Ultrasound imaging for the rheumatologist
X. Ultrasound imaging in crystal-related arthropathies

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ABSTRACT
This review aims to provide an update of the currently available data regarding ultrasound (US) imaging in crystal-related arthropathies (CA). US imaging allows the assessment of patients with CA showing synovitis, bone erosions, tendon, bursal and cartilage pathology. Moreover, the conformation and anatomical location of crystals may help distinguish the different clinical entities, improving the accuracy of diagnosis and sensitivity of disease activity and therapy monitoring.
Future topics for study include: consensus on scanning protocols and scoring systems, evaluation of greyscale and power Doppler US in the therapy monitoring of gout and evaluation of the role of 3D US in CA.

Introduction

In the field of rheumatology, ultrasound (US) imaging was first applied to rheumatoid arthritis (RA) patients but, in more recent times, its use has spread to practically all forms of arthritis and to the study of most of the articular joints (1-6). The crystal-related arthropathies (CA) are a group of disorders in which minerals are deposited in articular and periarticular tissues resulting in inflammation and damage of such structures. Many different species of crystals can be deposited such as monosodium urate (MSU), giving the clinical picture of gout, calcium pyrophosphate and hydroxyapatite. By using US, the conformation and anatomical location of crystals can be imaged thus helping to distinguish the different clinical entities.
This review provides an overview of the available data and discusses research issues of US imaging in CA.

Clinical applications

As well as in other inflammatory arthritides, the main indications for US examination in CA are: detection of synovitis (even when sub-clinical), demonstration of bone erosions (earlier than by plain x-ray), detailed assessment of tendon pathology, guided aspiration of fluid from joints (a very important tool for crystal identification in synovial fluid) and local injection of pharmaceutical substances (7-10). Besides these "traditional" applications, US in CA may help in the differential diagnosis between gout and calcium pyrophosphate dihydrate (CPPD) disease by characterisation of cartilaginous features, even if the "gold standard" for the diagnosis of crystal-related arthropathies remains the demonstration of crystals in synovial fluid.
To date, few rheumatologists have used high resolution US to more thoroughly investigate CA; however, the results are encouraging and some pathological findings imaged in this group of disorders and described in published papers are now part of the core knowledge of the most skilled rheumatologists or radiologists involved in musculoskeletal US.
High quality US machines allow accurate differentiation between synovial effusion and synovial proliferation using greyscale US, while power Doppler (PD) US provides information on the degree of synovial and soft tissue vascularisation, thus reflecting the activity of the inflammatory process.
US allows the detection of even minimal amounts of synovial fluid and serves as an excellent guide to improve the diagnostic yield in joint aspiration (7).
Furthermore, US may help in differentiating subcutaneous nodules and in the detection of even small tophaceous deposits (11, 12).

Sonographic findings

In CA, US makes it possible to detect joint effusion and synovial prolifera-

tion, while PDUS can disclose increased tissue signal, thus adding useful information on the inflammatory status of the anatomic structures. Also bone erosions, tendinopathy, cartilage involvement and bursitis are frequently imaged in CA by US.

Besides these common findings, there are some sonographic features which are of great help in the differential diagnosis of crystal-related disorders (Table I).

Gout
Gout is one of the most common forms of inflammatory arthritis, characterized by tissue deposition of MSU crystals. Patients with hyperuricaemia may develop acute attacks of gouty arthritis and, late in the disease course, chronic arthritis. Aggregated deposits of MSU, the so-called tophi, are frequently seen in the advanced stages of the disease (13). MSU crystals strongly reflect US waves and their presence can easily be confirmed especially at low levels of gain (14). Their deposition on the cartilage surface leads to hyperechoic enhancement of the superficial margin of the cartilage layer which is independent of the angle of insonation (14-16). Adhesion of MSU crystals to the cartilage surface can easily be verified by dynamic assessment. Sometimes thickening of the chondrosynovial interface is not homogenous but irregular due to focal deposition of MSU crystals.

During acute gout, synovial fluid may vary from complete anechogenicity to varying echogenicity. In the presence of multiple aggregates of MSU crystals, gentle pressure on the skin surface makes them float in the joint cavity, creating a "snowstorm" appearance (16).

Tophi appear as nodular deposits which may occur at virtually any site, with the most frequent locations being fingers and toes and olecranon bursae. According to the degree of compaction of the deposits, it is possible to distinguish soft, hard or mixed tophi. A soft tophus is visualized as an aggregate of inhomogeneous echogenicity, whereas hard tophi appear as hyperechoic bands generating a posterior acoustic shadow and mixed tophi show features of both soft and hard tophus (11, 17). It is possible

Table I. US imaging in CA: US patterns.

