Review

Therapeutic consequences of crystals in the synovial fluid: a review for clinicians

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ABSTRACT

Many crystals may be found in arthritic joints. Rheumatologists are able to diagnose, with a high degree of probability, which crystals induce arthritis in the individual case. A definite diagnosis supported by polarisation microscopy may provide a firm basis for adequate long-term treatment. Recently new insights in the inflammatory processes induced the development of targeted therapies. We review novel developments in crystal-induced arthritis and gout in particular.

Introduction

Diagnosing the cause of arthritis is often not easy but the detection of crystals is important as it can lead the way to adequate treatment. Antonie van Leeuwenhoek described the microscopic appearance of urate crystals in 1679. Only in 1848 the English physician Alfred Baring Garrod realised that excess uric acid in the blood caused gout. Diagnosis in crystal-induced arthritis often can be made with certainty by applying polarisation microscopy (1-3), or with a degree of probability by applying sets of clinical criteria or imaging techniques (4-7). Rheumatologists may find the cause of arthritis by microscopy Two crystals have major diagnostic and clinical relevance: monosodium urate (MSU) evoking gout (Fig. 1), and calcium pyrophosphate dehydrate (CPPD) crystals involved in pyrophosphate crystal arthritis or formerly called pseudogout (Fig. 2). Crystal induced arthritis may occur spontaneously without a clear cause, or following an event, such as surgery or weight loss. Clinicians always have to consider a coexisting bacterial arthritis. Microbiologists may tell us which microbe can be seen from Gram staining and/or culture.

Several other crystals may be found in an arthritic joint: hydroxyl apatite crystals are submicroscopic in size, invisible without specific staining and their presence is often difficult to interpret. Cholesterol monohydrate plates or rice bodies can be seen sporadically (8, 9), and their presence implies chronicity of synovitis with effusion (Fig. 3). A relevant finding can be iatrogenic glucocorticoïd crystals intra-articularly, as these imply a preceding therapeutic puncture (Fig. 4). A competence of the microscopist is to recognise not only these types of crystals but also certain artifacts (Fig. 5). Crystals such as calcium oxalate, haematoidin, Charcot-Leiden, cryoproteins are occasionally reported but can be considered as curiosities (1).

Crystal detection and identification is currently part of the European core curriculum in rheumatology (EULAR courses), as well as treatment guidelines. (http://www.eular-onlinecourse.org/) Before starting a therapeutic regimen a microscopically-proven diagnosis is often needed, only then treating to a predefined target can be realised. The understanding of chronic inflammation is growing and new therapeutic regimens have become available for the clinician.

We review the analysis of synovial fluid and the clinically most important crystals which should form a solid basis for an individual's diagnosis and therapy.

Analysis of synovial fluid

Synovial fluid (SF) analysis has long been recommended as a routine procedure to enable diagnosis of crystal-induced arthritis (2). Polarisation microscopy was introduced by Hollander and McCarty (3). This analysis should be performed on a droplet of fresh punctate. Examination of SF after several hours may still be adequate, though the fresher the analysate the better. Crystals will not degrade rapidly, but cellular

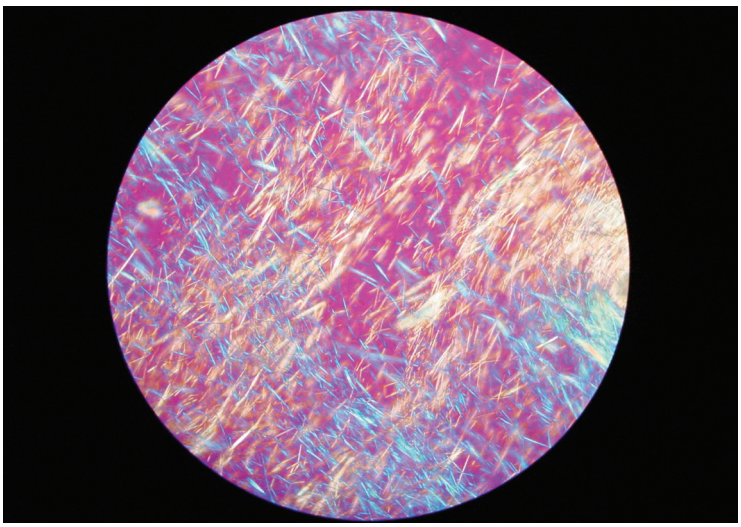

Fig. 1. Polarisation microscopy of urate needles (400x)

