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Diagnosis and Clinical Management of Gout Arthritis

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Abstract
Gout is an inflammatory joint disease caused by an inflammatory response to monosodium urate (MSU) crystals in the joint fluid, cartilage, bones, tendons, bursas, or other sites. High uric acid levels increase the likelihood of gouty arthritis, but not all high uric acid levels will develop into gout. Gout has a predilection for the lower extremities such as the first MTP, which is the most common site of acute gout known as podagra. The etiology of gout is usually multifactorial, including genetic risk factors, medical comorbidities, and dietary factors. gout has now been recognized as a global health problem and has gained attention due to its increasing incidence rate, multiple metabolic comorbidities, and high premature mortality, so patients with gouty arthritis need to be diagnosed and managed appropriately.
Keywords: Gout; Kristal Monosodium; Diagnosis; Treatment;

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Introduction

Gout is the most common type of joint inflammation. The incidence and prevalence of gout is increasing worldwide, with a prevalence of about 2-4% worldwide, especially in men over 40 years old and especially in those with comorbidities such as obesity, hypertension, coronary artery disease, diabetes, or metabolic diseases (Galozzi, Bindoli, Doria, Oliviero, & Sfriso, 2021). Gout affects approximately 2.1 million Americans, according to statistics from the National Health and Nutrition Examination Survey. Epidemiologic evidence also suggests that the incidence of GA is increasing dramatically worldwide or metabolic diseases

Gout affects about 2.1 million Americans, according to statistics from the National Health and Nutrition Examination Survey. Epidemiological evidence also shows that the incidence of GA is increasing dramatically worldwide. Gout has now been recognized as a global health problem and has gained attention due to its increasing incidence rate, multiple metabolic comorbidities, and high premature mortality (Zhang, Chen, Yuan, Xu, & Xu, 2022)

Gout is an inflammatory joint disease resulting from an inflammatory response to monosodium urate crystals (MSU) in the joint fluid, cartilage, bones, tendons, bursas, or elsewhere. These crystals can directly stimulate an acute inflammatory attack. In some patients, acute gout attacks become increasingly frequent, protracted and severe, and may eventually develop into a chronic inflammatory condition. In addition, in some patients, urate crystal deposits grow into larger collections, called tophi (single tophus) when seen clinically (Weaver et al., 2021)

Etiology

The etiology of gout is usually multifactorial, including genetic risk factors, medical comorbidities and dietary factors. In rare cases, a single genetic defect can cause gout, which is usually associated with other medical complications. Whatever the cause, the result is elevated serum uric acid, which in some patients eventually leads to clinical gout (Fenando, Rednam, Gujarathi, & Widrich, n.d.)

Food sources that may contribute to hyperuricemia and gout include consumption of animal foods such as seafood (e.g., shrimp, lobster), organs (e.g., liver and kidneys), and red meat (pork, beef). Some beverages such as alcohol, sugary drinks, sodas, and high-fructose corn syrup can also contribute to the disease (Fenando et al., n.d.). Consumption of plant-based purines, such as beans, lentils, mushrooms, peas, and legumes, and dairy products do not increase the risk of hyperuricemia and gout. In fact, vitamin C, low-fat dairy products, and olive oil have been reported to lower the risk of hyperuricemia. Alcohol can be a risk factor for hyperuricemia; however, the risk may vary depending on the amount and type of alcohol consumed (Cha et al., 2024)

Hypertension, diabetes mellitus, hyperlipidemia, and metabolic syndrome are often associated with gout. Individuals with psoriasis have increased urate production and are prone to gout. On the other hand, patients with renal insufficiency have decreased urate excretion, leading to gouty attacks (Fenando et al., n.d.)

