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Challenges in Diagnosing Infective Endocarditis: A Case Report

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ABSTRACT

Introduction: Infective endocarditis (IE) is an infection that affects the endocardial surface of the heart. Enforcing the diagnosis of IE is quite easy, but in some cases, it is sometimes very difficult to suspect the patient is experiencing an IE if the symptoms displayed are atypical or non-specific, so that the diagnosis and treatment are too late

Case illustrations: A 51-year-old man was first referred from a Type C Hospital to the Emergency Room of Type B Hospital with diagnosis of congestive hepatopathy, transaminitis, hyperkalemia, hyponatremia related retention, suspected hypoalbuminemia due to chronic inflammation and hepatopathy, mild normochromic normocytic anemia due to chronic disease, pneumonia, sepsis, AKI (acute kidney injury) with differential diagnose ACKD (acute on chronic kidney disease) because suspect of prerenal suspicion that had been improving. Infective Endocarditis (IE) was diagnosed with modified Duke criteria, in which this patient found vegetation on the aortic valve 1.70 cmx0.66 cm. Treatment for patients was given empirical antibiotics (ampicillin 3 grams every 6 hours by intravenous/IV and gentamicin 180 mg every 24 hours by intravenous/IV) while waiting for blood culture results and the patient was referred to the Central General Hospital/Type A Hospital for further treatment.

Conclusion: Infective Endocarditis is still a challenge in the field of medicine with its low incidence. In this case report, the patient experienced a clinical spectrum that was less specific for IE, causing difficulties in early diagnosis and management

Keywords: *Infective Endocarditis, Modified Duke Criteria, Aortic valve*

INTRODUCTION

Infective endocarditis (IE) is infection which occurs on the surface of endocardium.[1] Pathognomonic sign includes vegetation which form from group of platelets, fibrins, inflammation factors and microorganisms.[1] Most IE cases would involve cardiac valve (either prosthetic or natural valve), also could affect myocard's mural or septums.[2] In most studies, *Staphylococcus aureus* was the most common cause of IE (around 26.6% of cases), followed by *Streptococcus viridans* (18.7% of cases), other Streptococcus (17.5% of cases) and Enterococcus (10.5% of cases)[3]. Incidence occurs around 3-10/100.000 population, which ratio between men and women was 2:1.[3,4] Epidemiology of EI was shifted from younger patient with rheumatic fever to older one with various medical history.[5] Once, before antibiotic was introduced globally, EI was supposed to infected young adults to middle age patient with rheumatic heart disease (RHD) or congenital heart disease (CHD). But with the improvement in the medical fields and antibiotics enhancement, there was EI's risk factor changing which includes past medical history of EI; structural heart disease (CHD, valve diseases); prosthetic valve; usage of cardiac implants (pacemaker/defibrillator); patient on hemodialysis; patient with low immunity (diabetes, malignancy, HIV);

invasive oral procedure; intravenous medication abuse; bad oral hygiene and skin infection.[6]

IE was classified based on location, absent of intracardiac device or prosthetic valve, and the source of infection (either from community, nosocomial or intravenous). Patient with prosthetic valve had high IE risk. IE due to prosthetic valve was classified as early (below 1 year) or late (above 1 year) after valve procedure.[7] In present day, up until 40 to 50% of patient suffers IE will need valve surgery, with mortality rate of 20-25% per year.[8] IE incidence was still high even with better diagnostic facility, new antibiotic or early intervention procedure.[7]

IE diagnosing was established on combination of clinical picture, microbiology and imaging which based from Duke's modified criteria.[7] The criteria involved clinical findings, electrocardiography (ECG) also blood culture and serology. This criterion has sensitivity almost 80%, but the sensitivity would be lower in prosthetic valve endocarditis case or implantable electronic device infection related.[4,9] Based on Duke's modified criteria, IE classified into definite, possible and rejected IE (Table 1).[10] The classification was based on major and minor criteria from Duke's modified criteria (Table 2).[10]