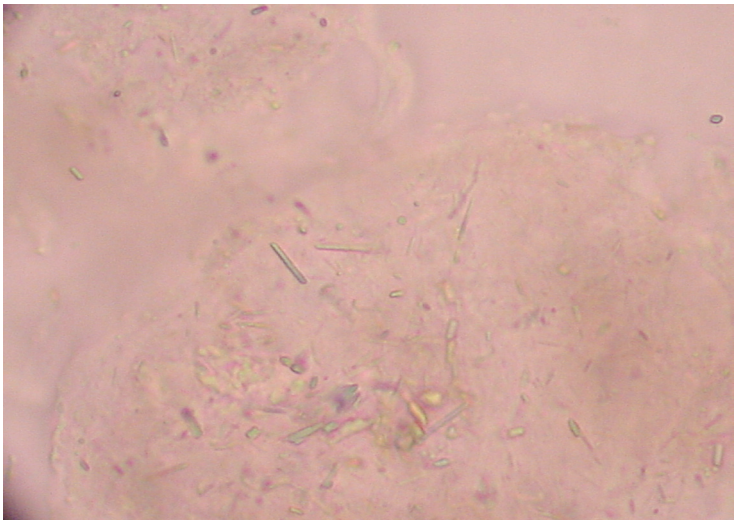

Fig. 2. calcium pyrophosphate crystals with tubules in normal light microscopy (1000x)

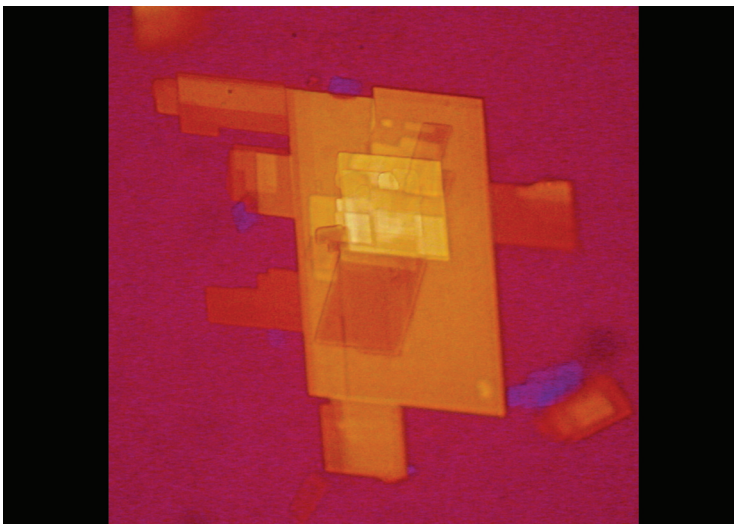

Fig. 3. Polarisation microscopy of cholesterol monohydrate plates (1000x)

components will deteriorate rapidly when outside the body. Cell integrity is especially important for detecting smaller intracellular CPPD crystals. The gross appearance and cell count of SF may help to distinguish between inflammatory and non-inflammatory swelling.

The recommended synovial fluid analysis (SF) includes: inspection of SF for gross appearance, a leukocyte count, a microbiologic analysis (Gram staining plus culture from a specialised microbiological laboratory even to be considered when crystals have been recognised) and polarisation microscopy searching for: urate needles with a negative birefringence and pyrophosphate rhomboids with a weakly positive birefringence, and other crystals (1-3).

The clinician has to consider a diagnosis such as gout or pyrophosphate crystal arthritis (formerly pseudogout) besides bacterial arthritis in any patient with severe arthritis (4). Sporadically, on microscopy one may encounter cholesterol monohydrate plates, rice bodies, or other crystals by surprise, (see Table I). Rice bodies are directly visible in the SF. By ultrasonography (US) and/or magnetic resonance imaging (MRI) rice bodies may be detected, but these techniques still have to prove their diagnostic validity in acute arthritis. A large percentage of patients with gout and normal plain radiographs have arthropathy that is only detected by advanced imaging. MRI appears to be more sensitive than US at detecting these findings (5).

