Clinical features of gout

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SUMMARY

Gout is a metabolic disease characterized by hyperuricemia and the deposition of monosodium urate (MSU) crystals in the joints and soft tissues, consisting of a self-limited acute phase characterized by recurrent attacks of synovitis and a chronic phase in which inflammatory and structural changes of the joints and periarticular tissues may lead to persistent symptoms. Acute gout is characterized by a sudden monoarthritis of rapid onset, with intense pain, mostly affecting the big toe (50% of initial attacks), the foot, ankle, midtarsal, knee, wrist, finger, and elbow. Acute flares also occur in periarticular structures, including bursae and tendons. The presence of characteristic MSU crystals in the joint fluid, appearing needle-like and showing strong negative birefringence by polarized microscopy, is pivotal to confirm the diagnosis of gout. The time interval separating the first attack from subsequent episodes of acute synovitis may be widely variable, ranging from a few days to several years. During the period between acute attacks the patient is asymptomatic even if MSU deposition may continue to increase silently. The factors that control the rate, location, and degree of ongoing deposition in gouty patients are not well defined. Chronic gout is the natural evolution of untreated hyperuricemia in patients with gouty attacks followed by pain-free intercritical periods. It is characterized by the deposition of solid MSU crystal aggregates in a variety of tissues including joints, bursae and tendons. Tophi can occur in a variety of locations including the helix of the ear, olecranon bursa, and over the interphalangeal joints. Their development is usually related with both the degree and the duration of hyperuricemia. About 20% of patients with gout have urinary tract stones and can develop an interstitial urate nephropathy. There is a strong association between hyperuricaemia and the metabolic syndrome (the constellation of insulin resistance, hypertension, obesity and dyslipidaemia), and gouty patients often have a medical history of kidney disease, diabetes mellitus and signs of vascular illness such as coronary artery disease, heart failure and stroke, resulting with a poor overall quality of life.

Key words: *gout, clinical feature, hyperuricemia, inflammation, MSU crystals, differential diagnosis.*

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INTRODUCTION

Gout is a metabolic disease characterized by hyperuricemia and the deposition of monosodium urate (MSU) crystals in the joints and soft tissues. The clinical picture consists of a self-limited acute phase characterized by recurrent attacks of synovitis and then a chronic phase in which inflammatory and structural changes of the joints and periarticular tissues may lead to persistent symptoms.

Although episodes of acute gout rarely extend beyond one week, they are usually associated with various degrees of functional impairment. In the chronic phase the episodes of synovitis increases in number and extends to several joints, being associated with shorter intercritical periods, persistent joint pain and swelling, tophi development, and increasing comorbidity.

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Inflammation can occur in any tissue in which MSU is deposited, as established by tophy and by urate nephropathy due to renal medullary deposition of MSU crystals. Hyperuricemia is the main factor that facilitates the formation of MSU crystals, although other factors, such as local temperature and trauma, may also play a role. Once formed, crystals are capable of raising an inflammatory response from leukocytes and synovial cells to trigger the release of cytokines that amplify the local inflammatory reaction.

ACUTE GOUT

Acute gout is usually characterized by episodic, self-limited inflammatory arthritis. Typically, gout produces an acute monoarthritis of rapid onset (approximately 80%

