A Case of Generalized Pustular Psoriasis with Organizing Pneumonia During Treatment for Rheumatoid Arthritis

Mizuho OTA, Michio TOKUYAMA, Tomomichi SHIMIZU,
Akio KONDOH and Tomotaka MABUCHI

Department of Dermatology, Tokai University School of Medicine

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Generalized pustular psoriasis (GPP) is a disease that presents with fever and multiple sterile pustules on flushed skin all over the body. GPP should be considered as systemic inflammatory response syndrome (SIRS), and is occasionally associated with respiratory failure. We encountered a case of GPP with organizing pneumonia (OP) during treatment for rheumatoid arthritis (RA). A 74-year-old Japanese woman with RA developed fever and erythema with small pustules on the trunk and extremities. She was diagnosed as GPP and admitted to our hospital. During the clinical course, she suffered hypoxia from OP. Although RA and OP are known to coexist, GPP and OP share the involvement of cytokines such as interleukin 8 in the pathogenesis. These cytokines are therefore also involved in the complications of GPP and OP.

Key words: generalized pustular psoriasis, rheumatoid arthritis, organizing pneumonia

INTRODUCTION

Generalized pustular psoriasis (GPP) is a relatively rare disease, accounting for about 1% of all psoriasis cases. This disease is characterized by acute fever, reddening of the skin, and frequent aseptic pustules along with one of the systemic inflammatory diseases, complicating mucosal symptoms, arthritis, respiratory failure, eye symptoms, and secondary amyloidosis [1]. Rheumatoid arthritis (RA) is another systemic disease with symptoms affecting the whole body, including joints, skin, and lungs. Secondary organizing pneumonia (OP) is known to occur in collagen diseases. However, in recent years, psoriasis and OP have been suggested to involve a common pathology [2–6]. Here, we report a case of GPP complicated by OP during treatment for RA.

CASE REPORT

A 74-year-old Japanese woman had been diagnosed with RA at 65 years old. At that time, she was treated with oral prednisone at 7 mg/day, bucillamine, and iguratimod in a department of rheumatology. She developed erythema on the back and buttocks more than 1 year before first visiting our department. Treatment with topical corticosteroid at a local doctor failed to achieve any improvement, so she visited our department. Clinical findings showed erythema with scaling around the margins of the lower back, flanks, and posterior surfaces of both thighs. Skin biopsy revealed hyperkeratosis, parakeratosis, and slight thickening of the epidermis and mild liquefied degeneration at the epidermal-dermal junction. Mild infiltration of inflammatory cells, including eosinophils and neutrophils, was observed around blood vessels in the deep dermis. Based on these findings, she was diagnosed as erythema multiforme at that point. Treatment was started with topical corticosteroid and oral anti-histamine drugs, after which the symptoms temporarily abated. Five months after the first visit, she developed pain and difficulty moving due to exacerbation of erythema and was transferred to our hospital by ambulance. Clinical findings showed erythema with lace-like scales on the trunk and extremities, with small pustules 2-mm in diameter scattered over the entire body, forming a pus-filled sea (Fig. 1a–c). No mucosal rash was observed. Vital findings on transport were: body temperature, 38.5°C; heart rate, 112 beats/min; blood pressure, 130/72 mmHg; respiratory rate, 20 breaths/min; and percutaneous oxygen saturation (SpO_2), 98% in room air. Laboratory findings were as follows: white blood cell count, 17,300/μL (normal, 4,000–8,000/μL); hemoglobin, 9.1 g/dL (normal, 13.7–16.8 g/dL); albumin, 1.7 g/dL (normal, 4.1–5.1 g/dL); Ca, 7.8 mg/dL (normal, 8.6–10.0 mg/dL); and C-reactive protein (CRP), 19.11 mg/dL (normal, < 0.30 mg/dL). No abnormalities were evident in hepatic or renal functions or levels of other electrolytes. Chest X-ray showed no evidence of pneumonia. Skin biopsy was performed to include a pustule on the left leg. Pathological findings revealed subcorneal pustule formation with numerous neutrophils and surrounding liquefied degeneration. Inflammatory cell infiltration with mixed lymphocytes and neutrophils was revealed from the dermis to the superficial layer of adipose tissue (Fig. 2a, b). The patient had no history of new drugs or drugs that could cause pustular drug eruption. We considered the possibility of GPP based on systemic expansion