Mono sodium urate (MSU) crystals

The clinical presentation of gout can be misleading and other diseases can present in similar ways. Sets of clinical criteria for diagnosing gout often fail due to limited value of the likelihood ratio of a negative test, see Table II. (4, 6). In chronic gout the same difficulty is encountered when using the ACR proposal and the EULAR recommendations. This means that in case of non-specific arthritis it is difficult to exclude gout due to poor specificity of clinical criteria (6, 7). Obtaining microscopic proof with specific findings of MSU needles is very helpful, although even in gouty arthritis absence of these nee-

dles may occur occasionally. In (micro) tophi birefringent needles can always be demonstrated (Fig. 1). In a diagnostic setting ultrasonography (US) may reveal classic findings, but it remains to be determined in what percentage of gout presentations US merits additional diagnostic value.

The treatment of a patient with gout can be very complex due to advanced age, renal dysfunction and comorbidity with potential drug-drug interactions (10). Modern fructose enriched drinks and purine rich diets may complicate treatment at the individual level (11). Gout occurs in the elderly more frequently than in the young, and is associated with cardiovascular mortality possibly due to suboptimal gout care (12, 13). In elderly women often a polyarticular arthritis is seen including the finger joints and the serum uric acid levels may be higher than in males (14). Currently, guidelines have been developed regarding diagnosis and management of gout (15-17).

Acute gouty attack

Conservative treatment for pain due to an acute attack consists of ice application for 20 to 30 minutes up to 4 times a day (16), plus an NSAID, orally or as suppository or intramuscular injection. Interestingly there is no significant difference on group level between NSAIDs regarding effectiveness (16). Improvement may be seen within 4 hours. A relative contraindication for NSAIDs is 1) advanced age with other health problems, and/or 2) gastrointestinal bleeding, 3) renal failure, 4) heart failure.

Glucocorticosteroids 35mg daily during a 5-day period have been found to be about as effective as NSAIDs (17, 18), and may thus be used if contraindications exist for NSAIDs. Intra-articular glucocorticosteroids have also been found to be effective, however in individual cases concurrent joint infection must be excluded. In many parts of the world, intramuscular corticosteroids are used to treat acute gouty attacks (18, 19).

In general there is no indication for high or increasing dosages of colchicine (20). The risk at developing diarrhoea and gastric upset can be decreased by using lower yet still effective daily dosages of 0.5–1.5 mg daily. In exceptional cases, colchicine up to 1.8 mg daily (if tolerated) may be considered for those with contraindications or intolerance for NSAIDs and corticosteroids: more than 50% pain reduction at 24 hrs can be reached in 38% of patients using 1.8 mg colchicine *versus* 16% in placebo patients indicating a number needed to treat (NNT) of 4.5 (20). An intravenous route for colchicine is never recommended. A contraindication for the use of colchicine is renal insufficiency, as it may result in nausea, diarrhoea, severe toxic hepatitis and severe bone marrow suppression. A caveat exists regarding pharmacological interactions: colchicine may interact with commonly prescribed atorvastatin and erythromycin (30-32).

For the management of acute gout and for preventing recurrent attacks, anticytokine therapy targeting at the inflammasome, particularly at interleukin (IL)-1β then may be effective, (Table III). Three IL-1-inhibiting drugs have

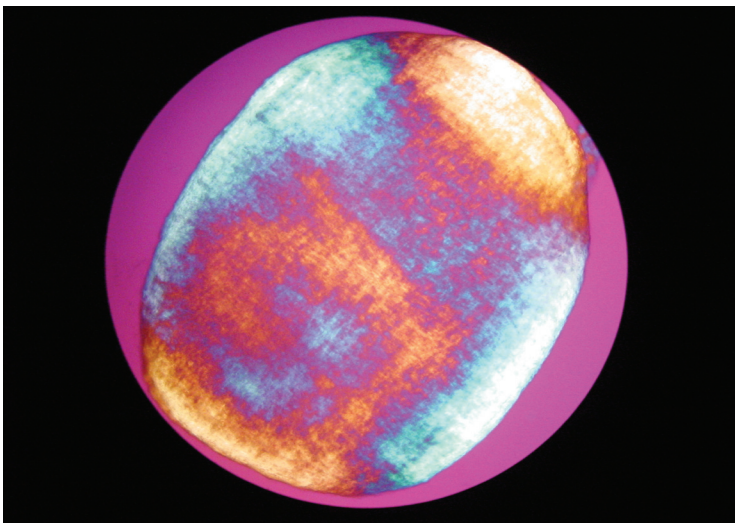

Fig. 4. Polarisation microscopy of a birefringent balloon, *i.e.* a rice body (400x)