Pathogenesis of acute gout arthritis

The accumulation of uric acid crystals in the joint cavity is the trigger for gout disease. These crystals initiate the inflammatory process by being engulfed by synovial phagocytic cells causing the release of lysosomal enzymes and the production of inflammatory chemokines. Another mechanism is that uric acid crystals alter the stability of cell membranes in phagocytic cells through direct cross-linking with membrane lipids and glycoproteins. This involves the triggering of G proteins, phospholipases A2, C and D, tyrosine kinases and other kinases such as mitogen-activated kinases (ERK1/ERK2, p38) and c-Jun N-terminal kinase. This interaction leads to an increase in IL-8 in phagocytes resulting in neutrophil activation (Ragab, Elshahaly, & Bardin, 2017)

The pathogenesis of gouty arthritis involves early activation of monocytes and mast cells followed by neutrophils. Before the first gout attack and in the inter-critical period, macrophages engulf uric acid crystals. Well-differentiated macrophages have the ability to store these crystals without causing an inflammatory response. While less differentiated monocytes produce large amounts of TNF, IL-1, IL-6 and IL-8 along with endothelial activation after phagocytosis of urate crystals. In addition, mast cells also play an important role in inducing an acute gout attack by producing histamine and IL-1. This leads to increased vascular permeability and vasodilation. Interestingly, this is thought to end the inflammatory phase by engulfing crystals and inflammatory debris (Ragab et al., 2017)

Signs and symptoms

Gout occurs when there is an increase in serum urate levels of more than 7 mg/dL or 420 μmol/L, which contributes to the formation of monosodium urate (MSU) crystal deposits. It usually affects the first metatarsophalangeal joint, but large joints such as the knee, wrist, and ankle may be involved as well, causing systemic acute inflammation (Parisa, Kamaluddin, Saleh, & Sinaga, 2023)

- *Acute Gout*

  Acute gout attacks are characterized by rapid onset and escalation with joint pain usually peaking within 24 hours of the onset of the attack with major signs of inflammation including redness, heat, tenderness, swelling, and loss of function. In large joints such as the knees and ankles, signs on the skin are rare, but swelling and pain can be very intense (Coburn & Mikuls, 2016), (Ragab et al., 2017)

  Gout has a predilection for the lower extremities such as the first MTP, which is the most common site of acute gout known as podagra. Other joints that may be affected are the tarsal and metatarsal joints, ankle, knee, wrist, MCP and interphalangeal joints of the hand. Rarely, the hip and shoulder joints may be affected (Ragab et al., 2017), (Weaver et al., 2021)

  Gout attacks generally occur at night and in the morning when the cortisol hormone is low. The pain is often sudden, waking the patient from sleep or may develop gradually over several hours before the onset of symptoms, with maximum pain intensity within 24 hours. Acute attacks often begin to subside after 5 to 12 days without intervention,

but full resolution may take longer in some patients. Serum uric acid may be normal during an acute gout attack, while inflammatory blood parameters may be elevated (Fenando et al., n.d.), (Weaver et al., 2021)

- *Intercortical period*
  After the acute attack is resolved, the patient is in the intercortical stage or remission stage. This period is characterized by the absence of symptoms. It may be abruptly interrupted by a more recent attack if appropriate treatment for hyperuricemia has not been undertaken. This remission stage may extend after the first attack. However, without proper treatment, attacks become more frequent and severe. These are clinically inactive disease phases between 2 flares. During these periods, gout patients also have hyperuricemia, which can lead to increased deposition of urate crystals in tissues (Engel, Just, Bleckwenn, & Weckbecker, 2017), (Ragab et al., 2017)
- *Chronic tophaceous gout*
  Untreated disease progresses to joint destruction with palpable tofi formation. Tophus are masses formed from many accumulated crystals. This occurs in chronic untreated gout. Tophi are non-soft soft tissue masses found in the subcutaneous soft tissues, intra-articular or periarticular soft tissues, tendons, ligaments, retinacula, and bursa, resulting from a chronic granulomatous reaction to MSU crystals. They have a fibrovascular matrix with MSU crystal centers surrounded by granulation tissue. Tophaceous gout often occurs on the hands and wrists as well as along the extensor surfaces of the knees and elbows and may eventually lead to bone erosion. Tophi tend to occur in areas subjected to mechanical stress, such as adjacent to the first MTP joint, Achilles and patellar tendons, and olecranon and prepatellar bursae. cruciate ligaments, peroneal tendons, popliteus tendons, and infrapatellar fat pads are common sites of MSU deposition. Tophi can also occur on the earlobe appendages and tip of the nose. This results in cosmetic abnormalities and may cause impaired joint mobility (Weaver et al., 2021)

Diagnosis

One-third of patients with acute gout have normal uric acid levels. A normal serum uric acid level in cases of acute arthritis does not rule out gouty arthritis. High uric acid levels increase the likelihood of gouty arthritis, but do not confirm the diagnosis (Weaver et al., 2021)

As recommended by all included reports, confirmation of MSU crystals in synovial fluid or tophi microscopically detected in negative birefringent and needle-shaped obtained has become the gold standard for definitive diagnosis.

