Lesson of the Week

Complications resulting from misdiagnosing pseudogout as sepsis

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Acute pyrophosphate arthropathy (pseudogout) is a common cause of acute monoarthritis in the elderly.¹ As in gout, acute attacks are not uncommonly provoked by surgery or intercurrent illness.^{1,2} We report on four patients who developed pseudogout in clinical circumstances which led to initial misdiagnosis as septic arthritis. In each case the correct diagnosis of crystal synovitis was delayed, permitting development of severe adverse side effects from treatment instituted for sepsis.

Case reports

Case 1—A 72 year old man with no history of joint disease underwent surgery for a strangulated femoral hernia. On the third postoperative day he developed an acutely painful, swollen left knee and a fever of 38.5°C. On examination the knee was warm and tender with tense effusion and overlying erythema. Aspiration produced 50 ml thin bloodstained fluid with a raised white cell count (58 000/mm³; polymorphs 95%); no organisms were seen on Gram staining and crystals were not specifically sought. Septic arthritis was diagnosed and he was given intravenous flucloxacillin and fusidic acid. Despite negative synovial fluid and blood cultures at 48 hours intravenous treatment was continued. Four days later he developed persistent bloody diarrhoea necessitating intravenous fluid replacement. Reaspiration of his knee then yielded plentiful calcium pyrophosphate dihydrate crystals detected by polarised light microscopy; crystals were also identified on re-examination of the initial aspirate. A radiograph of the knee showed faint fibrocartilage chondrocalcinosis. On sigmoidoscopy an inflamed mucosa but no pseudomembrane was seen. Clostridial toxin was not detected and culture of the stool grew no pathogens. The diarrhoea settled after stopping antibiotics; his knee improved after the second aspiration and was completely normal within five days.

Case 2—A 68 year old woman with osteoarthritis of knees, hands, hips, and shoulders underwent left hip replacement. On the third postoperative day she developed painful swelling of the right knee and right wrist and a fever of 39°C. The knee showed a warm, tense effusion with tenderness over the joint line; the wrist was similarly swollen with overlying erythema. Aspiration of the knee produced 60 ml thin, turbid fluid with a raised white cell count (50 000/mm³; polymorphs 90%); 2 ml pus (cell count 68 000/mm³; polymorphs 95%) was obtained from the wrist. Gram staining of both samples gave negative results. She was treated with intravenous flucloxacillin and fusidic acid plus daily aspiration of the knee. Synovial fluid and blood cultures were negative at 48 hours, but her intravenous treatment was continued. Four days later she developed diffuse pruritus and jaundice. Examination of the knee aspirate on the fourth day showed plentiful crystals of calcium pyrophosphate dihydrate (also identified on re-examination of previous aspirates). A radiograph of the knee showed hypertrophic tricompartmental changes typical of pyrophosphate arthropathy with faint calcification in the lateral fibrocartilage. Radiography of the right wrist showed radiocarpal changes typical of pyrophosphate arthropathy but no chondro-

Failure to detect calcium pyrophosphate dihydrate crystals in elderly patients with acute monoarthritis due to pseudogout may lead to severe consequences if prolonged antibiotic treatment is given for presumed sepsis

calcinosis. The antibiotics were stopped; her jaundice disappeared over two weeks and her joints improved within 10 days.

Case 3—A 68 year old woman was admitted with an exacerbation of chronic bronchitis. Two days later she developed an acutely painful left knee showing a tense effusion and tenderness over the joint line. After an orthopaedic consultation she underwent arthrotomy, which yielded 70 ml bloodstained synovial fluid with a white cell count of 75 000/mm³ (polymorphs 99%); the result of Gram staining was negative. A drainage system was left in situ and intravenous penicillin and gentamicin were begun. Cultures of synovial fluid and blood were negative after 48 hours. Seventy two hours after starting antibiotics she developed a widespread pruritic maculopapular rash, presumed to be an allergic response to penicillin. Examination of the draining synovial fluid then showed plentiful crystals of calcium pyrophosphate dihydrate (also identified on re-examination of previous aspirates). A radiograph showed only isolated patellofemoral osteoarthritis. Antibiotics were stopped and her rash rapidly resolved. Intensive physiotherapy was required to aid mobilisation, but her synovitis settled over 10 days.

