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REVIEW ARTICLE

Relevant imaging elements for gout diagnosis and treatment

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ABSTRACT

Gout is an arthritis characterized by the deposition of sodium monoacid crystals in the synovial membrane, articular cartilage, and periarticular tissues that leads to an inflamatory process. In most cases, the diagnosis is established by clinical criteria and analysis of the synovial fluid for MSU crystals. However, gout may manifest in atypical ways and make diagnosis difficult. In these situations, imaging studies play a fundamental role in helping to confirm the diagnosis or even exclude other differential diagnoses. Conventional radiography is still the most commonly used method in the follow-up of these patients, but it is a very insensitive test, because it only detects late changes. In recent years, advances in imaging methods have emerged in relation to gout. Ultrasound has proven to be a highly accurate test in the diagnosis of gout, identifying MSU deposits in articular cartilage and periarticular tissues, and detecting and characterizing tophi, tendinopathies, and tophi enthesopathies. Computed tomography is an excellent exam for the detection of bone erosions and evaluation of spinal involvement. Dual-energy computed tomography, a new method that provides information on the chemical composition of tissues, allows identification of MSU deposits with high accuracy. MRI can be useful in the evaluation of deep tissues not accessible by ultrasound. In addition to diagnosis, with the emergence of drugs that aim to reduce the tophaceous burden, imaging examinations become a useful tool in the follow-up treatment of gout patients.

Keywords: Gout; Ultrasonography; Magnetic Resonance Imaging; Dual-energy Computed Tomography

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1. Introduction

Gout is an arthritis characterized by periods of hyperuricemia and deposition of sodium monourate crystals (MUS) in the articular cartilage, subchondral bone, synovial membrane, capsule, periarticular tissues, and areas of lower temperature (such as the superficial tissues of the extremities), leading to inflammatory reaction[1,2]. Genetic and dietary factors have been implicated in the increased amount of MUS[2]. It occurs in approximately 0.2–0.35 per 100 inhabitants in the general population. The incidence is highest in the late third and early fourth decade of life, predominantly in males and about 5% in females, usually after menopause[2,3]. The diagnosis is usually established by clinical and laboratory evaluation, the gold standard method is synovial fluid analysis, but because it is an invasive technique, therapy can be started with the diagnostic criteria of the American College of Rheumatology (ACR)[4].

The importance of accurate diagnosis and treatment of gout should

not be underestimated, as patients require lifelong therapy to reduce the morbidities associated with hyperuricemia. Because of the multiple differential diagnoses, as well as the atypical presentations of gout, imaging may be useful at various stages of the disease[5]. In the last decade, there have been important advances in imaging techniques that aid in the noninvasive diagnosis and follow-up of gout treatment. To the best of our knowledge, there is no recent review in the Brazilian literature on imaging aspects of gout. This review intends to summarize recent advances in the literature involving imaging studies, showing relevant aspects for physicians of all specialties as regards diagnosis and imaging follow-up, considering the increasing prevalence of this disease.

2. Methods

Search made in the main databases (Medline, Lilacs, Cochrane Library and PubMed), with the terms *gout*, *arthritis*, *tophaceus gout* and *urate*. We limited the search to original articles from the last five years, but included in the search were review articles and case reports with significant clinical relevance. More than 700 articles and abstracts published on the theme proposed in this review were identified. The selection was based on clinical importance and articles that did not show any relation with imaging diagnosis were excluded, resulting in 39 articles.

3. Discussion

There are four possible clinical stages in hyperuricemic patients: asymptomatic hyperuricemia, acute gouty arthritis, intercritical gout, and chronic tophaceous gout[1,2] (the sequence of such events is not mandatory and asymptomatic patients are not diagnosed with gout). At each of these stages, imaging studies can be used. The typical clinical picture of acute gouty arthritis includes painful acute mono-arthritis of the 1st metatarsal or knee, with local flogging and swelling associated with elevated uric acid levels. Hyperuricemia is one of the clinical criteria used in the diagnosis of gout, but although this is the predominant risk factor for gout, elevated serum uric acid levels do not always lead to crystal deposition[6]. Serum urate levels above 6.8 mg⁄dL can lead to precipitation and deposition of urate crystals in joints and soft tissues, but acute gout can occur even in patients with normal serum urate levels, and in these cases clinical diagnosis is more difficult and can be aided by imaging methods. Imaging may also be used in atypical presentations, such as in cases involving unusual ages or locations, with prolonged and less intense symptoms at the time of presentation[5,6].

