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Opinion

On Synovial Fluid Cristallography Training for Arthrocentesis Performing Physicians

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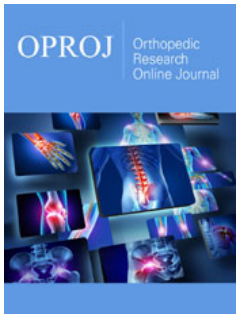

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Opinion

Synovial Fluid (SF) investigation should be a routine procedure for practitioners who perform arthrocentesis [1]. The most important reason to perform arthrocentesis is to check for joint infection, crystal deposition, autoimmunity, trauma or malignancy, as timely identification, treatment of a patient with septic arthritis are of paramount importance to a favorable clinical outcome. Also, arthrocentesis is indicated to gain diagnostic information through synovial fluid analysis in the case of a monoarticular or polyarticular arthropathy of unclear etiology presenting with joint pain and swelling [1]. Due to quality of relevant information obtained, the synovial fluid analysis has been referred as a "liquid biopsy" of the joint [2]. Proper SF investigation may decrease the number and cost of SF laboratory tests, shorten the time of recommended treatment initiation, and increase the odds of favorable prognosis [1,3].

As the most important indication for SF investigation is infection identification or exclusion, Gram stain and culture, total leukocyte count and differential are compulsory though not sufficient [4]. Besides infection, crystal deposition may also cause high grade joint inflammation [1]. In this setting SF crystal investigation is especially valuable in differential diagnosis of crystal deposition arthritis as the gouty arthritis is well controlled by urate-lowering treatment while pyrophosphate or hydroxyapatite related arthritis requires symptomatic approach.

Thus, every obtained SF sample should be evaluated for the presence of pathological crystals. Polarized microscopy is recommended as standard diagnostic method of crystals detection. This statement may decrease general practitioners motivation to evaluate SF in absence of polarized microscope. Meanwhile, the ordinary light microscope, used by trained observers, is a quite sensitive tool for detecting the presence of crystals (either monosodium urate (MSU) or calcium pyrophosphate dihydrate (CPPD) in synovial fluid [2]. Two series of studies comparing the diagnostic significance of plain light and polarization microscopy demonstrated 96.2 to 100% sensitivity and 100% to 97.1% specificity of crystal identification by light microscopy [pascual]. Thus, if polarized microscopy is not available, the synovial fluid should be investigated using a conventional light microscope.

If MSU crystals cannot be detected initially, the slide should be allowed to dry and reexamined 3 hours or more later. Besides, CPPD crystals have been reported to be only weakly birifringent and are probably better identified by non-polarized light and characterized by morphology than by their polarization properties [2,3]. Also polarized microscopy may even cause misdiagnosis. So, negative polarized light microscopy synovial fluid examination report, does not exclude the presence of small numbers of MSUM or CPPD crystals.

Main crystals detection and identification issues may be related to several following factors:

1. SF salts concentrations are unstable and crystals distribution may be irregular or sparse, so false negative search report may result from insufficient number of view fields investigated.

2. Ideally, SF crystals identification should be carried out in a native sample obtained from SF drawn into a dry test tube. The sample should be processed immediately after it is delivered to the laboratory and examined within 30 minutes after [4]. Failure to meet delivery deadlines may also cause diagnostic errors. To prevent coagulation of the LV during its transportation to the laboratory due to the presence of clotting factors in it, a number of authors recommend using test tubes containing EDTA or lithium - heparin as an anticoagulant [5,6].

3. Crystals, especially CPPD, are polymorphic. It is often difficult for a clinician or even diagnostic lab physician to differentiate crystals from artifacts. It is also important that at present in the regions of Russia an extremely insufficient number of doctors have experience in identifying crystals, and, therefore, there is often no one to share their experience with colleagues. Most laboratory diagnostics specialists rely only on images published in atlases, with no methodological support for direct image visualization.

4. Also, it should be accepted that there is no clear interaction and through co-operation between clinicians and laboratory diagnostics specialists. Often transferring a SF sample clinicians do not clearly indicate the task for lab specialists, as well as, neither symptoms nor current treatment being performed. Lack of information can also make results interpretation difficult.

