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Teaching Point
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A pilot in distress

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Introduction

Acute kidney injury in patients with chronic renal failure is a common scenario in clinical practice. In many cases, the cause is obvious, as in urinary tract infection, dehydration, use of non-steroidal anti-inflammatory drugs or recent therapeutic manipulation of the renin–angiotensin–aldosterone system. In some cases, however, the acute element can be more difficult to identify or remain elusive even after commencing dialysis. We present the case of a 77-year-old retired small-aircraft pilot with chronic renal failure, who returned from holidays with an acute, substantial and entirely unexplained deterioration in renal function. It was a tortuous journey, until we finally deciphered the underlying cause and avoided imminent dialysis. We discuss the presumed underlying mechanism and implications for the management of acute kidney injury in patients with pre-existing chronic renal failure.

Case

A 77-year-old man with known chronic renal failure presented unwell and with an acute deterioration of his renal function.

He had been known to have renal impairment since 2002 at which time his serum creatinine had been 141 μmol/l. There was a remote history of renal obstruction due to benign prostatic hyperplasia, but this had been successfully treated. The patient had a long history of hypertension. Therefore, hypertensive nephropathy, aggravated by the obstructive event, was felt to be the most likely underlying disorder. All immunology was negative and a renal biopsy was not performed. During the ensuing years, his renal function slowly deteriorated, and in early 2008, his serum creatinine was 254 μmol/l despite a creatinine clearance of up to 62 ml/min. At that time, he was on bisoprolol 5 mg, bendroflumethiazide 2.5 mg, atorvastatin 10 mg, finasteride 5 mg, ramipril 1.25 mg, quinine sulphate 300 mg as needed, tamsulosin 400 μg, sodium bicarbonate 500 mg bd and allopurinol 300 mg. None of the drugs had been started recently. He was a retired commercial pilot and flying small aircraft remained his favourite pastime.

In April 2008, he travelled to Cyprus while in good health. He enjoyed his holidays, but at his next follow-up appointment reported lassitude, a low-grade fever up to 37.8°C and occasional joint pains. On examination, he looked slightly worse that his usual self. There was no cardiac murmur and the chest was entirely clear; there was no lymphadenopathy and no rash. The C-reactive protein (CRP) was 36 mg/l. The serum creatinine had almost doubled to 485 μmol/l (estimated glomerular filtration rate 9 ml/min). Haemoglobin was 10.3 g/dl, without leucocytosis or eosinophilia. Urine dipstick was positive for leucocytes, but no growth was observed in culture. Blood cultures also remained sterile. Renal stones and other forms of obstruction were excluded by renal ultrasound. Another detailed history was obtained and the patient examined yet again, all to no avail. An infectious disease acquired in Cyprus was considered. Malaria was excluded by several thick blood films, as was Mediterranean spotted fever (fievre boutonneuse) by immunofluorescence. Blood cultures were repeated, a trial of oral augmentin was prescribed and ramipril was stopped. The patient remained unwell and the serum creatinine remained elevated just as before. Eventually, and in despair, a drug reaction was proposed and a decision was made to stop each drug sequentially, allopurinol being the first suspect on the list. Two days after the cessation of allopurinol, the patient phoned to report that all of his complaints had disappeared entirely. Of note, he had been on allopurinol for years. CRP levels normalized and his serum creatinine dropped substantially (Figure 1). When last seen in August 2009, he was very well indeed and his serum creatinine was back to 268 μmol/l.

Discussion

Allopurinol is usually prescribed in patients with established gout; additional indications include the prevention

