
Case report

Successful treatment of autoimmune chronic idiopathic urticaria with intravenous cyclophosphamide

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Background: A 45-year-old woman presented with a 20-year history of chronic idiopathic urticaria (CIU) unresponsive to H₁- and H₂-antagonists and combinations of other anti-inflammatory agents but controlled with daily prednisone (35 mg) for more than 13 years. Intracutaneous testing to autologous serum revealed an 8 × 10-mm wheal/flare reaction consistent with the presence of anti-FcεRIα autoantibodies. These autoantibodies have been reported to be present in >45% of patients with CIU. Their functional role in the pathogenesis of CIU remains poorly understood.

Objective: Because of the therapeutic refractory nature of this patient's CIU requiring high doses of corticosteroids, it was decided to initiate treatment with intravenous cyclophosphamide (CTX) in an attempt to eradicate autoantibody-producing B-lymphocyte clones. This therapeutic approach has been previously successful in other autoantibody-mediated disorders such as type II acquired angioedema and factor VIII deficiency.

Results: Initial treatment consisted of 500 mg CTX intravenously followed by increases of 100 mg every 2 weeks, with the maximum dose reaching 1,500 mg once a month, which represents approximately 20% of the dose administered during systemic cancer chemotherapy. Within 7 months there was a complete clinical remission and prednisone was discontinued. Repeat intracutaneous testing to autologous serum was negative, consistent with an abrogated autoantibody response. The patient has not experienced a recurrence of CIU at the time of this report.

Conclusion: This index case suggests that intravenous CTX may be effective in alleviating autoantibody-associated CIU in corticosteroid-dependent patients refractory to conventional therapies.

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INTRODUCTION

Chronic idiopathic urticaria (CIU) is a common skin disorder that is often responsive to H₁-antagonists alone or in combination with other agents that block specific mediators or activation of mast cells.¹ A smaller subset of patients may require several medications and in some cases, systemic corticosteroids (CS) to control or prevent the daily occurrence of hives. Approximately 45% of patients with CIU may have an immunoglobulin (Ig)G autoantibody directed toward Fcε I receptor α subunit (FcεRIα) that may play a role in the pathogenesis of their hives.^{2,3} This report describes our experience with cyclophosphamide (CTX) in a woman with CS-dependent CIU, associated with an autoantibody to FcεRIα. The rationale for using CTX, which is an alkylating agent that targets B-cell production of antibodies, was to eradicate the B-cell clone(s) producing the IgG antibody directed against FcεRIα, thereby preventing the recurrence of urticaria.^{4,5}

CASE REPORT

The patient is a 45-year-old female who was referred for further evaluation and treatment of CIU, which she has had for more than 20 years. Previous doctors had treated her unsuccessfully with various combinations of medications for the management of hives. To control the hives, a minimal effective CS dose of prednisone of 35 mg a day for the past 13 years was required. The hives were diffuse, coalescent, and extremely pruritic. There was associated angioedema of the lips and tongue, but no laryngeal involvement and no other respiratory symptoms. Extensive laboratory testing was unrevealing. She had normal blood counts, sedimentation rates, C-reactive protein, total IgE level, liver function tests, thyroid-stimulating hormone, antinuclear antibody, rheumatoid factor, extractable nuclear antibodies profile, C2, C3, C4, C1q, factor B, serum protein electrophoresis, and 24-hour urine histamine. She was hepatitis B surface antibody-positive and hepatitis B core antibody-positive; however, a hepatitis C virus immunoblot was nonreactive. Thyroid autoantibodies were not present, and a blood test for *Helicobacter pylori* was negative. Skin biopsy revealed a mild perivascular lymphocyte infiltrate but no evidence of neutrophilic infiltrates or vasculitis of dermal vessels.

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Her past medical history included bypass surgery for obesity without complications. She also had a history of mild, intermittent asthma and osteoarthritis. Her chronic CS requirement had resulted in a >100-pound weight gain despite her gastric bypass surgery.

Previous medications tried on this patient included first-generation antihistamines such as diphenhydramine and hydroxyzine. Second-generation antihistamines, such as cetirizine, loratadine, and fexofenadine, and H₂ antagonists including ranitidine and cimetidine were also ineffective. Other agents used in combination were doxepin, cyproheptadine, leukotriene D₄ antagonists (including montelukast and zafirlukast), a 5-lipoxygenase inhibitor (zileuton), mast cell stabilizers (including azatadine and oral albuterol), and calcium channel blockers. Disease-modifying agents included dapsone, hydroxychloroquine, colchicine, and danazol, the latter drug as part of a National Institutes of Health protocol.

Her evaluation included intracutaneous testing to her own serum (0.02 mL intracutaneously). This revealed an 8-mm wheal and 10-mm flare reaction in conjunction with a negative saline control and positive histamine reaction. This test was performed after all H₁-antagonists had been discontinued for 72 hours.

