Acute attack of gout precipitated by concomitant use of aspirin and diuretic in a rheumatic mitral stenosis patient

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DESCRIPTION

A 28 -year-old man from India, known to have rheumatic heart disease (RHD) with severe mitral stenosis (MS), presented with painful nodular swelling of multiple joints of hands and feet. He suffered rheumatic fever at 12 years of age and was on penicillin prophylaxis for 5 years and then stopped. He was diagnosed to have developed severe MS at the age of 20 years and is fairly asymptomatic on furosemide 20 mg 12 hours and metoprolol succinate 25 mg 12 hours. However, he had an exacerbation of shortness of breath with orthopnoea and pedal swelling 2 weeks ago. Cardiovascular examination revealed a thin built man with a blood pressure of 100/60 mm Hg and an irregular pulse of 90 beats/min. The jugular venous pressure was not elevated, and hepato-jugular reflux was absent. The pulmonary component of the second heart sound was loud, and a parasternal heave was noted. An opening snap was heard after the second heart sound, and a long apical mid-diastolic murmur was detected along with presystolic accentuation. The 12-lead surface ECG revealed normal sinus rhythm. Two-dimensional echocardiography revealed thickened mitral leaflets suggestive of severe MS with mitral valve area of 1 cm^2. The left atrium was enlarged (46 mm in end-systole) with the presence of spontaneous echo contrast. Mild mitral regurgitation was noted. The dose of diuretic was increased to torsemide 20 mg 12 hours, which diminished his congestive symptoms.

One week later, the patient presented with painful small joints of hands, wrist, elbows, feet and heel with restricted movements. Boggy swelling over both the elbows was also noted. However, there was no early morning stiffness. There was no recent upper respiratory tract infection or diarrhoea. There was no history of recent travel or unprotected sexual intercourse. There was no urethral discharge, redness of eyes or rashes anywhere in the body. He does not smoke or drink alcohol. There was no family history suggestive of any haemoglobinopathy. He did not have any significant previous medical history or any previous history of gout. The serum uric acid on admission was 5 mg/dL (normal range, 2.3–6.0 mg/dL). The serum creatinine concentration was 1.1 mg/dL (normal range, 0.6–0.9 mg/dL).

His haemoglobin level was 14.5 g/L (normal 14-16 g/L in male) and total leucocyte count was 12x10^9 /L (normal 4-11x10^9/L). Erythrocyte sedimentation (ESR) rate in the first hour was 32 mm (normal range is 0–22 mm/hour for men). C reactive protein (CRP) was 5 mg/dL (normal CRP levels are below 3.0 mg/L). Antistreptolysin O (ASO) titre was 120 Todd units (normal <166 Todd units). The worsening joint pain and congestive symptoms in a known patient of RHD without penicillin prophylaxis with high TLC, ESR and CRP were presumed to be due to acute rheumatic activity, and Aspirin was started in the dose of two 325 mg tablets three times a day.

The patient returned back after another week with nodular swelling of fingers and toes, red and tender, with ulceration. On examination of the joints, tender nodular swellings were noted in multiple small joints of both the hands, wrists, feet and ankle, mostly confined to the extensor surfaces (figure 1A). A nodule on his right foot drained chalky, sanguineous material. He also had leg ulcers formed at sites of draining tophi. Radiogram of the joints revealed the presence of multiple well-defined 'punched-out' erosions in the proximal interphalangeal joint of right little finger (figure 1B), the interphalangeal joint and metatarsophalangeal joint of the right big toe (figure 1C) with sclerotic margins in a marginal and juxta-articular distribution, with overhanging edges. Hyperdense soft tissue swellings were noted over the fingers of both the hands.

Joint aspirate was also taken from the tophi of right and left fingers and left great toe using a 21-gauge needle. It yielded white, chalky material which demonstrated slender needle-shaped crystals along with multinucleated giant cells and chronic inflammatory infiltrate on light microscopy of the Giemsa-stained smears. Polarising microscopy of the stained smears revealed negatively birefringent crystals, consistent with monosodium urate (MSU) deposition confirming diagnosis of gout.

