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Case Reports

Infective Endocarditis Due to Haemophilus parainfluenzae: A Case Report and Review of the Literature

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We present a 20-year-old male who was admitted with recurrent fevers. He was diagnosed with Haemophilus parainfluenzae mitral valve endocarditis with severe regurgitation and perforated leaflet. H. parainfluenzae was resistant to ceftriaxone but repeated sensitivities showed a sensitive organism. Despite endocarditis caused by H. parainfluenzae is rare, physicians should be vigilant of such diagnosis. Antibiotics sensitivity may be questioned if shows a resistant organism.

BACKGROUND

Infective endocarditis was first reported in the 17th century.[1] Most infective endocarditis cases are caused by *Staphylococcus*, *Streptococcus*, or *Enterococcus* species.[2] Endocarditis due to HACEK organisms (*Haemophilus* species, *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis, Eikenella corrodens*, and *Kingella* species) is rare and accounts for 0.8 to 6 % of cases of infective endocarditis.[3–5] In a study across 28 countries of 5,591 patients with infective endocarditis, 77 (1.4%) were due to HACEK bacteria.[6] In that study, the prevalence differed based on the country. The prevalence was low in North America (0.5%) and high in Austria/New Zealand (2.3%).[6] Furthermore, HACEK endocarditis was seen more at a younger age.[6]

CASE PRESENTATION

A 20-year-old male immigrant from Egypt presented with recurrent fevers, chills, and dysuria for one week. At an urgent care clinic, he was prescribed cephalexin for a urinary tract infection. The patient continued to have fevers and developed a dry cough associated with chest pain, intermittent headaches, lightheadedness, and vomiting. The patient had no pets at home, no animal exposure, recent travel, unpasteurized milk, or imported cheeses. He had been sexually active with one person and used contraception. The patient had no rash, but he had insect bites (three small spots on his left arm and right shoulder) that resolved independently. The patient denied any history of tick bites or hiking. The patient was from Egypt and immigrated to the United States seven months before the presentation.

The patient came to the emergency department one week after symptom onset with a temperature of 39.5 C° and a heart rate of 103/min. Physical examination revealed a new systolic murmur and tenderness in the left upper quadrant. The patient had dental plaques. Blood cultures were drawn and returned positive two days later; the gram stain showed gram-negative rods. White cell count (WBC) was 11,700/mcL on admission (normal WBC: 3,500/mcL – 11,000/mcL), and all components of the urinalysis were within normal limits. Influenza and rapid *Streptococcus pyogenes* tests were negative. Throat cultures grew 3+ normal throat flora. Borrelia burgdorferi IgG and IgM were negative. Urine culture was negative, and urine *Legionella* and *Strep pneumoniae* antigens were negative. Chest x-ray showed a left lower lobe consolidation. A transthoracic echocardiogram revealed a thickened posterior mitral leaflet prolapsing into the left atrium with a 0.5 cm x 0.6 cm mobile echodensity. There was significant mitral regurgitation and possible perforation of the posterior leaflet. Abdominal CT revealed a splenic infarct. Vancomycin and ceftriaxone were started for the treatment of endocarditis and pneumonia.

On day four, the gram-negative rods grew on chocolate agar only, indicating that the bacterium belongs to *Haemophilus sp*. On day seven, the organism was identified as *H. parainfluenzae* using the VITEK 2 system. Resistance to ceftriaxone and cefepime and sensitivity to ampicillin-sulbactam were determined by Kirby-Bauer disk diffusion. Antibiotics were adjusted accordingly. Repeat sensitivities at another laboratory revealed that the strain was sensitive to ceftriaxone and cefepime. He was placed on ceftriaxone again. The patient underwent surgical repair of his mitral valve (annuloplasty). He was eventually treated with oral levofloxacin on discharge to complete a total duration of eight weeks (including four weeks post-annuloplasty). A repeat echocardiogram one month later showed no residual vegetation.

DISCUSSION

Bacteria within the *Haemophilus* genus are pleomorphic and fastidious gram-negative coccobacilli that require supplementary factors for *in vitro* growth, particularly V-factor

(NAD) or X-factor (heme).[7] *H. parainfluenzae* is part of the human genitourinary and oropharyngeal microbiota. *H. parainfluenzae* was found to colonize the throat in 64.6% of healthy adult individuals and in 97% of children undergoing adenoidectomy.[8,9] Furthermore, *Haemophilus parainfluenzae* is emerging as an opportunistic multidrug-resistant pathogen.[7]

