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● *Original Contribution*

SONOGRAPHIC FINDINGS IN GOUTY ARTHRITIS: DIAGNOSTIC VALUE AND ASSOCIATION WITH DISEASE DURATION

AHMED M. ELSAMAN,* EMAN M. S. MUHAMMAD,† and FRANK PESSLER‡§

*Department of Rheumatology and Rehabilitation, Faculty of Medicine, Sohag University, Sohag, Egypt; †Department of Pathology, Faculty of Medicine, Sohag University, Sohag, Egypt; ‡TWINCORE Center for Experimental and Clinical Infection Research, Hannover, Germany; and §Helmholtz Centre for Infection Research, Braunschweig, Germany

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Abstract—The objective of this work was to evaluate the sonographic features of gouty arthritis and correlate findings with disease duration. The study was conducted on 100 patients in ambulatory care aged ≥40 y. Inclusion criteria included mono- or oligo-arthritis with effusion of the knee or the first metatarsophalangeal (MTP) joint and no known history of gout. A complete medical history was obtained with emphasis on the known risk factors or causes of gouty arthritis. A 12-MHz Medison linear probe was used for ultrasonography (US). Synovial fluid analysis with polarizing light microscopy was performed on all patients. Ninety-eight knee joints and 33 first MTP joints were examined. Gouty arthritis was found by US in four forms: (i) floating echogenic foci in effusion fluid or Baker cysts, (ii) deposits on the cartilage surface (double contour sign), (iii) erosions and (iv) mature tophus/tophi. These were found in 78.9%, 42.3%, 39.4% and 28.2% of patients, respectively. The overall sensitivity and specificity of US in detecting gout (as defined by the clinical gold standard, *i.e.*, detection of urate crystals by polarizing light microscopy) were 85.9% and 86.7%, respectively. Detection of echogenic foci in effusion fluid was associated with the shortest duration of symptoms (median duration 2 y) followed by double contour sign (3.5 y), erosions (4 y) and tophus (12.5 y). Sonographic findings in gout can be assigned a temporal pattern, with echogenic foci being associated with the shortest and full tophus formation with the longest disease duration. (E-mail: ahmed_elsaman@med.sohag.edu.eg) **© 2016 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Gout, Arthritis, Ultrasonography, Echogenic foci.**

INTRODUCTION

Gout affects around 1%–2% of the Western population at some point in their lifetime, and it is becoming more common. For instance, rates of gout approximately doubled between 1990 and 2010 (Ogdie et al. 2015). In 2012, in the United Kingdom, the prevalence of gout was found to be 2.5% and the incidence was 1.8% (Kuo et al. 2015). This rise is believed to be due to increasing life expectancy, changes in diet and an increase in disorders associated with gout, such as metabolic syndrome and high blood pressure. A number of factors have been found to influence the risk of developing gout, including age, sex and race. In men over the age of 30 y and in women over the age of 50 y, the prevalence is 2% (Schlesinger 2010).

Ultrasonography (US) is increasingly used to evaluate gout, and there has been particular interest in identifying gouty joint disease in the early stages before the development of irreversible complications (Kohler et al. 2015; Perez-Ruiz et al. 2009). The double contour sign, clusters of crystals floating in effusion fluid, and tophi are known sonographic features of gouty arthritis. In the present study, we aimed to evaluate the value of these findings, as well as erosions, for the sonographic diagnosis of gouty arthritis, to correlate them with proof of gout by microscopic identification of urate crystals and with the duration of symptoms and, thus, to identify findings that could serve as screening tools for the early detection of gouty joint disease.

