Interstitial Pneumonia in Psoriasis

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Abstract

Objective: To investigate the relationship between psoriasis and interstitial pneumonia (IP).

Patients and Methods: We analyzed the clinical data of patients with psoriasis treated with biologic agents from June 1, 2008, to June 30, 2017, retrospectively. Chest computed tomography was performed in 392 patients before treatment. The clinical characteristics and radiographic findings of these patients were evaluated.

Results: Of the 392 patients with psoriasis, IP was detected in 8 patients (2%). Bilateral ground-glass and/or irregular linear (reticular) opacity in the lower lung zone was the most common chest computed tomography finding. Five of the 8 patients with IP were treated with anti–interleukin (IL) 12/IL-23 or IL-17 antibodies, leading to decreased or stable IP activity.

Conclusion: Interstitial pneumonia was detected in 2% of patients with psoriasis who needed systemic treatments. Ground-glass and/or irregular linear (reticular) opacity in the bilateral lower lobes was characteristic of IP with psoriasis. The IL-23/IL-17 axis may play important roles in the pathogenesis of IP in psoriasis.

Psoriasis is a chronic inflammatory skin disease. Inflammation in psoriasis is not limited to the skin as surplus proinflammatory cytokines from inflamed skin affect systemic organs. Almost all blood flows into the pulmonary circulation, suggesting that the lung parenchyma is susceptible to systemic inflammation in psoriasis. However, no large studies demonstrating a link between psoriasis and interstitial pneumonia (IP) have been conducted.

Patients with psoriasis are routinely screened for prevalent well-known comorbidities, including cardiovascular diseases and diabetes mellitus. However, lung involvement, including IP, is not intensively investigated unless respiratory symptoms are obvious. Chest computed tomography (CT) is a useful tool for finding mild IP that is not detectable on chest radiography; however, CT is not routinely performed in all patients with psoriasis. Hence, asymptomatic, mild IP associated with psoriasis may have been underdiagnosed so far.

In our hospital, chest CT is routinely performed in patients with psoriasis who need biologic agents to exclude latent and active lung tuberculosis because tuberculosis is highly prevalent in Japan. We retrospectively evaluated lung lesions in these patients. We also evaluated IP activity in relation to psoriasis activity by chest CT and serum Krebs von den Lungen-6 (KL-6) assay. The aims of this study were to determine the prevalence of IP and to reveal the clinical and radiographic characteristics of IP in patients with psoriasis.

PATIENTS AND METHODS

Study Population

Five hundred twelve patients with psoriasis were treated with biologic agents at Jikei University Hospital from June 1, 2008, to June 30, 2017. Chest CT was performed in 392 patients, and the images were evaluated by 2 specialists of the Japanese Respiratory Society (H.H. and H.K.). Interstitial pneumonia was detected in 8 patients. The clinical characteristics of patients with IP and those without IP were compared. In the 8 patients with IP, the radiographic characteristics of IP...
were evaluated. The psoriasis area severity index (PASI) score and type of psoriasis were determined by specialists of the Japanese Dermatological Association.

This study was approved by the Ethics Committee of Jikei University (29-078 [8694]).

**Statistical Analyses**

Clinical indices were compared between patients with psoriasis with IP and those without IP using Welch t test, Fisher exact test, Mann-Whitney U test, and \( \chi^2 \) test. A 2-sided P value of less than .05 was considered statistically significant.

All statistical analysis was performed with EZR (Saitama Medical Center), which is a graphical user interface for R (The R Foundation for Statistical Computing). More precisely, it is a modified version of the R commander designed to add statistical functions frequently used in biostatistics.6

**RESULTS**

**Clinical Characteristics of Patients With Psoriasis With or Without IP**

Lung involvement of the 392 patients with psoriasis who were treated with biologic agents was evaluated by chest CT before starting biologic therapy. Interstitial pneumonia was detected in 8 patients (2.0%). The clinical characteristics of patients with psoriasis with IP and those without IP are summarized in Table 1.

