

# Successful treatment with rasburicase of a tophaceous gout in a patient allergic to allopurinol

Pascal Richette\* and Thomas Bardin

## SUMMARY

**Background** A 56-year-old white woman was referred to our institution with a 16-month history of severe, gouty, recurrent, acute polyarthritis involving the finger joints. She also had numerous small subcutaneous tophi in her hands. The patient was intolerant to allopurinol and had mild renal insufficiency attributed to uric-acid nephrolithiasis and interstitial nephropathy.

**Investigations** Physical examination, laboratory testing, X-rays of the hands, feet and pelvis, CT of the pelvis, microscopic analysis of an aspirate from a finger tophus.

**Diagnosis** Tophaceous gout associated with urate nephropathy in a patient intolerant to allopurinol.

**Management** Acute polyarthritis was successfully managed by intravenous bolus methylprednisolone combined with codeine, diclofenac and low-dose colchicine. Rasburicase infusions combined with fenofibrate and sodium bicarbonate achieved to maintain serum acid uric below 360  $\mu\text{mol/l}$ .

**KEYWORDS** allergy, allopurinol, gout, intolerant, rasburicase

## CME

This article offers the opportunity to earn one Category 1 credit toward the AMA Physician's Recognition Award.

## THE CASE

A 56-year-old white woman had a 16-month history of severe recurrent acute polyarthritis involving the finger joints. Her general practitioner diagnosed gouty arthritis because of a high serum uric-acid level (600  $\mu\text{mol/l}$ ; normal range 270–380  $\mu\text{mol/l}$ ) coexistent with tophi in her hands, and initiated allopurinol 100 mg daily. A few days after the introduction of allopurinol, the patient developed severe urticaria/angioedema, and allopurinol therapy was discontinued. The patient was hospitalized 7 months after allopurinol discontinuation, in order to manage subintract articular crisis that was resistant to colchicine therapy.

The patient's past medical history included a duodenal ulcer, hypertension, ischemic heart disease, hyperlipidemia and moderate, chronic renal insufficiency, which was previously attributed to uric-acid nephrolithiasis and interstitial nephropathy. She had also been suspected of anorectic behaviour and of intermittently taking diuretics for several years. Upon admission to hospital, her therapy consisted of acetaminophen 3 g daily, colchicine 1 mg daily, omeprazol 20 mg daily and bisoprolol 10 mg daily. Her height was 151 cm and her weight was 40 kg (BMI 17).

Physical examination revealed swelling and tenderness in both wrists and in many metacarpophalangeal joints, numerous small tophi in the subcutaneous tissue of the palmar aspect of her fingers, and severe finger flexor tenosynovitis. Laboratory evaluations showed a slightly raised uric-acid level of 445  $\mu\text{mol/l}$ , an elevated C-reactive-protein level of 50 mg/l (normal level <4 mg/l) and renal impairment with creatinine clearance of 29 ml/min (normal range 80–120 ml/min). The 24 h uric acid excretion rate was 1.09 mmol/day (normal range 2.4–4.8 mmol/day). Serum total cholesterol and triglycerides were 5.73 mmol/l (normal range

*P Richette is a Rheumatologist and T Bardin is a Professor of Rheumatology at the department of Rheumatology, Centre Viggo Petersen, Lariboisiere Hospital, University Paris VII, France.*

## Correspondence

\*Fédération de Rhumatologie, Centre Viggo Petersen, Hôpital Lariboisière, 2 rue Ambroise Paré, 75010 Paris, France  
pascal.richette@lrp.ap-hop-paris.fr

