

rhea and eczema, and the results of her physical examination were unremarkable. Laboratory studies revealed a platelet count of 4,000/ μ L, a positive Coombs antibody, and a positive antinuclear antibody. She was prescribed corticosteroids, which improved her platelet counts modestly. After recurrent bouts of ITP, further investigation revealed hypogammaglobulinemia and T-cell lymphopenia. Her antibody levels were 164 mg/dL of IgG, 10 mg/dL of IgA, and 21 mg/dL of IgM. Sequencing of the gene encoding Wiskott-Aldrich syndrome protein did not reveal any mutations, and CVID was diagnosed. Despite her hypogammaglobulinemia, the patient's B-cell counts were normal, indicating that her T-cell lymphopenia was unlikely to be attributable to corticosteroid therapy. At the age of 9 years, the patient presented to the emergency department in status epilepticus because of a lesion in the left parietal lobe. Chest computed tomography revealed several lung nodules. The intracranial mass was resected and biopsy specimens of the lung nodules were obtained; histopathologic analysis determined that the former was composed of loosely organized inflammatory tissue, whereas the latter contained many noncaseating granulomas. Lymphocytes were the predominant cell type.

Proliferation of the patient's T cells in response to a panel of specific antigens and nonspecific mitogens was greatly reduced, with the exception of phytohemagglutinin (Fig 1A, B). Proliferation of the patient's T cells to phytohemagglutinin antigen was normal, and proliferation to interleukin 2 was reduced by only 30% to 50%, indicating that the patient's proliferation defect is not explained by the relative paucity of T cells in the crude peripheral blood mononuclear cell preparations from the patient. The reduced proliferation to phorbol myristate acetate (PMA)/ionomycin suggested a relatively distal T-cell-intrinsic defect. We also found that the patient's T cells underwent activation-induced cell death (AICD) at a much higher rate than control cells; only 10% to 20% of the T cells remained viable after 12 hours of activation with PMA/ionomycin (Fig 1C). Furthermore, the T cells exhibited reduced NF- κ B activity shortly after activation with PMA/ionomycin (Fig 1D). Because NF- κ B activation is a critical step in T-cell proliferation and the avoidance of AICD,² this defect provides a possible explanation for the increased AICD and reduced proliferation.

Although the patient's lymphopenia might be explained by increased T-cell apoptosis, it did not provide an obvious explanation for the patient's autoimmunity. One possibility is that the patient's regulatory T-cell function may be impaired to an even greater extent than her conventional T-cell function. Regulatory T cells (Tregs) are critical for the suppression of inappropriate T-cell responses, and individuals lacking Tregs exhibit widespread autoimmunity. Several previous reports have noted Treg deficiencies in a subset of patients with CVID.³ We sought to characterize the patient's Treg compartment. Flow cytometric analysis revealed low numbers of CD4⁺ T cells but comparatively even fewer CD4⁺CD25⁺FoxP3⁺ Tregs (Fig 1E) and few CD4⁺CD25⁺CD127⁻ cells (data not shown). This pattern was observed consistently on several different occasions.

By the age of 13 years, the patient had been treated with corticosteroids for several years, and because of their adverse effects a steroid-sparing therapy was devised. Because several studies had shown that rapamycin increases Treg cell counts and suppressive function,^{4,5} we added rapamycin (1 mg/d) to the patient's regimen. Six months after beginning rapamycin therapy, the patient's Treg counts had nearly recovered to normal levels (Fig 1E). The patient had many more CD25low, FoxP3⁺ T cells after rapamycin treatment than did control samples; previous reports have indicated that this population may also represent Tregs.⁶ Her platelet count also in-

creased to 136,000/ μ L, and she reported reduced diarrhea. Her IgM level also returned to a normal value, whereas her IgA levels remained low.

Rapamycin is used as an immunosuppressive agent in organ transplant recipients and acts to suppress the AKT-mTOR signaling axis and consequently inhibit effector T-cell activity. To our knowledge, this is the first reported use of rapamycin for the treatment of CVID. Given the positive effects on the patient's Treg number and clinical status, we propose that rapamycin may serve as a useful therapy for individuals with CVID, particularly those with regulatory T-cell deficiency.

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ASPIRIN DESENSITIZATION IN A PATIENT WITH ASPIRIN SENSITIVITY AND CHRONIC IDIOPATHIC URTICARIA

Aspirin desensitization has proved to be beneficial in patients with aspirin-exacerbated respiratory disease, chronic rhinosinusitis, and aspirin-induced urticaria who require aspirin treatment for acute coronary syndrome.^{1,2} Desensitization in patients with a history of chronic idiopathic urticaria (CIU) with accompanying aspirin sen-

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sitivity has not been shown.³ We describe a patient who was successfully desensitized to aspirin despite a history of CIU.

