37. EROSIVE POLYARTICULAR TOPHACEOUS GOUT: A THERAPEUTIC CONUNDRUM

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Introduction: Gout is a common male predominant metabolic disease characterised by deposition of monosodium urate crystals in synovial membrane, articular cartilage and periarticular tissues leading to inflammation and irreversible joint damage. Nodular accumulation of urate crystals in soft tissue leads to the formation of tophi resulting in functional limitation and chronic pain. This can cause substantial morbidity and despite having readily available therapies, Gout continues to pose a therapeutic challenge. Long-term control requires dissolution of the existing monosodium urate crystals and measures to prevent future crystal formation.
Case description: A 47-year-old man was referred to rheumatology clinic in 2010 with 20-year history of severe destructive polyarticular gout. His main complaint was pain in small joints of hands, wrists, elbows and extremely painful flares. He was on gout treatment i.e. allopurinol 600mg; regular analgesics i.e. etoricoxib 60mg, analgesia (oral oxycodone and buprenorphine patch) and calcium channel blockers for hypertension. His personal history was remarkable for heavy alcohol use (100 units weekly), high purine diet intake and active smoking (40 pack-years). He was a taxi driver by profession. There was no family history of gout. Physical examination revealed morbid obesity (BMI 36.2 kg/m2) and multiple firm tophi over both hands, extensor surface of elbows and both shins. Laboratory workup revealed elevated serum uric acid 640 μmol/L, (normal: 286–518 μmol/L), with normal renal function test: blood urea 5.6 mmol/L (normal: 2.9-7.1 mmol/L) and serum creatinine 84 μmol/L (normal: 55–99 μmol/L). Radiographs of both hands showed periarticular soft-tissue swelling and punched-out erosions with sclerotic margins in a marginal and juxta-articular distribution, with overhanging edges in interphalangeal joints typical for gouty arthritis. Other inflammatory arthritides were excluded on clinical and laboratory data. Our patient clearly had severe chronic tophaceous gout that was sub optimally controlled. He was started on low dose regular prednisolone; his allopurinol was increased to maximum daily dose of 900 mg. On 3-month follow-up allopurinol was substituted with daily febuxostat 120 mg as serum Uric acid levels remained high (540 μmol/L) His analgesics were increased as he began to suffer increased frequency and severity of gouty flare. This helped his symptoms partially and brought his uric acid level down to the range of 340-495 μmol/L (normal: 286–518 μmol/L) over 10 months. He was admitted following left retinal detachment after a road traffic accident and it was noted that his BP was poorly controlled. ACE inhibitor and beta blocker were started at that stage. While an in-patient, he was reviewed by rheumatology for twice weekly gout flares and morning stiffness of $>$ 1hour. His uric acid level was 410μmol/L (normal: 286–518 μmol/L). He was commenced on colchicine 0.5 mg 12 hourly for one month, restarted on allopurinol that was titrated up to 600mg daily while continuing febuxostat 120mg, deltacortil 10mg and regular analgesics which reduced frequency of his gout flares to once per month and his uric acid level came down to 257 μmol/L (normal: 286–518 μmol/L) in one year. At this stage he also developed type 2 diabetes mellitus on a background of worsening peripheral vascular disease and hyperlipidaemia. After 4-years of rheumatology follow-up, he developed discharging tophi from the front and back of his shins, knees, an inflamed tophus of his right elbow and worsening digital damage. At that stage he had gout for 24 years and his uric acid despite obvious aggressive therapy still hovered above the target level (according to ACR 2012 guidelines, target serum uric acid level $<$ 360 μmol/L; and in severe cases $<$ 300 μmol/L). At that stage, we elected to treat him with a novel biologic therapy (rasburicase - an intravenous Uricase enzyme) to debulk his severe refractory chronic tophaceous gout. Bearing in mind that Uricase therapy could potentially precipitate severe flares and as our patient had previous incomplete response to the standard therapy, he was commenced on Anakinra (anti-IL 1 monoclonal antibody) 100mg daily subcutaneous injections to prevent gouty flare. He later received two infusions of Rasburicase (at dose of 0.2 mg/kg) intravenously two weeks apart and continued with anakinra injections. His uric acid level was reduced to to 300 μmol/L (normal: 200-430 μmol/L). He was hospitalised 2 months later due to left shin infected tophi leading to cellulitis (possibly aggravated by the Anakinra treatment) and was treated with intravenous antibiotics. While in hospital, he developed left middle cerebral artery and right basal ganglia infarct and was