Case 4—A 69 year old woman with no previous joint symptoms underwent laparotomy for perforated appendicitis. Two days later she developed a painful, swollen left knee and fever of 38.5°C. On examination her knee was warm and tender with a tense effusion and overlying erythema. Aspiration produced 35 ml turbid fluid with a white cell count of 70 000/mm³ (polymorphs 95%); Gram staining gave a negative result. Results of other investigations included a haemoglobin concentration of 120 g/l (7.5 mmol/l), sedimentation rate of 66 mm in the first hour, and serum C reactive protein concentration of 138 mg/l (normal <20). Septic arthritis was diagnosed and she was given intravenous penicillin and gentamicin. Synovial fluid and blood cultures were negative at 48 hours. Three days later she developed a widespread pruritic maculopapular rash, presumed to be due to the penicillin. Her knee was reaspirated on the third day and plentiful crystals of calcium pyrophosphate dihydrate identified; re-examination of the previous aspirate also showed these crystals. A radiograph of her knee showed meniscal chondrocalcinosis in both tibio-femoral compartments. Stopping the antibiotics led to disappearance of the rash, and her synovitis resolved within five days.

Discussion

Intra-articular deposition of calcium pyrophosphate dihydrate crystals is a common, predominantly age related phenomenon.^{1,3} Though often asymptomatic, deposition of these crystals has been associated with acute and chronic joint disease (pyrophosphate arthropathy or calcium pyrophosphate dihydrate crystal deposition disease).⁴ The diagnosis of pyrophosphate arthropathy is suggested by the nature and distribution of clinical abnormalities^{1,4} and confirmation is by finding calcium pyrophosphate dihydrate crystals in synovial fluid.^{1,4} Characteristic radiological features are

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commonly present, showing changes of osteoarthritis but with predominant cyst and osteophyte formation and a distribution within joints that is atypical of uncomplicated osteoarthritis.^{1,4,5} Calcification in cartilage (chondrocalcinosis) is usually but not always present, and its absence does not preclude the diagnosis.^{5,6}

It is well recognised that pseudogout may be difficult to distinguish from acute septic arthritis.⁷ Synovial fluid in both conditions may appear purulent owing to a pronounced increase in total cell count, predominantly polymorphonuclear cells (usually more than 90%), and both conditions may produce a severe acute phase response manifested by fever and malaise and a raised sedimentation rate, C reactive protein concentration, and other acute phase reactants. Blood staining of synovial fluid, however, is rare in septic arthritis but common in pseudogout;⁸ and a further point of differentiation is that acute pseudogout may be the first clinical manifestation of calcium pyrophosphate dihydrate crystal deposition (as in cases 1 and 2), whereas spontaneous joint sepsis is rare in adults without a definite history of pre-existing joint disease (usually rheumatoid arthritis) or systemic predisposition to infection.⁹ Diagnosis of septic arthritis is by Gram staining and, more important, by culture of aspirated fluid; diagnosis of pseudogout requires finding synovial fluid calcium pyrophosphate dihydrate crystals, which by comparison with monosodium urate crystals are small, only weakly birefringent, and thus easily missed unless carefully sought using suitable compensated polarised light microscopy.¹⁰ Failure to detect calcium pyrophosphate dihydrate crystals by routine examination of synovial fluid was well illustrated in each of our cases. Attacks of pseudogout may be precipitated by intercurrent illness, trauma, or surgery,^{2,4} and in such circumstances sepsis must be considered and specifically excluded. In our patients pseudogout was provoked by intercurrent illness in hospital; though pseudogout was the most likely diagnosis, septic arthritis was the only condition considered and parenteral antibiotic treatment continued despite lack of direct evidence to support infection. This led to serious antibiotic related side effects in all four and to unnecessary arthroscopy in case 3.

