Case Report

Leukocytoclastic vasculitis and interstitial nephritis with carbimazole treatment

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Introduction

Carbimazole is a common treatment for hyperthyroidism in the UK. Its main side effects include a rash, agranulocytosis and rarely a lupus-like syndrome. Although vasculitis associated with antineutrophil anticytoplasmic antibodies (ANCA) has been reported on several occasions following treatment with propylthiouracil, vasculitis with carbimazole appears to be less common. We report a case of leukocytoclastic vasculitis with carbimazole therapy accompanied by acute renal failure secondary to interstitial nephritis. Interstitial nephritis has previously been reported with propylthiouracil but not carbimazole.

Case

A 72-year-old male presented to another hospital with a rash over his feet and lower legs. Two weeks earlier he had been commenced on carbimazole 20 mg daily by his general practitioner who had requested thyroid function tests because of progressive weight loss. These had revealed free T4 of 65.7 nmol/l (10.0–32.0 nmol/l) and TSH < 0.01 mU/l (0.35–4.95 mU/l). He was previously fit and was on no other medication. He consumed six units of alcohol and smoked 20 cigarettes daily. The admitting team felt that the skin lesions were cellulitic in nature and commenced the patient on i.v. benzyl penicillin at a dose of 1.2g qds, flucloxacillin 500 mg qds and metronidazole 500 mg tds. However, the lesions progressed despite antibiotic treatment and, therefore, 4 days later, a dermatological opinion was sought. The dermatologist diagnosed a cutaneous vasculitis on clinical grounds and advised treatment with local potassium permanganate dressings and hence the antibiotics were discontinued after a total of 5 days. Over the following 3 weeks the rash gradually progressed to the upper legs, abdomen, back and upper limbs. During this time, there was a decline in renal function from a normal level on admission with urea 5.4 mmol/l and creatinine 80 mmol/l. Macroscopic haematuria was noted on a few occasions and midstream specimen of urine (MSSU) was sterile. The patient became more unwell with progressive nausea, anorexia and weight loss and, because of severely impaired renal function, nephrological advice was sought and the patient was transferred to our unit.

On assessment following transfer, the patient had a widespread vasculitic rash with several focal areas of necrosis (Figure 1). He was unwell, with nausea and obvious weight loss. Cardiovascular examination was unremarkable except for mild fluid overload and chest examination revealed a barrel-shaped chest with a few bilateral basal crepitations on auscultation. Examination of the abdomen revealed ptosis of the liver but was otherwise normal. Rectal examination was also normal. Urinalysis showed blood ++ + + and protein ++. Initially he was apyrexial but a fever developed shortly after admission. There were no complaints of arthralgia, epistaxis, haemoptysis or upper respiratory tract symptoms and no uveitis or episcleritis on examination.

Blood tests showed severe renal insufficiency with urea of 36.1 mmol/l (2.5–6.7 mmol/l) and creatinine of 632 mmol/l (70–120 mmol/l). Haematology revealed a normochromic, normocytic anaemia with haemoglobin

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of 9.7 g/dl, white cell count of $16.8 \times 10^{9}$ (neutrophilia) and platelet count of $225 \times 10^{9}$/l and an erythrocyte sedimentation rate (ESR) of 25 mm/h. Liver function tests including alkaline phosphatase and alanine transferase were normal. Plasma albumin was reduced at 18 g/l. C-reactive protein was significantly raised at 114 (normal <10). Anti-neutrophil cytoplasmic antibodies (ANCA) and anti-glomerular basement membrane antibodies were negative. Cryoglobulins of polyclonal IgG and IgA were detected in plasma. Measurement of complement showed a C3 level of 0.9 g/l (0.75–1.65) and a C4 level of 0.18 g/l (0.2–0.65). Serological investigations showed no hepatitis C infection. An ultrasound scan of the renal tract was normal.

An initial diagnosis of systemic vasculitis was made and because of the temporal relation of symptoms to the commencement of carbimazole, this drug was stopped.

The patient was haemodialysed and, because of the presence of a coliform growth in a catheter specimen of urine, i.v. cefuroxime was commenced (in view of the need to perform a renal biopsy to elucidate the cause of the acute renal failure). Skin biopsy confirmed a leucocytoclastic vasculitis; however, immunoperoxidase studies showed no evidence of significant immunoglobulin or complement deposition. A renal biopsy (Figure 2), performed 4 days after transfer, revealed an interstitial nephritis with a patchy, but heavy interstitial infiltrate including eosinophils and associated with acute tubular damage suggesting a possible allergic cause. There was also some tuft shrinkage but no definite glomerulonephritis and no evidence of vasculitis. Direct immunofluorescence showed no evidence of significant immunoglobulin or complement deposition. Electron microscopy confirmed the absence of glomerulonephritis. In neither skin nor renal biopsy was there evidence of cryoglobulin precipitation despite the presence of polyclonal IgA and IgG cryoglobulins in plasma. In view of the severity of the cutaneous vasculitis and interstitial nephritis, the patient was commenced on prednisolone 30 mg daily.

