Subacute Infective Endocarditis Secondary to Cardiobacterium hominis in a Patient with Mitral Valve Prolapse

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Abstract

We present the case of a 42-year-old man with a history of mitral valve prolapse (MVP) presenting with subacute native valve endocarditis secondary to *Cardiobacterium hominis* infection. He presented with non-specific symptoms of generalized fatigue and malaise subsequent to a complication-free dental cleaning. He was treated initially with 4 weeks of ceftriaxone, but ultimately required mitral valve replacement due to severe valvular degeneration. This case provides a review of the pathophysiology and presentations of infective endocarditis (IE) secondary to HACEK organisms. We will review risk factors, as well as the evidence and current guidelines for pre-procedural IE prophylaxis.

Résumé

Il s'agit du cas d'un homme âgé de 42 ans ayant des antécédents de prolapsus valvulaire mitral (PVM) lié à une endocardite sur valve native subaiguë attribuable à une infection causée par *Cardiobacterium hominis*. Le patient présente des symptômes non-spécifiques de fatigue générale et de malaise à la suite d'un nettoyage dentaire s'étant déroulé sans complications. Après 4 semaines de traitement à la ceftriaxone, il a finalement dû subir le remplacement de la valvule mitrale en raison d'une grave dégradation valvulaire. L'étude de ce cas fournit une rétrospective de la physiopathologie et des différentes présentations d'une endocardite infectieuse (EI) secondaire aux organismes HACEK. Nous passons en revue différents facteurs de risque, ainsi que les données probantes et les lignes directrices actuelles concernant les mesures préventives de prophylaxie relative à l'EI.

Case Presentation

A 42-year old man with a history of mitral valve prolapse (MVP) presented to the emergency department in August 2015 following direct referral by his cardiologist. A transthoracic echocardiogram (TTE) showed thickening of his posterior mitral valve leaflet, suspicious for a vegetation. He endorsed a history of worsening generalized fatigue and malaise over months that were beginning to impair his day to day function, but otherwise, a review of systems was negative. Of note, he denied any history of fevers, chills, night sweats or weight loss, and had no shortness of breath or chest pain. Four months prior to the onset of his symptoms, he had a complication-free dental cleaning, but no other procedures. As per AHA/IDSA guidelines, he did not take any antimicrobial prophylaxis prior

to his cleaning. His past medical history was unremarkable with no history of autoimmune disease, intravenous drug use or chronic indwelling devices such as catheters or lines. He was not taking any prescribed or over the counter medications and had no known allergies. On social history, there was no recent travel, he was a non-smoker, minimal alcohol drinker, and his family owned a dog, a gecko, and a new kitten that was a few weeks old and had recently given him a superficial bite on the arm that had not broken through his skin.

On examination, he looked systemically well. His vital signs were stable and he was afebrile. Precordial exam was normal except for the presence of a grade III/VI holosystolic murmur best heard at the apex, radiating to the axilla. There was no evidence of congestive heart failure. There were no stigmata of infective endocarditis (IE). The remainder of the exam was unremarkable.

Pertinent laboratory investigations included a white blood cell count of 13.4 (normal range 4.0–11.0 × 109/L) with an absolute neutrophil count of 11.4 (normal range 2.0–7.5 × 109/L) and an elevated C-reactive protein at 28.6 (normal < 5 mg/L). ESR was not ordered. The remainder of his bloodwork and a urinalysis was within normal limits. Serial ECGs showed transient sinus tachycardia without any signs of heart block. A chest radiograph showed no visible abnormalities. Three sequential sets of blood cultures were drawn. A transesophageal echocardiogram (TEE) revealed severe mitral regurgitation as well as thickening and possible myxomatous degeneration of the mitral valve (Figure 1). The presence of a vegetation on the mitral valve could not be ruled out.

