

# Acute Urticaria Induced by Oral Methylprednisolone

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Although corticosteroids have immunosuppressive, anti-inflammatory, and anti-allergic effects, allergic reactions are rare. We report a case involving a 52-year-old-female with acute urticaria caused by oral methylprednisolone. The patient had experienced aspirin-exacerbated respiratory disease (AERD) for 13 years with frequent asthma exacerbations. Symptoms of asthma exacerbations improved with short-term treatments of systemic steroids, including methylprednisolone or deflazacort, which had been well tolerated. However, the current admission was prompted by the development of acute generalized urticaria following the oral ingestion of methylprednisolone (8 mg) for relief of symptoms. An oral provocation test with 4 mg oral methylprednisolone led to generalized urticaria 20 minutes later, confirming the causal association. This is the first report of acute urticaria caused by oral methylprednisolone in a patient with AERD.

**Key Words:** Drug hypersensitivity; methylprednisolone; urticaria

## INTRODUCTION

Various manifestations of allergic reaction caused by steroids have been reported. Among these, delayed reactions to topically applied corticosteroids are more common, whereas immediate reactions to systemic corticosteroids are rare. Immediate reactions of urticaria with angioedema, and even anaphylaxis, have been reported.<sup>1</sup> Allergic reactions can occur via intramuscular, intraarticular, intralesional, oral, inhalational, and intravenous routes. Reactions to oral corticosteroids have been documented most commonly with prednisolone, but not with prednisone, betamethasone, triamcinolone, or methylprednisolone.<sup>2</sup> The present case is, to our knowledge, the first case of acute generalized urticaria caused by oral methylprednisolone.

## CASE REPORT

A 52-year old female had been diagnosed 13 years prior to the present admission with aspirin-exacerbated respiratory disease (AERD). The patient's asthma had been partly controlled using anti-asthmatic medications including inhaled corticosteroids, a long-acting  $\beta_2$  agonist, and a leukotriene receptor antagonist. At the first visit, the patient was non-atopic with a PC20 methacholine level of 0.55 mg/mL. A lysine aspirin bronchoprovocation test showed a positive response at 300 mg/mL of lysine aspirin. Pansinusitis with nasal polyps was demonstrated by rhinoscopy.

The patient was followed regularly with a maintenance medication regimen that included a combination of an inhaler and a leukotriene receptor antagonist. The patient had typically used a systematic steroid for several days for relief of asthma exacerbations; this regimen had been well-tolerated and proven effective in improving symptoms.

More recently, the patient experienced worsening of dyspnea and wheezing, and was diagnosed with asthma exacerbation due to an upper respiratory infection; therefore, a low dose (8 mg) of oral methylprednisolone was prescribed. Acute, whole body generalized urticaria developed after ingesting this medication.

An oral provocation test was performed to confirm the casual relationship between the urticaria and corticosteroids. No responses were observed following an oral provocation test to deflazacort, which is an alternative corticosteroid. However, 20 minutes after taking oral methylprednisolone (4 mg), generalized urticaria developed (Figure). The diagnosis was acute generalized urticaria caused by oral methylprednisolone.

The symptom-relieving therapy was changed from the use of

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**Figure.** Generalized urticaria that developed after 20 min of oral methylprednisolone exposure. (A) Photograph of the reaction on an ankle. (B) Photograph of the reaction in the lower extremities.

methylprednisolone to deflazacort. The patient has remained free from urticaria since that time.

To confirm the individual component of the steroid, we planned to perform allergic skin prick tests using pure methylprednisolone, other steroids, and their additives, but failed, as she refused to stop taking antihistamines due to her persistent rhinitis symptoms.

## DISCUSSION

Corticosteroid therapy involving a multitude of formulations is widely used in nearly all fields of medicine. A number of well-documented cases of steroid hypersensitivity have been reported. Delayed allergic reactions to topically applied corticosteroids are frequently observed (2.9%).<sup>3</sup> In contrast, immediate hypersensitivity reactions are very rare (0.3%)<sup>4</sup> and present various manifestations from a simple transient skin rash or contact dermatitis to respiratory distress and severe anaphylaxis.<sup>1</sup> Immediate hypersensitivity is generally found following intravenous administration and is commonly reported in asthmatic and renal transplant patients.<sup>5</sup> A close association with AERD has been reported,<sup>6,7</sup> because patients with AERD tend to present with more severe asthma symptoms and are likely to be hospitalized and treated with intravenous corticosteroids. Repeated exposure to intravenous corticosteroids increases the opportunity of sensitization to these drug antigens.<sup>8</sup> One study demonstrated the presence of specific immunoglobulin E (IgE) to methylprednisolone in a patient with an anaphylactic reaction after infusion of methylprednisolone.<sup>9</sup> In the present study, the patient had suffered from AERD and had frequently been exposed to a high dose of systemic corticosteroids for many years. An oral provocation test revealed the development of generalized urticaria after exposure to a low dose of methylprednisolone. Although we did not perform allergy skin prick tests with indi-

vidual components and did not confirm the presence of serum specific IgE to methylprednisolone, the pathogenic mechanism may be an IgE-mediated reaction, as the patient demonstrated immediate onset urticaria after the low dose steroid application. These findings suggest that even a low dose of oral methylprednisolone could induce an immediate allergic reaction in exposed patients.

Corticosteroid hypersensitivity may occur to the corticosteroid itself or to the preservatives, adjuvants, or stabilizers that are components of the preparation, making it difficult to quantify the risk. Succinate esters of hydrocortisone are the most frequently responsible additive for type 1 allergic reactions to systemic corticosteroids. The immunogenic role of succinate esters may involve their higher affinity to serum proteins, changing the steroid molecule from a hapten to a complete antigen.<sup>10,11</sup> Anaphylaxis induced by the carboxymethylcellulose component of an injectable steroid suspension has been reported.<sup>12</sup> There are an increasing number of reports describing anaphylactic reactions after an intra-articular injection of corticosteroids containing several mg of carboxymethylcellulose, prednisolone acetate, and triamcinolone acetonide.<sup>13</sup> In the present study, a very low concentration of carboxymethylcellulose was included in the methylprednisolone tablet and the patient's clinical manifestation was immediate onset of generalized urticaria. Therefore, the possibility of additive-induced urticaria may be extremely low.

Diagnostic testing to systemic corticosteroids include skin patch, intradermal, and provocation tests. However, these tests suffer from low sensitivity and there is no consensus concerning the most effective concentrations or vehicles to be used for skin testing. The most reliable method is a provocation test of the suspected systemic corticosteroid.<sup>2</sup> Possible cross-reactivities among hydrocortisone, methylprednisolone, and prednisone have been suggested.<sup>14</sup> Avoidance of hydrocortisone,

methylprednisolone, and prednisone in any formulation in patients displaying allergic reaction to systemic steroids has been recommended<sup>1</sup>. Instead, betamethasone, deflazacort, or dexamethasone can be used as alternatives. However, the provocation test is the best way to identify glucocorticoids that are safe options for future therapy. Presently, the patient's sensitivity was confirmed by an oral provocation test. No reaction to deflazacort was apparent, which was confirmed by the oral provocation test.

In conclusion, we report a case of oral methylprednisolone-induced urticaria that developed in a patient with AERD. Considering the cross-reactivity between the corticosteroids, it is important to identify safe alternative steroid(s) by the provocation test.

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