CHAPTER

39

Gout in 2017

Arup Kumar Kundu, Abhishek Kundu

INTRODUCTION

Gout is the commonest crystal arthropathy seen in day to day clinical practice though it is one of the medical ailments which is shrouded in mystery and plagued by misconception. Hyperuricemia is defined as serum uric acid level >6.8 mg/dL, while gout is the inflammatory response to monosodium urate (MSU) crystals formed secondary to hyperuricemia. All hyperuricemic patients do not suffer from gout and approximately one-tenth exhibit gout in the long run. In the last decade, there is an increasing trend of incidence of gout, especially in the elderly (Table 1). Gout usually affects the joints, periarticular soft tissues and kidneys. Articular gout usually has three distinct stages: acute gouty arthritis, intercritical (interval) gout and chronic tophaceous gout. Patients with long-standing hyperuricemia generally develops into acute gouty arthritis, which is usually monoarticular (the first attack is in metatarsophalangial joint of great toe in 75% patients – 'podagra') though it may be oligoarticular (2-4 joints) or polyarticular (>5 joints). Intercritical gout is the asymptomatic phases between acute gouty flares, which may last for several months to years. Chronic tophaceous gout usually develops after approximately 10 years of recurrent acute gouty arthritis with deposition of MSU crystals in tendons (tendo Achilles), ligaments, bursae, with concomitant tophi formation in fingers, toes, upper part of forearm and ears (Figures 1 to 4). In many of the patients, the second attack

Table 1: Increase in prevalence of gout and comorbidities in recent years

- Increased longevity
- Dietary trends (e.g., increased alcohol consumption)
- Systemic hypertension
- Epidemic of obesity and metabolic syndrome
- Rampant use of diuretics and low dose aspirin therapy
- Increased survival in congestive heart failure and coronary arterial disease (CAD)
- Increased chronic kidney disease and end-stage renal disease
- Major organ transplantations (need use of cyclosporin A or tacrolimus)

Fig. 1: Gouty tophi over proximal interphalangeal joint of thumb and distal interphalangeal joint of index finger (black arrows) along with deformity of hand in chronic gout

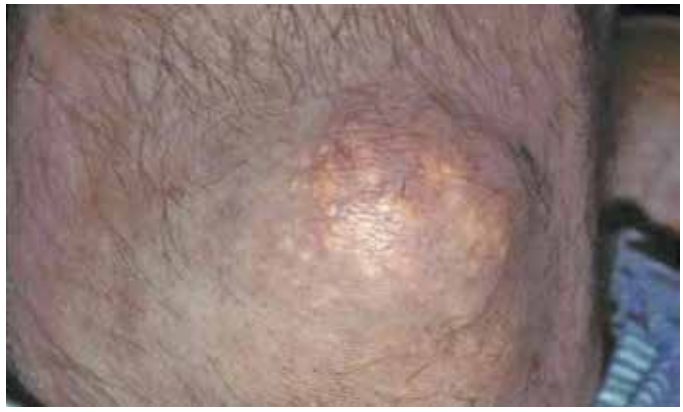

Fig. 2: White MSU crystals deposited in soft tissue of thigh in a patient of acute on chronic gout. The patient had acute arthritis in different joints too

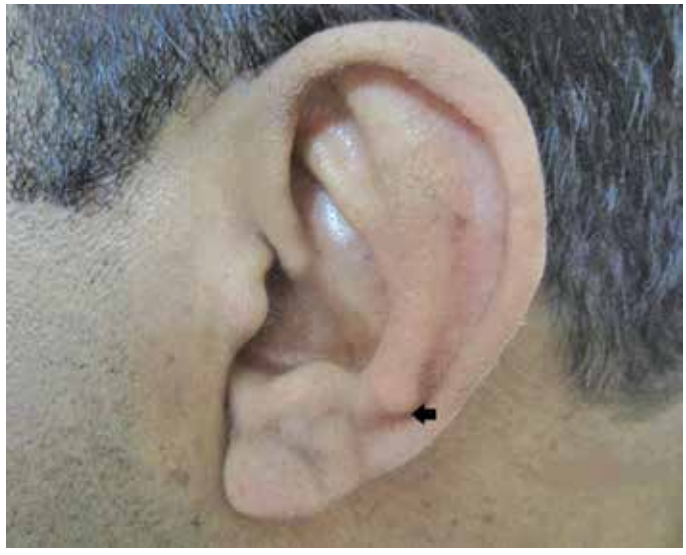

Fig. 3: Gouty tophi over pinna of left ear (black arrow)

