

Infective Endocarditis by Rare Organism *Granulicatella Adiacens*

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Abstract

Infective endocarditis (IE) is a life-threatening infection of the cardiac valves especially in patients with preexisted valvular disease. Having a rheumatic heart disease, congenital heart disease, prosthetic valves or previous episodes of IE are some of the traditional risk factors for infective endocarditis (Hoen & Duval, 2013).

Although most cases were reported by streptococci especially streptococcus viridans, which is one of the commensal bacteria isolated from the mouth, some of the cases of IE can be caused by fastidious extracellular bacteria such as Abiotrophia, HACEK group bacteria, Clostridium, Brucella, Legionella, Mycobacterium, and Bartonella spp. These organisms need supplemented media, prolonged incubation time, and special culture conditions to grow and be isolated.

Abiotrophia was reclassified in a new genus *Granulicatella*, as *Granulicatella adiacens*, balaenopterae, elegans and *G. para adiacens*. The genus *Abiotrophia* consists of only one species -*A. defectiva*.

Keywords: *Granulicatella Adiacens*, Infective endocarditis, modified Duke criteria, streptococci

1. Introduction

IE due to nutritional variant Streptococci (NVS) like *Abiotrophia* and *Granulicatella* accounts for approximately 5%-6% cases of all patients with IE (Werner, 1967).

The diagnosis of IE usually made in the presence of multiple findings rather than a single definitive test by using modified Duke criteria. The combination of clinical, microbiological and echocardiography form the cornerstone for the diagnosis. Having IE with blood culture negative organism like *Granulicatella* is usually challenging.

2. Methods

A 25 years old Hispanic female with past medical history significant for anemia and gastric acid reflux presented with symptoms of chest pain, fever and shortness of breath. She said her temperature was 100F few times during that week and had some chills. She also reported 2 months hx of persistent dry cough, fever and sore throat. She had history of dental visit around 1 year ago. However, one week before admission in 5/21/18, she started having symptoms of mild sharp central chest pain that is worse with breathing and associated with subjective fever and shortness of breath but denied any other symptoms otherwise. She went to see her PCP to evaluate her chest pain and she was told that she has new onset heart murmur. Patient works as a cop, married with no children. She doesn't smoke, drink alcohol, or use illicit drug. She reported taking ferrous sulfate for anemia and occasional ranitidine for dyspepsia.

In ED, patient was afebrile, hemodynamically stable BP 103/62 | Pulse 93 | Temp 96.7 °F (35.9 °C) (Oral) | RR 16, SpO2 99% | BMI 17.02 kg/m².

Examination was normal except for being pale with heart examination showed Normal S1,S2 with no gallop or rub with loud pansystolic murmur in mitral area, grade 4/6 radiating all over heart, and a systolic murmur in tricuspid area grade 1/6.

CBC showed microcytic, hypochromic anemia with Hb= 9.9 and MCV= 69 without leukocytosis.

Complete metabolic panel, and thyroid function test were normal. Chest X-ray was unremarkable. ECG showed NSR, HR 95, and biatrial enlargement was suggestive.

