# Aspirin-intolerant Chronic Urticaria Exacerbated by Cutaneous Application of a Ketoprofen Poultice

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Aspirin hypersensitivity results in distinct clinical syndromes, including aspirin-intolerant asthma and aspirin-intolerant chronic urticaria (AICU). Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) aggravate 20–30% of patients with chronic urticaria (1), but the pathogenesis of AICU is not completely clear. We describe here a case of AICU in a 52-year-old woman, which was aggravated by cutaneous application of a ketoprofen poultice, a representative NSAID.

## CASE REPORT

A 52-year-old woman had noticed an itchy erythema and wheals without any known cause 10 years previously. Of the many kinds of antihistamines tested, only olopatadine hydrochloride (5 mg × 2/day) was initially effective. However, the pinpoint-sized wheals and erythema had reappeared 6 months prior to presentation, and continued in spite of treatment with various antihistamines and tranexamic acid. Physical examination revealed no abnormalities. Laboratory tests, including blood counts, biochemical profiles, antinuclear antibody, and immunoglobulins were normal, except for a slightly elevated total IgE (347 IU/ml). Written informed consent was provided for this study prior to examination.

An intradermal injection of 0.05 ml autologous serum produced no response, suggesting that autoimmune pathogenesis may not be involved. Since the characteristics of the eruption were pinpoint-sized erythema and wheals, examinations for cholinergic urticaria and adrenergic urticaria were performed (2, 3). After 15 min of exercise on a treadmill, wheals or erythema did not appear. An intradermal injection of noradrenaline (1 µg/ml) did not induce any small erythematous wheals with a halo, which are a characteristic feature of adrenergic urticaria (4). Judging from the results of these examinations, this patient could not be diagnosed with either cholinergic urticaria or adrenergic urticaria, but was diagnosed with chronic urticaria. Because loxoprofen, a representative NSAID, had aggravated her wheal symptoms in the past, we next carried out challenge tests for AICU. A placebo (lactose) or aspirin 100 mg was administered orally. The placebo control did not induce any change in her eruptions, but aspirin 100 mg clearly aggravated the wheal response, especially on her palms and soles beginning 3 h after the challenge (Fig. 1 a, b).

Because reportedly a ketoprofen poultice had also aggravated her wheal response in the past, we decided to perform a provocation test with a 2% ketoprofen poultice. The small wheals and erythema gradually appeared on her palms and soles, but not on her back,

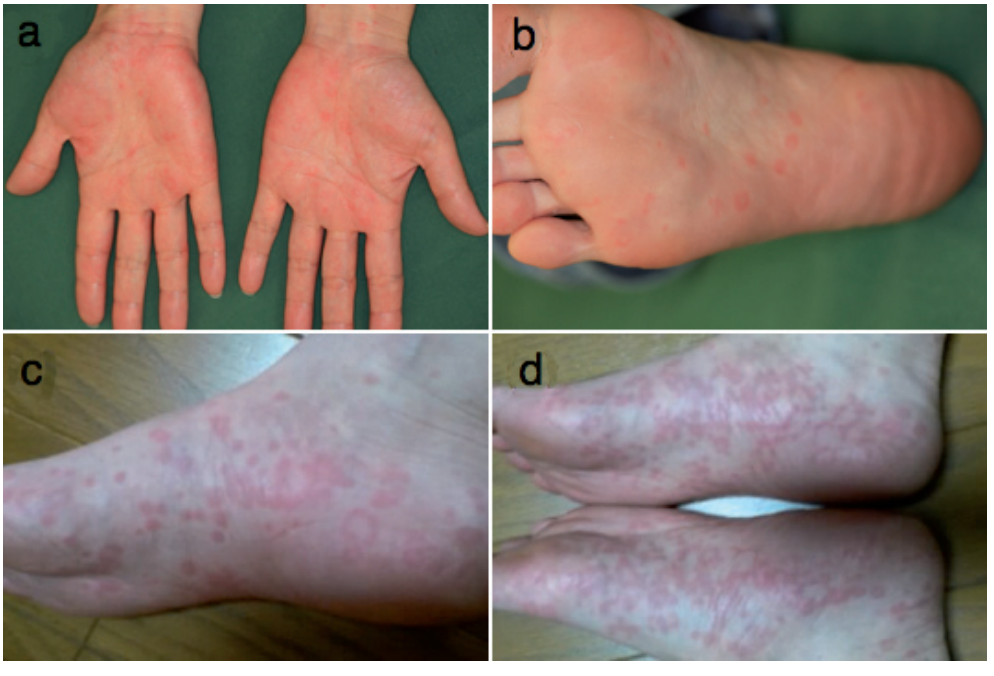


*Fig. 1.* (a, b) Small-sized erythema and wheals on the palms and soles 3 h after ingestion of aspirin 100 mg. (c) Small-sized erythema and wheals on the sole 5 h after application of the ketoprofen poultice. (d) Erythema and wheals were exacerbated on the soles 8 h after application of the ketoprofen poultice.

beginning 5 h after the ketoprofen poultice was applied to her back (Fig. 1c). The poultice was removed, but the symptoms continued to be exacerbated until 8 h after the ketoprofen poultice had first been applied (Fig. 1d). It has been reported that cyclo-oxygenase (COX)-2 inhibitors are generally tolerated well by patients with AICU (5). Therefore Celecoxib 100 mg, a COX-2 inhibitor, was administered, and it did not exacerbate her wheal response. Leukotriene receptor antagonists are effective in certain cases of AICU, but are ineffective or harmful in other cases (6, 7). Montelukast 10 mg, was tested but it did not affect any of her symptoms.

## DISCUSSION

It is thought that aspirin and non-selective NSAIDs act indirectly in AICU by inhibiting formation of prostaglandin via COX, for which there is some evidence of an inhibitory effect on immunological mast cell activation. The inhibition of COX-1 and COX-2 is common to all the classical NSAIDs, including aspirin and ketoprofen. AICU or aspirin-sensitive urticaria can occur within 15 min or up to 24 h after aspirin ingestion, but on average, it develops within 1–4 h (1, 8). In our patient, the ingestion of aspirin 100 mg clearly aggravated the wheal response within 3 h of the provocation test. Some reports have noted that patients with aspirin intolerance should not use NSAIDs at all, but it has rarely been reported that AICU is provoked by NSAID application to the skin. In our patient, a ketoprofen poultice obviously exacerbated the wheal reaction within 5–8 h of application. According to the interview form of a pharmaceutical company the serum concentration of ketoprofen is at least 100 ng/ml 4 h after an application of a ketoprofen poultice (20 mg) and reaches a peak 8 h after the application. In contrast, the serum concentration of aspirin reaches a peak 4 h after aspirin ingestion. This is consistent with the fact that ketoprofen is absorbed transcutaneously more slowly than the oral administration of aspirin, until the concentration of the agent becomes sufficient to provoke the wheal reaction systemically.

With regard to the management of patients with aspirin-sensitive urticaria, recent studies indicate that selective COX-2 inhibitors are generally well-tolerated in patients with aspirin-sensitive urticaria (5, 9). In our patient with AICU, celecoxib 100 mg, a selective COX-2 inhibitor, did not exacerbate her wheal response. We advised her that she should avoid ingestion and application of all NSAIDs except for selective COX-2 inhibitors.

*The authors declare no conflict of interest.*

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