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Paradoxical increase in uric acid level with allopurinol use in pyrazinamide-induced hyperuricaemia

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ABSTRACT We report the case of a 36-year-old man with psoriatic arthritis and miliary tuberculosis, whose serum uric acid (SUA) level increased after the initiation of antituberculosis treatment, which included pyrazinamide. Most strikingly and paradoxically, the patient's SUA level increased after treatment with allopurinol. On cessation of allopurinol, his SUA level decreased substantially, and complete normalisation was observed following the discontinuation of pyrazinamide treatment.

Keywords: allopurinol, antitubercular agents, tuberculosis, uric acid

INTRODUCTION

Factors that contribute to hyperuricaemia include genetics, diet, alcohol consumption, obesity, renal insufficiency, insulin resistance, hypertension, as well as the use of some drugs. The underlying mechanisms that cause hyperuricaemia may be underexcretion of uric acid due to defective renal clearance, overproduction of uric acid, or a combination of the two. Many drugs – notably diuretics, ciclosporin, nicotinic acid, vitamin B12, chemotherapeutic agents, salicylates (low dose) and levodopa – have been reported to alter the abovementioned processes and cause hyperuricaemia.[1,2]

The occurrence of hyperuricaemia and acute gouty arthritis have also been reported with the use of some antituberculosis (anti-TBC) drugs such as ethambutol and pyrazinamide (PZA), both of which decrease uric acid clearance. Hyperuricaemia was reported in 42%–66% of patients treated with ethambutol[3,4] and in 43%–100% of patients treated with PZA (alone or combined with other drugs).[5-7] Pyrazinoic acid, a major metabolite of PZA, can inhibit the renal tubular secretion of uric acid, which may cause hyperuricaemia. The hyperuricaemic effect of PZA is also acknowledged in the European Respiratory Society (ERS) Task Force's report on the management of tuberculosis in Europe.[8] According to ERS guidelines, uric acid monitoring in patients receiving PZA treatment is generally not recommended, except in cases where hyperuricaemia was previously documented. Treatment with allopurinol is recommended if symptoms of hyperuricaemia are present.[8] Herein, we describe a patient with miliary tuberculosis whose serum uric acid (SUA) level increased after the initiation of anti-TBC treatment that included PZA, and paradoxically, after treatment with allopurinol as well.

CASE REPORT

A 36-year-old man with a four-year history of psoriatic arthritis developed a high fever without any other symptoms while he was on prednisone (6 mg/day), naproxen (750 mg/day) and omeprazole (20 mg/day). He was treated with 12.5 mg weekly methotrexate (MTX). The drug was discontinued by a consulting dermatologist when the patient developed a penile skin lesion that was attributed to the drug.

Initial laboratory tests were notable for leucopenia (white blood cells 3.5 K/μL), high acute phase response (C-reactive protein 163 mg/L; erythrocyte sedimentation rate 75 mm/h) and moderately increased transaminase levels (aspartate aminotransferase 130 U/L; alanine transaminase 239 U/L). Extensive workup, which included chest radiography, did not reveal a specific cause for the fever, which recurred occasionally during the following three months. Repeat chest radiograph taken three months later showed multiple diffuse millimetre-sized nodules. Thus, a diagnosis of miliary tuberculosis was made. This diagnosis was later confirmed by a positive bronchoalveolar lavage culture for *Mycobacterium tuberculosis*. The patient was started on anti-TBC treatment, which consisted of PZA (2 g/day), isoniazid, rifampicin and streptomycin. On the sixth day of PZA treatment, the patient's SUA level rose to 15.6 mg/dL. Due to the nephrotoxic risk associated with high SUA levels,[9] allopurinol treatment (300 mg/day) was started, and aspirin (2 g/day) was added to the treatment regimen two days later. However, the progressive increase in the patient's SUA level continued (Fig. 1). Allopurinol and aspirin were discontinued on the tenth day of PZA treatment as recommended at a rheumatology consultation, and intravenous hydration therapy was initiated. Following the discontinuation of allopurinol and aspirin, the patient's SUA level decreased rapidly from 20.6 mg/dL to 11.9 mg/dL within a week and remained at approximately the same level during his remaining hospital stay. The patient was discharged with anti-TBC therapy and a recommendation of high fluid intake. His SUA level remained high until the cessation of PZA two