Gout	• *soft tophus-like lesion*: homogenously echoic "echotexture" (11).
	• *hard tophus-like lesion*: hyperechoic band generating a posterior acoustic shadow (11).
	• *mixed tophi*: features of both soft and hard tophus (11).
	• *double contour*: focal or diffuse enhancement of the superficial articular cartilage layer (independent from the deposition of MSU crystals), whose reflectivity is independent of the angle of insonation (15, 16).
	• *hyperechoic spots*: spots less than 1 mm in size with the same echogenicity of the bony cortex (11).
	• *"snowstorm" appearance*: hyperechoic spots in the synovial fluid floating within the joint cavity in acute inflammation (16).
CPPD disease	• *double contour*: thin hyperechoic band (either focal or diffuse) within the cartilage layer (14, 16, 18-20).
	• *"punctate" pattern*: hyperechoic rounded or amorphous-shaped areas in fibro-cartilage or tendons (16, 20).
	• homogeneous hyperechoic nodular or oval deposits in bursae or articular recesses (16, 20).
Hydroxyapatite crystal deposition disease	• hypoechoic pattern with associated posterior shadowing, even for calcification less than 2-3 mm (23).

to differentiate formed tophi from the deposition of MSU on the superficial layer of cartilage not solely by US characteristics but also because the former are imaged as firm aggregates while the latter move together with bone and cartilage layer (14). MSU microdeposits, with a small hypoechoic halo due to local inflammation, may be seen in tendons even in asymptomatic subjects. Tophaceous gout involving tendons can manifest as hypoechoic, (with occasional hyperechoic spots) nodules or, when longstanding, as hyperechoic bands with US (16).

CPPD disease
Patients with CPPD disease usually present with one of the following clinical entities: acute synovitis, chronic arthritis and asymptomatic findings of cartilage calcification. For diagnosis, the demonstration of calcium pyrophosphate crystals in synovial fluid and plain radiographs is desirable. More recently, US has been shown to be effective in demonstrating CPPD deposits. Sonographic findings suggestive of CPPD depositions are:
- a thin hyperechoic band (either focal or diffuse) within the cartilage layer (14, 16, 18-20)
- hyperechoic rounded or amorphous-shaped areas ("punctate" pattern) in

fibro-cartilage, typically in the triangular ligament of the wrist and in the menisci of the knee (16, 20)
- linear calcification (16, 21) (often with acoustic shadows) or ovoid-shaped hyperechoic densities in tendons (16)
- homogeneous hyperechoic nodular or oval-shaped deposits in bursae or articular recesses (20)

In all cases, calcification appears sparkling with posterior shadow if the dimension is >10 mm

In CPPD, crystals lie within the cartilage layer (22) ("double contour") unlike gout in which MSU crystals are located on the superficial margin of cartilage.

CPPD aggregations in synovial fluid show a sharply defined outer profile; by setting the US gain to a low level, it is possible to demonstrate the reflectivity of the crystals, thus distinguishing them from the debris and proteinaceous material floating in the joint cavity (16, 20).

