CASE REPORT

ACUTE ON CHRONIC LIMB-THREATENING ISCHEMIA ASSOCIATED WITH SEPTIC EMBOLISM IN PATIENT WITH INFECTIVE ENDOCARDITIS

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Abstract: Septic embolism associated with infective endocarditis (IE) is the occlusion of a blood vessel caused by an infected thrombus traveling through the bloodstream resulting in ischemia and/or infarction. Septic embolism can result in ischemia and/or infarction due to vascular occlusion and infection, resulting in inflammation and possible abscess formation. Systemic embolization generally occurs in left-sided IE, causing stroke, blindness due to embolism or endophthalmitis, splenic or renal infarct, limb ischemia, or even acute myocardial infarction. Here, we report a case of acute on chronic limb-threatening ischemia due to septic embolism in patient with IE.

Keywords: endocarditis, embolism, peripheral arterial occlusive disease

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INTRODUCTION

Septic embolism in infective endocarditis (IE) is one of the complications that can potentially cause vascular disorders.[1] Septic embolism can result in ischemia and/or infarction due to vascular occlusion.[1] An embolism can occlude or damage nearly any blood vessel in the systemic or pulmonary arterial circulation. Systemic embolization generally occurs in left-sided IE, causing stroke, splenic or renal infarct, limb ischemia, or even acute myocardial infarction.[2]

Septic embolism in IE remains a major cause of morbidity and mortality in recent decades despite the development of diagnostic and treatment modalities. Risk factors for septic embolism include using intravenous drugs, inserting vascular catheters, and patients with cardiovascular prosthetic devices (pacemaker and defibrillator implants).[1] A history of repeated intravenous drug use in patients is known to increase the risk of IE 100-fold compared to the general population.[3] Another risk factor is periodontal disease, which increases bacteremia risk and results in IE in those with predisposing factors such as valvular heart disease or implanted pacemakers.[4] Here, we report a case of acute on chronic limb-threatening ischemia due to septic embolism in patient with IE. A written consent form was obtained from the patient before collecting the medical information.

CASE REPORT

A 56-year-old Asian woman went to the rural hospital because of fever and worsening shortness of breath. The shortness of breath occurred when doing household activities and improved with resting. Past medical history included rheumatic mitral regurgitation, 5-year history of critical limb ischemia (CLI) with Rutherford category 3 on both legs, and intermit-tent toothache due to cavities. The patient did not routinely take medication.

Physical examinations found shortness of breath (26 breaths/minute), fever (38.1 ^{o}C), malnourished with a body mass index of 17.3 kg/m^2 (39 kg/150 cm), Osler's nodes, and Jane-way's lesions. The patient was suspected of having possible IE. Transthoracic echocardiography (TTE) was performed, and the mitral valve vegetations were seen with severe mitral regurgitation (MR). The diagnosis was definite IE by fulfilling 1 major and 3 minor criteria from the modified Duke criteria. The blood culture results were positive for the viridans group streptococcus. During the 2-week treatment at a rural hospital, the patient was treated with meropenem 1 gram every 12 hours, ramipril 2.5 once a day, paracetamol 500 mg three times a day, furosemide 40 mg once a day, and spironolactone 25 mg once a day, and also aspirin 100 mg once daily for the CLI.

The patient was referred to Dr. Soetomo Emergency Department (ED), Surabaya, for mitral valve surgery

after undergoing antibiotic therapy for two weeks. After 3 hours of traveling to our facility, the patient complained of tingling in his left leg. The patient is fully conscious, blood pressure 90/60 mmHg, heart rate 72 beats/minute, respiratory rate 18 breaths/minute, and body temperature 36.5°C. The cardiac apex was palpated with a thrill in the sixth intercostal space near the left anterior axillary line. Grade IV/VI holosystolic murmur was heard at the cardiac apex radiating to the axilla. The arterial pulse of the left femoral artery to the left dorsal pedis was weak with relatively low peripheral oxygen saturations (88%).

The electrocardiogram was normal. The chest X-ray showed cardiomegaly with cardiothoracic ratio 51.3% without any signs of pulmonary edema (Figure 1). Laboratory evaluation taken in the ED found leukocytosis 10,270/µL (reference: 3,370-10,000/µL), elevated procalcitonin 2.57 ng/mL (reference: <0.1 ng/mL), thrombocytosis 588,000/µL (reference: 150,000-450,000/µL), hypoalbuminemia (3 g/dL), and hypoglycemia (56 mg/dL).