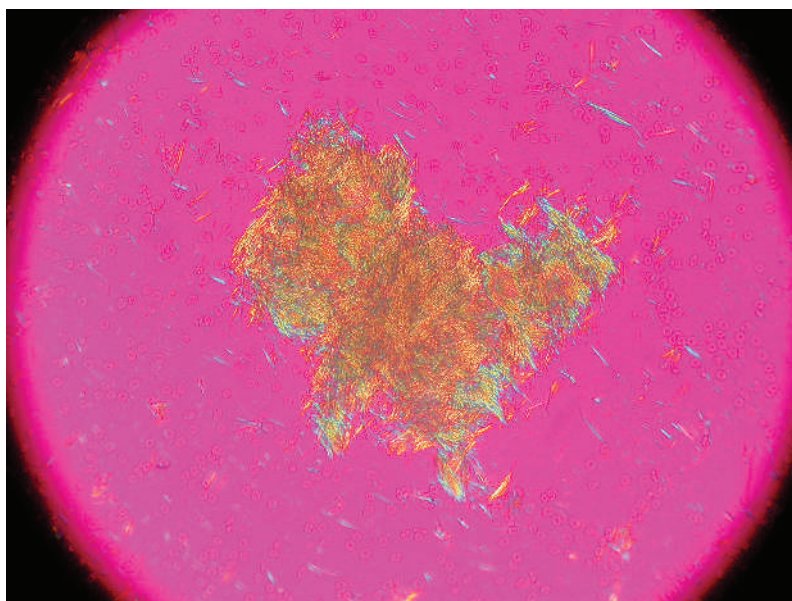
Received 18 January 2006 Accepted 12 April 2006

www.nature.com/clinicalpractice  
doi:10.1038/ncprheum0214

4.4–6.1 mmol/l) and 2.74 mmol/l (normal range 0.5–1.4 mmol/l), respectively. Glycemia was normal. A pelvic CT scan revealed intraparenchymatous renal calcifications with normal kidney size. X-rays of the hands, feet, pelvis and knees did not demonstrate features of urate arthropathy but revealed CHONDROCALCINOSIS in her knees and pubic symphysis. The chondrocalcinosis was asymptomatic, as the patient did not complain of arthritis in her knees.

A needle aspiration of a subcutaneous tophus located on the palmar aspect of the left forefinger allowed demonstration of needle-shaped, negatively birefringent monosodium urate (MSU) crystals by COMPENSATED POLARIZED-LIGHT MICROSCOPY (Figure 1).

The patient was given 1 mg colchicine every 4 h (maximum of 4 mg/day), but she developed diarrhea, so the colchicine dose was reduced to 1 mg daily, as was given previously. Despite concurrent treatment with diclofenac 75 mg daily and codeine 30–60 mg daily, her acute arthritis did not improve. Four days later, methylprednisolone 100 mg was administered intravenously, leading to a major improvement in joint inflammation. Sodium bicarbonate was prescribed in order to obtain a urinary pH of less than 6, and fenofibrate 160 mg daily was introduced in order to decrease uric-acid level and to manage hypertriglyceridemia. Following 1 month of treatment with fenofibrate, the patient's uric-acid level persisted above 360  $\mu\text{mol/l}$ , although triglycerides normalized. Intravenous therapy with recombinant urate oxidase rasburicase 0.20 mg/kg (Fasturtec<sup>®</sup>, Sanofi-Aventis, Paris, France) was then added. A total of 10 infusions were performed during a 16-month period. The patient's serum uric-acid level dramatically decreased in the days following rasburicase infusions, but progressively increased during the subsequent weeks, before the next infusion. After the third infusion, serum uric-acid level was maintained below 360  $\mu\text{mol/l}$  until the next infusion (Figure 2). Rasburicase treatment was well tolerated, without allergic side effects. The first three infusions were marked by recurrent, acute attacks, although these were successfully treated with oral prednisolone 20–40 mg day. No gout attack has occurred since the sixth infusion, and dramatic regression of hand synovitis was observed, with restoration of the patient's functional capacity of both hands. Gout tophi totally disappeared and renal function remained stable. The patient continues to receive rasburicase treatment.



**Figure 1** Microscopic analysis of an aspirate from a tophus. Numerous negatively birefringent needle-shaped monosodium urate crystals are detected by compensated polarized-light microscopy (original magnification  $\times 40$ ). Monosodium urate crystals are strongly birefringent when observed under polarized light, and negatively birefringent, appearing yellow when parallel, and blue when perpendicular, to the axis of slow vibration from the compensator.

