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Review

# Acute phospholipid microspherule associated arthritis: Is it rare?

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ABSTRACT

Joint fluid analysis must be performed as part of the diagnostic workup for acute arthritis, most notably to rule out septic arthritis and to allow the identification of crystal-induced arthritis (gout or calcium pyrophosphate deposition disease), which is one of the most common causes. However, the detection of monosodium urate or calcium pyrophosphate microcrystals is not the only goal of the polarized light microscopy examination of joint fluid. Other, less common microcrystals may be found. Among them are phospholipid microspherules, which are easily recognized microscopically based on their Maltese cross-like appearance. Phospholipid microspherules are a cause of acute arthritis that is often missed by rheumatologists and may therefore be more common than generally believed.

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## 1. Introduction

Joint fluid (JF) analysis is crucial to the diagnosis of acute joint effusions. A high cell count (> 2000/mm$^3$) indicates inflammation, positive cultures septic arthritis, and microcrystals visible by polarized light microscopy microcrystal-induced disease.

Monosodium urate (MSU) and calcium pyrophosphate (CPP) are only two of the many types of microcrystal that can be found in JF from patients with acute arthritis. Other types, generally believed to be rare, should be sought. They include calcium oxalate and Charcot-Leyden microcrystals, as well as lipid microspherules, which are undoubtedly the least uncommon. Many rheumatologists and clinical laboratories are unfamiliar with lipid microspherules, which are nevertheless easily identified. Thus, greater awareness of lipid microspherules would be expected to improve the etiological diagnosis of acute arthritis.

## 2. Definition and classification of microspherules found in joint fluid (JF)

Microspherules are microscopic spherical particles less than 2 mm in diameter, composed chiefly of mineral material usually in crystal form. The spherical shape indicates that the forces within the liquid content are in a state of equilibrium (water, air). Only spherules produced by naturally occurring physico-chemical processes (as opposed to biological processes or human activity) are classified as microspherules.

Chemical compounds that can organize into microspherules in the JF include MSU, carbonated apatite, and liposomes. A liposome is an artificially created spherical vesicle composed of concentric phospholipid bilayers between which aqueous compartments are trapped.

Microspherules found in JF can deflect polarized light, thus becoming visible as Maltese cross-like particles (Fig. 1). Under compensated polarized light, the deflection by microspherules may have positive polarity (e.g., liposomes) or negative polarity (e.g., MSU [1] or apatite [2,3]) (Fig. 1 and Table 1).

The identification by polarized light microscopy of microspherules in JF is not always abnormal [4]. Two common causes of microspherule-like artefacts should be borne in mind. Starch particles on the sterile gloves used by the physician performing the joint aspiration may produce irregular spherules with positive birefringence, which are consistently extracellular and often large. When blood-tinged JF is left too long in contact with air, mechanical hemolysis occurs during drying, causing the release of membrane phospholipids that may organize into liposomes seen as microspherules with positive birefringence. Therefore, spherules should not be considered abnormal when drying artefacts are visible (fern-like appearance).

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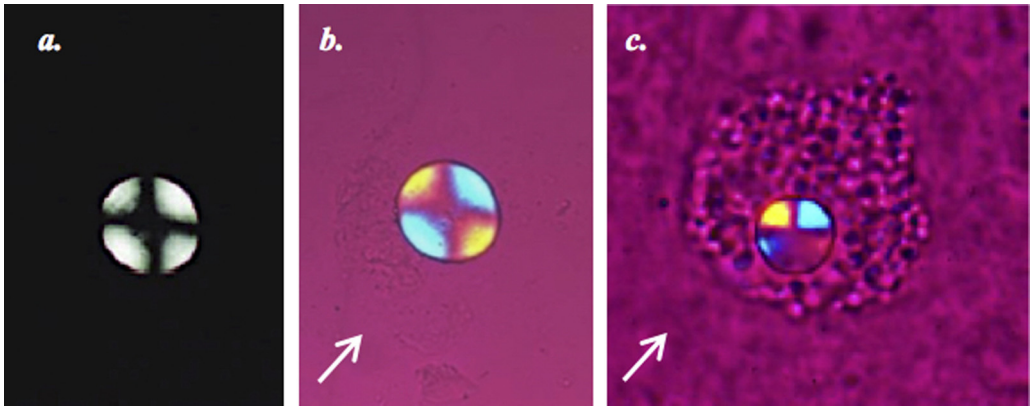


**Fig. 1.** Light microscopy appearance of a phospholipid microspherule (×1000): a: typical Maltese cross appearance under uncompensated polarized light; b: positive birefringence (blue along the axis of the compensator [arrow] and yellow perpendicularly); c: phospholipid microspherule within a leukocyte.