Mizuho OTA, Department of Dermatology, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan
Tel: +81-463-93-1121 Fax: +81-463-93-9387 E-mail: m.ota@tokai.ac.jp

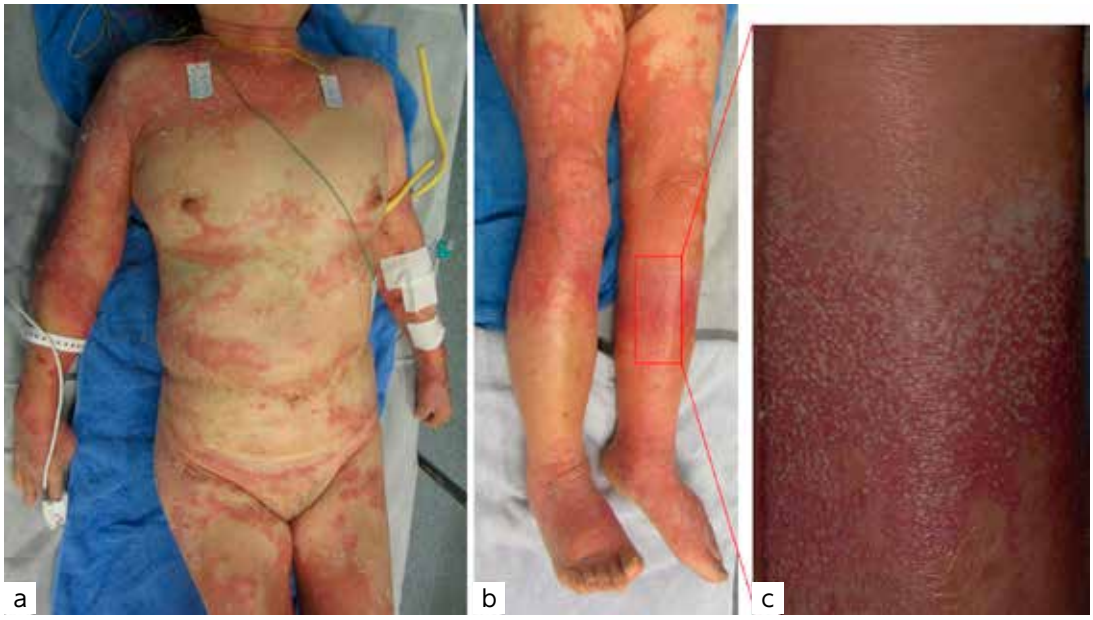

Fig. 1 Clinical findings
(a, b) Erythema with lace-like scales is observed on the trunk and extremities.
(c) Small pustules 1–2 mm in diameter are scattered over the whole body, forming a pus-filled sea.