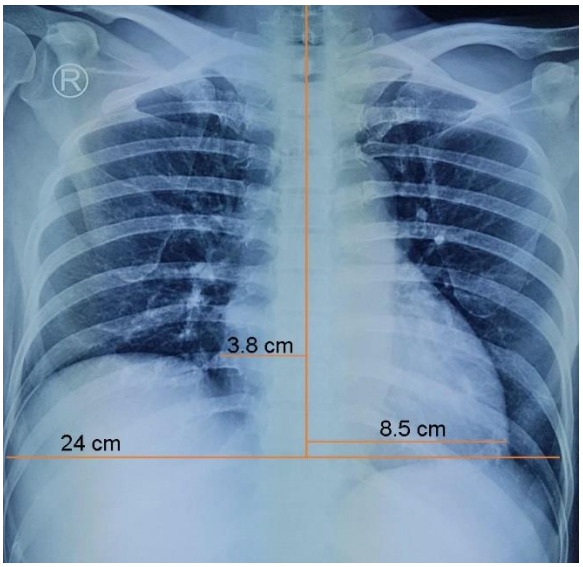

Figure 1: The chest X-ray showed enlarged cardiac silhouette with cardiothoracic ratio 51.3%

On repeat TTE evaluation, posterior mitral leaflet (PML) movement restriction was seen with severe mitral regurgitation (Carpentier type IIIA) and trivial tricuspid regurgitation. Left atrial and ventricular (LV) dilatation was seen with an internal diastolic diameter (LVIDd) of 6 cm. Multiple vegetations were found at the anterior mitral leaflet (AML) with size 1.4 cm x 1.0 cm and on the PML with size 0.9 cm x 0.7 cm, without intracardiac thrombus (Figures 2). There was eccentric LV hypertrophy, normal LV systolic function (EF 60%), and normal RV systolic function.

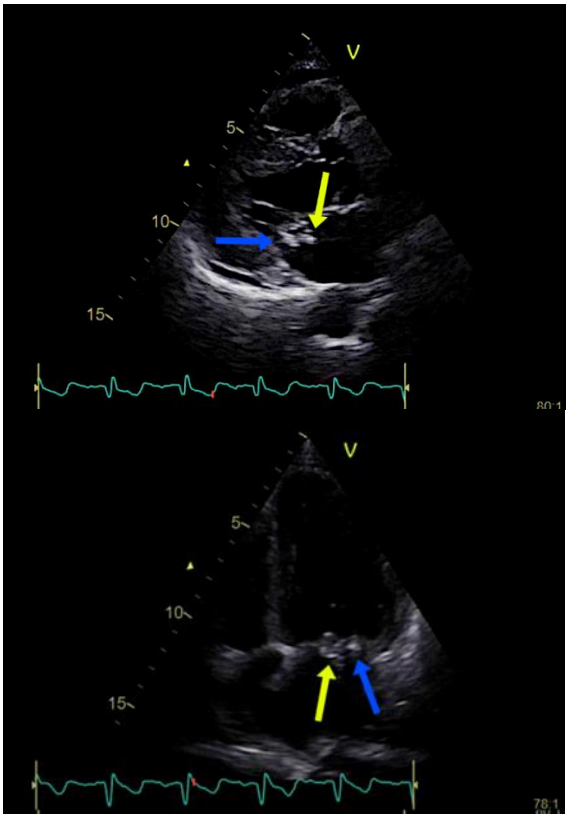

Figure 2: Left: Transthoracic echocardiogram parasternal long axis view showed vegetation at anterior mitral leaflet (yellow arrow) and posterior mitral leaflet (blue arrow). Right: Transthoracic echocardiogram apical four chamber view showed vegetation at anterior mitral leaflet (yellow arrow) and posterior mitral leaflet (blue arrow)

Two hours upon arrival in the ED, the patient complained of pain in the left leg again. Discoloration of the first and second digits of the left foot began to appear. The pulse of the popliteal artery to the left dorsal pedis was difficult to palpate. Vascular examination revealed resting ankle-brachial index (ABI) was 1.12 and 0.54 on the right and left leg, respectively. The left leg had lower blood pressure (65/52 mmHg). Doppler ultrasound (DUS) was performed and found a 1.92 cm x 0.92 cm mass suspected as vegetation embolism that caused occlusion of the left common femoral artery (CFA) branching (Figure 3).

The patient was assessed for acute limb ischemia (ALI) Rutherford IIA with septic embolic involvement from IE. The patient was treated with a bolus intravenous (IV) injection of 5,000 units of heparin, followed by a maintenance dose of 12-18 units/kg-

body-weight/hour until the activated partial thromboplastin time (APTT) reached twice the normal value. Antithrombotic therapy was also given, including aspirin 100 mg daily and cilostazol 50 mg twice daily. Antibiotic meropenem 1 gram per 12 hours IV was continued.

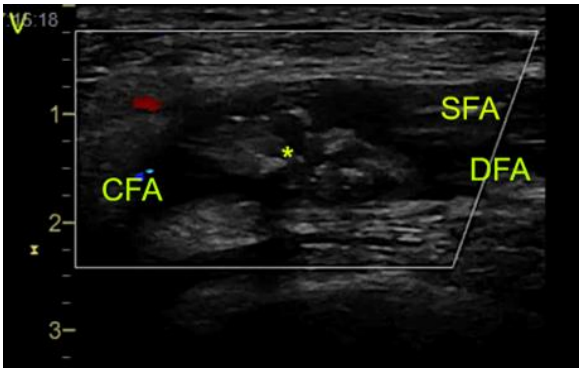

Figure 3: Doppler ultrasound of the left lower extremity showed a mass suspected of vegetation embolism (asterisk) in common femoral artery bifurcation

Six hours after heparin therapy, the patient complained of worsening pain and a motor deficit in the left toes. The discoloration extended, and the toes felt cold, referring to Rutherford IIB. To obtain a full anatomical view of the patient's lower extremity arterial flow and determine the revascularization strategy, an angiographic examination using computed tomography angiography (CTA) was performed immediately. The CTA of the lower extremity showed total occlusion of the superficial femoral artery (SFA) measuring 1.9 cm, with collateral vascularization distal to the left circumflex iliac artery and medial circumflex femoral artery (Figure 4).

