

***Neisseria meningitidis* serogroup C sepsis and septic arthritis in an HIV-positive man**

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Summary

A patient with well-controlled HIV-1 infection presented with fever and rigors, a widespread maculopapular rash, and severe generalised arthralgia. Sepsis of unknown aetiology was diagnosed, and treatment with broad-spectrum antimicrobials commenced. Following initial clinical improvement a right knee septic arthritis developed. Microscopy and culture of the joint aspirate was negative for organisms but 16S rDNA PCR identified *Neisseria meningitidis* DNA, subsequently verified as capsular genogroup C, thus confirming a diagnosis of disseminated meningococcal sepsis with secondary septic arthritis.

Keywords: *Neisseria meningitidis*, septic arthritis, HIV, 16S rDNA

Introduction

Meningococcal sepsis and septic arthritis are medical emergencies. While *Staphylococcus aureus* and other gram-positive bacteria such as streptococci are the most common causes of septic arthritis worldwide (1), *Neisseria meningitidis* must not be forgotten as an important pathogen in this setting. Reactive arthropathy complicating meningococcal sepsis is well recognised, typically occurring 1–2 weeks after bacteraemia; however early-onset septic arthritis is also seen in 2–10% of invasive meningococcal disease (2). Typically a mono-arthritis, the knee is most commonly affected (1, 3, 4) with concurrent bacteraemia in this context unusual (2).

Case report

A 52 year old white male with well-controlled HIV-1 infection (receiving tenofovir/emtricitabine and etravirine, HIV-1 viral load <50 copies/mL, CD4 count 670 cells/ μ l) presented with three days of fevers, rigors, severe generalised arthralgia and profuse watery diarrhoea. He had returned from the USA 16 days previously. While he was there, he had resided in the mid-west in a rural setting and had not visited any clubs or saunas. He was a man-who-has-sex-with-men (MSM) and denied any sexual exposures in the six months prior to presentation. Examination revealed an erythematous, maculopapular rash on the shins and severe symmetrical polyarticular arthralgia with tenderness most marked on palpation of the fingers, wrists, knees and ankles. At this point, there was no evidence of synovitis or joint effusion. There was no pharyngitis or urethral discharge. Respiratory and cardiovascular examinations were normal with no murmurs audible, and neurological examination was normal with no meningism or focal neurology. Observations at presentation revealed a peripheral pulse =120/min, regular, blood pressure =121/76 mmHg, respiratory rate =16/min, peripheral oxygen saturation =95% (on room air), and tympanic temperature =38° Celsius.

Initial investigations included a chest radiograph showing bibasal consolidation; markedly elevated inflammatory markers with C-reactive protein =560mg/L (normal <5mg/L) and total white cell count = 11×10^9 /L (of which, neutrophils = 9×10^9 /L); serum creatinine =103 μ mol/L and eGFR =68mL/min/1.73m² in keeping with acute kidney injury (baseline 70 μ mol/L and >90mL/min/1.73m² respectively); and an elevated alkaline phosphatase =139IU/L. Lumbar puncture was not performed as the patient was not clinically meningitic. Faecal microscopy and culture was negative for pathogenic enteric bacteria and parasites, and urine *Neisseria gonorrhoeae* (NG) and *Chlamydia trachomatis* (CT) nucleic acid amplification tests (NAATs) were negative. Pharyngeal and rectal NAATs were not performed as they were not felt to be indicated, given the sexual history.

The initial impression was of sepsis of uncertain origin. Empirical antimicrobial therapy with intravenous meropenem 1g eight-hourly and gentamicin 5 mg/kg once-daily was initiated due to a history of previous severe anaphylaxis to penicillin, meaning that a carbapenem was preferential to a cephalosporin. While aztreonam would be a suitable agent in cases of beta-lactam anaphylaxis such as this, it was unavailable for use in the hospital at the time of the patient's admission. The patient had no adverse reactions following initiation of meropenem and so it was considered safe to continue.

Over 24 hours the rash spread to the legs, arms and hands, becoming confluent with scattered petechiae. There was no hypotension, multi-organ failure or desquamation to suggest toxic shock syndrome. On day two, the clinical diagnosis was of presumed gonococcal sepsis with reactive arthritis. Blood cultures taken on admission, and days one and two of hospitalisation all remained negative. A transthoracic echocardiogram was normal.

