

CASE REPORT

Cyclosporine Treatment in a Patient with Concurrent Autoimmune Urticaria and Autoimmune Hepatitis

Hye Young Ju, M.D., Hei Sung Kim, M.D., Hyung Ok Kim, M.D., Young Min Park, M.D.

Department of Dermatology, College of Medicine, The Catholic University of Korea, Seoul, Korea

Patients with autoimmune urticaria show a higher rate of seropositivity for other autoantibodies and often have a history of autoimmune conditions. They also tend to have more severe symptoms and to have a poor response to conventional antihistamine treatment. Autoimmune hepatitis is a chronic inflammatory disorder in which progressive liver injury is thought to be the result of a T-cell-mediated immunologic attack against liver cells in genetically predisposed individuals. While the association between autoimmune urticaria and other autoimmune disorders such as thyroid disease is well known, there has been no reported case of autoimmune urticaria concomitant with autoimmune hepatitis. We report a case of autoimmune urticaria concurrent with autoimmune hepatitis, which was successfully treated with cyclosporine. (*Ann Dermatol* 21(3) 291 ~ 293, 2009)

-Keywords-

Autoimmune hepatitis, Autoimmune urticaria, Cyclosporine

INTRODUCTION

At least 40% of patients with unexplained chronic urticaria have clinically relevant functional autoantibodies to the high affinity immunoglobulin (Ig)E receptors on basophils and mast cells and show a positive reaction on the autologous serum skin test. The term "autoimmune

urticaria" is used for this group of patients, especially when there is evidence of underlying autoimmunity or dependence on oral corticosteroid therapy for disease control. Patients with autoimmune urticaria show a higher rate of seropositivity for other autoantibodies and often have a history of autoimmune conditions. They also tend to have more severe symptoms and to have a poor response to conventional antihistamine treatment¹. Autoimmune hepatitis is a chronic inflammatory disorder in which progressive liver injury is thought to be the result of a T-cell-mediated immunologic attack against liver cells in genetically predisposed individuals. The response rate to prednisone and azathioprine therapy is 80%, and non-responders may be considered for a trial of cyclosporine, tacrolimus, or mycophenolate mofetil². While the association between autoimmune urticaria and other autoimmune disorders such as thyroid disease is well known³, there has been no reported case of autoimmune urticaria concomitant with autoimmune hepatitis. We report a case of autoimmune urticaria concurrent with autoimmune hepatitis, which was successfully treated with cyclosporine.

CASE REPORT

A 45-year-old Korean woman presented with a six-month history of recurrent episodes of generalized pruritic erythema and wheals, often associated with swelling of her lips and eyes. Eleven months prior to presentation, she had undergone an evaluation for persistent asymptomatic elevation of serum aminotransferase levels, which had no association with viral infection or alcohol or drug use. Laboratory examination showed a 3-fold elevation in serum aminotransferases, a 1.5-fold elevation in serum Ig G, and positivity for antinuclear (ANA, 1 : 200) and anti-dsDNA antibodies, as well as negativity for mitochondrial antibodies and markers of viral hepatitis. Although a

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Reprint request to: Young Min Park, M.D., Department of Dermatology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 505, Banpo-dong, Seocho-gu, Seoul 137-701, Korea. Tel: 82-2-2258-6223, Fax: 82-2-594-3255, E-mail: ymmpark6301@hotmail.com

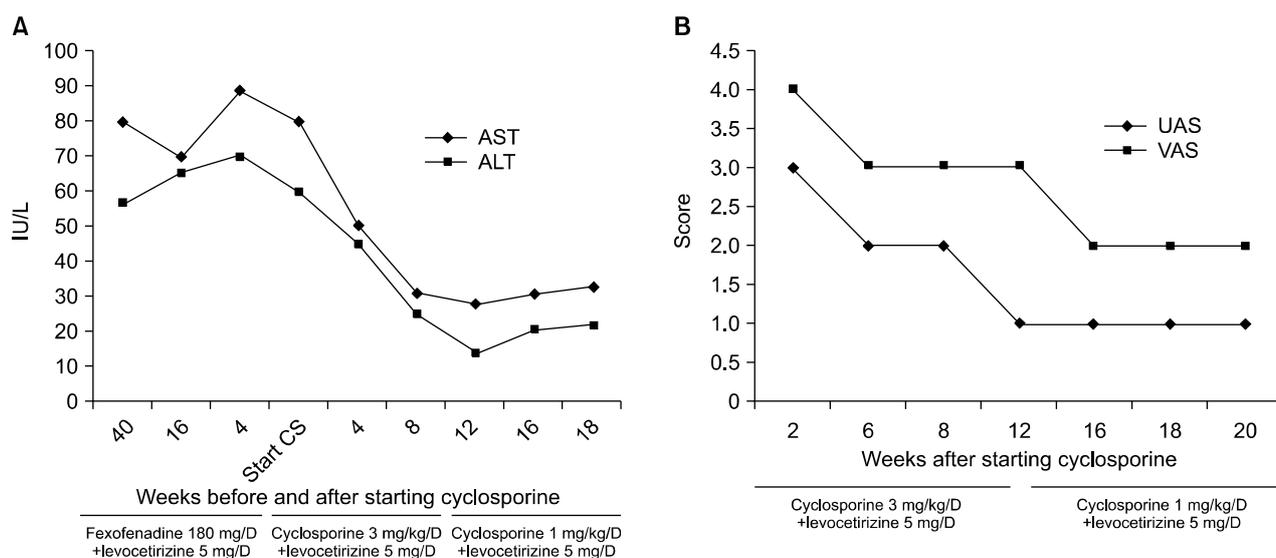


Fig. 1. (A) Serum transferases returned to the normal range after 2 months of cyclosporine treatment. (B) Both the urticaria activity score (UAS) and the visual analogue score (VAS) slowly decreased after cyclosporine treatment.

