Waterproofing spray-associated pneumonitis: review of 29 cases and comparisons with acute eosinophilic pneumonia and hypersensitivity pneumonitis

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Abstract

Purpose: Waterproofing spray-associated pneumonitis (WAP) proceeds to acute respiratory failure and is characterized by diffuse bilateral ground-glass opacities on computed tomography. These features are similar to those of acute eosinophilic pneumonia (AEP) and hypersensitivity pneumonitis (HP). This study identified the characteristics of WAP and compared them with those of AEP and HP.

Methods: We conducted a retrospective study of adult patients with WAP, AEP, and HP in Fukui University Hospital from 1990 to 2018. Furthermore, data from patients with WAP were collected from publications in PubMed and the Japan Medical Abstracts Society and combined with data from our patients.

Results: Twenty-nine patients with WAP, eleven patients with AEP, and thirty patients with HP were reviewed. There were no significant differences between the characteristics of WAP and AEP patients, such as age, sex, smoking habit, and laboratory findings. The features of WAP and HP were significantly different. The duration from symptom appearance to hospital visit was shorter in patients with WAP (median 1 day) than in patients with AEP (median 3 days, \( p = 0.003 \)) and HP (median 30 days, \( p < 0.001 \)). The dominant cells in the bronchoalveolar lavage fluid of patients with WAP, AEP, and HP were different (respectively macrophages, eosinophils, and lymphocytes).

Conclusions: It was easy to distinguish between WAP and HP because there were many different features. However, the features of WAP and AEP were similar, making differentiation between those two diseases difficult. To distinguish among WAP, AEP and HP, the speed of disease progression and a bronchoscopic examination are very important.

Introduction

The inhalation of waterproofing spray containing fluororesin causes acute poisoning and
lung injury [1–3], which is referred to as waterproofing spray-associated pneumonitis (WAP) in this report. The Japan Poison Information Center reported that WAP occurs in approximately 68 people per year in Japan [4]. Daubert GP et al. reported the following common clinical findings in twenty retrospectively reviewed cases: shortness of breath (63%), cough (60%), chest pain (44%), wheezing (33%), and rales (23%) [5]. Vernez et al. reported 102 cases of WAP in an outbreak. That study reported that 93% of the affected males and 71% of the females had a smoking habit and that the white blood cell count (WBC) and C-reactive protein (CRP) level were related to the inhaled maximum concentration of the waterproofing spray to which the subjects had been exposed [3]. A review of twenty-five cases indicated that WAP is associated with tobacco smoke exposure, including secondhand smoke, and is characterized by lung edema on computed tomography (CT) scans [1]. However, those reports did not describe the detailed laboratory, radiographic, or histopathologic findings. Furthermore, patients with WAP have acute respiratory symptoms and diffuse bilateral ground-glass opacities on CT [6–8]. These features are similar to those of acute eosinophilic pneumonia (AEP) and hypersensitivity pneumonitis (HP) [9,10]. Therefore, it is sometimes difficult to distinguish among WAP, AEP, and HP. This study was conducted to identify the various characteristics of WAP and to compare the features of WAP with those of AEP and HP.

Methods

Study Design and Setting

We retrospectively studied patients who were hospitalized for WAP in the Respiratory Disease Center of Fukujuni Hospital from April 1990 to March 2018. Furthermore, we collected past reports of WAP patients from PubMed and the Japan Medical Abstracts Society database and reviewed the combined data from those patients and our patients.
Additionally, patients with AEP and HP who were admitted to our hospital during the same period were analyzed. We compared patients with WAP to patients with AEP and summer-type HP. We selected adult patients (age ≥18 years old) with WAP, AEP, and summer-type HP. The data collected included symptoms, laboratory data, radiological findings, and any other relevant data. The serum Krebs von den Lungen–6 (KL–6) level was also collected as part of the laboratory data, and a normal range of serum KL–6 was defined as less than 500 U/mL. The study was approved by the Institutional Review Board of Fukukuji Hospital. It was determined that patient consent was not required. The decisions made by this board are based on and in accordance with the Declaration of Helsinki.

