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Urticarial Vasculitis Syndrome Effectively Treated with Dapsone and Pentoxifylline

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Urticarial vasculitis is difficult to treat. We report here on a 40-year-old woman with a 16-year history of idiopathic hypocomplementemic urticarial vasculitis syndrome. Her disease had been resistant to treatment with H1- and H2-blockers, indomethacin, dapsone and interferon alpha but responded to >25 mg/day prednisolone. Monotherapy with pentoxifylline was also of only minor benefit. Using a combination of dapsone (100 mg/day) and pentoxifylline (1,200 mg/day), we observed a gradual improvement resulting in a complete remission within 8 weeks. Complete control of symptoms could be maintained for 18 months without any serious side-effects. This type of treatment may be of benefit in other therapy-resistant cases of hypocomplementemic urticarial vasculitis syndrome, particularly in view of its excellent tolerance.

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Urticarial vasculitis syndrome (UVS) is defined as a distinct clinico-pathological entity, characterized by purpuric urticarial weals, histologically showing all the criteria of leukocytoclastic vasculitis. UVS represents a systemic disease that involves a number of organs, particularly the joints, lung and kidneys. In most of the afflicted individuals, UVS is associated with or results from underlying diseases, such as drug reactions, hepatitis B, or systemic lupus erythematosus. Consequently, if an underlying disease is detectable, the major therapeutic principle is to remove the stimulus or to treat the associated disease (1). In contrast, the treatment of idiopathic cases, classified as primary UVS, generally proves to be very difficult.

Attempts have been made to treat UVS with indomethacin, H1- and H2-blockers, dapsone and (hydroxy-)chloroquine as well as with steroids, but the results are varying (2, 3). An additional potential mode of treatment is the use of cytotoxic drugs, alone or in combination with steroids. Continuous therapy should, however, be restricted to short periods of time in order to avoid serious side-effects. At times, the use of these drugs is even contraindicated.

We report here on a patient who suffered from chronic UVS with typical urticarial weals, severe polyarthritis, conjunctivitis and gastrointestinal pain. All previous attempts using various treatment modalities had proven fruitless. After the patient had received a combination of 100 mg dapsone/day with 1,200 mg pentoxifylline (PTX)/day, all symptoms resolved completely within a period of 8 weeks.

CASE REPORT

A 40-year-old woman had suffered from multiple episodes of itching purpuric skin lesions for over 16 years. The skin lesions were characterized by indurated, erythematous weals with associated petechial bleeding. Individual lesions persisted for up to 3 days and were preferentially localized on the lower extremities. For 10 years, the patient had also developed episodic arthralgias with joint swellings, particularly on fingers, knees and toes, in association with the bouts of urticaria. In April 1984, the patient was hospitalized for evaluation of the palpable urticarial purpura and histologically diagnosed as having a leukocytoclastic vasculitis. She was treated with H1-antihistamines combined with penicillin, without any benefit. Also, no improvement was observed on an additive-free diet. In 1991, wealing spread to the upper extremities and the trunk and was associated with extracutaneous manifestations like abdominal pain, diarrhoea and painful conjunctivitis. Based on clinical and histological findings, the diagnosis of UVS was made and the patient was treated successfully with oral corticosteroids (40 mg prednisolone/day). However, after the steroid medication had been discontinued, skin and systemic manifestations recurred within 2 weeks. In 1992, the patient consulted our clinic again because non-steroidal medication gave no relief.

Laboratory data on admission

Laboratory values showed an elevated sedimentation rate (ESR) (60 mm/h), reduced levels of C3 (45 mg/dl; normal 55–120 mg/dl) with normal C4 (32 mg/dl; normal 22–50 mg/dl) and the presence of circulating immune complexes. Serum electrophoresis revealed an elevation of the gamma globuline fraction (24.1%; normal 11–19%). Rheumatoid factor, ANA, tests for DNA-, Sm-, RNP-, SS-A-, SS-B-antibodies, liverfunction tests, serum levels of Cl inhibitor, cryoglobulins, urinanalysis, chest X-ray, and ECG were all negative or within normal range. Pulmonary function tests showed no significant alterations.

Histopathology

A punch biopsy, taken from light-protected lesional skin, exhibited the typical signs of leukocytoclastic vasculitis: the upper dermal blood vessels showed fibrin depositions both within and around the vessel walls, infiltrates of neutrophils and lymphocytes and nuclear dust.

Direct immunofluorescence of the same lesion demonstrated deposition of IgG, IgA, IgM, C1q and C3 along the blood vessels. Immunoreactivity was found also along the dermo-epidermal junction.

