Urticarial vasculitis and syndromes in association with connective tissue diseases

Urticarial vasculitis is now recognised as a distinct entity comprising urticaria-like lesions which are categorised histopathologically by leucocytoclastic vasculitis. In association with connective tissue diseases it is most commonly seen complicating systemic lupus erythematosus and, less often, Sjögren’s syndrome. An editorial in the British Medical Journal in 1983 posed interesting questions about the relation between urticarial vasculitis and systemic lupus erythematosus, briefly discussing the chronic urticaria-angioedema syndromes as well as the simple chronic urticarias. These relations are still open to question and difficult to understand today, some eight years later. It is, however, abundantly clear, that a spectrum of clinical manifestations of urticarial vasculitis exists, occurring in patients who exhibit uncomplicated skin lesions only and ranging to those in whom the vasculitis is complicated by a systemic illness, often severe.

The coexistence of urticaria, angioedema/abdominal pain, and arthralgias has been well documented in patients with no evidence of a defined connective tissue disorder. These have recently been termed the AHA syndrome (arthralgias, arthritis (A), hives (H), angioedema (A)). An asymmetrical polyarthritis exists and it seems that symptoms might be precipitated by emotional stress, anxiety, exercise, and excessive alcohol ingestion. These patients may, indeed, form part of the same group recently reported by Pasero et al., suffering from the ‘urticaria/arthritis syndrome’, except that the latter patients did not have angioedema and all were shown to be B51 antigen positive. Arthralgias/arthritis in any event are not uncommon in association with the simple urticarias, and this combination has previously been reported. A study recently completed at St Thomas’s Hospital included all patients with urticarial vasculitic lesions over a five year period. A different spectrum of disease patterns from those found in patients recently reported from the St Johns dermatology centre was evident.

The diagnosis of urticarial vasculitis is essentially both clinical and histopathological. The condition is more frequently being recognised in association with connective tissue disease in rheumatology clinics today, and far fewer patients are being referred to dermatology centres for diagnosis or treatment, or both. It has also now become clear that treatment of the condition depends to a large extent on the nature of the underlying disease. Local treatment seems to be quite useless except for the symptomatic relief of the intense burning often felt at the site of the lesions.

The lesions vary from simple urticarial weals to ‘giant’ urticaria, accompanied in some by erythema multiforme lesions, purpura, or bullous lesions. They may last for several days, occurring in crops, or may be more or less permanent in some patients lasting for many weeks, months, or even years in a minority, with minor exacerbations and regression of the lesions. Some patients in the St Thomas’s series complained of symptoms for as long as 23 years.

Patients with systemic lupus erythematosus may develop rashes which may closely resemble simple urticaria, or which may be erythema multiforme-like and accompanied by a strong urticarial element, referred to as ‘urticated’ by dermatologists. Angioedema/abdominal pain may accompany these lesions. Although sometimes occurring with episodes of lupus activity, this is by no means true in all patients as recurrent, mild eruptions may punctuate the course of the systemic disease with little or no evidence of clinical or serological activity. The distribution of the lesions bears no relation to the typical vasculitic rash seen with systemic lupus erythematosus or other recognised connective tissue disorders—for example, the fingertips, nail folds, knuckles, elbows, knees, etc. The aetiopathogenesis of urticarial vasculitis may be different from classical vasculitis and the lesions may not have the same prognostic significance as non-urticarial vasculitic lesions, in that they are not often complicated by severe local or systemic vasculitic organ disease.

The serum complement concentrations may be low, either because of a C4 null allele or because of complement activation, and may also be associated with increases of circulating immune complexes or cryoglobulinaemia, or both. The hypocomplementaemia may be episodic, and systemic symptoms may precede the hypocomplementaemia by several years.

