SHORT COMMUNICATION

Effect of Dupilumab on Generalized Verrucosis in Refractory Bullous Pemphigoid

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Bullous pemphigoid (BP) is one of the most common bullous diseases. Many patients with BP experience various infections due to their immunosuppressive therapy for disease control. Generalized verrucosis (GV) is described as a chronic and progressive cutaneous human papillomavirus (HPV) infection resulting in more than 20 lesions. GV is always associated with immunodeficiency and resistance to conventional treatments (1). We report here a case of a man with BP and GV who was successfully treated with dupilumab.

CASE REPORT

A 63-year-old man presented to the dermatology department with a 1-year history of recurrent erythema and blisters and a 3-month history of progressive verrucous nodules on both hands. He had been diagnosed with BP 11 months previously and was being treated with oral glucocorticoids (0.5 mg/kg/day) and oral methotrexate (10 mg/day). However, he experienced multiple disease flares during the glucocorticoid tapering process. In the week prior to the current visit, erythema and blisters with

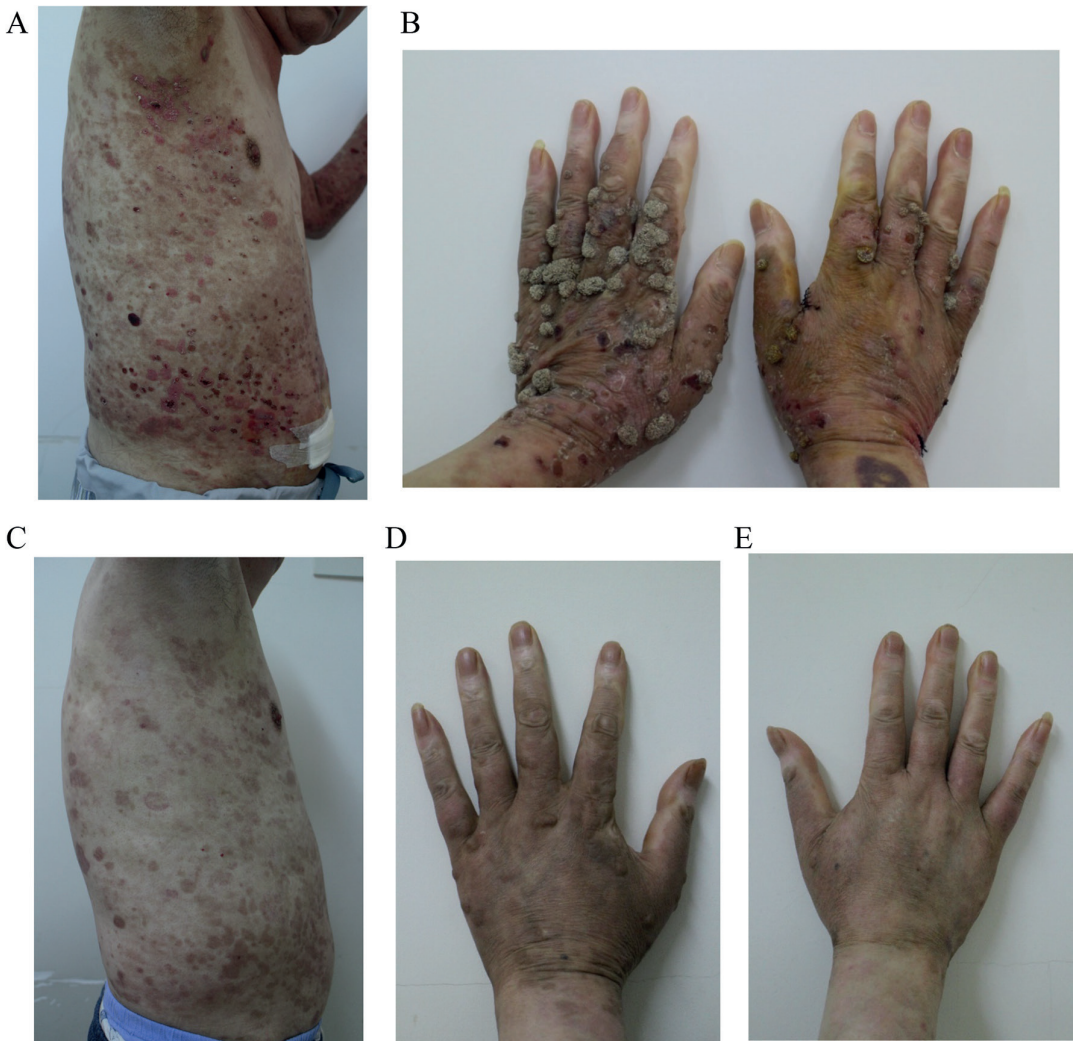

Fig. 1. Clinical images of bullous pemphigoid (BP) and generalized verrucosis (GV): (A, B) BP lesions and GV lesions before dupilumab treatment. (C, D, E) BP lesions and GV lesions 6 weeks after start of dupilumab treatment.

severe itching appeared again (**Fig. 1**A). Simultaneously, multiple nodules began to appear on both hands 3 months before this visit (Fig. 1B). The lesions responded poorly to topical imiquimod, and laser treatment was not possible due to the large area of distribution.

A skin biopsy of the hand skin lesions was performed, which confirmed verruca (Fig. S1). Given his refractory disease, he was treated with dupilumab (600 mg initially, followed by 300 mg every other week subcutaneously) without changing the dose of immunosuppressants (Fig. S2). His pruritus improved in 3 days, and the blistering stopped within 2 weeks (Fig. 1C). Surprisingly, the number of GV lesions began to decrease and the lesions disappeared completely after 6 weeks (Fig. 1D, E). At the 12-month follow-up, the patient was taking 10 mg/day prednisone and 300 mg dupilumab every month, and methotrexate was discontinued. No recurrence was observed.

DISCUSSION