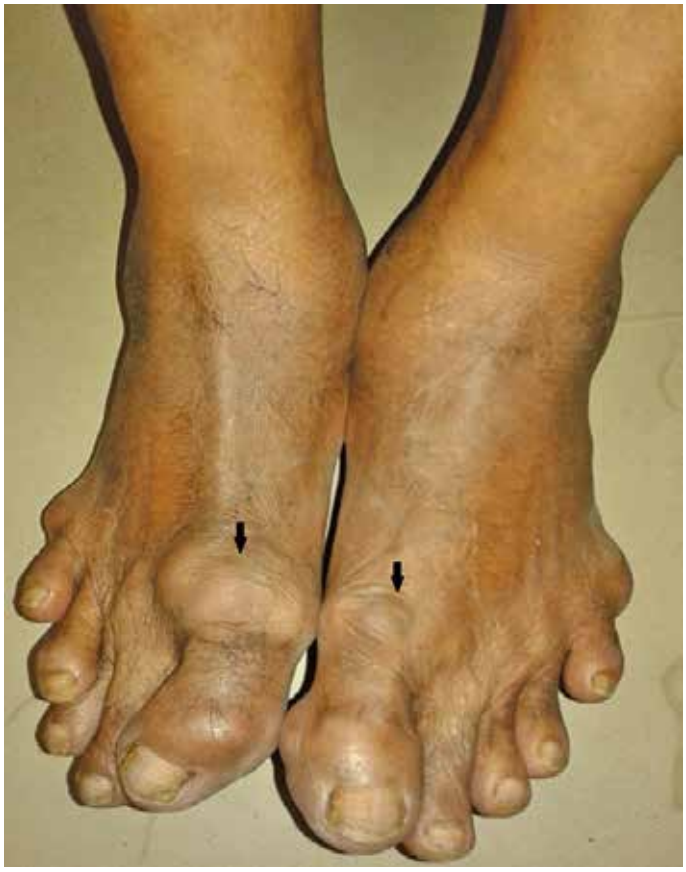

Fig. 4: A patient of chronic tophaceous gout with affection of first metatarsophalangeal joints of both feet (black arrows)

never occurs or occurs after many years. Gout is usually known as a chronic disease with recurrent acute flare. The renal involvement in gout may take three forms: acute uric acid nephropathy (precipitation of uric acid in the renal tubules or collecting tubules), urate nephropathy (deposition of urate crystals in the renal interstitium and pyramids) and uric acid stones (urolithiasis); it needs to be appreciated that other contributory factors for renal involvement in gout are hypertension, diabetes and long-continued use of nonsteroidal anti-inflammatory drugs (NSAIDs).

Differential diagnoses of gout in clinical practices are septic arthritis, trauma, cellulitis, reactive arthritis, psoriatic arthritis, palindromic rheumatoid arthritis and pseudogout.

DIAGNOSIS

A classical clinical presentation (Dr. Thomas Sydenham's classical description) clinches the presumptive diagnosis of acute gout (sudden appearance of red, hot, swollen and acutely tender joint at midnight). A rapid therapeutic response to NSAID or colchicine is often diagnostic but the gold standard for diagnosis of acute gout is demonstration of strongly negative birefringent needle- and rod-shaped crystals of MSU in the synovial fluid under polarized light microscopy. Ordinary light microscope can pick up MSU crystals but polarized microscopy for detection of birefringence characteristic is ideal. Joint effusions in acute gout is inflammatory (>2000 cells/ µl, mostly

