Restoration of aspirin tolerance following omalizumab treatment in a patient with chronic spontaneous urticaria

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Summary
Up to 30% of cases of chronic spontaneous urticaria (CSU) are exacerbated by COX-1 inhibiting nonsteroidal anti-inflammatory drugs (NSAID); this clinical picture is termed NECD (NSAID-exacerated cutaneous disease). On the other hand, multiple NSAID hypersensitivity may occur in the absence of an underlying CSU also, a situation that is termed NIUA (NSAID-induced urticaria / angioedema).
The present study reports a case of multiple NSAID hypersensitivity that occurred in a man much before he developed severe CSU. Omalizumab treatment eventually induced a remission of the cutaneous disease which was associated with aspirin tolerance, as assessed by open oral challenge with the drug. Altogether, this case suggests that it might be worth to investigate tolerance to aspirin or other strong COX-1 inhibitors in NECD patients showing a complete response to omalizumab, and maybe also the effects of omalizumab in NIUA patients as well.

Introduction
Chronic spontaneous urticaria (CSU) is a rather frequent disorder characterized by the recurrent occurrence of itchy wheals, in many cases associated with angioedema, for more than 6 weeks (1). The disease affects up to 1% of the general population and may severely impair the quality of life (2,3). In up to 30% of cases this condition is associated with an intolerance to nonsteroidal anti-inflammatory drugs (NSAID) which inhibit cyclooxygenase 1 (COX-1) (4). The intake of these drugs during the phases of clinical activity of the underlying skin disease leads to severe exacerbations that may pose the patient at risk of involvement of the upper respiratory tract (5). There are data suggesting that NSAID-hypersensitivity accompanies preferentially severe CSU (6), and that intolerance to NSAID reactivity might precede by years the onset of the spontaneous skin disease (7). In recent years the monoclonal anti-IgE antibody, omalizumab, has been introduced for the treatment of patients with severe CSU not responding to second generation antihistamines given even at higher than licensed doses, with excellent results in the majority of cases (8). The potentially beneficial effect of omalizumab treatment on NSAID hypersensitivity associated to CSU has not been evaluated so far, and will be considered in the present report.

Case report
A 65-year-old man presented at this allergy department with a 25-year-long history of acute, generalized urticaria/angioedema following the ingestion of chemically distinct NSAID (aspirin, metamizol, diclofenac, and paracetamol) taken in different occasions; the only analgesic drug that he was able to tolerate was the opioid tramadol. Adverse reactions occurred about 15-30 minutes after taking the offending drug. Further, during the
last one and a half year the man had been suffering from severe chronic spontaneous urticaria. The disease did not respond to second generation antihistamines at doses 3 times higher than the licensed dosage and the patient had to take 32 mg/day of methyl-prednisolone orally to control it. An autologous serum skin test (ASST) carried out in another hospital about 6 months before had scored frankly positive.

Baseline lab investigations showed elevated D-dimer plasma levels (1815 ng/ml; n.v. < 500) as well as elevated CRP (11.4 mg/100 ml; n.v. < 0.5), whereas thyroid autoantibodies were negative and ESR was normal. Therapy with omalizumab 300 mg/month was started, and the patient began to respond after the 3rd administration with a gradual drop of both D-dimer (657 ng/ml) and CRP (0.99 mg/100 ml; n.v. < 0.5), whereas thyroid autoantibodies were negative and ESR was normal.

The patient was kept under control for 1.5 hours after the last provocation challenge with aspirin in order to check its tolerability. The oral challenge was performed in the clinic under medical supervision. Increasing doses of aspirin were given 1 hour apart up to a normal dose of 500 mg (50 mg + 200 mg + 250 mg) in an open fashion. The patient was instructed and recommended to alert the personnel immediately in case of itching or discomfort; further, 60 minutes after each dose the patient underwent clinical examination looking for wheals and/or angioedema. The patient was kept under control for 1.5 hours after the last provocative dose. No reaction was noted, and the patient reported only a significant reduction of his orthopedic pain. It was concluded that aspirin was tolerated at this point.

**Discussion**

Recent studies from our group showed that serial measurements of D-dimer plasma levels are a simple and sensitive way to monitor disease activity in patients with chronic spontaneous urticaria (10). The mechanism of action of omalizumab in chronic spontaneous urticaria is still poorly understood. It has been hypothesized that early responders might have circulating IgE specific for self-antigens (11), while a late response is associated with an autoreactive/autoimmune disease, as shown by positive ASST (9). This patient was clearly a late responder. Further, he had a history of multiple NSAID hypersensitivity, that appeared well before the onset of spontaneous chronic urticaria. Thus, based on recent EAACI nomenclature (4), this patient had a NIUA (Nonsteroidal anti-inflammatory drugs-induced urticaria/angioedema). It is impossible to know whether, after the appearance of chronic spontaneous urticaria, he became a case of NECD (Nonsteroidal anti-inflammatory drugs exacerbated cutaneous disease), because he never took NSAIDs during the last 25 years. Nonetheless, the fact that he was able to tolerate a whole normal dose of aspirin after his severe chronic urticaria went into remission might suggest this possibility. However, the lack of a positive aspirin challenge prior to omalizumab treatment represents an important limitation, as a natural resolution of NSAID hypersensitivity, although unlikely, cannot be excluded. Altogether, this case suggests that it might be worth to challenge with aspirin or other strong COX-1 inhibitors NECD patients showing a complete response to omalizumab. In view of their frequent autoreactivity (12) it would be interesting to investigate the effects of omalizumab in NIUA patients as well.

**References**