H. parainfluenzae is increasingly recognized as an opportunistic pathogen causing genitourinary infections, respiratory tract infections, meningitis, endocarditis, pericarditis, bone and joint infections, and arthritis.[8,10–13] *Haemophilus* endocarditis is a rare disease caused mostly by *H. Parainfluenzae*.[14] A 20-year systemic review found 39 adult cases of endocarditis caused by H. *parainfluenzae* up to 2020.[15] The case fatality rate of *Haemophilu*s endocarditis has been reported to be 4.8% by Darras-Joly compared to 16-45% before the 1980s when optimal antibiotics were not available. As many as 60 % of patients develop embolic disease.[14] Olagunju et al. identified risk factors in 39 patients with infective endocarditis with H. *parainfluenzae*.[15] Ten percent had a previous history of endocarditis, 17.5% had a valve replacement, 20% had mitral valve disorders, 18% had aortic valve disorders, 17.5% had current IV drug use, 13% had a pacemaker and implanted cardiac defibrillator, 10% had poor dentition, 5% had recent genitourinary or gastrointestinal procedures, and 8 % had immunosuppression.[15] Seven patients had no known risk factors in that review.[15] Furthermore, Kelesidis et al. indicated that risk factors for the development of endocarditis with this organism included dental work, nasopharyngeal infection, and tongue piercing.[16] While our patient did not have any cardiac risk factors for infective endocarditis, he did have non-cardiac risk factors, including poor dentition and a recent urinary tract infection. Pneumonia also could have served as a source for *H. parainfluenzae*.

Heart failure is the most common complication of infective endocarditis, occurring in 50 to 60% of cases.[1] It has been reported to happen in 8% of H. *parainfluenzae* endocarditis in a recent review compared to 30.9 % in a previous review.[14,15] Other complications of H. *Parainfluenzae* endocarditis include septic emboli (28 of 39 patients), valvular regurgitation (28 of 39 patients), and death (5%).[15] This patient did not have heart failure, but he did experience a splenic infarct from embolization. Non central nervous system embolization did not differ between HACEK or non-HACEK endocarditis in the study done by Chambers et al. (21 vs 22%), however, the rate of stroke was higher in HACEK endocarditis (25% vs 17 %) with a relative excess of hemorrhagic stroke over embolic stroke in HACEK endocarditis compared to non-HACEK endocarditis (44% vs 17%).[6] Echocardiogram also revealed severe mitral regurgitation, which can be an indication for surgery, even without heart failure. Darras-Joly et al. described that 14/26 patients with *H.parainfluenzae* endocarditis required cardiac surgery.[14]

The slow growth of H. *parainfluenzae* delayed the patient's diagnosis and treatment. It took four days for the blood cultures to reveal the organism, which is not uncommon in HACEK organisms.[17] HACEK organisms are notoriously difficult to culture, which leads to delayed or missed diagnoses of endocarditis. Despite historically, HACEK organisms were associated with delayed growth on culture media, a recent retrospective study showed no added benefit from extending the incubation period beyond 4 days when using BacT/Alert Virtuo blood culture detection system (bioMérieux) using FA Plus (aerobic) and FN Plus (anaerobic) resin culture bottles.[18] Although advances have been made in DNA analysis of heart valve tissue specimens, these methods are not universally available, and there is still progress to be made in the efficient and accurate diagnosis of infective endocarditis. Andrzejczuk et al. reported that 34.5 % of all tested isolates were sensitive to all B-lactams, while 63.2 % were sensitive to ampicillin and 64.5% were sensitive to cefotaxime.[19] The *H. parainfluenzae* present in this patient's blood cultures was initially reported as resistant to the third-generation cephalosporin, ceftriaxone, and the fourth-generation cephalosporin, cefepime. However, repeat sensitivities were different, showing a more sensitive bacterium. This highlights the significance of questioning blood culture results if they are unusual. In this case, the discrepancies in the sensitivities prolonged the wait to find an appropriate treatment.

This case of endocarditis due to *H. parainfluenzae* serves as a cautionary tale for interpreting antibiotic sensitivities despite increasing resistance.[7] Physicians should repeat sensitivities at a different laboratory to confirm resistant strains. The significance of oral hygiene should be emphasized because of this case, even in the absence of traditional high-risk factors and high-risk procedures for endocarditis. Lockhart et al. reported that cumulative incidence of endocarditis-related bacteria in blood cultures was 23% compared to 60% for tooth extraction.[20] In conclusion, *H. parainfluenzae* is a significant organism for endocarditis despite being rare. Early diagnosis is essential to avoid the associated complications. Furthermore, sensitivity results should be interpreted carefully to avoid unnecessary antibiotics or delay in management.

DISCLOSURES/CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors have reviewed the final manuscript prior to submission. All the authors have contributed significantly to the manuscript, per the International Committee of Medical Journal Editors criteria of authorship.

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accu-

racy or integrity of any part of the work are appropriately investigated and resolved.

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