Definite IE
Pathological criteria • Microorganisms demonstrated by culture or on histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or • Pathological lesions; vegetation or intracardiac abscess confirmed by histological examination showing active endocarditis
Clinical criteria • 2 major criteria; or • 1 major criterion and 3 minor criteria; or • 5 minor criteria
Possible IE
• 1 major criterion and 1 minor criterion; or • 3 minor criteria
Rejected IE
• Firm alternate diagnosis; or • Resolution of symptoms suggesting IE with antibiotic therapy for ≤4 days; or • No pathological evidence of IE at surgery or autopsy, with antibiotic therapy for ≤4 days; or • Does not meet criteria for possible IE, as above

Table 1. IE definition based on Duke's modified criteia

Major criteria
1. Blood cultures positive for IE a. Typical microorganisms consistent with IE from 2 separate blood cultures: • *Viridans streptococci, Streptococcus gallolyticus (Streptococcus bovis), HACEK group, Staphylococcus aureus*; or • Community-acquired enterococci, in the absence of a primary focus; or b. Microorganisms consistent with IE from persistently positive blood cultures: • ≥2 positive blood cultures of blood samples drawn >12 h apart; or • All of 3 or a majority of ≥4 separate cultures of blood (with first and last samples drawn ≥1 h apart); or c. Single positive blood culture for Coxiella burnetii or phase I IgG antibody titre >1:800
2. Imaging positive for IE a. Echocardiogram positive for IE: • Vegetation; • Abscess, pseudoaneurysm, intracardiac fistula; • Valvular perforation or aneurysm; • New partial dehiscence of prosthetic valve. b. Abnormal activity around the site of prosthetic valve implantation detected by ^{18}F-FDG PET/CT (only if the prosthesis was implanted for >3 months) or radiolabelled leukocytes SPECT/CT. c. Definite paravalvular lesions by cardiac CT.
Minor criteria
1. Predisposition such as predisposing heart condition, or injection drug use. 2. Fever defined as temperature >38°C. 3. Vascular phenomena (including those detected by imaging only): major arterial emboli, septic pulmonary infarcts, infectious (mycotic) aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway's lesions. 4. Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor. 5. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE.

Table 2 Major and Minor Duke's modified criteria

In Indonesia, IE cases was considered as rare case, which its diagnosis was usually could be establish based on available criteria, but in few cases had difficult to establish IE if the symptoms was not specific, thus the diagnosing of IE and its

management would be delayed.[11] This would be the main reason of writer to up hold the case with focus of early diagnosing of IE patient.

CASE PRESENTATION

51 years old male referred from Type C Hospital to Emergency Department of type D Hospital diagnosed with hepatopathy congestive, transaminitis, hyperkalemia, retention-related hyponatremia, hypoalbuminemia suspected chronic disease, pneumonia, sepsis, acute kidney injury (AKI) dd acute on chronic kidney disease (ACKD) suspected prerenal-related which was improved condition. Patient was referred in order to get further treatment. During examination, patient felt shortness of breath and tenderness on right upper abdomen since 1 months ago, tenderness was on and off and worsen since 1 week before admission. He mentioned he had better breathing condition if applied 2 pillow while on lying position, and mentioned can't do heavy activities or walk in long distance. Patient also had decreased appetite, nausea and vomiting and since 3 days before admission, he noticed had swelling on both lower legs. Patient was recommended to be admit and consulted to Cardiologist for suspected of congestive heart disease. Patient had no significant past medical history. Had no family history of cardiac disease, congenital diseases, infection or immune-related disease. His social background was a self-employed person.

In general examination, he appeared weak, he was fully alert during examination (GCS E4V5M6), his body weight was 60 kgs, his blood pressure was 110/80 mmHg, pulse of 84 times per minutes, his temperature was 36.6^{o} C, respiratory rate of 20 times per minutes, oxygen saturation of 98% room air. Physical examination showed normal conjunctiva and pharynx. Cardiac examination showed right cardiac border 2 cm midclavicular line with systolic blowing murmur on apex with migration to axilla, also with early diastolic decrescendo murmur on erb's point. Lung examination showed ronkhi on both lung's base. Abdominal examination showed distended abdomen and sign of ascites, while on extremities showed swelling on both lower legs.