**Definitions**

There are no diagnostic criteria for WAP. Therefore, in this study, we defined a patient with WAP as one who showed respiratory symptoms after inhaling a waterproofing spray and in whom other diseases could be excluded. The diagnostic criteria used for HP were the Japanese diagnostic criteria [11] and patients with chronic HP were excluded based on the presence of respiratory symptoms for four months or more and fibrosis on CT scans [12]. Summer-type HP was identified by the presence of the antibody against *Trichosporon asahii* in patients diagnosed with HP. The diagnosis of AEP was based on Allen’s criteria [10]. We collected patients with AEP related to the inhalation of cigarette smoke. Patients with no laboratory data records were excluded.

**Statistical Methods**

All data were analyzed and processed using EZR, version 1.35 [13]. Student’s t tests, Mann–Whitney U tests, and Fisher’s exact tests were used to compare groups. The level of statistical significance was set at $p = 0.05$ (2-tailed).

**Results**
Two adult patients were diagnosed with WAP in our hospital. Thirty-six patients were collected from publications in PubMed and the database of the Japan Medical Abstracts Society, and 9 of those patients were excluded because of the lack of laboratory data records [8,14–37]. Finally, we combined and reviewed our two patients and twenty-seven patients from past case reports. Eleven patients with AEP and thirty patients with summer-type HP were hospitalized during the same period.

The patient’s baseline characteristics are shown in Table 1. Among patients with WAP, the median age was 40.5 years old (interquartile range (IQR): 32.3–49.5), there were nineteen males (65.5%), and twenty-three patients (82.1%) had a smoking history. The median duration from symptom appearance to hospital visit was 1 day (IQR 0.4–3.0 days). The common symptoms were dyspnea (96.6%), fever (55.2%), and cough (55.2%). Sputum was rare (6.9%). Six of 37 patients (20.7%) had other symptoms, such as nausea (n = 4, 13.8%), myalgia or arthritis (n = 3, 10.3%), headache (n = 2, 6.9%), and sore throat (n = 1, 3.4%). Comparing patients with WAP to patients with AEP and HP, there was a significant difference in the duration from symptom appearance to hospital visit (WAP vs AEP: median (IQR) 1 day (0.4–2.3) vs 3 days (2–4), p = 0.003, WAP vs HP: median (IQR) 1 day (0.4–2.3) vs 30 days (16.5–60), p<0.001). The features of WAP were similar to those of AEP with regard to age, sex, underlying comorbid diseases, and smoking history. Having a fever and chest pain were relatively less common in patients with WAP. Conversely, there were significant differences between patients with WAP and HP with regard to age (median (IQR) 41.0 years (33.0–51.0) vs 50.5 years (42.0–66.5), p = 0.011), sex (male n = 24 (64.9%) vs n = 8 (26.7%), p = 0.003), smoking history (n = 29 (78.4%) vs n = 5 (16.7%), p<0.001), and dyspnea (n = 35 (94.6%) vs n = 19 (63.3%), p = 0.002). No patient died in the three groups.

With regard to the laboratory findings, patients with WAP had high WBC in the peripheral
blood (median: 13550 /µL), high CRP levels (median: 4.90 mg/dL), and normal serum KL-6 levels (median: 241 U/mL). Figure 1 shows the comparisons of the WBC and eosinophil count in the peripheral blood, CRP level, lactate dehydrogenase (LDH) level, and serum KL-6 level among patients with WAP, AEP, and HP. Compared with patients with HP, patients with WAP had a significantly higher WBC (median (IQR): 13550 /µL (10250–21245) vs 8900 /µL (8070–10070), p<0.001), higher CRP level (median (IQR): 4.39 mg/dL (1.94–8.83) vs 1.56 mg/dL (0.78–2.90), p = 0.003) and lower serum KL-6 level (median (IQR): 237 U/mL (188–373) vs 1920 U/mL (1014–3157), p<0.001). The WBC, CRP level, and serum KL-6 level were not significantly different between patients with WAP and those with AEP. The eosinophil count in patients with WAP was lower than those in patients with AEP (median (IQR): 23.2 /µL vs 297.2 /µL, p<0.001) and HP (median (IQR): 23.2 /µL vs 282.5 /µL, p<0.001); however, there was no significant difference in eosinophil counts between patients with AEP and those with HP (p = 0.437).