The clinical, radiographic and histopathological features of the joint involvement were suggestive of gout, and the patient was put on colchicines. Aspirin was stopped, and torsemide was reduced to 10 mg 24 hours. The joint pain and swelling improved over a 72 hours and resolved over a period of 2 weeks without any further deterioration of shortness of breath. Penicillin prophylaxis was reinitiated. On follow-up, haemoglobin electrophoresis was done and was of normal pattern. HLA-B27 was also done, which was negative.

Young man with Asian enthnicity presenting with multiple swollen joints of hands and feet could be due to dactylitis secondary to haemoglobinopathies, gout, pesudogout, reactive arthritis and

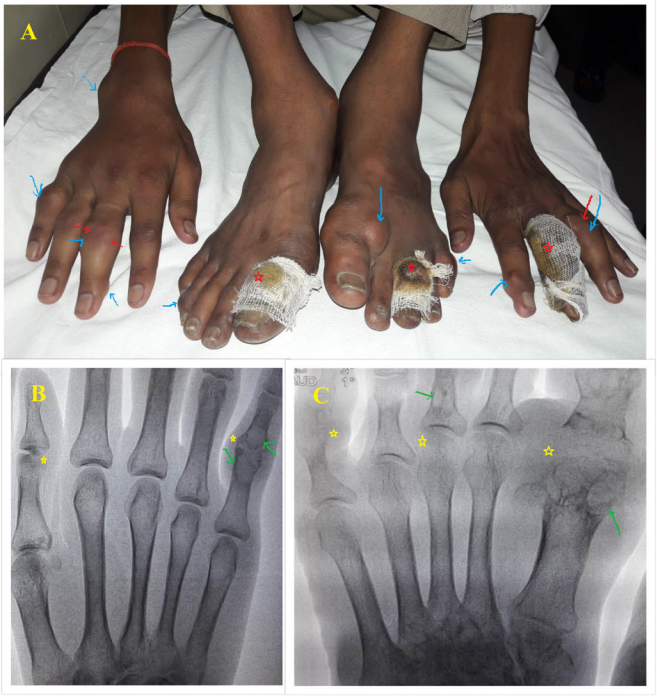

Figure 1 Image of multiple nodules (Tophi, blue arrows) overlying small joints of hands and feet (A) with overlying inflammation (red arrows) with discharging sinus (wrapped in gauzes, red stars). Radiogram of right hand (B) and feet (C) showing multiple well-defined 'punched-out' erosions (green arrows) with hyperdense soft tissue swellings (yellow stars).

rarely rheumatic arthritis. Normal haemoglobin electrophoresis ruled out heamoglobinopathy in our case. The absence of rash and preceding infection ruled out reactive arthritis. Rheumatic arthritis usually involves large joints, and dramatic response to aspirin is classical. Often subcutaneous nodules, worsening of cardiac symptoms and appearance of new (or musical) murmur, worsening regurgitation and pericardial effusion in echocardiography are associated. Moreover, rheumatic arthritis rarely causes erosion or deformity of joints. Recurrence of rheumatic arthritis was unlikely in our case to involve small joints of hands without elevation of ASO titre and, retrospectively, without response to aspirin. Moreover, the absence of calcification was noteworthy in the radiogram, which is common in pseudogout but absent in gout. However, joint aspirate demonstrating needle-shaped crystal with negative birefringence on polarised light is diagnostic of MSU deposition due to gout.