Patients with psoriasis with IP were significantly older than those without IP (P<.01). The serum sialylated carbohydrate antigen KL-6 levels in patients with psoriasis with IP were higher than those in patients without IP (P=.003). Generalized pustular psoriasis, the most severe type of psoriasis, was frequent in patients with psoriasis with IP. Sex, smoking status, family history of psoriasis, PASI scores, and underlying diseases were not different between the 2 groups. It is highly likely given the small sample size in the psoriasis with IP group that there is not sufficient statistical power to detect meaningful differences between the psoriasis with IP group and the psoriasis without IP group. The coexistence of any other connective tissue diseases that might cause IP was excluded by clinical evaluation and laboratory tests including autoantibodies.

Biologic agents were used in 392 patients (infliximab in 88 cases, adalimumab in 129

| TABLE 1. Characteristics of Patients With Psoriasis With or Without IP |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|                            | With IP (n=8)               | Without IP (n=384)          | P value                     |
| Age (y)                    | 72±5.98                    | 53.5±15.3                   | <.001                       |
| Sex male (%)               | 6 (75)                     | 271 (70.6)                  | >.99                        |
| Disease duration (y)       | 11±4.12                    | 139±10.4                    | .21                         |
| Ex-smoker (%)              | 5 (62.5)                    | 221 (57.9)                  | >.99                        |
| BI                         | 832±455                    | 551±478                     | .13                         |
| Family history of psoriasis | 0 (0)                       | 21 (5.5)                    | >.99                        |
| PASI score                 | 12.1±9.93                  | 12.2±8.48                   | .76                         |
| KL-6 (U/mL)                | 504±149                    | 261±172                     | .003                        |
| Type of psoriasis          |                            |                             |                             |
| PsV                        | 4 (50%)                     | 290 (75.52%)                |                             |
| PsA                        | 1 (12.5%)                   | 81 (21.09%)                 |                             |
| GPP                        | 2 (25 %)                    | 9 (2.34%)                   |                             |
| PsE                        | 1 (12.5%)                   | 1 (0.26%)                   |                             |
| PsG                        | 0 (0%)                      | 1 (0.26%)                   |                             |
| PPP                        | 0 (0%)                      | 2 (0.52%)                   |                             |

BI = Brinkman index; GPP = generalized pustular psoriasis; IP = interstitial pneumonia; KL-6 = Krebs von den Lungen-6; PASI = psoriasis area severity index; PPP = palmoplantar pustulosis; PsA = psoriatic arthritis; PsE = erythrodermic psoriasis; PsG = guttate psoriasis; PsV = psoriasis vulgaris.
cases, ustekinumab [UST] in 141 cases, secukinumab [SEC] in 33 cases, and brodalumab in 1 case).

Detailed characteristics of the 8 patients with psoriasis with IP are presented in Table 2. Of the eight patients, 6 were men and 2 were women (age range, 61-81 years; median age, 73.5 years). Psoriasis disease duration was 1 to 26 years, with a median of 11 years. Five patients were former smokers, and the other 3 were nonsmokers. One patient had respiratory symptoms, whereas the others had no symptoms. Four patients had a PASI score higher than 10 (average, 12.1; range, 0.6-20.4), and KL-6 levels were elevated in 4 patients (3 of the 4 patients with a PASI score of >10) (average, 504; range, 307-770). Of the 8 patients, 5 patients were treated with UST, 2 were treated with adalimumab, and 1 was treated with infliximab.

**Radiographic Findings in Patients With Psoriasis With IP**

Chest CT scans of the patients with psoriasis with IP are shown in Figures 1 to 4. A summary of the radiographic findings is presented in Table 3.

Lung lesions could be detected by chest radiography in 4 patients. Bilateral ground-glass and/or irregular linear (reticular) opacity was the most common CT finding in these patients. These opacities predominantly involved the lower lung zone in both lungs.

**Correlation Between IP Activity and Psoriasis Activity**

Interstitial pneumonia activity was evaluated by chest radiography, CT, and serum KL-6 periodically in patients with psoriasis with IP. Psoriasis activity was evaluated by PASI scores.