Laboratory results showed elevated leucocyte count of 15.44x10^{3}/uL, hemoglobin 9.6 g/dL, trombosit 210x10^{3}/uL, increased of liver function of AST of 571 U/L, ALT 1034 U/L. Elevated kidney function of ureum 70.6 mg/dL, creatinine 1.41 mg/dL, Low Albumin of 2.90 g/dL, Natrium count of 131 mmol/L, Potassium of 5.7 mmol/L, Chloride of 101 mmol/L, random blood glucose of 103 mg/dL, total bilirubin of 1.04 mg/dL, direct bilirubin of 0.72 mg/dL , indirect bilirubin of 0.32 mg/dL. Official reading of chest x-ray showed Cardiomegaly with Cardio-Thoracic Ratio of 77% and normal lungs condition. On ECG 12 Lead, showed normal sinus rhythm 97 times per minutes, left anterior fascicular block, axis deviation to left, poor wave progression on lead V1-V4.

Based on anamnesis, physical examination and laboratory also imaging findings, patient then diagnosed with congestive heart disease suspected with coronary heart disease.

Patient was treated with NaCl 0.9% 500 mls/24 hours. Oxygen supplementation 3 liter per minute on nasal canule, Ramipril 2.5 mg per oral once daily, Clopidogrel 75 mg per oral once daily, drip of Furosemide 10 mg/hours, Lovenox (Enoxaparin) 0.4 cc sub cutaneous once daily for 3 day, beta-blocker on hold due to congestive condition and postponed atorvastatin due to transaminitis. Patient then discharge from hospital after 8 days of admission. Patient was planned to have follow up as outpatient on Cardiology Department for Echocardiography.

13 days later, patient came to Emergency Department due to swollen on both lower legs. He also complaint of shortness of breath every night, which was worsen with lying down position also while on activity

but relief on sitting position. Patient also loss his appetite.

He mentioned he once treated on other goverment hospital due to cardiac disease at about 2 weeks ago. Denies other medical history, had no family history of cardiac disease, congenital diseases, infection or immune-related disease.

In general examination, he appeared weak, he was fully alert during examination (GCS E4V5M6), his body weight was 60 kgs, his blood pressure was 110/70 mmHg, pulse of 86 times per minutes, his temperature was 36 ° C, respiratory rate of 22 times per minutes, oxygen saturation of 98% 3 liter per minute on nasal canule. Physical examination showed icteric conjunctiva and pharynx. Cardiac examination showed right cardiac border 2 cm midclavicular line with systolic blowing murmur on apex with migration to axilla, also with early diastolic decrescendo murmur on erb's point. Lung examination showed ronkhi on both lung's base. Abdominal examination showed minimal distended abdomen and sign of ascites, while on extremities showed swelling on both lower legs.

Laboratory results showed leucocyte count of $8.19x10^3$/uL, hemoglobin 11.0 g/dL, trombosit $253x10^3$/uL, increased of liver function of AST of 197 U/L, ALT 218 U/L. Elevated kidney function of ureum 176.7 mg/dL, creatinine 3.26 mg/dL, Natrium count of 118 mmol/L, Potassium of 5.5 mmol/L, Chloride of 98 mmol/L. Official reading of chest x-ray showed Cardiomegaly with Cardio-Thoracic Ratio of 66% and right pleural effusion. On ECG 12 Lead, showed normal sinus rhythm 73 times per minutes, left anterior fascicular block, axis deviation to left, incomplete left bundle branch block.

On echocardiography showed dilatation on all cardiac's chamber, eccentric left ventricular hypertrophy, normal systolic function of left ventricle but decreased diastolic function of grade III, good contractility of right ventricle, global normokinetic, prolapse right coronary cuspic of aortic valve causing severe aortic regurgitation, seen mobile structure with sized 1.70x0.66 cm on aortic valve, severe mitral regurgitation due to anterior mitral leaflet prolapse, severe tricuspid regurgitation, eRAP 15 mmHg (Figure 1). Official reading of Abdominal Ultrasound showed sludge gallbladder, ascites and right pleura effusion.

