CASE REPORT

Management of Refractory Gout with Tumor Necrosis Factor Inhibitor and Febuxostat

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ABSTRACT

Gouty arthritis is a metabolic disorder associated with hyperuricemia and despite the availability of various pharmacotherapeutic agents, such as uricosuric, uric acid synthesis inhibitors, NSAIDs, corticosteroids and biologics – a new addition, some hyperuricemia patients are drug refractory. Refractory gout remains a persistent challenge for diagnosis and management for clinicians. We present a case of chronic gouty arthropathy was successfully treated by combining two different group of drugs such as xanthine oxidase inhibitor Febuxostat and TNF antagonists Etanercept.

Key words: Chronic rheumatic disease, Tumor necrosis factor, Refractory gout

INTRODUCTION

Gout is a debilitating chronic rheumatic disease condition caused by the deposition of monosodium urate crystals in and around joint tissue.[1] Refractory gout is a common problem faced by experienced rheumatologists. The diagnosis and treatment of complex and refractory gout are a major clinical problem to be solved. Incorrect and inadequate drug therapy may contribute to some cases of refractory gout, especially in physicians without CME.[2] The gold standard of diagnosis is identification of characteristic MSU crystals in the synovial fluid using polarized light microscopy. Management of gout includes management of flares, chronic gout, and prevention of flares, as well as management of comorbidities. In the acute outbreak of gouty arthritis as a local acute inflammatory process, tumor necrosis factor-alpha (TNF-α), interleukin-1, and other cytokines play an essential role in the occurrence, development, and persistence of local inflammation in gout acute stage.[3] Antigout drugs in the pharmacological armamentarium include non-steroidal anti-inflammatory drugs (NSAIDs) Colchicine Corticosteroids for acute flare. Chronic gout management is done by Uricosuric agents such as Probenecid, Sulfinpyrazone and Synthesis inhibitors Allopurinol and newer one is Febuxostat. Newer drugs in the pharmacological armamentarium are proving successful and supplement older ones.

We herein report the case of a patient with refractory gout that was successfully treated by combining two different group of drugs such as xanthine oxidase inhibitor Febuxostat and TNF antagonists Etanercept.

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CASE PRESENTATION

Presenting Complaints

A 65-year-old female patient was admitted to our rheumatology unit with a history of chronic tophaceous gout since 2019. Presenting complaints were severe pain in multiple joints affecting wrists, knees, ankles, right elbow, and first metatarsophalangeal joints for 2 weeks. On local examination there was fusiform swelling in proximal and distal interphalangeal joints of right hand, bilateral wrists, and knee joints. In addition, she complained of morning stiffness lasting for about 30 min.

Medical History

She had hypertension and hyperlipidemia 2 years before the admission. She was diagnosed as acute gouty arthritis, with uric acid 20.4 mg/dL at the age of 54 years. She had monoarticular

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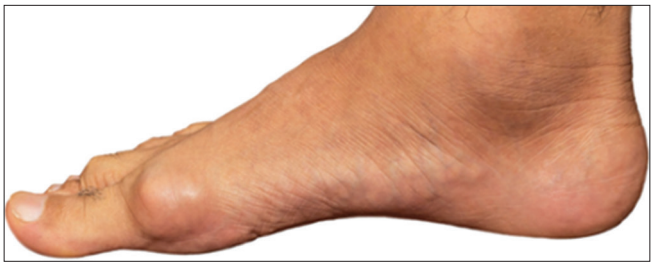

Figure 1: Right foot showing gouty arthritis with extreme swelling, erythema, and tophi

episodes that progressed over the years, difficult to control polyarticular attacks. She was regularly taking allopurinol 300 mg daily and colchicine, NSAIDs, or intramuscular corticosteroids during the acute attacks. She was on olmesartan + hydrochlorothiazide combination and atorvastatin.

Management

She was diagnosed as acute gouty arthritis (outbreak period) [Figure 1], hypertension Grade II, hyperlipidemia. She was started on a small dose of Colchicine to relieve joint pain, Febuxostat to reduce uric acid synthesis, For control of blood pressure, shifted on olmesartan + amlodipine combination. Atorvastatin to lower lipid. After 2 weeks her blood uric acid levels come to 6 mg/dl but joint swelling and pain occurred repeatedly. A selective cyclooxygenase (COX-2) inhibitor, a NSAID, celecoxib was added to treat the joint swelling and pain. A selective COX-2 inhibitor, a NSAID, celecoxib was added to treat the joint swelling and pain; however, multiple joint swelling and pain still did not relieve. Considering the ineffectiveness of celecoxib and colchicine in relieving the joint pain and inflammation treatment with the TNF-α inhibitor etanercept was initiated. It was initiated as 25 mg subcutaneously twice weekly for 2 weeks. There was marked reduction in frequency (gouty attacks per week) and the intensity (number of painful joints) of the gouty arthritis decreased considerably after four injections of etanercept.

Laboratory Test

Lab test	On admission	After etanercept therapy
WBC count	11.46×10^9/L	7.20×10^9/L
ESR	62 mm/1st h	10 mm/1st h
CRP	52.0 mg/L	8 mg/L
Uric acid	255 μmol/L	290 μmol/L

During Etanercept treatment, Febuxostat administration was withhold. There was marked reduction in joint pain after 1 day and joint swelling disappeared in 3–5 days. Patient was discharged 1 week after Etanercept treatment and started on Febuxostat 40 mg once a day, colchicine 0.5 mg b.i.d., Olmesartan+ amlodipine combination once a day and atorvastatin 20 mg once a day.

DISCUSSION

Symptomatic hyperuricemia can be treated by effective therapeutic options. Refractory and severe gouty arthritis is rarely seen. In most cases, standard treatment with colchicine, NSAIDs, and moderate doses of glucocorticosteroids is sufficient to control the inflammation of gouty attacks. Our patient suffered from severe polyarthritis, such as joints of hands, toes, and knees. The conservative treatment of gout, analgesics, did not control the attacks. The use of etanercept produced a noticeable decrease in all the pathological clinical and laboratory findings. TNF-α plays an important part in different inflammatory diseases. Today, anti-TNF-α is widely used in the treatment of different kinds of arthritis and primary vasculitis. Etanercept for injection is a recombinant human TNF receptor antibody fusion protein, which binds with TNF-α in blood competitively, blocks its binding with TNF-α receptor on the cell surface, reduces its activity, and effectively controls arthritis.[4-9] Etanercept alleviate the acute inflammatory response of gouty arthritis and achieve low uric acid treatment. It is still used off label for acute gout. Tausche *et al*.[10] reported that etanercept successfully treated one case of refractory gout in 2004, and the proposed etanercept was a new choice for refractory gout patients with low effect on common anti-inflammatory drugs. Furthermore Zhang *et al*. reported that etanercept successfully treated one case of refractory gout in 2020. We describe the first published case of severe, recurrent tophaceous gouty arthritis refractory to anti-inflammatory treatment in a patient who was subsequently treated successfully with a TNF-α inhibitor. Of particular interest is the possibility of maintaining anti hyperuricaemic treatment during the antiphlogistic protection of etanercept, especially as there is a massive excavation of uric acid from the depots owing to the antihyperuricaemic treatment.

CONCLUSION

This case is about refractory; severe gouty polyarthritis not responding to anti-inflammatory treatment and was subsequently treated successfully with a TNF-α nhibitor. TNF inhibitors help in reducing the acute inflammatory response of gouty arthritis.

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