METHODS

A descriptive cross-sectional study was carried out on male and female patients aged ≥40 y with episodic mono- or oligo-arthritis of the lower limb (defined as effusion in the knee or first MTP joint based on clinical evaluation). All patients enrolled in the study had a body mass index >23. Patients with any known cause of chronic

Address correspondence to: Ahmed M. Elsaman, Department of Rheumatology, Sohag University Hospital, Sohag University, Sohag, Egypt. E-mail: ahmed_elsaman@med.sohag.edu.eg

arthritis, including rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, scleroderma, neuropathic arthritis, seronegative spondyloarthropathy and similar conditions, were excluded from the study. Patients with known gouty arthritis were also excluded from the study. All enrolled patients had undifferentiated arthritis either not treated or treated with only non-steroidal anti-inflammatory drugs. Corticosteroid injections were delayed to avoid introduction of crystals into the synovial fluid. Subjects underwent US before joint aspiration, as effusion usually provides good contrast for crystal detection (Courtney and Doherty 2009). US was performed in both the anterior longitudinal suprapatellar median and paramedian (30° flexion, with quadriceps contraction) and transverse planes (with knee flexion and extension). Posterior longitudinal and transverse examinations were also done. The first MTP joint was examined from dorsal, lateral and plantar views in the longitudinal and transverse planes (Backhaus et al. 2001; Martinoli 2010; Schmidt et al. 2004). The bipolar method (with the left hand squeezing the suprapatellar space with the right thumb and the index fingers holding the joint line) facilitated in some cases the identification of crystal clusters. Erosions were considered to be present when visualized in both the longitudinal and transverse planes and with definite loss of bone cortex (D'Agostino et al. 2009). Echogenic foci were considered only when they had no posterior shadow and were smaller than 1 mm (Korkmaz 2011). Decreasing gain improved detection of echogenic foci (Ottaviani et al. 2012a, b).

Tophi were defined as hypo-echoic to hyper-echoic (with occasionally a posterior shadow), inhomogeneous material with poorly defined borders. Tophi can also be multigrouped (Thiele and Schlesinger 2007). The same US settings (frequency, depth, focusing) were used for all patients. A linear probe (Medison, Sonoace R3, made in South Korea) with a frequency of 8–12 MHz was used.

Polarizing light microscopy (Olympus SZX-10 microscope, made in Japan) was used as the gold standard for the diagnosis of gout. Slides were usually prepared in <48 h according to standard methodology (Gálvez et al. 2002; Zhang et al. 2006). Sterile technique was used (Newcombe 2013). An 18-gauge needle attached to a 20-mL syringe was used for the knee joint, and a 25-gauge needle attached to a 3-mL syringe, for the first MTP joint (Thomsen et al. 2006; Zayat and Wakefield 2011). Disease duration was defined as time elapsed from the onset of arthritis symptoms as reported by the patients.

Clinical and ultrasonographic examinations were done before polarizing light microscopy examination. The sonographer was therefore unaware of the results of the polarizing light microscopy examination, which was performed by a clinical pathologist.

All patients recruited into the study were informed of the methodology and goals of the study, and written consent was obtained from all included participants. The study was approved by the ethics committee of Sohag University. Personal and medical information was kept confidential and was not made available to a third party.

The data were analyzed using the program Statistical Package for Social Sciences (SPSS), Version 22 (IBM, Armonk, NY, USA). Initially, simple frequencies, means and standard deviations were described. To compare means, Student's *t*-test and analysis of variance (ANOVA) were used. Disease duration was not normally distributed. The Mann–Whitney *U*-test was therefore used to compare differences in disease duration between any two groups, and the Kruskal–Wallis test was used to compare the median differences among more than two groups. The χ^2 test was used to detect significance when comparing categorical data. In all tests performed, a level of significance of ≤ 0.05 was accepted.

RESULTS

The study included 100 participants, and a total of 131 joints were examined (one knee in 55 participants, two knees in 12 participants, one first MTP joint in 14 participants and one knee plus one first MTP joint in 19 participants, for a total of 98 knees and 33 first MTPs joints examined) (Table 1).

The mean age of the participants was 53.1 y (range: 40–75), and the mean age of those who had crystals (detected by polarizing light microscopy) was 55.1 y

Table 1. Demographic data of the study group

Variable	Total cases	Positive cases by PLM	Positive cases by US
Number of cases	100	47 (47%)	46 (46%)
Number of joints	131	71 (54.2%)	69 (52.7%)
One knee	55	23 (41.8%)	21 (38.2%)
Two knees	12	3 (25%)	5 (41.7%)
One first MTP	14	12 (85.7%)	10 (71.4%)
One knee + one first MTP	19	9 (47.4%)	10 (52.9%)
Joints aspirated			
Right knee	65	25 (38.5%)	28 (43.1%)
Left knee	33	18 (54.5%)	15 (45.5%)
Right first MTP	15	13 (86.7%)	13 (86.7%)
Left first MTP	18	15 (83.3%)	13 (72.2%)
Age			
Mean ± SD	53.07 ± 6.13	55.06 ± 6.42	54.61 ± 5.95
Range	40–75	42–75	45–75
Sex			
Male	55 (55%)	30 (63.8%)	31 (67.4%)
Female	45 (45%)	17 (36.2%)	15 (32.6%)

PLM = polarized light microscopy; US = ultrasonography; MTP = metatarsophalangeal joint.