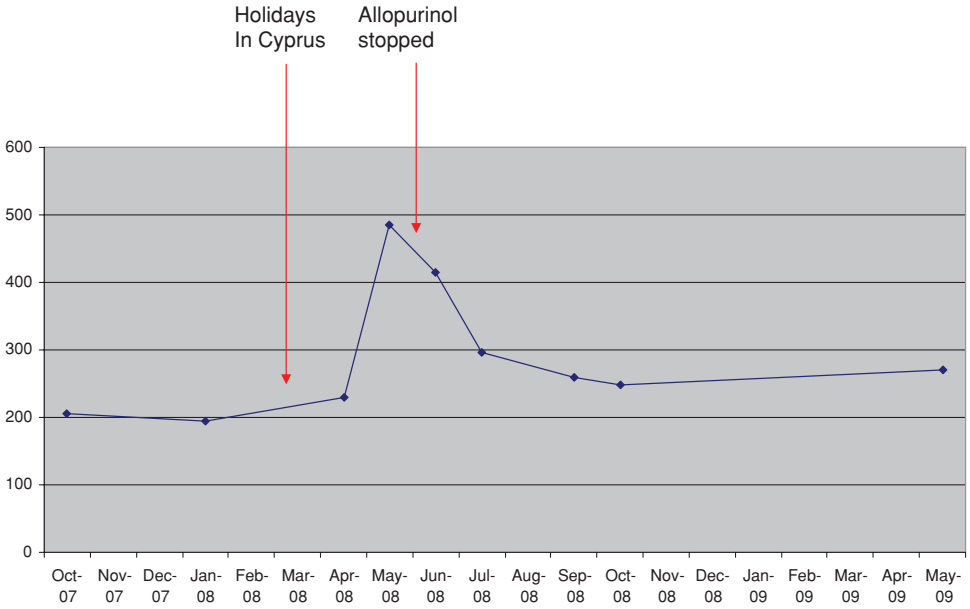

Fig. 1. Serum creatinine levels of patient from October 2007 to May 2009, detailing the association with vacation to Cyprus and cessation of allopurinol.

of the tumour lysis syndrome during chemotherapy or radiation. The action of allopurinol is best understood after a short detour into purine metabolism (Figure 2).

Purines are heterocyclic organic compounds consisting of a pyrimidine ring fused to an imidazole ring. Adenine and guanine are the chief purines. They are essential for the synthesis of two of the four deoxyriboncucleotides and ribonucleotides that make up DNA and RNA, respectively. Part of the purines is from our diet, but endogenous synthesis is also possible, the crucial precursor being inosine monophosphate (IMP).

Allopurinol and its main metabolite oxypurinol inhibit xanthine oxidase and thus prevent the conversion of hypoxanthine and xanthine to uric acid [1]. Both hypoxanthine and xanthine are easily excreted via the kidney. Allopurinol itself is well absorbed within the intestine [2] and rapidly undergoes renal excretion. In contrast, oxypurinol is actively reabsorbed at the kidney tubule and thus persists within the circulation, as evidenced by its long half-life (14–26 h) [3]. A newer drug used for tumour lysis syndrome, rasburicase, catalyses the reaction from uric acid to allantoin (Figure 2).

Our patient with stable chronic renal failure developed fever, lassitude and acute-on-chronic renal failure after a holiday in Cyprus. All of the symptoms, including the substantial deterioration in the glomerular filtration rate, disappeared abruptly after cessation of allopurinol. Of note, he had been on the drug for years. During several weeks of his illness, we repeatedly excluded all other potential causes. Of note, renal biopsy is not usually helpful in acute-on-chronic renal failure, as small kidneys tend to bleed and biopsies tend to be inconclusive. Here, the sudden disappearance of symptoms gave us confidence that allopurinol was the culprit.

Minor side effects of allopurinol occur in ~10% of patients and include rash, urticaria and gastrointestinal upset. Some patients, however, experience a serious reaction, the allopurinol hypersensitivity syndrome (AHS) [4]. This rare but feared syndrome can affect any organ system, and criteria for the diagnosis have been proposed [5] (Table 1). Skin involvement is very common although severity varies, as does the precise manifestation of this cutaneous involvement. Presentation may include a diffuse maculo-papular rash, exfoliative dermatitis or toxic epidermal necrolysis (TEN) in a Stevens–Johnson syndrome phenotype. AHS can be fatal with mortality rates up to 25% [6].