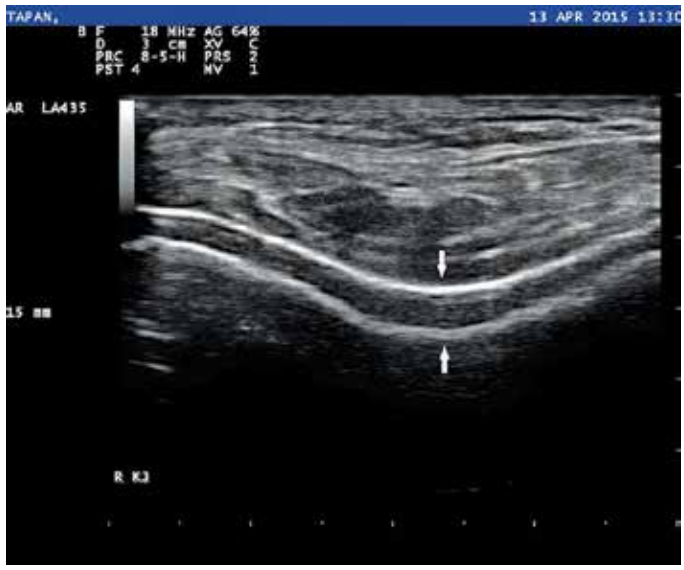

Fig. 5: The Double contour (DC) sign (white arrows). The DC sign is a hyperechoic delineation of the cartilage, caused by urate crystal deposits on the surface of the cartilage in chronic gout

polymorphs) in nature. Gram stain, cell culture, and cell count with differentials of the aspirated fluid are often required to exclude septic arthritis and cellulitis (gout mimickers). Serum uric acid (SUA) is usually raised (>10 mg/dL) but it is prudent to remember that up to 40% patients may have normal or low SUA during the acute attack as stress-induced liberation of ACTH and disease-induced secretion of cytokines are uricosuric. On the other way, a patient with acute arthritis and raised SUA may have many other diseases (Table 2); thus, a diagnosis of gout should never be based only on SUA level. To differentiate 'overproducers' from 'under excretors' (see Classification below), estimation of 24-hours urinary uric acid is sometimes required (normal value is < 800 mg on a regular diet). The ESR and CRP are typically elevated with a mild elevation of total WBC count. Complete blood count, urea and creatinine, lipid profile and glucose are important screens for comorbidities. Ordinary radiograph has little contribution in acute gout (only soft tissue swelling; in chronic gout, it may reveal 'punched-out' lesions with overhanging edges with or without severe joint destruction – "Martel's sign") but ultrasonography of the affected joint may exhibit 'Double contour sign' (Figure 5), which is often pathognomonic of acute gout. Dual-energy CT scan can identify uric acid accumulations but it is not routinely done.

CLASSIFICATION

In over 90% patients, the main abnormality is reduced excretion of uric acid by renal tubules and in around 10% patients, overproduction of uric acid is attributed to the cause of hyperuricemia. Gout is classified into primary (of unknown cause) and secondary gout (having an underlying illness). Primary gout is likely to be due to a genetic defect in renal urate handling. Secondary gout is due to:

A. Over-production of uric acid (overproducers)
   – Myeloproliferative and lymphoproliferative

Table 2: Differentials of arthritis with raised SUA level

- Gout
- Psoriasis
- Chronic hemolytic anemia
- Sarcoidosis
- Lymphoma, malignancy, myeloproliferative diseases
- Application of cytotoxic drugs

disorders, psoriasis, glycogen storage disease, haemolytic diseases, high purine diet, alcohol, tumour lysis syndrome, Lesch-Nyhan syndrome, glucose-6-phosphatase deficiency and phosphoribosyl pyrophosphate synthetase overactivity.

B. Diminished renal excretion (under excretors) – Renal failure, lactic acidosis, lead poisoning, sarcoidosis, Down's syndrome, alcohol, metabolic syndrome and drugs (thiazides, low-dose aspirin, pyrazinamide, cyclosporine, nicotinic acid).