Based on anamnesis, physical examination and laboratory also imaging findings, patient then diagnosed with acute decompensated heart failure due to infective endocarditis region aorta (ejection fraction 55.5%), heart valve disease with severe atrial regurgitation due to prolapse right coronary cuspis and severe mitral regurgitation due to prolapse anterior mitral leaflet.

Patient was treated with NaCl 0.9% 500 mls/24 hours. Oxygen supplementation 3 liter per minute on nasal canule, empirical antibiotics (Ampicillin 3 gram intravenously every 6 hours combined with Gentamicin 180 mg intravenously once daily), Ramipril 5 mg per oral once daily, Nitrokaf 2.5 mg per oral every 12 hours, Clopidogrel 75 mg per oral once daily, Furosemid 40 mg bolus intravenously then maintenance with drip 20 mg/hours, Carvedilol was postponed due to congestive condition and also with atorvastatin due to transaminitis. Patient was done blood culture and planned to refer to general hospital for further treatment.

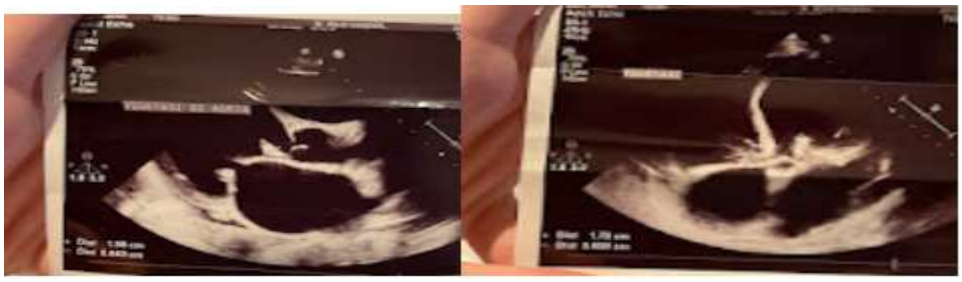

Figure 1. Echocardiography of patient's second admission

DISCUSSION

Infective endocarditis (IE) described as infection on cardiac's endocardium surface, with vegetation as its lesion characteristic. Cardiac valve became the most affected organ due to infection, also involved mural endocardium and septum. Endocardium surface normally resist to microbes colonization, but due to turbulence trauma, high pressure flow (as described as valve defect or heart structure such as rheumatic heart disease, congenital heart disease, past endocarditis history, prosthetic valve), and hypercoagulability condition or inflammation which cause thrombus contain fibrin and platelets on cardiac's valve. Microbes could attach on cardiac's valve while on bacteremia, viremia or fungemia which developed colonization and vegetation formation (consist of platelets, fibrins, inflammation and bactery) which commonly formed biofilm.[2]

The most common etiology IE is *Staphylococcus aureus* (25-30% cases). Other microbes such as oral Streptococcus (viridans group), negative coagulase Staphylococcus (11%), *Enterococcus faecalis* (10%) and negative-gram bacteria (5%) includes Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella and Kingella (HACEK group).[6] IE's characteristic was shift based on ages, cases was found more on prosthetic valve and other cardiac devices, and decreased proportion on rheumatic heart disease.[10] Clinical picture of IE was diversed, from acute sepsis symptoms until low-grade fever, heart failure syndrome or stroke.[12] IE could manifest as acute or subacute disease. Acute IE was progressing fast, present with sudden high fever, shivers, sepsis or systemic complication. Clinical presentation was difficult to differs with other cause of sepsis, but if there is new-onset heart murmur, IE must be considered. Otherwise, subacute IE was too difficult to diagnose due to possibilities of patient came with unspecific symptoms such as weakness/ tiredness, shortness of breath, decreased body weight with or without fever. Although IE commonly related with cardiac's murmur due to valve regurgitation, new onset heart murmur present on half of cases (Table 3). Janeway lesion or Osler nodule was classic diagnostic findings (Figure 2), but only less than 5% of cases.[13] As of those data, IE diagnosing sometimes was easier in few patients, but in other cases was difficult to suspect patient with IE if patient present with unspecific symptoms, so then to diagnose and the treatment would be delayed.[11] Delayed diagnosis and treatment initiation triggers complication and clinical worsening.[12]