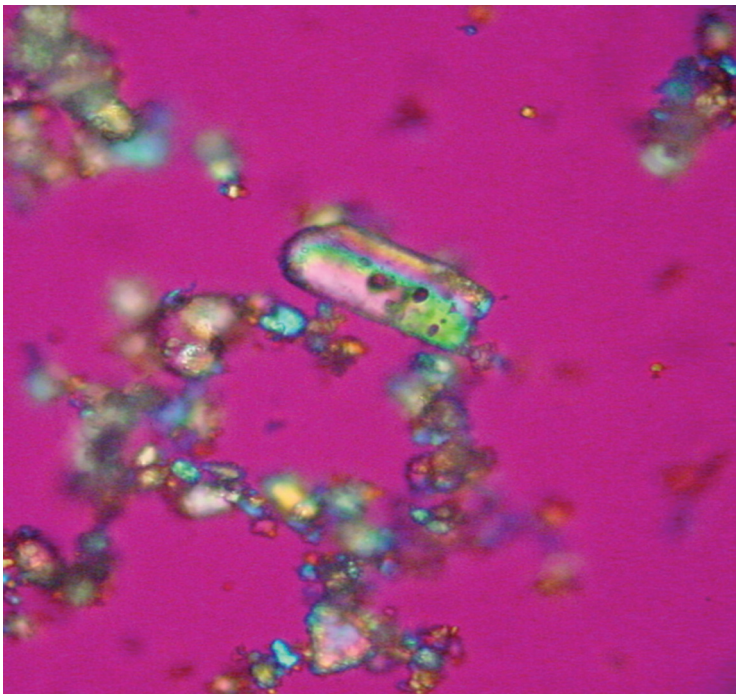

Fig. 5. Polarisation microscopy of multiform birefringent crystals, *i.e.* depomedrol (400x) in polarised light with compensator

been tested in small series with promising results, anakinra (21, 22), rilonacept (23) and canakinumab (24). The role these agents may play in clinical practice of gout, once approved, is to be determined. These monoclonal antibodies to IL-1 could prove to be well applicable in patients with (renal/gastrointestinal) contraindications or intolerance for the currently available medications. It will however be hard to improve on performance of glucocorticosteroids, particularly regarding the issue of costs. If IL-1 blockade may help to prevent clinical admissions the costs of this novel therapy may easily become acceptable.

Chronic gout

General measures are commonly known like diet (poor in purines), no alcohol (beer in particular), weight reducing diets and abstinence from fructose-containing fluids. Many doctors and patients think that these low-calorie drinks are innocent, but they are not (25). If no clear contraindication exists, any patient with tophi and/or more than 2 gout attacks per year should be offered urate lowering therapy, (Table IV): commonly allopurinol is the first choice as a xanthine oxidase inhibitor (XOI), if needed plus a uricosuric (26, 27); in cases with intolerance/allergy the novel XOI febuxostat can be prescribed (28-31), see Table IV for the efficacy table of XOI. An additional role has been suggested for febuxostat in mild renal insufficiency, though more extensive studies are warranted. In the case that serum uric acid levels have not been lowered adequately, an additional uricosuric has to be considered: the availability of sulfinpyrazone or probenecid or benzbromarone varies greatly from country to country. The evidence in the long-term for these therapies is rather scarce, however. Next to benzbromarone, a new uricosuric lesinurad is looming on the horizon.

When starting urate lowering therapy (ULT), colchicine 0.5mg bd or glucocorticosteroids is highly recommended to prevent gout flares, particularly in a period during which the serum urate concentration fluctuates, as occurs in the first half year during ULT (12, 14). A caveat exists regarding pharmacological interactions: colchicine may interact with commonly prescribed atorvastatin and erythromycin (30-32). The dosage of allopurinol should be increased slowly to 100 mg at 2–4 weeks guided by the serum uric acid levels. In cases of tophaceous gout, prophylaxis of colchicine daily 1.0 mg (if tolerated, when diarrhoea occurs the dose should be reduced) for aperiod of about six months is recommended, often even longer.