(range: 42–75). There was a positive association between older age and crystal-induced arthritis; of the 47 patients with crystals, 40 (85%) were older than 50 y, and 32 of the 53 patients with no crystals (60%) were older than 50 y (odds ratio = 3.75, $p = 0.006$) (Table 1).

The male-to-female ratio was 11:9 (1.22) for all participants, whereas the ratio was 5:3 (1.76) in patients diagnosed with gout by polarizing light microscopy and 2:1 (2) for those diagnosed with gout by US. Of the 131 joints examined, 71 gout-affected joints (43 knee joints and 28 first MTP joints) were identified by polarizing light microscopy, and 69 (43 knee joints and 26 first MTP joints) by U/S (Fig. 1a). Non-mono-sodium urate (MSU) crystals only (calcium pyrophosphate dihydrate [CPPD] n = 7, apatite n = 3, overlap crystals n = 1) were detected in 11 joints, and no crystals in 49 joints (Table 1).

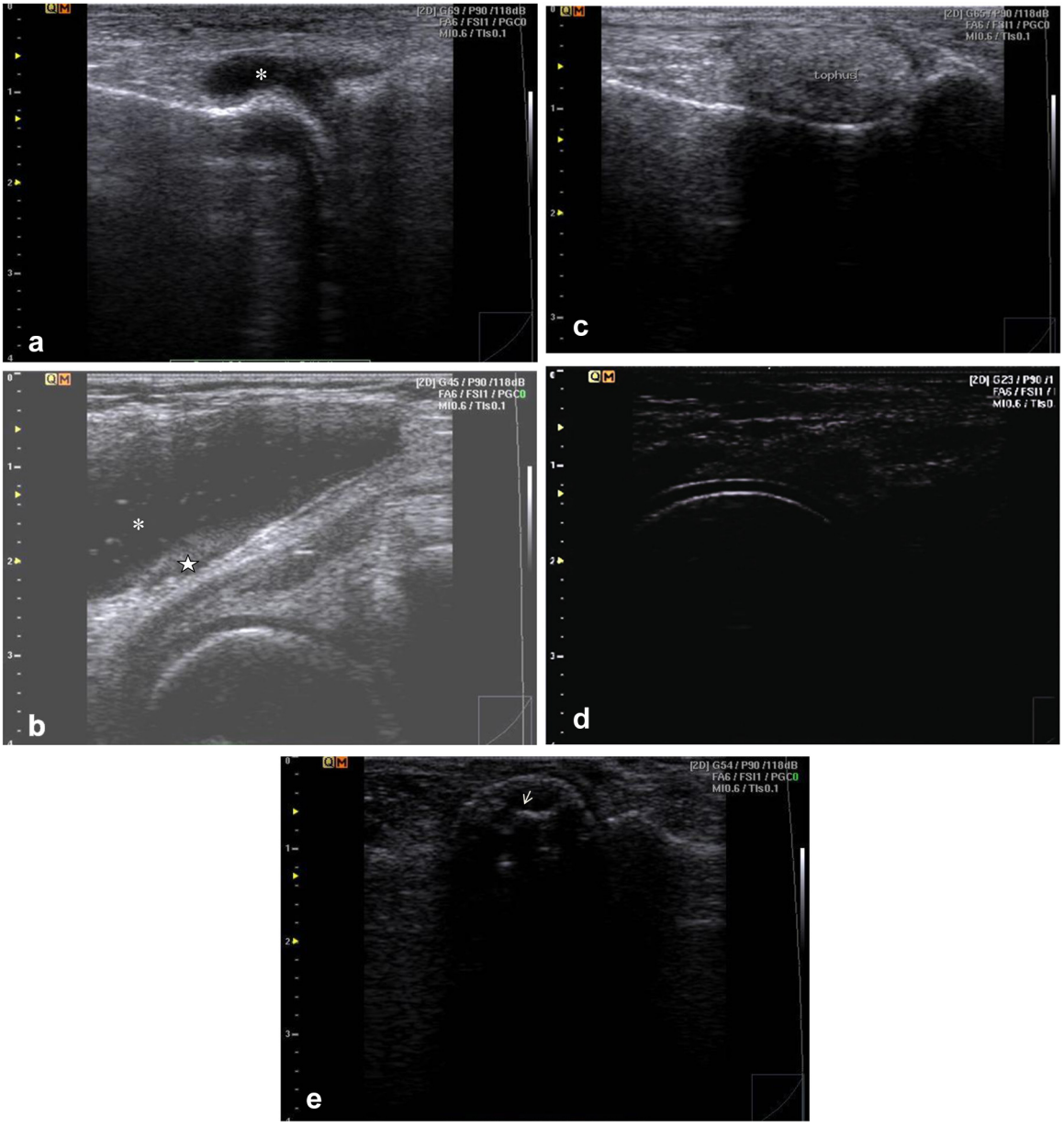

Fig. 1. Ultrasonographic findings in crystal-induced arthropathy. (a) Effusion of first MTP dorsal longitudinal view, grade 3, B-mode with synovial fluid making a convex bulge (*white asterisk*). (b) Echogenic foci inside a Baker cyst (knee, posterior longitudinal medial view, *white asterisk*) with synovial proliferation evident at the bottom of the cyst (*white star*). (c) Tophus near the first MTP joint (longitudinal dorsal view) with a posterior shadow and juxta-articular position. (d) Double contour sign (knee, posterior longitudinal view of the femoral condyle) parallel to synoviochondral enhancement along its full length. (e) Periarticular erosion of the first metatarsal bone (longitudinal dorsal view, *white arrow*).

The most common sonographic sign of gout was crystals floating in effusion fluid (77 joints, 59%, 53 knees, 24 MTP joints), especially inside Baker cysts (34/53 knee joints) (Fig. 1b), followed by erosions (51 joints, 39%, 37 knees, 14 MTP joints) (Fig. 1e) and the double contour sign (32 joints, 24%, 22 knees, 10 MTP joints) (Fig. 1d). Tophus was found in 20 joints (15%, 8 knees, 10 MTP joints) (Fig. 1c).

