

Ultrasonography shows disappearance of monosodium urate crystal deposition on hyaline cartilage after sustained normouricemia is achieved

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Abstract This study aimed at determining whether lowering serum urate (SU) to less than 6 mg/dl in patients with gout affects ultrasonographic findings. Seven joints in five patients with monosodium urate (MSU) crystal proven gout and hyperuricemia were examined over time with serial ultrasonography. Four of the five patients were treated with urate lowering drugs (ULDs) (allopurinol, $n = 3$; probenecid, $n = 1$). One patient was treated with colchicine alone. Attention was given to changes in a hyperechoic, irregular coating of the hyaline cartilage in the examined joints (double contour sign or “urate icing”). This coating was considered to represent precipitate of MSU crystals. Index joints included metacarpophalangeal (MCP) joints ($n = 2$), knee joints ($n = 3$), and first metatarsophalangeal (MTP) joints ($n = 2$). The interval between baseline and follow-up images ranged from 7 to 18 months. Serial SU levels were obtained during the follow-up period. During the follow-up period, three patients treated with ULD (allopurinol, $n = 2$; probenecid, $n = 1$) achieved a SU level of <6 mg/dl. In two

patients, SU levels remained above 6 mg/dl (treated with allopurinol, $n = 1$; treated with colchicine, $n = 1$). At baseline, the double contour sign was seen in all patients. In those patients who achieved SU levels of <6 mg/dl, this sign had disappeared at follow-up. Disappearance of the double contour sign was seen in two knee joints, two first MTP joints, and one MCP joint. In contrast, disappearance of the double contour sign was not seen in patients who maintained a SU level ≥ 7 mg/dl. In one patient treated with allopurinol, SU levels improved from 13 to 7 mg/dl during the follow-up period. Decrease, but not resolution of the hyperechoic coating was seen in this patient. In the patient treated with colchicine alone, SU levels remained >8 mg/dl, and no sonographic change was observed. In our patients, sonographic signs of deposition of MSU crystals on the surface of hyaline cartilage disappeared completely if sustained normouricemia was achieved. This is the first report showing that characteristic sonographic changes are influenced by ULDs once SU levels remain ≤ 6 mg/dl for 7 months or more. Sonographic changes of gout correlate with SU levels and may be a non-invasive means to track changes in the uric acid pool. Larger prospective studies are needed to further assess these potentially important findings.

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Introduction

Gout is a systemic metabolic disease. Humans do not express the enzyme urate oxidase (uricase), due to a mutation of the uricase gene during evolution, which converts

urate to the more soluble and easily excreted compound allantoin. Among mammals, only humans and other primate species excrete uric acid as the end product of purine metabolism. Uric acid is a weak organic acid that exists mainly as the urate ion at pH > 5.75 and as the un-ionized uric acid form at more acidic (lower) pH levels. Thus, the urate form predominates in all extracellular fluids, including serum, in which the physiological pH is 7.4. When the serum urate (SU) concentration exceeds the solubility of urate (a concentration above 6.8 mg/dl), supersaturation of urate in the serum and other extracellular spaces results. This state is hyperuricemia and imparts a risk of crystal deposition of urate in tissues from the supersaturated fluids [1].

A preferential crystallization on hyaline cartilage was first described 150 years ago by Sir Alfred Garrod. Garrod found “*more or less complete incrustation of the surfaces of the bones with the white matter*” in gouty patients with extensive tophaceous deposits. “*Similar, but less severe infiltration of articular cartilage was also present in cases with only a few external deposits as well as in subjects who had remained completely free of tophi*” [2]. In the 1950s and 1960s, Sokoloff [3, 4] and McCarty [5] found the articular cartilage to be the site of crystal precipitation “*par excellence*”. The reasons for this predilection remain unclear. Tissue factors of cartilage and synovial fluid have been examined with varying results [6, 7]. Chondroitin sulfate and phosphatidylcholine, constituents of hyaline cartilage, were found to influence growth kinetics of monosodium urate (MSU) crystals in vitro [8]. MSU crystals can form crusts that cover large areas of the articular cartilage [9–11]. Crystal deposition on hyaline cartilage, the hallmark feature of gout, is found on gross pathological specimens and seen with polarizing microscopy on histopathological specimens [12, 13] and in vivo during arthroscopy. We have previously shown that ultrasonography is able to visualize these MSU crystal deposits within joints [14].

We herein describe the changes of crystal deposits on hyaline cartilage over time, with and without therapeutic intervention, and with and without achieving normouricemia. Our goal was to determine whether lowering SU to less than 6 mg/dl in patients with gout affects ultrasonographic findings.

