

Methotrexate-responsive chronic idiopathic urticaria: a report of two cases

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Summary Chronic idiopathic urticaria (CIU) may be severe and refractory to standard therapies. We describe two patients with CIU, neither of whom had detectable autoantibodies, in whom control of the disease was achieved with methotrexate.

Key words: chronic idiopathic urticaria, methotrexate

Chronic idiopathic urticaria (CIU) can be extremely disabling in its severe form,¹ and may be unresponsive to antihistamine therapy.² It is now well established that about one-third of patients with CIU have autoantibodies to the high-affinity IgE receptor (FcεRIα) and/or against IgE.^{3–6} Evidence for an immunological pathogenesis stimulated the use of immunomodulatory treatment, including cyclosporin, plasmapheresis and intravenous immunoglobulin, in severely affected patients with antihistamine-resistant disease.^{7–9} We report two patients with CIU, neither of whom had detectable autoantibodies, in whom methotrexate successfully controlled symptoms. Only one patient with CIU and one with urticarial vasculitis have previously been reported as responsive to methotrexate.^{10,11}

Case reports

Patient 1

A 42-year-old Egyptian housewife presented in September 1994 with a 3-week history of severe urticaria and angio-oedema, which had started 1 week after a tetanus injection. Urticarial weals lasted for less than 24 h and left no residual purpura. They occurred daily at any site, but with a slight predilection for pressure

areas. There were no other physical precipitants. Episodes of angio-oedema occurred daily with facial and throat swelling. Attacks of urticaria were associated with fever, bone pain, arthralgia, myalgia, eye soreness, breathlessness and prostration. The patient was not on any medication and did not take aspirin. She had a previous history of intermittent urticaria in childhood, thought to be related to dairy products and strawberries. These episodes ceased when she reached the age of 20 years, at the time of the birth of her first child.

Challenge tests confirmed delayed pressure urticaria and excluded dermographism. An autologous serum skin test was negative,¹² and functional autoantibodies to FcεRIα or IgE were not detected in basophil histamine release assays.³ A skin biopsy showed a neutrophilic infiltrate with no evidence of urticarial vasculitis. She had a mild microcytic anaemia (minimum haemoglobin 10.1 g dL⁻¹, mean cell volume 75 fL) with normal ferritin levels, suggesting a β thalassaemia trait (although haemoglobin electrophoresis was not performed). C-reactive protein was elevated at 157 mg L⁻¹ (normal < 5) and erythrocyte sedimentation rate was raised at 28 mm in the first hour (normal < 20). The following investigations were negative or normal: urea and electrolytes, liver function tests, immunoglobulins and protein electrophoresis, antinuclear factor, extractable nuclear antigen, organ-specific autoantibodies, complement factors C3 and C4, Coomb's test and thyroid function tests. A raised

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temperature was not recorded, but in view of the self-reported fever an infection screen was performed and the following tests were negative: serology for hepatitis A, B and C, toxoplasmosis and antistreptolysin antibody, a Mantoux test, chest X-ray and abdominal ultrasound. Cytomegalovirus and Epstein–Barr virus IgG antibodies were detected, indicating previous infection. Liver biopsy was not undertaken prior to methotrexate therapy as both liver function tests and abdominal ultrasound findings were normal.

Treatment with antihistamines (cetirizine and loratidine with cimetidine), dapsone and doxepin was unsuccessful; indeed, acrivastine caused a serum sickness-like reaction. Adrenaline injections and 2% ephedrine spray were needed, sometimes daily, for the angio-oedema. The patient required prednisolone 40–60 mg daily to control symptoms, and became cushingoid. Cyclosporin 300 mg daily (3 mg kg^{-1}) was introduced in April 1995, given in combination with prednisolone, but although there was an initial improvement, the patient relapsed within 3 months while still on cyclosporin. In September 1995, methotrexate 15 mg weekly was commenced. There was a marked improvement after 1 week, and within 2 months the patient was symptom free except for mild delayed pressure urticaria. The cyclosporin was stopped in October 1995 and the prednisolone was gradually reduced and withdrawn by January 1996. The patient remained symptom free, and in March 1996 the methotrexate was stopped. Both the angio-oedema and the urticaria returned within 2–3 weeks. In April 1996, the methotrexate was reinstituted, and again the patient responded within 1 week. She continues on methotrexate 12.5 mg weekly, with fexofenadine 180 mg daily.

