Dear Editor

Does Drug-induced Hypersensitivity Syndrome Elicit Bullous Pemphigoid?

A 68-year-old Japanese woman presented to our hospital for disseminated erythema on the whole body, lymphadenitis and high fever on 10 August 2003 (Fig. 1a). The erythema developed with a sudden onset after taking minocycline hydrochloride for pharyngitis and 38-degree fever on 6 August 2003 (day 0). She had taken carbamazepine and zonisamide for one year to control trigeminal neuralgia. Histopathological examination demonstrated perivascular dermatitis, and infiltration cells mainly consisted of eosinophils and lymphocytes in the upper dermis. She was given a diagnosis of drug eruption, and all the medication was stopped (day 4). However, erythema continued to develop, and we administered 60mg/day of oral prednisolone (day 8), after which the fever and erythema gradually ameliorated. Laboratory data showed leukocytosis (20.14 × 10⁹/L), hypereosinophilia (23%), atypical lymphocytes (4%), elevated γ-glutamyltranspeptidase (385U/L) and elevated liver enzymes (aspartate transaminase 19U/L, alanine aminotransferase 61U/L). Thereafter, titer for human herpes virus 6 (HHV-6) IgG increased from ×10 (day 8) to ×1280 (day 25). Collectively, a diagnosis of drug-induced hypersensitivity syndrome (DIHS) was established. We could not perform patch testing, and results of drug-induced lymphocyte stimulation tests for carbamazepine, zonisamide and minocycline hydrochloride were negative. It remained unclear which drug elicited the eruption. While tapering oral prednisolone, we started cyclosporine (3mg/kg) because we found slight recurrence of erythema (day 58), and we finally reduced oral prednisolone to 20 mg/day, with slight erythema remaining (day 68). However, 9 days later (day 77), itchy edematous erythema and tense bullae developed on the trunk and extremities, and there was no relationship between the distribution of the DIHS eruptions and the new eruptions (Fig. 1b). Biopsy specimens revealed subepidermal blisters with eosinophil and lymphocyte infiltration. Direct and indirect immunofluorescence showed lesional and circulating IgG autoantibodies at the basement membrane (Fig. 2). The laboratory data demonstrated hypereosinophilia (36.6%) and high index of anti-BP 180 (2780) antibody by ELISA (day 92). Anti-nuclear antibody was negative. Thus, we diagnosed bullous pemphigoid (BP). Despite of the combination therapy with oral prednisolone (50mg/day), cyclosporine (3–5mg/kg), azathio-
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prine (100 mg/day), cyclophosphamide pulse (500 mg/day), or double filtration plasmapheresis, the eruptions were recalcitrant. Finally a remission was achieved by starting mycophenolate mofetil (3 g/day) and the titer of anti-BP 180 antibody began to decrease markedly (Fig. 3).

To the best of our knowledge, this is the first report of BP developing consecutively after DIHS. The pathological or immunological linkage as to whether BP occurred incidentally after DIHS or was induced by DIHS remains unclear. However, Kano et al. reported a case of sclerodermaid graft-versus-host disease-like lesions occurring after DIHS. They suggested that the autoimmune manifestations observed in patients with chronic GVHD could also be seen in patients with DIHS in view of clinical similarity between GVHD and DIHS. Although a recent report showed that a decrease in immunoglobulin levels and B-cell counts can be associated with HHV-6 reactivation and the subsequent onset of DIHS, our present case suggests that this disease may involve or evolve into other immunological events including autoimmunity.

Akiko Kijima1, Shigeki Inui2, Toshiaki Nakamura2, Satoshi Itami2 and Ichiro Katayama2
1 Department of Dermatology, Osaka Prefectural Medical Center for Respiratory and Allergic Disease, Japan and 2Department of Dermatology, Osaka University Graduate School of Medicine, Osaka, Japan

Email: akiko-kijima@kawachi.zaq.ne.jp

REFERENCES

Fig. 2 Positive deposition of IgG at the basement membrane zone on direct immunofluorescence (DIF) studies.

Fig. 3 Clinical and laboratory course of DIHS (a) and BP (b). HHV-6, human herpesvirus 6; PSL, prednisolone; CyA, cyclosporine; CYC, cyclophosphamide; DFPP, Double filtration plasmapheresis; AZP, azathioprine; MMF, mycophenolate mofetil.