By controlling hyperuricaemia the prognosis of gout, comorbidity and early death improves (19). The primary aim of treatment is to reduce the level in tissues below the saturation point at which gout crystals are formed. These should be reached with serum uric acid concentrations stable, *i.e.* <0.36 mmol/l according to EULAR guidelines, or <0.30 mmol/l according to British guidelines. If these targets cannot be reached (15-17), it may be useful to combine XOI (mostly allopurinol) with the uricosuric that is locally available (23): benzbromarone in Eurozone or probenecid in USA. For about 10% of gout patients an alternative to allopurinol is needed due to lack of efficacy or evidence of intolerance/allergy; then febuxostat is to be considered. In such cases 500 mg vitamin C can be prescribed daily, which has a moderate uric acid lowering effect (35).

Human beings are lacking in the uricase enzyme that converts uric acid into hydrophylic allantoin. New drugs have been developed based on uricase. In sporadic cases like cytotoxic treatment of leukaemia or Hodgkin's disease, uricase derivatives, such as rasburicase (36), may be indicated for debulking or possibly even for chronic maintenance therapy. Uric acid concentrations will fall instantly to undetectable levels when uricase is administered (36-37). For chronic maintenance, PEGylated uricase, with a prolonged halftime, has been developed (36-37). However, many patients had infusion reactions and developed flares of arthritis and kidney stones. Antibodies to PEG-uricase occur in 76% (31/41) at week 14 and 38% at 1 year, but increase to 89% in the long-term. In a six-month, placebo-controlled clinical trial, pegloticase 8 mg every 2 weeks induced a lytic decrease of serum urate concentrations leading to dissolution of tophi in 40% of patients at their final visit. However, 58% are non-responders to the defined target serum urate of 0.36 mmol/l (at 80% of the time during month 3 and 6), also possibly due to antibody formation. Moreover 26–31% experienced infusion reactions and 77% suffered from gout flares. While long-term data are awaited, an anti-immunologic/anti-inflammatory strategy is needed to prevent pegloticase antibody formation leading to infusion reactions and diminished/shortened efficacy, and might also prevent gout flares. According to current clinical data, pegloticase might have an important role as a (bridging) treatment in serum urate-responsive patients for rapid urate debulking in severe chronic refractory gout.

Even more important, in pivotal trials PEG-uricase has been associated with a possible increase in cardiovascular death: at the ACR 2008 meeting it was reported that mortality data revealed 4% mortality in PEG-uricase *versus* 1% in placebo in 225 treatment failure gout patients. The association of mortality in PEG-uricase-treated gout patients remains controversial, as gout is be associated with comorbidity and with a poorer clinical situation. Since the Framingham study and the Multiple Risk Factor Intervention Trial (MRFIT) gout and/or hyperuricemia are associated with coronary heart disease possibly via stimulated rennin-angiotensin-aldosterone system, or via endothelial dysfunction (39). The role of BMI in inducing hyperuricaemia, hypertension as well as hyperlipidaemia needs clarification. The potentially increased cardiovascular death risk due to lytic lowering of uric acid concentrations has to be clarified before widespread use of uricase derivatives can be propagated.

Calcium pyrophosphate dehydrate (CPPD) crystals

CPPD-associated arthritis is due to crystals deposited in fibro- and hyaline cartilage and often seen in degenerative joint disease, especially in the knee. A rapid onset of inflammatory symptoms and signs is suggestive but not proof of

CPPD-associated crystal arthritis.

Radiographic chondrocalcinosis is not highly sensitive nor specific for the diagnosis of CPPD-associated arthritis (pseudogout). Ultrasonographic calcific reflections from within the cartilage appear more sensitive and specific for CPPD arthritis with an excellent diagnostic value in cases where crystals are visualised: likelihood ratio for positive test result is 24 (95% CI 3.5, 168.0). A definitive diagnosis relies on the identification of CPPD crystals by polarisation microscopy from the punctate, derived from intra-articular fluid: weakly positive birefringent crystals with a rhomboid configuration (see Table I and Fig 2). Ultrasonography is a very promising technique to demonstrate calcific reflections highly suggestive for calcium pyrophosphate arthritis. For diagnosis a bacterial infection should always be excluded by performing a culture.

CPPD crystal arthritis is the third most common inflammatory rheumatic disease after RA and gout (40). CPPD-associated arthritis with or without chondrocalcinosis is often seen in degenerative joint disease, particularly in the knee and wrist. Recently, a EULAR Task Force developed recommendations for diagnosis and management of CPP crystal arthritis (41, 42). The prevalence of chondrocalcinosis in adults aged 40–79 years is 4.5% (40). CPPD deposition is seen more frequently in association with hyperparathyroidism (odds ratio OR: 3.0), hypomagnesaemia (OR 13.5) and (repetitive) trauma (OR 5.0) or after surgery or myocardial infarction (39).

