Case Report

Six Cases of Erythrodermic Pemphigus Foliaceus: A Case Report

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Abstract
Pemphigus foliaceus (PF) is one of the causes of erythroderma; however, to date, there have been relatively few reported cases. We herein describe 6 cases of erythrodermic PF. In all 6 cases, PF was a direct cause of erythroderma because the patients had not undergone any medical treatments and neither had any other skin diseases nor were taking any drugs that typically cause erythroderma. Serum levels of IgE and thymus and activation-regulated chemokine were elevated in 5 of the 6 cases, whereas soluble interleukin-2 receptor and squamous cell carcinoma-related antigen were markedly increased in all cases, suggesting that those markers are strong indicators of skin surface damage. All patients were treated with predonisolon (PSL), of which PSL pulse was added in 4 patients and intravenous immunoglobulin was added in 4 patients. Furthermore, all patients except for one were older adults, among whom 2 cases developed Kaposi’s varicelliform eruption, and died, and another 2 patients, respectively, died of gastrointestinal bleeding and sepsis. Kaposi’s varicelliform eruption is a complication of erythrodermic PF associated with poor prognosis, and thus caution is necessary when considering the diagnosis. Furthermore, elderly people are more likely to have complications due to PSL, which may result in death. Inappropriate treatment and delay in treatment may cause erythroderma, so early diagnosis and treatment are necessary.
Introduction

Pemphigus foliaceus (PF) is characterized by scaly, crusted, and erosive erythematous lesions, which rarely develop into erythroderma. We herein report 6 cases of PF, presenting as generalized erythroderma with scales and erosions.

Case Report/Case Presentation

Case Report

Case 1

A 46-year-old woman visited our department, complaining of diffuse erythema with scales and erosions in various locations around her body. The symptoms had gradually worsened over the previous 6 months. Physical examination revealed severe edematous erythematous lesions with abundant exudates, profuse scaling, and erosions covering her whole body (Fig. 1a). A biopsy specimen from the erythema on the trunk showed acanthosis and a parakeratotic stratum corneum with neutrophilic infiltration. Acantholytic lesions were observed in the granular layer. Infiltration of neutrophils was found not only in the epidermis but also in the dermis, with a perivascular pattern. After admission, 45 mg/day of oral prednisolone (PSL) was administered and improved the erythroderma; following treatment, however, annular erythemas with collarette scales and pin-head sized pustules emerged on the patient’s bilateral flanks and waist. KOH examination and bacterial culture both yielded negative results. The second skin biopsy showed that the subcorneal pustules consisted of many neutrophils and acantholytic cells in the granular layer, results which were similar to those of the first biopsy. Direct immunofluorescence (DIF) showed deposition of IgG and C3 on the epidermal intercellular space, and enzyme-linked immunosorbent assay (ELISA) showed increased levels of anti-Dsg1 antibody (>3,000 U/mL, cutoff: <10). This case responded well to oral prednisolone without dose-escalation, and thereafter, there has been no relapse of symptoms.

Case 2

An 88-year-old woman presented to our department with generalized eruptions that had appeared 2 months previously. She was treated with oral PSL (30 mg/day) under suspicion of pemphigus 1 month previously. However, no effect was observed and was hospitalized in our hospital. Physical examination showed diffuse erythema and erosions on the face, trunk, and extremities (Fig. 1b). In addition, erosions were observed on the hard palate in the mouth. Serum titer of the anti-Dsg1 antibody measured by ELISA was >1,000, whereas that of anti-Dsg3 antibody was 9.7 U/mL. DIF of the biopsied skin showed deposition of IgG and C3 on the epidermal intercellular space. The patient was treated with oral PSL (50 mg/day), but on the fourth day after admission, a number of small vesicles appeared on the face and oral mucosa. Tzanck test revealed ballooning cells, and fluorescent antibody method detected herpes simplex type 1. Aciclovir was started and in parallel methylprednisolone pulse therapy (1,000 mg for consecutive 3 days) was carried out; however, the patient suffered from methicillin-resistant Staphylococcus aureus infection and died of multi-organ failure on the 22nd day after admission.

