

Characteristics of Patients with Generalized Pustular Psoriasis and Psoriatic Arthritis: A Retrospective Cohort Study

Yukari MANOME-ZENKE^{1,2}, Yuri OHARA³, Sho FUKUI³, Daiki KOBAYASHI⁴, Kazumitsu SUGIURA⁵, Shigaku IKEDA² and Satoru ARAI¹

¹Department of Dermatology, ²Immuno-Rheumatology Center, ³Department of Epidemiology, Graduate School of Public Health, St Luke's International University, 9-1 Akashi-cho, Chuo-ku, Tokyo 1048560, ⁴Department of Dermatology and Allergology, Juntendo University Graduate School of Medicine, Tokyo and ⁵Department of Dermatology, Fujita Health University, Toyoake, Japan. E-mail: yukazen@luke.ac.jp Accepted Feb 17, 2022; Epub ahead of print xx

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Generalized pustular psoriasis (GPP) is a rare disease that accounts for <3% of all cases of psoriasis, and GPP with psoriatic arthritis (PsA) accounts for 30.0–34.7% of all cases of GPP (1, 2). GPP with PsA is rare, and knowledge about this condition is limited. This study examined the severity of skin lesions and musculoskeletal manifestations between patients with GPP with PsA, GPP alone, and PsA alone, in order to provide insights into the timing and choice of treatment for patients with GPP and PsA.

MATERIALS AND METHODS

A retrospective analysis was performed of 7 patients with GPP with PsA, 20 patients with GPP without PsA, and 148 patients with PsA without GPP at St Luke's International Hospital, Tokyo, Japan, between July 2003 and March 2021. GPP diagnosis was performed based on the ERASPEM criteria (3) and the clinical guidelines of the Japanese Dermatological Association (JDA) (1). PsA diagnosis was based on the Classification Criteria for Psoriatic Arthritis (CASPAR). In this report, "GPP+PsA" is defined as GPP with PsA, "PsA-only" as PsA with skin manifestations without GPP, and "GPP-only" as GPP without arthritis. The baseline characteristics and GPP severity when the pustular lesions initially developed were evaluated. GPP severity was evaluated according to the JDA guidelines for pustular psoriasis (Table SI) (4). The severity of musculoskeletal manifestations in patients with PsA was evaluated at their first visit for joint pain, based on core domains (spinal diseases, dactylitis, peripheral arthritis, and enthesitis)

according to the modified Composite Psoriatic Disease Activity Index (CPDAI) (5), and bone erosion and deformation were assessed on X-ray radiography, and chronic bone changes on magnetic resonance imaging (MRI) (Table SII). Direct-sequencing analyses were performed using the Sanger method for the entire coding regions of *IL36RN* and exons 2–4 and the exon-intron boundaries of *CARD14*. The study was approved by St Luke's International Hospital Ethics Committee (approval number 15-R042). Fisher's exact test and the Mann–Whitney *U* test were used to compare the characteristics of GPP+PsA patients, PsA-only patients, and GPP-only patients. All statistical analyses were performed using SPSS Version 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Overall, 1,359 patients with all types of psoriasis were included in the analysis, of whom, 27 (2.0%) had GPP, including 7 patients (0.5%) with GPP+PsA. The proportion of PsA patients was significantly higher among GPP patients than among other psoriasis patients (25.9% and 10.9%, respectively, $p < 0.01$). Among the 7 GPP+PsA patients (Table I), 4 were male. The median age of onset of the psoriatic skin lesions was 39.0 years, the median duration of psoriatic skin lesions was 12.0 years, and 85.7% of the patients developed psoriasis vulgaris skin lesions before developing GPP. No mutations in *IL36RN* or *CARD14* were found. Organ involvement occurred in

Table I. Baseline characteristics, severity of skin lesions, and musculoskeletal involvement in patients with generalized pustular psoriasis (GPP) with psoriatic arthritis (PsA), GPP alone, and PsA alone

| | GPP+PsA (n = 7) | GPP-only (n = 20) | p-value ^a | PsA-only (n = 148) | p-value ^b |
|---|-------------------------|---------------------------|----------------------|-----------------------|----------------------|
| Female, n (%) | 3 (42.9) | 13 (65.0) | 0.391 | 66 (44.6) | > 0.999 |
| Age at psoriatic onset, years, median (IQR) | 39.0 (22.0–48.0) | 48.5 (0.5–77.0) | 0.314 | 37.0 (25.5–50.0) | 0.785 |
| Time since psoriatic onset, years, median (IQR) | 12.0 (2.0–14.0) | 6.0 (0.5–40.0) | 0.231 | 9.0 (3.0–17.0) | 0.898 |
| Preceding psoriasis vulgaris, n (%) | 6 (85.7) | 10/16 (62.5) | 0.366 | 113 (76.4) | > 0.999 |
| <i>IL36RN</i> gene mutation, n (%) | 0/6 (0.0) | 1/7 (14.3) | – | – | – |
| <i>CARD14</i> gene mutation (exon 2–4), n (%) | 0/6 (0.0) | 0/7 (0.0) | – | – | – |
| Total severity score during pustular flare-ups on the JDA, median (IQR) | 8.0 (7.75–9.25) (n = 6) | 12.5 (10.0–13.0) (n = 12) | 0.003 | – | – |
| Skin severity score, median (IQR) | 5.5 (4.75–6.25) | 7.0 (6.0–8.0) | 0.017 | – | – |
| Laboratory score, median (IQR) | 3.0 (1.75–4.0) | 5.0 (3.25–6.0) | 0.041 | – | – |
| Prevalence of severe GPP on the JDA, n (%) | 0/6 (0) | 9/12 (75.0) | 0.010 | – | – |
| Severe disease in ≥3 of the 4 domains on the modified CPDAI, n (%) | 3 (42.9) | – | – | 7 (4.7) | 0.006 |
| Spinal disease, n (%) | 5 (71.4) | – | – | 43 (29.3) | 0.031 |
| Dactylitis ≥ 3 digits, n (%) | 2 (28.6) | – | – | 4 (2.7) | 0.024 |
| Peripheral arthritis ≥ 4 joints, n (%) | 4 (57.1) | – | – | 60 (40.8) | 0.450 |
| Enthesitis ≥ 3 sites, n (%) | 3 (42.9) | – | – | 17 (11.5) | 0.046 |
| Bone erosion and deformation, n (%) | 5 (71.4) | – | – | 40 (27.0) | 0.022 |

