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Case Report

Microbiology Section

Infective Endocarditis by *Aggregatibacter paraphrophilus*: Case Report and Literature Review

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ABSTRACT

Aggregatibacter paraphrophilus (former name, *Haemophilus paraphrophilus*) is a normal inhabitant of the naso- and oropharynx and has been rarely reported as a cause of human infections. A case of infective endocarditis by this organism is being reported and literature of endocarditis cases caused by Aggregatibacter paraphrophilus is being reviewed.

Keywords: *Aggregatibacter paraphrophilus*, *Haemophilus paraphrophilus*, endocarditis

INTRODUCTION

Endocarditis is a common severe medical entity for which guidelines are being continuously updated; its aetiology can at times be vague, because of the involvement of certain rare pathogens. Some of these organisms have been categorized jointly as a part of the HACEK group of rare bacteria (*Haemophilus* spp., *Actinobacillus actinomy cetemcomitans*,*Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella kingae*) which are responsible for small but recognizable percentage (roughly 3%) of endocarditis cases [1,2]. The estimated incidence of infective endocarditis (IE) caused by *Haemophilus* species is 0.8-1.3% [3]. The various *Haemophilus* species which have been implicated in the aetio-pathogenesis of endocarditis include *Haemophilus influenzae*, *H. aphrophilus*, *H.paraphrophilus* and *H. parainfluenzae*. Of these, *H. parainfluenzae* is the most common pathogen in endocarditis, followed by *H. aprophilus* [3]. The objective of this report is to highlight the rare occurrence of IE caused by *Haemophilus paraphrophilus*. This case is the first report from India, implicating Aggregatibacter paraphrophilus as a causative agent of infective endocarditis.

CASE HISTORY

A 30–year–old male, resident of Ratangarh tehsil in Churu district of Rajasthan, presented to the Cardiology OPD of a tertiary care private hospital in Jaipur, India with history of fever, moderate grade, off and on for past one and a half months, associated with progressive breathlessness on exertion, progressive weight loss and sweating. The patient was brought to hospital's OPD by one of his cousin brothers who was the hospital's employee. At the time of OPD consultation; no earlier investigation reports were available with the patient. His vitals were as follows: temperature- 100.8 ˚F, blood pressure-110/78mmHg, and pulse-112/min sinus tachycardia. On physical examination, mild icterus and grade 2 clubbing were noted. No cyanosis, pedal oedema or lymphadenopathy were observed. Jugular venous pressure was normal. On auscultation, a pan systolic murmur was heard.

The transthoracic 2D echocardiography findings were as follows- Mitral valve thickened, stenosed and calcified, aortic valve thickened, tricuspid and pulmonary valve-normal, left atrium, right atrium and right ventricle –dilated and left ventricle-normal in size and function. The aorta, pulmonary artery, pulmonary vein, superior vena cava, inferior vena cava, pericardium were all normal. No intra-cardiac masses were observed. No left atrium clot or left atrial appendage clot were seen, no vegetations were seen. A diagnosis of rheumatic heart disease with mitral stenosis and mild aortic stenosis with minimal raised gradients was provided.

The lab investigations revealed CRP- >=4.8<9.6mg/dl, ESR- 48mm at 1 hour, ASLO -< 200IU/ml,RBC- 5.11 mil/ microlitres, Hb- 11.5 g/dl, Hct- 34.8%,MCV- 68fL, MCH- 22.6pg, MCHC- 33.2g/dl, platelets -284 thousand/microlitres, WBC- 7.9 thousand /microlitres and WBC differential -N70, E01,L25, M04, B00. The blood for culture was collected from the right hand and the left hand, inoculated in brain heart infusion broth (HiSafe TM Blood culturing system, HiMedia, India) and was sent for processing to the Microbiology laboratory, with provisional diagnosis of Infective endocarditis being mentioned in the microbiology culture requisition form.