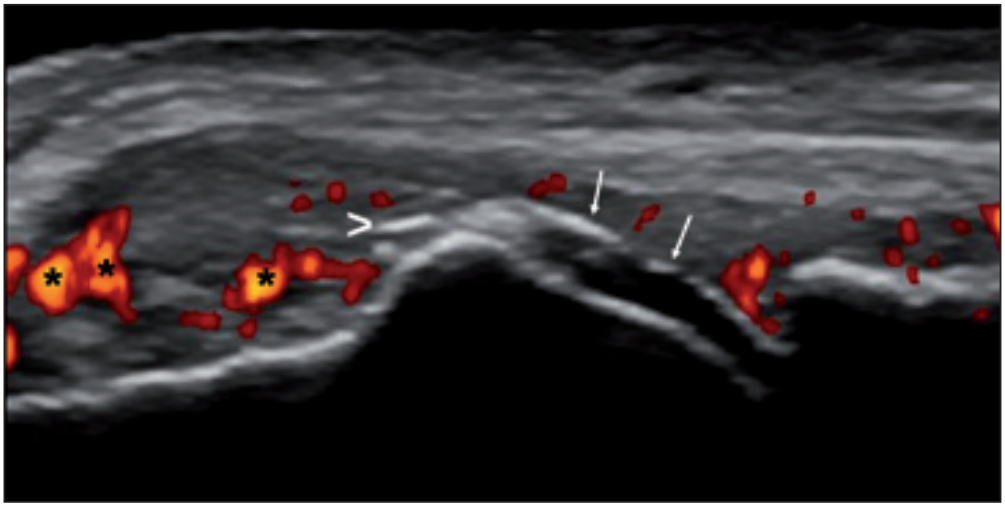

Figure 1 - Acute gout involving the first metatarsophalangeal joint. The key elements are represented by intraarticular power Doppler signal (*) indicating an intense inflammation and by hyperechoic aggregates of monosodium urate crystals (>) inside the synovial fluid and around the outer margin of the cartilage surface of the metatarsal head (⇓) generating a double contour sign.

of initial attacks), often waking patients from sleep, reaching a peak within 24 to 48 hours. The pain is intense, and patients often cannot wear socks or touch bedsheets during flare-ups. The marked exacerbation of pain even at the simple touch of the affected limb significantly interferes with the common activities of daily living (Figure 1). The most commonly affected joints, in addition to the big toe (50% of initial attacks), are foot, ankle, midtarsal, knee, wrist, finger, and elbow. Acute flares also occur in periarticular structures, including bursae and tendons. The olecranon bursa, the tendons around the ankle, and the bursae around the knee are among the locations where acute attacks can take place.

The classic symptom of gout affecting the big toe, also known as podagra, has been recognized since antiquity. The most powerful witness to the drama of the pain of gout comes from the ancient Sophocles' Philoctetes. Sophocles, in describing the terrible evil that afflicts the foot of Philoctetes must have been inspired by acute gout attacks (1). Clinical features supporting this diagnosis are the quick increase of the pain (Neoptolemus: What is it? So suddenly coming upon you … These terrible cries … It tortures you … Philoctetes: Torture … I cannot tell you … O for pity!), the self-limiting course of the attacks (The demon comes from time to time after letting me alone for a little while), the characteristics of the pain (Curse you, foot; must you torment me so! There it again … now! … O the agony!), the unbearable level of suffering (Oh! Oh! It goes right through me like a knife. I'm done for, boy … it's come for me now … (racked with agony) Pfff! Your sword, if you have it … For God's sake, boy. Cut off my foot! Off with it! Quick! O son! O son! O let me die!).

However, the most impressive and realistic description of symptoms of an acute attack of gout which still retains a special charm is that of Thomas Sydenham in his "Tractatus de gout et hydrope" published in 1683. Sydenham, besides being an excellent physician, was himself a victim of gout and it is not surprising therefore that the way in which he analyzes the various facets of the disease hits us so much compared to the descriptions, not less complete, but certainly not as detailed than those of the great English physician. This is his memorable description of acute gout:

The patient goes to bed, and fleeps quietly, till about two in the morning, when he is awakened by a pain, which usually seizes

the great toe, but sometimes the heel, the calf of the leg, or the ankle. The pain resembles that of a dislocated bone, and is attended with a sensation, as if water just warm were poured upon the membranes of the part affected; and these symptoms are immediately succeeded by a chillness, shivering, and a slight fever. The chillness and shivering abate in proportion as the pain increases, which is mild in the beginning, but grows gradually more violent every hour, and comes to its height towards evening, adapting itself to the numerous bones of the tarsus and metatarsus, the ligaments whereof it affects; sometimes resembling a tension or laceration of those ligaments, sometimes the gnawing of a dog, and sometimes a weight and coarctation, or contraction, of the membranes of the parts affected, which become so exquisitely painful, as not to endure the weight of the cloaths, nor the shaking of the room from a person's walking briskly therein. And hence the night is not only passed in pain, but likewise with a restless removal of the part affected from one place to another, and a continual change of its posture. Nor does the perpetual restlessness of the whole body, which always accompanies the fit, and especially in the beginning, fall short of the agitation and pain of the gouty limb".

The affected joints show features of all the expressions of intense inflammation becoming red, shiny and tender in a few hours after the first appearance of symptoms. An intense inflammation of periarticular soft tissue is common especially when the acute attack is localized at the ankle, olecranon or olecranon bursa. The intensity and extent of inflammation may be so relevant as to lead to suspicion of an infective cellulitis or septic arthritis (2). An extensive exfoliation of the skin overlying the affected joint is frequent as the inflammatory process begins to regress. Concurrent systemic features are usually mild or absent. However, fever and systemic symptoms can occur in some patients.

