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Case report

Cardiobacterium hominis endocarditis incidentally diagnosed following an aortic valve replacement surgery

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ABSTRACT

Background: Cardiobacterum hominis (*C. hominis*) is the part of the HACEK group (*Haemophilus spp, Actinobacillus spp, C. hominis, Eikenella, and Kingella spp)* that accounts for the majority of the Gram-negative infective endocarditis cases. Historically, the fastidious characteristics of these microorganisms proved challenging to many clinicians. Advances in microbiological identification of culture-negative endocarditis; however, may be the reason for the rising incidence of these infections. Here, we report an incidentally diagnosed *C. hominis* endocarditis following an aortic valve replacement.

Case report: A healthy 54-year-old gentleman presented after several months of generalized weakness and exertional intolerance. He was found to have a bicuspid aortic valve with regurgitation and underwent aortic valve replacement surgery. Intraoperatively, the patient was found to have a large perforation of the fused leaflet associated with abnormal pink tissue in the aortic valve area. The aortic valve tissue was cultured. Gram-negative rods were isolated 48 h later and were ultimately identified as *C. hominis*. He was successfully treated with 6 weeks of intravenous ceftriaxone with sterile blood cultures throughout the hospital stay. In retrospect, the patient's valve failure was likely secondary to subacute endocarditis from *C. hominis* complicated by leaflet perforation.

Conclusion: C. hominis is a rare cause of infective endocarditis with an excellent prognosis when timely diagnosed and managed. By reporting this case, we wish to raise awareness of potential asymptomatic infection, particularly amongst patients with underlying native valve abnormalities, new leaflet perforation, and valve insufficiency.

Introduction

Cardiobacterium hominis (*C. hominis*) is a Gram-negative pleomorphic and fastidious rod-shaped bacterium first described in 1964 by Slotnick and Dougherty in a patient with endocarditis caused by a previously unknown microorganism with characteristics similar to Pasteurella multocida [1]. Afterwards, based on its characteristics, *C. hominis* became a part of the HACEK group (*Haemophilus species, Actinobacillus species, C. hominis, Eikenella corrodens, and Kingella species*), with *Capnocytophaga* species added in recent reports (*C. ochracea, C. sputigena and C. gingivalis* for the human species) [2,3]. These microorganisms are grouped based on their similarities, such as: being predominantly oropharyngeal microbiota; their low virulence; and their similar infectious profile including periodontal infections, bacteremia, and occasionally infective endocarditis (IE) [2,4]. Aside from *viridans* streptococci, HACEK bacteria are the second most common oral pathogen group to cause bacteremia and subsequent IE [5]. Although infrequently encountered in clinical practice, understanding of the role of HACEK bacteria in IE etiology has grown over the past few decades concomitant with increasing knowledge of the microorganisms'

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characteristics, advancements in precise identification, culture techniques, and management.

Here, we report a *C. hominis* IE case incidentally diagnosed after culturing aortic valve tissue due to a concerning intraoperative valve finding.

Case presentation

We present a healthy 54-year-old gentleman with an unremarkable annual examination as of July 2021. Within several months he developed generalized weakness and exertional intolerance which rapidly progressed. Once he was unable to tolerate even walking short distances, he presented for evaluation by his family physician in December of 2021. No systemic or constitutional symptoms such as chills, fevers, night sweats, or unintentional weight loss were reported. On physical examination, he was found to have a new prominent systolic and diastolic murmur, which further prompted outpatient workup with transthoracic echocardiography (TTE) accomplished in January of 2022. The TTE revealed new heart failure with reduced left ventricular ejection fraction (LVEF) of 35%, and bicuspid aortic valve with severe aortic regurgitation; but without significant stenosis or apparent valvular vegetations. Subsequently, the patient underwent replacement of the aortic valve with a mechanical prosthesis in March of 2022. Perioperative transesophageal echocardiography (TEE) was negative for apparent aortic valve vegetations but revealed a perforation of the fused leaflet (Fig. 1). During the surgery, an area of abnormal pink tissue along with the leaflet perforation were noted in the native aortic valve area and was subsequently sent for cultures (Fig. 2). After 48 h, bacterial cultures of the aortic valve tissue grew Gram-negative fastidious bacillus prompting blood cultures to be obtained. While awaiting identification of the microorganism, a beta-lactamase disk test was performed for antibacterial therapy guidance. Thus, the patient was initiated on intravenous (IV) ceftriaxone 2 g every 24 h. Eight days after the surgery, *C. hominis* was identified using Bruker matrix-assisted laser desorption/

