Case report

Infective endocarditis and brain abscess secondary to Aggregatibacter aphrophilus

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ABSTRACT

Aggregatibacter aphrophilus is a rare cause of infective endocarditis that was first described in 1940 by Khairat et al. and is now classified under the HACEK group of bacteria (Haemophilus spp., Aggregatibacter spp., Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae). There is limited literature describing the extracardiac complications of infective endocarditis caused by this organism. We report a case of a 53-year-old male with no significant past medical history who developed acute infective endocarditis complicated by a brain abscess caused by A. aphrophilus. The patient underwent aspiration of the abscess and treated with a long course of intravenous antimicrobials. This case represents a rare complication of infective endocarditis caused by A. aphrophilus and to the best of our knowledge, is the second reported case in the literature describing such a complication in a previously healthy patient. Although neurological sequelae is associated with higher mortality and may be the presenting symptom of infective endocarditis, it may also be clinically silent – only detected upon imaging.

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Introduction

HACEK endocarditis (HE) refers to infective endocarditis caused by a group of five fastidious gram-negative species: Haemophilus spp., Aggregatibacter spp., Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae. They are considered a rare cause of infective endocarditis, responsible for less than 3% of cases [1]. Although neurological manifestations are the most common non-cardiac manifestation of infective endocarditis, brain abscesses are considered rare [2]. Here we report a case of a 53-year-old male who presented to the emergency department with confusion and was found to have a brain abscess on imaging. Further diagnostic workup revealed severe mitral valve regurgitation, and blood cultures grew Aggregatibacter aphrophilus (formerly Haemophilus aphrophilus and H. paraphrophilus), a HACEK organism with a tendency to cause both endocarditis and brain abscesses.

Case report

A 53-year-old Caucasian male with no significant past medical history presented to the emergency department with complaints of confusion and word finding difficulty for three days prior to admission. A few weeks prior to the admission, he was treated for infectious mononucleosis and streptococcus pharyngitis and completed his course of treatment. In addition to his chief complaints, he also reported fevers, night sweats, chills, and unintentional weight loss of twenty pounds over the preceding two months. He reported being told in the past that he had a benign heart murmur. He denied any accompanying chest pain, shortness of breath, palpitation, nausea, vomiting, abdominal pain, diarrhea, urinary complaints, recent travel, or sick contacts. On admission his vitals were stable. Initial laboratory results were significant for hemoglobin of 9 g/dL with a mean corpuscular volume of 79.7 fL (MCV). Leukocyte and platelet counts were normal. ESR and CRP were both elevated at 105 mm/hr. and 12 mg/dL, respectively, and urinalysis was normal. A comprehensive metabolic panel (CMP) was normal except for serum albumin of 2.6. An iron panel revealed a low serum iron of 43 mcg/dL, low TIBC of 162 mcg/dL, normal iron saturation, and a normal ferritin level. Both B12 and folate levels were also normal. His thyroid stimulating hormone (TSH) level was found to be normal, and Epstein-Barr virus (EBV), human immunodeficiency virus (HIV), and monospot tests all were negative.

A chest x-ray showed a rounded density noted in the right retrocardiac region measuring 2.7 cm in diameter. Computed tomography (CT) scan of the brain without contrast showed a 3.1 x 3.4 cm thin-walled cystic lesion in the left frontal lobe with surrounding vasogenic edema and a 4 mm midline shift to the right. A subsequent magnetic resonance imaging (MRI) of the brain...
confirmed a $3.8 \times 3.7 \times 3.4$ cm necrotic mass in the left frontal lobe with thick wall enhancement and intense central restricted diffusion with a 3 mm midline shift to the right – highly suspicious for an abscess with a necrotic tumor considered less likely – and leptomeningeal enhancement in the right parietal region that could be secondary to meningitis with meningeal metastasis considered less likely (Fig. 1).