Evaluation of clinical signs, laboratory results, and imaging results is generally required for the diagnosis of gout when MSU crystals have not been detected in gout attacks (Cha et al., 2024), (Galozzi et al., 2021), (Li et al., 2022), (Ragab et al., 2017). The serum uric acid level required for the diagnosis of hyperuricemia varies among studies. In general, cut-off levels of 6.8 to 7.0 mg/dL of serum uric acid have been reported. When suggesting standards according to gender, 6.0 mg/dL (or ~360 μmol/L)

for women and 7.0 mg/dL (or ~420 μmol/L) for men are recommended (Fenando et al., n.d.). During an acute gout relapse, serum urate levels may be high, normal, or low. Clinicians should repeat serum urate levels in patients with an uncertain diagnosis of gout after a relapse. Hyperuricemia is helpful in the clinical diagnosis of gout in symptomatic patients, but hyperuricemia alone cannot definitively confirm the diagnosis. The most accurate time to assess serum urate levels to determine baseline values is two weeks or more after the gout attack has completely subsided (Fenando et al., n.d.)

Typical radiologic features of an established diagnosis of gout include bony erosions with prominent edges and sclerotic margins, bony hyperplasia, joint space narrowing, and soft tissue masses (tophis) that may be calcified

Musculoskeletal ultrasonography can aid the diagnosis of gout, especially in cases of atypical symptoms and when obtaining microscopic evidence of MSU crystals is not possible. In the results of a systematic review, ultrasound findings of double contour signs, tophi, punctate deposits on the synovial membrane, and hyperechoic spots in the synovial fluid showed good specificity ranging from 0.65 to 1.00 for the diagnosis of gout, using the identification of MSU crystals as the reference standard (Cha et al., 2024)

Dual energy CT (DECT) can reveal small deposits of uric acid crystals but should only be considered if the findings for differential diagnosis are unclear, as it involves radiation exposure, is expensive, and has low overall sensitivity (Cha et al., 2024)

Management

The main goal of an acute gout attack is to relieve pain quickly and safely. Although a gout attack may resolve if left untreated within a few days or weeks, the symptoms may resolve more quickly with the use of various medications. The long-term goal is to lower serum urate levels to achieve suppression of recurrence and regression of tophi (Fenando et al., n.d.), (Weaver et al., 2021)

Lifestyle Modifications

Gouty arthritis has been referred to as "arthritis of the rich" due to its association with rich foods and excessive alcohol consumption. Lifestyle modifications alone have little effect in lowering uric acid. Obesity is the most common comorbidity risk with gout. Therefore, lifestyle and dietary modifications are key components in the management of gout. Many epidemiologic studies have shown an association between gouty arthritis and various foods and beverages, including beer, meat, seafood, and fructose, while a high intake of low-fat foods, coffee, and ascorbate is thought to be protective. Vitamin C supplementation is reported to reduce serum urate concentrations (Fang & Waizy, 2013)

Dietary recommendations include reducing alcohol consumption, limiting purine-rich foods (meat, seafood, high fructose corn syrup, and sugary soft drinks), and replacing low-fat or non-fat dairy products with dairy products that are higher in fat content. Weight loss and adequate hydration will also help reduce the frequency of gout attacks (Fenando et al., n.d.)

Acute Gout Flare

Management of acute flares aims to reduce the inflammation and pain they cause. Clinicians should initiate treatment within the first 24 hours after the onset of the disease to reduce the severity and duration of recurrence. Non-pharmacological management such as rest with topical ice packs can be combined with medications that reduce inflammation. First-line treatments for gout attacks are (nonsteroidal anti-inflammatory drugs) NSAIDs, colchicine, or systemic glucocorticoids. The duration of treatment should be at least 7 to 10 days to prevent recurrence of the disease (Cha et al., 2024), (Fenando et al., n.d.)