The intercritical period is the period after an acute episode of gout crisis, in which the patient remains asymptomatic. Advances in imaging techniques have shown that tophaceous deposits can be detected in patients in the intercritical period where up to 50% of the joints have already been affected by acute episodes[5]. It has also been shown that asymptomatic patients have tophaceous deposits in the spine detected by computed tomography (CT)[7]. Knowing that even asymptomatic patients may already have tophaceous deposits that are often not detected clinically, the question arises whether it is important to evaluate early joint, bone and tendon damage, or even the tophaceous burden, by imaging examinations in the intercritical phase. Imaging assessment in this phase, to the best of our knowledge, is not yet recommended in the literature.

It takes several years for the tophi to become clinically apparent after the first attack, and it is rarely identified at the time of that first episode[1]. Chronic tophaceous gout is characterized clinically by the presence of tophi, secondary to the accumulation of uric acid, protein matrix, inflammatory cells, and foreign body giant cells in tendons, ligaments, cartilage, pouches, subcutaneous cellular tissue, and periarticular regions[5]. The tophi are most frequent on the extensor surfaces of the hands, elbows, feet, knees, auricular appendages, and the tip of the nose. Although chronic tophaceous gout usually has a simple clinical diagnosis, it can pose a challenge in some cases when associated with unusual symptoms or atypical disease. Atypical clinical manifestations are seen more frequently in certain segments of the population, including the elderly, patients who have undergone organ transplants, and those with tumors[6].

The toph nodes may also be non-typical and have differential diagnoses, such as ganglia,

cysts, bursitis, hematoma, amyloidosis, thrombophlebitis, sarcoidosis, psoriatic and pyrophosphate deposition arthritis, neoplasms, tenosynovitis, rheumatoid nodules, and osteoarthritis and infection[8,9]. Imaging may be useful at this stage to assess the severity of the disease, the extent of MSU deposition and the presence of chronic inflammation. In addition, it can be a useful tool to monitor the response to uric acid reduction therapy[10].

3.1 Follow-up and response to treatment

Several methods have been developed and evaluated by Outcomes Measures in Rheumatology (Omeract) to quantify tophi in patients with chronic tophaceous gout, from simpler methods by physical examination to more sophisticated means with imaging examinations. In patients with chronic tophaceous gout, quantification of tophi and documentation of regression with treatment are important monitoring measures, with the goal of preventing joint destruction. Patients with high uric acid levels do not necessarily have larger masses of tophi than patients with low uric acid levels[11,12].

Among the methods that use a physical examination are mainly tophi counting, measuring with a tape measure, using a specific instrument called a Vernier meter, and using digital photography[13]. Ultrasonography (US) is a good tool in the evaluation of response to treatment, since it is available and has good sensitivity. Computed tomography and magnetic resonance imaging, although less available, provide some advantages, such as the possibility of storing data for later reading and visualization of intra-articular tophi, even in the absence of subcutaneous tophi[14-16].

Dual-energy computed tomography (DTC) is a good tool for demonstrating MSU deposits even in asymptomatic patients. Although the quantification capability of tophi of this technique is a potentially useful tool for assessing small changes in tophus burden and the technique has a role in monitoring treatment response, due to the cost and, albeit low, radiation exposure, the main role in treatment monitoring is limited to clinical trials of new therapeutic agents rather than clinical practice[16].

3.2 Imaging methods

The most commonly used imaging methods for the evaluation of gout are plain radiography (X-ray), ultrasonography (US), dual-energy computed tomography (DTC), computed tomography (CT), and magnetic resonance imaging (MRI).