This case taught us many lessons. First, the presumptive diagnosis of acute rheumatic activity on the basis of worsening symptoms and elevated TLC, ESR and CRP was wrong. As in acute gouty arthritis, the inflammatory markers are also elevated. Second, a normal serum urate level misled us to rule out gout. But, serum uric acid level can be normal in acute attack of gout. In a study by Schlesinger *et al*, in 70% of patients, the serum uric acid was lower during the acute episode.[1] Moreover, the low uric acid level has been found to be correlated with increased inflammatory factors, which is also true in our case.[2] Third, high-dose diuretic inducing gout is a known entity but rarely encountered and should be remembered by the cardiologists, while prescribing diuretics in RHD, heart failure or hypertension patients. It is usually associated with hyper-uricaemia but normal serum urate level does not exclude gout.[3] Fourth, recurrent rheumatic activity is not uncommon in established RHD (even without the elevation of ASO titre in indolent cases), and 90% patients suffer recurrence in their lifetime. However, it should be remembered that small joint involvement is a red-flag sign for rheumatic arthritis.[4] Fifth, aspirin is the most effective treatment for acute rheumatic activity but it is also known to precipitate gout. Aspirin doses up to 1–2 g/day reduce uric acid excretion.[5] In our patient, total dose of aspirin was 1950 mg daily, which precipitated acute attack of gout probably with an additive effect of loop diuretic. Sixth, the radiological features of gout consist of well-defined 'punched-out' erosions with sclerotic margins without peri-articular osteopenia unlike non-erosive changes of rheumatic arthritis.[6] Seventh, rheumatic arthritis is diagnosed retrospectively by the dramatic response of aspirin, likewise, gout is retrospectively diagnosed by its dramatic response with colchicine. Arthritis in our patient did not respond to aspirin but colchicines remarkably relieved the pain within 72 hours. Finally, our patient presented with tophi as an initial presentation of gout, which is very rare, but has been reported in the context of acute illness.[7] In our case, concomitant recurrent rheumatic activity might play role, though there was no musical murmur, pericardial effusion, nodularity of mitral leaflets or elevation of ASO titre.[8] In this regard, it is worthwhile to mention that there are cases which reported tophi in mitral valve in severe tophaceous gout.[9 10] However, tophaceous deposits in the mital valve were not seen in our case.

From a pharmacological point of view, loop diuretics inhibits, involved in the active uptake of plasma uric acid in renal proximal tubules. Loop diuretics increases serum uric acid levels by inhibiting Organic Anion Transporters (OAT1 and OAT3) located in basolateral portion of renal proximal tubules, inhibiting NPT4 which is located at the apical side of renal proximal tubules and also by inhibiting Multidrug Resistance Protein 4 (MRP4)-mediated uric acid transport.[11] Moreover, diuretics cause sufficient salt and water loss that may to lead to volume contraction, which stimulates uric acid reabsorption.[11] Also, furosemide induces hyperlactacidaemia sufficient to suppress tubular excretion of uric acid.[11] In low dosages (60–300 mg once daily), aspirin reduces uric acid excretion and may induce hyperuricaemia, whereas higher doses are uricosuric.[12] This paradoxical effect of salicylate can be explained by two modes of salicylate interaction with the urate monocarboxylate exchanger (URAT1): acting as an exchange substrate to facilitate urate reabsorption at low dose and acting as an inhibitor for urate reabsorption at high dose. In addition, salicylate may exert its hyperuricaemic effect through inhibiting MRP4-mediated urate transport as well as inhibiting OAT1 and OAT3.[12]

In our case, rheumatic MS patient presenting with worsening congestive symptoms with painful small joints was misdiagnosed as recurrence of rheumatic activity and was treated with aspirin

Learning points

- Serum uric acid level can be normal in acute attack of gout in up to 70% of cases and low uric acid level has been found to be correlated with increased inflammatory factors.
- Although 90% patients with rheumatic heart disease suffer recurrence of rheumatic activity in their lifetime, small joint involvement is a red-flag sign for rheumatic arthritis.
- Aspirin can precipitate acute attack of gout specially when used concomitantly with high-dose diuretics.
- Gout usually flares up during an acute illness, and rarely it can also present with tophi as an initial manifestation.

and high dose of loop diuretics that precipitated gouty arthritis, which was later diagnosed correctly by its radiological appearance and was treated successfully with colchicines and diminution of dose of diuretics. In this regard, it is prudent to mention that, if diagnostic dilemma between gout and rheumatic arthritis cannot be resolved with confidence, it is worthy to give a trial of steroids, though, we did not try that in our case.

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