- NSAIDs

  NSAIDs are most effective when therapy is started within 48 hours of the onset of gout symptoms. Strong oral NSAIDs, such as indomethacin (50 mg three times daily) or naproxen (500 mg twice daily), are given. Other NSAIDs include meloxicam (15 mg daily), ibuprofen (800 mg three times daily), diclofenac (50 mg two to three times daily, and celecoxib (200 mg twice daily). Usually NSAID treatment for gout attacks lasts for five to seven days. There is no data to favor one NSAID over another. High-dose, fast-acting NSAIDs such as naproxen or diclofenac are preferred, and indomethacin is not preferred due to its toxicity profile. NSAIDs are usually given in full doses for the first three days and then gradually reduced according to progression. COX2 selective inhibitors such as celecoxib may be given to prevent GI side effects (Fenando et al., n.d.)

  Contraindications to the use of NSAIDs include active duodenal or gastric ulcers, cardiovascular disease (uncontrolled hypertension or heart failure), NSAID allergy, and chronic kidney disease with creatinine clearance (CrCl) less than 60 ml/min per 1.73 square meters (Fenando et al., n.d.)

- Glucocorticoids

  Oral glucocorticoids are often used in patients with typical gout attacks who can take oral medications but have contraindications to the use of nonsteroidal anti-inflammatory drugs (NSAIDs). A common regimen is prednisone which is started at 30-40 mg per day, once daily or given in divided doses twice daily until resolution of the flare begins. This is then reduced over 7-10 days; however, the duration of reduction may be required up to 21 days. Glucocorticoids have similar (or even better) efficacy and have no greater risk of side effects compared to other drugs used to treat acute gout (Weaver et al., 2021)

  The 2016 European Society of Rheumatology guidelines recommend the administration of prednisolone and glucocorticoids 30-35 mg in equal doses for 3-5 days as the primary treatment of gout attacks). [yonghan,] it has been shown to be at least comparable to the efficacy of NSAIDs. High initial doses of systemic steroids (>0.5mg/kg body weight) are required for acute gout, especially in patients with polyarticular presentation. depot preparations of triamcinolone (60mg once) or methylprednisolone have been reported to be effective (Fenando et al., n.d.)

- Colchicine
  Colchicine relieves joint pain and inflammation during a gout attack. Immediately after a gout attack, 1.2 mg of colchicine should be taken, followed by 0.6 mg 1 hour later, then 0.6 mg 12 hours later, which is the preventive dose of gout and can be repeated 1-2 times a day. Common side effects are diarrhea and abdominal cramps, especially in high-dose therapy (Cha et al., 2024)
  For substantial clinical improvement, oral administration of colchicine especially when started within the first 24 hours of an acute gout attack, is very beneficial as it reduces the frequency of gastrointestinal side effects, which can sometimes be severe. Colchicine may have a very narrow therapeutic window compared to other drugs used to treat acute attacks of gouty arthritis (Parisa et al., 2023)
- Interleukin 1 Inhibition
  While IL-1 inhibitors may be beneficial for certain patients experiencing acute gout attacks, they are usually reserved for patients who have failed other treatments or who have contraindications to them. Anakinra (100 mg daily) is the IL-1 inhibitor treatment of choice for acute gout due to its short half-life and relatively low cost compared to other IL inhibitors (Weaver et al., 2021)

Non-acute Flares

Physicians should not initiate urate-lowering therapy (ULT) in patients with asymptomatic hyperuricemia or gout with infrequent attacks (1 flare/year). American College of Rheumatology (ACR) 2012, Guidelines for starting ULT include the following: (1) Frequent or disabling gout flares (greater than or equal to two per year) that are difficult to treat, (2) gout with chronic kidney disease (stage 3 or higher), (3) tophus diagnosis on physical examination or imaging, (4) past urolithiasis, (5) chronic tophaceous gout (Fenando et al., n.d.), (Weaver et al., 2021)