The patient underwent a stereotactic aspiration of the cystic brain lesion via a left–sided bur hole in which purulent drainage was noted. Both blood cultures and abscess cultures grew *Aggregatibacter aphrophilus*. A transthoracic echocardiogram (TTE) was suggestive of a large mitral valve vegetation consistent with endocarditis, but a transesophageal echocardiogram (TEE) showed a flail posterior leaflet with severe regurgitation but no clear vegetation (Figs. 2 and 3). He was started on intravenous (IV) steroids, vancomycin, ceftriaxone, and acyclovir.

Given the organism is part of the normal oral flora, dentistry was consulted but their exam was unremarkable without signs of infection or disease. Additional imaging with a CT scan of the chest, abdomen, and pelvis was also unremarkable for possible sources of infection. The patient underwent an esophagogastroduodenoscopy (EGD) and a colonoscopy that were remarkable only for a single polyp. No source of infection was identified. Repeat blood cultures were negative. The patient’s antimicrobial regimen was deescalated to IV ceftriaxone for six weeks, and the patient was also started on levetiracetam for seizure prophylaxis. He was eventually transferred to rehab, and then underwent a mitral valve replacement with a bioprosthetic valve after his functional status improved. Subsequent pathology studies of the anterior mitral valve leaflets showed degenerative changes without vegetations.

**Discussion**

HACEK endocarditis (HE) refers to infective endocarditis caused by a group of five fastidious gram-negative species: *Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*. These organisms classically are part of the normal oropharyngeal flora, have a comparable infectious profile, and a low virulence. Dental procedures and valvular diseases are common risk factors and they preferentially affect the mitral valve [1]. Our patient had an unremarkable dental

**Fig. 1.** Magnetic resonance imaging (MRI) of the brain with and without contrast showing a $3.8 \times 3.7 \times 3.4$ cm necrotic mass in the left frontal lobe highly suspicious for an abscess with vasogenic edema and compression of the left lateral ventricle.

**Fig. 2.** Transthoracic echocardiogram (TTE) suggestive of a $1.5 \times 1.0$ cm loosely associated echogenicity on the atrial aspect of the posterior leaflet of the mitral valve, highly suspicious for a vegetation, with moderate regurgitation also noted (left = parasternal long axis view, right = modified apical three-chamber view).

**Fig. 3.** Transesophageal echocardiogram (TEE) midesophageal four-chamber view showing a mildly thickened mitral valve with severe flail motion of the posterior leaflet due to rupture of one or more chords with linear densities that could represent endocarditis.
exam and did not have a known history of valvular disease prior to admission. Whereas gram-positive bacteria cause most cases of infective endocarditis (>80%), particularly Streptococci and Staphylococci spp., gram-negative bacteria are thought to cause less than 10% [3,4]. HACEK species have been reported to cause 1.4–3% of all infective endocarditis cases [1]. In a large multi-national cohort study, the prevalence of HE by regions was: Africa (1/19, 5.3%), Australia/New Zealand (23/279, 2.3%), Asia/Middle East (5/277, 1.8%), Europe (35/2806, 1.2%), North America (5/992, 0.5%), and South America (8/518, 1.5%) [5]. HE tends to differ from non-HACEK endocarditis (non-HE) in the following ways: younger age of presentation; fewer comorbidities (like our patient); community acquired; more vascular/immunological manifestations; and better outcomes. In the multi-national cohort study, the HE group had lower in-hospital and one-year mortality rates than the non-HE group with a cumulative

### Table 1

The Duke criteria for diagnosing infective endocarditis listing the major and minor criteria.