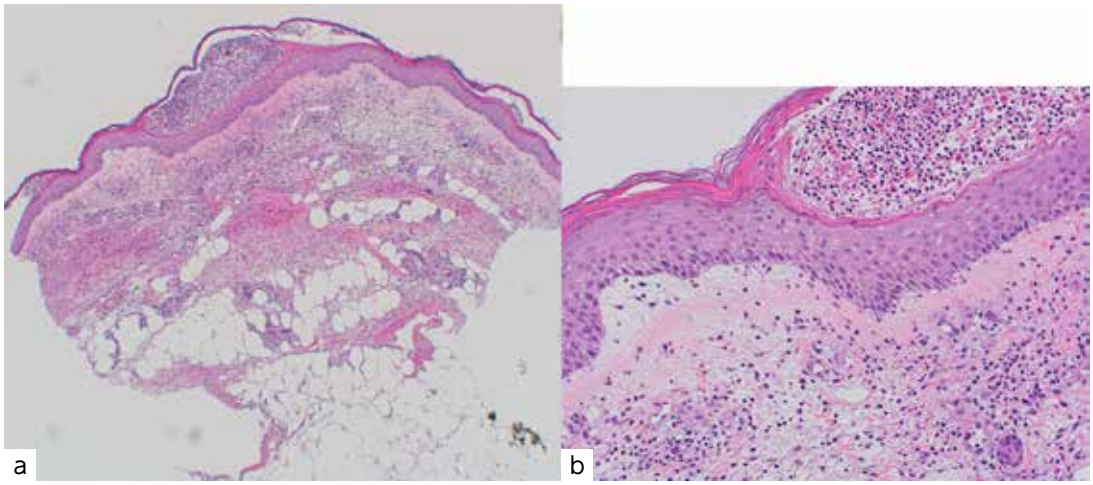

Fig. 2 Pathological findings (skin)
(a) Subcorneal pustule formation and superficial and deep mixed inflammatory cells infiltrate the dermis. (Hematoxylin-eosin [HE], ×20)
(b) Subcorneal pustule formation with numerous neutrophils and surrounding liquefied degeneration. Inflammatory cell infiltration with mixed lymphocytes and neutrophils is revealed from the dermis to the superficial layer of adipose tissue. (HE, ×400)

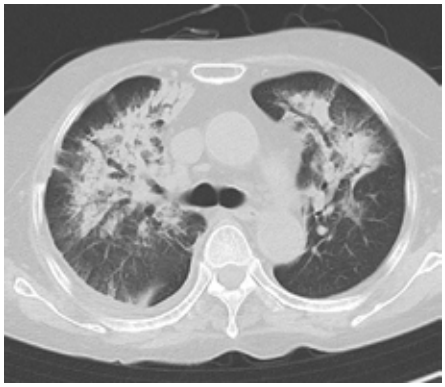

Fig. 3 Computed tomography findings
Bilateral infiltrative shadows newly appeared on day 7 of admission.

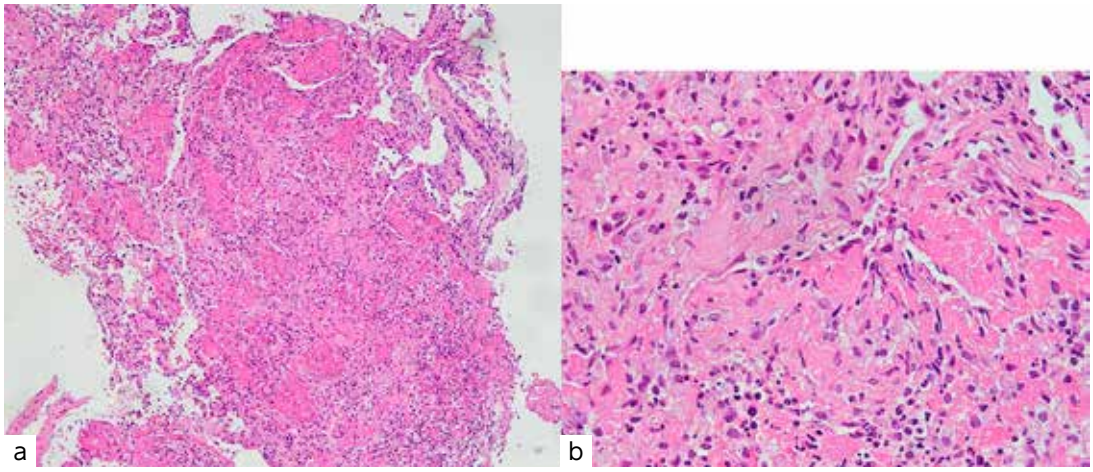

Fig. 4 Pathological findings (lung)
Bronchiolar lung biopsy showed an organized image with infiltration of neutrophils, macrophages, lymphocytes, and exudation of fibrin into the alveolar space. (a: HE, ×20, b: HE, ×400)

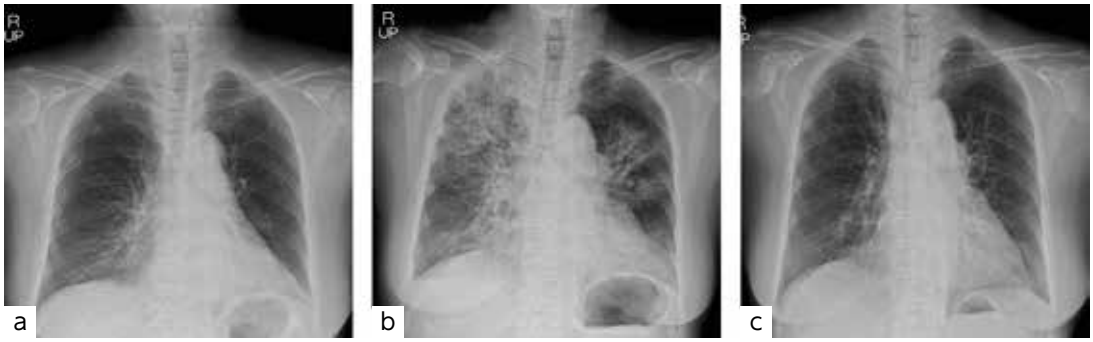

Fig. 5 Chest X-ray findings
(a) On admission.
(b) On Day 7 of admission.
(c) On Day 30 of admission.