Patient 2

A 37-year-old caucasian man presented in August 1998 with an 8-month history of severe urticaria requiring prednisolone 50 mg daily for symptomatic control. Urticarial weals occurred daily at any site and lasted for 24–48 h, resolving without residual purpura. Attacks of lip swelling occurred weekly but there was no history of angio-oedema of the airways. There were no other symptoms accompanying the attacks, but the patient suffered independently from headaches, facial flushing and heartburn (perhaps as a result of high-dose corticosteroids). There were no symptoms of any of the physical urticarias. There was no history

of insect bite, vaccination or any medication taken prior to the first attack of urticaria.

On examination, the patient was cushingoid and had scattered urticarial weals on his trunk. Challenge tests were negative for dermographism but revealed delayed pressure urticaria. Skin biopsy was not performed because the longer lasting lesions were thought to be a result of delayed pressure urticaria. No functional anti-Fc ϵ RI α or anti-IgE autoantibodies were detected in basophil histamine release assays. A synacthen test showed a baseline cortisol of 312 mg L^{-1} , rising to 421 mg L^{-1} 1 h after intramuscular tetracosactrin $250 \text{ }\mu\text{g}$, consistent with adrenal insufficiency secondary to the long-term use of corticosteroids. Bone mineral densitometry showed osteopenia of the spine (T score = -1.3). An oesophagogastroduodenoscopy confirmed oesophagitis and duodenitis. C-reactive protein was slightly elevated at 14 mg L^{-1} . The following investigations were negative or normal: full blood count, erythrocyte sedimentation rate, serum ferritin, urea and electrolytes, liver function tests, immunoglobulins and protein electrophoresis, anti-nuclear antibody, organ-specific antibodies, complement factors C3 and C4, thyroid function tests, hepatitis B and C serology and a chest X-ray.

The urticaria was unresponsive to antihistamines (chlorpheniramine, astemizole, fexofenadine), doxepin, and to a low salicylate, dye and preservative-free diet, and the patient required prednisolone 40–50 mg daily to relieve the symptoms. Cyclosporin 200 mg twice daily (3.5 mg kg^{-1}) was introduced in December 1998 and the dose of prednisolone gradually reduced. Although there was an initial improvement, the cyclosporin was discontinued after 1 month because of hair loss and retrobulbar pain. In April 1999 methotrexate 20 mg weekly was introduced in combination with prednisolone 5 mg daily, cetirizine 10 mg daily, hydroxyzine 25 mg daily, omeprazole 20 mg daily, and daily vitamin D and calcium supplements. There was a marked improvement in the symptoms, with fewer and shorter attacks occurring within 2 weeks. Methotrexate (at least 15 mg weekly) was required to prevent relapse. The patient remains in remission on methotrexate 15 mg weekly, prednisolone 2 mg daily and cetirizine 10 mg daily.

Discussion

We describe two patients with severe antihistamine-resistant, corticosteroid-dependent CIU, who responded to treatment with methotrexate. Methotrexate has been

reported as an effective treatment in one previous case each of CIU¹⁰ and urticarial vasculitis,¹¹ although in the latter there was little histopathological evidence of urticarial vasculitis. Both cases were very similar to ours, with severe disease requiring high doses of corticosteroids and response to methotrexate within 2 weeks of commencing treatment.

The self-reported pyrexia in patient 1 is unusual for ordinary CIU, but the most frequent causes of pyrexia occurring with CIU, such as underlying lymphoma, Schnitzler's syndrome or common infective causes, were excluded. Both patients had associated delayed pressure urticaria, and in patient 1 this was poorly responsive to cyclosporin, a common finding in our experience when using cyclosporin or intravenous immunoglobulin (unpublished data). In patient 2, the weals were of more than 24 h duration. These weals could have been due to delayed pressure urticaria, but as a skin biopsy was not performed, urticarial vasculitis cannot be excluded. The severity of symptoms in both patients and the self-reported pyrexia in patient 1 makes these cases of urticaria rather unusual and necessitated more extensive investigations than are normally required in CIU.