Methods

Seven joints in five patients with MSU crystal proven gout and hyperuricemia were examined sonographically. Four of the five patients were treated with urate lowering drugs (ULDs) (allopurinol, $n = 3$; probenecid, $n = 1$). One patient was treated with colchicine alone. Attention was given to

changes in a hyperechoic, irregular coating of the hyaline cartilage in the examined joints (double contour sign or “urate icing”). This coating was considered to represent precipitate of uric acid crystals. Index joints included metacarpophalangeal (MCP) joints ($n = 2$), knee joints ($n = 3$), and first metatarsophalangeal (MTP) joints ($n = 2$). The interval between baseline and follow-up images ranged from 7 to 18 months. Serial SU levels were obtained during the follow-up period.

IRB approval was obtained. All studies were performed by a rheumatologist certified in musculoskeletal ultrasound, with 15 years of ultrasound experience (R.G. Thiele). A second rheumatologist (N. Schlesinger) reviewed all joint ultrasound images.

Images were obtained following published guidelines for ultrasound in rheumatology [15]. Images of patient 1 were obtained on a General Electric Logiq 200 ultrasound machine. Images of patients 2, 3, 4, and 5 were obtained on a General Electric Logiq 3 ultrasound machine. On both machines, a high-frequency, linear transducer was used (10 Lb, 5–10 MHz, footprint 40 mm × 9 mm, GE Medical Systems, Milwaukee, WI, USA). Images obtained on the Logiq 200 machine were stored on a magneto-optic disk; images obtained on the Logiq 3 machine were stored on the hard drive of the machine.

Metacarpophalangeal joints were examined from dorsal and volar in long and short axes. In addition, second MCP joints were visualized from a radial aspect, and fifth MCP joints were visualized from an ulnar aspect. Femoral cartilage was visualized in a suprapatellar, long and short axis view with the knee in maximal flexion. First MTP joints were examined in long and short axes from dorsal, plantar, and medial aspects. All studies were performed in a dynamic fashion, scanning across the joints in a medial–lateral sweep for long axis views and proximal–distal sweep for short axis views. Joints were also gently led through range of motion, with the probe kept steady. Representative still images and cine-loops were saved and stored on the ultrasound machine.

Patient 1

The patient is a 59-year-old male with past medical history significant for diabetes mellitus (DM), hypertension (HTN) and peptic ulcer disease. His medications included hydrochlorothiazide, rosiglitazone maleate, potassium supplements, and aspirin 81 mg/day. He had MSU crystal proven gouty arthritis for 4 years affecting his right knee and left hand, in particular the third left MCP joint. For his acute attacks he received different nonsteroidal anti-inflammatory drugs as well as colchicine with relief of his pain. Allopurinol was prescribed as an ULD at an initial dose of 150 mg/day; this was increased to 300 mg/day after 1 week.

At presentation with acute gouty arthritis of his left hand, a conventional radiograph of his left hand was found to be unremarkable; however, an ultrasound examination showed a small effusion in this joint, tophaceous material, and an erosion. Echogenic material was seen coating the hyaline cartilage of the metacarpal head. An ultrasound-guided injection was performed. He had not had a gouty attack after the initial attack. He was seen again 18 months after the initial attack. At that time, he continued to have slight difficulty with flexion in left third MCP joint, but was pain free. An US examination revealed a decrease in synovial thickening, complete resolution of tophaceous material and disappearance of the hyperechoic material that had coated the cartilage of the metacarpal head (Fig. 1).

Patient 2

The patient is a 69-year-old male with a 10-year history of hyperuricemia and recurrent MSU crystal proven gouty arthritis. He has had no other medical history. His gouty flares affected his ankles and feet, including his first MTP joints. His attacks responded to short courses of oral steroids. He was placed on allopurinol 300 mg daily; however, allopurinol was stopped after worsening of liver function tests (an increase in transaminase levels). He was seen for olecranon bursitis and pain in his first MTP joints. Radiography and MRI studies of both feet with particular attention to the first MTP joint showed a small amount of fluid and mild changes of osteoarthritis. No gouty changes were seen. An ultrasound study of his first MTP joints showed a thick, irregular, echogenic band paralleling the contour of the metatarsal heads superficial to hyaline cartilage. Probenecid therapy was started. The dose was titrated up to

2,000 mg daily in divided doses. A repeated US study of his first MTP joints performed 8 months later showed complete resolution of this irregular band (Fig. 2).

