

Non-complementaemic urticarial vasculitis: successful treatment with the IL-1 receptor antagonist, anakinra

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Urticarial vasculitis (UV) is a clinical and pathological entity characterized by recurrent episodes of urticaria with the histopathological features of leucocytoclastic vasculitis (1). This condition is idiopathic in many patients but can also occur in the context of autoimmune disorders, infections, drug reactions, or as a paraneoplastic syndrome. The variability in the clinical presentation may be due to the presence or absence of hypocomplementaemia (2). Here we describe a case of non-complementaemic UV (NUV) successfully treated with anakinra.

A 54-year-old man was referred to our department for a second opinion because of fever of 3 years' duration. The patient also complained of recurrent urticaria for approximately 4 years. Prior to presentation at our clinic, he had been treated for 6 months with cyclosporin (5 mg/kg/day) and for the past 2 months with up to 40 mg of daily prednisone without improvement. The urticarial lesions were located on the trunk and extremities. No arthritis or

splenomegaly was evident. Laboratory data were significant for elevated erythrocyte sedimentation rate (70 mm/h) and C-reactive protein (83 mg/L). Cryoglobulins and circulating immune complexes were absent, serology for hepatitis C was negative, and complement profile was normal.

Biopsy of an urticarial lesion revealed swelling of endothelial cell nuclei with disruption of the vessel wall, extravasation of red blood cells, fibrin deposition, and an infiltrate of neutrophils and lymphocytes with occasional eosinophils. Bone marrow biopsy was unremarkable. Multiple cultures of blood, urine, and sputum were negative. A diagnosis of NUV was made and the patient was started on methotrexate (15 mg/weekly i.m.), prednisone (25 mg/daily), and naproxen (500 mg twice a day). After 6 months of this regimen, fever and urticaria were reduced but persisted. The patient reported a dramatic remission in all symptoms following the initiation of anakinra (100 mg/daily s.c.). After 2 weeks of anakinra, methotrexate and naproxene were stopped, and

prednisone was reduced to 5 mg/daily and subsequently discontinued. Upon reduction of anakinra to alternate days, urticaria and fever reappeared. Daily anakinra was reintroduced and the patient has been disease free for 13 months.

The recombinant form of the naturally occurring interleukin-1 (IL-1) receptor antagonist anakinra is the only agent currently approved for reducing IL-1 activities (3).

The mechanism(s) underlying the pathogenesis of cutaneous NUV remains unknown. In patients with this form of vasculitis, the infiltrate in the vascular lesion is rich in activated lymphocytes, which is consistent with a role for cellular mechanisms (4). However, in other vasculitides with a leucocytoclastic pattern, a role for tumour necrosis factor- α (TNF α), IL-6, and IL-1 has been proposed in mediating the vascular inflammation (5). Nevertheless, it is clear from the rapid and near complete responses of the present case that IL-1 is likely to be the primary mediator of systemic as well as local inflammation in NUV. There was a rapid reduction in fever, urticarial lesions, and acute phase reactants following the initiation of anakinra, but each reappeared upon a dose reduction only to remit upon returning to daily dosing. The half-life of 100 mg of subcutaneous anakinra is less than 4 h and explains the requirement for daily treatment. Others have reported a similar reoccurrence of systemic disease upon cessation of anakinra in adult (6) as well as in juvenile (7) Still's disease. Thus, anakinra represents an effective treatment option for steroid- and immunosuppressive therapy-refractory NUV.

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