The rash had started to improve on cessation of carbimazole and continued to improve rapidly with steroid treatment. Unfortunately, he has remained dialysis dependent after 6 months and a repeat renal biopsy performed 6 weeks after the first still showed interstitial infiltrate but associated with considerable tubular loss and chronic damage. Repeat immunology shows normal complement and no plasma cryoglobulins are detectable.

![Fig 2. Renal biopsy showing acute tubular interstitial nephritis.](image.png)

**Discussion**

This report documents the occurrence of a severe cutaneous vasculitis and interstitial nephritis secondary to carbimazole therapy in the absence of circulating ANCA. Vasculitis associated with carbimazole treatment is reported but as an infrequent side effect. D'Cruz et al. [1] reported the onset of a Wegener's like granulomatosis illness with a biopsy-proven crescentic glomerulonephritis (MPO-ANCA positive) 1 month after discontinuing carbimazole therapy. There are two reports of a leukocytoclastic vasculitis occurring shortly after the commencement of carbimazole treatment [2,3], and in one case atypical pANCA were present [3]. Leger et al. [4] reported a polynephropathy, in which a microvasculitis was revealed on nerve biopsy, and Pasquier et al. [5] report on a biopsy-proven myositis with microvasculitis [5] both associated with carbimazole use.

In our patient, the presence of demonstrable polyclonal IgG and IgA cryoglobulins in the plasma at presentation is interesting. However, there was no direct evidence to suggest that the cutaneous vasculitis (or interstitial nephritis) was secondary to the cryoglobulinaemia. Histologically there was no evidence of vascular intra-luminal cryoglobulinaemic deposits, and immunoperoxidase studies were negative for immunoglobulins and complement. However, plasma complement C4 was slightly low, and C3 low normal, compatible with low-grade complement consumption. It is possible that complement activation was secondary to the cryoglobulinaemia and thus it is possible the vasculitis may have been caused by the polyclonal cryoglobulinaemia. However, these possibilities remain speculative. One would speculate that the polyclonal IgG and IgA cryoglobulin production was either directly related to carbimazole exposure or a non-specific response of B cells/plasma cells to the inflammatory state, given that the patient no longer has demonstrable circulating cryoglobulins present. There are no previous reports of carbimazole causing a cryoglobulinaemic vasculitis.

The cause of the interstitial nephritis in our patient is most probably carbimazole related but the association with antibiotic therapy cannot definitely be excluded. However, the course of antibiotics was short and the renal failure progressed despite their discontinuation. It is also very unlikely that the renal failure was related to urinary tract infection/pyelonephritis, as the first
MSSU (collected during the initial deterioration of renal function), was sterile. The cause of the initial macroscopic haematuria remains unclear but has not recurred and is a recognized feature of acute allergic interstitial nephritis. Carbimazole and propylthiouracil (PTU) are structurally related drugs, both being thioureylenes and they appear to have similar pharmacological activity. There are two reports of interstitial nephritis associated with PTU treatment. Reinhard et al. [6] report a 41-year-old male who developed acute renal failure 4 days after commencing treatment with PTU. Renal biopsy revealed an acute interstitial nephritis, but despite drug withdrawal and treatment with corticosteroids, significant renal impairment remained. In a case reported by Nakahama et al. [7], acute renal impairment and interstitial nephritis occurred 18 months into treatment with PTU. There was subsequently good improvement of renal function following withdrawal of PTU and treatment with corticosteroids. Interstitial nephritis has not previously been reported to be associated with carbimazole. An ANCA-positive vasculitis associated with PTU is increasingly recognized [8]. It has recently been identified that patients taking anti-thyroid medication have a higher prevalence of circulating ANCA and it has been proposed that there may be some merit in testing for the presence of ANCA in patients on such medication and withdrawing treatment if ANCA is present in order to prevent the future development of vasculitic complications [9]. In summary, we report the case of a 72-year-old male who developed a florid leukocytoclastic vasculitis and acute renal failure secondary to interstitial nephritis shortly after commencing treatment with carbimazole. Because of the temporal relationship with the commencement of carbimazole, and the absence of ANCA we propose that the leukocytoclastic vasculitis and interstitial nephritis were caused by an acute, allergic drug reaction. This response has not been reported previously, but because of the widespread use of carbimazole, it is an important potential side effect.

References


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