Without specific treatment gout usually resolves within 7-10 days. After the initial acute attack patients may be clear of symptoms for months or years, but some go on to have more frequent attacks that tends to last longer, involving more joints and/or tendons thus developing eventual chronic tophaceaous gout or permanent joint damage, or both. A second attack may develop after a time interval usually ranging between 6 months to 2 years. The frequency of attacks increases in untreated patients. Subsequent acute attacks may occur more frequently and usually tend to persist longer and to involve more joints.

Common factors triggering for acute gout are acute illness, infections, contrast media injections, acidosis, and rapid raise and fall in serum uric acid concentrations as can happen with trauma, surgery, psoriasis flare-ups, chemotherapy, and stopping or starting allopurinol or febuxostat (2).

Women are almost a decade older at the onset of gout arthritis, have more associated comorbidities such as hypertension and renal insufficiency, and use less alcohol. The typical location in the first toe is less frequent, and women are more likely to take diuretics (3). Diuretics therapy is one of the most frequent precipitating factor for an acute gouty attacks in the elderly.

Gouty arthritis can be polyarticular and more indolent in the elderly. The coexistence in the same joints with osteoarthritis is not rare. Polyarticular attacks are usually more frequent in patients with established and poorly controlled gout.

The presence of characteristic MSU crystals in the joint fluid play a key role to confirm the diagnosis of gout. MSU crystals typically appearing needle-like and showing strong negative birefringence by polarized microscopy are likely to be positive in an acute gout attack, but their identification varies according to the skill of the observer (positive LR 567; 95% CI 35.5-9053). The presence of hyperuricemia may also be a useful diagnostic finding when compared with the normal range of the local healthy population (positive LR 9.7, 95% CI 7.5-12.7) (4). Although serum uric acid levels are the most important risk factor for gout, they neither confirm nor exclude it. Many people with hyperuricemia do not have gout; conversely, during acute attacks of gout, serum uric acid levels may be normal.

In patients with gout, fluid collections can show ultrasound features ranging from homogeneous anechogenicity of the synovial fluid (early phase of the disease) to MSU crystal aggregates of variable echogenicity (after multiple acute attacks).
Sometimes, gout can be difficult to distinguish clinically from pseudogout. However, based on expert opinion, an analysis of synovial fluid for crystals should also include an assessment for calcium pyrophosphate dihydrate (CPPD) crystals, the presence of which helps to confirm the diagnosis of pseudogout. CPPD crystals are polymorphic and often intracellular. They can also be small showing only weak positive birefringence, so it is suggested that the detection of crystals may be carried out in 2 phases (5). Common light microscopy should be used first to distinguish crystal morphology (e.g., needle-like MSU crystals against polymorphic CPPD crystals). Once crystals have been detected, uncompensated polarized light can be used to distinguish birefringence (e.g., the strong negative birefringence of MSU crystals against the weakly positive birefringent of CPPD crystals) (5). When crystals are strongly suspected but are not seen in a sample of synovial fluid, the detection rate may be improved by centrifugation and a repeat search for crystals in the pellet (5).

INTERCRITICAL GOUT

The time interval separating the acute attacks may be widely variable, ranging from a few days to several years. During the period between acute attacks the patient is asymptomatic even if MSU deposition may continue to increase silently. The factors that control the rate, location, and degree of ongoing deposition in a particular patient are not well defined. Crystals may still be found in the synovial fluid of previously involved joints until the serum urate level is reduced for a significant period to a level less than 6.8 mg/dl. Any systemic factor that increases the risk of hyperuricemia may together increase the risk of symptomatic gout, even if patients with hyperuricemia not necessarily may have a gouty attack. Modifiable risk factors include a high-purine diet, alcohol use, obesity, and diuretic therapy. Some data show an increased risk of gout with consumption of red meat and seafood but show a potentially protective effect with consumption of dairy products. Among men with gout, the type of alcohol consumed may be important. Whereas both beer consumption and alcohol consumption appear to be associated independently with the risk of gout, wine does not (6).
Incomplete resolution of the attacks indicates the evolution to the chronic phase of the disease.