## DISCUSSION

Management of a patient allergic to allopurinol can be considered a therapeutic challenge. This article highlights the diversity of medications that can be used to manage hyperuricemia during this situation.

### Discussion of diagnosis

Gout is related to the deposition of MSU monohydrate crystals within the joints. It is the most common inflammatory joint disease in men, affecting at least 1% of the Western population.<sup>1,2</sup> Gout is best diagnosed by the presence of MSU crystals in synovial fluid or tophus specimen (Figure 1). The risk of crystal formation increases as urate concentration is elevated above the limit of urate solubility (about 420  $\mu\text{mol/l}$  at 37 °C). Population studies indicate a direct, positive association between serum urate levels and the risk of developing gout;<sup>3</sup> therefore, hyperuricemia is the most important risk factor for gout. Other factors such as obesity, hypertension, use of diuretics and high alcohol consumption contribute independently and additively to the risk of gout.<sup>2,3</sup>

Gout is a rare condition in premenopausal women. This is proposed to be due, in part,

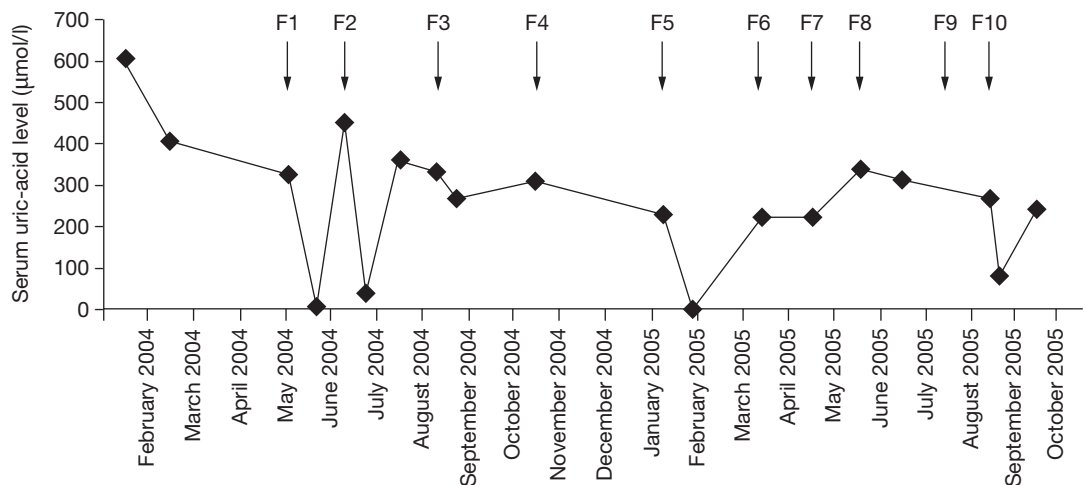
## GLOSSARY

### CHONDROCALCINOSIS

Calcification of cartilage caused by the deposition of calcium pyrophosphate dihydrate crystals in cartilage and fibrocartilage. It can present as acute synovitis (pseudo gout attack) or chronic arthropathy; more often than not it is asymptomatic

### COMPENSATED POLARIZED-LIGHT MICROSCOPY

Uses a first-order red compensator filter in the polarized-light microscope that is used to enhance the color differences between birefringent crystals; this allows for easier identification of the crystal using the change of polarity



**Figure 2** Course of serum uric-acid levels during long-term rasburicase treatment. Rasburicase infusions are indicated as F. A total of ten infusions were performed between May 2004 and October 2005.

to the enhancing effects of estrogens on renal urate clearance.<sup>2</sup> By contrast, the prevalence of gout is identical in both sexes in patients older than 60 years.<sup>2</sup> In postmenopausal women, a careful search for secondary factors needs to be carried out, in particular, the use of thiazides and loop diuretics, renal insufficiency and hypertension.<sup>2,4,5</sup> Renal insufficiency and hypertension were present in our patient. Because of unexplained hypokalemia episodes, we strongly suspected that she had been taking diuretics, but she denied any diuretic abuse. Her clinical presentation with numerous finger tophi was also consistent with diuretic-induced gout.<sup>2,4</sup>