3.2.1 Plain radiography

Claude Boch *et al.*[2] classified radiological changes into early, intermediate and late. Radiographic changes are more frequent in the feet, especially in the first metatarsophalangeal joint[2,10]. In the early presentation of gout, there are no specific radiographic signs, only increased volume and soft tissue density. X-ray is unable to evaluate early soft tissue changes such as effusion, early erosions, synovial hypertrophy, hypervascularization, or small tophi, while MRI that shows these changes does not always allow the exact differentiation between gout and some of its differentials.

X-ray is a rapid method and usually the first used in the investigation of gout. It has low sensitivity for diagnosis, and there can be a delay of 6 to 12 years before radiological changes are presented[2]. In 2008, Rettenbacher *et al.* found a sensitivity of 31% to 55% and a specificity of 93% for X-Ray in the diagnosis of gout[17]. In chronic tophaceous gout the radiographic signs include the visualization of tophi as soft tissue or intraosseous masses, which may or may not have calcifications and the presence of a non-demineralizing arthropathy, with erosions that have margins that may be sclerotic or prominent. Martel's reaction (**Figure 1**) consists of a protruding bony border separated from and inclined over the tophum[18,19]. The joint space is usually preserved at X-ray[10]. According to Bloch[16], X-ray is a method of little use in treatment assessment, primarily because of its low sensitivity in detecting disease in early stages and because it is based on the presence of late findings, such as soft tissue enlargement, cortical erosions, and lytic lesions.

3.2.2 Ultrasonography

The high resolution of US allows the identification of the several forms of gout presentation and its relation with different tissues, beneficial to the early and non-invasive diagnosis, therapeutic decision and treatment control. Moreover, it is a very useful method to evaluate the extent and measure-

ment of lesions and involvement of adjacent structures, with low interobserver variability, and fulfills the necessary characteristics to evaluate the therapeutic response. For histopathological confirmation of gout, US is useful to guide a puncture or biopsy[19,20].

US detects early soft tissue changes in the gout and is primarily used when clinical and laboratory findings and radiographic studies are negative or inconclusive. Other advantages include noninvasiveness, repeatability, ability to differentiate solid from cystic lesions, low cost, patient contact, absence of ionizing radiation, high resolution multiplanar imaging, dynamic assessment of the joint and tendons, and effectiveness in guiding invasive procedures[9,19,21]. Some studies comparing the sensitivity and specificity of US with X-ray have shown that US is more sensitive and earlier than X-ray, because the ultrasound-graphic changes are present in stages before the typical X-ray signs[17,19,22].

One sonographic feature that is characteristic for the diagnosis of gout is the "double contour sign" (**Figure 1**), characterized by the presence of an irregular linear hyperechoic layer over the superficial margin of the anechoic hyaline cartilage parallel to the bone cortex, with no posterior acoustic shadowing. This sign was seen in 92% of the patients with biopsy-confirmed gout and in none of the controls in Thiele's 2007 study[19]. However, patients with asymptomatic hyperuricemia may present the double contour sign, observed in the study by Pineda *et al.* in 25% of the metacarpophalangeal joints[20]. Moreover, with the reduction of uric acid levels, this sign tends to disappear in up to seven months[22].

