

Case Report

TREATMENT OF URTICARIAL VASCULITIS WITH OMALIZUMAB

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CASE REPORT

A 45-year-old woman with an eight-year history of chronic urticaria was reviewed in our multidisciplinary allergy and dermatology clinic for worsening symptomatology. The evolution of her chronic urticaria included: initial typical urticarial plaques on trunk and limbs (lasting less than 48 hours) with intermittent angioedema of her lips. She experienced flaring of urticaria prior to menstruation; flare-up after a trial of medroxyprogesterone acetate for worsening menorrhagia; progressively increasing size and duration (up to 96 hours) of the urticarial plaques with associated blistering; and resolution with post-inflammatory hyperpigmentation (see Figures 1–3).

She had no known co-morbid medical conditions, and a three-pack-year smoking history. Family history included breast cancer in both grandmothers. Relevant gynaecological history included two normal pregnancies, a tubal ligation after the second pregnancy and menorrhagia ten years after the last pregnancy.

On examination she was overweight with a body mass index (BMI) of 44. She had tender, large indurated erythematous plaques with areas of coalescing blisters. The largest plaque was over the upper back with smaller ones scattered on the

upper body and to a lesser extent lower limbs (see Figures 1 and 2). The plaques were noted to resolve with post-inflammatory hyperpigmentation (see Figure 3). Laboratory results included a normal full blood count, liver profile, C3 and C4 complement levels and appropriate follicle-stimulating, luteinising and oestrogen hormone levels. An autoimmune screen was negative.

We considered progesterone-associated urticaria, due to the history of worsening symptoms with menstruation and flaring



Figure 1: Large urticarial plaque on the mid back with peau d'orange (small arrow) and vesicles (large arrow) on the upper back.



Figure 2: Large indurated urticarial plaque surrounded by smaller erythematous plaques.



Figure 3: Urticarial plaques in different stages of evolution. Larger arrow highlights fresh lesions and the smaller arrows those that have resolved with post-inflammatory hyperpigmentation.

during medroxyprogesterone acetate treatment. Patch testing using 30% dilutions of medroxyprogesterone acetate in two vehicles (sterile water and petroleum jelly) was negative both at 20 minutes and 48 hours. Persistence of the plaques and resolution with post-inflammatory hyperpigmentation prompted us to perform another skin biopsy. A skin biopsy performed during her initial presentation, seven years prior, showed mild superficial oedema in the papillary dermis, ecctatic vessels and no vasculitis – features consistent with urticaria. In contrast, the second biopsy showed epidermal spongiosis with intracorneal blister formation and papillary dermal oedema. Abundant eosinophils with admixed neutrophils and lymphocytes were present within the superficial and deep dermis in a perivascular and periadnexal distribution. Leucocytoclasia and dermal flame figures were noted. In addition, there was evidence of vascular damage, manifested by focal fibrinoid necrosis of vessels and erythrocyte extravasation (see Figure 4). These features were consistent with leukocytoclastic vasculitis and our final diagnosis was urticarial vasculitis (UV).

Over the preceding eight years her chronic urticaria had been managed with different classes of high-dose antihistamines, including cetirizine, desloratadine, and fexofenadine; adjunctive H2-receptor antagonist ranitidine; and low-dose oral prednisone with only partial resolution. We considered the risk–benefit of:

- attempting more aggressive progesterone suppression with gonadotropin-releasing hormone agonists;
- immunosuppression with cyclosporine, or
- anti-IgE therapy.

We decided on a trial of anti-IgE therapy with omalizumab, a humanised anti-IgE monoclonal antibody. A dose of 300 mg was administered subcutaneously. The response was a complete resolution of her urticarial plaques within days following the injection. Two weeks after the injection she developed shortness of breath and an increased blood pressure requiring hospitalisation. She was diagnosed with a pulmonary embolus. She recovered fully and is now on lifelong warfarin therapy and antihypertensives. In consultation with haematologists and pharmacologists we decided to recommence omalizumab therapy as the test dose had resulted in a dramatic improvement of her symptoms and quality of life. She has since received four doses of omalizumab, four weeks apart, with no recurrence of her urticarial plaques.

In parallel to our diagnosis of UV, gynaecological work-up for menorrhagia found a left ovarian cyst measuring 50 × 40 × 30 mm. Initial management was conservative, but due to persistent heavy bleeding she elected to have a left oophorectomy. Histology confirmed this to be a benign cystic teratoma. In the three months following the removal of the

teratoma and off omalizumab, she had continued to have cyclical urticaria. This resolved on reinitiating of omalizumab.

DISCUSSION

Chronic urticaria is the occurrence of wheals and/or angioedema lasting longer than six weeks.¹ UV is a clinico-pathologic entity characterised by recurrent episodes of wheals that have the histopathologic features of leukocytoclastic vasculitis.² Neutrophilic urticaria has been proposed to represent a type of urticarial reaction pattern in between ordinary urticaria and urticarial vasculitis, although this is still debated.³ UV is classified as normocomplementaemic or hypocomplementaemic based on the presence of complement consumption (decreased C3, C4 and C1q).⁴ In both subtypes, urticaria and angioedema are often accompanied by other symptoms including chest or abdominal pain, fever and joint pain. These extra-cutaneous features are most prominent in the hypocomplementaemic subtype, most frequently associated with systemic

