Rare disease

Aortic homograft endocarditis caused by *Cardiobacterium hominis* and complicated by agranulocytosis due to ceftriaxone

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Summary

The present report describes a very rare case of an aortic homograft valve endocarditis caused by *Cardiobacterium hominis*. The case was complicated by an agranulocytosis after 3 weeks of antibiotic treatment induced by ceftriaxone. Alternative oral treatment with ciprofloxacin and rifampicin was successful, no surgical intervention was needed and homograft function could be preserved.

BACKGROUND

Cardiobacterium hominis, a fastidious, Gram-negative bacillus belonging to the *Haemophilus parainfluenzae*, *Aggregatibacter* spp., *C hominis*, *Eikenella corrodens* and *Kingella kingae* (HACEK) group was first isolated in 1962 from four patients with endocarditis.¹ It is present as a commensal of the normal flora of the oropharynx in most individuals.² It was also detected in stool samples by fluorescent antibody analysis and may colonise the gastrointestinal tract of humans.³ In one study *C hominis* was isolated from cervical and vaginal culture and therefore could be an intermittent colonising bacteria of the urogenital tract.⁴ *C hominis* is a rare cause of endocarditis. Recently, a second species of the genus *Cardiobacterium*, *Cardiobacterium valvarum*, was described as an infectious agent of endocarditis.⁵ Only 3% to 6% of all community acquired endocarditis cases are caused by the HACEK group.² Das *et al* described *C hominis* as the aetiological pathogen in 27% of endocarditis cases caused by members of the HACEK group.⁶ To date only 80 cases have been reported.^{7–9} The most common site of infection is the native heart valve.⁸ The primary focus of the infection is rarely identifiable. A previous dental procedure or oral infection has been reported in approximately 50% of the reported cases.¹⁰ With new blood culture systems, extended incubation to recover HACEK bacteria is not necessary.¹¹ Detection of *C hominis* by broad range PCR has recently been described.^{12–13} The vast majority of *C hominis* cases are sensitive to penicillin, but two cases of endocarditis caused by β lactamase-producing *C hominis* from blood cultures have been reported (both infections occurred on native valves).^{14–15} The current recommendation for preferred treatment is a third-generation cephalosporin for 4 to 6 weeks.^{16–17} However, randomised clinical trial data is lacking. Surgical treatment, mostly valve replacement, was needed in 45% of published cases.⁷ The main complications of *C hominis* endocarditis include congestive heart failure, peripheral embolic events, arrhythmia, mycotic

aneurysm, glomerulonephritis, vertebral osteomyelitis and severe thrombocytopenia.^{9 18} The clinical outcome of *C hominis* endocarditis is favourable, in almost 95% of reported cases the patients were cured.^{6–7 9} However, this number most likely overestimates positive outcomes because a considerable bias of under-reporting of unfavourable cases is likely.¹⁹ Here, we report a case of a *C hominis* homograft endocarditis that was further complicated by ceftriaxone-induced agranulocytosis.

CASE PRESENTATION

A 61-year-old man was admitted to our hospital with a history of fatigue, lethargy and weight loss for many months and chills and night sweats for 2 months. His medical history was remarkable for a Carpentier–Edwards bioprosthetic aortic valve replacement at the age of 34 years due to a bicuspid aortic valve with aortic insufficiency.

Some 14 years after the valve replacement, three episodes of *Streptococcus sanguis* endocarditis occurred, with the last one complicated by penicillin-induced agranulocytosis. At that time the prosthetic aortic valve was replaced by a homograft because of valvular leak with insufficiency due to mechanical destruction of the prosthetic valve. In addition, chronic unspecific colitis of unknown aetiology was diagnosed 1 year before the current admission. Colonoscopy at this time showed a one-segmental unspecific colitis of unknown aetiology. At 6 months prior to admission no dental procedures were performed. Then, 5 days before admission, three sets of blood cultures were drawn in a private laboratory on initiative by the patient because the symptoms of increasingly profuse night sweats requiring changes of bed linen, fatigue during the day and extreme weakness reminded him of the three earlier episodes of endocarditis 14 years ago. Furthermore the transthoracic echocardiogram (TTE) showed a change in comparison with the TTE from 1 year ago with minimal calcifications

and an aortic insufficiency with jet at the non-coronary commissure in addition to the known minimal central aortic insufficiency. On admission day, the private laboratory results showed growth of Gram-negative bacilli of yet unknown specificity, confirmed in all three aerobic bottles from three sets of blood cultures.