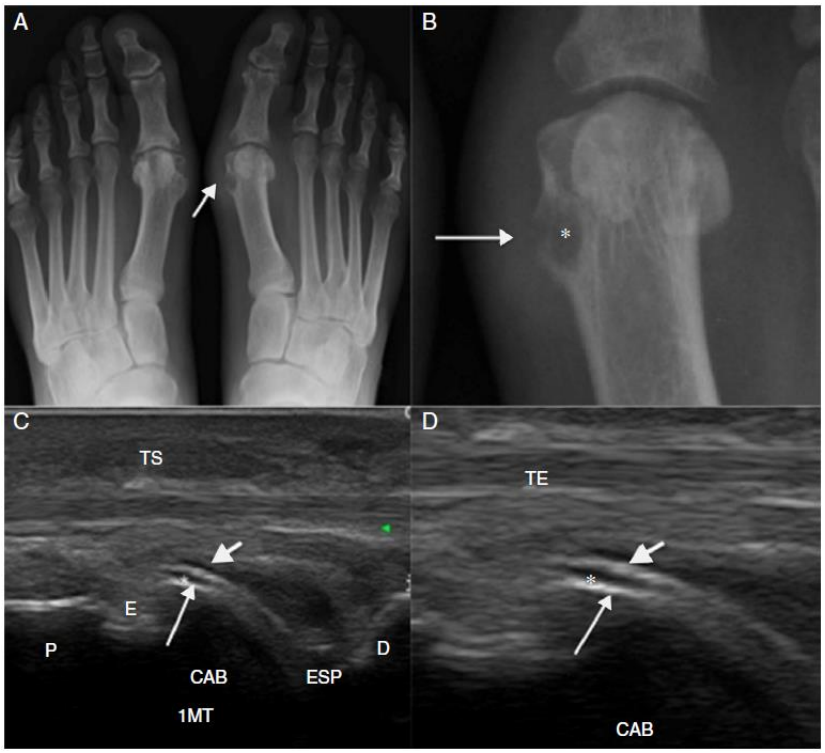

Figure 1. A: anteroposterior radiograph of the feet of a patient with gout showing increased volume and soft tissue density adjacent to the1[a] MTF joint (arrow). Bone erosion is also noted in the distal metaphysis of the 1st metatarsal; **B**: detail of the previous image showing the head of the 1st left metatarsal, evidence of bone erosion marked with an asterisk (*) with raised borders and Martel's reaction (arrow); **C**: ultrasound image with longitudinal section of the foot at the level of the 1st metatarsophalangeal joint of the 1st toe, showing the bony cortical bone of the 1st metatarsal head (larger arrow), the metatarsophalangeal joint space of the hallux (ESP), the cartilage of the 1st metatarsal head (*) and a thin hyperechoic layer covering the lining cartilage (smaller arrow), characterize the double contour sign; **D**: detail of the previous image showing the bone surface (arrow) of the 1st metatarsal head, the articular cartilage (*) and the thin hyperechoic layer (setamenor), characterizing the double contour sign (P–proximal, D–distal, TS–subcutaneous tissue, ESP–phalangeal hallux, TE–extensor hallucis tendon).

In 2008, Rettenbacher *et al.*[17] found a sensitivity and specificity of respectively 80% and 75% for hyperechoic bright foci in synovial tissues (microtophos) and 79% and 95% for hyperechoic areas in the diagnosis of gout. Considering the presence of any of the two findings, ultrasound had a sensi-

tivity of 96% and specificity of 73%. The specificity is not higher because hypoechoic punctiform foci, which may represent microtophosphates, can also be seen in cases of arthrosis, chondrocalcinosis, and rheumatoid atritis[23]. When hyperechoic bright foci are seen in combination with the double outline signal, the specificity reaches 100%, but with considerably reduced sensitivity[24].

In cases where imaging study is necessary, knowledge of the sonographic characteristics of the lump is important to differentiate lumps from nodules of other etiologies (**Figure 2**). US uses criteria that help in differentiating nodules caused by neoplasms, inflammatory and infectious processes. Nalbant[10], when comparing tophi nodules and rheumatoid nodules, demonstrated that 80% of tophi were heterogeneous, and of these 75% were hyperechoic, and only 15% heterogeneity and hyperechogenicity were observed in rheumatoid nodules. The rheumatoid nodule is more homogeneous and may have a well-defined, hypoechoic central area due to necrosis. Since rheumatoid nodules rarely calcify, this also helps differentiate them from tophi, which can calcify.

The presence of calcifications with posterior acoustic shadowing and irregularity of the cortical bone underlying the nodules also favors the diagnosis of tophi. There is no correlation between the time of disease and the presence of calcifications in the tophi. The tophi are hyperechoic in 96.3% of cases and hypoechoic in 3.7%[12]. The hyperechogenicity observed in the tophi represents either urate deposits or calcifications. Small hyperechoic particles or bright foci measuring less than 1 mm in size represent synovial microtophos[17]. The agglomeration of hyperechoic microtophils form the tophus, so hyperechogenicity and heterogeneity are strong indicators of tophus.