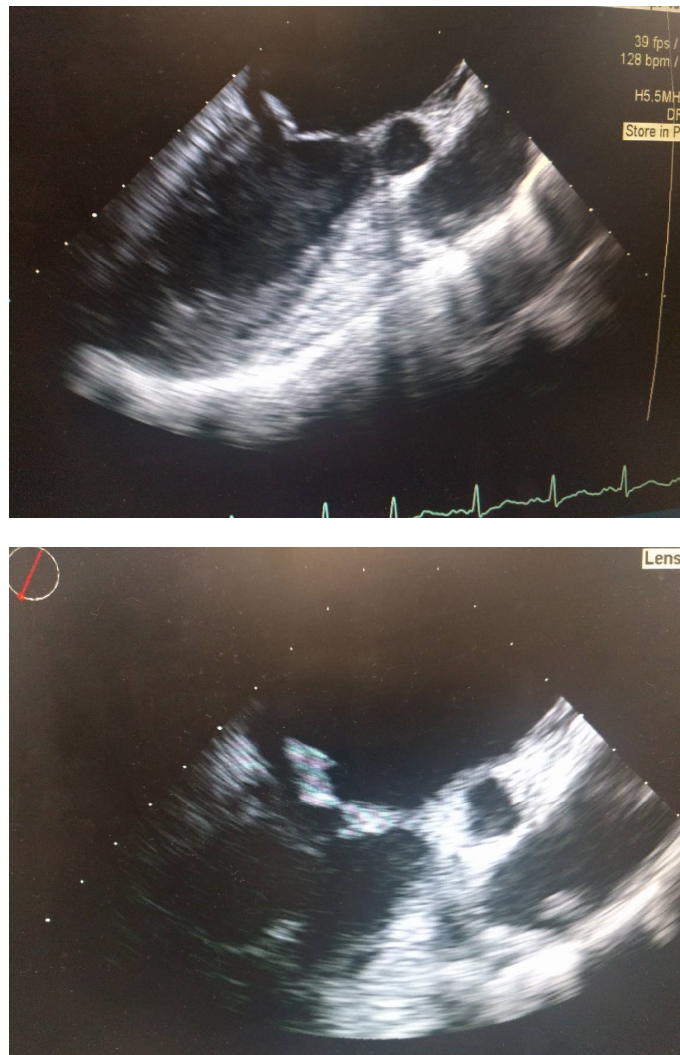
She received one dose of Ceftriaxone and Vancomycin for empiric infective endocarditis coverage and admitted to medicine floor for evaluation of possible endocarditis.

Transthoracic Echo done showed normal LVEF of 60% with moderately severe 3+ mitral regurgitation and a 1.2 x 0.7cm mobile vegetation on anterior leaflet of mitral valve, Mild tricuspid regurgitation with an estimated RV systolic pressure of 47 mm Hg. Flow reversal to the pulmonary veins was noted.

Further work up showed Anti streptolysin O Ab titer <100, Strep A throat culture was negative, CRP 1.40, ESR 51, Rheumatoid Factor <10.0, ANA was negative.

2 sets of Blood cultures showed Gram positive cocci in chains. *Granulicatella Adiacens* identified by MALDI TOF mass spectrometry.

Transesophageal Echo showed LVEF was 60% with normal mitral valve mobility and thickness with linear mobile echo density measured (1.48cm) attached to the tip of the anterior leaflet of the mitral valve suggestive of a vegetation. Moderately severe mitral regurgitation (+3) was present as below:



Few days later patient developed dyspnea. On examination blood pressure was 94/59, HR 102, temperature 98.8 °F (37.1 °C), RR 29 with Spo2 was dropping necessitating oxygen supplement. Neck examination showed jugular venous distention with lungs examination demonstrated scattered rales with diminished lung sounds in the bases especially on the right side.

Repeated Chest X-ray showed development of extensive bilateral interstitial pulmonary edema with thickened interlobular septa bilaterally. There was also ground glass opacities bilaterally with blunting of both costophrenic angles consistent with pleural effusions. These findings were new compared to prior study.

Diagnosis with Acute heart failure with pulmonary edema was made and patient transferred to ICU. Repeated ECHO showed LVEF=51% with ruptured and friable mitral valve without perivalvular abscess. Decision was made by cardiothoracic surgeon to proceed with mitral valve replacement with bioprosthetic valve.

Due to difficulties in reaching early bacteriological confirmation and high prevalence of beta-lactam and macrolide resistance (Tuohy, Procop & Washington, 2000), this patient was started on vancomycin 1 gram twice daily and meropenem 1 gram twice daily.

Another complication happened during her hospital course, patient had histamine reaction to vancomycin and decision to switch her to meropenem and levofloxacin was done by Infectious disease team.

Patient condition stabilized afterwards but one of the challenges that she has faced is the need for long term anticoagulant use with risk of bleeding giving her job as a cop.

3. Results

Granulicatella is one of the nutritional variant Streptococci (NVS) along with Aerophilina. This means these organisms need cysteine or vitamin B6 active form to grow to in the medium. It is a Gram-positive, catalase-negative oxidase negative facultatively anaerobic cocci that are considered part of the normal flora of the human throat, intestine and urogenital tracts (Ruoff, 1991). Their importance came from their risk of causing serious infections like endophthalmitis or keratitis, osteoarticular infections, pancreatic abscesses and postpartum sepsis (Cerceo, Christie, Nachamkin, et al., 2003; Carey, Gross & Roberts, 1975).