Traditional treatment for BP includes topical/systemic corticosteroids and tetracyclines. Due to the older age of the patient population, the side-effects related to glucocorticoids are of concern. Short-term control of blisters with tetracycline treatment is less than optimal. Recently, biologics, including rituximab and omalizumab, have shown promise in treating BP that is refractory to conventional therapies (2). However, the efficacy and safety of these novel therapies remain controversial (3, 4).

Dupilumab is a monoclonal antibody that can inhibit the T helper 2 (Th2) cell immune response by targeting interleukin (IL)-4Rα and blocking both IL-4 and IL-13 signalling. Previous studies have demonstrated the potential of dupilumab to treat BP since Th2 proinflammatory cytokines play a role in the pathogenesis of BP (5).

In the current case, remission of GV was achieved, and his BP was treated successfully with dupilumab. Although remission has been observed similarly in patients with atopic dermatitis, authors tend to attribute the phenomenon to the improvement in skin barrier function (6, 7). In the current patient, all GV lesions occurred in the BP-free area. Therefore, it is assumed that restoration of the Th1/Th2 balance plays a more important role.

The elimination of HPV is mostly based on the host's cellular immune response, in which Th1 immune response-related cytokines play a significant role (8). Immunotherapy based on the Th1 immune response, such as imiquimod and interferon, showed a curative effect in HPV infection. Studies have also shown that the failure of immunotherapy is related to Th2 cytokine profiles, such as IL-4 and IL-10, which indicates that topical Th1/Th2 imbalance might lead to warts (9). However, in patients with atopic dermatitis, the use of the IL-4 inhibitor dupilumab may lead to the aggravation of diseases dominated by the Th1/Th17 axis, such as psoriasis and multiple sclerosis (10). Therefore, we assume that dupilumab may relieve the inhibition of the Th1 response by blocking IL-4 signalling, which might lead to clearance of HPV. Since the skin lesions of GV began to improve before the dose of immunosuppressants was reduced in the current case, we do not believe that the reduction in drug dose is related to this finding (Fig. S2).

In conclusion, dupilumab is an option for the treatment of Th2 diseases combined with HPV infection. This case suggests that IL-4 inhibition might be a new biologic therapy target for immunosuppression-associated GV.

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