



Letter to the Editor

Effectiveness of omalizumab in two cases of normocomplementemic urticarial vasculitis due to perivascular mast cell infiltration

Dear Editor,

Urticarial vasculitis (UV) is characterized by long-lasting urticarial rashes and the histopathologic finding of leukocytoclastic vasculitis or lymphocytic vasculitis. UV comprises normocomplementemic urticarial vasculitis (NUV), which has normal serum complement levels, hypocomplementemic urticarial vasculitis (HUV), which has low serum complement levels, and hypocomplementemic urticarial vasculitis syndrome (HUVS), which is associated with pulmonary or renal disease, episcleritis, and uveitis. Previous studies found that 6–12.5% of UV cases were related to infection^{1,2} and that 7–7.8% of UV cases were related to malignancy.^{1,2} Herein we present two cases of normocomplementemic urticarial vasculitis with increased perivascular mast cell infiltration which were successfully treated using omalizumab.

Case 1 was that of a 49-year-old Japanese male patient who experienced recurrent episodes of wheal-like erythema for four weeks. His symptoms failed to respond to a double dose of second-generation antihistamine at the previous clinic. A clinical examination revealed that the erythema on the face and trunk had left slight, post-inflammatory hyperpigmentation (Fig. 1a). Laboratory analysis demonstrated normal levels of complement proteins (C3 and C4) and antinuclear antibodies (ANA). The serum total IgE was 842 IU/ml. He had no history of infection or malignancy. A skin biopsy revealed leukocytoclastic vasculitis with perivascular infiltrates and neutrophil predominance (Fig. 1b). Direct immunofluorescence (DIF) detected IgG and C₃ deposition on the vessels in the upper layer of the dermis. A combination of prednisone 0.5 mg/day and cyclosporine 3 mg/kg/day was administered for two weeks without effect. Thereafter the treatment regimen was switched to omalizumab 300 mg/months for five months. After switching to omalizumab, the skin eruptions improved immediately. The UCT (Urticarial Control Test) changed from 0 to 16 after the treatment.

Case 2 was that of a 61-year-old Japanese female patient who had recurrent episodes of wheal-like erythema for four weeks. Corticosteroids and a double dose of second-generation antihistamines at the previous clinic were ineffective. Clinical findings showed wheal-like erythema on the trunk which later resolved, leaving slight, post-inflammatory hyperpigmentation (Fig. 1c). Laboratory analysis demonstrated normal C3 and C4 levels and negativity for ANA. The serum total IgE was 127 IU/ml. She had no history of infection or malignancy. A skin biopsy showed leukocytoclastic vasculitis (Fig. 1d) but denied DIF, IgM, IgG, and C₃ deposition on the vessels in the upper layer of the dermis. Based on the patient's

medical history, omalizumab 300 mg/monthly was administered, and her eruptions resolved within one month after the start of treatment. Omalizumab administration was terminated after five additional doses. The UCT changed from 0 to 16 after the treatment.

To understand the mechanism of omalizumab's activity against NUV, mast cells were examined by toluidine blue (TB) staining. The results showed an increased number of mast cells around the vessels in the dermis (Fig. 2a, b). The number of mast cells in NUV is comparable to that in HUVS (Fig. 2c), but fewer mast cells are observed in IgA vasculitis (Fig. 2d). Generally, TB stains both mast cells and basophils. Confocal laser microscopy using anti-mast cell tryptase antibody and anti-basophil antibody (Supplementary Fig. 1) confirmed that mast cells, but not basophils, had increased around the vessels in both NUV and HUV. In these cases, the TB-positive cells were identified as mast cells. IgA vasculitis and