**Table 1**
Description of the different microspherules that can occur in joint fluid.

| | Positive birefringence | Negative birefringence |
|---|---|---|
| Abnormal crystals | Phospholipids within leukocytes (immediate examination of fresh sample) | Apatites (immediate examination of fresh sample)<br>Monosodium urate (rare) |
| Artifacts | Starch (sterile gloves)<br>Phospholipids outside the leukocytes (after a few minutes on the slide, hemolysis) | |

Positive birefringence under compensated polarized light is defined as blue along the axis of the compensator and yellow perpendicular to this axis; negative birefringence is the opposite.

## 3. Clinical presentation

A search of PubMed using the terms "lipid liquid crystals" or "lipid microspherules" or "birefringent Maltese cross" retrieved 16 case-reports [5–17]. In addition, 2 cases have been managed in our department (See the supplementary material associated with this article online). Six other cases of acute monoarthritis have been reported as abstracts that do not provide clinical details [18]. Table 2 lists the clinical features in reported cases of phospholipid microspherule (PL-MS) arthritis. Females were predominantly affected (78% of cases, sex ratio of 4.5) and mean age was 41 ± 13.5 years (range: 14–63 years).

Most patients (90%) presented with acute monoarthritis, of abrupt onset, usually with no remarkable circumstances. A fever was present in some cases. The large joints were the most common targets (knee, 66.5%; wrist, 16.5%; shoulder; ankle; and metacarpophalangeal joints). Radiographs of the affected joints were normal, with no evidence of arthropathy, chondrocalcinosis, or periarticular calcification. The JF was often blood-tinged and sometimes cloudy, with the high cell counts characteristic of inflammation (mean: 38,000 ± 37,500/mm$^3$ nucleated cells and over 90% of neutrophils in 83.3% of cases). Under polarized light microscopy, numerous PL-MS were visible as particles with strong positive birefringence located within the leukocytes and measuring 2 to 6 μm in diameter. No MSU or CPP microcrystals were visible.

In all patients, the microbiological cultures were negative and a full recovery was achieved within 2 weeks of starting antiinflammatory therapy (colchicine, nonsteroidal antiinflammatory drug [NSAID], or intraarticular glucocorticoid injection). A single patient experienced a recurrence, at a different joint site [13]. Furthermore, distal symmetric polyarthritis with PL-MS in JF samples has been reported in 2 patients [6,12], including 1 with a chronic course [6]. Nevertheless, a causal role for the microspherules remains unclear, given the short follow-up of less than 1 year. Thus, PL-MS may conceivably be found in joints with chronic inflammatory synovitis, as demonstrated for cholesterol crystals, particularly in rheumatoid arthritis. Support for this possibility comes from a description of 2 patients who had villonodular synovitis of the knee and recurrent episodes of hemarthrosis, with PL-MS in the JF samples [9]. In these 2 cases, inflammation was mild, with less than 10,000/mm$^3$ leukocytes including fewer than 5% of neutrophils, and the PL-MS were located within the synovial phagocytes and the macrophages.

## 4. Pathophysiological hypotheses

In reported cases of acute arthritis with PL-MS, the lipid composition of the microspherules was established based on specific staining with Sudan Black B and/or Oil Red O combined with absence of staining by alizarin red S (ruling out apatite microspherules) and of dissolution by uricase (ruling out MSU microspherules).

By transmission electron microscopy, PL-MS are seen as uniformly clear lipid inclusions surrounded by finely granular protein material. The protein component is associated with darker inclusions consisting in concentric multilayered membranes (membrane debris). The PL-MS are located within the synovial macrophages. The serum lipid profile was normal in the vast majority of patients.

Hemarthrosis is a common clinical finding in acute PL-MS arthritis. In a rabbit model, injecting 0.5 mL of autologous blood into the knee induced acute arthritis with intracellular PL-MS under polarized light microscopy [19]. The Sudan Black B stain was positive and the microspherules had the same electron microscopy appearance described in humans with acute PL-MS arthritis. Thus, hemarthrosis may be the cause, as opposed to a consequence, of acute PL-MS arthritis. Nevertheless, of the cases reported in humans, only half were characterized by hemarthrosis. Furthermore, using the same rabbit model, the same investigators found that injecting 0.5 mL of a liposome preparation into the knee induced the development within 6 hours of arthritis with an inflammatory JF profile characterized by high neutrophil counts and by chiefly extracellular PL-MS [20]. After 2 days, most of the PL-MS were intracellular and the synoviocyte/macrophage count was higher. In this experimental study, the various phases of the inflammatory process were identical to those seen in animal models of arthritis induced by intraarticular injections of MSU or apatite microcrystals.

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