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Single Case

A Case of Papuloerythroderma Successfully Treated with Dupilumab

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Keywords
Papuloerythroderma · Dupilumab · Th2 · IL-4 · IL-13

Abstract
Papuloerythroderma is an erythroderma characterized by the composition of dense paving stone shape papules and intertriginous uninvolved skin on the abdominal wall and is often intractable and accompanied by itching. Topical or oral corticosteroids are treatment measures, but immunosuppressive drugs are sometimes required. Herein, we report a case of papuloerythroderma treated with dupilumab, a completely humanized immunoglobulin monoclonal antibody against interleukin-4 receptor subunit α (IL-4Rα) of IL-4 and IL-13 receptors, with rapid and marked improvement. Dupilumab is one of the treatment options to treat refractory papuloerythroderma.

Introduction

Papuloerythroderma was described by Ofuji et al. [1] in 1979 as an erythroderma characterized by dense papules that form a paving stone shape accompanied by itching. Eruption is composed of areas of papules or erythema and intertriginous uninvolved skin on the abdominal wall and is often intractable. Topical or oral corticosteroids are treatment measures, and immunosuppressive drugs are sometimes required. Herein, we report a case of papuloerythroderma treated with dupilumab, a completely humanized immunoglobulin monoclonal antibody directed against the interleukin-4 receptor subunit α (IL-4Rα) of IL-4 and IL-13 receptors, with rapid and marked improvement.

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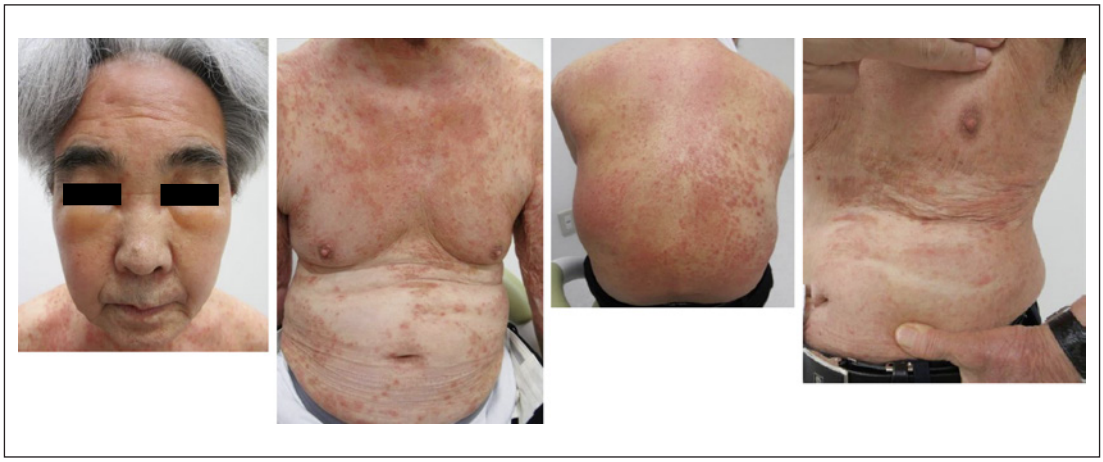

Fig. 1. Clinical pictures at the first visit to our department. **a** Marked edema of both lower eyelids were observed. **b**, **c** Irregular papules, erythema, and eruptions, ranging from the size of a needle head to that of a pea on the trunk were obvious. **d** Intertriginous uninvolved areas on the abdominal wall (deckchair sign) were seen.

Case Report/Case Presentation

A man in his 80s with a medical history of hypertension, atrial tachycardia, chronic cardiac insufficiency, and cataract visited our hospital in April 2021 with a complaint of erythema and papules on the extremities and trunk, accompanied by severe itching. A generalized pruritic skin rash started in 2010 and was diagnosed as eczema and folliculitis. The medication prescribed included antihistamines, topical steroids, minocycline, sodium azulene sulfonate hydrate, tocopherol nicotinate, roxithromycin, and topical ketoconazole lotion, although the outcome was ineffective. The patient was treated with cyclosporine 100 mg daily, starting in October 2020. The eruption was almost in remission in December 2020, but cyclosporine was discontinued in April 2021 due to complications, such as hypertension and renal dysfunction. The eruption reoccurred and the patient was subsequently referred to our department.