Because of the refractory nature of her hives and continuous requirements for a moderately high daily dose of oral CSs with attendant associated side effects, it was decided to treat her with low-dose intravenous CTX, which has previously been demonstrated to be effective in eradicating B-cell clones producing autoantibodies in a variety of diseases.⁴⁻⁷

After the patient signed an informed consent approved by the University of Cincinnati Institutional Review Board, a Port-a-Cath (Deltec, St. Paul, MN) was placed and an intravenous fusion of 500 mg of CTX was initiated. During each infusion, she was pretreated with anti-emetics and dexamethasone (Decadron; Merck, West Point, PA). The CTX dose was increased by 100 mg every 2 weeks until a maximum dose of 1,500 mg was achieved. The patient was then maintained at 1,500 mg every 4 weeks for a total duration of 8 months. In general, the therapy was well tolerated except for mild nausea.

After 4 weeks of treatment, prednisone tapering was initiated by 2.5 mg every week. Six months later, the patient had complete resolution of her hives and was able to discontinue prednisone. One month after the CTX infusions were discontinued, repeat intracutaneous testing to autologous serum was negative. Subsequent 12-month followup of this patient revealed residual mild pruritus with an occasional, mild transient episode of hives readily controlled with diphenhydramine 25 mg on an as-needed basis. She has not required further treatment with CSs, nor has she required daily prophylactic medications to control CIU. Clinical evaluation revealed no evidence of side effects from the CTX treatment.

CONCLUSION

Anti-FcεRIα autoantibodies have been detected in numerous chronic skin disorders including CIU, pemphigus vulgaris,

dermatomyositis, systemic lupus erythematosus, and bullous pemphigoid.⁸ These autoantibodies have been estimated to be present in up to 45 to 50% of patients with CIU.^{3,9-11} Interestingly, studies have demonstrated that only anti-FcεRIα autoantibodies associated with CIU demonstrate significant basophil and mast cell histamine-releasing activity.³ One theory explaining this difference is that FcεRIα autoantibodies associated with CIU are of the IgG1 and IgG3 antibody subclasses, which can activate complement, whereas FcεRIα autoantibodies associated with other chronic skin disorders are of the IgG2 and IgG4 antibody subtypes, which do not fix complement.⁸ However, the precise pathogenic role of these antibodies in this disorder remains unclear.^{3,9-11}

It has been demonstrated that positive autologous serum skin test responses correlate well with basophil histamine release. This suggests that skin testing to autologous serum may be a simple method for screening patients with CIU for the presence of anti-FcεRIα autoantibodies.¹² The ability to detect the presence of autoantibodies by this simple test may provide a rational basis for the clinician to consider alternative treatments, including a more robust immunosuppressive approach in CS-dependent patients. The clinical utility of this test has been questioned by a recent study that reported a poor correlation with a positive autologous serum skin test and basophil histamine release.¹³ Hypothetically, this could be explained by the presence of histamine-releasing factors that selectively activate tissue mast cells rather than basophils. Another possibility for a positive autologous serologic skin test could be attributable to complement byproducts in the serum, such as C5a, which can directly activate mast cells.¹³ However, in this patient there was no detectable evidence of complement activation. Further, the shift from a positive to a negative autologous serum skin test after treatment with CTX, which targets B-cell production of antibodies, is consistent with the presence of an anti-FcεRIα antibody in our patient.

This index case indicates that patients with CS-dependent CIU with anti-FcεRIα antibodies and a lack of response to other medications can be successfully treated with low-dose CTX infusions, presumably with the goal of eradicating B-cell clones producing these autoantibodies. The rationale for pursuing this aggressive therapy in this patient was based upon our previous experience in a patient with type II acquired angioedema, a rare condition in which patients produce autoantibodies against C1 esterase inhibitor.⁴ In this case, the patient underwent a similar treatment course with CTX, which was successful in eliminating the C1 esterase inhibitor autoantibody and preventing recurrences of angioedema.⁴ This patient has now been followed for 9 years without a recurrence of C1 esterase autoantibody or angioedema episodes. Further, CTX has also been used safely and successfully for the treatment of hypocomplementemic urticarial vasculitis and other autoimmune chronic skin disorders such as pemphigus vulgaris.^{7,8}

Although treatment of patients with CIU with CTX may seem overly aggressive, it is important to emphasize that this patient could only be controlled with prednisone 35 mg daily

and suffered significant side effects, including a 100-pound weight gain and osteoarthritis of her knees. The patient received the CTX treatment in an oncology outpatient center under the supervision of an experienced oncologist. The treatment course was well tolerated.

This current experience, along with our previous report of type II acquired angioedema, indicate that low-dose CTX treatment can be used effectively in improving clinical outcomes of selected patients with minimal risks. The successful treatment of this patient with CTX provides indirect support for a functional role of FcεRIα subunit autoantibodies in the pathogenesis of a subpopulation of patients with CIU. A larger case series of patients with autoimmune CIU should include in vitro histamine release assays in conjunction with in vivo autologous serum intracutaneous testing before and after treatment to confirm the effectiveness of this treatment in eradicating autoantibodies directed toward anti-FcεRIα subunit.

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