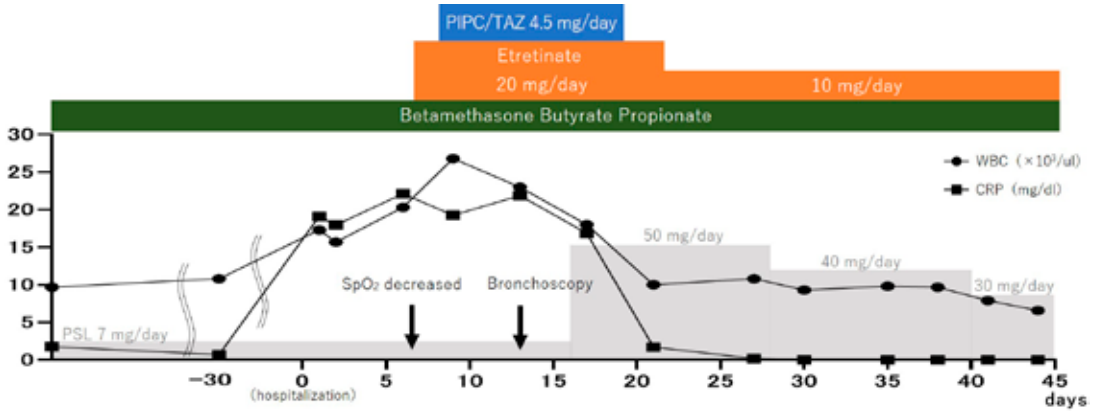

Fig. 6 Clinical course

of pustules accompanied by systemic symptoms such as fever, and pathological findings. The *IL36RN* gene mutation was not measured because the patient declined testing. Her severity of GPP was classified as severe with a total score of 15 out of 17 from rating skin symptoms (erythema, pustules, and edema) and systemic inflammation accompanied by certain laboratory findings (fever, white blood cell count, and serum CRP and albumin levels) [1]. Topical corticosteroid was continued after admission and oral etretinate was started at 20 mg/day on hospital day 6. On hospital day 7, she suffered hypoxia and bilateral infiltrative shadows, predominantly in the right lung field, were confirmed by chest X-ray and computed tomography (CT) (Fig. 3). Since antibiotic therapy was ineffective, bronchoscopy was performed. Bronchiolar lung biopsy revealed an organized image with infiltration of neutrophils, macrophages, lymphocytes, and exudation of fibrin into the alveolar space (Fig. 4a, b). Based on these findings, OP associated with RA was diagnosed. Oral prednisolone was started at 50 mg/day for OP. After increasing the dose of prednisolone, both clinical symptoms and

Table 1 Cytokines involved in GPP, RA, and OP

Generalized pustular psoriasis (GPP)	TNF-α, IL-1β, IL-6, IL-8, IL-17, IL-23, IL-36	[13]
Rheumatoid arthritis (RA)	TNF-α, IL-1β, IL-2, IL-6, IL-7, IL-17, IL-18, IL-21, IL-23, IL-33	[14]
Organized pneumonia (OP)	TNF-α, IL-8, IL-17, PDGF	[2]～[6]

laboratory findings improved rapidly. Chest X-rays showed marked improvements in lung lesions (Fig. 5). Prednisolone was continued at 50 mg/day for 2 weeks, then tapered off (Fig. 6). Erythema and pustules disappeared, and the dose of etretinate was reduced to 10 mg/day. The patient has continued to receive oral and topical treatments on an outpatient basis.