Though pseudogout is by far the most common cause of acute monoarthritis or oligoarthritis in the elderly,¹ pseudogout and sepsis may occasionally coexist in the same joint (such concurrence has lent support to "crystal shedding" as a mechanism of crystal

induced synovitis).^{11,14} In elderly patients with acute synovitis the joint should be aspirated and the fluid examined for both crystals and organisms. If calcium pyrophosphate dihydrate crystals are identified and the result of Gram staining is negative antibiotics should not be given unless the possibility of sepsis is extremely high, as in severely ill patients or when the attack has been provoked by an intercurrent infective illness. In such high risk circumstances it seems reasonable to begin parenteral antibiotic treatment pending the results of synovial fluid culture; if subsequent culture at 48 hours is negative, however, then antibiotics should be stopped and the diagnosis of pseudogout accepted alone. This approach should avoid the complications from prolonged, inappropriate antibiotic treatment and surgical drainage reported in our cases.

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MATERIA NON MEDICA

What would Hippocrates have done?

He died last year, and so perhaps I can now tell the story. He was professor of surgery and chief of staff in his hospital in Belgium at the time when it was overrun by the Germans. He was instructed by them to carry on with his daily work. If he himself was in touch with the underground it must have been only in a very minor way, although his wife, we must admit, was deeply involved, being one of the now famous "White Ladies."

One Sunday he was asked by a nice greyhaired old lady to come to her house for afternoon tea so that he could meet there a young man whom the old lady (she was the local link of the "escape chain") would be launching on his journey down the escape route to freedom in Switzerland. One should say that each person only knew the name of the person in the next town who would supply the escapee with a safe overnight lodging.

At the afternoon tea party the visitor spoke in almost impeccable English, but he did make one or two minor mistakes. One of these was when he said to the professor, "I will be in England in a week or two, and I could if you wish deliver a 'brief' for you to a friend." Although the professor himself spoke with an appalling English accent he had a very correct knowledge of English. The word 'brief' he knew was wrong. He realised that the man was a spy. If he was allowed to go down the escape route every person in this complicated chain would be shot or imprisoned and the whole escape line would be blown wide open. The spy must be liquidated.

The professor in his surgical team had only one assistant whom he could fully trust, and so he suggested to this registrar that he should take the visitor for a very interesting walk along a high path overlooking the Meuse and show

him the sights. At one corner on this narrow path there was a sharp bend, and if the registrar could possibly slip at that point his companion could easily and "accidentally" fall into the river. The whole affair was carried out two days later according to plan. Sadly, instead of the Meuse being in flood it was frozen over, and so instead of being carried away Mr X received a head injury only. He was brought into hospital and was put under the care of our own professor. After a few days it appeared that he was going to make a full recovery, and so the professor suggested that a lumbar puncture might be advisable. This was done, some CSF was removed and replaced by some infected fluid. Next day the patient was considerably worse; all the team now rallied round with all the antibiotics available, but the patient finally died. It was interesting that on several occasions during this period inquiries came from the Germans regarding his progress, which proved that he was part of their team. Just before he died he admitted that he was a spy—he was in fact a citizen of a still uninvolved country.

Shortly afterwards the professor began to realise that he was now rather suspect and perhaps it might be wise if he silently slipped away. So it was soon after this that I made my first contact with him, when a foreign gentleman in a brand new RAMC uniform appeared for breakfast in the officers' mess at the Royal Herbert Hospital at Woolwich. His uniform was better than his English. From this contact a friendship of 40 years started, which ended only with his death last year.

If faced with a problem of this sort, I wonder what Hippocrates would have done?—IAN FRASER, Belfast.