The patient is a 49-year-old man with a history of diabetes mellitus, childhood asthma, hypertension, gastroesophageal reflux disease, myocardial infarction, and intermittent hives. He first noticed the hives when he was 16 years old. He developed generalized pruritic lesions that lasted 24 hours and spontaneously disappeared. At the age of 33 years, he was prescribed an adult dose of a nonsteroidal anti-inflammatory drug (NSAID) for a leg injury. A few days later, he noticed hives that began on his legs and spread upward 10 to 15 minutes after taking the NSAID. He took diphenhydramine, and the hives resolved. A few months later, the patient was having mild arthritic pain and took an adult dose of aspirin. Ten minutes later he began to develop hives. The hives again were relieved by oral diphenhydramine treatment. Since that time, despite avoiding NSAIDs and aspirin, the patient reports having outbreaks of hives 5 to 6 times per year with no apparent triggers. He had no respiratory complaints, swelling of eyes or lips, or gastrointestinal problems associated with the hives.

The patient was referred to us for aspirin desensitization because of his history of myocardial infarction. Physical examination findings were normal. There were no hives or evidence of dermatographism. Spirometry showed normal lung function, and autologous serum skin test results were negative. The patient was diagnosed as having CIU and aspirin sensitivity. He was advised of the risks of desensitization and agreed to the procedure.

Aspirin desensitization treatment began with 40 mg given at 10 AM. The patient had some mild itching of his ears, but this spontaneously abated. At 11:30 AM, he was given aspirin, 81 mg. He was observed for 2 hours and had no reaction. Later that afternoon, 3.5 hours after the aspirin administration, the patient had a severe flare-up of generalized urticaria. He took diphenhydramine, 25 mg, and the hives subsided. The next day, he was given aspirin, 81 mg, at 8:30 AM. He had no reaction after 2 hours and was given aspirin, 162 mg, at 10:30 AM. At 12:30 PM, the patient began to have a mild flare of hives, with a few lesions seen on his neck. He was given cetirizine, 10 mg, and the hives resolved in 30 minutes. The next day he was given aspirin, 162 mg, at 8:30 AM. At 11:15 AM he was given aspirin, 325 mg, and remained asymptomatic. The patient was advised to continue with the aspirin, 325 mg/d, and cetirizine, 10 mg nightly. Since the patient's desensitization, his dose of aspirin was reduced from 325 to 81 mg/d after 2 months by his cardiologist, and he is taking cetirizine only as needed. In the 5 months after his desensitization, he had 2 mild urticarial outbreaks that readily resolved with cetirizine treatment.

Aspirin desensitization has been proved to be a safe and effective office procedure,⁴ but its use in patients with aspirin-induced urticaria remains controversial. Grzelewska-Rzymowska et al⁵ and Asad et al⁶ demonstrated that patients with urticaria or angioedema reactions solely related to aspirin could be desensitized in a few days. Wong et al² studied 11 patients, most of whom had acute coronary syndrome and a history of aspirin-induced urticaria and angioedema. They underwent a rapid desensitization protocol, which was successful in 9 patients. This illustrates the possibility that desensitization is possible in single drug-induced urticaria/angioedema.

Simon³ studied aspirin desensitization in patients with a history of chronic urticaria. He desensitized 25 patients to aspirin, 650 mg. However, within 1 day of desensitization, the hives flared. This outbreak was severe, and prednisone was administered to adequately control it. Further aspirin desensitization attempts after the initial

trial only triggered more exacerbations of the hives. Our patient experienced acute urticaria with desensitization but was controlled with oral antihistamines.

The present case demonstrates that aspirin desensitization may be possible in patients with a history of aspirin sensitivity and CIU. We should emphasize that this patient may represent the milder end of the spectrum in that he was responsive to a histamine₁ antihistamine and the autologous serum skin test result was negative. Further studies with more patients are needed to better characterize the possibility of aspirin desensitization in this difficult-to-treat population.

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EMPOWER YOUR PATIENTS: SAVE LIVES

Epinephrine is the initial drug of choice in anaphylactic reactions. Some patients, such as those allergic to foods, latex, or Hymenoptera venom, are at such a high risk for systemic reactions (SRs) that they should always carry an epinephrine autoinjector. Proper treatment depends on the availability of epinephrine, knowledge of indications, and accurate use of the device when needed.¹ Several studies^{2–4} have shown that many patients do not always carry their epinephrine device, are deficient in their knowledge of indications for use (84% of parents), and cannot use the device correctly (63%). One survey¹ of patients' parents showed that training, previous use of epinephrine, and empowerment improved comfort with parental administration of epinephrine autoinjectors. In the severe anaphylactic reactions that have occurred, a delay in administration, inaccurate use, and lack of availability of epinephrine have been cited as contributing to the severity of the reaction.⁵ Physicians are already encouraged in practice parameters to educate patients on the importance of always having an epinephrine autoinjector available.^{1,5} Education by the physician or team is typically achieved using a training device,^{1,3,6,7} but patients may still fear the needle and medication from the autoinjector itself. A survey by Kim et al¹ showed that parental comfort was not affected by their child's previous

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