Once a definite diagnosis has been made one should consider treatment which is restricted to symptomatic control.

Treatment in acute CPP crystal arthritis may consist of NSAIDs orally or in suppository form or even intramuscularly, intra-articular glucocorticosteroid injection and sometimes colchicine or corticosteroids orally or intramuscularly (42). Every clinician knows this but few systematic studies have been done and the evidence to support their use is mainly by extrapolation from studies on gout. Even interleukin-1 inhibitors in CPPD case series have proven to be effective. For classic colchicine, the intravenous route is not advised in CPPD arthritis (43).

Despite the sparse evidence regarding efficacy, there is abundant evidence concerning side effects of NSAIDs: gastrointestinal ulcer or bleeding, cardiovascular events, and renal impairment due to NSAIDs, and of colchicine: diarrhoea and nausea. These side effects restrict their use in elderly patients. A small non-randomised controlled trial compared the efficacy of a single intramuscular injection of 7mg betamethasone in 10 patients, *versus* a single intravenous injection of 125 mg methylprednisolone in 7 patients, *versus* diclofenac 150 mg daily for 3 days in 10 patients (40, 44). The number needed to treat is only 3 to reach a 50% improvement for glucocorticosteroid injection *versus* diclofenac, and was only significant on day 1, but not on days 3, 6 and 15, suggesting that glucocorticosteroids may be more effective at gaining a quick control of severe CPPD-associated arthritic pain. These data are supported by an uncontrolled study in 14

Table I. Clinically important crystals which can be seen by applying polarisation microscopy.

Geometry	Birefringence	Pathogenecity	Diagnosis
Needles	yes: negative	yes	gout: MSU-associated arthritis
Rhomboids	yes: weekly positive	sometimes	CPP-associated arthritis
Plates	yes: negative	yes if bulky	cholesterol monohydrate
Irregular rods	yes: negative	?	cholesterol anhydrate*
Balloons	yes	no, epiphenomenon	chronic arthritis
Rare			
polymorph artifacts	yes	no?	iatrogenic glucocorticoid
Bipyramids	yes	yes	oxalosis

*crystals probably not intra-articular but present in bile ducts.

Table II. Limited validity of the American College of Rheumatology (ACR) criteria (1-More than one attack of acute arthritis; 2-Maximum inflammation developed within one day; 3-Mono- or pauciarticular attack; 4-Redness observed over joint; 5-MTP1 painful or swollen; 6-Unilateral arthritic attack in MTP1; 7-Unilateral tarsal arthritic attack; 8-Tophus (proven or suspected); 9-Hyperuricemia; 10-Asymmetric swelling within a joint; 11-Complete remission of an attack) for classifying patients with gout, as no test combines a low (<0.5) LR_{neg} with a high (>2.0) LR_{pos} (6, 7).

N_{ACR}	PPV	NPV	LR_{pos}	LR_{neg}
>3	0.70	0.97	1.3	>100
>4	0.72	0.79	1.5	7
>5	0.80	0.65	2.2	3.2
>6	0.85	0.52	3.2	1.9
>7	0.87	0.42	3.7	1.3
>8	0.94	0.38	7	1.1

N_{ACR}: number of positive ACR criteria; PPV: positive predictive value; NPV: negative predictive value; LR_{pos}: likelihood ratio of a positive test result (optimal: >2); LR_{neg}: likelihood ratio of a negative test result (optimal: <0.5).

Table III. Inflammatory syndromes and their targeted therapies.

Disease/syndrome	Mechanism	Targeted therapy
Cryopyrin-associated periodic syndr./ Familial Mediterranean Fever (FMF)	NALP3-inflammasome	anti-IL1: Anakinra
Gout, or CPP-associated arthritis	NALP3-inflammasome	Rilonacept, Canakinumab
Chronic (rheumatoid) arthritis	B- lymphocytes	Rituximab
+ cholesterol plates	T-lymphocytes	Abatacept
+ rice bodies	synoviocytes	Anti-TNF anti-IL6 or anti-IL1

Table IV. Therapeutic options in crystal-associated arthritis.