Thus, rheumatologist and laboratory specialist may require viewing the SF samples together to gradually master the technique from the obvious to more complex images. Our multiannual experience of non-polarized light crystallography implementation into current medical practice routine has revealed three most frequent patterns of SF crystals.

Monosodium urate crystals

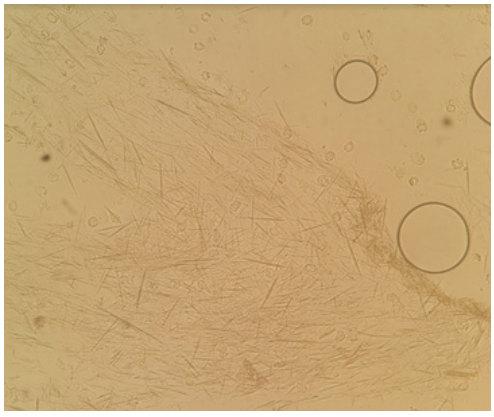

Figure 1: Niddle shaped crystals of monosodium urate (non polarized light microscopy).

MSU crystals are clearly visible in plain light, they are needle-shaped, their size ranging from very small to about twice the diameter of a neutrophilic leukocyte. Tofus contents microscopy may be useful for learning how to identify these crystals. To do this, a white crumb-like material is placed on a slide and examined as a native preparation (Figure 1).

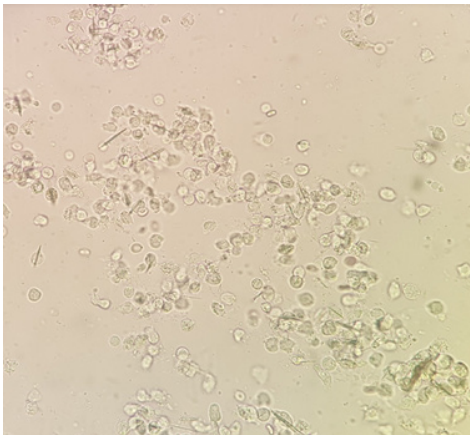

Figure 2: Phagocytosis of monosodium urate crystals (non polarized light microscopy).

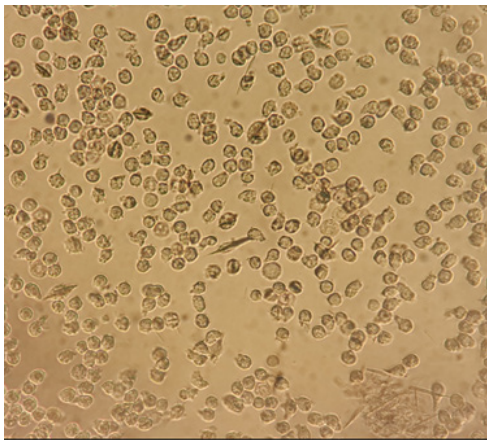

Figure 3: Intracellular monosodium urate crystals (non polarized light microscopy).

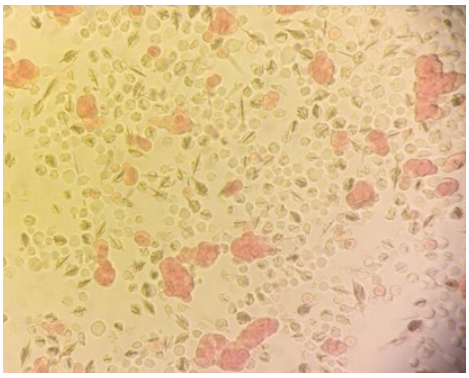

Figure 4: Monosodium urate crystals and RBC clots in SF (non polarized light microscopy).

Detection of MSU crystals in the SF samples depends on the duration of the arthritis. Initially, the crystals are determined in

large quantities and are located freely. Over time, the number of phagocytic crystals increases, and their total number decreases in the SF (Figure 2 & 3). When puncturing synovial bags in gouty bursitis, along with MSU crystals, it is quite often possible to detect clusters of red blood cells associated with damage to the capillaries (Figure 4). Azur-eosin staining of the SF smears does not change the pattern MSU (Figure 5).

