



Infective Endocarditis Caused by *Neisseria mucosa* – A Case Report & Review of Literature

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Abstract

Despite advances in management, Infective Endocarditis (IE) remains a serious disease that carries a considerable risk of morbidity and death. There is an increasing trend in the incidence of IE caused by uncommon microorganisms with low pathogenicity. We herein report a case of IE caused by *Neisseria mucosa* (*N. mucosa*) in a young boy with Chronic Rheumatic Heart Disease (CRHD) with previously damaged mitral and aortic valves. The IE was successfully treated with intravenous penicillin G and gentamicin. More cautious efforts to detect and identify this unusual opportunistic pathogen should be made. Despite its rarity, clinicians should consider IE due to *N. mucosa* as a severe infection, especially in young patients with underlying valvular disease and treat with appropriate and adequate antibiotic therapy.

Introduction

IE remains a serious disease that carries a considerable risk of morbidity and death. While *Streptococci* or *Staphylococci* species are the most common pathogens causing endocarditis, occasionally non-pathogens, such as Non-gonococcal non-meningococcal *Neisseria* species have also been reported and remain unrecognized as a cause of severe disease [1].

Non-pathogenic *Neisseria* species comprise part of the commensal bacterial microbiota of the human and animal oropharynx. These commensal *Neisseria* spp. have generally been regarded as harmless organisms of little clinical importance [2-4]. Majority of these organisms colonize mucosal surfaces, usually without causing overt pathology, and are therefore regarded as components of the host normal microbiota. Hence, their isolation is usually not considered relevant to a pathological process [5]. However, several clinical reports have shown that they can occasionally disseminate from their commensal niche and occupy, survive and proliferate in other anatomical niches and cause serious infections in a wide variety of anatomical sites. Including the heart, nervous system (meningitis). Invasion of the bloodstream by *Neisseria* from the oropharynx may lead to endocarditis and meningitis [6].

In the present case, IE due to *N. mucosa* was diagnosed in a young boy with CRHD and damaged mitral and aortic valves. *N. mucosa* was repeatedly isolated from the Blood cultures, indicating a significant bacteremia [7]. The clinical case fulfilled the Duke criteria for clinically definite endocarditis [8]. However, the primary source of these organisms could not be established in the patient. The IE was successfully treated with adequate antibiotic therapy. The literature was reviewed for similar reports of IE due to *N. mucosa*. To the best of our knowledge, the present case is probably the first report of IE due to *N. mucosa* from India.

Case Presentation

A 16-year-old male presented to the emergency department of Kamineni Hospitals, Hyderabad, Telangana, India, with a history of intermittent fever for the past 10 days, associated with cough with mucoid expectoration. There was no history of cold, burning micturition, chills, rigors, abdominal pain, and vomiting, loose motions. The patient did not give any history of drug abuse, smoking or alcoholism. He was not a known diabetic. At the age of 6 years, the patient was diagnosed to have mitral regurgitation with IE. However, no further case details could be obtained due to the unavailability of the treatment records. The patient also gave a history of jaundice, one month ago. On physical examination, the patient was found to be well built, conscious, and coherent. There was no fever, pallor, edema, clubbing. His temperature was 98.0F, pulse rate was 76/mt and regular with no missed beats, blood pressure was 130/70 mmHg, respiratory rate was 18/mt and regular.

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Received Date: 18 Jun 2020

Accepted Date: 03 Jul 2020

Published Date: 13 Jul 2020

Citation:

Vemu L, Anisha CK, Shyam Sunder MN. Infective Endocarditis Caused by *Neisseria mucosa* – A Case Report & Review of Literature. *Ann Clin Case Rep.* 2020; 5: 1859.

ISSN: 2474-1655

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On examination of the cardiovascular system, all peripheral signs of aortic regurgitation were present. S1, S2+, prominent carotid pulsations were present, pansystolic murmur grade 3/6 was present at apex radiating to the axilla and early diastolic murmur of moderate intensity at aortic area was present with a loud P2. There were neither skin lesions nor any nodules. The lungs were clear, abdomen was soft with no masses and central nervous system was normal. The patient had no other risk factors for endocarditis. All the joints were supple with no swellings or effusions. His oral hygiene was well preserved with no stomatitis, gingivitis nor cavities. With a provisional clinical diagnosis of Chronic Rheumatic Heart Disease (CRHD) with severe Aortic (AR) & Mitral Regurgitation (MR) and IE, the patient was transferred to the General Medicine Department, Kamineni General Hospital, for further workup and management. Laboratory investigations revealed hemoglobin of 10.6 gms %, total count 8670 cells/cmm, ESR 30 mm for 1 h, Liver function tests and a complete urine examination were within normal limits. The Electrocardiogram (ECG) showed Left Ventricular Hyperplasia (LVH). A 2D ECHO was reported as CRHD with thickened aortic valve with severe AR, thickened Mitral valve with moderate eccentric MR, Left Ventricular (LV) and atrial dilatation with concentric LVH, Global Hypokinesia, mild LV dysfunction, mild Tricuspid Regurgitation (TR) with mild Pulmonary Artery Hypertension (PAH) and minimal pericardial effusion. There were no LV clots. Chest radiography showed dilatation of the main pulmonary artery and left atrial appendage. Dual valve replacement was advised after 10 days by the consultant cardiovascular surgeon. Three sets of blood culture (each set had BacT/Alert FA aerobic and FA anaerobic bottle) were collected over 24 h and incubated in the BacT/Alert 3D (bioMérieux, Marcy Etoile, France) system in Microbiology Department. The patient was empirically started on intravenous Cefoperazone-sulbactam 1.2 mg thrice daily with other supportive care and management.

