

Received Date: 27-Jan-2017

Accepted Date: 13-Feb-2017

Article Type: Letter to Editor

**Omalizumab does not improve skin lesions in a patient with
Hypocomplementemic Urticarial Vasculitis Syndrome**

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Keywords: urticaria, urticarial vasculitis, hypocomplementemia, glomerulonephritis, omalizumab

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jdv.14202

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Funding

The authors declare that no funding was received for the present study.

Conflict of interest

The authors declare that they have no conflict of interest.

Hypocomplementemic urticarial vasculitis syndrome (HUVS) is a rare immune complex-mediated disease being characterized by persistent urticarial lesions, hypocomplementemia and possible organ involvement [1]. Therapy of HUVS is reported to be challenging [2].

We report on a 36 year old non atopic female who first presented in our university allergy centre with 18 months history of recurrent urticarial flares. There was no focal infection and total serum IgE was within normal range. She was treated for five months with several oral antihistamines with no effect, even after up dosing. After having been lost to follow-up for eighteen months she presented with persisting urticarial flares and newly diagnosed nephrotic syndrome due to histologically proven membranoproliferative glomerulonephritis (GN) of unknown origin. A skin biopsy showed perivascular neutrophilic infiltrates with fibrinoid necrosis confirming urticarial vasculitis.

Blood tests showed persistent serum hypocomplementemia (C3 0,401 g/l, normal range 0.84-1.6, C4 0.030 g/l, 0.16-0.46) and elevated C1q-antibodies 66.4 U/l (<10) but no antinuclear antibodies, anti-double-stranded DNA antibodies or anti-cyclic citrullinated peptides.

Diagnostic criteria for HUVS with membranoproliferative GN were fulfilled (table 1) [3]. The patient complained about recurrent arthralgia of the fingers but had no suspicion of any other organ involvement. Oral therapy with mycophenolate mofetil (MMF, 720 bid) and prednisolone (80 mg/d being tapered to 5mg/d within 19 months) led to full recovery of GN but urticarial flares persisted . We added omalizumab subcutaneously (300-600mg once a month) which did not result in any significant change of skin lesions within 19 months. Subsequently we switched her from omalizumab to cyclosporine A (CSA, 3 mg/kg bodyweight) while keeping MMF and low dose prednisolone. As there was only mild improvement of urticarial flares and worsening of kidney function, we decided to stop CSA after four weeks and kept her under MMF and low dose prednisolone with skin lesions still persisting. Further treatment options were not started until now due to stable renal situation and the patient being reluctant.

HUVS is a rare form of UV with unknown prevalence and incidence being first described in 1973 [4]. It is based on development of immune complexes with activation of humoral autoimmune complex cascade. Diagnostic criteria were established in 1982 (Table 1) [3].

Systemic manifestations of HUVS (table 2 [1, 3, 5 ,6, 7]) can be very similar to systemic lupus erythematosus (SLE) including renal involvement in up to 50 % of the patients, ranging from mild proteinuria to nephrotic syndrome [8]. 54% of HUVS patients are diagnosed with SLE in a follow-up period, and 7-8% of SLE patients are reported to have HUVS [6].

Some patients with HUVS were reported to respond to low dose steroid, hydroxychloroquine or dapsone but others required high doses of glucocorticosteroids, cyclophosphamide, cyclosporine, azathioprine, MMF or methotrexate [1].

A recent review identified rituximab and cyclophosphamide as being the most effective therapies, followed by MMF and azathioprine [2]. Only few reports exist showing omalizumab to be effective in urticarial vasculitis [9; 10]. The mechanisms of action of omalizumab in this entity and in chronic spontaneous urticaria (CSU) are not fully understood and may include reduction of activity of IgG autoantibodies against FcεRI and IgE as well as of mast cell releasability [11]. To the best of our

knowledge, we report for the first time upon the application of omalizumab in a patient with HUVS, which turned out to be ineffective.

In summary, we present a case of HUVS with skin lesions not responding to antihistamines, MMF, CSA or omalizumab. This suggests the pathogenesis of urticarial skin lesions in HUVS being markedly different from that in CSU.

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Table 1: Diagnostic criteria for Hypocomplementemic urticarial vasculitis syndrome: Two major and at least two minor criteria are required for diagnosis [3]. Bold: Criteria being present in our patient

Table 2: Reported organ involvement and estimated frequency in patients with HUVS

Major criteria	Minor criteria
recurrent urtikaria > 6 months	Biopsy proven vasculitis of dermis
hypocomplementemia	Positive C1q-antibodies and/or suppressed C1q-level
	glomerulonephritis
	arthralgia/arthritis
	ocular inflammation
	recurrent abdominal pain

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Organ system	Lung [6]	Kidney [5]	Joints [3]	Gastrointestinal tract [6]	Ocular [7]	Central nervous system [1]	Cardiac [1]
Symptom	dyspnea, coughing, hemoptysis, pleural effusion, COPD	Proteinuria, hematuria, glomerulo-nephritis	Arthralgia, arthritis	abdominal pain, nausea, vomiting diarrhea, ascites, hepatomegaly, splenomegaly	Inflammation of uveal tract, conjunctivitis, episcleritis	seizure, aseptic meningitis , peripheral neuropathy, pseudotumor cerebri	Valvular abnormalities, congestive heart failure
Frequency (%)	50	50	50	30	30	rare	rare

Table 2: Reported organ involvement and estimated frequency in patients with HUVS