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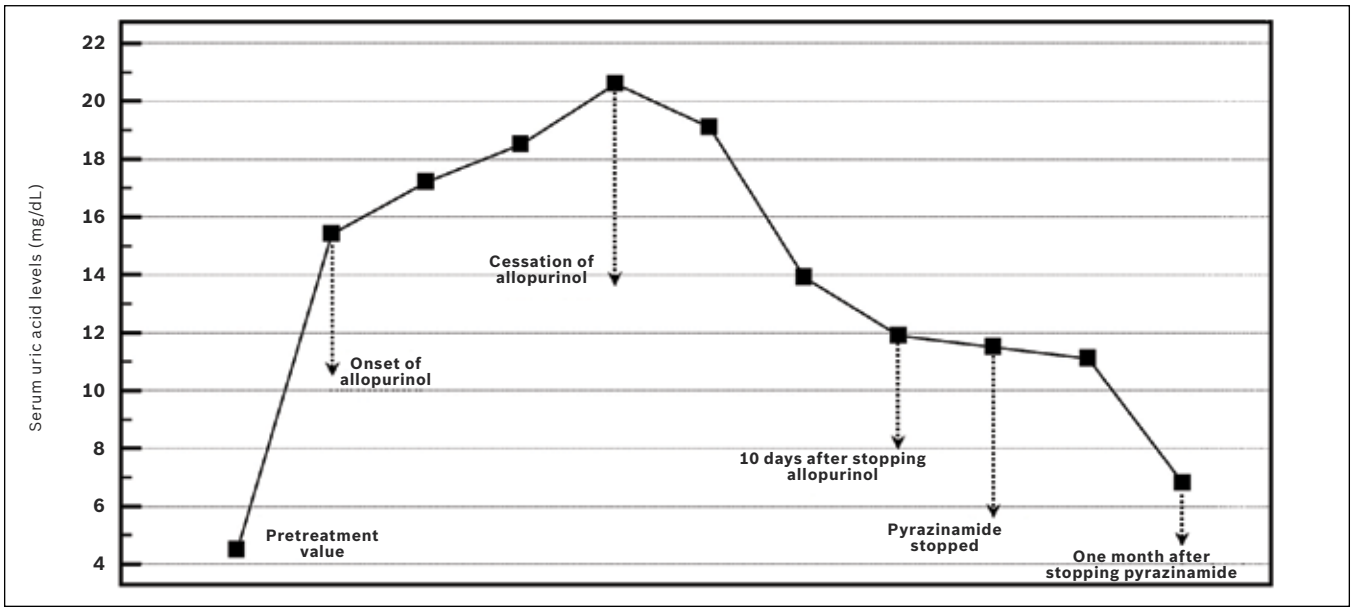

Fig. 1 Relationship between the patient's serum uric acid levels and medications.

months later, following which there was a dramatic reduction in his SUA level to 6.8 mg/dL. The patient was still taking other anti-TBC drugs at the time of this writing.

DISCUSSION

Although the management of hyperuricaemia due to PZA has not been clearly described, there are a number of studies that suggest that aspirin may be effective in reducing PZA-induced hyperuricaemia.[5,6,10,11] In a small, double-blind, placebo-controlled study of aspirin and allopurinol, a reduction in SUA levels was observed with aspirin, but not with allopurinol.[12] Moreover, in a pharmacokinetic study involving six healthy subjects, allopurinol was shown to increase plasma concentrations of pyrazinoic acid, a chemical that is directly responsible for the inhibition of renal urate secretion.[13] In our case, we believe that allopurinol induced the accumulation of pyrazinoic acid and was responsible for the paradoxical increase of our patient's SUA level after the initiation of allopurinol treatment. Therefore, we recommend that allopurinol not be used in the treatment of PZA-induced hyperuricaemia. Our findings support the study conducted by Taki et al, which suggested that an increase in SUA levels due to PZA therapy can be managed by simple observation without specific drug therapy and dose modification.[2]

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