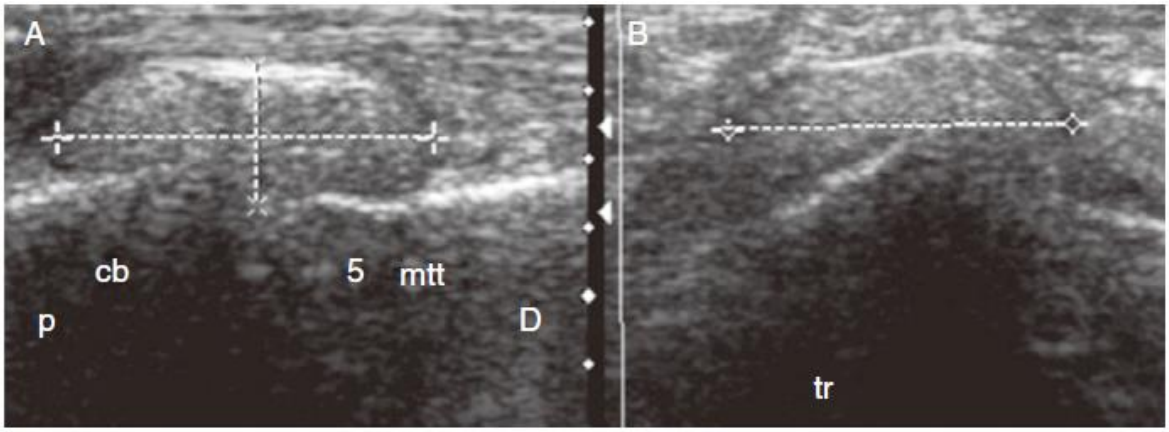

Figure 2. MTT (5th metatarsal).
Note: A and B: ultrasound image. Longitudinal (A) and cross-sectional (B): views of an amorphous, hyperechogenic nodule located in the soft tissues adjacent to the metatarsocuboid joint; structures deep within the nodule are defined by acoustic beam attenuation; R: proximal; D: distal.

The hypoechoic halo peripheral to the tophus is a hypoechoic band seen partially or completely around the tophus and may correspond to an inflammatory process, fibrosis, or edema. It is observed in most parts of the tophi and may be another marker of a tophaceous nodule[12].

The sonographic characteristics of the tophi in relation to tendons may help to explain the clinical presentations with motion restriction in patients with chronic tophaceous gout, and their knowledge may avoid invasive procedures such as biopsies. A classification of the relationship of the tophus to the tendon in chronic tophaceous gout into five types has been proposed[25] based on their location: tendon surrounded by tophi, no relationship between tophi and tendon, tophi at the tendon insertion site (enthesopathy), extrinsic compression, and tophi within the tendon.

Enthesopathy secondary to tophi is a recent finding in the literature and, although described in only 7% of cases of chronic tophaceous gout, should be kept in mind in the differential diagnoses, depending on the clinical context. The differential diagnosis of enthesopathies is broad and includes calcium pyrophosphate deposition disease, degenerative disease, acromegaly, hyperparathyroidism,

hypoparathyroidism and rheumatoid arthritis, among others. The intratendinous tophi tends to evolve to rupture of the tendon[26] and the early ultrasonographic diagnosis may help the doctor to institute an effective treatment, avoiding damages that, if not clinically treated, may evolve to surgical treatment. Within the tendon, tophi may have microdeposits demonstrated by bright, ovoid, hyperechoic spots. Chronic intratendinous tophi may appear as hyperechoic bands, occasionally with posterior acoustic shadowing[27].

US allows showing the changes in the inflammatory process of gout. Evaluation of gout by US with color Doppler shows increased flow in the acute phase of the gout crisis, which partially normalizes within seven days. Color Doppler usually shows no flow when out of gout crisis[10], but it has been observed in the author's clinical practice that painful periarticular areas in patients with known diagnosis of gout may present hyperechoic tophi and flow at Doppler, even without signs of classic crisis, which explains atypical clinical pictures of gout arthralgia, but this finding needs further studies to be used (**Figure 3**).