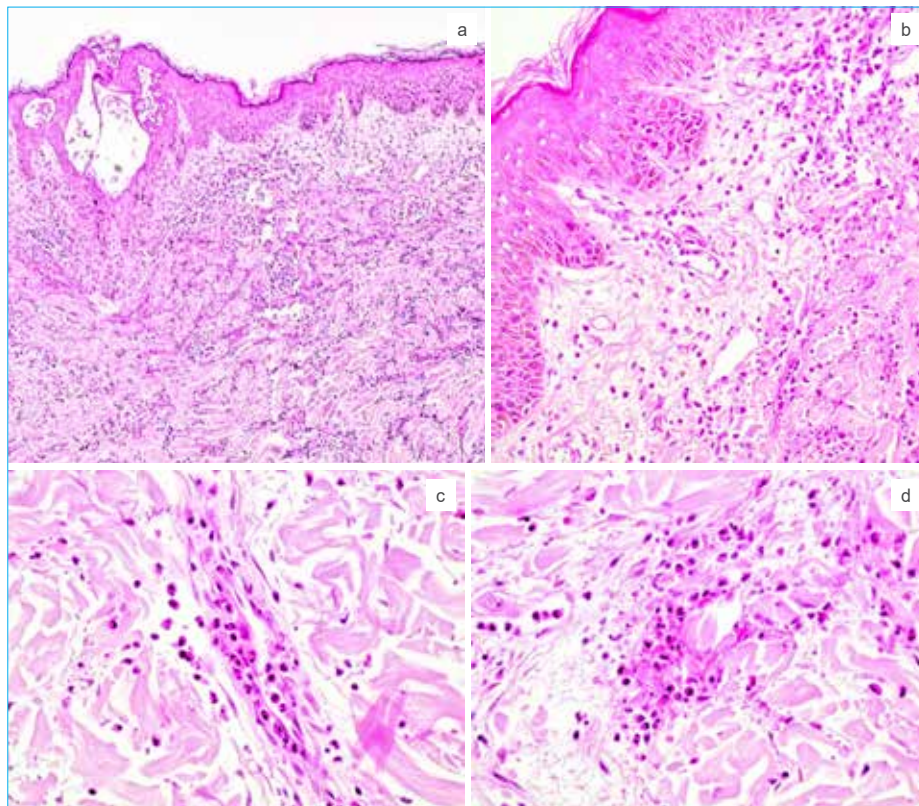


Figure 4: Haematoxylin and eosin stains of sections of the skin punch biopsy shows: **a)** an intracorneal blister, with epidermal spongiosis, papillary dermal oedema and moderately dense superficial and deep dermal inflammation, **b)** numerous eosinophils, neutrophils and lymphocytes are noted in the dermis, with evidence of leucocytoclasia and red blood cell extravasation, **c)** prominent perivascular eosinophils, **d)** a conspicuous flame figure and fibrinoid necrosis

lupus erythematosus.⁴ UV can be associated with infections, drug reactions or part of paraneoplastic syndrome.²

UV is immune-complex mediated, where circulating antigen-antibody complexes are deposited in cutaneous vascular walls activating complement, generating anaphylatoxins, which in turn causes mast cell degranulation and neutrophil chemotaxis.² It is interesting to postulate a connection between our patient's UV and her ovarian teratoma. A teratoma derives from all three embryonic tissue types – ectoderm, mesoderm and endoderm.⁵ Thus, it is possible that auto-reactive antibodies directed against tumour antigens (paraneoplastic) led to the development of UV. The persistence of symptoms post-resection argue against the teratoma as the disease driver, although circulating antibodies may persist for up to six months post-removal and close follow-up will be required.⁶

Efficacious off-label use of omalizumab for UV treatment has been reported in case series and case reports.^{4,7} The specific mechanism of action in UV remains uncertain. Omalizumab inhibits IgE by binding to the IgE C3 domain.⁷ It also produces immunomodulatory effects, including a decrease in IgE cell receptors in mast cells and basophils as well as reducing B-cell activation and homing.⁷ Dosing in UV is similar to that in chronic urticaria (150–300 mg/month).^{4,7} The maintenance dose of omalizumab in UV, duration of treatment and tapering protocols are still unclear. No adverse effects were reported in the previous cases of UV treated with omalizumab.^{4,7}

We were concerned by the temporal relationship between omalizumab administration and pulmonary embolus in our patient. A prospective real world epidemiologic study that evaluated clinical efficacy and long-term safety of omalizumab in asthma showed omalizumab to increase the risk of pulmonary embolisms/venous thrombosis with an incidence event rate of 3.2 (95% CI 2.4–4.3) per 1 000 patient years versus 1.5 (95% CI 0.8–2.5) in non-omalizumab group.⁸ However, the adjusted

hazard ratio was 1.32 (95% CI 0.91–1.91) thus suggesting no significance between the two groups.⁸ Narukonda et al reported on a 53-year-old male patient with severe asthma on omalizumab for two years who developed an acute pulmonary embolism.⁹ They attributed the pulmonary embolism to omalizumab as they could not find any other identifiable cause.⁹ Our patient had other thromboembolic risk factors including obesity (BMI 44), recent surgery, and undiagnosed hypertension; her elevated d-dimer also indicated excess turnover of her coagulation pathway. Thus the contribution of omalizumab to her pulmonary emboli is uncertain; nevertheless, clinicians using omalizumab should be aware of this data in similar patients with high thromboembolic risk.

CONCLUSION

This complex case highlights the spectrum of severe chronic urticaria and important clinical role of histology in the management of such patients. The link to a benign ovarian teratoma is a rare association that may drive a paraneoplastic aetiology of UV. The case adds to the literature on the successful use of omalizumab in UV, as well as highlighting for clinicians the possible link of omalizumab with thromboembolic events. Further studies are required to understand the role, adverse effects and long-term outcomes of UV treatment with omalizumab.

INFORMED CONSENT

Written informed consent was provided by the patient for this case report and pictures to be published.

DECLARATION OF CONFLICT OF INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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