^aGPP+PsA vs GPP-only. ^bGPP+PsA vs PsA-only.

CPDAI: Composite Psoriatic Disease Activity Index; DIP: distal interphalangeal joint; IQR: interquartile range; JDA: Japanese Dermatological Association; PASI: Psoriasis Area and Severity Index.

p-values in bold indicate statistically significant differences between groups.

3 cases, which included interstitial pneumonia, primary biliary cholangitis, and ulcerative colitis, respectively. Four of 7 GPP+PsA patients were diagnosed with PsA before the first pustular flare-up, and the other 3 patients were diagnosed concurrently or later.

The severity of the skin lesions and laboratory abnormalities was milder in GPP+PsA patients than in GPP-only patients. In the evaluation of the severity of GPP, the total severity score ($p=0.003$), skin severity score ($p=0.017$), and laboratory score ($p=0.041$) were all significantly lower in GPP+PsA patients ($n=6$) than in GPP-only patients at the time of pustular lesion flare-ups ($n=12$). Moreover, 9 of 12 (75%) patients in GPP-only group were classified as severe. However, there were no severe cases among GPP+PsA patients ($p=0.01$).

In contrast to the severity of skin lesions in GPP+PsA vs GPP-only patients, GPP+PsA patients had more severe musculoskeletal involvement than PsA-only patients ($n=148$) (Table I). GPP+PsA group was significantly more likely to have a severe musculoskeletal manifestation in 3 or 4 clinical domains on the modified CPDAI than PsA-only group ($p=0.006$). The prevalence of spinal disease ($p=0.031$), dactylitis ($p=0.024$), and enthesitis ($p=0.046$), and the ratio of bone erosion and deformation ($p=0.022$) were all significantly higher in GPP+PsA patients than in PsA-only patients.

DISCUSSION

In this study, 62.5% of all GPP patients and 85.7% of GPP+PsA patients had psoriasis vulgaris skin lesions preceding GPP. Choon et al. (3) reported that 77.8% of GPP patients had a history of preceding psoriasis vulgaris or a similar skin condition. The frequency of *IL36RN* mutations in GPP patients has been reported to be 23.7–38.7% (6, 7), and the majority of cases of *IL36RN* mutations manifest as GPP with psoriasis vulgaris (4). None of GPP+PsA patients had mutations in the *IL36RN* and *CARD14* genes in the current study; only 1 GPP-only patient had an *IL36RN* gene mutation.

In the evaluation of GPP severity, the baseline characteristics in GPP+PsA patients and GPP-only patients were not significantly different. However, the total skin severity scores in GPP+PsA patients were significantly lower than those in GPP-only patients. We hypothesized that the majority of GPP+PsA patients would have preceding psoriasis vulgaris skin lesions, and might be less likely to develop acute skin eruptions, such as the typical Zumbush-type generalized pustular lesions. To test this hypothesis, we examined these 2 groups, excluding patients showing Zumbush-type extensive pustular lesions. However, we observed the same results (data not shown), suggesting that most GPP and PsA patients do not experience severe skin inflammation.

Conversely, the prevalence of 4 severe domains of PsA in GPP+PsA patients was considerably higher than

that in PsA-only patients, and GPP+PsA patients were significantly more likely to develop severe spinal disease, dactylitis, and enthesitis than PsA-only patients. Furthermore, although age, sex, and disease duration between the GPP+PsA patients and PsA-only patients did not differ significantly, GPP+PsA patients were significantly more likely to develop bone erosion and deformation. These results suggest that GPP+PsA patients are more likely to develop severe musculoskeletal involvement and progress earlier than PsA patients alone, and that joint inflammation, rather than skin inflammation, is the predominant pathology in patients with GPP+PsA.

In 8 previous reports of GPP+PsA cases (8–15) (Table SIII), the median age at onset was 29.0 years, with an equal incidence in males and females. Preceding psoriasis vulgaris skin lesions were present in 6 cases (75%), 4 cases (50%) were diagnosed with PsA before the first pustular flare-up, and 6 cases (75%) had polyarthritides. Severe dactylitis, enthesitis, and bone erosion and deformation were reported in 2 (25%), 4 (50%), and 2 cases (25%), respectively. However, it was challenging to evaluate arthritis appropriately because some case reports did not provide detailed information on joint pain.

A key limitation of this study is that only a small number of patients with GPP+PsA were included. Furthermore, a few patients had to be excluded owing to missing data.

In conclusion, to our best knowledge, this is the first in-depth analysis of patients with GPP+PsA. The severity of psoriatic skin lesions was milder in patients with GPP+PsA patients than in patients with GPP alone. In contrast, joint inflammation was more severe in patients with GPP+PsA than in patients with PsA alone. The results suggest that adequate monitoring and early interventions for musculoskeletal manifestations are required in patients with GPP+PsA.

The authors have no conflicts of interest to declare.

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