Waterproofing spray-associated pneumonitis review
Comparison with acute eosinophilic pneumonia and hypersensitivity pneumonitis

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Abstract

Waterproofing spray-associated pneumonitis (WAP) proceeds to acute respiratory failure and is characterized by diffuse bilateral ground-glass opacities on computed tomography; however, the detailed characteristics of WAP are unknown. Therefore, this study identified the characteristics of WAP from comparisons with those of acute eosinophilic pneumonia (AEP) and hypersensitivity pneumonitis (HP), which show similar features to WAP.

Adult patients with WAP, AEP, and HP treated in Fukujuji Hospital from 1990 to 2018 were retrospectively enrolled. 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.

Thirty-three patients with WAP, eleven patients with AEP, and thirty patients with HP were reviewed. Regarding age, sex, smoking habit, and laboratory findings (white blood cell count, C-reactive protein level, and serum Krebs von den Lungen-6 level), WAP and AEP were not significantly different, while 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 = .006) or HP (median 30 days, P < .001). The dominant cells in the bronchoalveolar lavage fluid of patients with WAP, AEP, and HP were different (macrophages, eosinophils, and lymphocytes, respectively).

The characteristic features of WAP were rapid disease progression and macrophage dominance in the bronchoalveolar lavage fluid, and these characteristics can be used to distinguish among WAP, AEP, and HP.

Abbreviations: AEP = acute eosinophilic pneumonia, BALF = bronchoalveolar lavage fluid, CRP = C-reactive protein, CT = computed tomography, HP = hypersensitivity pneumonitis, IQR = interquartile range, KL-6 = Krebs von den Lungen-6, WAP = waterproofing spray-associated pneumonitis, WBC = white blood cell count.

Keywords: acute eosinophilic pneumonia, bronchoalveolar lavage fluid, hypersensitivity pneumonia, Krebs von den Lungen-6, waterproofing spray

1. 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.\(^{[4]}\) Some
previous studies reported various characteristics of WAP; the common clinical findings were shortness of breath (63%), cough (60%), chest pain (44%), wheezing (33%), and rales (23%).[13] The white blood cell count (WBC) and C-reactive protein (CRP) level were related to the maximum concentration of the waterproofing spray inhaled by the subjects.[13] WAP is associated with tobacco smoke exposure, including secondhand smoke, and WAP is characterized by lung edema on computed tomography (CT) scans.[1] However, those reports did not describe the detailed characteristics. Partly because the detailed characteristics are unknown, the diagnosis of WAP is usually based on the exclusion of other diseases with similar symptoms. In particular, patients with WAP have acute respiratory symptoms and diffuse bilateral ground-glass opacities on CT.\(^6\)\(^–\)\(^8\) and these features are similar to those of acute eosinophilic pneumonia (AEP) and hypersensitivity pneumonitis (HP).[9,10] It is sometimes difficult to distinguish among WAP, AEP, and HP. Therefore, this study was conducted to identify the characteristics of WAP from comparisons with those of AEP and HP.

2. Methods

2.1. Study design and setting

Patients who were hospitalized for WAP in the Respiratory Disease Center of Fukujuji Hospital from April 1990 to March 2018 were enrolled. Furthermore, past case reports of WAP patients from PubMed and the Japan Medical Abstracts Society database were collected, using the keywords “waterproofing spray,” “water repellent,” “fluoropolymer”, and “leather protector” in English and Japanese only. Those keywords in Japanese were used to search the Japan Medical Abstracts Society database, and reports without English abstracts were excluded. Furthermore, patients with no laboratory data were excluded. The combined data from those patients and our patients were reviewed. Eleven patients with AEP and thirty patients with summer-type HP were diagnosed with WAP in our hospital. Finally, thirty-one patients from past case reports and our two patients were reviewed. Additionally, two patients from past case reports and our two patients were reviewed.

2.2. Definitions

There are no diagnostic criteria for WAP. Therefore, in this study, a patient with WAP was defined 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.\(^10\) Patients with AEP related to the inhalation of cigarette smoke were collected. Patients with no laboratory data records were excluded.

