

An atypical cutaneous presentation of vasculitis with features of Churg–Strauss syndrome, associated with anti-neutrophil cytoplasmic antibodies and anti-glomerular basement membrane antibodies

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Summary

We report the case of a 59-year-old woman who presented with a persistent papular and nodular cutaneous eruption and new-onset asthma, with normal renal function but persistent haematuria and proteinuria. Investigations revealed eosinophilia, both antineutrophil cytoplasmic antibodies and antglomerular basement membrane antibodies on serological testing (double-positive vasculitis), and a focal necrotizing glomerulonephritis on renal biopsy. Histological examination of a skin biopsy showed a dense neutrophilic infiltrate with focal fibrinoid necrosis and few eosinophils. The clinical and pathological features suggested a double-positive vasculitis/Churg–Strauss overlap syndrome presenting with a predominantly neutrophilic dermatosis. Specific cutaneous features in patients with double-positive vasculitis have not been documented previously. The patient has responded extremely well to immunosuppressive treatment and her disease is currently in remission.

The small vessel vasculitides include a number of clinical diseases such as Wegener's granulomatosis (WG), microscopic polyangiitis and Churg–Strauss syndrome (CSS). Most of these diseases have been found to be associated with a specific serological marker, antineutrophil cytoplasmic antibodies (ANCA).¹ These are mainly IgG autoantibodies directed against neutrophil proteinase 3 [(PR3)-ANCA or cytoplasmic staining (c)ANCA] and myeloperoxidase [myeloperoxidase (MPO)-ANCA or perinuclear (p)ANCA]. The ANCA-associated vasculitides represent a histological and clinical disease spectrum.

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Histologically, ANCA-associated vasculitides are characterized by the varying presence of a pauci-immune necrotizing small vessel vasculitis, necrotizing and crescentic glomerulonephritis, and extravascular granuloma formation. In CSS, the histological features often include a prominent eosinophilic infiltrate. It has become increasingly recognized that a proportion of patients with vasculitis have circulating antglomerular basement membrane (anti-GBM) antibodies, as found in classic Goodpasture's disease, in addition to ANCA. These cases have been labelled double-positive vasculitis. These patients usually present indistinguishably from other small-vessel ANCA-associated vasculitides.² Rapid diagnosis of these diseases is important as they usually require aggressive immunosuppression to prevent major morbidity or death.

We report a patient with ANCA and anti-GBM antibody-associated (double-positive) vasculitis, with

features of CSS, in whom multiple cutaneous nodules comprising a predominant neutrophilic infiltrate were an early and persisting clinical feature. The patient had cutaneous, renal, ocular and pulmonary involvement. The cutaneous features and prognostic implications of this rare double-positivity are discussed.

Report

A 59-year-old woman presented with a 5-month history of a cutaneous eruption mainly affecting her limbs. The rash first began on her lower legs during a hospital admission for a lower respiratory tract infection. A diagnosis of adult-onset asthma was made at that time. Three months later she developed bilateral anterior uveitis, which resolved with topical steroid treatment. Over the next 4 weeks, her cutaneous eruption worsened, with umbilicated, necrotic papules and nodules emerging on her limbs and face (Fig. 1a,b). These were most prominent over the extensor surfaces of the elbows and knees.

She was noted to have haematuria and proteinuria on urinalysis and 24 h urinary protein of 0.3 g/day. Renal function was preserved. Full blood count showed eosinophilia of $2.5 \times 10^9/L$ (normal range 0.0–0.4). She was positive for cANCA (IgG subtype) at a titre of 286 (normal < 25) and anti-GBM antibodies were present at a titre of 47 (normal < 25). Pulmonary function tests showed an obstructive defect with significant bronchodilator reversibility, consistent with a diagnosis of asthma. Radiography and computed tomography of the chest gave normal results.

