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## Hypocomplementemic urticarial vasculitis in mixed connective tissue disease

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### Abstract

Urticarial vasculitis is characterized clinically by urticaria-like skin lesions and histologically by leukocytoclastic vasculitis. It may be idiopathic or associated with various conditions such as infections, hematologic disorders, drugs, and connective tissue diseases, primarily systemic lupus erythematosus; an association with mixed connective tissue disease (MCTD) has rarely been reported. We present a case of hypocomplementemic urticarial vasculitis in a patient with MCTD that responded to hydroxychloroquine after a period of corticosteroid dependence.

### Introduction

Urticarial vasculitis is characterized by episodes of persistent urticarial skin lesions, with or without angioedema, and histological evidence of leukocytoclastic vasculitis. Patients can be divided into two groups, those with normal complement levels and those with hypocomplementemic urticarial vasculitis. The latter are more likely to have systemic compromise including arthralgia, progressive lung disease, ocular inflammation, and renal involvement [1]. Urticarial vasculitis is frequently idiopathic but may be associated with serum sickness, drugs, physical urticaria, Schnitzler syndrome, infections, hematologic disorders, and connective tissue diseases, primarily systemic lupus erythematosus. Nevertheless, the association with mixed connective tissue disease (MCTD) has been rarely reported. We present a case of hypocomplementemic urticarial vasculitis in a patient with MCTD that responded to prednisone followed by maintenance treatment with hydroxychloroquine.

### Case report



Figure 1

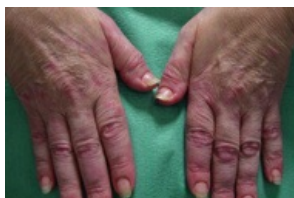


Figure 2

**Figure 1. Urticarial papules and plaques on the trunk.**

**Figure 2. Edema of the hands.**

A 56-year-old woman presented to the Dermatology department with a 3-week history of recurrent generalized urticarial papules and plaques, unresponsive to antihistaminic treatment (Figure 1). The eruption had a purpuric quality, and was associated with mild pruritus. Individual lesions persisted beyond 48 hours. She also had a 5-year history of edema of the hands (Figure 2), Raynaud phenomenon, and hand and foot arthralgias for which she was receiving intermittent treatment with indomethacin. The patient denied difficulty in swallowing, dyspnea, myalgia, muscle weakness or other symptoms. She was otherwise healthy and no other drug intake was mentioned. The histopathologic examination of a skin biopsy specimen revealed damage of the small vessels in the dermis with neutrophilic infiltrate, and presence of leukocytoclasia and red blood cells extravasation, consistent with leukocytoclastic vasculitis (Figure 3).

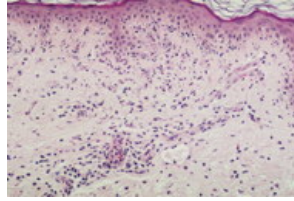


**Figure 3**

**Figure 3. Small vessel vasculitis in the dermis (left), with neutrophilic infiltrate, presence of leukocytoclasia and red blood cells extravasation (inset, right), consistent with leukocytoclastic vasculitis (H&E).**

Complete blood cell count, erythrocyte sedimentation rate, chemistry panel including aldolase and creatine kinase, C-reactive protein, and urinalysis were within normal range. The antibody serologies of hepatitis B, hepatitis C, HIV, cytomegalovirus, and Epstein Barr virus were negative. Rheumatoid factor, anti-double stranded DNA, anti-cardiolipin, anti-centromere, and antineutrophil cytoplasmic antibodies were all negative. The protein electrophoresis showed an elevated level of gamma globulins (25%; normal range 10.5-19.5%) with increased immunoglobulin G (1890 mg/dl; normal range 650-1500 mg/dl). The C1q level (4 mg/dl; normal range, 18 – 45 mg/dl), C3c level (27 mg/dl; normal range, 83-177 mg/dl), C4 level (7 mg/dl; normal range, 12-36 mg/dl) were decreased, whereas the circulating immune complex (CIC) level was markedly increased (100 µg/ml; normal < 4.4 µg/ml). An elevated titer of antinuclear antibodies (ANA) was detected (>1/1000; speckled). There was a high titer of autoantibodies against U1-ribonucleoprotein (U1RNP), as shown by the immunoblot test. The other anti-extractable nuclear antigen (ENA) antibodies (anti-Jo1, anti-SCL70, anti-Sm, anti-Ro, anti-La) were negative. Nailfold capillaroscopy and chest radiography were unremarkable. HLA-DR4 typing was negative.