Case 3

A 91-year-old male was referred to our hospital complaining of generalized eruptions that had appeared three months previously. He had increased levels of anti-Dsg1 antibody and was suspected of having PF. He was treated with oral PSL (20 mg/day) and admitted to
our hospital. He had a past history of gastrointestinal perforation and had stoma for about 20 years. Physical examination showed diffuse erythema and erosions on the face, trunk, and extremities (Fig. 1c). Serum titer of the anti-Dsg1 antibody measured by ELISA was >1,000. A biopsy specimen revealed subcorneal acantholytic cleavage. DIF showed deposition of IgG and C3 on the epidermal intercellular space. The PSL dose was increased to 60 mg/day, but erosions did not improve, so mPSL pulse therapy and intravenous immunoglobulin (IVIg) were started. Gradually, serum titer of the anti-Dsg1 antibody was degraded, and the erosions were epithelized. However, about 1 month after admission, the patient developed gastrointestinal bleeding and died on the 53rd day after admission.

Case 4

A 76-year-old male was admitted to our hospital, complaining generalized eruptions with 1 month’s duration. Physical examination showed diffuse coalesced erythematous lesions and scales all over the face trunk and extremities (Fig. 1d). A biopsy specimen revealed subcorneal acantholytic cleavage, and DIF showed deposition of IgG and C3 on the epidermal intercellular space. Serum titer of the anti-Dsg1 antibody measured by ELISA was 1,750, whereas that of anti-Dsg3 antibody was <5. The patient was treated with mPSL pulse therapy, followed by oral PSL and plasma exchange; however, during the course, he developed iliopsoas abscess and sepsis and died after being transferred to another hospital.

Case 5

An 89-year-old female was referred to our department, complaining of generalized bullae and erosions which appeared 3 months previously. She had been treated with PSL 15 mg/day for the previous 2 months but without effect. She had histories of rheumatoid arthritis, and
she was being treated with PSL 2 mg/day. Physical examination showed coalesced erythematous lesions, scale, and erosions on the trunk and extremities (Fig. 1e). Scales and erosive erythemas were also observed on the face. Histological examination revealed subcorneal acantholytic cleavage. DIF showed deposition of IgG and C3 on the epidermal intercellular space. Serum titer of the anti-Dsg1 antibody measured by ELISA was 3,340, whereas that of anti-Dsg3 antibody was <5. On day 7 after admission, a number of small vesicles appeared on the face and oral mucosa. Tzanck test showed ballooning cells. Aciclovir was started and in parallel IVIg therapy was carried out; however, the patient died of multi-organ failure on day 14 day after admission.

Case 6
A 72-year-old male was treated for leg ulcer and elephantiasis once a week at a nearby dermatology clinic. He was admitted to our hospital after developing generalized erythema and erosions on the face 1 month previously (Fig. 1f). Serum titer of the anti-Dsg1 antibody measured by ELISA was >1,000. A biopsy specimen revealed subcorneal acantholytic cleavage (Fig. 1g). DIF showed deposition of IgG and C3 on the epidermal intercellular space (Fig. 1h). He was treated with PSL (60 mg/day), but the generalized erythema and erosions did not improve, hence mPSL pulse therapy and IVIg were started. Erythema reappeared due to PSL taper 2 months after the start of treatment, so cyclosporine was started. The erythema and erosions were resolved with no recurrence.

Serum Levels of IgE, TARC, sIL2, and SCC
Serum levels of IgE, thymus and activation-regulated chemokine (TARC), soluble interleukin-2 receptor (sIL2-R), and squamous cell carcinoma-related antigen (SCC) were examined. All cases except for one showed increased levels of serum IgE and TARC. By contrast, sIL-2R and SCC serum levels were markedly elevated in all cases, suggesting that both markers significantly reflected skin surface damage (Table 1).