Clinical Symptoms

The trunk was covered with irregular papules, erythema, and eruptions, ranging from the size of a needle head to that of a pea, with central excoriation, necrosis, and crusting. Intertriginous uninvolved areas were also detected on the abdominal wall. Both the lower eyelids showed marked edema (Fig. 1). The entire body was intensely pruritic.

Clinical Laboratory Findings

White blood cells; 11,430/μL (segmented neutrophils; 53.1%, eosinophil; 24.8%, basophil; 0.6%, monocytes; 10.8%, lymphocytes; 10.7%), red blood cells; 3.94 × 104/μL, hemoglobin; 11.3 g/dL, platelet count; 357 × 104/μL, aspartate transaminase; 31 IU/L, alanine aminotransferase; 22 IU/L, lactate dehydrogenase; 393 IU/L, total protein; 5.9 g/dL, creatinine; 1.05 mg/dL, blood urea nitrogen; 25.6 mg/dL, blood glucose levels (2-h postprandial value); 138 mg/dL, HbA1c; 5.7%, C-reactive protein; 0.06 mg/dL, anti-nuclear antibodies <40×, thymus and activation-regulated chemokine (TARC); 51,630 pg/mL, immunoglobulin E (IgE); 5,529 mg/dL, sIL-2R U/mL, erythrocyte sedimentation rate 1 h: 8 mm, 2 h: 19 mm. Urinalysis was within the normal range.

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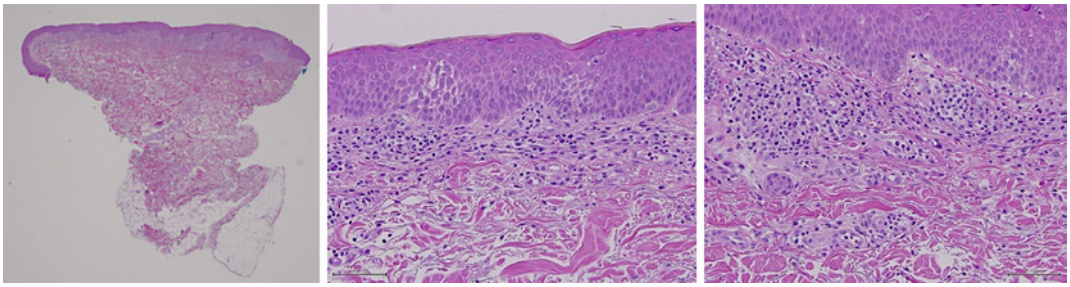

Fig. 2. Histopathological findings taken from the trunk at the first visit. **a** Epidermal thickening and prolongation of the epidermal processes were unremarkable. There were no significant changes in the adnexa or subcutaneous fatty tissue (hematoxylin and eosin staining, ×20). **b**, **c** The epidermis showed spongiosis and mild liquid degeneration. In the dermis, there was moderate lymphocytic infiltrate with histiocytes in a shallow perivascular area. The vascular endothelium was mildly enlarged, and neutrophils and eosinophils were distributed within the vessels (HE staining, ×100).