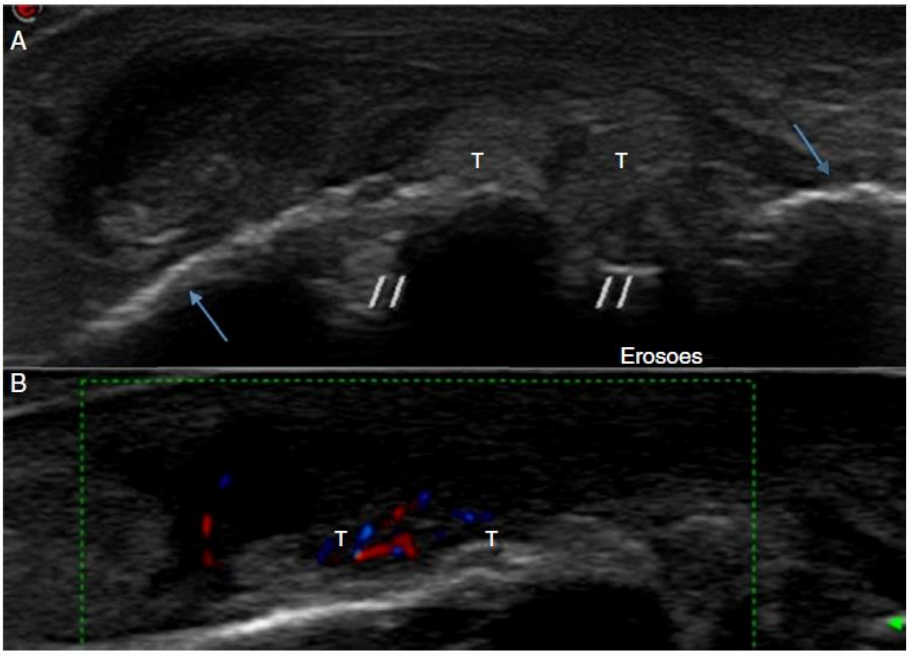

Figure 3. A: ultrasound image in the longitudinal plane at the 1st metacarpal bone. Patient with pain without evidence of gouty crisis. Note the presence of bone erosions (//) and tophi (T) next to the erosions; B: color Doppler study shows increased vascularization in the tophi. Cortical bone (arrows).

Bone erosions are defined as cortical discontinuities observed in two perpendicular planes. It is a late finding and has low sensitivity in the diagnosis of tophaceous gout, but they are slightly better detected by US than by radiographic study (24% versus 20% of cases)[17].

The dimensions of the gouty tophi assume importance in the evaluation of the response to treatment, therefore, to be useful in practice, the method used for this purpose must have good reproducibility. Perez-Ruiz *et al.* showed that US is able to detect all periarticular tophi identified by MRI[10,28]. Omeract, after these studies, considers US as a possible useful method in the measurement of gouty tophi, but clinical trials need to be conducted to validate the method.

3.2.3 Computed tomography (CT)

CT allows visualization of tophi in both subcutaneous and intra-articular cellular tissue. This method also helps to identify bone erosions and is more sensitive than X-ray and MRI for this purpose. A systematic review has shown that CT detects intraosseous tophi in 81% of eroded joints and in 100% of cases when the erosion is greater than 7.5 mm[29].

CT can also show MSU deposits inside the tophi, because it has an attenuation close to 160 HU, compared to calcium deposits, which have higher attenuation, around 450 HU[30], it can help in the differentiation with other types of soft tissue nod-

ules. It can be used as a complementary imaging method in the evaluation of damage to deep structures, when non-ionizing radiation examinations cannot confirm it. In cases of involvement of deep structures, such as the spine, it can eventually complement an MRI study and demonstrate masses of tophi with compression of nerve structures.

Although CT can be useful, it is not recommended as the method of choice in the evaluation of gout in surface structures because of the dose of ionizing radiation used.