Gout: MSU-associated arthritis	
Acute atack	Cold packs 3–6 times daily 10-20 minutes NSAID max for 6 weeks Prednisolone 30-35 mg for 10 days Prednisolone intra articular or i.m. colchicine 2dd 0.5mg, max up to 1 year (also to prevent flares) anakinra off-label/rilonacept/canakinumab in progress
Prophylaxis by ULT	1st choice: allopurinol 100–600 (max 900) mg/dy* 2nd choice: febuxostat 40–120 mg/dy* 3rd choice: allopurinol+benzbromarone <200mg/dy 4th choice: any XOI+uricosuric rasburicase off-label/ PEG-uricase in progress
CPP-associated arthritis	
Acute attack	Cold packs 3–6 times daily 10–20 minutes NSAID and/or colchicine
Prophylaxis	Colchicine 2dd0.5mg, or daily NSAID or prednisolone 5–10mg/dy
Cholesterol monohydrate synovitis	Reduce general activity of inflammatory arthropathy Consider: statin
Rice bodies	Reduce general activity of rheumotoid arthritis

*see Table V.

Table V. Potency table of xanthine oxidase inhibitors in gout with percentage of patients reaching the predefined target of serum uric acid <0.30 mmol/l.

	European RCTs	USA RCTs
Allopurinol 100mg/dy	ND	0%
Allopurinol 300mg/dy	25%	13%
Febuxostat 40mg/dy	ND	21%
Febuxostat 80mg/dy	ND	48%
Allopurinol 600mg/dy	78%	ND
Febuxostat 120mg/dy	ND	66-88%
Febuxostat 240mg/dy	ND	>69%

patients who responded well to 1–2 intramuscular injections of triamcinolone acetonide 60 mg (45).

For chronic CPPD crystal arthritis, oral NSAID (with GI protection if indicated) or colchicine 0.5–1.0 mg daily, low-dose glucocorticosteroid or methotrexate or hydroxychloroquine may be considered (46, 47). Uncontrolled studies examined the effect of methotrexate 5–10 mg weekly in 5 patients, and of hydroxychloroquine in 36 patients, both suggesting some additional value for these treatment options: NNT of 2 reflecting hydroxychloroquine (48, 49). No data for low-dose glucocorticosteroids in chronic CPPD-associated arthritis can be found.

Prophylaxis against frequent recurrent acute CPPD crystal arthritis can be achieved by administering low-dose colchicine such as 0.5–1.0 mg daily, or low-dose NSAIDs: in one uncontrolled trial 10 patients with recurrent attacks received 0.6 mg colchicine daily during a 1-year period and this reduced or prevented the number and severity of attacks (46).

One double-blind placebo-controlled trial has proven clinical efficacy of colchicine 0.5 mg bid for 8 weeks in 39 patients with knee osteoarthrosis plus persistent inflammation caused by CPPD: NNT for 30% pain reduction was 2 at 4 months and 4 at 5 months (47). Thirty-two episodes of acute arthritis were recorded in the year before starting the drug and only 10 after taking colchicine 0.6 mg daily: $p<0.001$, indicating that 90% of patients benefitted from colchicine prophylaxis. Whether different NSAIDs or low-dose prednisolone are equipotent in their prophylactic efficacy remains to be investigated.

Cholesterol monohydrate plates

Cholesterol plates are found only sporadically in the SF of patients with chronic synovitis or longstanding arthritis (8). Many doctors do not recognise these: out of 658 responses from NEJM readers with 59% practicing clinicians only 27% correctly identified cholesterol plates from the synovial fluid (8).

Such crystals may appear in two morphologic forms (Table I): large, flat, rectangular plates with negative birefringence and characteristic notched corners, ranging from 8 to 100 μm long and consisting of monohydrate cholesterol, or rod-shaped, helical birefringent crystals, ranging from 2 to 20 μm long and consisting of anhydrate cholesterol (Fig. 3). Since the large cholesterol plates are supposedly only cleared with difficulty from the intra-articular space, they are thought to play a role in the perpetuation of local synovitis or arthritis.

Treatment

Once correctly recognised, a therapeutic regimen has to be tried, aiming at reducing inflammation and, if tolerated, increasing the dosage of DMARDs (50).