2.3. Statistical methods

All data were analyzed and processed using EZR, version 1.35.\(^13\) Student t tests, Mann–Whitney U tests, and Fisher exact tests were used to compare groups. The level of statistical significance was set at \(P = .05\) (2-tailed).

3. Results

Forty-one patients were collected from publications in PubMed and the database of the Japan Medical Abstracts Society, and 3 articles without English abstracts and 7 patients with no laboratory data records were excluded (Fig. 1).\(^8,14–19\) Additionally, two patients were diagnosed with WAP in our hospital. Finally, thirty-one patients from past case reports and our two patients were reviewed. 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 twenty-three males (69.7%), and twenty-six patients (83.9%) had a smoking history. The median duration from symptom appearance to hospital visit was 1 day (IQR 0.2–2.5 days). The common symptoms were dyspnea (97.0%), fever (60.6%), and cough (60.6%). Sputum was rare (6.1%). Eight of 33 patients (24.2%)...
had other symptoms, such as nausea (n = 5, 15.2%), myalgia or arthrits (n = 3, 9.1%), headache (n = 2, 6.1%), and sore throat (n = 2, 6.1%). 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 (0.2–2.5) vs 3 days (2–4), P = .006, WAP vs HP: median (IQR) 1 day (0.2–2.5) vs 30 days (16.5–60), P < .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 was relatively less common and having dyspnea was more common in patients with WAP. Conversely, there were no significant differences between patients with WAP and HP with regard to age (median (IQR) 40.5 years (32.3–49.5) vs 50.5 years (42.0–66.5), P < .001), sex (male n = 23 (69.7%) vs n = 8 (26.7%), P < .001), smoking history (n = 26 (83.9%) vs n = 5 (16.7%), P < .001), and dyspnea (n = 32 (97.0%) vs n = 19 (63.3%), P < .001). One patient with WAP did not survive, while none of the patients with AEP and HP died.

With regard to the laboratory findings, patients with WAP had high WBC in the peripheral blood (median: 14065/μL), high CRP levels (median: 4.90 mg/dL), and normal serum KL-6 levels (median: 241 U/mL). Figure 2 shows the comparisons of the WBC and eosinophil count in the peripheral blood, CRP level, lactate dehydrogenase 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): 14065/μL (10825–21058) vs 8900/μL (8070–10070), P < .001), higher CRP level (median (IQR): 4.90 mg/dL (1.65–9.74) vs 1.56 mg/dL (0.78–2.90), P = .002) and lower serum KL-6 level (median (IQR): 241 U/mL (171–384) vs 1920 U/mL (1014–3157), P < .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 < .001) and HP (median (IQR): 23.2/μL vs 282.5/μL, P < .001); however, there was no significant difference in eosinophil counts between patients with AEP and those with HP (P = .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): 89.0% (77.9–91.7%), 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 CDS+ cells in patients with WAP was 1.2 (IQR 1.0–1.5), which was not significantly different compared with the ratio in patients with AEP (median (IQR): 2.1 (1.4–3.0), P = .054), although it was significantly higher than the ratio in patients with HP (median (IQR): 0.3 (0.2–0.6), P < .001). Thirteen patients with WAP underwent histopathologic examinations. Ten of the 13 patients had alveolitis, and three 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 = 1.000) or those with HP (n = 10 (76.9%) vs n = 19 (90.5%), P = .648). Alveolar hemorrhage and granulomas were found only in patients with WAP and HP, respectively.