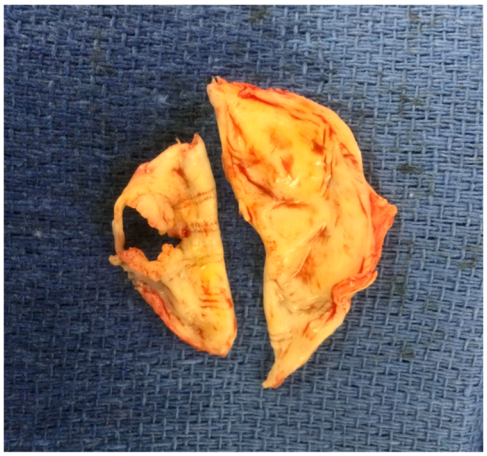

Fig. 2. Bicuspid aortic valve following aortic valve replacement surgery demonstrating perforation of the leaflet.

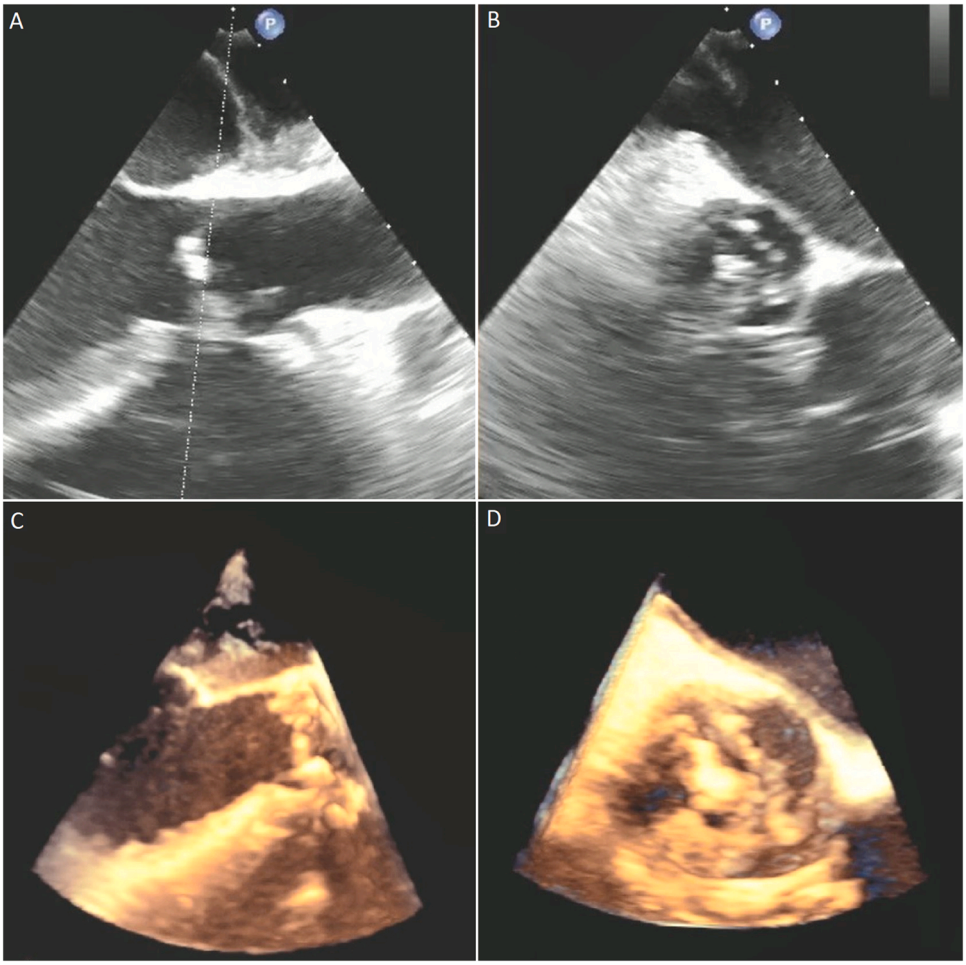

Fig. 1. Transesophageal echocardiography (TEE) shows a long-axis (A) and short-axis (B) view of thickened aortic valve leaflets, along with 3D reconstruction (C and D).