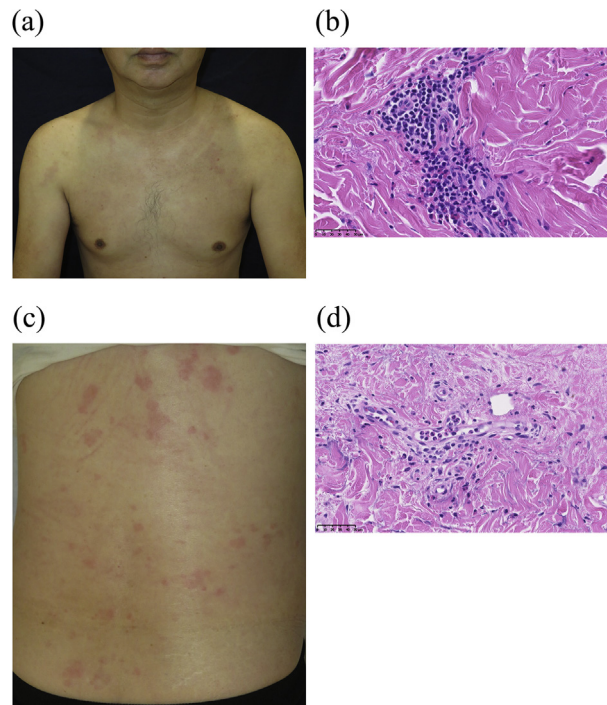


Fig. 1. Clinical features and pathological findings. Case 1. (a) Wheal-like erythema appeared on the trunk. (b) Skin biopsy revealed leukocytoclastic vasculitis with perivascular infiltrates with neutrophil predominance. Case 2. (c) Wheal-like erythema appeared on the trunk. (d) Skin biopsy revealed leukocytoclastic vasculitis.

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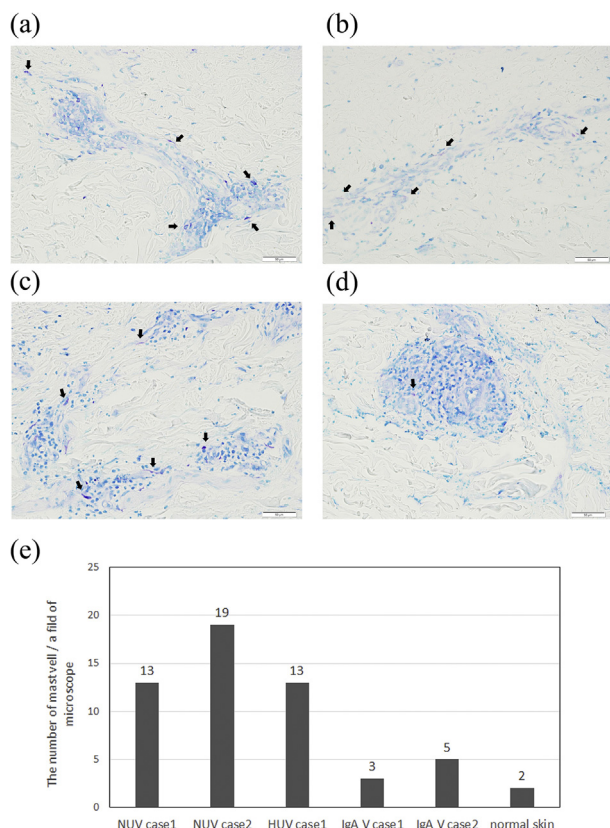


Fig. 2. Pathological findings on toluidine blue staining. (a) Case 1 with NUV; (b) Case 2 with NUV; (c) HUV; (d) IgA vasculitis; (e) Mast cells/field at indicate magnification.

normal skin used for comparison with UV showed no increase in mast cells or basophils in IgA vasculitis or normal skin.

More than a century has passed since Wills and Lond first described two, young, male patients with UV presenting with fever, arthritis, purpura, angioedema, and wheals.³ The worldwide prevalence of UV is unknown. In the US, the UV incidence is reportedly 0.5 per 100,000 person-years. In a recent study, two researches have been reported with total 261 patient eligible studies and 789 unique patients with UV. Corticosteroids were shown to be effective for both cutaneous and extracutaneous symptoms in most UV patients,² but a few unresponsive cases have been reported. Corticosteroids and H1-antihistamines were ineffective in the present two present cases. However, recent studies demonstrated the efficacy of omalizumab in UV treatment.⁴ One report showed that omalizumab was effective not only for HUV^{5,6} but also for NUV.^{1–4} The mechanism of omalizumab activity in the treatment of these conditions is unknown. Some reports suggested that the drug may act through reducing IgE levels and affecting cellular activation mechanisms.⁷ The number of perivascular mast cells increases in both HUV

and NUV (Fig. 2e), and UV shares some features with neutrophilic vasculitis and urticaria. One study found that the mast cell infiltration in vasculitis was related to protease,⁸ suggesting that mast cell infiltration improved in UV via suppression of degranulation by omalizumab, which resulted in a decrease in protease. The present study is the first to report that UV infiltrate contains not only neutrophils but also mast cells. The efficacy of omalizumab in UV treatment makes this drug a potentially viable, first-choice alternative to corticosteroid therapy, given the latter's adverse effects, such as diabetes, and hypertension. More data are needed to verify the efficacy of omalizumab in the treatment of UV.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2020.09.012>.

Conflict of interest

The authors have no conflict of interest to declare.

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