The patient's urticarial skin lesions with histological evidence of leukocytoclastic vasculitis and decreased complement levels were diagnosed as hypocomplementemic urticarial vasculitis. The diagnosis of MCTD was established because of the presence of Raynaud phenomenon, edema of the hands, and arthralgias (synovitis) associated with a high titer of anti-U1RNP autoantibodies.

Treatment with oral prednisone was started, initially 0.5 mg/kg/day and then 1 mg/kg/day; resolution of the skin lesions and improvement in arthralgias was achieved. Laboratory improvement included an increase of the C1q level (from 4 to 14 mg/dl), and decrease of the CIC level (from >100 to 22 µg/ml). The attempts at tapering the corticosteroid dose were accompanied by the recurrence of the urticarial papules and plaques, therefore, after 4 months, hydroxychloroquine 400 mg/day was added. The prednisone was slowly tapered and, at

one year follow-up, the patient was free of symptoms while receiving prednisone 10 mg every other day and hydroxychloroquine 400 mg/day. During follow-up, high titers of ANA (>1/1000, speckled) and anti-U1RNP antibodies were still detected.

## Discussion

The association between urticarial vasculitis and MCTD has been rarely reported. There are two reviews describing 3 patients with MCTD among 68 cases of urticarial vasculitis [2], and one patient among 27 [3].

The initial description of MCTD as a distinct connective tissue disease was made by Sharp and colleagues in 1972 [4]. Since then, the concept has been controversial, but now is evident that MCTD is a distinct entity. The presence of high titers of autoantibodies to U1RNP influences the expression of connective tissue disease in ways that are relevant to prognosis and treatment [5]. Mixed connective tissue disease is characterized by overlapping features of lupus erythematosus, systemic sclerosis, polymyositis / dermatomyositis, and rheumatoid arthritis. There are various published criteria for the diagnosis of MCTD. The Alarcon-Segovia criteria include high titers of antibodies against U1RNP as well as the presence of at least 3 of 5 of the following clinical features: edema of the hands, synovitis, myositis, Raynaud phenomenon, and acrosclerosis [6]. This criteria set has a sensitivity of greater than 90 percent, a specificity of greater than 98 percent [7]. It was evaluated as one of the best classification criteria to define MCTD [8]. Other clinical features are pulmonary interstitial fibrosis, pulmonary hypertension, esophageal reflux or dysmotility, small-vessel vasculitis with palpable purpura, leg ulcers, alopecia, facial erythema, and periungueal telangiectasias. Renal involvement is rare and usually mild. Anti-U1RNP antibodies are detectable in 25-47 percent of SLE patients, but high titers of anti-U1RNP are diagnostic of MCTD [9]. There is a strong association of MCTD with HLA-DR4, which is found in 52 percent of the patients [10]. The prognosis varies from a benign course to severe progressive disease. In approximately one-third of patients the clinical symptoms go into long-term remission and the anti-RNP antibodies disappear. One-third of patients have a severe and progressive disease course [11]. The primary disease-related cause of death is pulmonary involvement [12].

Systemic corticosteroid is the most effective treatment of hypocomplementemic urticarial vasculitis. Management also includes indomethacin and antihistamines for symptomatic relief, dapsone, colchicine, and hydroxychloroquine. For refractory cases azathioprine, methotrexate, cyclophosphamide, and rituximab have also been used [1]. However, therapy of HUV involves management of the underlying cause, when identified. Because no controlled studies have been performed to guide the therapy in MCTD, the conventional therapies used in other rheumatic conditions are employed. Corticosteroids, antimalarials, methotrexate, cytotoxics, and vasodilators have all been used [13]. Hydroxychloroquine inhibits chemotaxis of eosinophils and locomotion of neutrophils; in addition, it impairs complement-dependent antigen-antibody reactions. Our patient responded favorably to oral steroids (1 mg/kg/day) but the frequent relapses with tapering, in the setting of mild systemic involvement, made hydroxychloroquine an appropriate choice.

This case illustrates the relevance of searching for underlying disease in patients with urticarial vasculitis, especially when it occurs with hypocomplementemia.

The diagnostic criteria for MCTD are based on a specific

serologic marker (U1-RNP), the association with HLA-DR4, the mild renal involvement, and the predisposition to pulmonary disease. These seem to delimit a clinically distinct and stable condition, but the longitudinal follow-up of MCTD patients must take into account the possible evolution to another entity in the connective tissue spectrum, such as systemic sclerosis, systemic lupus erythematosus, and dermatomyositis.

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