Blood cultures: All the three sets of blood culture bottles flagged positive within 24 h of incubation. A direct Grams stain from the broth showed thin short Gram-negative *Diplococci*. Subculture of the blood culture broth was done on 5% sheep blood agar plates (COS, bioMérieux, Marcy Etoile, France), CromID agar plate (CPSE, bioMérieux) and MacConkey agar and incubated at 37°C for 24 h. The following day, the blood agar plate showed pale, about 1 or 2 mm in diameter, circular, convex with a flat border, smooth, moist, non-pigmented and non-hemolytic colonies. Minimum growth was obtained on CromID agar after 48 h of incubation, with similar colony morphology as described on blood agar. There was no growth on MacConkey agar. Grams stain of the colony from blood agar showed thin short Gram-negative *Diplococci*, similar to the direct examination from the blood culture broth. The isolate was non-motile and positive for Oxidase and Catalase enzymes. The culture was processed in the VITEK2 (bioMérieux, Marcy Etoile, France) using the IDGN. The VITEK2 gave a report as unidentified species. The antibiotic susceptibility was done by the disc diffusion method. The isolate was found to be susceptible to Ampicillin, Amoxicillin/clavulanic acid, gentamicin, amikacin, cefazolin, ceftriaxone and ciprofloxacin. For a definite identification, the isolate was processed on Vitek-MS (Mass spectrometry microbial identification system) (bioMérieux, Marcy Etoile, France) and was identified as *N. mucosa*.

A final diagnosis of IE due to *N. mucosa* was made. Based on the antibiotic susceptibility of the isolate, the patient was administered intravenous Co-Amoxiclav (Amoxicillin 1000 mg and Clavulanic acid 200 mg) 6th hourly. The patient's status rapidly improved and

after 10 days, the infection completely resolved with no residual vegetations. Repeat blood cultures 3 days before discharge were sterile. He was discharged with an advice to take oral therapy with capsule Augmentin 625 Duo (Amoxicillin 500 mg/clavulanate potassium 125 mg) twice daily for the next 10 days. At the follow-up review after 10 days, patient was free of the infection.

Discussion

Despite advances in management, IE remains a serious disease that carries a considerable risk of morbidity and death [1]. While Streptococci or Staphylococci species are the most common pathogens causing endocarditis, occasionally other organisms such as non-pathogenic *Neisseria* have also been reported and remain unrecognized as a cause of severe disease by the clinicians [1].

Over the years, there have been occasional case reports of several commensal *Neisseria*, of the oropharynx with a high propensity to cause serious systemic infectious, such as meningitis, bacteremia, endocarditis, pericarditis, empyema lung, pneumonia, as opportunistic pathogens in immune suppressed patients [9-11].

The first recorded case of endocarditis caused by a 'presumably' commensal *Neisseria* species was probably from Coulter in 1915 [6,12]. Schultz described the first confirmed case of endocarditis as a consequence of infection with a commensal species of *Neisseria* in 1918 [6]. Species of non-pathogenic *Neisseria* that have been shown to be associated with IE include *B. bacilliformis*, *N. elongata*, *N. mucosa*, *N. cinerea*, *N. sicca*, *N. flava*, *N. flavescens* and *N. subflava*. [1,6,3]. A case of *Neisseria* sp. group AK105 induced pacemaker endocarditis that resolved after a combination of antibiotic and surgical treatment was also reported [3]. From an epidemiological perspective, infections with commensal *Neisseria* spp. occur as singular events rather than as outbreaks [6]. There is minimal person-to-person transmission. Development of the disease may probably be due to endogenous spread of the organism from a primary infected site (oropharynx). The outcome of the disease is determined by the hosts' immunity and/or enhanced virulence of the particular infective strain [6]. *Neisseria*-induced endocarditis usually results in acute febrile endocarditis with large vegetations and a destructive process that often causes severe cardiac and systemic complications, as was seen in our patient. Surgical valve replacement is required in half of the patients [3]. Pilmis et al. [1] reported a case of IE with secondary arthritis due to *N. mucosa* and reviewed similar case reports available on Pubmed. They found 20 published reports between January 1966 and August 2013 in 17 articles from Europe, North America, Oceania, Asia and Latin America. There were no reported cases of IE due to *N. mucosa* from India. The present case is probably the first case of IE due to *N. mucosa* reported from India. With the present case, the total number of IE cases due to *N. mucosa*, reported between 1971 to 2020, would increase to 22.