G. adiacens appears to have higher degree of infectivity with high mortality rate of (around 9.5%) compared to other NVS in general and genus *Granulicatella* specifically. Although Most cases affect preexisting pathological valves, there have been several noted cases of normal valves being affected by NVS as in our case, of which aortic and mitral valve are the most commonly affected. Infection due to NVS has indolent course, more severe, and required longer duration of antibiotics with high risk of treatment failure given the slow growth of the bacteria and production of exopolysaccharide.

One of the features that these organism express and involve in the endovascular infectivity is it's ability to bind to extracellular membrane proteins which is attributed to Fn-binding abilities of *Abiotrophia* species. The higher the Fn binding capacity the high virulent strain as expressed in *G. adiacens* compared to *G. para-adiacens* and *G. elegans* strains (Giuliano, Caccese, Carfagna, et al., 2012; Perkins, Osorio, Serrano, et al., 2003).

Given these organisms are nutritionally variant, supplementation of pyridoxal hydrochloride and L-cysteine is necessary for them to grow. another characteristic of these organisms is having the satellate phenomenon which is form of commensalism, in which growth of *Granulicatella* spp. is dependent on the nutrients released by other bacteria like *Staphylococcus aureus* on blood agar.

4. Discussion

The first clue that leads to the diagnosis of endocarditis as in our patient is finding of heart murmur that was heard at the physical exam on basis of fever. Studies have shown that at the initial presentation $\leq 15\%$ of patients may have high fever or a murmur, but eventually almost all patients develop both as the disease progress (Lin & Hsu, 2007).

Although most cases of IE occur after oral or dental work especially if there is underlying valve or structural heart disease, our patient did not have any underlying cardiac or immunosuppressive illness and did not undergo recent dental manipulation.

Biomedical testing and/or molecular confirmation are used to identify *Granulicatella* isolates like (MALDI-TOF) matrix-assisted laser desorption/ionization time-of-flight mass spectrometry as in our case.

Accelerating the identification of *Granulicatella* has been challenging, many methods such as the ribosomal 16S-23S intergenic spacer region and fluorescence in situ hybridization has been use to confirm the diagnosis (Tung, Teng, Vaneechoutte, Chen & Chang, 2007).

These organisms exhibit significant tolerance to penicillin demonstrated by some isolates with the minimum bactericidal concentration of penicillin greatly exceeds the MIC, usually by 32-fold with up to 60 and up to 47 % of the strains may be resistant to ceftriaxone and cefepime respectively. This may be the reason for delayed initiation of the appropriate antibiotic regimen and treatment failure. (Liao, Teng, Hsueh, Chen, Huang, Chang & Ho, 2004)

As per guidelines Combinations of either benzylpenicillin (penicillin G) or amoxicillin

or vancomycin with gentamicin for 4-6 weeks are the most frequent antibiotic interventions used to treat infections due to *Granulicatella* species.

Complications which may necessitate surgical intervention includes valvular damage, heart failure, distal embolization, cerebral mycotic aneurysm and extension of vegetations to the atrial wall which seems to be higher compared to IE caused by streptococci viridans (Stein & Nelson, 1987).

A vegetation size may also contribute to these risks. Vegetation length greater than 15 mm is recognized as a strong predictor of embolic events and death in patients with IE in the first year after diagnosis. It has previously been reported that nearly 30% of NVS strains show resistance to penicillin and that nearly 41% of cases fail medical therapy with antibiotics (8 up to 50 % of patients require prosthetic valve replacement for complication especially congestive heart failure).

As conclusion *Granulicatella* can cause severe infective endocarditis that is usually difficult to be identified due to blood culture negative nature in most cases. Given the rarity of the infection and the challenges of diagnosis, prolonged antibiotic treatment course, high risk of complications and treatment failure, reporting such cases are of clinical significance.

Abbreviation

ED: emergency department; 9F: Fahrenheit; BP: blood pressure; BMI: Body mass index; CBC: complete blood count; MCV: Mean corpuscular volume; ECG: Electroencephalogram; NSR: normal sinus rhythm; HR: heart rate; LVEF: Left ventricular ejection fraction; RV: right ventricular; CRP: Carbon reactive protein; ESR: erythrocyte sedimentation rate; ANA: Antinuclear antibody; RR: respiratory rate; ICU: intensive care unit

Author's Contributions

Co-authors helped write or edit the manuscript. All authors read and approved the final manuscript.

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