needle biopsy specimen of the liver failed to show characteristic histological features, the patient was ultimately diagnosed with autoimmune hepatitis according to the scoring system established by the International Autoimmune Hepatitis Group⁴. Because she had minimal histological changes and no symptoms, she was followed closely without specific treatment. Five months later, recurrent episodes of urticaria and angioedema developed, and the patient was referred for a dermatology consultation. Despite 1 month of treatment with fexofenadine (180 mg/day) and levocetirizine (5 mg/day), she had no therapeutic response. One week after cessation of antihistamine therapy, an intradermal injection of autologous serum was performed; its positive effect led us to the diagnosis of autoimmune urticaria unresponsive to conventional therapy. Cyclosporine is known to bring about clinical improvement in chronic idiopathic urticaria patients with positive autologous serum skin tests⁵, so cyclosporine (3 mg/kg/day) was given to the patient. After 2 months of therapy, the patient had become almost completely free of lesions, and serum aminotransferase levels had decreased to normal (Fig. 1). After 5 months, the cyclosporine dose was decreased to 1 mg/kg/day and maintained for 2 months without any side effects.

DISCUSSION

Leznoff et al.³ first suggested an autoimmune basis for chronic idiopathic urticaria (CIU) in 1983 after noting that there was an association between thyroid disease and CIU. This concept has been confirmed in several subse-

quent reports^{6,7}. At least 40% of patients with CIU possess functional autoantibodies that cause cross-linking of IgE receptors on basophils and mast cells, leading to the release of inflammatory mediators and cytokines⁸; this subgroup of patients is classified as having autoimmune urticaria. A history of autoimmune conditions is confirmed significantly more often by patients with anti-FcεRI or anti-IgE than it is by patients without such a history⁹. The autologous serum skin test (ASST) is the *in vivo* clinical test used to detect *in vitro* basophil histamine-releasing activity. The ASST has a reasonably high specificity (80%) and sensitivity (70%) for functional autoantibodies detected by *in vitro* histamine release from basophils of healthy donors with chronic idiopathic urticaria¹⁰. Although the current gold standard diagnosis depends on functional release assays with basophils or mast cells, these investigations remain confined to a few research centers. In practice, the diagnosis of autoimmune urticaria relies primarily on clinical suspicion, which is supported by tests when available¹.

Neither the pathogenesis of autoimmune urticaria nor autoimmune hepatitis is fully understood, but these two conditions seem to share autoimmune mechanisms. The proposed underlying immune mechanisms are actually quite different. Autoimmune urticaria may be related to antibodies against the high affinity IgE receptor or to anti-IgE IgG antibodies, whereas autoimmune hepatitis appears to be cell-mediated. However, both generally respond to immunosuppressive treatment.

The mainstays of initial therapy for autoimmune urticaria include antihistamines with the possible addition of H2-

blockers, but some patients are refractory to these therapies, and they may need systemic corticosteroids or other immunosuppressive agents to control their disease. There are various potential side effects associated with long-term treatment. Cyclosporine inhibits cell-mediated autoimmune responses by downregulating the Th1 lymphocyte response and T-cell-dependent antibody formation in B-lymphocytes. This treatment has proven to be effective in a double-blind controlled study in chronic idiopathic urticaria patients with positive ASSTs⁵. The authors suggested that the reduction in *in vitro* serum histamine releasing antibodies and the reduced ASST responses to post-treatment sera indicate that histamine-releasing autoantibodies may be directly involved in disease pathogenesis and support the concept of autoimmune urticaria⁵. Cyclosporine's exact mechanism of action in urticaria is still unknown, but it could be related to inhibition of anti-IgE-induced histamine release from basophils and mast cells⁵. Prednisone and azathioprine are effective in the treatment of autoimmune hepatitis, but they both have serious side effects. Low-dose cyclosporine has been reported to be safe and effective, although randomized controlled trials have not been performed^{11,12}. Our case suggests that patients with concurrent autoimmune urticaria and autoimmune hepatitis can be successfully treated with cyclosporine. There are limitations in our case. We did not performed functional release assays with basophils or mast cells to confirm diagnosis of autoimmune urticaria, and it remains unclear whether normalization of serum aminotransferase levels were related to cyclosporine treatment or were due time alone. However, the current case is worthy of discussion because it is the first reported case in which another autoimmune condition was associated with autoimmune urticaria. The details of this case also suggest a possible treatment option other than systemic corticosteroids. The optimal cyclosporine treatment protocol should be addressed in further studies.

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