Patient 3

The patient is an 88-year-old female with past medical history significant for DM, chronic renal failure (CRF) and congestive heart disease. Medications included carvedilol, lasix, aspirin, glimepiride and oxybutynin. She first noted pain and swelling in her fingers 2.5 years prior to being seen when she was gardening. She denied having had gouty attacks in her knees or feet. She had since noticed the development of whitish nodules over her fingers. One of the nodules led to a skin break that healed poorly. When seen in our clinic, she had multiple tophi over the DIP joints of both hands. She had ulceration over one of her DIP joints. One of the tophi was unroofed, and large amounts of uric acid crystals were found under polarizing microscopy.

Treatment with allopurinol was started at a dose of 50 mg/day in an attempt to facilitate healing of her skin lesion. The dose was increased to 100 mg daily 2 weeks after initially being seen, then to 200 mg daily 3 months later and to 300 mg/day 5 months from her initial visit. At that time, an US study showed tophaceous material over DIP joints, deposition of a layer of MSU crystals on the cartilage of MCP joints of both hands and in the humeroradial joint on the right side. She had a thick, irregular, hyperechoic band over the cartilage of the distal femur on both sides. A year after her initial visit a repeat US study showed a complete resolution of the crystal layer over the distal humerus in the right humeroradial joint and over the cartilage of the distal femur bilaterally (Fig. 3).

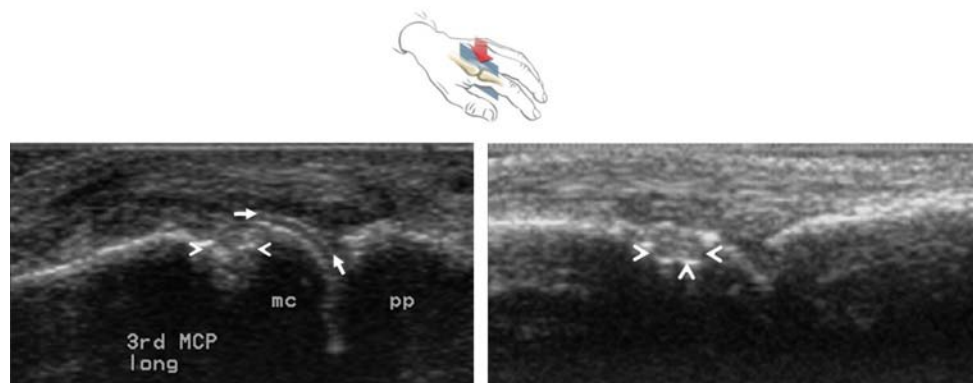


Fig. 1 Patient 1: dorsal longitudinal view centered over the third metacarpal phalangeal joint. The *left image* shows the joint in slight flexion. More hyaline cartilage is exposed. The contour of the metacarpal head is hyperechoic. The layer of hyaline cartilage over the bone appears anechoic (“black”). An irregular, hyperechoic (“white”) band covers the cartilage (between *arrows*). Erosion is seen at the level of the anatomic neck (between *open arrowheads*). A thin, regular hyper-

echoic line is seen overhanging this erosion (“egg shell overhang” or Martel reaction). Tophaceous material and fluid is seen within the joint capsule. On the *right image*, taken 17 months later with the same equipment, the hyperechoic band over the hyaline cartilage has disappeared. An erosion remains at the level of the anatomic neck of the metacarpal head (between *open arrowheads*)

Fig. 2 Patient 2: plantar longitudinal view centered over the first metatarsal phalangeal joint of left and right feet. *Top left* MTP 1 joint and *bottom, right* MTP 1 joint. Superficial to both metatarsal heads, which appear as a hyperechoic outline, anechoic hyaline cartilage is seen. On the images on the *left side*, after more than 1 year of documented hyperuricemia, a thick hyperechoic, irregular band coats the cartilage (*arrows*). On the images on the *right side*, which were taken after 6.5 months of well-documented, sustained normouricemia, this layer of echogenic material has disappeared