Histological examination of a skin biopsy showed a dense neutrophilic infiltrate in the superficial and mid dermis with prominent leucocytoclasia (Fig. 2a). Focal fibrinoid deposition was noted (Fig. 2b). No granulomas were seen. Direct immunofluorescence was negative. In view of the persistent urinary abnormalities, a renal biopsy was taken. This showed focal and segmental necrotizing glomerulonephritis with crescent formation (Fig. 3a,b). There was linear capillary wall staining for IgG. A diagnosis of ANCA-associated vasculitis was made, but with serological double-positivity for ANCA and anti-GBM antibodies, and with features of CSS.

The patient was started on oral prednisolone (1 mg/kg) and pulsed intravenous cyclophosphamide every 2 weeks (500 mg/pulse). After six infusions of cyclophosphamide she was started on maintenance treatment with oral azathioprine (100 mg). Her skin eruption resolved within 4 weeks of starting treatment. At the last follow-up, the skin eruption had not recurred, renal function and peripheral eosinophil count

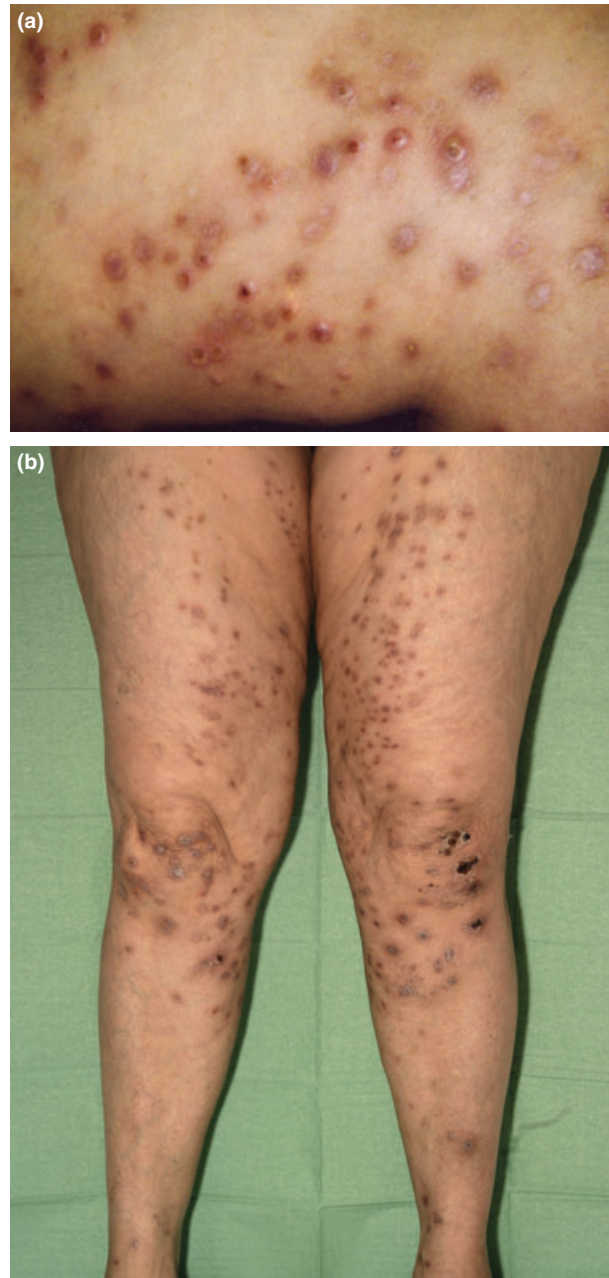


Figure 1 (a) Ulcerated papular lesions on the knee at presentation; (b) distribution of the eruption on knees and inner thighs 3 months later.

were normal, asthma had improved and uveitis had not recurred. Urinalysis had normalized, and ANCA and anti-GBM antibodies were no longer detectable.