In this case, patient was referred from type C hospital, patient was not yet diagnosed with IE, where he was referred with hepatopathy congestive, transaminitis, hyperkalemia, hyponatremia-related retention, hypoalbumin suspected chronic inflammation and hepatopathy, mild anemia normochromic normocytic due to chronic disease, pneumonia, sepsis, improved acute kidney injury dd acute on chronic kidney disease. He presents with differs and unspecified symptoms and clinical findings also laboratory results for IE. Patient present on emergency department and consult to Internist and was moved to general ward. After 1 day admission, he then consulted to Cardiologist due to suspicion of congestive heart disease due to heart failure syndrome. After 10 days of admission, patient was clinically and laboratory improved, and discharged from hospital with diagnose of congestive heart disease suspected with coronary artery disease. He was not yet diagnosed with IE.

13 days after dischargement, patent came to emergency department with complaints of swelling on both lower legs since morning (on admission day) accompanied with breathlessness every night, which worsen with lying position and activity, but relief with sitting position. While consulted by ER doctor, early diagnosis was acute decompensated heart failure (ADHF) suspected coronary artery disease due to symptoms related with heart failure syndrome. After 7 days admission, he was

done echocardiography on Cardiology polyclinic and showed mass with suspected as vegetation on aortic valve, then he diagnosed with ADHF due to IE. He was done blood culture and plan to be refer to central government hospital for further treatment. Patient was infected by negative coagulase Staphylococcus, which this group was the third most cause of IE.

Signs	**Patient, %**
Fever	86-96
New murmur	48
Worsen old murmur	20
Hematuria	26
Vascular embolism	17
Splenomegaly	11
Splinter Hemorrhages	8
Osler Nodes	3
Janeway lesion	5
Roth spot	2
Complication	
Stroke	17-20
Nonstroke embolization	23-33
Heart failure	14-33
Intracardial Abcess	14-20
New Conduction Abnormalities	8

Table 3. Clinical symptoms and IE complication

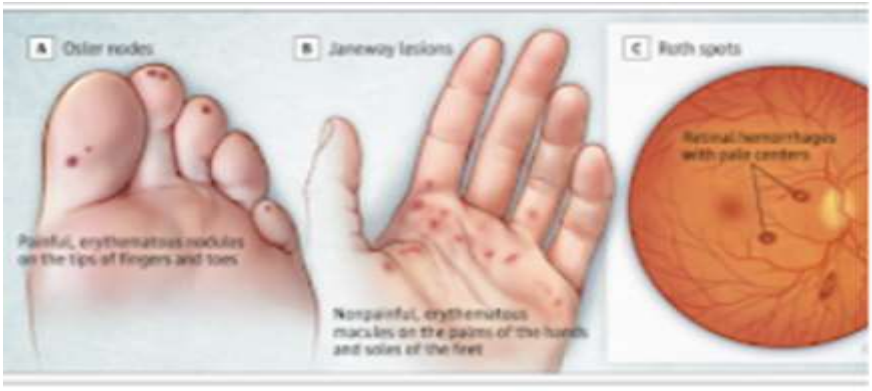

Figure 2 Rare clinical picture on Infective Endocarditis

Diagnosis of IE was established based on Duke's modified criteria, which classified as definite, possible or rejected IE.[14] Definite IE was established if fulfil one of pathology criteria or clinical criteria (2 major criteria or 1 major and 3 minor criteria or 5 minor criteria).[9] Duke's modified criteria was developed to evaluated patient with left-sided native valve IE, and diagnostically correct was more lower on right-sided native valve IE, IE prosthetic valve, IE with pacemaker and defibrillator-related, where echocardiography give normal or inconclusive reading.[14] On this case, definite IE was established after echocardiography was done on second admission, where the case was already fulfil 2 major criteria which is positive blood culture from blood sample also endocardial involvement (sign of mass on aortic valve which suspected as vegetation from echocardiography).