Discussion/Conclusion
We herein report 6 cases of PF presenting with exfoliative erythroderma on the face, trunk, and extremities. All cases exhibited erythroderma at the time of initial visit to our hospital. To date, cases of PF presenting with erythroderma are relatively rare [1–3], and PF is estimated to cause erythroderma at a frequency of 5% [4]. In our cases, PF was the direct cause of erythroderma because the patients had undergone no medical treatments and had neither any other skin diseases nor factors, i.e., drugs, that might be causes of erythroderma. The patient in Case 1 was treated with herbal medicine and had had undiagnosed as having PF for a long time, leading to erythroderma. In Case 4 and 6, it took time from the appearance of the skin rash to the consultation. All patients were treated with PSL, to which PSL pulse was added in 4 patients and IVIg was added in 4 patients. In many cases of previously reported

Table 1. Serum levels of IgE, sIL2R, TARC, and SCC

| Cutoff | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 |
|--------|--------|--------|--------|--------|--------|--------|
| IgE    | 173    | 826    | 1,115  | 553    | 3,376  | 170    |
| TARC   | 450    | 2,745  | 2,079  | 697    | 3,829  | 200    |
| sIL2-R | 613    | 1,250  | 2,410  | 1,340  | 3,040  | 1,320  |
| SCC    | 1.5    | 139    | 57.7   | 58.4   | 307    | 46.6   | 31.1   |
cases, PF with erythroderma was difficult to treat. In our series, all but 5 cases were in elderly patients. In addition, in our cases, 4 patients died. Kaposi’s varicelliform eruption was developed in 2 cases, both of which died, and the other 2 patients respectively died of gastrointestinal bleeding and sepsis, respectively. Therefore, we suggest that erythrodermic PF occurring in aged patients has a poor prognosis.

Miyamoto et al. [5] retrospectively examined 30 patients with erythrodermic PF, 24 of which (80%) already developed erythroderma at the initial presentation. Both bacterial and viral infections were observed, and herpes simplex infection (36.7%) resulted in longer hospitalization. Kaposi’s varicelliform eruption has been reported to be an occasional complication of PF [6], which sometimes resulted in fatal outcome [7].

Serum vascular endothelial growth factor (VEGF) concentration is known to be elevated in patients with erythroderma. A recent study examined serum VEGF and soluble VEGF receptor in 19 of 30 patients with erythrodermic PF [5]. Increased VEGF levels were observed during the course of erythroderma, as compared with non-erythrodermic phase PF and healthy controls. We examined serum IgE, TARC, sIL-2R, and SCC, all of which were increased in the patients included in the current study. In erythroderma, T cells are activated and Th2 becomes dominant, and IgE and TARC are increased [8]. Elevated SCC expression derives from the activity of epidermal cells [9]. In our cases, serum IgE, TARC, sIL-2R, and SCC were increased in all cases except for Case 5. We suspect that this was because Case 5 had started PSL treatment before the visit to our department.

In conclusion, we reported 6 cases of PF presenting generalized erythroderma with scales and erosions. Elderly people are more likely to have complications due to PSL, which may result in death. Inappropriate treatment and/or delay in treatment may cause erythroderma, so early diagnosis and treatment are necessary.

Statement of Ethics

This study protocol was reviewed and approved by the Fukushima Medical Hospital, approval number C-T2022-0002. Written informed consents were obtained from the patients for publication of the details of their medical case and any accompanying images. In cases (2–5) written informed consent was obtained from the patient’s next of kin for publication of the details of their medical case and any accompanying images.

Conflict of interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Shohei Igari, Masato Ishikawa, Tatsuhiko Mori, Tomoko Hiraiwa, Nobuyuki Kikuchi, and Yuka Hanami collected the data and wrote the initial manuscript. Toshiyuki Yamamoto evaluated and revised the manuscript. Toshiyuki Yamamoto provided critical feedback and
contributed to the final version of the manuscript. Natsumi Norikawa examined the patient, collected the anamnesis, treated the patient, and participated in the writing of the manuscript.

**Data Availability Statement**

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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