By day 3 of hospitalisation, consideration was given to adding a macrolide to treat presumed gonococcal infection, but as the patient was systemically improving this was not done. At this time the patient developed significant right knee pain. Marked swelling with significant effusion and increased temperature of the overlying skin were present. Passive flexion was reduced markedly, associated with significant supra-patellar tenderness. Plain radiographs demonstrated significant effusion but no bony anomaly. Septic arthritis was suspected, and after review by Rheumatology and Orthopaedics a right knee joint aspiration was undertaken, demonstrating turbid, straw-coloured fluid. Microscopy revealed numerous polymorphonuclear leukocytes; no crystals were seen. Gram staining showed no organisms. NG/CT NAATs of the aspirate were negative, as was extended bacterial culture at five days. The right knee joint aspirate was repeated on day 12 with similar results.

On day 13, magnetic resonance imaging of the right knee demonstrated a large joint effusion with marked synovitis in keeping with septic arthritis, mild pre-patellar bursitis and an extensive horizontal oblique tear of the right medial meniscus. Subsequent right knee arthroscopic washout and synovial biopsy on day 15 showed nonspecific inflammation only.

At this juncture, investigations thus far had failed to yield a microbiological diagnosis, and so both knee aspirates were analysed using polymerase chain reaction (PCR) to detect broad-range bacterial 16S ribosomal DNA (rDNA). Sequencing of the amplified product identified *Neisseria meningitidis*-specific rDNA on day 16. This was subsequently confirmed by a second in-house organism-specific PCR and finally by the National Reference Laboratory where *Neisseria meningitidis* capsular genogroup C was identified. As a notifiable disease, the Public Health England local Health Protection Team were informed of the diagnosis of meningococcal septicaemia.

The patient completed a ten-day course of intravenous meropenem and made good progress post-discharge, although at three months he continued to have recurrent non-inflammatory effusions in his right knee related to the meniscal tear, and has subsequently been followed up by both the Rheumatology and Orthopaedics teams.

Discussion

On reflection following this case, it was felt that patient's status as an HIV-infected MSM played a large role in the initial clinical suspicion of gonococcal sepsis, with the finding of symmetrical polyarticular arthralgia on examination leading the clinicians to consider associated reactive arthritis. The patient's denial of recent sexual activity, negative urine NAAT for NG, and lack of urethritis or pharyngitis failed to dissuade the treating clinicians of this presumed diagnosis, however the emergence on day three of isolated right knee pain prompted reinvestigation, eventually leading to a diagnosis of meningococcal sepsis with early-onset septic arthritis.

This case is particularly interesting as the patient's capsular genogroup probably reflects the epidemiology of his recent travel, as approximately a third of adult meningococcal disease in the USA is serogroup C whereas in the UK this serogroup is responsible for only 4% of current invasive meningococcal disease (5, 6). This is well illustrated by a recent outbreak of serogroup C meningococcal disease in men who have sex with men (MSM) in Southern California (7). The diagnosis of meningococcal disease might have been considered sooner if the patient had visited a city in the USA with an ongoing meningococcal outbreak among MSM (e.g. Chicago, New York, Los Angeles) or if he had frequented crowded venues that could have increased his risk of acquiring meningococcal carriage/disease. Of note, MSM are known to have high rates of *Neisseria meningitidis* carriage (42.5% in one study) (8, 9) and an increased risk of invasive meningococcal disease has been associated with HIV-infection (10-13) and worse outcomes (14, 15). Thus in cases of HIV-infected MSM presenting with septic arthritis, clinicians may wish to consider empirical antimicrobials which cover against both *N. gonorrhoeae* and *N. meningitidis*.

Of note, the patient had not been vaccinated against meningococcus, and this illness caused by *Neisseria meningitidis* serogroup C may have been prevented had he previously received the MenC or MenACWY vaccine. This is an important learning point, and a reminder that all HIV-infected MSM should be offered meningococcal vaccination as per UK national guidelines (16).

This case also underscores the utility of PCR-based techniques in the microbiological diagnosis of septic arthritis, especially when joint aspiration is performed after antimicrobial initiation. Gram stain and culture may become negative shortly after initiation of antimicrobial therapy whereas bacterial rDNA persists and may be detected by molecular methods several weeks later (17). Addition of 16S rDNA PCR to routine processing of joint specimens increases diagnostic yield over culture alone in paediatric septic arthritis (18).

In conclusion, in cases of HIV-infected MSM presenting with sepsis or septic arthritis, it is important to keep a broad range of aetiological agents in mind, including less typical causes of septic arthritis such as *Neisseria meningitidis*, an important notifiable organism. A thorough travel, sexual and vaccination history is invaluable, especially in this group of patients. 16S rDNA PCR can be a useful adjunctive investigation in septic arthritis, and can be of particular use both early in the course of the disease if initial microscopy and culture fails to yield a microbiological diagnosis, or at a later juncture if joint aspiration is performed after the initiation of antimicrobial therapy.

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