MANAGEMENT

A. Acute Gout – The drugs used are NSAID, colchicines, corticosteroids (intra-articular / systemic), and majority of patients response. According to researchers in this field, IL-1 inhibitors like anakinra, rilonacept or canakinumab (all are very expensive) may be used in 'acute' gouty patients unresponsive to NSAID or colchicines. Urate lowering therapy (ULT) is generally initiated when the patient is stable i.e., after 2-4 weeks after the acute attack, and continued lifelong. It is judicious to initiate ULT after the 2nd or 3rd attack of gouty arthritis if it occurs within a year. The target uric acid level is <6 mg/dL in general and <5 mg/dL in patients with tophi.

B. Chronic Gout – The drugs (ULT) are categorised into three groups:

1. Uricostatic drugs (xanthine oxidase inhibitors) – Allopurinol (100-800 mg/day in single morning dose), oxypurinol, febuxostat (40-120 mg/day, single dose).
2. Uricosuric agents – Probenecid (500-2000 mg/day), sulfinpyrazone, benzbromarone, losartan, fenofibrate, amlodipine (cyclosporine-induced hyperuricemia), vitamin C (500 mg/day).
3. Uricolytic drugs – Uricase, rasburicase, pegloticase.

Along with pharmacotherapy, dietary restrictions [avoid alcohol, red meat, sea foods and fructose but protein restriction is not necessary; intake of low-fat dairy products, vitamin C (500 mg/day) and coffee reduces SUA level], lifestyle modifications (overweight patients should restrict calorie and cholesterol) and controlling comorbid conditions are 'target to treat' chronic gout. Acute on chronic flare can be treated by Colchicine (0.6 mg/day for 6 months, or NSAID for one month) along with ULT. ULT dissolves preformed crystals and prevent new crystal formation, which should be intimated to the patients for proper motivation of their chronic treatment.

Lesinurad is a novel uricosuric agent (urate transporter inhibitor), which prevents uric acid reuptake and increases its secretion. It was approved by FDA in late 2015. It is given in addition to either allopurinol or febuxostat if the target SUA level is not attained by taking one of those drugs; lesinurad should not be used alone.

Benzbromarone, sulphinpyrazone, lesinurad and IL-1 inhibitors are not available in India. Rasburicase, by short-term IV, is used for prevention of tumour lysis syndrome in haematological malignancy, and IV pegloticase (pegylated uricase) is helpful in severe, recalcitrant gout for debulking incapacitating tophi.

COMPLICATED GOUT

- Polyarticular Gout – Gout is basically a monoarticular disease but polyarticular affection is common in elderly, postmenopausal women on diuretics, in transplant patients and chronic tophaceous gout. Initial acute gouty attack may be polyarticular in 3-14% patients.
- Gout in the Elderly – Usually above 65 years with a male: female ratio of 1:1. The gouty attack may be polyarticular and the patient may have history of diuretic overuse with or without renal insufficiency; tophi formation is early. Comorbidities (obesity, hypertension, alcohol abuse) are usually not associated with.
- Organ Transplant Related Gout – Transplant patients (cardiac or kidney transplant) are treated by anti-rejection therapy (cyclosporine), often with diuretics. Approximately 10% develop gout with a mean SUA level of 12 mg/dL where the presentation is atypical, polyarticular, with extensive tophi formation along with involvement of upper extremity and occasionally the spine. These patients are resistant to therapy. Many a time glucocorticoid, present in immunosuppressive regimen, delays overt inflammation of gout. It is important to remember that allopurinol has severe drug interaction with azathioprine, which is metabolized by zanthine oxidase.
- Gout in the Women – Above the age of 50 years, gout is the most common cause of inflammatory arthritis in men; gout is rare in children and premenopausal women. After the menopause, excretion of uric acid is reduced due to lack of oestrogen; and thus 50% gouty patients above 60 years of age are women.
- Gout in Renal Failure – Urate nephropathy may lead to chronic renal failure (CRF) and end-stage renal disease (ESRD). In CRF, NSAID and colchicine are avoided. Systemic (in polyarticular disease) and intra-articular (in monoarticular disease) corticosteroid are helpful. Colchicine-induced myelosuppression and myopathy may develop; colchicines-induced side effects are managed by granulocyte colony stimulating factor (for nutropenia), simvastatin, erythromycin and

cyclosporine. Allopurinol may be used in CRF in a reduced dose of 50-100 mg/day to twice weekly; instead febuxostat can be used safely.