The relationship between gout and renal insufficiency is complex. Severe gout can cause uric-acid nephrolithiasis and medullary deposition of MSU, leading to interstitial nephropathy (as diagnosed in our patient). On the other hand, renal insufficiency increases serum urate levels and accounts for roughly 10% of cases of gout; however, uratic nephropathy is a rare event, as its frequency has been decreased by the efficient management of gout.<sup>1,6,7</sup>

Subcutaneous and intradermal tophi can be mistaken for rheumatoid nodules or pyogenic pustules.<sup>8,9</sup> In the clinical setting of acute inflammatory monoarthritis, differential diagnosis of gout includes septic arthritis and pseudogout. The presence of crystals in synovial fluid or tophus samples is a key diagnostic tool for diagnosis of both polyarthritis and monoarthritis. Bacterial analysis should be carried out even in the presence of crystals, as septic arthritis can

occur in a patient with gout.<sup>2</sup> Gout and chondrocalcinosis can coexist in the same patient.<sup>10</sup> Chondrocalcinosis was undoubtedly asymptomatic in this case, because the patient did not experience arthritis of the wrists or knees (where calcium pyrophosphate dihydrate calcifications were deposited), and because her arthritis was resolved with urate-lowering therapy alone.

#### Discussion of treatment options

Treatment of gout takes a two-pronged approach, comprising treatment of acute flare-ups of gouty arthritis, and urate-lowering therapy in some patients. Several medications can be used for the treatment of acute, gouty arthritis. Whatever the medication used, the time of treatment initiation is of great importance: the earlier medication is introduced, the more rapidly a complete response will be obtained. The recommended dose of colchicine for the treatment of acute arthritis starts at 1 mg, followed by 0.5–1 mg every 2–4 h as needed until pain is relieved. The total daily dose should not exceed 4 mg in France, although higher doses are accepted in some countries. The most prevalent adverse effect of colchicine is dose-related gastrointestinal intolerance as experienced by the case patient. Toxicity of colchicine is also increased by renal or hepatic failure, and by coprescription of drugs such as macrolide or ciclosporin, which interfere with colchicine metabolism.<sup>1</sup>

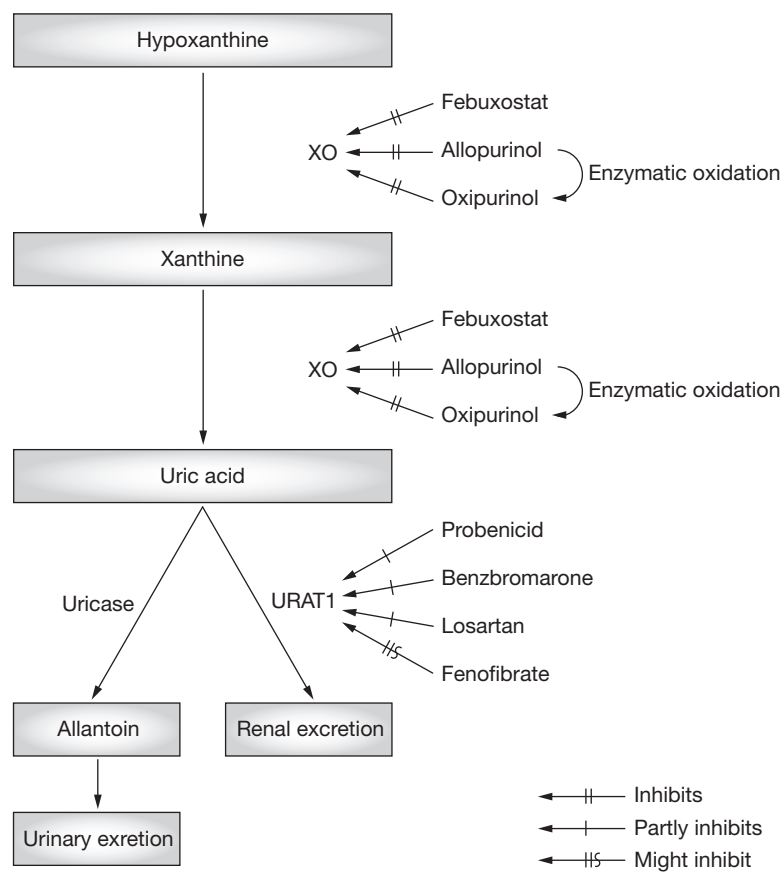
Nonsteroidal anti-inflammatory drugs (NSAIDs) are the standard treatment for acute gout in many countries, and are very effective; however,