INVESTIGATIONS

Physical examination revealed a middle-aged man without respiratory distress with blood pressure of 150/70 mm Hg, a heart rate of 80 beats/min and a temperature of 36.9 °C (taken in the ear). Cardiac examination demonstrated a slightly increased murmur. No peripheral signs of endocarditis were observed. Laboratory investigation demonstrated a white blood cell count of 8.2×10^3 cells/ μ l (no leucocyte left shift), his C reactive protein (CRP) level was only slightly elevated (17 mg/litre) and a full blood count, urine analysis, blood urea and electrolyte levels were all normal. An additional three sets of blood cultures were drawn. Transoesophageal echocardiography (TOE) revealed no signs of endocarditis but confirmed the new insufficiency at the non-coronary commissure with jet, compared with the TTE performed by the same examiner 1 year earlier.

TREATMENT

An empirical intravenous treatment with vancomycin, gentamicin, rifampicin and ceftriaxone was given. At 2 days after admission the three aerobic bottles from the three sets of blood cultures taken at admission revealed again growth of Gram-negative rods. Within 3 days the Gram-negative rods were identified as *C hominis* by conventional methods, that is, Gram-negative rods arranged in rosette clusters, positive for indole and oxidase but negative catalase reactions.²⁰ Meanwhile, the external laboratory confirmed the identification by molecular means. We performed 16S rRNA gene sequencing as described previously.²¹ The results confirmed *C hominis* with 99.1% base pair homology. *C valvarum* was also found with 94.7% base pair homology. The antibiotic treatment was simplified to just ceftriaxone 2 g per day and the patient was discharged home, receiving daily intravenous treatment in our outpatient clinic. The patient quickly improved clinically and his CRP level normalised after 4 days. Then, 3 weeks after admission, the patient reported subfebrile episodes with changes of vision. The laboratory examination showed an elevated CRP level (46 mg/litre) and neutropoenia of 0.02×10^3 cells/ μ l, induced by the betalactam antibiotic ceftriaxone that was immediately stopped. Antibiotic treatment was switched to oral ciprofloxacin 750 mg twice daily and rifampicin 450 mg twice daily according to low minimal inhibition concentrations (MIC) and very good oral bioavailability of those two drugs (MIC of ciprofloxacin 0.012 mg/litre, MIC of rifampicin 0.125 mg/litre; these MIC values are considered to be susceptible according to the Clinical and Laboratory Standards Institute).²² A positron emission tomography CT scan showed only a slightly enlarged spleen but no signs of septic emboli. New blood cultures drawn remained fully negative. During agranulocytosis the patient developed severe gingivostomatitis and a submandibular abscess. Oral clindamycin was added at a dose of 900 mg three times a day for 14 days. At 10 days after stopping ceftriaxone, his leucocyte count normalised

and the stomatitis and submandibular abscess rapidly disappeared. During the next few weeks the patient reported several episodes of severe pain in the right shoulder, in the vertebral column and in the left leg, and also had presumably increased activity of the colitis as reflected by abdominal pain and increased frequency of diarrhoea. In addition CRP values fluctuated between 7 mg/litre and 144 mg/litre and febrile temperatures up to 38.5 °C were repeatedly measured. An additional TOE performed 5 weeks after diagnosis revealed new nodular vegetation on the aortic valve and a minimal insufficiency of the aortic valve of the homograft. At this point the endocarditis could be unambiguously confirmed according to the modified Duke criteria.²³ To rule out possible embolic events, an MRI of the brain and a CT scan of the abdomen were performed, which both remained negative. The cause of the painful episodes remained unclear and they were classified as most probably of muscular or inflammatory origin due to potential paraimmunological phenomenon resulting from the endocarditis or the colitis.

OUTCOME AND FOLLOW-UP

After a total treatment course of 6 months antibiotics were stopped. Another TOE at this time confirmed the vegetation seen before at a similar size. At 8 months after completion of the antibiotic treatment the patient continues to do well without any signs of a relapse of the endocarditis.

DISCUSSION

Here, we report a rare case of *C hominis* endocarditis that presented with several unique features: to the best of our knowledge this case represents only the second reported case of a homograft endocarditis caused by this organism reported to date. The course of treatment was complicated by severe agranulocytosis induced by ceftriaxone. For this reason, we could not continue standard treatment with this drug and had to switch to an alternative regimen. We chose high-dose oral ciprofloxacin and rifampicin according to very favourable MICs and excellent oral bioavailability, being fully aware that this is not an established treatment for this bacterium and outcome data are missing. Although we knew that this patient had an increased risk of ceftriaxone-induced agranulocytosis due to his former episode of penicillin-induced agranulocytosis 11 years ago during treatment for *S sanguis* prosthetic valve endocarditis, together with the patient we decided to take the risk of initial ceftriaxone treatment because no other standard treatment is recommended. We wanted to save the still well functioning homograft to omit new cardiac surgery at this point if possible. We performed frequent monitoring of the patient's white cell count (2–3 times per week). This strategy allowed us to apply standard treatment for 3 weeks and led to the diagnosis of agranulocytosis very early on. We believe that the early detection of agranulocytosis and immediate cessation of ceftriaxone led to a much shorter duration of agranulocytosis of only 10 days when compared to the first episode 12 years ago when agranulocytosis persisted for 3 weeks. The antibacterial efficacy of ciprofloxacin in one case of endocarditis due to *C hominis* had been previously reported by Vogt *et al.*²⁴ The American Heart Association (AHA) also suggest that fluoroquinolone can be considered as alternative regimen in patients unable

