Cerebral vasculitis following allopurinol treatment

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Summary
A 45-year-old man developed cerebral vasculitis associated with a systemic hypersensitivity response shortly after commencing treatment with allopurinol. The illness settled on withdrawal of the drug and no other cause was found.

Keywords: allopurinol, cerebral vasculitis

Allopurinol is a xanthine oxidase inhibitor which is widely used in the treatment and prophylaxis of hyperuricaemia. Common side-effects include skin rash and gastrointestinal symptoms, but less commonly hypersensitivity may occur in the form of a generalised vasculitis causing eosinophilia, fever, exfoliative dermatitis and, if severe, hepatic, ocular and renal damage. Neurological manifestations are rare, although there have been isolated reports of peripheral neuropathy. We report a case of vasculitis associated with allopurinol treatment with prominent central nervous system (CNS) manifestations.

Case report
A 45-year-old man suffering from low grade small cell follicular lymphoma was commenced on chlorambucil (10 mg/day for two weeks) and prophylactic allopurinol (300 mg/day). Three weeks later he developed frontal headache, nausea and a maculopapular rash on trunk and limbs, followed by progressive weakness of his right arm and left leg and paraesthesia in both hands. The allopurinol was stopped, he was treated with antihistamines and referred for neurological investigation. There were no other medications, and no significant past medical history or family history.

Examination revealed mild fever (37.5°C), purpuric lesions on the limbs and hands, and nail bed capillary infarcts. He was confused (Mini Mental Score = 17/30), had impaired short-term memory, acalculia, right-left disorientation and word-finding difficulty. Cranial nerve examination and fundoscopy were normal. He had a flaccid right upper limb monoparesis (MRC grade 0/5 for distal extensors, 2/5 finger and wrist flexion, 4/5 biceps, triceps and shoulder abduction), and a mild left hemiparesis mainly affecting the leg. Reflexes were symmetrically brisk but plantars were flexor. Sensation and cerebellar function were normal.

Investigation revealed a marked eosinophilia (23 × 10⁹/l), an elevated erythrocyte sedimentation rate (45 mm/h) and C-reactive protein (13.1 mg/dl). Serum IgA, IgM and IgG were reduced, and immune complexes were detected in the blood. Cryoglobulins were not detected. Anti-nuclear factor, rheumatoid factor, and anti-neutrophil cytoplasmic antibody were negative. Anti-streptolysin O titre, plasma viscosity, and B12 and folate were normal, and blood cultures, tests for hepatitis B, mycoplasma and toxoplasma infection were negative. An electrocardiogram, chest X-ray and echocardiogram were normal. Urea, creatinine and urine microscopy were normal, and liver function tests were within normal limits. A computed tomography (CT) brain scan was normal, but magnetic resonance imaging (MRI) revealed multiple large discrete periventricular lesions of high signal intensity on T-2 weighted images, compatible with vasculitis or demyelination (figure). Cerebrospinal fluid pressure, microscopy, culture, cytology, protein, glucose and electrophoresis were normal, with a low IgG concentration and no oligoclonal bands. Sural and median nerve sensory action potentials were absent and electromyography showed an excess of polyphasic units, consistent with a distal axonal neuropathy.

Within days of stopping the allopurinol the headache and rash subsided, and after one week the patient's general condition had improved. A repeat MRI scan at two weeks showed a reduction in the size of the lesions with complete resolution of the vasculitis 15 months after stopping the drug.

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Accepted 28 June 1995

Figure MRI scan showing multiple high intensity white matter lesions on T-2 weighted imaging.
month cognitive function had returned to normal, the only residual abnormality being impairment of fine movement in the right hand. A repeat MRI six months later showed resolution of the previous abnormalities. Over the subsequent year he required further treatment for his lymphoma but had no further neurological symptoms.

Discussion

The patient's systemic upset began shortly after starting allopurinol treatment, was similar to previously reported allopurinol hypersensitivity reactions, and resolved rapidly on withdrawal of the drug. Chlorambucil is not reported to cause vasculitis. Vasculitis can occasionally occur in association with systemic lymphoma in the absence of other potential causes, but is usually limited to the skin, although a vasculitic sensorimotor polyneuropathy has been reported. In this case, the rapid resolution of symptoms without further treatment suggests that lymphoma was not the cause. The MRI scan appearance was not that of primary CNS lymphoma, and the rapid neurological improvement was not consistent with cerebral involvement. The MRI appearance could be due to demyelination, but the clinical syndrome was not typical, there was no history of previous episodes, and analysis of the cerebrospinal fluid revealed no evidence of demyelination. The detection of immune complexes in the serum is consistent with the finding of immune complex deposition in allopurinol hypersensitivity vasculitis.

We are not aware of any previous reports of symptomatic cerebral vasculitis in association with allopurinol treatment. Retinal vasculitis and biopsy-proven temporal arteritis were reported in one case, and a patient with renal carcinoma taking deoxycoformycin and allopurinol developed generalised small vessel arteritis which was found to involve the cerebral vessels at post mortem, although this had not been clinically evident. A 17-year-old boy with Lesch–Nyhan syndrome developed focal seizures after nine years of prophylactic treatment with allopurinol. Cerebral angiography was reported to show some features compatible with vasculitis, but there was no clinical or laboratory evidence of either vasculitis or a generalised hypersensitivity reaction.

The majority of hypersensitivity reactions associated with allopurinol occur within four to six weeks of starting the drug. The condition may be severe with up to 50% of patients having hepatic and/or renal involvement, in which case it is associated with a significant mortality. This case suggests that cerebral involvement may occur, and that neurological symptoms may dominate the clinical picture in the absence of any evidence of renal or hepatic involvement. However, in this case the symptoms resolved rapidly following withdrawal of the drug.

### Side-effects of allopurinol

- hypersensitivity reactions are common and may sometimes be severe. Fatal cases have been reported. Hypersensitivity is manifest as a generalised vasculitis with fever, lymphadenopathy, eosinophilia and exfoliative dermatitis. Rarely, hepatic necrosis may ensue
- leukopenia and neutropenia may occur
- mild granulomatous hepatitis
- allopurinol blocks conversion of xanthine to uric acid. There is therefore a danger of xanthine-based crystal formation (xanthine, hypoxanthine, oxypurinol). Crystals have been found in muscle and may also predispose to renal disease
- skin rashes occur in up to 10% of patients

### Learning points

- allopurinol treatment may induce an immune–complex-mediated hypersensitivity reaction
- systemic hypersensitivity reactions usually resolve on withdrawal of allopurinol
- allopurinol hypersensitivity may involve symptomatic cerebral vasculitis

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doi: 10.1136/pgmj.72.844.119

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