CASE REPORT

Helicobacter cinaedi knee infection after arthroscopy in an immunocompetent patientHans Linde Nielsen,^{1,2} Jørgen Prag,³ Karen Angeliki Krogfelt⁴¹Department of Clinical Microbiology, Aalborg University Hospital, Aalborg, Denmark²Department of Infectious Diseases, Aalborg University Hospital, Aalborg, Denmark³Department of Clinical Microbiology, Viborg Hospital, Viborg, Denmark⁴Department of Microbiology and Infection Control, Statens Serum Institut, Copenhagen, Denmark

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SUMMARY

An otherwise healthy 36-year-old man was hospitalised due to a traumatic tear of the meniscus in the left knee. An arthroscopy was performed and his meniscus was partially resected. Thirty days later, he was rehospitalised with arthritis in the left knee and cellulitis on the left tibia. *Helicobacter cinaedi* was isolated from the synovial fluid, which was incubated in a BACTEC Paediatric bottle. The patient was treated with oral rifampicin and moxifloxacin for 6 weeks with good clinical response without relapse. The source of the infection was not found. The case emphasises the importance of incubating the synovial fluid in a rich medium such as a BACTEC Peds Plus/F bottle. Physicians and microbiologists should be aware of *H. cinaedi* as a human pathogen causing a range of disease manifestations, including infective arthritis and cellulitis, particularly if symptoms evolve in the weeks following a surgical procedure.

BACKGROUND

Helicobacter spp are Gram-negative, microaerophilic, motile and curved spiral (S-shaped) rods, and the gastric *Helicobacter pylori* is the most well-known species.¹ However, other species such as *H. bilis*, *H. cinaedi*, *H. canadensis*, *H. canis*, *H. fennelliae* and *H. pullorum*, classified as 'enterohepatic *Helicobacter* species', have also been isolated from humans.¹

The most frequently isolated non-pylori *Helicobacter* spp is *H. cinaedi*, first isolated in 1984 from HIV positive homosexual men with proctitis.² Since then, *H. cinaedi* infections have also been described in immunocompetent patients with symptoms such as fever, enteritis, erysipelas, cellulitis, bacteraemia and other clinical symptoms, after *H. cinaedi* entered the body, likely through the intestinal mucosa.^{3–6} However, to the best of our knowledge, there have only been three reported cases of *H. cinaedi* monarthrititis.^{7,8}

Kitamura *et al*⁴ reported a case series of 11 immunocompetent Japanese patients who all had *H. cinaedi* bacteraemia and postoperative cellulitis on average 30 days after orthopaedic surgery. Similarly, we describe the first Danish case of *H. cinaedi* arthritis 30 days after arthroscopy in an immunocompetent patient.

CASE PRESENTATION

An otherwise healthy 36-year-old man was hospitalised at the department of orthopaedics, due to a traumatic tear of the meniscus in his left knee. An arthroscopy was performed and the meniscus was

partially resected. Thirty days later, the patient was readmitted due to cellulitis with a diffuse, pale pink skin colour on the left tibia and pain in his left knee. Moreover, he presented a history of loose stools for weeks, but the patient's stools were not examined for pathogenic enteric bacteria. He was treated with oral penicillin V and discharged.

Seven days later he was rehospitalised due to increased localised pain and a synovial effusion in his left knee. The patient was afebrile and laboratory findings showed white cell count (WCC) $11.7 \times 10^9/L$, C reactive protein (CRP) 20 mg/L and erythrocyte sedimentation rate of 33 mm. A sterile puncture of the knee was followed by intravenous cefuroxime for 2 days followed by oral dicloxacillin, and the patient was discharged without a surgical debridement. Unfortunately, the dicloxacillin gave no clinical improvement, and therefore the antimicrobial therapy was changed to roxithromycin in an outpatient setting; this also, however, had no significant clinical effect.

After the identification of *H. cinaedi*, the antimicrobial therapy was finally changed to oral rifampicin 450 mg two times per day and moxifloxacin 400 mg once a day for 6 weeks. This combination therapy had a clear effect, and synovitis of the knee disappeared without any joint sequelae during 6 weeks follow-up. Moreover, by telephone after 6 months follow-up, the patient also reported no joint sequelae. The patient had no close contact with animals.

INVESTIGATIONS

The initial microscopy of the synovial fluid (wet smear, Gram-staining and Methylene blue staining) was negative. Furthermore, primary culture on conventional solid agars, Columbia 5% sheep blood agar (Becton Dickinson, Maryland, USA), chocolate agar (SSI Diagnostica, Copenhagen, DK), lactose agar and thioglycolate broth incubated in an aerobic atmosphere with 5% CO₂ and an anaerobic atmosphere at 35°C, were culture-negative after 4 days. There was not enough synovial fluid to make a primary incubation in the BACTEC standard aerobic/anaerobic blood culture bottles (Becton Dickinson), but approximately 1 mL of synovial fluid was incubated in a BACTEC Peds Plus/F bottle (Becton Dickinson). After 5 days, incubation in the BACTEC 9240 Ped bottle was positive with small, mobile, Gram-negative, catalase-positive, spiral rods. Secondary incubation of the isolate in the BACTEC standard aerobic or anaerobic blood culture bottles remained negative. The isolate was urease and nitrate negative, but oxidase positive.