Table 1. Criteria for the diagnosis of allopurinol hypersensitivity syndrome [5]. Two major criteria or one major and at least one minor criterium are required for the diagnosis

Major criteria	Minor criteria
Rash (includes exfoliative dermatitis, erythema multiforme, maculopapular rash and toxic epidermal necrolysis)	Fever
Declining renal function	Leucocytosis
Acute hepatic toxicity	Eosinophilia

The precise mechanism behind AHS is unclear. The average duration of treatment before the hypersensitivity occurs is 2–6 weeks, although time periods from 1 day up to 8 years have been documented [7]. Most investigators have proposed a type III hypersensitivity reaction, and circulating immune complexes are often detectable [8]. It is possible that allopurinol itself or its metabolites are targets of the immune reaction; alternatively, the drug may cause the formation of a neo-antigen. AHS is difficult to treat, and immediate cessation of allopurinol is mandatory [4,5,7]. Patients with epidermolysis are best treated in a dedicated burns unit. The use of steroids has been advocated in severe cases [5]. However, steroids will often be required for a long period of time as recurrences, particularly of the dermatological manifestations, are a frequent occurrence when the steroid dose is tapered too abruptly [4,5]. Haemodialysis has been utilized to remove the remaining oxypurinol from the blood in the hope of halting