| Major Criteria | Minor Criteria |
|----------------|---------------|
| 1 Positive Blood Cultures (one of the following) | 1 Intravenous drug use or presence of a predisposing heart condition (e.g., prosthetic heart valve). |
| 2 Two separate blood cultures positive for “typical” IE microorganisms consistent with consistent with IE: Staphylococcus aureus, Viridans streptococcus, Staphylococcus gallolyticus (S. bovis), HACEK bacteria, community-acquired enterococcus without primary focus. | 2 Fever: Temperature ≥38.0 °C (100.4 °F). |
| 3 Persistently Positive Blood Cultures | 3 Vascular phenomena: Major arterial emboli, septic pulmonary infarcts, mycotic aneurysms, intracranial hemorrhage, conjunctival hemorrhages, or Janeway lesions |
| 4 “Typical” organisms causing IE: At least two positive blood cultures from blood samples drawn >12 hours apart. | 4 Immunologic phenomena: Glomerulonephritis, Osler nodes, Roth spots, or rheumatoid factor |
| 5 For organisms that are more commonly skin contaminants: Three or a majority of ≥4 separate blood cultures (with first and last drawn at least one hour apart). | 5 Microbiologic evidence: Positive blood cultures that do not meet major criteria OR serologic evidence of active infection with organism consistent with IE |
| 6 Single positive blood culture for Coxiella burnetii or phase 1 IgG antibody titer >1:800. | |
| 7 Evidence of Endocardial Involvement | |
| 8 Positive echocardiography: Vegetation or abscess or prosthetic valve with new partial dehiscence. | |
| 9 New valvular regurgitation. | |

**Definite IE** = 2 major clinical criteria OR 1 major and 3 minor clinical criteria OR 5 minor clinical criteria

### Table 2

Reported cases of infective endocarditis secondary to A. aphrophilus (or H. aphrophilus).

| Author | Age | Sex | Underlying Structural Heart Disease | Extra-cardiac Complications | References |
|--------|-----|-----|------------------------------------|-----------------------------|------------|
| Ayotte et al. | 43 | M | Rheumatic heart disease with aortic valve incompetence. | None. | [19] |
| Bauer et al. | 24 | M | Rheumatic heart disease with mitral insufficiency. | None. | [20] |
| Broa et al. | 50 | M | None. | None. | [21] |
| Deleixhe et al. | 65 | F | Rheumatic heart disease status post mitral and aortic valve replacement with mechanical prosthesis. | Embolic stroke, papillary and retinal hemorrhages (Roth’s spots). | [22] |
| Farrand et al. | 31 | M | Suspected rheumatic heart disease with mitral insufficiency. | Petechial rash and hemorrhuria. | [23] |
| Fortune et al. | 26 | M | Rheumatic heart disease with aortic stenosis, aortic insufficiency. | Embolic stroke and subconjunctival hemorrhages. | [24] |
| Guttott et al. | 26 | M | Unknown. | Septic emboli to the right popliteal artery and mycotic aneurysm of the left femoral artery. | [25] |
| Hidalgo-Garcia et al. | 4 | F | D-transposition of the great arteries with ventricular septal defect and pulmonary stenosis was corrected according to the Rastelli procedure. | None. | [26] |
| Hirano et al. | 72 | F | Unknown. | Mycotic cerebral embolism and hemorrhage without neurological symptoms and acute renal failure with hematuria. | [27] |
| Jung et al. | 42 | F | None. | Brain: Pyogenic ventriculitis (PV) (i.e. ventricular empyema) | [13] |
| Keith et al. | 60 | M | Unknown. | Petechiae. | [28] |
| Liao et al. | 47 | M | None. | Retinal hemorrhages. | [29] |
| Patel et al. | 62 | M | Complete heart block status post dual-chamber pacemaker with subsequent lead manipulation. | None. | [30] |
| Pine et al. | 57 | M | None. | Splinter, retinal, and conjunctival hemorrhages, and hematuria. | [31] |
| Sutter et al. | 44 | M | Rheumatic heart disease and mitral insufficiency. | Retinal hemorrhages and extensive subarachnoid hemorrhages. | [32] |
| | 73 | M | Mitral regurgitation. | Autopsy findings: Septic emboli to spleen, brain abscess, subarachnoid hemorrhage, and disseminated intravascular coagulation (DIC). | [33] |
| Wassef et al. | 61 | M | Bicuspid aortic valve with stenosis. | Splinter hemorrhage under the third right fingernail. | [34] |
| Wright et al. | 51 | M | None. | Embolic stroke. | [34] |

References:

[1] [2019]
mortality rate that was 6% and 39%, respectively (p=0.001) [5]. Given the subacute nature of HACEK infections (average of 13 weeks of symptoms before diagnosis), HE tends to present with larger vegetations at the time of diagnosis [6,7].