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Electron microscopy, using a FEI Morgani D268 electron microscope at 80 kV, showed a *Helicobacter*-like organism with bipolar unsheathed flagella. The final identification was made by matrix-assisted laser desorption ionisation time-of-flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonics, GmbH, Bremen, Germany) with an identification score of >2.0 as well as 16S ribosomal RNA analysis on lysates of the pure culture using a MicroSeq ID kit (Applied Biosystems, California, USA), as described by Fontana *et al.*⁹ Although no clinical breakpoints exist for *H. cinaedi*, susceptibility testing was performed using McFarland standard 0.5 on *Brucella* sheep blood agar and E-test (AB Biodisk, Solna, Sweden) in a microaerophilic atmosphere. The susceptibility test gave the following results: ampicillin minimum inhibitory concentrations (MIC): 0.25 µg/mL, ciprofloxacin MIC: 0.064 µg/mL, moxifloxacin MIC: 0.002 µg/mL, tetracycline MIC: 0.032 µg/mL, rifampicin MIC: 0.032 µg/mL and erythromycin MIC: 4.0 µg/mL.

DISCUSSION

This is the first reported Danish case of an *H. cinaedi* knee infection after arthroscopy in an immunocompetent patient. The patient did not have fever, and he only had slightly elevated WBC and CRP, and a surgical debridement was not performed probably due to the few objective findings of severe knee infection. The patient did not improve on roxithromycin, a finding that corresponds to the *in vitro* susceptibility testing. The antibiotic treatment was, therefore, changed to a combination therapy with oral rifampicin and moxifloxacin resulting in a very good clinical response.

In general, rifampicin should never be administered by itself, due to the risk of resistance; therefore, quinolones are excellent combination agents because of their bioavailability, antimicrobial activity and tolerability.¹⁰ The case reported by Lasry *et al.*⁸ was also treated with rifampicin in combination with ciprofloxacin for 12 weeks, and the synovitis disappeared with no sequelae. However, we chose to combine the rifampicin with moxifloxacin instead of ciprofloxacin due to the lower MIC. Moreover, our patient recovered after 6 weeks of combination therapy. We were not able to identify the infection route of *H. cinaedi* in our case. Zoonotic transmission from animals to humans has been reported for *H. cinaedi*,^{11 12} but our patient had no close contact with animals, and we were not able to cultivate any *Helicobacter* spp in the patient's stools. Unfortunately, the stools were examined after the antimicrobial therapy was initiated. Whether the infection had an iatrogenic cause was unclear. Kitamura *et al.*⁴ reported 11 immunocompetent patients who all had postoperative cellulitis and spontaneous pain close to the operated site as well as *H. cinaedi* bacteraemia on average 30 days after orthopaedic operation. Our case, besides having infective arthritis in his left knee, also had cellulitis on the front of his tibia. This occurred 30 days after his arthroscopy, a period of time identical to the average time observed in the Japanese patients. In the Japanese outbreak, Kitamura *et al.* tried to identify the source of the *H. cinaedi* infections, and therefore tested for *H. cinaedi* carriers among the hospital staff and other patients. However, surveillance testing was negative and the route of infection remained unclear. Nevertheless, observations showed a strong trend for the appearance of cellulitis at the area of the skin where cold compresses had been applied. Our patient also had cold compresses around his left knee in the hours immediately after the arthroscopy. These cold compresses also involved the patient's tibia to some degree. The pathogenetic mechanism of cellulitis is poorly understood, but Kitamura *et al.* discussed the risk of *H. cinaedi* invasion to the tissue via

the vasculature, when there is a cold-induced stress on the local blood flow.

Isolation of *Helicobacter* spp requires a microaerobic atmosphere and the growth of *H. cinaedi* is accelerated by adding hydrogen gas (5–10%) to the microaerobic gas.¹³ The BACTEC blood culture system (Becton Dickinson), particularly the paediatric BACTEC Peds Plus/F bottle, has proven to be superior to conventional agar plate methods, for the detection of microorganisms from synovial fluid.¹⁴ Our case emphasises the importance of incubating part of a synovial fluid in a rich medium such as the BACTEC Peds Plus/F bottle. This isolate showed no growth on the primary agar plates, nor did it show growth on a secondary incubation in the aerobic or anaerobic blood culture bottle. The paediatric bottle is supplemented by extra animal tissue digestion and has less sodium polyanethol sulfonate compared with the aerobic or anaerobic bottle. The advantage of the former in stimulating growth of enteric *Helicobacter* spp corresponds to the earlier finding by Prag *et al.*¹⁵ The incubation time is also very important as it took 5 days before the paediatric bottle was positive.

Clinicians as well as microbiologists should be aware of *H. cinaedi* as a human pathogen causing a range of disease manifestations, including infective arthritis and cellulitis, particularly if symptoms evolve in the weeks following a surgical procedure. Moreover, if there has been a history of enteritis or loose stools, clinicians should be aware of the risk of an extra-intestinal *H. cinaedi* infection. Antibiotic therapy for *H. cinaedi* arthritis should be individualised but, so far, a combination of rifampicin and a quinolone has been well tolerated with good clinical response.

Learning points

- ▶ Physicians and microbiologists should be aware of *Helicobacter cinaedi* as a human pathogen causing a range of disease manifestations including infective arthritis and cellulitis, particularly if symptoms evolve in the weeks following a surgical procedure.
- ▶ The case emphasises the importance of incubating the synovial fluid in a rich medium such as the BACTEC Peds Plus/F bottle.
- ▶ Antibiotic therapy for *H. cinaedi* arthritis should be individualised but, so far, a combination of rifampicin and a quinolone has been well tolerated with good clinical response.

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Contributors All the authors contributed to the manuscript. HLN wrote the paper. HLN, JP and KAK performed the bacterial identification and susceptibility testing and revised the paper.

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