Table 2 compares the cellular analyses of bronchoalveolar lavage fluid (BALF) and histopathologic findings on bronchoscopic examination among WAP, AEP, and HP patients. The BALF samples of patients with WAP, AEP, and HP were dominated by macrophages (median (IQR): 89.5% (73.5–92.1)), eosinophils (median (IQR): 50.4% (46.0–64.0)), and lymphocytes (median (IQR): 64.0% (50.4–75.2)), respectively. The ratio of CD4+ to CD8+ cells (CD4/8 ratio) in patients with WAP was 1.3 (IQR 1.1–1.6), which was not significantly different compared with the ratio in patients with AEP (median (IQR): 2.1 (1.4–3.0), p = NS), although it was significantly higher than the ratio in patients with HP (median (IQR): 0.3 (0.2–0.6), p<0.001). Twenty-six patients with WAP underwent histopathologic examinations. Ten of the 26 patients had alveolitis, and four patients had alveolar hemorrhage. Two of them had both alveolitis and alveolar hemorrhage. In terms of alveolitis, there was no significant difference between patients with WAP and those with
AEP (n = 10 (76.9%) vs n = 5 (83.3%), p = NS) or those with HP (n = 10 (76.9%) vs n = 19 (90.5%), p = NS). Alveolar hemorrhage and granulomas were found only in patients with WAP and HP, respectively.

Discussion

The study identified some characteristics of WAP and compared them to those of AEP and summer-type HP. The duration from symptom appearance to hospital visit and BALF findings on bronchoscopic examination were useful for distinguishing among the patients with WAP, AEP, and summer-type HP. Between patients with WAP and HP, there were many different features, such as age, sex, smoking habit, dyspnea, and laboratory findings (WBC, CRP level, and serum KL-6 level). However, the features of WAP were similar to those of AEP. Therefore, we thought that asking patients about their history of exposure to waterproofing spray, determining the disease progression, and performing a bronchoscopic examination are very important steps.

The three diseases (WAP, AEP, and HP) are common acute pulmonary inflammatory diseases [10,38,39]. In our study, WAP had the fastest progression of the three diseases, and the WBC and CRP level of patients with WAP and AEP were higher than those of patients with HP. Similar to our report, Daubert GP et al. reported that the symptoms of patients with WAP appear rapidly within three hours after exposure [5], and Hays HL et al. demonstrated that patients with WAP have high WBCs and CRP levels as characteristic laboratory findings [40]. AEP is a severe, rapidly progressive lung disease due to exposure to inhalational agents, such as cigarette smoke. The onset of symptoms in patients with AEP is within a few weeks and often only days [10]. Summer-type HP, the most prevalent type of HP in Japan, is caused by seasonal mold contamination in the home environment, often by *T. cutaneum* (*T. asahii*) [38]. The symptom duration of acute HP is usually a few weeks or months [9]. The disease progression of WAP, AEP, and HP typically occurs within
a few hours, days, or weeks/months, respectively, similar to the results in our report. In addition, the three diseases have alveolitis in common; however, only summer-HP had granulomas in our report. Generally, HP is a granulomatous lung disease that is caused by the repeated inhalation of antigens [41,42]. The granulomas are defined as chronic inflammation [43]; therefore, it is reasonable that patients with HP have a slower disease progression than patients with WAP and AEP.