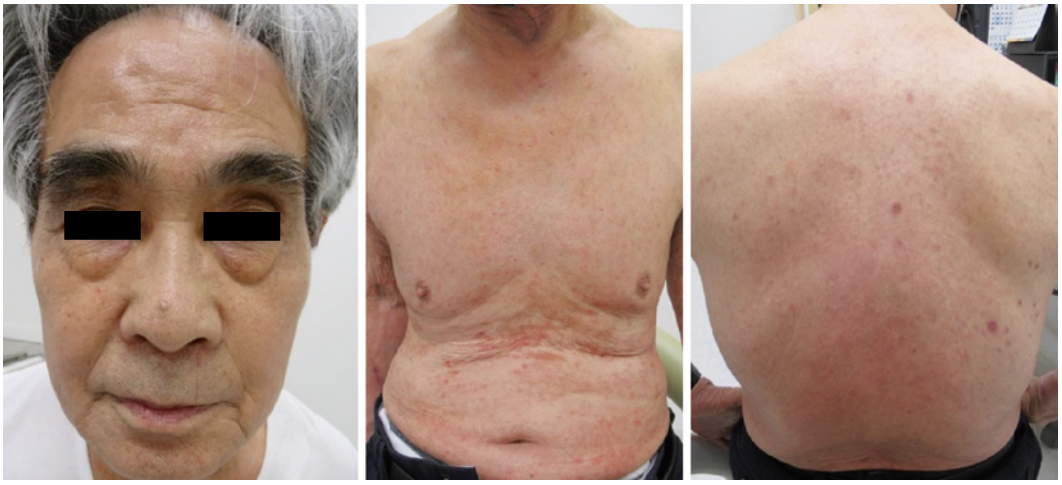

Fig. 3. Clinical pictures after 2 months of dupilumab administration. **a** Significantly improved edema of both lower eyelids. **b**, **c** Erythema and eruptions with improving trend.

Histopathological Findings

The epidermis had spongiosis and mild liquid degeneration. Epidermal thickening and prolongation of the epidermal processes were unremarkable. In the dermis, there was moderate lymphocytic infiltrate with histiocytes in a shallow perivascular area. The vascular endothelium was mildly enlarged, and neutrophils and eosinophils were distributed within the vessels. There were no significant changes in the adnexa or subcutaneous fatty tissue (Fig. 2).

Treatment and Outcomes

Based on the clinical symptoms and pathological findings, the patient was diagnosed with papuloerythroderma, and dupilumab was administered. Two months after the administration, erythema and eruptions improved, and TARC was decreased to 1,277 pg/mL (Fig. 3). Four months after the treatment, the patient did not experience any itchiness, TARC was 825 pg/mL, and the blood eosinophil count decreased to 530/μL. Six months after the start of treatment, the patient was still free of pruritus and papules, and his symptoms continued to improve without apparent adverse effects (Fig. 4).

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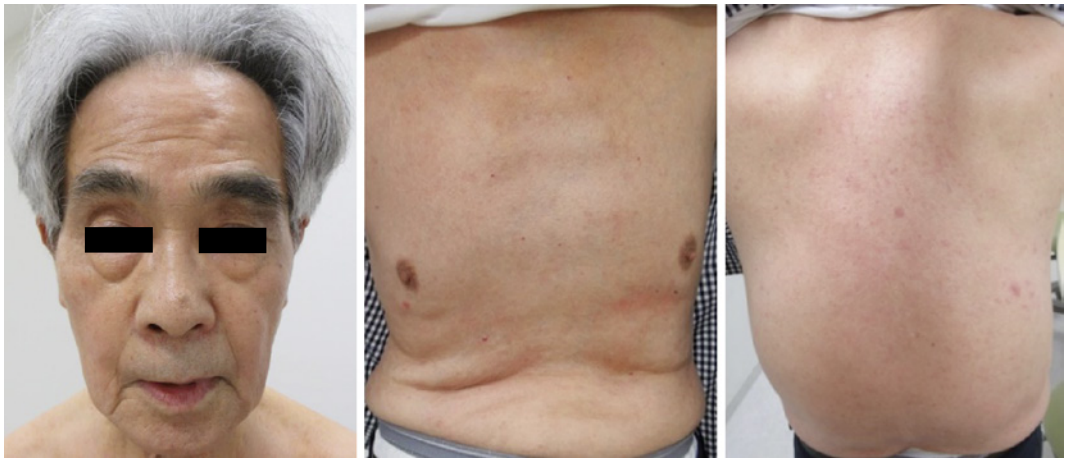

Fig. 4. Clinical pictures after 6 months of dupilumab administration. **a** Edema of both lower eyelids that continues to improve. **b**, **c** Erythema and eruptions that have completely disappeared.