3.2.4 Dual-energy computed tomography (DTC)

DTC is a method that provides information on the chemical composition of tissues and allows their differentiation. By means of DTC it is possible to distinguish MSU crystals from gout, bone or dystrophic calcification[6]. Some studies that have examined articular and periarticular crystal deposition with CTD have shown high sensitivity and specificity. Variations in the data obtained may be due to the different joints evaluated, different protocols and different stages of disease analyzed[30-34].

In the early stages of the disease, when MSU deposits are microscopic and intra-articular, rather than macroscopic tophi, CTP may not be able to detect them, as it has a size limitation of usually 2 mm, and is not able to distinguish deposits below this limit[35]. Besides the size-related limitations of the deposits, the CTP is susceptible to some artifacts, mainly related to metal devices, corns, nails, and areas of skin thickening such as the heel. Most studies have not explored the diagnostic accuracy of DTC in the first presentation of gouty arthritis. From the limited data available, the diagnostic sensitivity of the first episode of gouty arthritis is low, around 50%[36]. A study of 21 patients comparing the diagnostic accuracy of US and DTC in cases with suspected gout observed similar sensitivity of the two methods, with false negative results on DTC accurately detected by US[16].

DTC can be used to evaluate gout, independently of serum uric acid levels, and can confirm the disease in patients with normal serum uric acid levels or exclude it in patients with hyperuricemia. The overall burden or volume of uric acid deposition can be calculated on individual lesions, joints or the whole scan area. A potential disadvantage of CTD could be the exposure of the patient to ionizing radiation, but the dose used is lower than the annual dose received naturally and much lower than the values that could induce malignancy[22]. Its main role, although low in cost and radiation exposure, is that treatment monitoring is limited to clinical trials of new therapeutic agents, not clinical practice[16].

3.2.5 Magnetic resonance imaging

MRI is not routinely used to evaluate tophacea gout. It can be used to recognize the cause of motion limitation, motor dysfunction, or pain secondary to changes in deep structures or those covered by bone, when US access is not adequate (**Figure 4**).

MRI is also useful for evaluating the differential diagnosis of soft tissue masses in the extremities[31]. MRI tophi usually presents as a juxta-articular soft tissue mass, causes periarticular erosions and synovial thickening. The appearance of tophi on MRI is variable. On T2-weighted sequence it varies from low to high signal, with a homogeneous or non-homogeneous pattern, depending on the degree of hydration and calcification. The most common appearance on a T2-weighted sequence is a low to intermediate, heterogeneous signal. Its T1 appearance is more consistent, usually showing low to intermediate signal. The pattern of enhancement is also variable. Another feature is the enhancement that surrounds the fovea, probably related to the adjacent granulation tissue (**Figure 5**)[37].

MRI also provides information about the morphology of the tophi, which can range from small ill-defined nodular masses deposited on anatomical planes to having a permeative appearance[38]. Perez-Ruiz *et al.* evaluated the measurement of tophi comparatively between US and MRI, including the change in tophi size and its association with serum urate concentrations over the course of 12 months. The diameters assessed on MRI in this study were larger than US diameters and this may be related to a better MRI image of the soft tissue component of the tophus, which may

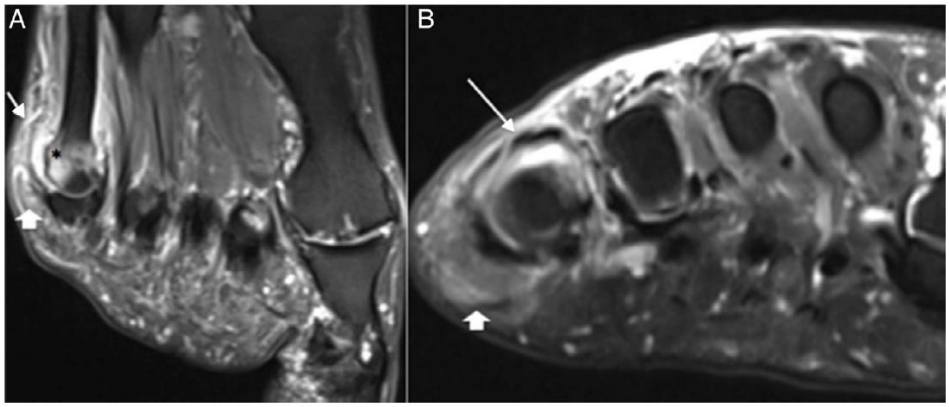

Figure 4. Long **(A)** and short **(B)**: axis MRI images of the foot showing joint effusion (arrow) at the 5[a] metatarsophalangeal joint, associated with a pattern of medullary bone edema at the head and distal metaphysis of the 5[th] metatarsal (*), and densification of the adjacent fat planes (arrowhead).