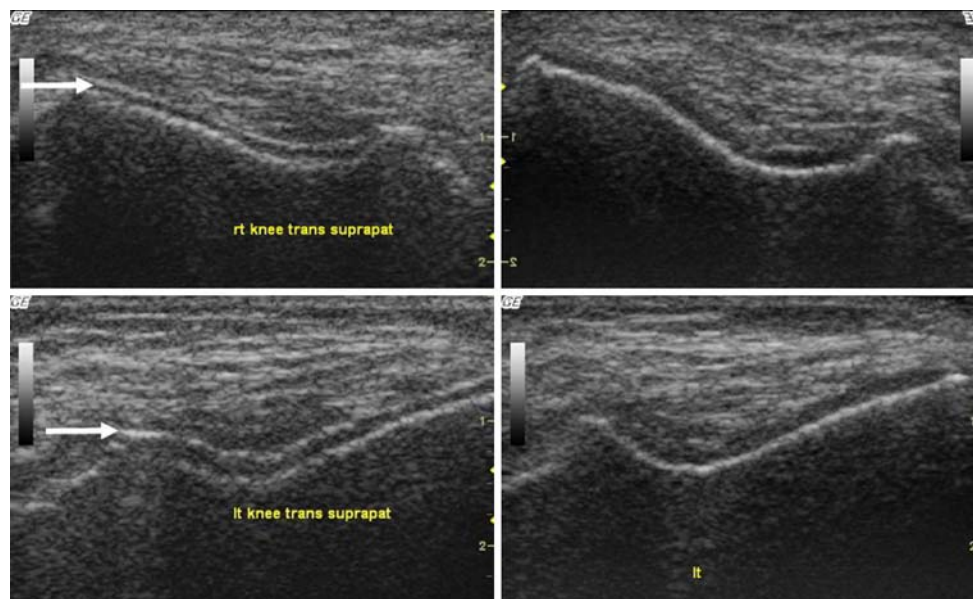
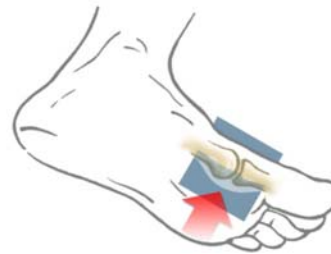
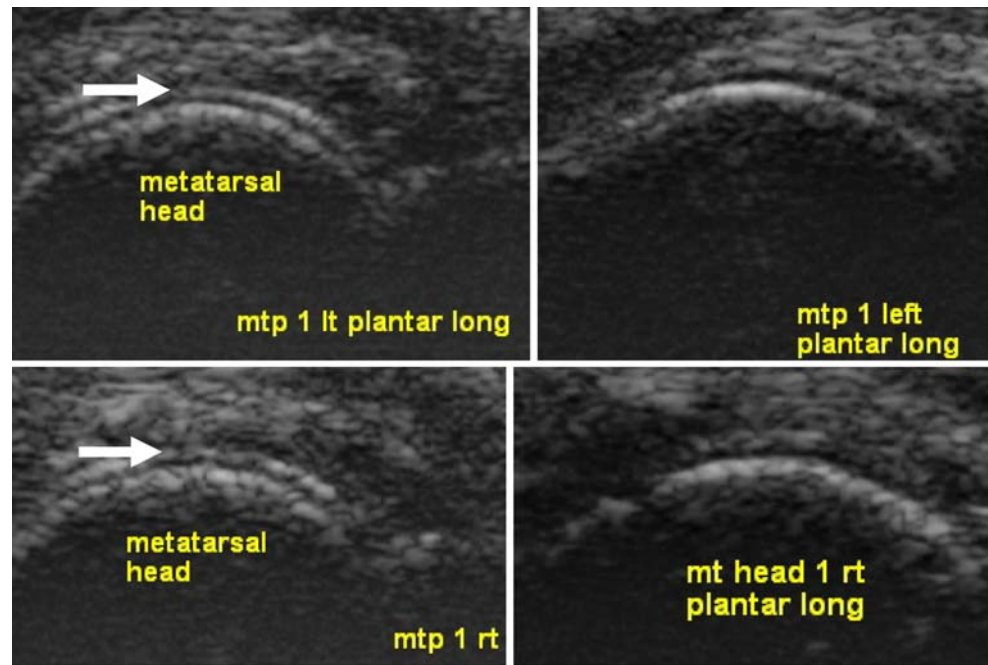
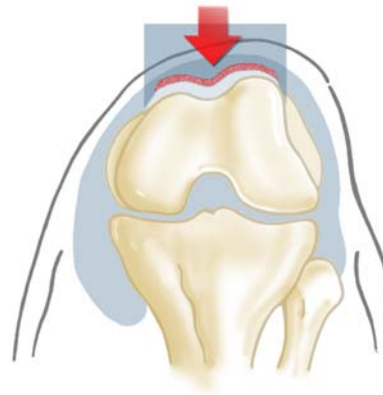
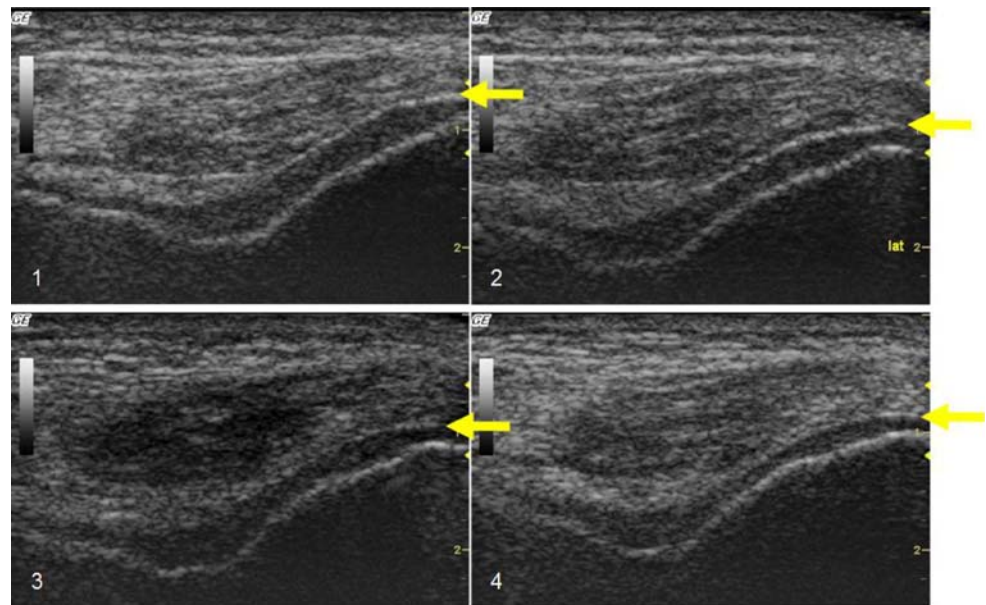