- Gout and Hepatic Disorder – Gout and alcohol are inseperable. NSAID (G.I. hemorrhage), alcohol and even colchicine (with a loading dose) are very unsafe in this situation. Allopurinol in prophylaxis, and parenteral corticosteroids are relatively safe in acute attack. Stoppage of alcohol intake is crucial and life-saving. Febuxostat should better be avoided in severe hepatic dysfunction.
- Gout in Active Peptic Ulcer Disease – NSAIDs are contraindicated and if nothing is allowed per mouth (e.g., in recent upper G.I. hemorrhage), intra-articular or systemic corticosteroid can be tried in a desperate situation. Supportive measures like misoprostol or proton-pump inhibitors should be continued; specific cox-2 inhibitor (e.g., etoricoxib) can be used cautiously for a short period with allopurinol (for prophylaxis).
- Asymptomatic Hyperuricemia – It has been shown to be associated with increased cardiovascular morbidity though many authorities are in the opinion that increased morbidity is due to the presence of other cardiovascular risk factors rather than high SUA level. Controversy still persists whether asymptomatic hyperuricemia should be treated or not but consensus is in favour of initiation of treatment if it is associated with arthritis, renal calculi, tophi, tumour lysis syndrome, with very strong family history of gout, patients to receive chemo- or radiotherapy, and with very high SUA level (i.e., men >12mg/dL and women >10 mg/dL).
- Normouricemic Gout – Around 40% patients may have normal or low SUA during acute attack. The fall in the SUA often precipitates acute episodes due to tophi dissolution. Demonstration of urate crystals in joint fluid makes the diagnosis. Otherwise a classical history, a positive family history and therapeutically favourable response to colchicine establish the diagnosis.
- Gout and Metabolic Syndrome – Hyperuricemia occurs as a part of metabolic syndrome (obesity, hypertension, diabetes, hyperlipidemia and CAD) and in this situation, drug interaction is of major concern. Colchicine increases the toxicity of statins by developing rabdomyolysis or myoglobinuria. Allopurinol prolongs the half life of warfarin though febuxostat has no interaction with warfarin. Diuretics are better avoided; losartan and amlodipine are chosen for treating hypertension, and fenofibrate for hypertriglyceridemia (all are uricosurics). Aspirin in the range of 600-2400 mg/day cause uric acid retention while doses >4000 mg/day are uricosuric; and thus a very low dose aspirin (75-150 mg/day) used for cardiovascular prophylaxis may not have clinically meaningful untoward effects, and may be continued if needed.
- Gout in Patients Hypersensitive to Allopurinol – Around 1-2% patients on allopurinol develop hypersensitivity reactions (in 2nd -3rd week), and 20% of them may develop vasculitis or renal failure. This occurs in patients who are on diuretics, or allergic to penicillin/ampicillin/sulphonamides, or is an Asian expressing HLA-B*5801. The other choices for the patient are attempt at desensitization to allopurinol, or addition of febuxostat, probenecid, losartan or uricase. It is always better to start with low dose allopurinol depending on the creatinine clearance to avoid hypersensitivity reactions.
- Non-rheumatological Controversial Associations – Renal involvement, bursitis, tendonitis, enthesitis and carpal tunnel syndrome are recognised non-arthritic manifestations of gout.

  Though uric acid is the most abundant natural antioxidant in human body, hyperuricemia may be a true independent risk factor for CAD. Hyperuricemia is a strong marker of endothelial dysfunction and insulin resistance, and an independent risk factor for systemic hypertension. Associations among hyperuricemia, and atherosclerosis and/or dyslipidemia remain controversial.

CONCLUSION

Presence of gout in a patient should be taken very cautiously. It is the duty of a physician to try to recognise the conditions associated with gout, particularly in the presence of growing evidences that gout increases the risk of cardiovascular diseases.

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