N. mucosa (*Diplococcus mucosus*) was described in 1906 but was not recognized again until 1959, when Veronetal characterized five bacterial isolates from the pharynx or sputum of patients and named it *N. mucosa* [5]. *N. mucosa* is an encapsulated Gram-negative *Diplococcus*, belonging to the family *Neisseriaceae* [5,12,13]. Like the rest of the members of this family, *N. mucosa* also has a high affinity for mucosal membranes and is known to be a normal part of nasopharyngeal flora in human [9]. Recently it has been reported as a probable urinary pathogen [14]. *N. mucosa* optimally grows under aerobic conditions (35°C to 37°C) as large, mucoid, non-pigmented adherent colonies. *N. mucosa* was established as an independent

species and differentiated from other *Neisseria* by the characteristics of encapsulation, mucus production and the very active reduction of nitrates with gas formation [5]. It demonstrates pathogenicity to mice following intraperitoneal inoculation. This species appears capable of colonizing a broad range of hosts in addition to the environment. *N. mucosa* has been cultured or identified in dogs, cats, ducks, the woodlouse, water and sediment [11]. Thus, Animal isolates can rarely act as zoonotic pathogens and cause disease in humans [11].

N. mucosa induced IE has distinctive identifiable clinical characteristics [1,15]. Patients are younger than those with endocarditis due to other pathogens. Median age is 40 years and reaches 58 years. [1,2]. The symptoms manifested by an infected individual with *N. mucosa* include myalgia, fatigue, arthralgia and intermittent fever.

The incidence of IE by *N. mucosa* is 38% following a recent and or extensive dental manipulation or infection. This is higher than that for endocarditis caused by *Viridans streptococci* [2,16,17]. The *Neisseria* probably enter the blood stream following a minor trauma in the oropharynx. A case of a patient developing bacteremia after undergoing a flexible bronchoscopy procedure, which in turn led to endocarditis, was reported [18]. A case of *N. mucosa* IE following tongue piercing was reported [19]. The patient had no other risk factors for IE. He had a healthy oropharynx, gums and teeth and no manipulations were done in the oral cavity prior to the episode of IE.

N. mucosa survives in the blood and escapes killing as they may resist the bactericidal action of the blood or the patient's blood is defective in killing the organisms [6]. After an initial adhesive interaction between the bacterium and the mucosal epithelial cell, the bacteria aggregate and form microcolonies and a biofilm resulting in a heavy colonization of the endothelial surfaces of the valve leaflets [6]. The adhesion of *Neisseria* to the exposed epithelia depends on an abundant repertoire of diverse adhesion/invasion molecules (Opacity-associated (Opa) embedded within the bacterial Outer Membrane (OM) and their interplay with specific host cell receptors. Opa protein is abundantly expressed and regulated in *N. mucosa* [6].

Though a few cases of *N. mucosa* IE involving normal valves were reported [15,17,20], *N. mucosa* predominantly causes IE in patients with previously abnormal cardiac valves due to its low pathogenicity [2,15]. Majority of the patients report underlying cardiopathies, especially rheumatic heart disease (as in the present case), unlike in IE due to other pathogens [15]. The incidence of underlying heart disease is 77%, which is at the high end of the range of 60% to 80% [2]. *N. mucosa* generally involves abnormal mitral or prosthetic valves. The aortic valve was reported to be involved in only 8% of patients with *N. mucosa* endocarditis compared with 38% of those with endocarditis in general [2]. In one case a previously damaged tricuspid valve was involved [16]. Both the mitral and aortic valves were involved in the present case.

Systemic antibiotic regimen and duration for *N. mucosa* endocarditis are not defined [2]. There is no available Antimicrobial Susceptibility Testing (AST) interpretative criteria for *N. mucosa*. It has an intermediate susceptibility to penicillin, amoxicillin, cefotaxime, ciprofloxacin and ceftriaxone. Due to its variable susceptibility profile, the choice of antibiotic therapy should be supported by an *in vitro* AST [9,17]. The most commonly used treatment in *N. mucosa* related endocarditis is a combination of a beta-lactam and an aminoglycoside, which is recommended in this

setting, given its efficacy in endocarditis.

Conclusion

A prompt recognition of IE due to *N. mucosa*, an uncommon pathogen, in a young patient with underlying CRHD and valvular disease was possible with meticulous microbiological processing, including multiple sets of blood cultures and advanced identification systems for bacteria, have contributed to the successful diagnosis and outcome. The infection successfully resolved with prompt and appropriate antibiotic therapy. Despite its rarity, clinicians should consider IE due to *N. mucosa* as a severe infection, especially in young patients with underlying valvular disease and treat with appropriate antibiotic therapy.

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