Subsequent clinical course

The patient's skin lesions and systemic affections were not controlled by H1-blockers, indomethacin or aspirin. With prednisolone, 40 mg/day, the patient's skin lesions and systemic manifestations cleared, but the drug was discontinued to avoid undesirable long-term side-effects. Since IFN-α had been found to be of benefit in a patient with urticarial vasculitis and plasmocytoma (4), treatment with IFN-α2b (3×3 Mio IU/week) was started. Since an initial decrease in itching was not sustained and since the systemic manifestations of the disease were not altered, treatment was stopped at the request of the patient after 5 weeks. A course of dapsone, 100–150 mg/day, resulted in a slight improvement of the skin lesions, but purpura as well as systemic manifestations were unaffected. In August 1992, the patient was treated with 3×400 mg PTX in combination with 2×50 mg dapsone daily. Two weeks later, the skin lesions had improved, and over the next 6 weeks all skin and systemic manifestations resolved completely. Reduction in dapsone medication resulted in occurrence of urticarial lesions,

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suggesting that monotherapy with PTX was not sufficient to maintain the improvement. We observed no side-effects. Therapy with dapsone and PTX induced no alterations of the routine blood tests. Elevated ESR, reduced levels of C3 and circulating immune complexes persisted.

In October 1993, on relapse of the patient's skin lesions, we transiently increased the dose of PTX up to 3×600 mg daily, with again good control of all symptoms.

DISCUSSION

Two decades ago, McDuffie et al. (5) reported on a case of cutaneous vasculitic syndrome that was characterized by chronic urticaria-like lesions of more than 6 months' duration with associated arthritis or arthralgias and a broad spectrum of additional systemic symptoms. Since this initial report, at least 100 patients have been described with hypocomplementemic UVS, and a variety of different medications have been used for treatment, including antihistamines, indomethacin, chloroquine, dapsone, colchicine, prednisolone, azathioprine, cyclophosphamide and plasmapheresis. So far, there is, however, no generally effective therapeutic agent for this disease (2), as might be expected from the broad spectrum of clinical manifestations. The patient presented here was initially treated with diverse regimens including antihistamines and an additive-free diet, IFN-α and penicillin, with no benefit. Prednisolone at higher doses (> 25 mg/day) led to complete clearance of all symptoms, but treatment was discontinued because of potential long-term side-effects. Dapsone resulted in a slight improvement of urticarial skin manifestations, but the purpura as well as the systemic manifestations persisted. The patient experienced, however, continuous improvement within only 2 weeks of a combined therapy with 1,200 mg PTX and 100 mg dapsone daily. After 8 weeks, the vasculitis was totally controlled. During therapy, no change in the patient's serological parameters was noted, and the treatment was well tolerated.

The subjective and objective improvement observed in our patient is most probably due to the combined therapeutic effect of both medications, since discontinuation of one component resulted in a prompt relapse.

Sulfones and sulfonamides have been used to treat a variety of vasculitic disorders. Dapsone has been employed in the therapy of numerous dermatologic and systemic disorders, including hypocomplementemic UVS (6–8). In vitro studies have suggested various effects on neutrophil function: dapsone inhibits myeloperoxidase-mediated iodination (9, 10), neutrophil-lysosomal activity (11), and generation of active oxygen metabolites (12). Besides these anti-inflammatory effects, some authors have proposed also suppression of neutrophil chemotaxis (13–15), but this effect has been controversally discussed by others (16). Recently, Booth and co-workers (17) showed that dapsone inhibits neutrophil adherence mediated by integrins, and Thuong-Nguyen et al. (18) described suppression of neutrophil adherence to antibodies (IgA, IgG) at the basement membrane in a dose-dependent manner.

All these effects may contribute to the clinical efficacy of dapsone in antibody-mediated diseases (8), resulting in inhibition of neutrophil accumulation in the skin. Nevertheless, an analysis of the literature reveals that in UVS responsiveness to dapsone is variable and generally unsatisfactory (2).

PTX was originally introduced for the treatment of peripheral vascular diseases, cerebrovascular disease, and for a number of other disorders with defective micro- or macrocirculation (19). In this context, the observed effects were related to general hemodynamic or oxygenation effects on the tissue. Recently, it was reported that PTX additionally exerts profound influences on granulocyte functions similar to dapsone. PTX has also been shown to inhibit free radical generation (20, 21) and both basal and stimulated neutrophil adhesion to bovine endothelium (22), probably via the downregulation of neutrophil functional antigens (e.g. CD11 a-c, CD18). In addition, PTX acts as a selective inhibitor of TNF-α in vitro and in vivo (23). Since TNF-α increases the adherence of polymorphonuclear leukocytes to endothelial cells (24), PTX may inhibit neutrophil adherence at sites of inflammation via the modulation of cytokine expression.

Treatment with PTX has until now been reported in 3 patients with chronic leukocytoclastic vasculitis (25, 26). Two patients had complete clearing of their lesions after 2 months of therapy. A third patient, suffering from Hodgkin's disease, responded as well, so that his steroid medication could be reduced from 40 to less than 10 mg daily. We have recently reported for the first time preliminary results on the effect of the combined use of PTX and dapsone in 3 patients with leukocytoclastic vasculitis which also included results on the present patient and data from two other patients with associated Sjögren's syndrome and rheumatoid arthritis (27). In the patient presented here, monotherapy with 3×400 mg PTX or 100 mg dapsone daily had been ineffective, and only the combination of both drugs brought the desired long-term benefit. We recommend that this therapeutic regimen should be tried in additional patients with hypocomplementemic UVS, in order to confirm the present good results.

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