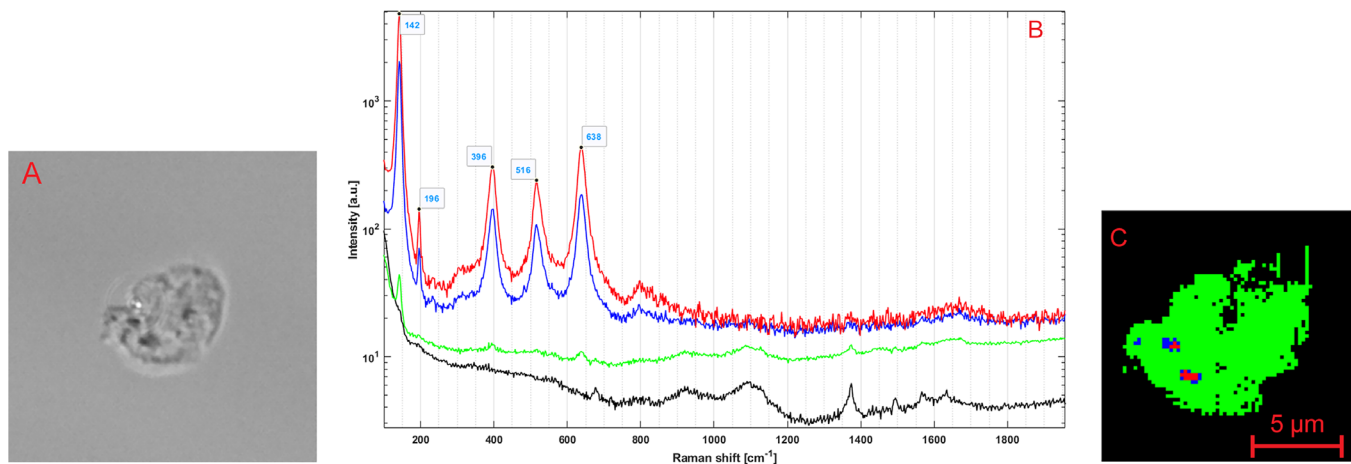


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Clinical Images: Detection of titanium dioxide particles by Raman spectroscopy in synovial fluid from a swollen ankle

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 (TiO_2). The black spectrum (B and C) has peaks at 676 and 1,374 cm^{-1} , which are linked to oxidized cytochrome b_{558} . Cytochrome b_{558} 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 TiO_2 endocytosis can trigger interleukin- 1β 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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Tom Niessink 
 Jasper Ringoot
 Cees Otto, PhD
 University of Twente
 Enschede, The Netherlands
 Matthijs Janssen, MD, PhD
 VieCuri Medical Center
 Venlo, The Netherlands
 Tim L. Jansen, MD, PhD
 University of Twente
 Enschede, The Netherlands
 and VieCuri Medical Center
 Venlo, The Netherlands