Urate-lowering therapy is initiated with low doses to monitor side effects and response to treatment. Dose titration is done every 2 to 6 weeks to achieve serum urate levels of less than 6 mg/dl or 5 mg/dl in patients with tophi. During ULT administration, there is an increased risk of gout attacks, so low-dose recommended colchicine prophylaxis is the first choice. This is started 1 or 2 weeks before the use of urate-lowering drugs and continued for up to 6 months after normalization of uric acid levels or until clinically apparent tophi are resolved. Low-dose NSAIDs and low-dose corticosteroids are rarely used. The recommended dose of colchicine is 0.5mg once or twice daily in the absence of renal or hepatobiliary impairment. ULT can categorize into three classes (Fenando et al., n.d.):

Xanthine oxidase inhibitors (XOI)

Xanthine oxidase inhibitors (XOI). work by inhibiting the synthesis of uric acid. This class includes allopurinol and febuxostat. Allopurinol is the recommended first-line pharmacologic ULT in gout disease

- Allopurinol
  Allopurinol is an oral xanthine oxidase inhibitor, first introduced to the clinic in the sixties. Allopurinol is a purine, which is rapidly converted to its active metabolite, oxprenolol, by the enzyme xanthine oxidase. The accumulation of xanthine is rarely reported to cause urinary xanthine stones which can be prevented completely by adequate fluid intake. Since oxprenolol has a long half-life, allopurinol can be prescribed once daily. Worldwide, allopurinol is prescribed at a dose of 300 mg/day or less in more than 90-95% of gout patients. At a daily dose of 300 mg, allopurinol is used to reduce uricemia to less than 6 mg/dL (Ragab et al., 2017)
- Febuxostat
  Febuxostat is an alternative xanthine oxidase inhibitor that can also be used for the treatment of hyperuricemia. Daily doses (40 mg or 80 mg) produce reductions equivalent to or better than those seen in patients treated with allopurinol 300 mg once daily. jeniffer It can be given safely in patients with renal insufficiency, but the cost of treatment tends to be higher than allopurinol (Weaver et al., 2021)
  Potential side effects include transaminitis, nausea, arthralgia, and rash. Of particular concern is that febuxostat, compared to allopurinol, is associated with a higher risk of cardiovascular death and all-cause mortality. The drug currently comes with a boxed warning for increased risk of death. In CKD patients, the uric acid-lowering effect of febuxostat is superior to that of allopurinol. Patients taking azathioprine, 6-MP, and theophylline are considered contraindications to the use of febuxostat (Cha et al., 2024), (Fenando et al., n.d.), (Weaver et al., 2021)

Uricosuric Drugs

Uricosuric agents work by enhancing renal urate clearance. Patients with low or normal urinary uric acid excretion accompanied by hyperuricemia are potential candidates for uricosuric therapy. These agents are not effective as monotherapy in patients with low creatinine clearance (less than 30 ml/min) and are contraindicated in patients with a history of nephrolithiasis

Probenecid is the only agent approved for use as monotherapy. Probenecid is started at a dose of 250 mg twice daily, and dose increases are titrated according to the level of serum urate concentration. The dose is usually increased every few weeks to a usual maintenance dose of 500 to 1000 mg (taken 2 to 3 three times daily), with a target urate level goal of <6 mg/dL (<357 micromol/L). The main side effects of uricosuric drugs are the onset of gout attacks, uric acid urolithiasis, gastrointestinal intolerance, and rash

Uricase Pegloticase (urate oxidase)

Uricase is present in non-primates and lower primates. Pegloticase (a pegylated recombinant form of uricase) is a potent agent that rapidly reduces serum urate levels. It directly degrades uric acid to highly soluble allantoin. Uricase is only reserved for patients with intractable gout. Patients should discontinue urate-lowering therapy when starting this medication as they may develop antibodies to uricase. Pegloticase is given as an

intravenous infusion every two weeks, and before each infusion, serum urate levels should be monitored to ensure urate-lowering efficacy. For at least the first six months of treatment, all patients treated with pegloticase should receive gout attack prophylaxis

Conclusion

The management of gouty arthritis is complex as it needs to consider side effects, drug interactions, comorbidities and contraindications. A major barrier to successful management is the need to weigh the risks and benefits associated with various gouty arthritis therapies. Additional new drugs such as IL-1 inhibitors have been developed to improve the management of resistant gout. A thorough understanding of the pathology, diagnosis and various treatment modalities is essential for individualization of an optimal management regimen.

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