We suggest that the cellular analysis of BALF is the best examination for distinguishing WAP from AEP and HP because the dominant cells in the BALF are different for each disease. The BALF of patients with WAP, AEP, and HP is dominated by macrophages, eosinophils, and lymphocytes, respectively. We thought that the BALF findings are the result of the different mechanisms underlying the three diseases. Generally, patients with AEP have eosinophil infiltration into the alveolar interstitium, which induces respiratory failure [44]. In addition, patients with HP have lymphocytes and plasma cells with interstitial infiltration [41]. Therefore, the BALF findings in patients with AEP and HP show dominant eosinophils and lymphocytes, respectively [10,41]. In our study, patients with WAP had alveolitis and/or alveolar hemorrhage on histopathological examination, and macrophages constituted the dominant cell type in the BALF. In a past report, the mechanism underlying WAP, namely, the inhalation of fluororesin in a waterproof spray, induces macrophage infiltration and thickening of the alveolar septum, increased airway resistance, and reduced expiratory flow rate in mice [45,46]. These mechanisms might induce the macrophage domination in the BALF findings of patients with WAP.

We demonstrated that serum KL-6 levels were also able to distinguish WAP from HP. Conversely, there was no significant difference in serum KL-6 levels between WAP and AEP patient in our report. However, no report has discussed serum KL-6 levels in patients with WAP. Serum KL-6 is a mucinous high molecular weight glycoprotein classified as human
MUC1 mucin, which has been reported to serve as a sensitive marker for interstitial lung diseases [47,48]. Generally, serum KL–6 levels were highly elevated in patients with HP (median 2700 U/mL, IQR 1510–5710 U/mL) [49]. On the other hand, serum KL–6 levels in patients with AEP were reported to be within the normal range (median 161±74 U/mL) [48] because nonfibrotic interstitial lung diseases do not demonstrate elevated serum KL–6 levels [47]. In our study, the serum KL–6 levels of patients with WAP were also within the normal range. This might be because WAP does not induce lung fibrosis. Two patients with WAP in our study had not improved after more than a month of follow-up despite treatment with steroids. Follow-up CT scan and a histopathologic examination by TBLB or a video-assisted thoracoscopic lung biopsy a month after starting steroid therapy in those patients did not indicate fibrotic findings [8,26]. Therefore, WAP can be considered a respiratory disease with alveolitis, alveolar hemorrhage, and no fibrosis.

This investigation had several limitations. The study was conducted retrospectively in a single center, and some medical data were not recorded. Only two patients with WAP participated from our hospital. There might be publication bias because of the limited number of cases with WAP included from published reports. Some medical data such as the duration from symptom appearance to hospital visit were not described in careful detail.

Conclusions

This study aimed to demonstrate the characteristics of WAP and to compare the features of WAP with those of AEP and HP. It was easy to distinguish between WAP and HP because there were many different features. However, the features of WAP were similar to those of AEP, and it was difficult to differentiate between those two diseases. To distinguish among patients with WAP, AEP, and HP, the history of exposure to a waterproofing spray, the progression of the disease, and a bronchoscopic examination are very important.
Declarations

Ethics approval and consent to participate:

The study was approved by the Institutional Review Board of Fukujuji Hospital. It was determined that patient consent was not required. The decisions made by this board are based on and in accordance with the Declaration of Helsinki.

Consent for publication: Not applicable

Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Authors’ contributions:

YT had the conception and designed of the work with co-responding author. KF, KF, TO, KM, RY, HK, YS, KY, and KO collected data of patients with WAP, AEP, and HP. All authors read and approved the final manuscript.

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Tables
Due to technical limitations, tables are only available as a download in the supplemental files section

Figures
Figure 1

Comparisons of WBC, eosinophil count and CRP, LDH, and serum KL-6 levels among patients with waterproofing spray-associated pneumonitis (WAP), acute eosinophilic pneumonia (AEP), and summer-type hypersensitivity pneumonitis (HP) WAP: waterproofing spray-associated pneumonitis, AEP: acute eosinophilic pneumonia, HP: hypersensitivity pneumonitis, WBC: white blood cell count, CRP: C-reactive protein, LDH: lactate dehydrogenase, KL-6: Krebs von den Lungen-6

Supplementary Files

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Table 2.docx