Two days following the patient's admission, two sets of blood cultures grew Gram-negative bacilli after 43.2 hours. The long incubation time was inconsistent with most Gram-negative organisms, and given the microbiology lab's comment on the inconsistency of the Gram stain with areas of under-colourization,
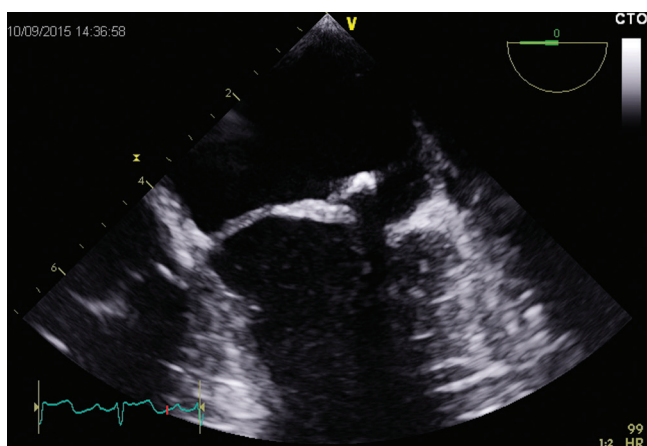
the patient was treated with vancomycin and ceftazidime for broad spectrum coverage. The following day, *Cardiobacterium hominis* was isolated. The strain was susceptible to beta-lactams. The patient remained clinically stable and was discharged with a PICC line and a 4-week course of ceftriaxone for *C. hominis* infective endocarditis (IE). Blood cultures drawn a day after the initiation of treatment were negative. The patient was provided with antimicrobial prophylaxis for future appropriate procedures.

The patient began to experience symptoms of shortness of breath on exertion and palpitations in the months after his initial diagnosis. Repeat echocardiography continued to demonstrate severe degeneration and regurgitation of the mitral valve. His progressive symptoms prompted a referral to cardiac surgery and he underwent a mitral valve replacement in March 2016. Pathology from the surgical tissue sample showed chronic inflammation, fibrosis and myxomatous degeneration but was culture negative several months after his course of antimicrobials.

Discussion

The HACEK Group

IE has a diverse pathophysiology and is caused by a variety of mechanisms. The most common etiology is secondary to bacterial infection. *Streptococcus* and *Staphylococcus* species are responsible for approximately 70-80% of cases of IE (Table 1). A group of fastidious Gram-negative organisms referred to as the HACEK organisms (*Haemophilus parainfluenzae, Aggregatibacter* species, *Cardiobacterium* species, *Eikenella corrodens* and *Kingella kingae*) are well-established, albeit infrequent causes of IE (1–3%). There have been recent changes to the nomenclature as certain several members of the *Haemophilus* species have been reclassified as *Aggregatibacter* species.[1] Distinguishing features of HACEK IE, as identified in a large database review, include a younger patient population and a weaker association with health care associated infections.[2] Major causes of IE are outlined in Table 1.[3,4]

Figure 1. Transesophageal echocardiogram showing a lesion suspicious for a vegetation on the anterior leaflet of the mitral valve.

Table 1. Major Causes of Infective Endocarditis

Microorganism	Approximate proportion of cases
Streptococcus species	38%
Staphylococcus species	36%
Enterococcus species	11%
HACEK	1–3%
Other	5–7%
Culture negative	5–7%

The long incubation time required to culture HACEK organisms has been well-documented, almost exclusively taking in excess of 2 days. Previous studies suggested that long incubation times of at least five to seven days were required to culture *C. hominis*; however, recently published cases and reviews have demonstrated consistent growth within five days.[5] Similarly, a review of laboratory incubations showed that all cases of HACEK IE were diagnosed within 5 days, and all incubations beyond 5 days yielded no growth.[6] This is important given the ever-increasing demands on microbiology labs and the extra costs incurred from prolonged incubation with no evident benefit. Current IDSA guidelines recommend three sets (including 8–10 ml of blood each into both an aerobic and anaerobic culture bottles) of sequential blood cultures be drawn to increase the diagnostic yield when investigating for endocarditis.[7] Our patient's strain of *C. hominis* was susceptible to beta-lactams, as are approximately 93% of reported cases.[8]

Cardiobacterium hominis

This case highlights a few classic features of *C. hominis* IE. *C. hominis* is a Gram-negative bacterium which commonly colonizes the oropharynx. Of note, the bacteria are pleomorphic rods and parts of the cell may actually stain Gram-positive.[9] A retrospective study of HACEK IE showed that *C. hominis* had a predominance for late disease presentation with the majority of reported cases (10/12) occurring three or more months following symptom onset.[3] The common symptoms are constitutional, including fever, chills, fatigue and weight loss. Symptoms of congestive heart failure are more common in cases of *C. hominis* than other HACEK organisms, and approximately 40% of cases ultimately require surgery on the affected valve.[8]

Risk Factors for C. hominis IE:

Established risk factors for IE caused by HACEK organisms, and specifically *C. hominis*, include structural cardiac abnormalities as well as dental procedures, which is understandable given that the bacteria are oral commensals. However, in contrast to the Gram-positive bacteria commonly causing IE, intravenous drug use does not seem to be a risk factor for *C. hominis* IE likely due to its absence on the skin at points of vascular injury.[5] Dental manipulation has been classically associated with the development of transient bacteremia even in immunocompetent hosts.[10] More recently, even mild dental manipulation from brushing has been shown to cause transient bacteremia.[11] While transient bacteremia is typically innocuous, it serves as a risk factor for IE particularly in the setting of structural cardiac abnormalities.