CHRONIC TOPHACEOUS GOUT

Chronic gout is the natural evolution of untreated hyperuricemia in patients with gouty attacks followed by pain-free intercritical periods. It is characterized by the deposition of solid MSU crystal aggregates in a variety of locations including joints, bursae and tendons. Tophi are deposits of MSU crystal aggregates in different tissues. They can occur in a variety of locations including the helix of the ear, olecranon bur-

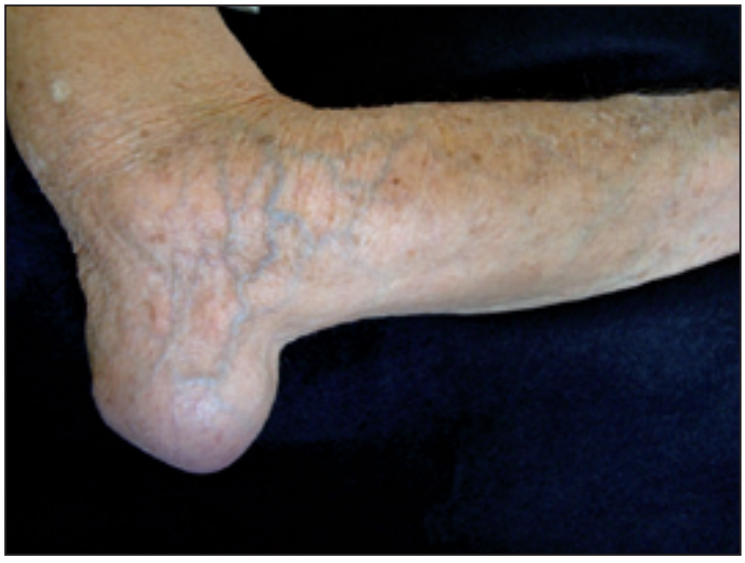

Figure 2 - Chronic gout. Giant tophus inside the olecranon bursa.

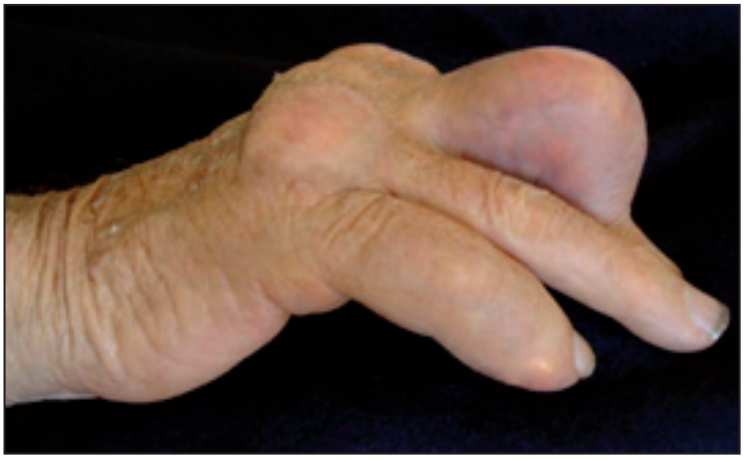

Figure 3 - Chronic gout. Extensive tophaceous deposits with relevant functional impairment but no spontaneous pain.

sa (Figure 2), and over the interphalangeal joints (Figure 3). Their development is usually related with both the degree and the duration of hyperuricemia. Long duration of active untreated disease, frequent attacks, upper extremity involvement, and polyarticular diseases are also associated with more aggressive tophaceous gout. Tophi tipically progress insidiously but the rate of their formation can be much faster in patients treated with diuretics or with severe renal disease. Tophaceous gout may lead to significant morbidity and, if untreated, can cause a prominent joint damage and marked functional impairment. At times, polyarticular tophaceous gout presents as subcutaneous nodules that can mimic rheumatoid arthritis (2). Tophi generally develop after an average of 11.6 years of gouty arthritis before uric acid lowering therapy became available. They were reported to occur in 12% of patients after 5 years, and 55% after 20 years of untreated disease (7). Tophi can also develop without a concomitant arthritis. Some authors used the term 'gout nodulosis' to describe the subcutaneous deposits of MSU in the absence of initial manifestation of gouty arthritis (8). Tophi may also develop over osteoarthritic Heberden's (Figure 4) or Bouchard's nodes in the distal and proximal interphalangeal joints, especially in older women often treated with diuretics (9). Biopsy of a tophus reveals a chronic granulomatous inflammatory response around the crystals. However, the tophi are not inert; the uric acid can be mobilized by mass action effect if the urate in surrounding fluids is reduced. If tophi are adjacent to bone, erosion into bone may occur (10). As a rule, intradermal tophi are asymptomatic and frequently not recognized, even though they are rare in severe untreated gout. Such tophi may be particularly common in transplant patients and appear as white or yellowish deposits which brings up with the overlying skin taut (10). Ultrasonography can be helpful to demonstrate even minimal MSU crystal aggregates in otherwise asymptomatic patients (Figure 5).