The mechanism of action of methotrexate has mainly been studied in patients on high-dose methotrexate as chemotherapy for neoplastic disease or in patients on low-dose methotrexate for rheumatoid arthritis. The mechanism of action in CIU is not known. The classic mechanism of action of methotrexate is the inhibition of dihydrofolate reductase, decreasing the supply of reduced folate cofactors for RNA and DNA synthesis. Intracellular polyglutamates of methotrexate inhibit thymidylate synthetase and 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase, the key enzymes in the synthesis of pyrimidines and purines, respectively. It has been shown that methotrexate promotes intracellular AICAR accumulation, thereby enhancing release of adenosine into the extracellular fluid, which diminishes stimulated neutrophil adhesion.¹³ Methotrexate has also been shown to reduce the accumulation of neutrophils at inflamed sites.¹⁴ Other reported effects of methotrexate in rheumatoid arthritis include decreased intracellular leukotriene B₄ biosynthesis by neutrophils,¹⁵ alteration of cytokine levels [suppression of interleukin (IL)-1 and IL-6 release, but increase in IL-2 production],¹⁶ and reduction in the effects of proteolytic enzymes.¹⁷ The effects of methotrexate on folate-dependent enzymes and some of the other effects of methotrexate are shared with sulphasalazine,¹³ a

drug which has also been reported as a successful treatment in three patients with corticosteroid-dependent CIU.¹⁸ However, sulphasalazine has also been reported to inhibit IgE-mediated mast cell degranulation,¹⁹ which may be its more relevant mode of action in CIU.

The pathogenesis of CIU has not been fully elucidated. Elevated levels of histamine have been found in urticarial weals, and mast cell degranulation has been demonstrated.²⁰ However, as weals often last for longer than the duration of a histamine-induced weal and flare response, and as urticaria in some patients is resistant to antihistamine treatment, it seems likely that other mediators released from mast cells or other infiltrating cells are important in weal formation or maintenance.²¹ It has been shown that eosinophils, neutrophils and CD4+ T lymphocytes accumulate in some, but not all, urticarial weals.²² The effects of methotrexate on neutrophil adhesion, accumulation and leukotriene B₄ synthesis may therefore be relevant to CIU. The chemokine and cytokine profile of urticarial weals is not yet known.

It has been shown that about one-third of patients with CIU have circulating functional autoantibodies to FcεRIα and/or IgE,^{3–6} but such autoantibodies were not detected in either of our patients. The pathogenesis of CIU in the remaining two-thirds of patients has yet to be determined, and the cause of mast cell degranulation is not known in the two patients described. However, the absence of detectable autoantibodies suggests that the successful effect of methotrexate in these patients was independent of currently recognized autoantibody production or function.

The adverse effects of methotrexate are well known and include bone marrow suppression, teratogenicity, hepatic toxicity, gastrointestinal intolerance, interstitial pneumonitis, pulmonary fibrosis and small vessel vasculitis.^{23–25} Of note, although rare, there are at least 20 reported cases of anaphylactoid reactions to methotrexate, including cases of urticaria and angio-oedema.²⁶ Most such patients were receiving high-dose methotrexate as chemotherapy for neoplastic disease, but three were on relatively low doses for psoriasis. Methotrexate has also been reported to be responsible for exacerbation of urticarial vasculitis in one patient.²⁷

In summary, we report two patients with antihistamine-resistant corticosteroid-dependent CIU who responded to treatment with methotrexate. However, we are aware of patients in whom this treatment has been unsuccessful, and adverse effects of methotrexate may be serious. We therefore suggest that a trial of

methotrexate be reserved for patients with severe CIU, in whom other treatments such as antihistamines and cyclosporin have been unsuccessful or are contra-indicated. Methotrexate may then provide a useful alternative.

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