Five of the 8 patients were treated with anti–interleukin (IL) 12/IL-23p40 antibodies; UST or anti–IL-17 antibodies; SEC or anti–IL-17 receptor antibodies; or brodalumab, and disease activity decreased in 3 patients (cases 6, 7, and 8) and was stable in 2 patients.

Details on the clinical course of cases 6, 7, and 8 are as follows. In case 6, UST induction treatment improved not only skin lesions but also IP lesions. After the recurrence of skin lesions during UST maintenance treatment, IP became worse. An increased dose of UST ameliorated both skin and lung lesions (Figure 2). The IP became worse again with further relapse of psoriasis, which was improved by treatment with SEC (data not shown). In case 7, lung lesions (ground-glass and irregular linear [reticular] opacity) on chest CT regressed with UST treatment, which was effective for psoriasis skin lesions (Figure 3). In case 8, both lung and skin lesions regressed with UST treatment. Both lesions were exacerbated after the discontinuation of UST (Figure 4).

In these 3 patients, IP activity was aligned with psoriasis activity. Intriguingly, patients who were treated with biologic agents other than an IL-23/IL-17 axis blocker showed no
clear association between IP activity (assessed by CT and KL-6) and psoriasis activity (PASI score).

DISCUSSION
In this study, we demonstrated that IP was detected in patients with psoriasis who needed biologic agents (8 of 392 [2%]). Bilateral ground-glass and irregular linear (reticular) opacity in the lower lobes was the most common chest CT finding in these patients. Most of the IPs were mild without respiratory symptoms, and half of the IPs were not detectable by chest radiography. The activities of IP were aligned with the activities of psoriasis in 3 of 5 patients treated with anti-IL-12/IL-23 or IL-17 antibodies, suggesting an intimate link between psoriasis and IP.

Increasing evidence suggests that psoriasis has systemic effects and is associated with several systemic comorbidities, including cardiometabolic diseases.\(^{1,3-5}\) Although the high prevalence of chronic obstructive pulmonary disease\(^{8,9}\) and pneumonia\(^{10}\) in psoriasis has been demonstrated by population-based studies, the association between psoriasis and IP remains to be determined. Indeed, there are only a few case reports demonstrating the simultaneous existence of psoriasis and IP\(^{11-15}\), including case 6 in this report.\(^7\) No epidemiologic studies searching for comorbidities in psoriasis have revealed a high prevalence of IP in psoriasis, indicating that clinically relevant IP might be rare in patients with psoriasis. However, in this study, we showed that IP was involved in 2% of patients with psoriasis who needed biologic agents. Considering that the prevalence of idiopathic pulmonary fibrosis, one of the most common idiopathic forms of IP, is 0.01% in the general population in Japan,\(^{16}\) the prevalence of IP in psoriasis in this study seems high.

The high prevalence of IP in patients with psoriasis in this study is partly due to the high detection rate of asymptomatic and subclinical IP by chest CT. In previous studies, chest CT would not be performed in most patients because IP has not been recognized as a comorbidity in psoriasis. Subclinical IP associated with psoriasis might be underdiagnosed in those studies. Intriguingly, Scherak et al\(^{17}\) reported that lymphocytes in the bronchoalveolar
lavage fluid of asymptomatic seronegative patients with arthritis (8 patients with psoriasis of a total of 13 patients were included) increased. The lung might be affected insidiously in psoriasis.

Another reason for the high prevalence of IP in this study was that the study population included patients with severe psoriasis who needed biologic agents. In particular, generalized pustular psoriasis, the most severe type of psoriasis, was more frequent in patients with psoriasis with IP than in those without IP. The severity of psoriasis is associated with the high prevalence of comorbidities of psoriasis. A large surplus of proinflammatory cytokines from inflamed skin might have affected the lungs in the patients with severe psoriasis in this study.

In this study, we investigated the radiographic characteristics of IP associated with psoriasis. Most of the IPs associated with psoriasis were mild and affected only a small part of the lung; hence, half of the IPs were not detectable by chest radiography. Bilateral ground-glass and/or irregular linear (reticular) opacity in the lower lung zone on CT scans was a characteristic radiographic finding.