The sensitivity and specificity of US in detection of gouty arthritis, compared with polarizing light microscopy, were 86% and 87%, as US detected gout in 61 of the 71 positive gouty arthritis cases and excluded 52 of the negative 60 cases, with false-positive findings seen in 8 negative cases and false-negative results seen in 10 positive cases. Both parameters differed significantly among the four major sonographic signs. The sensitivity and specificity of US in detecting gout were 79% and 65% for microtophi, 42% and 97% for the double contour sign, 39% and 62% for erosions and 28% and 100% for true tophi (Table 2 and Fig. 2). A patient who had one or more of the four sonographic signs was considered to have gout as diagnosed by sonography. Controls in this study were considered patients with joint effusion who did not have urate crystals on polarizing light microscopy examination.

There was a strong positive association between disease duration and the presence of tophus, as median disease duration was 12.5 y in patients with tophus and 2 y in patients without tophus ($p < 0.001$, Mann–Whitney *U*-test). On the other hand, median disease duration was shortest in cases with echogenic foci inside effusion fluid (2 y with and 5.5 y without echogenic foci, $p = 0.003$, Mann–Whitney *U*-test). Median disease duration was 3.5 y among patients with the double contour sign and 4 y among patients with erosions. Kruskal–Wallis analysis revealed that median disease duration differed significantly among patients with the four ultrasonographic signs ($p < 0.001$). Table 3 and Figure 3 outline the distribution of disease duration for each of the four ultrasonographic findings. These results allowed us to define the temporal trend of appearance (from earliest to latest) as floating echoes (echogenic foci) < double contour < erosions < tophi.