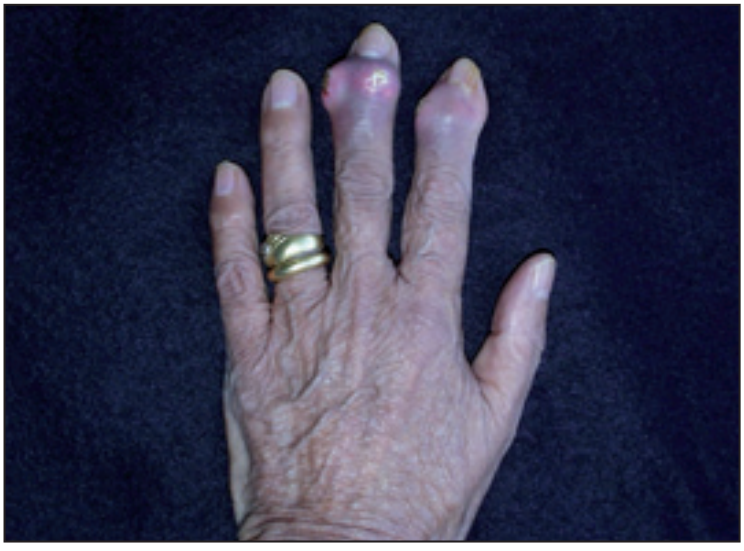

Figure 4 - Chronic gout. Ulcerated tophi localized at the interphalangeal joints in a woman with coexistent Heberden's nodes.

OTHER MANIFESTATIONS

Gout rarely involves the axial joints and the literature on axial gout is limited to case reports and case series. Radiologic changes of axial gout were more common than recognized clinically, with a frequency of 14% (11). Since not all patients had CT images, it is possible that the frequency of axial involvement is even greater. Axial gout may include vertebral erosions mainly

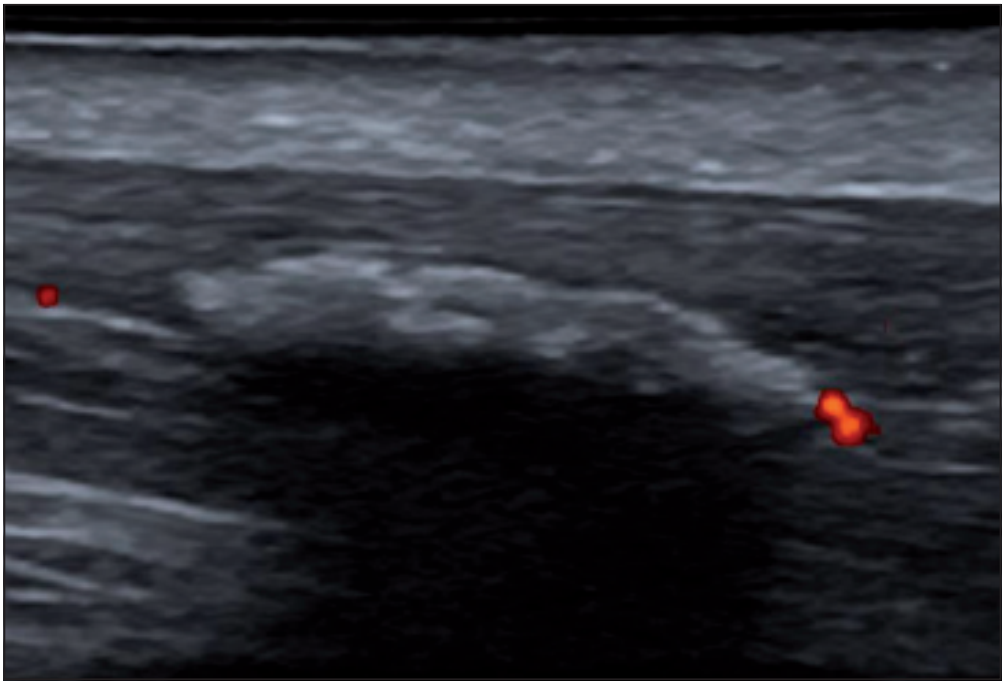

Figure 5 - Chronic gout. Large tophus generating a posterior acoustic shadow inside the Achilles tendon. The circumscribed power Doppler signal indicates the presence of localized inflammation.

at the discovertebral junction and the facet joints, deposits of tophi, and erosions in the vertebral body, epidural space, ligamentum flavum and pars interarticularis (11, 12). Temporomandibular joint involvement is uncommon, with only 10 reports in the English-language literature (13).