they can be contraindicated in elderly patients, particularly those with hypertension or renal impairment. Although a risky prescription in this case, the NSAID diclofenac was administered for a very brief period during which creatinine level was carefully monitored. Systemic corticosteroids (oral or intravenous) are a safe alternative when colchicine and NSAIDs are contraindicated or not effective, as was the situation with this patient. The initial dose of prednisolone should be at least 20–30 mg, but relapses can occur when tapering the daily dose. Intravenous bolus methylprednisolone, as performed in the patient, has been shown to be efficacious<sup>1</sup> and can discourage automedication. Intra-articular corticosteroid injections appear to be a safe and effective option, but could not be applied in the polyarticular involvement of this patient.<sup>1,11</sup>

#### Urate-lowering therapy

The aim of urate-lowering therapy is to allow dissolution of urate deposits. The principal indications for urate-lowering therapy are frequent attacks of gouty arthritis, tophi, urate-induced arthropathy or uric-acid renal lithiasis. Allopurinol is the most widely available and frequently used antihyperuricemic agent. Intolerance is rare; however, severe skin reactions, as described in this case, require permanent treatment discontinuation, because re-exposure to allopurinol will induce a life-threatening hypersensitivity syndrome in about 20% of cases.<sup>12</sup> A recent study has suggested that these severe cutaneous adverse reactions might be genetically driven.<sup>13</sup> A history of allopurinol allergy contraindicates the use of oxipurinol, an allopurinol metabolite, as cross-allergies exist between the two compounds.<sup>12</sup>

Hyperlipidemia and hypertension are commonly associated with gout. When such comorbidities are present, the use of fenofibrate to control serum lipids and losartan for the control of blood pressure, in combination with dietary treatment, should be considered because each of these agents has weak uricosuric effects.<sup>1,11,12</sup> When these measures are insufficient, several treatment options are available, depending upon the level of uric-acid excretion in urine. In patients with normal uric acid-excretion, uricosuric drugs such as probenecid and benzbromarone can be used, but they are contraindicated in patients with urate nephropathy or with a history of urate



**Figure 3** Drugs affecting urate levels and their underlying mechanisms.

Uricase degrades relatively insoluble uric acid to the more soluble compound allantoin. Urate reabsorption by urate transporter-1 is partly suppressed at the proximal tubule lumen membrane by the uricosurics benzbromarone, probenecid and losartan. Fenofibrate could also inhibit urate transporter-1. Xanthine oxidase, the enzyme that catalyzes the oxidation of hypoxanthine to xanthine and xanthine to uric acid, is inhibited by allopurinol, oxipurinol and febuxostat. Allopurinol is a structural analog of hypoxanthine. It is both a substrate for and a potent inhibitor of xanthine oxidase. The product of the enzymatic oxidation of allopurinol is oxipurinol. URAT1, urate transporter-1; XO, xanthine.

nephrolithiasis.<sup>12</sup> In patients with high uric-acid excretion, use of potent uricosuric drugs is not permitted, because of the risk of renal lithiasis. Moreover, in the presence of uric-acid urolithiasis, alkalinization of urine should be achieved by use of sodium bicarbonate or potassium citrate.

Uricase (urate oxidase) therapy is highly effective in decreasing serum urate levels by degrading urate to allantoin (Figure 3). Recombinant uricase (rasburicase) is indicated for the prevention of hyperuricemia that can follow chemotherapy for malignancies, but it has not been approved for the management of

**Acknowledgments**

Written consent was obtained from the patient reported in this Case Study. We thank Dr K Ea for providing photos of monosodium urate crystals detected by compensated polarized-light microscopy.

