to diagnose AEP, as follows: (1) acute respiratory illness of  $\leq 1$  month's duration; (2) pulmonary infiltrates on chest radiography or CT; (3) pulmonary eosinophilia as demonstrated by  $>25\%$  eosinophils in the BAL fluid or eosinophilic pneumonia on a lung biopsy; and (4) the absence of other specific pulmonary eosinophilic diseases, including eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndrome, and allergic bronchopulmonary aspergillosis. The precise cause of AEP is unknown, but identifiable causes include cigarette smoke, medications, and certain infections (9). Most patients with AEP with identifiable causes are current smokers, and changes in smoking habits, such as newly starting smoking, increasing the number of cigarettes smoked, or changing the cigarette brand, can cause AEP (9, 10). Epithelial injury following inhalational exposure is postulated to trigger eosinophilic inflammation by releasing epithelial cytokines, such as IL-33 and thymic stromal lymphopoietin, that initiate type 2 inflammation (9).

Recently, two cases (7, 8) were reported that suggested a correlation between HTP smoking and AEP onset. In the case of a 20-year-old man (7), a rapid increase in daily HTP use 2 weeks before admission was presumed to have caused the AEP, which required oxygen therapy. In the case of a 16-year-old man (8), HTP smoking commencement 2 weeks before hospitalization was presumed to have triggered the AEP, which required respiratory ventilation. In our case, the change from conventional cigarette smoking to HTP smoking was suspected to have triggered the AEP, as the cough, low-grade fever, and chest radiographic abnormalities developed soon after the change in smoking habits. None of the other potential causes of AEP or eosinophilic disorders, including medication, parasitic infections, allergic bronchopulmonary aspergillosis, and eosinophilic granulomatous with polyangiitis, were present in our patient. Consistent with the previous reports, our patient responded to systemic corticosteroid treatment. However, our patient did not present with the respiratory failure that was reported in the previous

two cases. The reason for this is unclear, but continuous ICS treatment for asthma may have reduced the respiratory symptoms in our patient.

No specific single additive or substance in cigarette smoke has been determined to be responsible for causing AEP. HTPs release lower levels of toxic chemicals and harmful substances than conventional cigarettes; however, the toxic compounds are not completely eliminated (11). Five randomized controlled trials showed that switching from conventional cigarettes to HTPs reduced but did not eliminate exposure to harmful and potentially harmful compounds (HPHCs) (3). The levels of several substances, such as propylene glycol, glycidol, acetol, and 2-propen-1-ol, were actually elevated in HTP emissions compared with cigarette smoke (12). HTP users rated HTPs as less satisfying than conventional cigarettes (13) and puffed more frequently than the specified doses, even though the nicotine levels of HTPs are comparable to those in conventional cigarettes (11, 13, 14). There is a lack of evidence that HTPs are indeed less harmful than conventional cigarettes. Further studies are thus needed to clarify the potential effects of HTPs on human health.

E-cigarettes are marketed as harm-reducing tobacco products, but there is a lack of evidence to support this description. A recent randomized clinical trial of e-cigarettes versus nicotine-replacement therapy showed no serious adverse events related to product use in either group (15). However, a recent review (16) described 58 cases of e-cigarette-related respiratory disease, including acute lung injury, organizing pneumonia, eosinophilic pneumonia, and acute respiratory distress syndrome. Among these 58 patients, 1 presented with acute lung injury after switching from conventional cigarettes to e-cigarettes (17). While no single ingredient in e-cigarettes has yet been identified as responsible for respiratory diseases, cannabinoids, nicotine, and the e-liquid constituents are potential causes (16).

We herein report for the first time a case of AEP that developed after switching from conventional cigarette smoking to HTP smoking. Because HTP use has been growing, especially among younger generations (5), physicians should consider HTPs as a possible cause of AEP.

**The authors state that they have no Conflict of Interest (COI).**

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