ionization-time of flight (MALDI-ToF) mass spectrometry. Antimicrobial susceptibility was performed using gold standard agar dilution for the drugs (bioMérieux VITEK 2 XL instrument, Mayo Clinic Laboratories) and results were reported according to Clinical Laboratory Standard Institute (CLSI) M100 guidelines. Minimum inhibitory concentrations (MICs) was $\leq$ 0.5 mcg/mL for ceftriaxone. Beta-lactamase chromogenic assay was negative. The patient was continued on IV ceftriaxone 2 g every 24 h. His leukocyte count was within normal limits before and remained stable after surgery, but his C-reactive protein (CRP) was elevated at 29.9 mg/L (reference less than 10 mg/L) 12 days after the surgery (no CRP was done before or immediately following the surgery). His fibrinogen was 337 mg/dL on the day of surgery (reference rang 200–400 mg/dL). Throughout the hospital course, the patient was asymptomatic without any sign of infection. His blood cultures remained sterile. At the time of this case writing, he was completing a 6-week course of IV ceftriaxone 2 g every 24 h with plans to initiate prophylactic amoxicillin afterwards.

Discussion

IE is a rare infection with an annual incidence ranging from 3 to 10 cases per 100,000 people [6]. While Gram-positive cocci, such as streptococci and staphylococci, are the predominant IE etiology (80–90% of the cases), the incidence of Gram-negative IE ranges from 1.3% to 10% with most cases attributed to HACEK microorganisms [2,6,7]. Despite constituting the majority of Gram-negative IE, the lack of randomized-controlled clinical trials in diagnosing and treating IE makes it difficult to optimally manage these infections [2]. One of the first studies that reviewed 45 HACEK-IE cases over 23 years in the Mayo Clinic (Minnesota, USA) reported an incidence of 0.14 per 100,000 person-years or 3% of all IE cases [7]. Similar prevalence was reported worldwide, from 0.5% in Africa and Australia, to 1.8% in the Middle East and Asia, to 6.1% in Argentina [8,9]. It appears that the incidence of HACEK-IE cases has been rising, but this may be secondary to increased awareness of these microorganisms, as well as advancements in laboratory (molecular) techniques to appropriately identify the etiology of culture-negative endocarditis cases, principally via the use of Bruker MALDI-ToF mass spectrometry [2,3]. In general, HACEK group microorganisms share similar characteristics including epidemiology, risk factors, clinical manifestations, treatment, and prognosis; however, each carries some unique characteristics [2]. Among HACEK microorganisms, the incidence of individual bacteria varies among studies, with the *C. hominis* share ranging from 13% [8] to 27% [7]. The other *Cardiobacterium* species to cause IE is the significantly less frequent *Cardiobacterium valvarum* which has been reported in less than dozen published cases thus far [8]. Differentiation between these two *Cardiobacterium* species can be done by using a broad-range 16 S rRNA PCR/sequencing test [3]. While some studies showed no gender difference in the HACEK-IE [8], others do find a male predominance [10]. Previous studies found a younger patient population in HACEK-IE compared to non-HACEK-IE [2,8], and this is also observed with *C. hominis IE* [10]. Native valves are more commonly affected in older patients compared to prosthetic valves [8]. Unlike other HACEK bacteria, *C. hominis* IE rarely occurs in children [10].

Clinical presentation of HACEK-IE is often indolent with the duration of preceding symptoms measured in weeks or even months [10]. When contrasted with non-HACEK-IE, it tends to have a subacute presentation and to be acquired from the community [2]. A limited review of *C. hominis* IE from 2006 found a preceding symptom duration of 138 $\pm$ 128 days, with the most reported symptoms being fever (74%), fatigue and malaise (53%), weight loss/anorexia (40%), night sweats (24%), and arthralgia/myalgia (21%) [10]. Many other *C. hominis* case reports describe a similar array of symptoms [3,10]. Our patient; however, was asymptomatic without any of these symptoms. Common risk factors include oral infection or recent dental procedures along with underlying acquired or congenital valvular disease, with pre-existing aortic valve abnormalities strongly associated with *C. hominis* infection [2,3,8]. In retrospect, our patient's symptoms of generalized weakness and exertional intolerance appeared to be a consequence of valve failure due to a leaflet perforation that likely occurred because of subacute IE.