Data from the literature on treatment options of cholesterol crystal synovitis are lacking, and should be deduced from individual case reports (8, 50). If deposition occurs in rheumatoid arthritis it occurs most frequently in structures with synovial lining and without concomitant hyperlipidemia. General interest in the use of statins in RA has increased over the last years after a trial of atorvastatin in RA (TARA) showing beneficial effects (51). Interestingly, statins have a cholesterol lowering effect, as well as immunomodulatory and anti-inflammatory properties (52-54). They appear to act as direct repressors of class II major histocompatibility complex (MHC)-mediated T-cell activation while not affecting constitutive expression of class II MHC in dendritic cells and B-lymphocytes. Statins selectively block β_2 integrin and lym-

phocyte-function-associated antigen I (LFA-1) by binding to a novel allosteric site within LFA-1 (52-54). One may hypothesise that loco-regional monohydrate cholesterol production or suppression of class II MHC or Th1-Th2 switch plays a pivotal role in the etiopathogenesis of cholesterol synovitis associated with long-term arthritis disease activity (50).Cholesterol plates are thermodynamically stable and not easily cleared. In our experience, in only 1 case, a firmer suppression with DMARDs plus a statin may resolve the chronic cholesterol synovitis in a shoulder joint (50).

Rice bodies

They are commonly encountered in chronic synovitis, especially in rheumatoid arthritis, and, macroscopically, they look like edible rice (9). Rice bodies, described in 1895 by Reise were originally associated with tuberculous arthritis (9), consist of collagen, fibrinogen, fibrin, fibronectin, mononuclear cells and amorphous material (Fig. 4). Using polarisation microscopy, amorphous material is not birefringent, but many of the other collagen and fibrin components may be birefringent. This explains the presentation of rice bodies as huge semicircular balloons with birefringent edges.

It is thought that rice bodies are formed due to chronic inflammation, supposedly producing synovial microinfarcts: infarcted tissue or debris will be drifting in a joint space, and they can then be coated with a thin layer of fibrin. An alternative theory is that they result from synovial inflammation, proliferation and degeneration. The frequency of occurrence of rice bodies in the knee is not exactly known: loose bodies commonly occur at lavage from inflamed knee joints. In 1982, the era prior to modern MTX therapy, a 72% occurrence in RF-positive RA patients was reported (55). Kirkley *et al*. recently reported in osteoarthritis loose bodies in 12 out of 86 patients who underwent knee arthroscopy (56).

Therapy

Rice bodies have been implicated as a stimulus for continuing synovial inflammation. Therefore, adequate suppression of chronic inflammation by local glucocorticosteroids plus methotrexate once weekly for an additional time period may have a therapeutic effect on synovitis. Surgical debridement or arthroscopic debridement, as was the therapeutic advice in former days of loose/rice bodies, may not be needed.

Glucocorticosteroid injectate and other artifacts

If previously an intra-articular glucocorticosteroid injection with *e.g*. triamcinolonacetonide (Kenacort) or methylprednisolone (Depomedrol), has been administered, a number of multiform birefringent crystals can be seen in the SF sometimes even up to 6 months afterwards. Other artifacts may be starch-like particles (from gloves) or glass slivers from the fabrication process. Sporadically synovial proteins with a negative birefringent pattern may lead to confusion due to similarity with MSU needles.

Calcium oxalate

In specific metabolic disorders, *i.e*. oxalosis, or severely diminished renal function with ingestion of an overdose of vitamin C one may encounter biconcave birefringent crystals during polarisation microscopy of SF. Depending on the calcium content, these crystals can be visualised by performing radiography.

Hydroxyl apatite or basic calcium phosphate (BCP)

Periarthritis or arthritis may occur when BCP crystals are deposited in or around a joint. In rapidly destructive omarthritis such as the Milwaukee shoulder (McCarty) polarisation microscopy may not reveal any crystal at all. If hydroxyl apatite is suspected, one has to consider specific staining via alizarin red. If enough calcium is bound, these crystals can easily be seen using plain radiography.

Conclusions

Clinicians using a polarisation microscope are able to make a correct diagnosis and start adequate treatment in crystal-induced arthritis. This includes cooling of affected joints plus NSAIDs, glucocorticosteroids, colchicine, as well as preventive measures. Studies are needed to compare the promising technique of ultrasonography in crystal proven cases of acute arthritis. The ACR and EULAR recommendations for treatment of gout and the availability of a novel non-purine xanthine oxidase inhibitor, a novel URAT-1 blocking uricosuric and uricase derivatives will give relief to millions of sufferers. New insights in the inflammatory process including the role of the inflammasome and the role of IL-1 and may result in new treatment modalities for acute arthritis.

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