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Case Report

Pyrazinamide-induced acute gouty arthritis: a case report

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ABSTRACT

Gout is a common inflammatory and metabolic disease caused by the deposition of monosodium urate crystals in articular and non-articular tissues. Drugs used to treat tuberculosis, such as pyrazinamide and ethambutol, have been linked to hyperuricaemia. However, acute gout is uncommon. We report a case of a 28-year-old female who developed acute gouty arthritis of the left knee joint as a result of taking pyrazinamide as part of a tuberculosis therapy regimen. Although pyrazinamide-induced hyperuricemia is frequently regarded as asymptomatic, the clinician should be aware of the likelihood of acute gouty arthritis, which can result in significant morbidity and an impaired quality of life.

Keywords: Acute gout, Hyperuricemia, Pulmonary tuberculosis, Pyrazinamide

INTRODUCTION

Gout is a common metabolic and inflammatory disease caused by monosodium urate crystal deposition in articular and non-articular tissues.[1] There has been an increasing prevalence of gout in Europe, the United States, and developing countries. This is due to the increasing use of diuretics and low-dose aspirin.[2-4] The major risk factor for the development of gout is hyperuricaemia, which is defined as blood urate levels above 6.8 mg/dl.[1] Although increased uric acid levels are often asymptomatic, they can result in crystal deposition and may result in three primary disorders: gout, urolithiasis, and urate nephropathy.[5] Hyperuricaemia can be caused by excessive production or reduced excretion of uric acid in the body.[1]

A number of drugs have been implicated in the development of hyperuricaemia and/or gout.[1] Pyrazinamide and ethambutol are common anti-tuberculosis drugs used in the intensive phase of treatment. They are known to induce hyperuricaemia; however, pyrazinamide induced gout is rarely reported. In this article, we report the case of a 28 year old female spatient who developed an acute attack of gouty arthritis while being treated with anti-tuberculosis drugs. The aim of the report was to highlight the morbid, rare adverse effects of pyrazinamide.

CASE REPORT

A 28-year-old female presented to the rheumatology clinic of our facility with a three-day history of pain and swelling of her left knee joint.

The joint pain was said to be worse at night and associated with some joint stiffness. It was severe enough to affect the mobility of the patient. She had not had any similar symptoms before. There was no history of fever or trauma. The patient was not on diuretics and does not take alcohol or smoke cigarettes. There was no history of diarrhoea, eye symptoms or symptoms suggestive of a sexually transmitted infection. There was no history of rashes. She had been diagnosed with pulmonary tuberculosis six weeks earlier and commenced on anti-tuberculosis drugs which included pyrazinamide. She was not a known hypertensive or diabetic patient.

On physical examination, she was in painful distress, had a temperature of 37.1°C, 97 percent oxygen saturation in room air, a pulse rate of 101 bpm, a respiratory rate of 18

breaths per min, and a blood pressure of 122/78 mmHg. Her body mass index was 23.3 kg/m^2.

The left knee joint was erythematous, swollen and tender with a reduced range of motion. The overlying skin was shiny. An initial impression of suspected acute gout following pyrazinamide therapy was entertained. The possibility of septic arthritis was also considered. The knee joint effusion was aspirated and sent for analysis.

Her initial serum uric acid before the commencement of anti-tuberculosis drugs was 4.8 mg/dl (range 3.5-6.5). At this current presentation, serum uric acid was 12.8 mg/dl. Other laboratory findings included; erythrocyte sedimentation rate (ESR) 104 mm/hr (1-20), C-reactive protein (CRP) 10.7 mg/l (0-7.4), White blood cell count (WBC) 8.6×10^9/l (4-11), haemoglobin 13.8 g/dl (12.0-18.5), platelets 219×10^9/l (150-450), serum creatinine 78 umol/l (57-113), Fasting blood glucose (FBS) 98 mg/dl, and a urinalysis that was normal. Serological tests for HIV, hepatitis B and C were negative.

The liver function test was also normal. Analysis of knee effusion revealed a cloudy fluid with a leucocyte count of 15600 cells/ul, and cultures were sterile. We were able to assess for monosodium urate crystals as our facility was unable to do that. She was negative for Antinuclear antibody (ANA), Rheumatoid factor (RF), and anti-Cyclic citrullinated peptide (anti-CCP).