The modified Duke criteria for IE diagnosis still apply to this group of microorganisms, although HACEK-IE remains a frequently overlooked infection due to the difficulty in isolating HACEK bacteria in the standard blood culture media due to their prolonged incubation period (from 3 to 6 days, but often exceeding 1 week) [7,10]. Thus, it is not unusual to extend blood culture incubation to 14 or 21 days to improve HACEK detection in cases of culture-negative endocarditis. Some studies find the incubation extension unnecessary and advise nonculture-based techniques, such as serology or nucleic acid amplification, when unusual microorganisms are suspected [11]. Given that culture-negative endocarditis is present in 5–10% of IE cases, often delaying effective and timely management, these nonculture-based methods would yield earlier detection and appropriate intervention [2,5]. As *C. hominis* bacteremia is not detected in many of IE cases, there have been attempts of establishing the IE diagnosis by the presence of one major and two minor criteria, thereby reducing the modified Duke criteria [3]. Conversely, if HACEK bacteremia is present in the absence of an infection source, it is highly suggestive of IE [5]. Our patient did not have typical IE physical exam findings, nor positive blood cultures, but aortic valve tissue grew *C. hominis*, thus undoubtedly confirming the diagnosis. Blood cultures were not done before the surgery, rather following the bacteria isolation from the valve tissue cultures and this source control probably was the reason for sterile blood cultures. The possibility that the bacterium was just an "innocent bystander" in the valve tissue is unlikely.

While up to 40% of patients with HACEK-IE require surgical management (similar to non-HACEK-IE), the majority of cases are successfully treated with solely medical therapy that consists of a 4–6 week course of IV ceftriaxone or ciprofloxacin for native and prosthetic valve IE, respectively [5,8]. There have been reports of penicillin and third-generation cephalosporin resistance due to beta-lactamase production, particularly with *C. hominis* [12]. This raises the problem of potential treatment and prophylaxis failure with amoxicillin as recommended by the American Heart Association (AHA). Despite amoxicillin's effectiveness against the most common IE causative bacteria (i.e. Gram-positive cocci, including viridians streptococci), it is ineffective in beta-lactamase HACEK producers [5]. Therefore, based on the latest AHA recommendations, HACEK microorganisms should be considered ampicillin-resistant, unless adequate susceptibility testing is available [5]. Hence, fluoroquinolone (e.g. ciprofloxacin) utilization is recommended unless adequate susceptibility testing is available [5].

Mortality of HACEK-IE varies depending on the source and ranges from 4% [8] to 15% [13]. *C. hominis* mortality is estimated to be around 7% and appears to be similar in both native and prosthetic valve endocarditis [10]. A large multi-national study from 2013 analyzed 77 HACEK-IE cases and found the overall mortality of 4% which was significantly better compared to non-HACEK-IE which was 18% ($p < 0.001$) [8]. The same study found that HACEK-IE is associated with higher embolization risk and subsequent stroke compared to non-HACEK-IE (25% vs 17%, $p = 0.05$), particularly in native mitral valve IE and younger age [8]. Other reported *C. hominis* IE complications are congestive heart failure, arrhythmia, mycotic aneurysm, and systemic septic emboli [10]. Only one case of perforated aortic valve leaflet secondary to *C. hominis* IE has been reported thus far, although the patient had undergone valve-sparing aortic root replacement for aortic regurgitation 5 years prior [14]. Our patient had an excellent short-term outcome with source control and 6 weeks of IV ceftriaxone. Besides heart failure with reduced LVEF that was attributed to bicuspid aortic valve insufficiency with severe aortic regurgitation secondary to leaflet perforation (which we believe occurred due to subacute IE), no other complications were observed. A repeat TTE is scheduled to assess if there

is LVEF improvement following the aortic valve replacement.

Conclusion

C. hominis endocarditis is a relatively rare infection with an excellent prognosis if the microorganism is timely diagnosed and managed. By reporting this case, we wish to raise awareness of potential asymptomatic infection, particularly amongst patients with underlying native valve abnormalities, new leaflet perforation, and valve insufficiency. Amoxicillin prophylaxis may be ineffective as it would not cover beta-lactamase-producing strains, so utilization of a different antibiotic class, like fluoroquinolone, may be reasonable in high-risk patients.

Consent

Written, informed consent for publication was obtained from the patient for the case report and imaging.

Source(s) of financial support

None to be reported.

Conflict of interest

None to be reported.

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