DISCUSSION

The role of US in the diagnosis of gout is well known. Commonly found signs are erosions, crystal deposition on the cartilage (double contour sign), hyper-echoic spots in effusion fluid, Baker cysts ("snowstorm appearance") and tophus. However, little is known about the sequential appearance of these signs, except that tophus develops late in well-established disease (Carter et al. 2009; Grassi et al. 2006; Howard et al. 2011; Ottaviani et al. 2012a, b; Peiteado et al. 2012; Slot and Terslev 2010). Thus, this study provides additional data on earlier sonographic features of gout and, in particular, identifies echogenic foci ("snowstorm") as the earliest finding in many cases.

Diagnostic value of US

In our study, the overall sensitivity of US in detecting gouty arthritis was lower than the 96% reported in the study on asymptomatic patients with hyperuricemia by

Table 2. Sensitivity studies

Variable	Positive by PLM	Negative by PLM	Total cases	Sensitivity	Specificity
Cases diagnosed by US					
Positive by US	61	8	69	85.9%	86.7%
Negative by US	10	52	62		
Total	71	60	131		
Echogenic foci by US					
Positive	56	21	77	78.9%	65.0%
Negative	15	39	54		
Erosions by US					
Positive	28	23	51	39.4%	61.7%
Negative	43	37	80		
Double contour sign by US					
Positive	30	2	32	42.3%	96.7%
Negative	41	58	99		
Tophi by US					
Positive	20	0	20	28.2%	100.0%
Negative	51	60	111		
Echogenic foci + double contour					
Positive	24	2	26	33.8%	96.7%
Negative	47	58	105		
Echogenic foci and/or double contour					
Positive	61	21	82	85.9%	65.0%
Negative	10	39	49		

PLM = polarized light microscopy; US = ultrasonography.

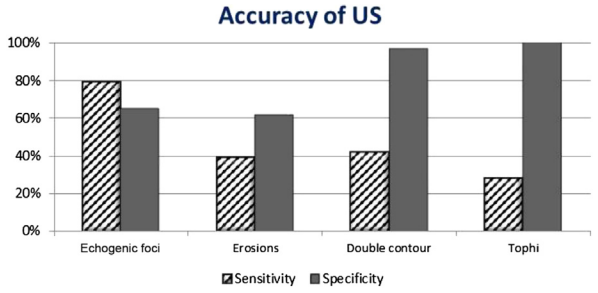

Fig. 2. Accuracy of US in the diagnosis of gouty arthritis. Detection of echogenic foci has the highest sensitivity (>80%), followed by double contour sign, erosions and tophi. On the other hand, detection of tophi has the highest specificity, followed by double contour sign, echogenic foci and erosions. US = ultrasonography.

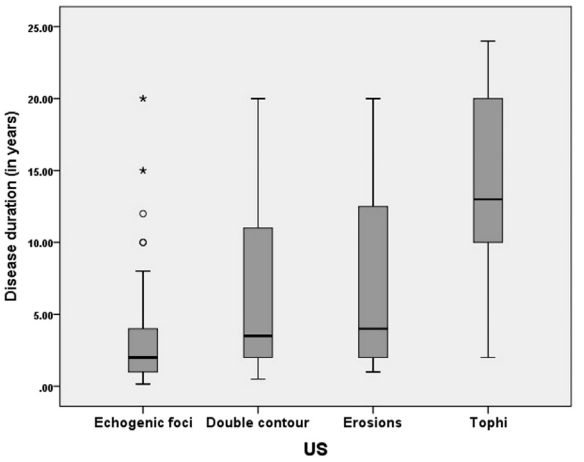

Fig. 3. Differences in median disease duration among the four cardinal sonographic findings. The differences between tophi and the other three signs and between echogenic foci and the other three signs were significant (Mann–Whitney *U*-test). The comparison of median disease duration across all four signs (Kruskal–Wallis test) was also highly significant.

Perez-Ruiz et al. (2009), but the difference may be explained by the fact that these authors used power Doppler as an additional sonographic tool.