Fig. 3 Patient 3: suprapatellar, transverse views of right (*top images*) and left (*bottom images*) knees in flexion. These views allow assessment of the femoral cartilage. The bony outline of the distal femur appears as a bright, hyperechoic line. Above it and parallel to it lies the anechoic layer of hyaline cartilage. The images on the *left side*, which

were taken after an episode of hyperuricemia, show a hyperechoic, irregular white band that parallels bony contour and hyaline cartilage (*arrows*). On the images on the *right side*, which were taken after 7 months of normouricemia, this band has completely disappeared

Fig. 4 Patient 4: suprapatellar transverse view in flexion. Image 1 is taken at baseline. Images 2–4 are taken at months 5, 8 and 10, respectively. A fine, coarse hyperechoic band overlies the anechoic hyaline cartilage (*arrows*). Although there is a slight decrease seen in image 3, this band does not disappear entirely on image 4. Serum urate levels never fell below 6 mg/dl



Patient 4

This is a 60-year-old African American male with a 6-month history of polyarthritis. During a hospitalization for acute knee pain and elbow pain, an aspiration of an olecranon bursa and the right knee yielded MSU crystals. A SU level at that time was 12.9 mg/dl. His symptoms improved with a combined treatment with prednisone, colchicine, and ibuprofen. His past medical history included mild CRF (creatinine 1.5–1.6 mg/dl) and HTN. His HTN was treated with amlodipine. Treatment with allopurinol 100 mg daily was initiated upon discharge from the hospital. Oral colchicine 0.6 mg twice daily and prednisone 10 mg daily were continued upon discharge from the hospital. Ibuprofen was discontinued. When first seen in our clinic 1 month later, an US study of his right knee showed hyperechoic lining of the hyaline cartilage of the distal femur. Prednisone was discontinued at that time. One month later SU levels dropped to 10.2 mg/dl. Allopurinol was increased to 300 mg daily 2 months after his first US study. Five months after his initial US study, SU levels had dropped further to 9.2 mg/dl. At

that time, a repeated US study of his right knee showed unchanged hyperechoic lining of the femoral cartilage. Allopurinol was increased to 600 mg daily. 9 weeks later, his SU level had dropped to 7.0 mg/dl. An US study performed at this time showed a decrease, but not a complete resolution of the echogenic layer over his femoral cartilage. Three months later, his SU level was 7.4 mg/dl. A repeat US study failed to show a complete resolution of the hyperechoic layer (Fig. 4).

Patient 5

This patient is a 76-year-old white male with a 4-year history of recurrent gouty attacks in his hands and feet. His past medical history includes CRF with creatinine levels between 1.5 and 2.1 mg/dl. He has had hyperuricemia with SU levels between 8.1 and 11.3 mg/dl over the last 4 years. He has had several episodes acute gouty attacks in his first MTP joints and left second MCP joint during the last 4 years. Aspiration of the MCP joint revealed MSU crystals. The patient was intolerant to allopurinol and was started on

colchicine 0.6 mg twice daily. His last gout attack in the second MCP joint started a week before the first US image was taken. The US examination showed tophaceous material within the joint capsule and coating of the hyaline cartilage of the metacarpal head. Erosion at the radial aspect of the second metacarpal head was seen, as well. The erosion measured 0.40 cm × 0.28 cm in width and height; and 0.38 cm in depth. Hyperechoic, tophaceous material surrounded by an anechoic rim was seen entering the erosion. A conventional radiograph of the hands taken at the same time showed only osteoarthritis. No changes suggestive of gout were reported.