Gouty panniculitis is an unusual clinical manifestation, characterized by the deposition of MSU in the lobular hypodermis. Clinically, it is represented of indurate subcutaneous plaques, which may precede or appear subsequently to the articular clinical expression of tophaceous gout (14). Smoking and high alcohol intake are relevant risk factors and, on physical examination, patients exhibit the presence of erythematous, irregular surface, deep indurate subcutaneous plaques. Patients with gouty panniculitis generally show high levels of serum uric acid and are non-complant to treatment with allopurinol, NSAIDs, and colchicine. Gouty panniculitis should be considered in the differential diagnosis of panniculitis, especially in the presence of high levels of uric acid (14).

About 20% of patients with gout have urinary tract stones and can develop an interstitial urate nephropathy. Patients with gout typically present acidic urine secondary to a defect in the renal production of ammonia, which may be due to the tubular damage from MSU deposition (15). Moreover, gouty patients have a higher risk for uric acid stone formation because of the low urine pH, which promotes uric acid precipitation. Gout may also increase the risk for calcium oxalate stone formation, the most common type of kidney stones (15).

Chronic urate nephropathy is seen in patients with chronic hyperuricemia with or without clinical gout (16). In patients with symptomatic gout chronic interstitial nephritis, pyelonephritis and/or stone formation and glomerulosclerosis are often present, but the incidence of "classic" gouty nephritis appears diminished due to use of efficacious drugs to treat hyperuricemia. Use of antineoplastic drugs and radiation therapy for lymphoproliferative tumors is now increasing and may cause urate nephropathy (16).

Gouty patients have an increased cardiovascular risk. There is a strong association between hyperuricaemia and the metabolic syndrome (the constellation of insulin resistance, hypertension, obesity and dyslipidaemia), potentially explained by dietary and lifestyle changes (17). This is deeply demonstrated by the typical gouty patient being an obese, middle-aged man with a hedonistic lifestyle and a medical history of hypertension, kidney disease, diabetes mellitus and signs of vascular illness such as coronary artery disease, heart failure and stroke. A high number of patients with a first episode of gout had a statistically higher prevalence of one or more signs of cardiovascular disease (35 vs 26%) compared with healthy controls.

Established data revealed a statistically higher prevalence of hypertension (39 vs 14%), hypercholesterolaemia (8 vs 4%), diabetes mellitus (5 vs 1%) and obesity (52 vs 27%) among the gouty patients (18). Several large epidemiological studies have found that serum urate level predicts the development of hypertension. One of the most recent showed that the serum urate level independently predicts the occurrence of hypertension when using age adjusted and multivariate models that include body mass index, abdominal girth, alcohol use, serum lipid levels, plasma glucose level, and smoking status (19). Gout associates with poor overall quality of life mainly resulting from related co-morbidity. Physical health-related quality of life, however, remains impaired after adjustment for co-morbidities (20).

DIFFERENTIAL DIAGNOSIS

Acute gout can imitate a number of other acute inflammatory monoarthritis including calcium pyrophosphate dehydrate deposition disease (pseudogout), septic arthritis, reactive arthritis, and other crystalline arthropathies.

Chronic tophaceous gout can be misdiagnosed as chronic pseudogout, rheumatoid arthritis, seronegative spondyloarthropathy, osteoarthritis and erosive osteoarthritis. Tophi can sometimes be mistaken for rheumatoid nodules.

Definitive diagnosis of gout usually rests on demonstration of MSU crystals in the joint fluid and/or inside a tophus. Ultrasound has revealed to play a useful role in differential diagnosis especially with respect to pseudogout as it may detect both MSU and calcium pyrophosphate crystals aggregates (21). Although the distinction between MSU and calcium pyrophosphate crystals remains a prerogative of the polarized light microscopy, the identification of ultrasound patterns defined by the topographic distribution of crystal deposits at hyaline cartilage level, showed to be accurate in distinguishing between MSU and calcium pyrophosphate crystal aggregates. MSU crystals deposit is typically localized on the outer hyaline cartilage margin generating a characteristic double contour aspect (Figure 1). Conversely, calcium pyrophosphate crystal aggregates are embedded within the cartilage layer. However, even in calcium pyrophosphate dehydrate deposition disease the presence of crystal deposition in the middle part of the cartilage may be linear and homogeneous thus generating a double contour (22).

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