The most common non-cardiac complications of infective endocarditis are neurologic sequelae, which may be seen in 25–70% of cases, are associated with higher mortality, and may be the presenting symptom (as in our patient). Neurological manifestations may include embolic stroke (most common), brain abscesses, infected intracranial aneurysm, meningitis, spinal epidural abscess, neuropathy, and seizure [2]. One prospective study found that clinically silent neurologic complications occurred in 30% of patients, only detected by imaging [8]. Brain abscesses are a rare complication, seen in approximately 1–7% of infective endocarditis cases, and may produce edema, mass effect, or hemorrhage. Although they can present as a solitary lesion like in our case, multiple ring-enhancing lesions are usually seen [2].

The two most common invasive A. aphrophilus infections are infective endocarditis and cerebral abscesses, although epiperal and intravertebral infections may also be seen. The first known case of A. aphrophilus central nervous system infection appears to be in 1932 when a child with a brain abscess was found to have the organism growing in his spinal fluid, and the first known case of A. aphrophilus endocarditis was first reported in 1940 by Kharat et al. [9,10]. It accounts for 2 to 7% of bacteria grown from brain abscesses. It is thought the organism has unique virulence characteristics that predispose to brain abscess formation [9]. Interestingly, several case reports have described patients that were regularly licked by their pets developing A. aphrophilus brain abscesses [11]. Of note, abscesses are not solely restricted to the central nervous system as cases of a liver, spleen, and lung abscesses have also been reported [12]. The brain abscess may subsequently rupture into the ventricles causing pyogenic ventriculitis/ventricular empyema. Deep-seated infections, an immunosuppressed host, presenting with a Glasgow Coma Score less than 9, and abscess rupture are all associated with increased mortality. Although IE secondary to A. aphrophilus may have devastating consequences, it usually has a mild clinical course – as in our patient – with a less than 10% mortality rate [13].

HE uses the same modified Duke criteria to diagnose non-HE (Table 1) [14]. Although our patient grew A. aphrophilus on the first obtained blood cultures, the HACEK organisms are typically difficult to grow and therefore are categorized within the “culture-negative endocarditis” group. An enriched blood culture media or exposure to carbon dioxide is typically needed for growth [15]. We suspect our patient meets the criteria through two major criteria: two separate positive blood cultures with a HACEK organism and a new valvular regurgitation.

Endocarditis secondary to HACEK organisms generally has an excellent prognosis. Intravenous third or fourth generation cephalosporins and fluoroquinolones are considered first-line therapy by both the American Heart Association (AHA) and European Society of Cardiology (ESC). The routine duration of treatment is four-weeks for non-valvular endocarditis (NVE) and six-weeks for prosthetic-valve endocarditis (PVE) [16,17]. Brain abscesses complicating the disease may require abscess drainage or surgical resection and a longer course of antimicrobials [2,18] (Table 2).

**Conclusion**

Compared to non-HE, HE usually has a younger age of presentation in patients with fewer comorbidities and presents with more vascular/immunological complications. Additionally, HE has a better prognosis and responds well to treatment. Both types can be complicated by neurological sequelae which is associated with higher mortality and may be the presenting symptom or be clinically silent – only detected upon imaging. Brain abscesses are considered one of the rarer neurological manifestations and will require a long course of intravenous antimicrobials, and possibly drainage or surgical resection.

**Conflicts of interest**

The authors declare no conflicts of interest.

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The authors have no sources of funding to declare.

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