The patient continued his colchicine treatment without ULD. Over the next year, his SU levels remained >8 mg/dl. Repeated US studies showed no resolution of the tophaceous material that coated the cartilage of the metacarpal head (Fig. 5).

Results

Four of the five patients were treated with ULD (allopurinol, $n = 3$; probenecid, $n = 1$). One patient was treated with colchicine alone. Attention was given to changes in a hyperechoic, irregular coating of the hyaline cartilage in the examined joints (double contour sign). This coating was considered to represent precipitate of MSU crystals. Index joints included MCP joints ($n = 2$), knee joints ($n = 3$), and first MTP joints ($n = 2$). The interval between baseline and follow-up images ranged from 7 to 18 months. Serial SU levels were obtained during the follow-up period.

During the follow-up period, three patients treated with ULD (allopurinol, $n = 2$; probenecid, $n = 1$) achieved a SU level of <6 mg/dl. In two patients, SU levels remained above 6 mg/dl (treated with allopurinol, $n = 1$; treated with colchicine, $n = 1$).

At baseline, the double contour sign was seen in all patients. In those patients who achieved SU levels of <6 mg/dl, this sign had disappeared at follow-up. Disappearance of the double contour sign was seen in two knee joints, two first MTP joints and, one MCP joint. In contrast, disappearance of the double contour sign was not seen in patients with a SU level ≥ 7 mg/dl. In one patient treated with allopurinol, SU levels improved from 13 to 7 mg/dl during the follow-up period. Decrease, but not resolution of the hyperechoic coating was seen in this patient. In the patient treated with colchicine alone, SU levels remained >8 mg/dl, and no sonographic change was observed. Conventional radiographs obtained in all patients were not diagnostic for gout. In patients 1 and 5, gouty erosions were seen on ultrasound but not on conventional radiographs (Fig. 6). Patient 2 had, in addition, MRI studies of both first MTP joints that did not show changes suggestive of gouty arthritis, whereas

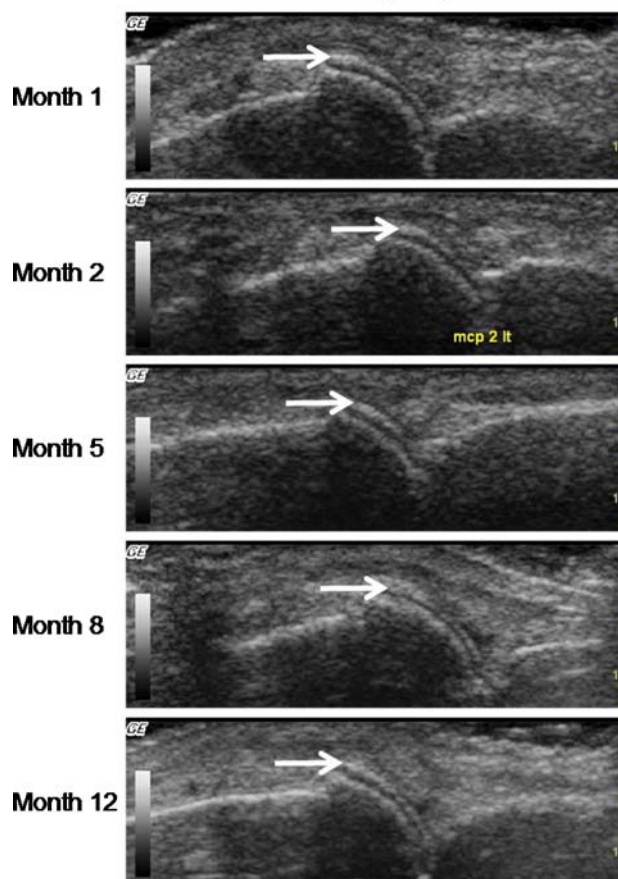
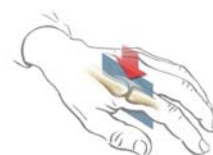


Fig. 5 Above: MCP 2, dorsal longitudinal view. A strong, hyperechoic band is seen overlying the anechoic hyaline cartilage of the metacarpal head. This band does not significantly change over time. The patient's serum urate level remained above 8 mg/dl during the examination period