also diagnosed as having alcohol related memory disorder requiring community neuro-rehabilitation. He was strongly advised to cut down alcohol (reduced to 20 units/week) and smoking (reduced to 10-15 cigarettes/day). Our patient tolerated anakinra injections well for 10-months with no reported adverse events resulting in significant clinical improvement and serum uric acid in the target range. In December 2014, he developed right big toe osteomyelitis requiring washout, debridement and further prolonged course of intravenous antibiotics for 6 weeks according to microbiology advice with good clinical outcome. In last 3-years he has had excellent control of gout, marked reduction in the size of tophi and normalization of uric acid concentration (170-249 μmol/L; Normal: 200-430 μmol/L) on single maintenance xanthine oxidase inhibitor (febuxostat 120 mg daily).

Discussion: Gout is characterized by recurrent attacks of red, tender, hot, and swollen joints due to hyperuricemia that results from accelerated purine metabolism. Other potential contributors are alcohol, genetic predisposition, diet and coexisting metabolic syndrome. As in our case, patient had history of heavy alcohol abuse; high purine-diet consumption and metabolic syndrome .Gouty tophi are the chronic manifestations of the disease progression. Concordant with the history of our patient, tophi are usually present in patients who have had gouty arthritis for at least 10-years. Gout is associated with increased frequency of obesity, chronic kidney disease, hypertension, type 2 diabetes, dyslipidemias, cardiac diseases, stroke and peripheral arterial disease(PVD). Interestingly our patient was obese and hypertensive; and over the course of his disease he developed type-2 diabetes, dyslipidemias, stroke and PVD. Gout management can impose significant therapeutic challenges. NSAIDs, corticosteroids, or colchicine are used in an acute attack. Recent literature suggests IL-1 inhibitors (e.g. anakinra) as fourth-line beneficial therapy for acute attacks after NSAIDs, colchicine, and steroids due to their high cost and limited clinical experience. Anakinra acts as potential anti-inflammatory agent in refractory gout. It is also useful in tophaceous gout by reducing breakthrough flares during initiation of standard chronic urate-lowering therapies i.e. xanthine oxidase inhibitors (allopurinol and febuxostat) and uricosurics (probenecid and benzbromarone). In certain cases, these therapies are not enough as they only prevent further formation but do not dissolve existing uric acid. Novel biologic agents have been approved for use in such refractory cases. Rasburicase, a recombinant urate oxidase enzyme, breaks down uric acid to allantoin, which is highly soluble and easily excreted in the urine. Certainly our patient had severe destructive tophaceous gout and was a poor responder to standard gout treatment till he received novel therapies i.e. anakinra and resburicase that helped dramatically to control his symptoms.

Key learning points: 1. Gout is a rheumatologic condition associated with elevated serum uric acid levels and deposition of monosodium urate crystals in joints and soft tissues. 2. Longstanding and untreated recurrent attacks of acute gout may lead to advanced tophaceous gout. 3. Heavy alcohol consumption, genetic predisposition, high purine diet and coexisting metabolic syndrome are potential contributors to hyperuricemia 4. Screening and care of gout related comorbidities as well as of cardiovascular risk factors are of outmost importance in patients with gout 5. Although gout is an ancient disease, best practices for treatment of acute gout flares, chronic refractory gout and hyperuricemia continues to evolve with traditional agents for mild-to-moderate disease and novel therapeutic agents as a potential treatment option for individuals with severe or refractory symptoms.