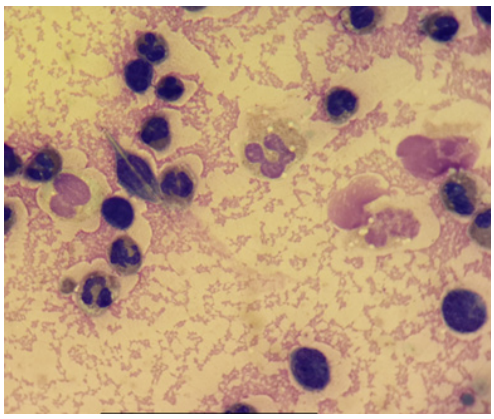

Figure 5: Intracellular monosodium urate crystal (Azur-eosine staining).

Thus, MSU crystals can be detected during routine SF microscopy and shorten the time between symptoms onset and diagnosis verification.

Calcium pyrophosphate dihydrate crystals

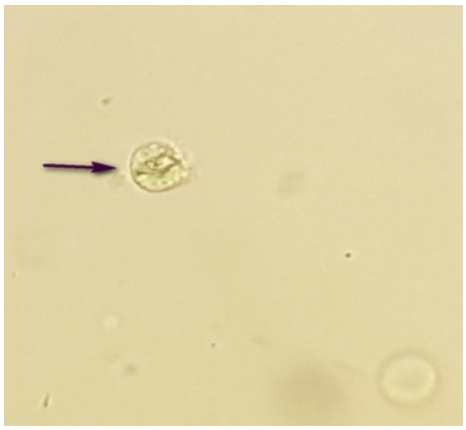

Figure 6: Intracellular calcium pyrophosphate dihydrate crystals (non polarized light microscopy).

CPPD crystals are more difficult to identify, since the threshold for their detection is a concentration of about 10-100MK/ml, while in natural conditions the concentration of crystals can be only 2-3MK/ml [7]. CPPD crystals size can range from 0.4 to 20 microns, most of them being less than 1 microns. This is exactly the threshold that allows them to be detected using non-polarized light microscopy [8]. CPPD identification can be performed by radiogram in advanced cases of the disease. We suggest that CPPD identification training should be performed using SF smears of patients with a previously established diagnosis of CPPD deposition disease.

CPPD crystals are polymorphic and can range from diamond-shaped to brick-shaped (Figure 6), as well as needle-shaped crystals, difficult to differentiate from MSU (Figure 7). CPPD crystals are often located intracellularly (usually looking as small squares or needles) [9], even in the absence of inflammation (Figure 8). It should be emphasized that, unlike MSU, CPPD microcrystalline arthropathy does not exclude septic arthritis [10], so the detection of CPPD crystals in the SF does not exclude the need for gram staining and bacteriological research. Azur-eosin staining also helps to identify CPPD crystals in SF (Figure 9).

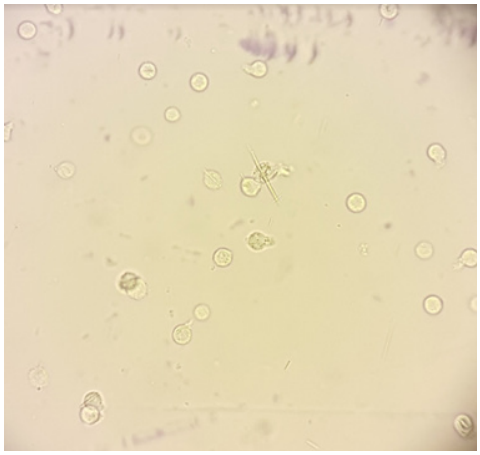

Figure 7: Multiple patterns of calcium pyrophosphate dihydrate crystals (non polarized light microscopy).