Hydroxyapatite deposition disease
Intra-articular and peri-articular deposits of apatite (mainly hydroxyapatite) are frequently asymptomatic but sometimes may result in clinically relevant disorders (calcific periarthritis, acute synovitis, Milwaukee shoulder syn-
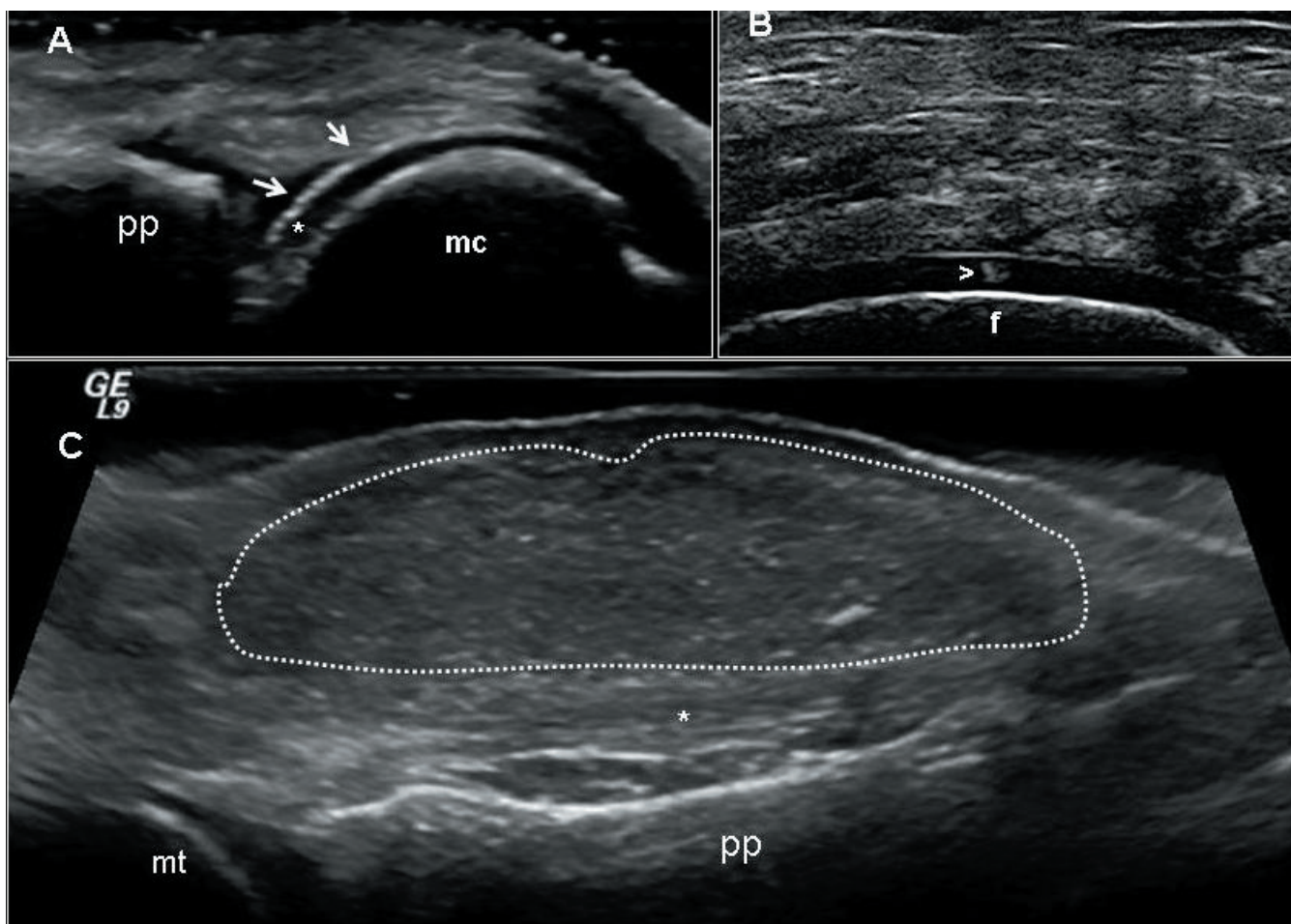
Fig. 1. A. Gout. Longitudinal dorsal scan of the metacarpo-phalangeal joint showing MSU crystal over the superficial margin of the articular cartilage ("double contour"). *: cartilage layer; mc: metacarpal head; arrow: double contour. Image obtained with a Logic 9 (General Electrics Medical Systems, Milwakee, WI) with a 9-14 MHz broadband linear probe.
B. Calcium pyrophosphate deposition disease. Femoral condyle on longitudinal view with knee in maximal flexion. The arrowhead indicates a pyrophosphate deposit within the cartilage layer. Image obtained using a My Lab 70 (Esaote Biomedica, Genova, Italy) with a 6-18 MHz broadband linear probe.
C. Gout. Longitudinal dorsal scan of the first metatarso-phalangeal joint (trapezoid view) showing a soft tophus (inside the dotted line) lying over the extensor hallucis longus tendon. *: extensor hallucis longus tendon; mt: metatarsal head; pp: proximal phalanx. Image obtained with a Logic 9 (General Electrics Medical Systems, Milwakee, WI) with a 9-14 MHz broadband linear probe.

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drome, severe osteoarthritis). Whilst the US features of apatite deposits are non-specific, they are often less sparkling and have posterior shadowing detectable even if the dimensions are < 2-3 mm (23).

Literature review
Very few papers have described the US features of crystal-related arthropathies. Nevertheless, it is well-known that US is a very sensitive technique in the detection of joint effusion, synovitis, bone erosions, bursitis and tendinopathy. Also, deposits of crystals, particularly calcified materials, in hyaline cartilage and in periarticular tissues are easily depicted by US examination (24).

Gout
Recently, three studies highlighted the principle features of gouty arthritis which can be detected by US (11, 14, 16). In 2006, Grassi *et al*. (16) studied 26 patients with crystal-proven gout and described the spectrum of abnormalities observed in such cases: the deposition of MSU on the surface of articular cartilage, the presence of aggregates of different shapes and echogenicity in synovial fluid, the deposition of crystals within tendons and the appearance of the tophi. More recently, to establish the usefulness of US in gouty patients and to verify if there are sonographic findings which are typical for gout and not for other arthropathies,