DISCUSSION

GPP presents with fever and multiple sterile pustules against a background of generalized flushed skin, forming subcorneal pustules histopathologically characterized by Kogoj spongy pustules [1]. Repeated recurrences are characteristic of this disease. A study of cases showing familial onset revealed that the causative gene encodes an interleukin (IL)-36 receptor antagonist that regulates the action of IL-36, which is involved in the production of inflammatory cytokines such as IL-8, which in turn is important for neutrophil migration. Most sporadic cases of GPP (not preceded by plaque psoriasis) reportedly show mutations in the *IL36RN* gene [1].

In GPP, increased levels of vascular endothelial growth factor in plasma and skin are known to cause increased vascular permeability, resulting in capillary leak syndrome [7]. A similar phenomenon in the lungs causes respiratory failure due to pulmonary edema, representing acute respiratory distress syndrome (ARDS). In our case, capillary leak syndrome or ARDS were the differentials, but based on the histological findings of the bronchiolar lung biopsy, it was diagnosed as OP. OP which is a specific type of interstitial lung disease, is characterized by inflammation from the alveoli to the bronchioles near the alveoli and polyp-like organized tissue in the air spaces [8]. This pathology can be cryptogenic or secondary, with secondary cases often seen in connective tissue diseases such as RA [9], as in our case. Cryptogenic and secondary OP display similar treatment responses, relapse rates, and mortality rates [9]. On the other hand, inflammatory rheumatic disease-related cases also reportedly show a lower complete recovery rate with a tendency toward a higher recurrence rate compared with cryptogenic OP cases [10]. Our case was considered secondary OP had arisen as a complication of RA. The prevalence of clinically significant interstitial pneumonias in RA patients is reported to be 7.7－12.0%, while OP in RA patients is less common compared with usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP) [11]. A case series from single hospital reported that 14.3% preceded articular symptoms of 19.0% developed simultaneously with the onset of RA, and 66.7% occurred during follow-up periods [11]. In cases of OP developing after the diagnosis of RA, 71% had maintained low disease activity by the onset of OP [11]. In our case, no exacerbation of RA disease activity was seen.

In recent years, OP has also been suggested to be related to psoriasis. Activated Th17 cells are known to produce several mediators, including IL-17A, IL-17F, and IL-22 associated with psoriasis. IL-17 produced by Th17 cells is also believed to contribute to alveolar inflammation and enhance cytokine production in pulmonary fibroblasts [2]. In addition, some reports have suggested that tumor necrosis factor-α (TNF-α), IL-8, and platelet-derived growth factor (PDGF) may be involved in the pathogenesis of OP and psoriasis [2]. Indicates common mediators associated with psoriasis, RA, and OP (Table 1). Multiple common cytokines may thus be involved and the possibility of common pathologies and complications has been suggested [3－6].

In a retrospective study of 447 patients with interstitial pneumonia, Ishikawa *et al.* reported that 4.7% (21 cases) of patients with interstitial pneumonia had antecedent or comorbid psoriasis, of which 9.5% (2 cases) had OP [2]. This study only includes psoriasis vulgaris and psoriatic arthritis and does not include GPP. Only one case of GPP and interstitial lung disease has been reported [12], but it has not been discussed in detail regarding coexistence of GPP and IP. To the best of our knowledge, our case represents the first case of GPP and RA, OP.

Cytokines such as IL-17, IL-23, IL-1, TNF-α, and IL-36 are known to be involved in the pathology of GPP, and IL-36 in particular has attracted attention in recent years [13]. IL-36 is mainly secreted from epidermal keratinocytes and dermal dendritic cells upon stimulation with IL-1, TNF-α, and IL-17. IL-36 is then activated to IL-36α, β, and γ. These bind to the IL-36 receptor and produce cytokines and chemokines such as CXCL1 and CXCL8 (IL-8), which are important for neutrophil migration. As described above, IL-8 is also involved in OP. Although the relationship is unclear, common cytokines such as IL-8 may be involved in both OP and GPP (Table 1). We thought that the OP in our case was associated with RA, but the association may instead have been with GPP. As mentioned above, common cytokines may be involved in OP and psoriasis, suggesting common pathological processes and even complications. Reported cases remain scarce, but the pathophysiology is expected to be elucidated in the future.

We encountered a case of GPP and OP in a patient with RA. ARDS is a well-known pulmonary complication of GPP, but OP should also be considered in patients with a history of RA. GPP and OP share cytokines such as IL-8 in the pathogeneses. These cytokines may therefore also be involved in the coexistence of GPP and OP.

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