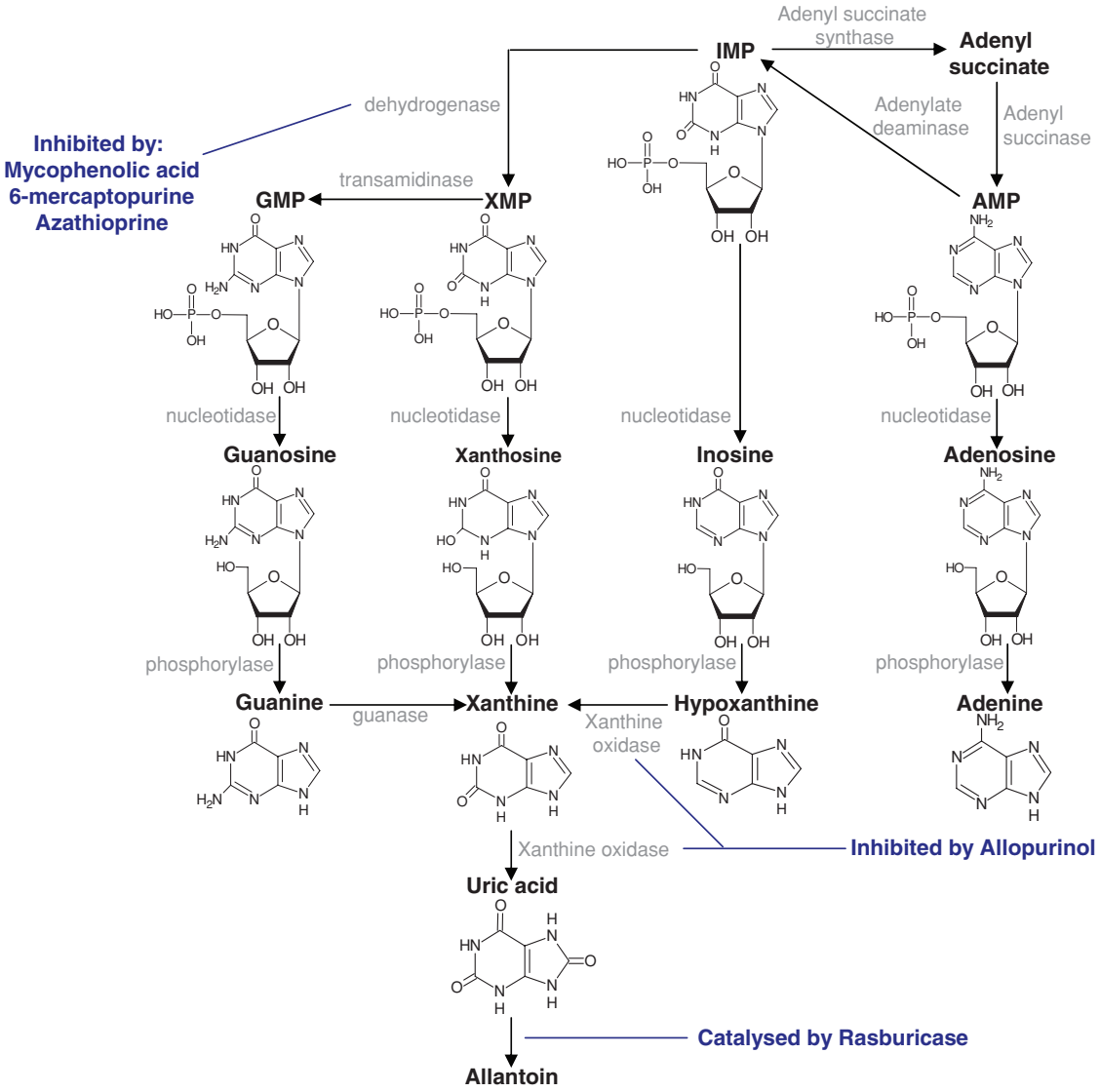

Fig. 2. Inosine monophosphate is the first nucleotide to be produced. Guanosine monophosphate (GMP), xanthosine monophosphate (XMP), inosine monophosphate (IMP) and adenosine monophosphate (AMP) result from further reactions catalysed by specific enzymes. These nucleotides undergo further reactions to result in their respective nucleosides by removal of a phosphate group. These nucleosides undergo further reactions to result in xanthine (AMP must first be converted to IMP). Xanthine is the main metabolite of all purines and a precursor of uric acid, which is the final degradation product of purines in humans. Allopurinol inhibits xanthine oxidase, resulting in rapid excretion of water-soluble xanthine and hypoxanthine. Rasburicase, a novel treatment option for the tumour lysis syndrome, is a recombinant uric acid oxidase. This enzyme is present in many mammals but absent in humans and results in breakdown of uric acid to water-soluble allantoin.

the progression of the condition [5]. Despite the logic behind such approaches, scepticism has been voiced as well [5].

It is well documented that renal patients may be more prone to allopurinol hypersensitivity: A normal rate of oxypurinol excretion requires preserved renal function. The half-life of the drug and particularly its main metabolite oxypurinol is markedly prolonged in renal failure, with a half-life of 250 h in the anuric patient [5]. The co-administration of drugs that interfere with the removal of oxypurinol such as thiazide diuretics will also prolong the drug's half-life [5]. Of note, our patient had both renal impairment and was receiving a thiazide diuretic. Hande and colleagues reported as many as 78 patients with renal impairment and life-threatening allopurinol toxicity [2].

In addition to the co-administration of other medications affecting the metabolism of allopurinol, allopurinol itself may affect the side-effect profile of other medications. Ampicillin is such an example, and concomitant use of the two drugs increases the frequency of ampicillin-induced skin rashes [9]. It is also important to remember that concomitant use of allopurinol and azathioprine is contra-indicated, leading to bone marrow depression with potentially fatal leucopaenia. Of note, the likely cohort of patients to be prescribed allopurinol will be those of advancing age, where polypharmacy is common.

Our patient, we believe, had allopurinol hypersensitivity somewhere in between the simple rash and the life-threatening variant. We have to be chided for not stopping allopurinol earlier—the drug is indeed one of the usual suspects when a drug reaction is assumed. To our defence, one may say that delays are not infrequent in making a diagnosis of AHS. Such delays are often attributable to ignorance of the condition, particularly in light of the variable lag between the initiation of allopurinol and the onset of AHS, and also due to the lack of specificity of the presentation. The broad range of manifestations, and the rarity of the syndrome, may lead the physician to first consider more likely alternative diagnoses, such as infection, a reaction to an alternative drug, or sepsis.

In this case, the apparent onset of symptoms after the vacation to Cyprus was particularly misleading. An infectious cause was suspected initially, and even malaria was considered despite Cyprus being declared free of the disease in the 1950s. Further unnecessary expenses were incurred by utilizing an immunofluorescence test to exclude Mediterranean Spotted Fever or fievre boutonneuse. This rickettsial infection with *Rickettsia conorii* is anthropod-borne and transmitted through ticks and/or mites. Patients often present with fever and lassitude, but rash and headache, two salient features of the disease, were absent in our case. Additionally, the distinctive tache noire, a black eschar at the inoculating site, was absent (though looked for repeatedly). Finally, rickettsiosis is often acquired by younger travellers during wild camping or during contact with stray dogs—neither were favourite pastimes of our 77-year-old patient. In retrospect, we probably expended considerable time and money before we even considered a drug reaction and returned to square one.