Thiele *et al*. (14) studied 37 joints of 23 patients with gout confirmed by the detection of MSU crystals in synovial fluid. They observed in 92% of the patients and in none of the controls the irregular band over the superficial margin of the articular cartilage of the metatarsal and metacarpal heads, femoral condyles and humeral head ("double contour"). Tophaceous material was shown in all the metacarpo-phalangeal and metatarso-phalangeal joints (MTPJ); erosions were frequently adjacent to the tophaceous material, maximally in MTPJ. Synovial hypertrophy was imaged as a concentric thickening of the synovial membrane but no villous hypertrophy or hypertrophic synovial

tissue invading subchondral bone was demonstrated (14). Even more recently, Wright *et al.* (11) carried out an investigation aiming at comparing US with plain radiographs in the detection of bone damage at the first MTPJ in 39 patients with gout. As in RA, US is more effective than x-ray in detecting bone erosions in gout in 67% and 28% of MTPJ respectively. Erosions were also detected by US in 22 joints which had never been subjected to a clinical attack of gout. Tophus-like lesions were shown in 50% of the first MTPJ but also in 14% of disease controls, the latter result probably reflecting the difficulties in the distinction between soft tophi and extensive synovial proliferation (11).

Very few cases of gouty tenosynovitis, sometimes mimicking infection, have been reported (25, 26).

PD has demonstrated increased perfusion in 79% of the examined joints in gouty patients (15), even when inflammation had just entered clinical remission (27). With colchicine therapy, PD signal decreased and finally disappeared (28).

Some authors have studied US reliability for the measurement of tophi in chronic gouty patients. They reported good sensitivity to change, associated with urate-lowering therapy (29) and good intra-observer correlation (30) at follow-up, so tophi measurement could become an outcome measure for urate lowering therapy in chronic gout (31).

CPPD disease

In 1995, Coari *et al.* (18), showed the presence of calcification within condylar cartilage in 43 knees of 28 patients with chondrocalcinosis. These results were

confirmed by Foldes (19) in a study with 21 subjects with chondrocalcinosis and by Sofka (32) who described a case of US detected men-iscal calcification not visualized by conventional radiograph. Moreover, Monteforte *et al.* (33) visualized calcification also in 6 patients with elbow enthesopathy.

Frediani *et al.* (20) and Grassi *et al.* (16), in two different papers, proposed the US criteria for the diagnosis of CPPD deposition (previously reported, see sonographic findings). In particular Grassi *et al.* (16) focused attention on the different pattern of crystal deposition in gout and CPPD disease. The presence of hyperechoic material within the substance of hyaline cartilage is typical of chondrocalcinosis.

Frediani *et al* (20) studied the relationship between the presence of such crystals in articular and periarticular structures and the presence of crystals in synovial fluids in 11 patients with US evidence of CPPD deposition; moreover, they compared US with the x-ray findings. CPPD crystals were present in the synovial fluid of all the patients but 2 out of 11 plain x-rays did not succeed in imaging the calcification visualized by US

In 2004, Falsetti *et al.* (21) studied the Achilles tendon and plantar fascia in 57 patients with proven (radiographic or microscopic evidence) CPPD disease. Calcification was imaged in 57.9% of the Achilles tendons and in 15.8% of the plantar fascia. The US features seen included multiple thin linear bands in the majority of cases (72.4%), less frequently fine linear bands (17.2%) or thick solid bands (10.3%). No homogeneous rounded hyperechoic deposits were observed. Plantar fascial

calcification was always present as a single fine linear echoic band in the superficial region of the insertional tract, apparently not in contiguity with the cortical bone (21). Additionally, postero-inferior and inferior calcaneal enthesophytosis was shown in CPPD disease patients but without a significantly different prevalence from the control group of osteoarthritis subjects. Interestingly, the authors observed that frequently there were no acoustic shadows behind the calcifications, probably because CPPD crystal deposits in the tendons are unstructured and allow US penetration (21).

Hydroxyapatite crystal deposition disease

To the best of our knowledge, studies on the US appearance of hydroxyapatite crystal deposition disease are still lacking in the international medical literature.

Research agenda

The use of US in CA has similar limitations previously reported for the other arthritides including: lack of an accepted scanning protocol and scoring system for the main abnormalities which can be visualized; lack of standardization of the PD tool.

Great efforts are being made to reach an international consensus on the methods for the evaluation of bone damage and synovitis in RA (34) but very few US researchers have focused their attention on CA. There are, therefore, a limited number of papers on such topics.

In Table II, we report the principal "hot research topics" related to US and CA.

Link

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Table II. US imaging in CA: research agenda.

To develop a specific training programme for rheumatologists performing US examination of patients with CA.

To develop international consensus on scoring systems for assessing joint and peri-articular soft tissue pathology related with CA.

To assess the specificity and sensitivity of US findings for the diagnosis of CA; in particular to investigate the "other" crystal deposit characteristics (*i.e.* hydroxyapatite).

To evaluate the role of both greyscale and PD US in therapy monitoring of gout.

To investigate the potential of 3D US with the volumetric probe in assessing patients with CA.

To investigate the link between CA and osteoarthritis.

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