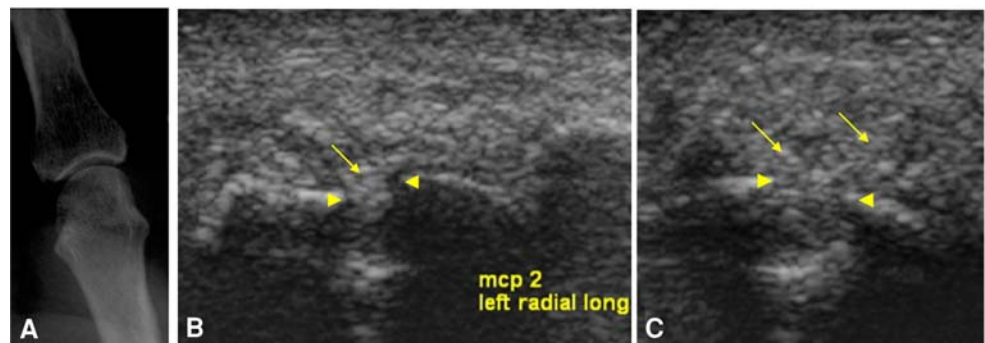
ultrasonography of his first MTP joints revealed typical changes of gouty arthritis.

Serum urate levels are shown on graphs in Fig. 7.

Discussion

Monosodium urate crystals have distinct sites of precipitation in gout; in particular, the articular cartilage. Garrod first described deposition of MSU crystals on the surface of cartilage with the aid of a polarized light in 1859. Over the past several decades there have been very few descriptions of this feature of gout, possibly because it escapes frequently used diagnostic imaging modalities including conventional radiography (CR), CT scans and MRI imaging. When urate deposits are found on the surfaces of articular

Fig. 6 Patient 5: plain radiograph of both hands. No gouty arthritis was detected. Radiograph and sonograms were taken at the same time. **a** Radiograph. Close-up of MCP 2 left. **b** Sonogram. Longitudinal scan over radial aspect. A bony erosion is seen as a break in the cortical contour (between *arrowheads*). A hyperechoic tophus is seen entering the erosion (*arrow*). The tophus is surrounded by an anechoic rim. **c** Short axis, transverse sonogram over radial aspect of left second metacarpal head. The same erosion is seen as a cortical break (between *arrowheads*). Tophaceous material is marked with *arrows*



cartilage with arthroscopy, these are difficult to identify on MRI and CT images, even retrospectively [16].

We have previously shown that US is superior in detecting changes of gouty arthritis compared to CR, MRI, and CT scanning [17]. Others, too, found US to be superior to conventional radiographs in evaluating small bone changes in gout [18]. Rettenbacher et al., on the other hand, suggested that US was much more sensitive than conventional X-ray but possibly less specific [19]. Similar to studies that compare detection of erosions with ultrasound and CR in rheumatoid arthritis [20], we found erosions with US where they were not seen with CR.

It is also notable that significant deposits of MSU crystals were found in joints that had not endured acute gouty attacks and were assumed to be unaffected (patient 3). MSU crystal deposition on hyaline cartilage in asymptomatic joints has been described in an arthroscopy study [21]. Another study suggested that ultrasonography can aid in identifying sonographic features that may be representative of the disease even in clinically silent joints [22].

In our patients, sonographic signs of deposition of MSU crystals on the surface of hyaline cartilage disappeared completely if sustained normouricemia was achieved. This is the first report showing that characteristic sonographic changes are influenced by ULD once SU levels remain ≤ 6 mg/dl for 7 months or more. Ultrasonography is the only imaging modality that shows deposits of MSU crystals as a layer on hyaline cartilage. This layer is distinct from aggregates of these crystals which form tophi.

In contrast to gout, calcium pyrophosphate crystals, which are also readily seen by ultrasound, tend to deposit in lacunae in the mid-zonal area of hyaline cartilage. They give a characteristic appearance of a hyperechoic bony outline, coated by a layer of anechoic cartilage, in the center of which irregular hyperechoic crystals are embedded [23–25]. A recent study showed that ultrasound findings are highly specific for gout and calcium pyrophosphate deposition [26].

The incidence of gout is increasing. New ULD are on the horizon [27]. Pegylated urate oxidase shows promise