There are several cardiac structural lesions that predispose a patient to bacterial seeding leading to IE. Population-based studies in North America have shown that MVP has superseded rheumatic heart disease as the most common predisposing cardiac condition.[11] As well in patients with IE and no prior cardiac diagnosis, mitral valve prolapse with or without valvular regurgitation is the most commonly diagnosed underlying cardiac structural abnormality on echocardiography.[12] The pathophysiology of regurgitant valvular disease predisposing to IE involves turbulent flow through the valve leading to endothelial damage and the development of a vegetation through the aggregation of platelets, fibrin, and clotting factors at the site of the exposed endothelium.

Antibiotic Prophylaxis for IE Prevention

The utility of antibiotic prophylaxis prior to dental procedures for the prevention of infective endocarditis in patients with MVP has long been debated. Current major guidelines do not recommend prophylaxis for patients with MVP based on the lack of robust evidence for the effectiveness of prophylactic antibiotics in preventing endocarditis.[11,13] A Cochrane review of pre-procedural antibiotic prophylaxis, updated in 2013, only found one study suitable for inclusion in their analysis: a Dutch case-control study published in 1992.[14] There was a non-significant increase in the risk of developing IE 180 days post procedure for patients who did not receive antibiotic prophylaxis compared to those who did (odds ratio 1.62 with a 95% CI of 0.57–4.57).[14,15] To date, there have not been any randomized controlled trials examining the use of antibiotic prophylaxis in the prevention of IE. Such a study would be challenging to undertake as relatively low event rates would require large numbers of enrolled patients to ensure adequate power. It is clear that this is an area that would benefit from further study in order to further our understanding about the prevention of IE.

Based on the lack of strong evidence supporting antimicrobial prophylaxis, the United Kingdom's 2008 NICE guidelines for IE recommended no prophylaxis ahead of dental surgery for any indication. A subsequent temporal cohort study of the years before and after this guideline showed both a decrease in prescriptions for antimicrobial prophylaxis, as well as an increase in the incidence of IE after the guideline change.[16] Although this result does not suggest causation, it prompted an amendment to the NICE guidelines in 2016 to recommend against *routine* antibiotic prophylaxis, but to consider a case-by-case approach.[17] In comparison, the AHA/IDSA guidelines recommend prophylaxis only to patients at high risk of developing IE (Table 2).[11] Although the utility and efficacy of prophylaxis is still somewhat unclear, studies have shown that modern methods of prophylaxis with amoxicillin are safe and well-tolerated.[18] While our patient would not have previously met the 2007 AHA/IDSA criteria for pre-procedural prophylaxis prior to his dental cleaning, his

episode of endocarditis would qualify him for future prophylaxis with amoxicillin.

Table 2. Cardiac Conditions for which Pre-procedural Antibiotics are Recommended to Prevent IE as per the AHA/IDSA Guidelines

Conditions for which IE Prophylaxis is Recommended
Prosthetic heart valve (mechanical or tissue)
Previous history of IE
Valvulopathy in cardiac transplant patients
Unrepaired cyanotic congenital heart disease
Repaired congenital heart disease with residual defects and in the first 6 months post procedure

Conclusion

In summary, our case of native valve *C. hominis* IE represents a classic presentation of an uncommonly-occurring disease process. The case emphasizes the importance of a thorough history, physical exam, and laboratory investigations in the workup of potential IE. In patients presenting with fever of unknown origin or new-onset heart failure one should not neglect to ask about major risk factors for IE such as cardiac structural disease and IV drug use, but also enquire about other routes of bacterial exposure including dental procedures and ownership of pets. A review of the literature shows that there is minimal evidence regarding the efficacy of antibiotic prophylaxis prior to dental procedures for all-comers at risk of IE. Further research should focus on specific populations in which procedural prophylaxis would be effective.

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