**Competing interests**

P Richette declared he has no competing interests. T Bardin declared competing interests; go to the article online for details.

gout. The effectiveness of rasburicase in a kidney transplant patient with tophaceous gout has been reported,<sup>14</sup> although the immunogenic properties of rasburicase raise concern about safety in long-term use.<sup>7</sup> The case patient displayed no recurrence of hyperuricemia during the last part of the treatment period. This was most probably because of the rate of rasburicase infusions, but other factors like urate-pool depletion, and potential diuretic misuse withdrawal, could also have affected uric-acid levels. This case shows that rasburicase is safe and effective in a patient intolerant to allopurinol, although this experience with rasburicase for managing gout cannot be generalized to practice without clinical trials. The high cost and parenteral administration of rasburicase also limit its use.

New medications can be expected to expand treatment options in allopurinol-intolerant patients. The orally administered nonpurine inhibitor febuxostat has demonstrated efficacy and safety in phase II and III trials. Its efficacy and tolerance were reported in a short series of allopurinol-intolerant patients.<sup>15</sup> Finally, a novel uricase, coupled to polyethylene glycol, is currently undergoing clinical trials. The incorporation of polyethylene glycol should reduce antigenicity and prolong half-life of the enzyme.<sup>7,11,12</sup>

**CONCLUSION**

Gout in postmenopausal women can have an atypical presentation, with numerous subcutaneous tophi of the hands and acute arthritis predominantly involving the upper limbs. In this case, the diagnosis of gout prompted a search for associated medical conditions such

as hypertension, hyperlipidemia and diuretic intake. In this patient, who was intolerant to allopurinol, rasburicase therapy lowered serum-urate levels and appeared to promote rapid tophus dissolution.

**References**

- 1 Terkeltaub RA (2003) Clinical practice. Gout. *N Engl J Med* **349**: 1647–1655
- 2 Rott KT and Agudelo CA (2003) Gout. *JAMA* **289**: 2857–2860
- 3 Choi HK *et al.* (2005) Pathogenesis of gout. *Ann Intern Med* **143**: 499–516
- 4 Puig JG *et al.* (1991) Female gout. Clinical spectrum and uric acid metabolism. *Arch Intern Med* **151**: 726–732
- 5 De Souza AW *et al.* (2005) Female gout: clinical and laboratory features. *J Rheumatol* **32**: 2186–2188
- 6 Johnson RJ *et al.* (2005) Essential hypertension, progressive renal disease, and uric acid: a pathogenetic link? *J Am Soc Nephrol* **16**: 1909–1919
- 7 Bieber JD and Terkeltaub RA (2004) Gout: on the brink of novel therapeutic options for an ancient disease. *Arthritis Rheum* **50**: 2400–2414
- 8 Fam AG and Assaad D (1997) Intradermal urate tophi. *J Rheumatol* **24**: 1126–1131
- 9 Vazquez-Mellado J *et al.* (1999) Intradermal tophi in gout: a case-control study. *J Rheumatol* **26**: 136–140
- 10 Jones AC *et al.* (1992) Diseases associated with calcium pyrophosphate deposition disease. *Semin Arthritis Rheum* **22**: 188–202
- 11 Wortmann RL (2005) Recent advances in the management of gout and hyperuricemia. *Curr Opin Rheumatol* **17**: 319–324
- 12 Bardin T (2004) Current management of gout in patients unresponsive or allergic to allopurinol. *Joint Bone Spine* **71**: 481–485
- 13 Hung SI *et al.* (2005) HLA-B\*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci USA* **102**: 4134–4139
- 14 Vogt B (2005) Urate oxidase (rasburicase) for treatment of severe tophaceous gout. *Nephrol Dial Transplant* **20**: 431–433
- 15 Becker MA *et al.* (2004) Febuxostat, a novel non-purine selective inhibitor of xanthine oxydase, therapy in allopurinol intolerant patients [abstract]. *Arthritis Rheum* **50 (Suppl)**: S803