Discussion

Papuloerythroderma was described by Ofuji et al. [1] in 1979 as a disease that begins with lichenoid papules and presents with erosive erythroderma-like lesions. They listed eight disease characteristics [1]: (1) it is more common in elderly men; (2) the basic skin rash is a red, full-blown papule that becomes dense and coalesces into a diffuse lesion resembling erythroderma; (3) there is often no rash on the face, and even if there is, it is mild; (4) large wrinkles in the axillae, elbows, knees, groin, and abdomen lack a rash with clear borders; (5) there is itching but no general discomfort; (6) the main histopathological finding is perivascular inflammatory cell infiltration with eosinophils in the upper dermis, which is not specific for both papules and erythema; (7) eosinophilia in peripheral blood; and (8) painless lymphadenopathy in the axilla and inguinal region. In the current case, the diagnosis of papuloerythroderma was made because the patient fulfilled almost all the characteristics except lymphadenopathy.

The major treatments include topical corticosteroids, oral antihistamines, and antiallergic agents. Other treatments have been attempted, such as oral steroids, cyclosporine, etretinate, and ultraviolet light therapy for refractory cases. In a report by Tanei and Hasegawa [2], cytokine production and expression of skin-homing receptors in circulating T cells of patients with 2 cases of papuloerythroderma were investigated, suggesting that Th2 cells may be involved in the pathogenesis [3]. The reason for this is that the percentage of CD4+ and CD8+ T cells producing IL-4, IL-13, and IL-22 in the peripheral blood of patients with this disease was significantly higher than that in healthy subjects, and the percentage was significantly reduced after remission [3, 4]. Th2 cytokines are important mediators that affect the production of specific and nonspecific IgE antibodies and the survival of eosinophils [5]. Based on the above report, Th2 type immune response was considered to be predominant in this disease. Eosinophil count and TARC and IgE levels were increased in the current case. There are various factors that lead to Th2 predominance; aging and decreased testosterone levels are thought to be among them. These factors may be related to the fact that the disease tends to occur in elderly men [2]. In general, the disease onset tends to occur in people older than 80 years. In refractory cases, topical steroids, oral steroids, and cyclosporine are used, but it is important to note that immunosuppression associated with these therapies may lead to infection and unfortunate outcomes, especially in the elderly. Since he was 84 years old and his activities of daily living were independent, we considered that the use of oral steroids

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might induce wide range of side effects including infection and osteoporosis, which could lead to bone fractures and a decrease in activities of daily living. He was not suffering from diabetes mellitus, but it was necessary to consider the possibility that oral steroids could cause glucose intolerance in his treatment choice. Therefore, we focused on Th2 cytokines, such as increased eosinophils and IgE, as one of the pathogenesis mechanisms, and tried to suppress the Th2 immune response by inhibiting signal transduction by IL-4/13 using a monoclonal antibody against the IL-4Rα of IL-4 and IL-13 receptors. As a result, the papules, erythema, and eruptions mainly on the trunk improved dramatically. In addition, the serum TARC level, which has been reported to be useful as a biomarker of Th2 immune response because it stimulates the CC chemokine receptor 4 expressed on Th2 cells [6], decreased significantly along with a decrease in itchiness. In other reported cases, itching and TARC improved rapidly after the first administration of dupilumab, which can be regarded as a therapeutic advantage [7, 8]. In the current case, marked edema of both the lower eyelids, presumably induced by Th2 cytokines, also improved with a single dose of dupilumab. After 9 months from the start of the treatment, the symptoms continued to improve and stabilize. Based on the results of this study, we believe that a treatment focusing on specific cytokines may be one of the treatment methods chosen from the standpoint of safety, considering the concern about immunosuppression caused by the systemic administration of steroids and cyclosporine, especially in refractory cases in the elderly. In summary, dupilumab is one of the treatment options that can be used to treat papuloerythroderma refractory to topical steroids.

Statement of Ethics

The research was conducted in accordance with the Declaration of Helsinki. The patients provided a written informed consent to publish their case studies, including publication of images. The paper is exempt from Ethical Committee approval, because of the single case study and accordance with local or national guidelines.

Conflict of Interest Statement

The authors have declared that no competing interests exist.

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The authors did not receive any financial support for the present study.

Author Contributions

Ayaka Mizuno and Keiichi Yamanaka treated the patient. Ayaka Mizuno, Koji Habe, Yoshiaki Matsushima, Makoto Kondo, and Keiichi Yamanaka wrote 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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