Beside heart failure, IE could trigger complication which affect central nerve system, spleen, kidneys and blood vessels with mycotic aneurysm formed. About 20% of patient present with neurologic complication which commonly caused by septic emboli.[15] Elevated liver enzyme commonly identified when IE was complicated with tricuspid regurgitation and/or mitral and acute right heart failure, severe congestive heart failure which caused congestive hepatopathy, or septic shock with ischemic hepatitis component. Heart failure on IE could be sign of poor outcome, especially for valve surgery.[16] Almost 30% of patient could fell into acute heart failure due to acute tubular nephrosis (due to sepsis or hemodynamic problems), immune complex-mediated glomerulonephritis, renal infarct due to emboli, drug toxicity or drug-related nephritis.[15] On this case, patient had elevated liver enzyme which possibly caused by severe congestive heart failure which caused congestive hepatopathy and also elevated kidney function which

triggered by acute tubular nephrosis or drug-related nephritis.

Suspected or confirmed IE's treatment needs multidisciplinary team which consist of Cardiologist, Thoracic and Cardiovascular Surgeon also Internist/infectious disease specialist. Treatment's goal always related with causative eradication, which needed long term bactericidal antibiotics. Surgery might contribute to treatment goals to eradicate infection materials and to abscess drainage.[4] IE treatment needs to have immediate administration. Blood culture needs to be taken at least 30 minutes prior to antibiotic initiation. Empirical antibiotics regiment would based on few consideration, such as previous antibiotic regiment; natural or prosthetic valve, infection location (community, nosocomial or nosocomial healthcare-associated IE). Antibiotic regiment for Natural Valve IE (NVE) and Prosthetic Valve IE (PVE) must be effective for Staphylococcus, Streptococcus and Enterococcus also non HACEK negative-gram pathogen. Should the pathogen identified, antibiotic regiment needs calculation with antibiotics-resistance patterns.

===TABEL 2 ANTIBIOTICS REGIMENT

Surgery decision/indication would be complex and based on clinical and prognostic factors, which varies among patients, includes infected organisms, vegetations, perivalvular infection, embolism or heart failure, ages, non-cardiac comorbid.[10] Early surgery while on active phase (while patient on antibiotic treatment) done to prevent worsen heart failure condition and irreversible structure damage which caused by severe infection/ uncontrolled also to prevent systemic embolism. On the contrary, surgery on active phase could triggers significant risk.[9] In this case, initially patient only treated with heart failure management, but after second admission (after done echocardiography and found mass on aortic valve which suspected with vegetation), then the patient had additional management of empirical antibiotics (combination of Ampicillin 3 grams every 6 hours intravenously and Gentamicin 180 mg once daily intravenously). Patient then done blood culture which range 12 hours. Patient then planned to be referred to Government Hospital for further treatment. Due to agreement of patient's referral before blood result finish, then definitive management of antibiotics and further treatment will be done on referred hospital.

CONCLUSION

Infective Endocarditis (IE) still became challenging in medical field. Although it had low incidence, varies clinical presentation and causative organism with wide spectrum microbes, which cause delayed diagnosis and treatment. Although EI's management already had it's enhancement, IE still cause high mortality and morbidity. In the case presentation, patient was referred with unspecified clinical spectrum, then on first admission, medical team was had difficulty to diagnose IE. After vegetation was found from echocardiography, patient was given empirical antibiotics, heart failure management and blood culture. Patient had IE with blood culture result found negative coagulase Staphylococcus. Due to agreement of patient's referral before blood result finish, then definitive management of antibiotics and further treatment will be done on referred hospital. And because of clinical wide spectrum triggers difficulty to diagnose and initial treatment.

Declaration by Authors

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