The double contour sign is specific for gouty arthritis (Thiele and Schlesinger 2007) and was observed with similar frequency (43.7%) by Filippucci et al. (2009) in a study of knee joints, but substantially more often (69%) in the study by Peiteado et al. (2012), which included examination of bilateral knees and first MTP joints in patients with known gouty arthritis. We found the double contour sign to be highly specific (96.7%) in our study, compared with 83.3% reported by Naredo et al. In the latter study, the radiocarpal joints were also included (Naredo et al. 2014), which may explain the difference. Hyper-echoic spots were observed in 78.9% of our patients in comparison to the 97% in the studies of Peiteado et al. (2012) and Grassi et al. (2006) and to the 32% reported by Lei and Ling-Yan (2011). The wide difference in results may be due to inclusion of Baker cysts as part of the joint examination and to the fact that all the patients in our study had a joint effusion (Fig. 1b). The presence of echogenic foci and or the double contour sign increased the sensitivity to 85.9%, but the specificity was 65%; however, considering both together increased the specificity to 96.7%, but sensitivity decreased to 33.8% (Table 2). We observed erosions at a somewhat lower frequency than others, who reported a frequency of 39.4% (Ottaviani et al. 2012a, b). This may, among other reasons, be due to the higher prevalence of other erosive joint disorders such as osteoarthritis and chronic inflammatory arthritis such as rheumatoid arthritis in their cohort (Zhang et al. 2012). Indeed, as expected, erosions were neither sensitive nor specific for the diagnosis in our study. The specificity of tophus for the sonographic diagnosis of gout in our study was 100%, which agreed well with the findings of Ottaviani et al. (2012a, b). Tophus was reported in 19% of their cases, and in another study, it was found in 35% (Howard et al. 2011). This difference may be related to disease duration in both studies. The strong positive correlation between disease duration and tophus means that it is not a suitable sign for early diagnosis (Howard et al. 2011). However, its high specificity suggests that it can be considered a pathognomonic sonographic sign of established gout.

Table 3. Relation between disease duration and ultrasonographic findings

Ultrasonographic finding	Median disease duration (y)		
	Patients with negative sign	Patients with positive sign	*p* Value (Mann–Whitney test)
Echogenic foci	5.5 (0.5–24)	2.0 (0.15–20)	0.003
Double contour sign	2.0 (0.15–24)	3.5 (0.5–20)	0.101
Erosions	2.5 (0.15–24)	4.0 (1–20)	0.050
Tophi	2.0 (0.15–20)	12.5 (2–24)	<0.001

In our study, the first MTP joint was found to be more frequently affected than the knee joint, which agrees well with results obtained by Carter et al. (2009) and is likely explained by the well-known observation that the first MTP joint has a lower temperature, which facilitates crystal precipitation (Doherty 2009).

Temporal associations of sonographic findings

To our knowledge, a correlation between sonographic features of gout and disease duration has only been reported for tophus. In our study, the temporal progression of sonographic features of gout was as follows: floating echoes, double contour, erosion and finally tophus. However, there was significant overlap in

duration, suggesting that the rate of progression varies from patient to patient.

Limitations

Disease duration was estimated in our study as arthritis duration, but this represents an underestimation, as hyperuricemia may go on for a considerable time before a first gout attack (Perez-Ruiz et al. 2009; Sivera et al. 2014). A prospective study design would be needed to detect the onset of hyperuricemia and put it into perspective with the onset of joint symptoms and US findings. A second difficulty was the suboptimal specificity of echogenic foci, as some patients had more than one type of crystal. To compensate for this, only echogenic foci without posterior shadow and ≤1 mm in diameter were considered (Korkmaz 2011). This increases specificity, but other types of crystals such as CPPD can have the same sonographic appearance (Filippucci et al. 2012). A third difficulty is that few patients had only one sonographic sign, which makes statistical assessments less accurate. The bipolar method was helpful in some cases to mobilize echogenic foci and also to differentiate them from the tips of the synovial villi, as synovial villi move in a wavy pattern (to and fro) but not freely like echogenic foci (Carotti et al. 2002).

CONCLUSIONS

It can be said that US is achieving progress in the early diagnosis of gout. The "snowstorm sign" and floating echoes are early, sensitive signs that can be used for screening purposes. Synovial fluid analysis, a test with high specificity, should be done to confirm the diagnosis in these cases.

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