It is worthwhile to remember the renal lesions caused by allopurinol. The typical biopsy finding in such cases is acute tubulointerstitial nephritis [10]. Some cases may have a granulomatous phenotype [11]. Crescentic glomerulonephritis in association with allopurinol has been described as well [12]. Despite the use of allopurinol to prevent precipitation of uric acid crystals, oxypurinol itself may accumulate into stones [13], which in addition may contribute to deterioration in renal function. However, in this case, there was no evidence of renal stones on renal ultrasound. A renal biopsy was not deemed appropriate after consideration of his pre-existing chronic renal failure. Notably, our patient had sterile leucocyturia, in keeping with acute interstitial nephritis. This clue, too, was missed. We should be reprimanded for not studying the urinary sediment ourselves or else the occasional urinary eosinophil could have pointed towards the correct diagnosis.

An important learning point from cases such as ours is that allopurinol is not a simple or harmless drug. Allopurinol should not be prescribed without a clear indication; many of those reported to have acquired AHS were receiving the drug for asymptomatic hyperuricaemia, for which allopurinol offers little benefit [4]. It is disturbing to read about fatal AHS in such patients [6]. Five percent of the general population may have some degree of hyperuricaemia and it is frequent in renal patients, whether they are in one of the various stages of chronic renal failure, on dialysis or following renal transplantation. Among those, however, only a small minority has true gout and benefits from allopurinol treatment. Renal patients are clearly prone to AHS and clinicians should exercise caution when prescribing the drug in such individuals. If indicated, the dose of allopurinol should be reduced according to renal function as described elsewhere [7].

It is also worthwhile to remember that a variety of infectious agents have been claimed to trigger AHS [14], and a viral infection sustained on holiday may have played a role in our case. Our case also carries an important lesson for the management of acute-on-chronic renal failure. If the cause is not obvious then drug effects should be high on the list of suspects. In this regard, allopurinol should be regarded as a known offender and stopped, just as other potentially nephrotoxic drugs.

Very recently, high doses of allopurinol have been proposed as treatment for endothelial dysfunction, supposedly through mechanisms that are independent of a reduction in uric acid [15]. It remains to be seen whether the medical community adopts this approach. If so, then this treatment is likely to be used irrespective of renal function. Such an effect was indeed observed in the aftermath of the RALES study, with a substantial increase in emergency admissions and even fatalities due to injudicious use of spironolactone in patients with impaired renal function [16]. It is, therefore, conceivable that we will see more renal patients with side effects of allopurinol [17]. This may be particularly relevant, as cardiovascular disease and chronic renal failure are associated with one another.

Conclusion

After years of slow deterioration and regular uneventful visits to the renal clinic, our retired pilot ended up in considerable turbulence after return from Cyprus. In hindsight, it took us quite some time to regain control and re-discover an old wisdom in internal medicine: Side effects of drugs are common. Allopurinol is a notorious suspect and should have been stopped much earlier. In the end, we were delighted to get it right, avoid dialysis and learn a great deal on allopurinol. Not surprisingly, the patient returned to the skies with renewed energy (Figure 3).

Teaching points

1. Allopurinol is a xanthine oxidase inhibitor, preventing the production of uric acid. It is commonly used in the treatment of gout and to prevent tumour lysis syndrome.
2. The half-life of allopurinol and its main metabolite, oxypurinol, depends on renal function. Dose reduction is recommended in relation to the glomerular filtration rate.
3. Allopurinol has a well-described range of side effects, ranging from an isolated rash, to life-threatening toxic epidermal necrolysis. The typical renal lesion is acute interstitial nephritis.

Fig. 3. The patient as copilot in Florida, USA, in 2008 (note that the orientation of the picture is correct). With permission.

4. Allopurinol should be stopped immediately if a patient develops a rash after the drug has been initiated. However, allopurinol hypersensitivity can also occur after years of uneventful therapy.
5. Allopurinol should be considered as a potentially nephrotoxic drug and stopped if the cause of acute or acute-on-chronic renal failure remains unclear.

Conflict of interest statement. None declared.

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