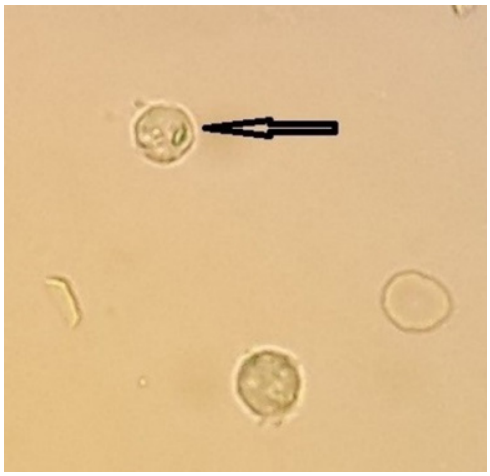

Figure 8: Intracellular calcium pyrophosphate dihydrate crystals (non-polarized light microscopy).

Microscopic patterns of intra-articularly administered substances

Not rarely SF investigation reveals artifacts of administered substances, such as betamethasone or hydrocortisone suspension and lidocaine (Figure 10 & 11) which are visually like CPPD crystals. Therefore, it is extremely important to follow the arthrocentesis procedure and carefully collect the patient's medical history. Hyaluronic acid preparations are not detected by light microscopy and do not produce artifacts.

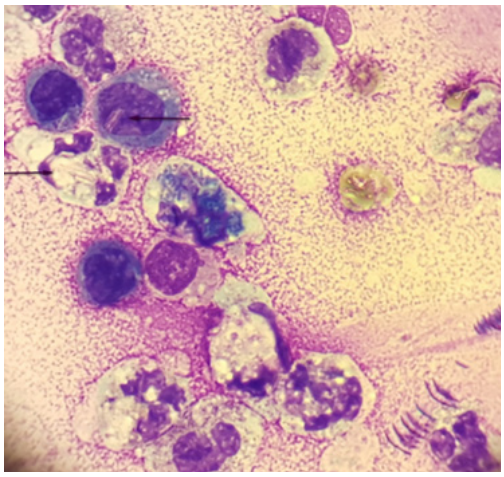

Figure 9: Intracellular deposits of calcium pyrophosphate dihydrate crystals (Azur-eosine staining).

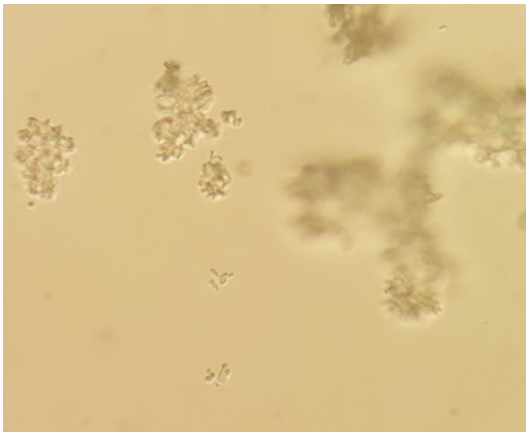

Figure 10: Hydrocortisone suspension crystals in synovial fluid sample.

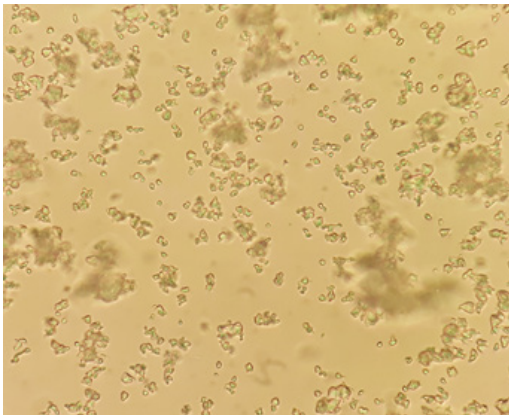

Figure 11: Lidocain crystals in synovial fluid sample.

Conclusion

Thus, non-polarized light microscopy searching for SF crystals should be performed in every case of SF evacuation and should be estimated as up to date procedure. Besides, polymorphonuclear cells count, Azur-eosin and Gram staining, SF culture are also mandatory to exclude septic arthritis, plain light crystal search can shorten time from symptoms onset to proper diagnosis and treatment initiation. Training in crystallography is not much complicated and time-consuming and should be available for every clinician performing intra-articular procedures.

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