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Clinical Images: Detection of titanium dioxide particles by Raman spectroscopy in synovial fluid from a swollen ankle



The patient, a 71-year-old man, presented with a swollen ankle joint. Review of the patient's history revealed gout flare in 2011 (diagnosed by a general practitioner) and receipt of titanium alloy hip implants in 2016. The general practitioner's diagnosis of suspected gout could not be confirmed by compensated polarized light microscopy. Brightfield microscopy of a synovial fluid specimen from the ankle joint showed dark, smooth objects inside a synovial leukocyte (**A**). We used Raman spectroscopy to measure the chemical composition of these objects. The red and blue spectra (**B** and **C**) are typical of anatase crystals, with peaks at 142, 196, 396, 516, and 638 cm⁻¹ (1); anatase is a polymorph of titanium dioxide crystals (TiO₂). The black spectrum (**B** and **C**) has peaks at 676 and 1,374 cm⁻¹, which are linked to oxidized cytochrome b₅₅₈. Cytochrome b₅₅₈ is part of the NADPH oxidase complex, which plays a critical role in inflammation. Anatase is a known component of paints, drugs, toothpaste, and ointments, and the release of titanium dioxide from dental and orthopedic implants is suggested (2). To our knowledge, this is the first example of anatase crystal detection in synovial fluid. Anatase has a low birefringence ($\pm 20\%$ of the value for monosodium urate monohydrate crystals), and the morphology of crystal surfaces is smooth. Experiments have shown that TiO₂ endocytosis can trigger interleukin-1 β release in cultures of leukocytes (3). Whether the anatase crystals contributed to the inflammation in this case is unknown. There were no clinical signs of metallosis or osteolysis. The patient responded well to prednisone (10 mg orally every other day for 6 weeks) and fully recovered.

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