Some investigators have looked at the association between skin lesions and genetic deficiencies of complement, and this subject has been well reviewed by Agnello. Rashes associated with genetic complement deficiencies are, however, usually of the lupus type, resembling those of subacute cutaneous lupus erythematosus or perhaps discoid lupus erythematosus. The predominant clinical feature is angioedema. A deficiency of the early components of complement may, however, predispose to a ‘lupus-like’ disease.

Urticarial vasculitis rashes and angioedema may be seen in those patients who do not fulfil four of the 1982 revised American Rheumatism Association criteria for the classification of systemic lupus erythematosus and who have been termed ‘lupus-like’ but who in reality have mild/moderate lupus, as well as in patients with ‘mixed’ connective tissue disease. Patients with Sjögren’s syndrome or essential cryoglobulinaemia usually have a different pattern of skin lesions, which may have an urticarial element but are predominantly purpuric and are seen mainly over the legs. They are often precipitated by exercise and have been termed ‘purpura hyperglobulinaemia/anaphylactoid purpura’.

Urticarial vasculitis, arthralgias, myalgias, and angioedema may also be encountered in patients with ‘primary’ vasculitis. Other manifestations of systemic vasculitis may be prominent in these patients, such as episcleritis, uveitis, iridocyclitis, and, perhaps, retinal vasculitis. When the urticarial vasculitis is associated with severe hypocomplementaemia (particularly of Clq, but also C4, C2, and C3) the term hypocomplementaemic urticarial vasculitis syndrome has been used. This syndrome is often accompanied by chronic obstructive pulmonary disease, immune complex nephritis, and central nervous system complications, particularly pseudotumour
cerebri. Rarely, patients with hypocomplementaemic urticarial vasculitis syndrome may progress to systemic lupus erythematosus.

A group of patients with normocomplementaemic urticarial vasculitis/arthritis syndrome also exists. This was initially recognised by Sanchez et al. and several patients with this type of disorder have been identified in the St Thomas's series. This seems not to be a lupus associated condition, but forms part of the primary vasculitis spectrum. Differences between this condition and hypocomplementaemic urticarial vasculitis syndrome are the absence of lowering of complement components, and particularly the absence of renal disease.

Urticarial vasculitic lesions may also appear with necrotising or granulomatous vasculitides—for example, with polyarteritis nodosa or Wegener's granulomatosis, but the predominant appearance is purpuric rather than urticarial.

What of the conditions associated with Clq esterase inhibitor to urticarial vasculitic lesions? A deficiency of Cl inhibitor, either genetic or acquired (for example, with lymphomas), leads to a deficiency of C4 and C2. The rashes in this condition are of the 'lupus' type, affecting the butterfly area of the face, and may be discoid or subacute cutaneous lupus erythematosus-like. Angioedema is the clinical hallmark of this condition, and urticarial vasculitis usually does not occur. Treatment with danazol (an impeded oestrogen) in this condition has resulted in clearance of the skin lesions as well as elimination of photosensitivity.

The existence of IgG antibodies to Clq in hypocomplementaemic urticarial vasculitis syndrome has been recently confirmed by Wniesnisi and Naff. Precipitins, 7S as well as 19S, had been found earlier by Agnello et al. The existence of Clq antibodies is not unique to patients with this syndrome, however, as they have also been shown in patients with systemic lupus erythematosus without any vasculitic manifestations.

The treatment of urticarial vasculitis is, to say the least, problematical. There is usually no response to antihistamines alone, indicating that urticarial vasculitis is not caused by mast cell-histamine mechanisms as is simple urticaria. Parenteral high dose oral steroids of intravenous 'pulse' cyclophosphamide may be effective in some, but repeated 'pulses' may be necessary to maintain a satisfactory response. Too rapid a reduction in steroid dosage may precipitate a 'flare'. The use of azathioprine is usually without effect. Antimalarial drugs reduce in steroid dosage may precipitate a 'flare'. The use of this condition and hypocomplementaemic urticarial vasculitis syndrome: the role of Clq esterase. J Allergy Clin Immunol 1987; 80: 104-16.


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