### 4. Discussion

The study identified some characteristics of WAP and compared them to those of AEP and summer-type HP. As in previous reports, patients with WAP had common clinical characteristics, such as dyspnea, cough, and fever,[1] a history of smoking,[1] and bilateral ground-glass opacities on CT scans.[1] The features characteristic of WAP were rapid disease progression and macrophage dominance in the BALF. The duration from symptom onset to hospital admission and BALF findings on bronchoscopic examination were useful for distinguishing among WAP, AEP, and summer-type HP. There were many differences.
in characteristics between patients with WAP and HP, such as age, sex, smoking history, dyspnea, and laboratory findings (WBC, CRP level, and serum KL-6 level). However, the characteristics of WAP were similar to those of AEP. Therefore, it is 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 acute pulmonary inflammatory diseases.[10,40,41] 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 WBC counts and CRP levels as characteristic laboratory findings.[42] 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).[40] The duration of symptoms of acute HP is usually a few weeks or months. 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

Table 2

Comparisons of waterproofing spray-associated pneumonitis (WAP), acute eosinophilic pneumonia (AEP), and summer-type hypersensitivity pneumonitis (HP) according to bronchoscopic examination.

|                      | WAP | AEP | P-value | Summer-type HP | P-value |
|----------------------|-----|-----|---------|----------------|---------|
| BALF                 | n = 15 | n = 9 |         | n = 29         |         |
| Lymphocyte, median (IQR), % | 3.0 (2.5–3.4) | 14.8 (13.2–16.8) | .001* | 64.0 (50.4–75.2) | <.001* |
| Neutrophil, median (IQR), % | 8.0 (2.1–35.0) | 1.4 (0.2–2.4) | .021* | 3.0 (1.2–14.0) | .204 |
| Eosinophil, median (IQR), % | 3.0 (0.1–6.4) | 50.4 (46.0–64.0) | <.001* | 2.0 (0.8–4.0) | .970 |
| Macrophage, median (IQR), % | 69.0 (77.9–91.7) | 35.2 (19.4–37.6) | .001* | 24.2 (18.2–29.8) | <.001* |
| CD4/8 ratio, median (IQR) | 1.2 (1.0–1.5) | 2.1 (1.4–3.9) | .004 | 0.3 (0.2–0.6) | <.001* |
| Histopathologic findings | n = 13 | n = 6 |         | n = 22         |         |
| Alveolitis, n (%) | 10 (76.9) | 5 (83.3) | 1.000 | 19 (90.5) | .648 |
| Alveolar hemorrhage, n (%) | 3 (23.1) | 0 (0) | .517 | 0 (0) | .044* |
| Granulomas, n (%) | 0 (0) | 1.000 | 12 (54.5) | <.001* |

AEP = acute eosinophilic pneumonia, BALF = bronchoalveolar lavage fluid, CD4/8 ratio = ratio of CD4+ to CD8+ cells, HP = hypersensitivity pneumonitis, IQR = interquartile range, WAP = waterproofing spray-associated pneumonitis.
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.[43,44] The granulomas are defined as chronic inflammation[45]; therefore, it is reasonable that patients with HP have a slower disease progression than patients with WAP and AEP.

The results of our study 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. Generally, patients with AEP have eosinophilic infiltration into the alveolar interstitium,[46] and patients with HP have the interstitial infiltration of lymphocytes and plasma cells.[43] Therefore, the BALF findings in patients with AEP and HP show the dominance of eosinophils and lymphocytes, respectively.[10,43] 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, induced macrophage infiltration and thickening of the alveolar septum, increased airway resistance, and reduced expiratory flow rate in mice.[47,48] These mechanisms might induce the macrophage domination in the BALF findings of patients with WAP.

Our study 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.[49,50] Generally, serum KL-6 levels were highly elevated in patients with HP (median 2700 U/mL, IQR 1510–5710 U/mL).[51] 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).[50] Because nonfibrotic interstitial lung diseases do not demonstrate elevated serum KL-6 levels.[49] 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 transbronchial lung biopsy or a video-assisted thoracoscopic lung biopsy a month after starting steroid therapy in those patients did not indicate fibrotic findings.[6,26] 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.

5. Conclusion

This study demonstrates the unique characteristics of WAP that could be used to differentiate WAP from AEP and HP. There were many features that differed between WAP and HP, while the clinical features of WAP were similar to those of AEP. To distinguish among patients with WAP, AEP, and HP, the history of exposure to a watering spray, the progression of the disease, and a bronchoscopic examination are very important. Supplementary digital content, Book1, http://links.lww.com/MD/F853.

Author contributions

YT conceived of and designed 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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