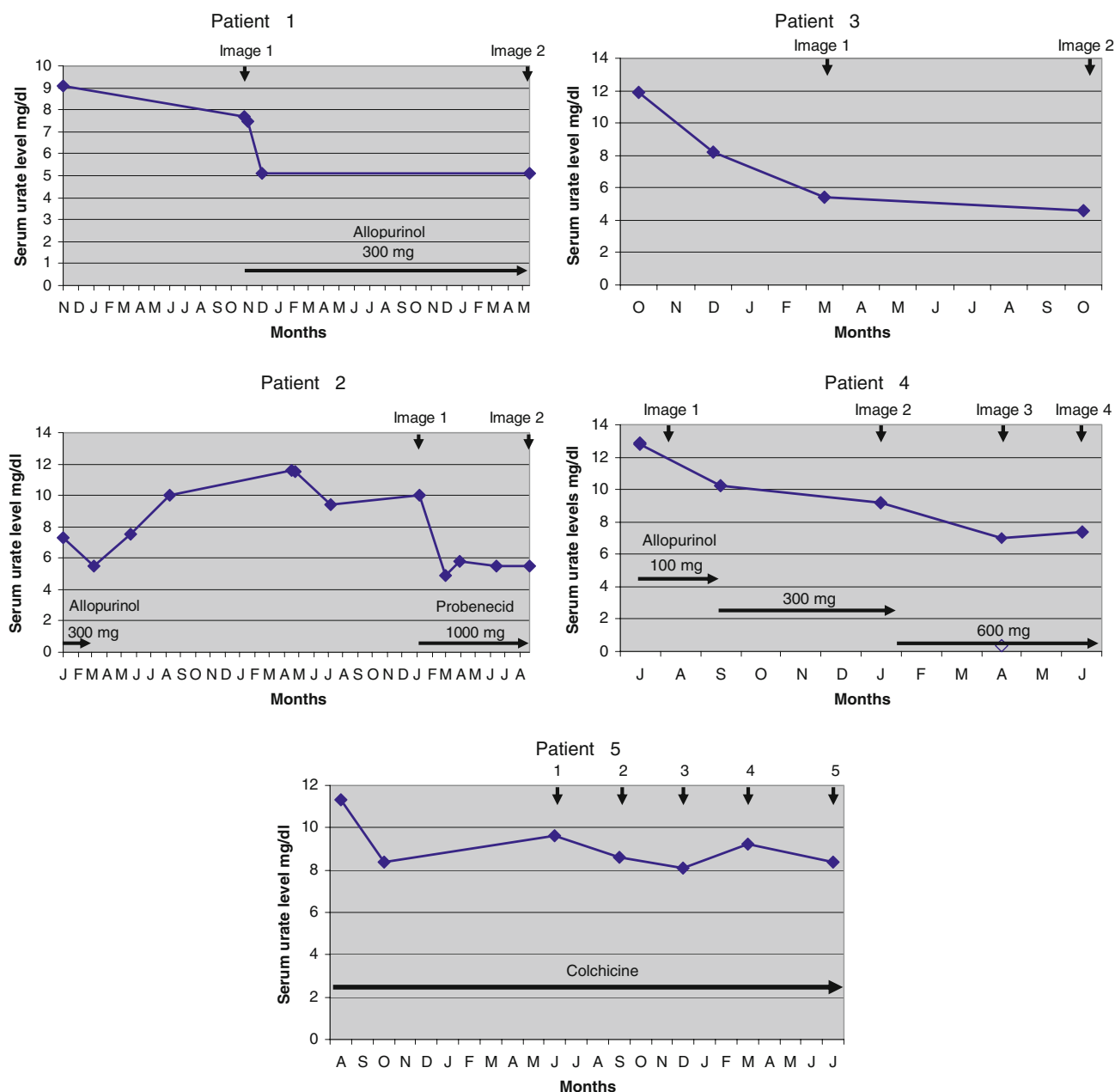


Fig. 7 Blue line denotes SU levels in mg/dl. Arrows mark date of ultrasound image taken

in patients with hyperuricemia and gout as does febuxostat, a new oral xanthine oxidase inhibitor. This is an opportune time to have a new method to follow response to treatment with ULD in patients with an increased uric acid pool, MSU crystal deposition, and gout. Ultrasonography appears to be a sensitive imaging modality for the detection of MSU crystal-induced arthritis. Herein, we described how the target lesion, as viewed by ultrasonography, in gouty arthritis disappears after sustained normouricemia is achieved. It is of interest that changes can occur within half a year of achieving a SU of ≤ 6 mg/dl using ULDs.

Similar to our ultrasound findings, one study used serial arthrocentesis and found disappearance of intra-articular MSU crystals over time when normouricemia was achieved [28].

Limitations of our study include the small number of examined joints and variation in type and duration of treatment. However, we believe that in principle ultrasonography can be a non-invasive way to track changes in the uric acid load in individually affected joints. It is a simple, safe, inexpensive, and non-invasive method to follow treatment response to ULD. Large prospective trials of patients with crystal proven gout are needed to further evaluate the use of

ultrasonography as a way to follow response of patients with gouty arthritis to treatment with ULDs.

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Conflict of interest statement The authors have declared no conflicts of interest.

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