Increasing evidence suggests that the IL-23/IL-17 axis plays central roles in the pathogenesis of psoriasis, and clinically available anti–IL-23 or IL-17 antibodies improve psoriasis skin lesions. In this study, we showed that the disease activities of IP were aligned with the activities of psoriasis in 3 of 5 patients treated with anti–IL-12/IL-23 or IL-17 antibodies. Inhibition of the IL-23/IL-17 axis ameliorated not only psoriasis skin lesions but also IP, indicating that this signaling pathway is involved in the development of both psoriasis and IP. In addition to the 3 patients in this report, Miyachi et al recently reported a case showing the improvement in IP during psoriasis by IL-23/IL-17 inhibition. Inhibition of this pathway with biologic agents may be effective for IP associated with psoriasis, although biologic agents also potentially induce IP. Intriguingly, inhibition of the IL-23/IL-17 axis also ameliorated inflammation-induced lung fibrosis in mouse models through several mechanisms. The IL-23/IL-7 axis is also upregulated in many autoimmune diseases,
including rheumatoid arthritis and inflammatory bowel diseases, although the pathogenetic roles of the IL-23/IL-17 axis remain unknown. Rheumatoid arthritis and inflammatory bowel diseases frequently affect the lungs, suggesting that the IL-23/IL-17 axis may play some roles in the development of lung involvement in these diseases. The precise mechanisms of the intimate relationship between IP and autoimmune diseases, including psoriasis, need further studies.

This study has several limitations. First, this study was retrospectively designed and performed in a single center. In addition, the sample size was small. Larger studies are necessary to confirm our results. Second, psoriasis affects 2% to 3% of the general population in Europe, whereas it affects 0.34% in Japan. The genetic background may differ between patients in Japan and those in other countries. Hence, our conclusions might not be applicable to patients in other countries. Finally, our study population consisted of patients with severe psoriasis who needed the biologic agents described. The prevalence of IP in psoriasis will be lower in patients with mild or topical psoriasis than in patients with severe psoriasis in this study.

CONCLUSION
Mild asymptomatic IP was detected in 2% of patients with psoriasis who needed biologic agents. Ground-glass and/or irregular linear (reticular) opacity in the bilateral lower lobes

<table>
<thead>
<tr>
<th>Case</th>
<th>Abnormal chest radiography findings</th>
<th>Distribution</th>
<th>GGO</th>
<th>Reticular opacity</th>
<th>Emphysema</th>
<th>IP activity during psoriasis treatment</th>
<th>Respiratory failure due to IP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>Bilateral lower lobe</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Stable</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Stable</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>Bilateral lower lobe</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Stable</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>Bilateral lower lobe</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Stable</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
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<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Stable</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>No</td>
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<td>Yes</td>
<td>Yes</td>
<td>Improved</td>
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</tr>
<tr>
<td>7</td>
<td>No</td>
<td>Bilateral lower lobe</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Improved</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>Yes</td>
<td>Bilateral lower lobe</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Improved</td>
<td>No</td>
</tr>
</tbody>
</table>

GGO = ground-glass opacity; IP = interstitial pneumonia.
was characteristic of IP with psoriasis. Individuals with severe psoriasis should be counseled and screened for IP by chest CT and serum KL-6. The intimate relationship between psoriasis and IP indicated that common pathways were involved in the development of both psoriasis and IP. The IL-23/IL-17 axis may play important roles in the pathogenesis of both psoriasis and IP although a direct role for this pathway in the IP observed in the patients with psoriasis remains to be elucidated. Inhibition of this pathway may be effective treatment for IP associated with psoriasis. Additional therapy for IP with immunosuppressants can be avoided in some cases.

ACKNOWLEDGMENTS
Drs Kawamoto and Hara contributed equally to this work.

Abbreviations and Acronyms: CT = computed tomography; IL = interleukin; IP = interstitial pneumonia; KL-6 = Krebs von den Lungen-6; PASI = psoriasis area severity index; SEC = secukinumab; UST = ustekinumab

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