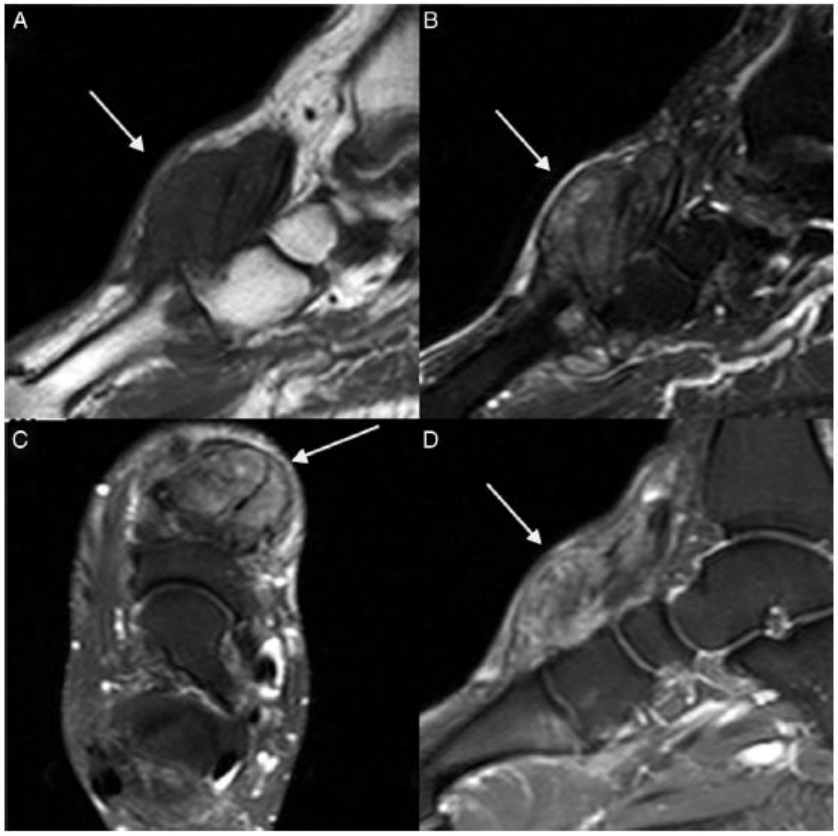

Figure 5. Sagittal T1-weighted **(A)**, T2-weighted **(B)**, axial T2-weighted **(C)** and contrast-enhanced sagittal **(D)** MRI sections of the foot showing heterogeneous material with isosignal on T1, heterogeneous hypersignal on T2, with heterogeneous enhancement after IV injection of paramagnetic contrast, on the dorsal aspect of the foot (arrows).

contain regions of inflammation and hypervascularization[10].

Recent studies have shown that MRI can detect early joint erosions that are not radiographically apparent[39]. In acute gouty arthritis, periarticular edema, synovitis, and joint effusion are common, as well as high bone marrow and periarticular soft tissue signal, but these changes can be seen in any inflammatory arthropathy and are nonspecific. MRI has no relevant role to play in the initial diagnosis of gout. For these reasons, we do not suggest the routine use of MRI for the diagnosis of early-stage gout in cases of typical or atypical clinical presentation.

4. Conclusion

Imaging methods may be useful to aid in the diagnosis and follow-up treatment of patients with gout, especially the use of ultrasonography, which is an affordable, non-invasive tool with good results. The potential of ultrasound diagnosis has increased

physicians' interest in it.

Conflict of interest

The authors declared no conflict of interest.

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