Radiograph of the knee joint was unremarkable. The above results confirmed the diagnosis of acute gout with the culprit likely being pyrazinamide. The patient satisfied the 2015 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) classification criteria for gout.

She was commenced on oral colchicine at a dose of 1mg stat, then 0.5 mg an hour later and intraarticular steroid was administered to the affected joint. She was continued on daily oral colchicine. The pyrazinamide-based anti-tuberculosis drugs were, however, continued.

The symptoms of joint pain had subsided fully one week after the commencement of anti-inflammatory. The examination of the knee joint was normal. Her serum uric acid at this time was 11.7 mg/dl and ESR was 78 mm/hr. Further review at two weeks, her serum uric acid was 8.7 mg/dl.

At this time, pyrazinamide had been discontinued for about a week due to the completion of the intensive phase of treatment. The ESR was 48 mm/hr. Two weeks later her serum uric acid had normalized with a value of 5.8 mg/dl and an ESR of 29 mm/hr. The patient was closely monitored until her tuberculosis treatment was completed, and she had no further episodes of this nature. At the completion of tuberculosis treatment, her uric acid was 4.2 mg/dl which was still normal, and the patient was discharged from care.

DISCUSSION

Gout is characterized by hyperuricemia, which is caused by an increase in the production and/or decreased excretion of serum uric acid.[6] Many persons with hyperuricemia do not develop gout or even crystallise uric acid, even though hyperuricemia is the main pathogenic defect in gout. Indeed, only 5% of individuals with hyperuricaemia greater than 9 mg/dl develop gout.[7] As a result, other factors such as genetic susceptibility, obesity, alcohol, and hypertension are thought to have a role in the occurrence of gout.[6,7]

Drugs play a role in the pathogenesis of hyperuricaemia as well. They increase uric acid reabsorption and/or decrease uric acid secretion. Some drugs may also promote uric acid production.[1] Table 1 shows common drugs that cause hyperuricaemia. In clinical practice, drug-induced hyperuricaemia and/or gout are emerging and increasingly common conditions.[1]

Even though the true prevalence of drug-induced hyperuricaemia and gout remains unknown, Paulus et al reported that drugs accounted for increased serum urate levels in up to 20% of hyperuricaemic individuals.[8] Appropriate medical history is necessary for patients with drug-induced hyperuricaemia and/or gout to ascertain the presence of any underlying or related disease condition and the type of drugs used. Our patient was on treatment for pulmonary tuberculosis with a drug regimen containing pyrazinamide, so it was thought to be the likely cause of the gouty arthritis.

Pyrazinamide and to a lesser extent, ethambutol are two anti-tuberculosis drugs that induce hyperuricemia.[1] Studies have shown that the estimated incidence of hyperuricemia has ranged from 43.4% to 86.3% in patients treated with combination therapy or pyrazinamide alone.[9-11]

Shapiro et al even recorded an incidence as high as 100% due to pyrazinamide alone.[12] Despite these findings, acute gout seems rare from pyrazinamide therapy. Inoue et al reported that acute gout occurred in only one of 44 patients with serum uric acid greater than 8 mg/dl. The patient, however, had hyperuricemia and a predisposition to gout prior to pyrazinamide treatment.[11]

Pyrazinamide not only causes hyperuricemia but can also trigger acute gout episodes. At a therapeutic dose, it is a potent urate retention medication, that reduces renal uric acid excretion by more than 80%.[1,13] Pyrazinoate, an active metabolite of pyrazinamide, causes urate reabsorption from the luminal side into tubular cells by having a trans-stimulatory impact on Urate transporter in the human kidney (URAT1).[14] Ethambutol, like pyrazinamide, causes hyperuricemia by lowering renal uric acid clearance. However, it does so less consistently and to a lesser extent.[13] Withdrawal of these drugs frequently results in a return to normal serum uric acid levels, and reintroduction

typically results in the resurgence of hyperuricemia, as documented in certain studies.[15,16]