The ANCA-associated vasculitides represent a clinical and histological spectrum of disease and not all patients are easily classified into the recognized clinical syndromes of WG, CSS, and microscopic polyangiitis and its

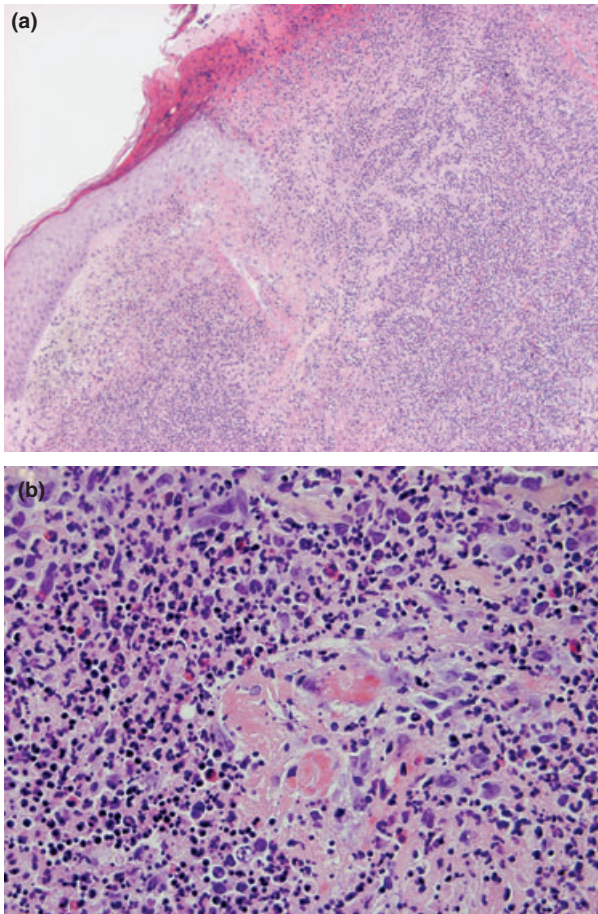


Figure 2 Ulceration of the epidermis with underlying mixed (neutrophil-rich) inflammatory infiltrate; (b) vessel with fibrin deposition. Haematoxylin and eosin, original magnification (a) $\times 50$; (b) $\times 250$.

renal-limited form. Our patient had clinical features consistent with CSS, a multisystem vasculitis associated with asthma and eosinophilia in which renal involvement is common.³

Mucocutaneous features are not uncommon in ANCA-associated vasculitides and may be an early presenting feature in 15–30% of cases, potentially facilitating early diagnosis and treatment.⁴ A cutaneous eruption is seen in 40–70% of patients with CSS and it is the presenting feature in approximately 6% of cases.^{3,5} The lesions may appear as macules, papules, nodules and papulovesicles occurring in crops. Other reported lesions include palpable purpura, petechiae, livedo reticularis and urticarial plaques.⁶ Umbilicated nodules are the most common, occurring mainly on the extensor surfaces of the limbs.

Three main histological patterns have been identified in CSS: (i) a dermal eosinophil-rich inflammatory

