

blood sampling for assessment of serum IL-9 were performed in all patients as previously reported. All patients were polysensitized to some pollens, including *Parietaria*, birch, olive tree, and grasses. Clinical severity was also evaluated by assessing the following symptoms: nasal obstruction, sneezing, rhinorrhea, and itchy nose. Each symptom was evaluated on the following scale: 0 indicating absent; 1, mild (symptom was present but was not annoying or troublesome); 2, moderate (symptom was frequently troublesome but did not interfere with either normal daily activity or sleep); and 3, severe (symptom was sufficiently troublesome to have interfered with normal daily activity or sleep) as previously reported.<sup>7</sup> AR was diagnosed according to validated criteria.<sup>8</sup> The study was approved by the local ethics committee and performed with the written informed consent of all participants.

The human IL-9 (Human IL-9 ELISA Ready-SET-Go!; eBioscience, Rome, Italy) reagent set contains the necessary reagents, buffers, and diluents for performing quantitative enzyme-linked immunosorbent assays. The purity is greater than 97%, and the sensitivity is 1 pg/mL, with a standard curve ranging from 1 to 100 pg/mL.

Descriptive statistics were first performed and quantitative parameters were reported as medians with first and third quartiles (interquartile range). The package S-Plus (MathSoft Corp, Needham, Massachusetts) was used for all analyses.

The median serum IL-9 value was 6.12 pg/mL (interquartile range, 0.09–7.86 pg/mL). A significant positive relationship between IL-9 serum values and symptom severity was observed for all nasal symptoms as reported in Figure 1. In particular, there was a moderate positive relationship between IL-9 and itching, sneezing, and rhinorrhea and a weak negative relationship with obstruction.

Itching, sneezing, and rhinorrhea are typical AR symptoms and are mainly sustained by histamine effects on histamine<sub>1</sub> receptors; they may also be called *irritative* symptoms. Obstruction depends on enlargement of the turbinates, which is mainly dependent on chronic inflammation. These findings show that the serum IL-9 levels are closely associated with the severity of irritative symptoms, mainly rhinorrhea. This phenomenon might support the pathogenic role of IL-9 in inducing mucous production, even though further studies should address this issue. In addition, irritative nasal symptoms may be considered expression of acute allergic reaction, whereas nasal obstruction may be mainly dependent on chronic inflammation. Therefore, serum IL-9 might be considered a surrogate biomarker for acute AR, which may be useful for assessing patients during the pollen exposure. However, further functional studies should be performed to confirm these results. In conclusion, this study provides evidence that serum IL-9 is related to irritative nasal symptoms.

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## DAPSONE HYPERSENSITIVITY SYNDROME DURING DELAYED PRESSURE URTICARIA TREATMENT

Dapsone is a compound with potent anti-inflammatory and antimicrobial effects. It has been used as a first-line drug for Hansen disease since the 1950s. Dapsone has also been useful for the treatment of other conditions, such as dermatitis herpetiformis, polyarteritis nodosa, cutaneous mycetoma, and bullous dermatoses, and for chemoprophylaxis of *Pneumocystis carinii* infection and malaria.<sup>1</sup> More recently, dapsone has been used in the treatment of urticarial vasculitis, chronic idiopathic urticaria and angioedema, and delayed pressure urticaria and in patients with poor response to conventional therapy.<sup>2</sup>

However, dapsone use may be associated with a variety of adverse effects, most commonly lethargy, headache, hemolytic anemia, and methemoglobinemia but also hepatic involvement, cutaneous involvement, agranulocytosis, nephritis, pneumonitis, peripheral neuropathy, and hypothyroidism.<sup>1</sup> A serious idiosyncratic reaction to dapsone has been described in less than 5% of patients using this drug in the long term, which has been known as dapsone hypersensitivity syndrome. This report describes a woman who developed dapsone hypersensitivity syndrome during treatment of delayed pressure urticaria.

A 35-year-old woman presented with fever (temperature of 38°C), abdominal pain, weakness, oral ulceration, and pruritic rash after 13 days of using dapsone for treatment of delayed pressure urticaria. She was evaluated by the emergency physician, who diagnosed dengue fever. Once her clinical condition worsened, she came to our immunology clinic. On examination, she had erythematous papular rash that involved the face, trunk, and limbs (Figure 1). Multiple bilateral cervical and retroauricular tender lymph nodes measuring 1 to 2 cm were noted. Her pharynx was hyperemic, and she had ulcerations in the oral cavity. There was no palpable organomegaly, and she was hemodynamically stable.

She underwent a complete blood cell count, which revealed the following laboratory values: hemoglobin, 12.9 g; hematocrit, 38.9%; white blood cell count, 9,000/mm<sup>3</sup> (eosinophils, 15%; neutrophils, 36%; lymphocytes, 44%; and monocytes, 5%); platelet count, 341,000/

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Figure 1. Erythematous papular rash.

mm<sup>3</sup>; and erythrocyte sedimentation rate, 25 mm in the first hour. Her liver function test results were abnormal: direct bilirubin, 0.4 mg/dL; indirect bilirubin, 1.3 mg/dL; aspartate aminotransferase, 63 U/L; alkaline aminotransferase, 281 U/L; alkaline phosphatase, 81 U/L;  $\gamma$ -glutamyl transferase, 95 U/L; and serum albumin, 4.1 g/dL.

A diagnosis of dapsone hypersensitivity syndrome was thus based on the patient's medical history, clinical findings, and laboratory test results. Then, dapsone treatment was discontinued and corticosteroid therapy was started. Prednisone was given orally (40 mg/d), and we tapered off this dose during a period of 6 weeks. Hydroxyzine, 25 mg/d, and ranitidine, 300 mg/d, were added. Her clinical condition improved, and laboratory test results returned to normal levels within 3 months.

Dapsone hypersensitivity syndrome was first described by Alday and Barnes in 1951.<sup>3</sup> Its incidence ranges from 0.5% to 3%, and it typically presents with sudden onset of fever, malaise, lymphadenopathy, skin eruption, and internal organ involvement, often within 8 weeks of commencement of dapsone therapy.<sup>1,4</sup> The clinical manifestations may mimic a viral infection.<sup>4</sup> The most common

cutaneous manifestations are exfoliative dermatitis, erythematous maculopapular eruption, and Stevens-Johnson syndrome-like lesions.<sup>5</sup> The severity of cutaneous manifestations may not correlate with the severity or extent of internal organ involvement.<sup>1</sup>

Dapsone hypersensitivity syndrome can be considered a manifestation of the so-called DRESS syndrome (drug rash with eosinophilia and systemic symptoms), which may be caused by several other drugs, including anticonvulsants, sulfonamides, allopurinol, minocycline, and gold salts.<sup>6</sup> The internal organ most commonly involved is the liver, but pulmonary, pancreatic, renal, and cardiac involvement have also been reported.<sup>7,8</sup> Hyperbilirubinemia present in dapsone syndrome may partly be due to hemolysis in addition to hepatotoxicity. Both hepatocellular and cholestatic injury have been described. Hepatitis may progress to liver failure and death.<sup>7</sup>

Our patient presented with a characteristic history of delayed drug hypersensitivity that mimicked a viral illness. The diagnosis of delayed hypersensitivity was supported by the history, evolution, time of exposure to the drug, abnormal liver function test results, and resolution of the symptoms after withdrawing dapsone and corticosteroid treatment.

Because of the increasing use of dapsone in the treatment of conditions other than Hansen disease, dapsone hypersensitivity syndrome may become more common. Therefore, allergists and dermatologists should be aware of this severe hypersensitivity reaction to dapsone.

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