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Pompholyx as a clinical manifestation suggesting increased serum immunoglobulin G (IgG) levels in a patient with drug-induced hypersensitivity syndrome / drug reaction with eosinophilia and systemic symptoms (DiHS/DRESS)

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SIR, To date, the pathogenesis of pompholyx is still unknown although there are many theories about the etiology of pompholyx. It is very likely that several aggravating factors, such as atopy, contact allergy, allergy to ingested metals, psychological stress, and drug eruption, influence the development and formation of pompholyx in a predisposed individual¹. It has been well known

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to be associated with intravenous immunoglobulin infusion (IVIg)²⁻⁴, suggesting the possibility that a rapid increase in serum IgG levels may be involved in the development of pompholyx. In this regard, we hypothesized that pompholyx may develop in patients with the alterations of serum IgG levels. We previously demonstrated that decreased serum IgG levels are common in the initial stage of drug-induced hypersensitivity syndrome / drug reaction with eosinophilia and systemic symptoms (DiHS/DRESS) and that they are rapidly restored upon withdrawal of the causative drugs⁵. Nevertheless, there have been no previous reports describing the occurrence of pompholyx in these patients. We describe here a 39-year-old woman who developed pompholyx on palmoplantar surfaces during the course of DiHS/DRESS coincident with the increase in IgG levels.

A 39-year-old woman had been treated with carbamazepine for epilepsy. On day 35 of this treatment, she developed skin rashes and fever. On physical examination, erythematous rashes were observed on the trunk and extremities. Cervical lymphnode swelling was detected. Multiple tiny reddish vesicles were observed on both her palms. The patient did not have a personal history of atopy, eczema or pompholyx and neurological conditions. The rash and fever temporarily subsided in a few days, but worsened again with leukocytosis and liver dysfunction. Her laboratory findings showed leukocytosis 20,600/mm³ (normal range 3,500-9,000) with eosinophilia of 13%, and liver dysfunction (aspartate and alanine aminotransferases values of 213 and 322 IU/l [normal range 8-33 and 3-30, respectively]). After admission, she improved steadily after initiation of prednisolone 50 mg daily. Virological investigations were carried out by measuring viral DNA loads in peripheral blood leukocytes using quantitative polymerase chain reaction (PCR) method. HHV-6 DNAs were detected in the leukocytes at 23 days after onset. Based on these findings, she was diagnosed as having DiHS/DRESS. Using the RegiSCAR scoring system⁶, this case is classified as definite DRESS. At 18 days after onset, pompholyx appeared again on palmoplantar surfaces (Fig.1). In this patients, hypogammaglobulinaemia, particularly a profound decrease in serum IgG level (716mg/dl), was observed at 14 days after the onset, and the decreased serum IgG levels was restored to normal at

6 days, at which time pompholyx developed (Fig.2). Thus, the dramatic increase in serum IgG levels to restore the decrease was coincident with the development of pompholyx. Moisturizer was prescribed, and the skin lesions subsided without recurrence in 2 weeks.

As we reported previously, DiHS/DRESS patients are characterized by a decrease in the serum IgG level a week after onset⁵. The serum IgG levels continue to decrease for at least several days to a week after drug therapy is discontinued. Immediately after the nadir in the decrease, however, the overshoot in the IgG levels is observed within 1 to 2 weeks⁵. In this patient, pompholyx on palmoplantar surfaces occurred, coincident with overshooting increases in the serum IgG level. However, one may argue that the first episode of pompholyx appeared to develop at the time when serum IgG levels started to decrease. Although this possibility cannot be excluded due to our unavailability of serum samples before onset of the pompholyx, it is likely that the first episode may have also occurred coincident with the possible increase in serum IgG levels before onset in view of the second episode. According to previous reports^{2,3}, pompholyx typically occurred 5 to 7 days after initiating IVIg in patients with chronic inflammatory demyelinating polyneuropathy, Guillain-Barre syndrome, Stevens-Johnson syndrome, idiopathic thrombocytopenic purpura and Kawasaki disease : a time frame is quite similar to that in this patient. The range of the increase in the serum IgG levels after the nadir in our case (12.8mg/kg b.w.) was equivalent to that (9.9 to 65.6mg/kg b.w.) achieved in the serum of patients treated with high doses of IVIg who were diagnosed as Stevens-Johnson syndrome or pemphigus vulgaris and treated in our dermatology department from 2008 to 2014. Interestingly, vesicles were observed at the time, when serum IgG levels were the same as the development of pompholyx. Although the mechanism of the induction of pompholyx by IVIg is unknown, these similarities led us to consider the possibility that pompholyx might represent an immunological reaction in response to a dramatic increase in serum IgG levels. Consistent with this view, pompholyx has been reported to occur in the setting of HIV infection after the introduction of antiretroviral therapy⁷, in a similar timing as demonstrated in our patient. If so, pompholyx-like reactions occurring after treatment of severe atopic dermatitis⁸ might also occur, coincident with

the increase in serum IgG levels. Because similar pompholyx-like eruptions have been previously reported to occur as an early manifestation of DiHS/DRESS^{9,10}, these lesions could also be interpreted as representing a cutaneous symptom in the course of DiHS/DRESS. However, from the longitudinal viewpoint of immune responses, thinking of “pompholyx” as a reaction to increased B cell responses rather than as a mere distinct clinical symptom of the disease might be more productive in terms of understanding the pathogenesis. Indeed, the pompholyx developed at 18 days after onset, at which time rashes had resolved, but serum IgG levels profoundly increased. Thus, we would like to interpret the finding as indicating that pompholyx-like lesions, which have been reported to occur during the early stage of the disease, may reflect a reaction to overshooting B cell responses occurring after the decrease in serum IgG levels. Recognition of this cutaneous manifestation as a sign of the rebounding increase in serum IgG levels may prove helpful in understanding of the pathogenesis and treatment of DiHS/DRESS. Despite the high prevalence of the rebounding IgG responses in many patients with DiHS/DRESS, pompholyx or pompholyx-like lesions have rarely been reported in the literature. This is likely because its subtle and transient eruption would be overlooked because of lack of recognition: if special attention is called to pompholyx on palmoplantar surfaces and the time course of appearance of the eruption in relation to serum IgG levels is examined carefully in any patient with DiHS/DRESS, the occurrence of pompholyx coincident with the rebounding increase in serum IgG levels would be much more common than generally thought. The pompholyx points to immunopathologic pathways previously unexplored in DiHS/DRESS patients. Dermatologist should be aware of pompholyx that can occur at the time when serum IgG levels increase.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

FINANCIAL DISCLOSURE

The authors have no financial disclosure.

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TABLE AND FIGURE LEGENDS

Fig. 1. Pompholyx affecting palmoplantar surfaces at 18 days after onset.

Fig. 2. Clinical course of the patient. IgG and PSL indicate immunoglobulin G and prednisolone.