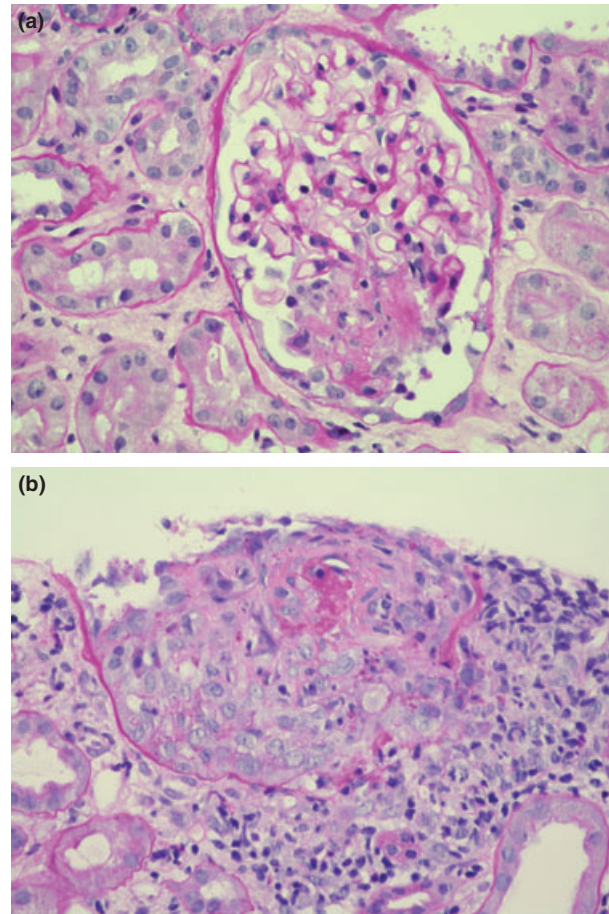


Figure 3 Glomerulus showing (a) a segmental area of fibrinoid necrosis; (b) a circumferential cellular crescent with rupture of Bowman's capsule. Periodic-acid-Schiff (a,b) $\times 400$.

infiltrate; (ii) extravascular necrotizing, palisaded granulomas, often with abundant eosinophils, most commonly found on histological assessment of cutaneous nodules; and (iii) necrotizing vasculitis with fibrinoid changes occurring in small to medium sized vessels. In contrast, the main histological finding in this case was a dense neutrophilic infiltrate in the dermis. There were no granulomas and no significant eosinophilic infiltrate. Focal areas of fibrinoid deposition were seen.

Antineutrophil cytoplasmic antibodies of the IgG subtype have established clinical and diagnostic relevance for WG, CSS, microscopic polyangiitis and periarthritis nodosa. There have been reports of ANCA positivity occurring in association with neutrophilic dermatoses such as Sweet's syndrome and erythema elevatum diutinum.⁷ Many of these cases had IgA rather than IgG ANCA and it remains to be established whether these are an epiphenomenon of neutrophil

activation or are pathogenic triggering factors. The development of ANCA in association with a neutrophilic dermatosis has been reported in patients taking propylthiouracil.⁸ Gürses *et al.*⁹ reported a case of WG presenting with a neutrophilic dermatosis in which granulomatous skin lesions later developed. Our case was clinically consistent with CSS, and presented with a neutrophilic dermatosis. These cases suggest that patients presenting with neutrophilic dermatosis-like skin lesions associated with systemic symptoms should be monitored for the development of ANCA-associated diseases such as WG or CSS.

Interestingly, our patient had anti-GBM antibodies in addition to serum ANCA. Examination of a renal biopsy confirmed the specificity of the anti-GBM antibodies, as they could be seen bound to the basement membranes of glomeruli. Previous studies have estimated that up to 15% of patients with ANCA also have anti-GBM antibodies.^{2,10} It has been suggested that patients who develop an ANCA-related illness leading to glomerular damage subsequently mount an immune response to the exposed glomerular basement membrane. Both antibodies are usually present at the time of clinical presentation. Up to 50% of patients with anti-GBM antibodies have pulmonary haemorrhage. Pulmonary involvement is nearly universal in CSS, with most patients having asthma, typically occurring early in the course of the disease. Pulmonary infiltrates are also present in most patients with CSS but are often fleeting. Alveolar haemorrhage has been reported in a minority of cases. Cutaneous features have been reported in 22% of cases of double-positive vasculitis, but to our knowledge, this is the first report documenting the specific skin lesions seen.² The prognosis in patients with double-positive vasculitis remains unclear.^{2,10}

In conclusion, we present a patient with a double-positive vasculitis and clinical features of CSS who presented with early and persistent cutaneous features

comprising a neutrophilic dermatosis. The ANCA-associated vasculitides represent a spectrum of vasculitic disorders in which prompt diagnosis, leading to early initiation of appropriate immunosuppressive treatment, may be life-saving.

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