to tolerate betalactam treatment.¹⁶ The current recommendation regarding duration of treatment is a 4-week intravenous course with a third-generation cephalosporin for native valve endocarditis, and a 6-week course with prosthetic valves.¹⁷ Due to the fact that our patient had an atypical course of a rare infection that was complicated by agranulocytosis with oral infection, followed by a need to switch to a non-standard antibiotic treatment, relapsing colitis and a homograft in situ with new vegetation, we chose a total treatment course of 24 weeks.

The first case of homograft aortic valve endocarditis due to *C hominis* was published by Currie *et al* in 2000, reporting on a 17-year-old man with previous aortic valve replacement due to congenital aortic stenosis and positive blood cultures of *C hominis* but no growth of the organism from the excised graft.²⁵ In contrast to that patient, in our patient surgery could be omitted. In 1995 the AHA recommended that HACEK microorganisms should be considered ampicillin resistant and the third-generation cephalosporins should be considered the antibiotics of choice,¹⁷ although ampicillin-resistant strains have been reported only rarely,^{14 15} in contrast to other members of the HACEK group. As in our patient, structural abnormalities of the heart valve are predisposing factors for infection with *C hominis* and were present in more than 75% of all cases reviewed.⁷ The source of infection, however, is less clear. According to the literature in most cases a primary focus cannot be found.⁸ Neither intravenous drug use nor infection at other body sites have been described as risk factors for *C hominis* endocarditis, in contrast to endocarditis caused by other pathogens.⁷ Most likely the oral tract is the main source of infection, as previous dental procedures have been reported in approximately 50% of patients with *C hominis* endocarditis.¹⁰ Our patient had an unclear chronic colitis. We hypothesise that it is most likely translocation of *C hominis* from the colonised bowel through the colonic wall occurred, leading to bacteraemia and colonisation of the homograft aortic valve. In two reported cases, *C hominis* endocarditis occurred after upper endoscopy and colonoscopy, respectively.^{9 26} In contrast to the previous AHA guidelines, the newest guidelines published in 2007 no longer recommend antibiotic prophylaxis in patients undergoing endoscopy at a high risk for endocarditis.²⁷ Both patients had a prosthetic heart valve and received no prior endocarditis prophylaxis. Our patient underwent colonoscopy 1 year before endocarditis and therefore a link to this procedure can most likely be excluded. However, the colitis presented a diagnostic complication because the patient had had fatigue for several months, which was attributed to episodes of colitis but could have been an early symptom of endocarditis. Clinical symptoms of *C hominis* endocarditis are often unspecific and typically present with unspecific subacute symptoms such as night sweats, weight loss, chills, arthralgias and subfebrile temperatures in approximately 75% of all reported cases.⁷ These characteristics may be explained by a low virulence of the pathogen. In an experimental study an inoculation of 10⁹ microorganisms into mice led to no evidence of infection.¹ In a recent review, the mean duration of symptoms before diagnosis was found to be 145 days (range 1 week to 11 months).⁷ Laboratory findings do not differ from endocarditis caused by other organisms.^{7 9 18} The most common physical findings

are a cardiac murmur (94%), peripheral embolic lesions (51%) and splenomegaly (40%).⁹ The fact that we did not find any septic emboli, described to occur in approximately 50% of *C hominis* endocarditis cases,¹⁰ might potentially be explained by the relatively early presentation compared to cases reported in the literature.^{12 28–31} The diagnosis is usually established by clinical and echocardiography findings and positive blood cultures. In a review by Das *et al* regarding infective endocarditis caused by HACEK microorganisms, vegetations were present in 60% in patients evaluated by TTE and TOE (low positive predictive value of 29% and negative predictive value of 76% for embolic events).⁶ Malani *et al* found that vegetations were detected in 80% of cases by TOE and in 56% of cases by TTE.⁹ In our case, initial echocardiography was unremarkable but echocardiography performed 4 weeks later showed new vegetations. This fact supports the current recommendation to routinely perform echocardiography in the course of treatment when initial echocardiography was negative. Prognosis of endocarditis due to *C hominis* is favourable, with reported cure rates of almost 95%. However, valve replacement was required in 40% to 45% of cases.^{6–7 9}

Learning points

- Prolonged non-standard treatment with ciprofloxacin and rifampicin of a very rare case of an aortic homograft endocarditis caused by *Cardiobacterium hominis* due to ceftriaxone-induced agranulocytosis was successful in preserving the homograft.

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Competing interests None.

Patient consent Obtained.

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