Inj. Augmentin 2g i.v. 8 hrly and Inj. Amikacin 500mg i.v. BD were prescribed with the advice, for getting admitted to the cardiology unit for close monitoring. Due to financial constraints, the patient's family refused to get him admitted at our hospital and he was referred to the Cardiology Unit of the Government Medical College Hospital in the city. In the Microbiology laboratory, after 7 days of incubation at 37 ˚C, at the time of final subcultures of both the blood culture bottles (under CO_2 incubation in candle jar) identical minute colonies were obtained on sheep blood agar, with no growth on Mac Conkey's agar. The organism was oxidase positive gram negative coccobacilli. The antibiotic susceptibility test results as per disc diffusion method were as follows: Ampicillin-resistant, Cefuroxime, Ceftriaxone, Cephotaxime, Ceftazidime, Amikacin, Levofloxacin, Amoxyclav, Gentamycin, Ciprofloxacin and Levofloxacin –sensitive. Both the isolates were identified as *Haemophilus paraphrophilus* by miniAPI (Biomerieux, Marcy-l'Etoile, France) using the API NH panels at a Reference laboratory. The patient remained in follow-up for 2 weeks with the hospital's cardiologist. However, he failed to show up after that. After 2 months, on enquiring to his cousin brother, it was found that the patient had expired.

DISCUSSION

The first description of Hemophilus paraphrophilus was given by Zinneman et al. It was described as a fastidious, catalase- negative, oxidase -positive, V-factor dependant, gram negative cocco-bacillus that needed a carbon dioxide enriched atmosphere for supporting its growth [4]. A recent reclassification has placed these organisms in a new genus of Aggregatibacter, as they are independent of factor X and variably dependent on factor V for their growth in vitro [5].

This organism is a normal commensal inhabiting the oro- pharynx, nasopharynx and lower gastrointestinal tract [6]. Human diseases

caused by *Haemophilus paraphrophilus* are unusual. This organism has been implicated in causing cerebral abscesses, meningitis, subacute endocarditis, larynogo-epiglottitis, pneumonitis, hepato-biliary infections, endophthalmitis, peritonitis, parotid gland abscess, osteomyelitis and septic arthritis in adults [7,8]. Clinical infection caused by *H.paraphrophilus* is the result of local or blood stream invasion from the site of colonization [9].

The first case of *H.paraphrophilus* endocarditis was reported by De Silva et al., [10]. As has been described for other *Haemophilus* species, it is possible that *H.paraphrophilus* causes some of the cases of endocarditis in which blood cultures are persistently negative, thereby explaining the small number of clinical reports of infections caused by this organism [11]. Mis–identification of this organism has been reported, because it causes pitting in agar, which is commonly associated with Eikenella corrodens and due to its morphological similarity to *H.parainfluenzae* and *H.aphrophilus* [12].

Literature review on *Haemophilus paraphrophilus* endocarditis cases revealed that the highest incidence of endocarditis caused by this organism was seen among young or middle aged adults. More males than females have been affected [11]. There appears to be a predilection solely for mitral valve involvement. However, similar to the findings of this case, involvement of both aortic valve and mitral valves has also been previously reported [3,13]. Mitral valve prolapse has been reported as the commonest underlying cardiac pathology among the endocarditis cases caused by *H.paraphrophilus*. Apart from native valve involvement, *Haemophilus paraphrophilus* also affects prosthetic valves [12]. The portal of entry of the offending organism has not been known with certainity in the reported cases of endocarditis.

Endocarditis caused by *Haemophilus* species has been associated with one of the highest rates of large vessel embolization among the cases of gram negative endocarditis [14]. Due to the preferential involvement of mitral valve by this microorganism, embolism occurs in the systemic vascular system. Central nervous system has been reported to be the commonest site of large vessel embolization [12]. Since some HACEK group bacilli produce β-lactamases; Ampicillin is no longer the first-line treatment option. Conversely, they are susceptible to Ceftriaxone, other third-generation cephalosporins, and quinolones—the standard treatment is Ceftriaxone 2 g/day for 4 weeks. If these bacteria do not produce β- lactamase, intravenous Ampicillin (12 g/day i. v. in four or six doses) plus gentamicin (3 mg/kg/day divided in two or three doses) for 4 weeks is a treatment option. Ciprofloxacin (2 x 400 mg/day i.v. or 1000 mg/day orally) is a less well validated option [15].

The outcome of *H.paraphrophilus* endocarditis depends on the presence or absence of complications and organ damage, which are responsible for high morbidity and moderate mortality caused by this illness.

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