Gout usually manifests as a self-limiting inflammatory monoarthritis affecting the lower limb joints.[7] Gout is diagnosed using a variety of classification criteria, the most recent of which being the ACR/EULAR.[17] The presence of monosodium urate crystals on polarised microscopy of aspirated fluid gives a definitive diagnosis.[17] The index patient presented with an acute painful swollen left knee joint about 6 weeks following the initiation of anti-tuberculosis drugs. She was unable to walk due to the extreme discomfort in her joint, and her serum uric acid level was elevated (12.8 mg/dl). Though we were unable to assess for crystals due to our facility's limitations. Gout was diagnosed in this patient using the ACR/EULAR criteria.[17]

Treatment for asymptomatic hyperuricemia is usually unnecessary.[13] Gout flares are commonly treated with anti-inflammatory drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroids.[18] Anti-IL 1 agent (anakinra) is also effective in acute gout.[18] For intercritical gout and gout prophylaxis, colchicine has been utilised.[13,18] To decrease the body's uric acid production, xanthine oxidase inhibitors such as allopurinol and febuxostat are frequently used. Prolonged urate-lowering therapy results in the dissolution of monosodium urate crystals, thereby preventing gout flares and tophi and improving the overall quality of life.[7,19]

Probenecid, benzbromarone and sulfinpyrazone are all uricosuric agents that are used to treat patients who under secrete uric acid.[6,18] Other urate-lowering agents include Lenisurad, rasburicase and pegloticase.[7,18] Purine restriction in the diet and lifestyle changes are crucial measures in uric acid regulation.[6]

There are no published treatment guidelines for drug-induced hyperuricaemia and/or gout. Patients on drugs that promote hyperuricaemia should be encouraged to stay hydrated and have their urate levels checked regularly.[1] When gout develops, the decision to continue therapy, and/or commence a urate -lowering agent must be made on an individual basis. Withdrawal of the offending agent should be determined by a benefit-risk analysis.[1] Pyrazinamide-induced hyperuricemia and/or gout can be controlled without necessarily stopping the medication. As in the case of our patient, she was treated with intra-articular steroids and oral anti-inflammatory drugs.

The anti-tuberculosis regimen containing pyrazinamide is widely used. The incidence of asymptomatic hyperuricemia is often high in these patients. Additional conditions that alter the production and/or excretion of serum uric acid may precipitate an acute gout attack. It is therefore critical to consider this when prescribing these medications.

Table 1: Common drugs that promote hyperuricemia.[1]

Drugs	Mechanisms
Anti-tubercular drugs	Increased uric acid reabsorption (pyrazinamide)
	Decreased uric acid secretion (pyrazinamide)
	Reduction in the fractional excretion of uric acid (ethambutol)
Diuretics	Increased uric acid reabsorption in the proximal tubules
	Increased uric acid secretion
	Volume contraction
Aspirin (low dose)	Increased uric acid reabsorption
	Decreased uric acid secretion
Cytotoxic chemotherapy	Massive disruption of tumour cells
Immunosuppressant drugs	Increased uric acid reabsorption in the proximal tubules (ciclosporin)
	Decreased glomerular filtration rate secondary to afferent arteriolar vasoconstriction (ciclosporin)
	Reduced urate excretion (tacrolimus)
	Inhibition of the synthesis of guanine nucleotide (mizoribine)
Nicotinic acid	Increased uric acid reabsorption
	Decreased uric acid secretion
	Increased uric acid synthesis
Fructose	Increased nucleotide turnover and nucleotide synthesis
	Increased uric acid tubular reabsorption
Lactate infusion	Increased uric acid reabsorption
Xylitol	Increased purine degradation
	Increased production of lactate
Testosterone	Increased uric acid reabsorption

CONCLUSION

Anti-tuberculosis drug regimen containing pyrazinamide has been associated with hyperuricemia. Though often asymptomatic, the likelihood of acute gout occurring should be kept in mind. This can result in significant

morbidity and a lower quality of life. There are several treatment modalities/principles documented for drug-induced hyperuricemia. Clinicians must have a high index of suspicion to institute appropriate therapy.

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