The Rutherford IIB classification with total occlusion of the superficial femoral artery strongly indicates revascularization. Thrombectomy was scheduled, but the patient's family postponed any surgery for personal and cost reasons. The patient's first and second digits of the left foot became necrosis 14 days later despite adequate heparin and antibiotics. The blood culture evaluation also showed sterile isolate after a total of 4 weeks of antibiotic. After permanent nerve and major tissue damage, according to Rutherford III classification, the patient and family agreed to surgery. Revascularization with end-to-side bypass from the left CFA to the left SFA using a graft from the saphenous vein and amputation of the first and second necrotic digits of the left leg were performed 4 weeks since the beginning of antibiotics treatment.

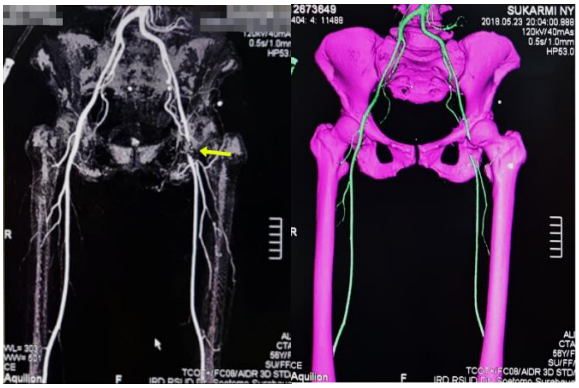

Figure 4: Computed tomography angiography of the left lower extremity showed a total occlusion of the superficial femoral artery (yellow arrow)

After the surgery, the patient underwent rehabilitation for six days and showed improvement in left leg muscle strength by walking without pain or using a walking aid. The patient was also referred to the dental clinic to evaluate the source of bacteremia, which was previously believed to be odontogenic. Oral examination revealed multiple chronic apical periodontitis with pulp gangrene at the 16th tooth.

The patient was then discharged 35 days after hospitalization in our facility. Four weeks later, the patient went to the outpatient clinic for a consultation regarding mitral valve replacement (MVR) surgery. After dental treatment and multiple tooth extraction, the Heart Team decided to perform MVR using a mechanical valve prosthesis. The MVR procedure was carried out 11 weeks after leg surgery with a good result.

DISCUSSION

Suspicion of IE in this present case was made based on the Duke-modified criteria; one major criterion was vegetation on the mitral valve by TTE, and three minor criteria include fever (>38°C), Janeway lesion (vascular phenomenon), and Osler's node (immunological phenomenon). To date, the Duke-modified criteria have been used as a diagnostic guide in conjunction with clinical assessment and should be interpreted as probabilities of IE. The index of clinical suspicion for IE increases with a predisposing cardiac condition, new or changing murmurs, progressive heart failure or hemodynamic compromise, bacteremia, and clinical evidence of embolic phenomena.[5]

Typical pathogens consistent with IE are *Staphylococcus aureus*, *Viridans streptococci*, *Streptococcus gallolyticus* (formerly *Streptococcus*

bovis), HACEK group (*Haemophilus aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae*), and fungi (*Candida species, Aspergillus species*, and *Histoplasma species*).[1,4] The most frequent portal of entry for IE is cutaneous, associated with the administration of therapy such as vascular access or surgical site. The second most frequent portal of entry for IE is oral or dental.[6]

Periodontitis is associated with bacteremia in IE patient.[4] The leading cause of IE is *Viridans streptococi*, the dominant commensals in oral cavity. Bacteremia is more frequently inducible in patients with severe periodontal disease than those with a healthy periodontium.[4,7] Bacteremia can occur not only from dental infections, but also from tooth extractions and other oral surgery procedures. Antibiotic prophylaxis is the only way to prevent IE in high risk patient undergoing dental procedure involving manipulation of gingival or periapical region of teeth or manipulation of oral mucosa.[4] The American College of Cardiology/American Heart Association (ACC/AHA) recommends dental examinations prior to valve intervention to rule out potential sources of infection.[8]

Vascular complications during IE are defined as the occurrence of embolic and/or hemorrhagic during IE. Vegetation (septic thrombus) is usually located upstream of the valve or shunt, an area of lower pressure.[9] Septic thrombus can dislodge into smaller particles and then migrate through the bloodstream and block blood vessels, resulting in ischemia and inflammation/infection.[1] The presentation of peripheral vascular embolism as a complication of IE is acute limb ischemia of varying severity, from transient ischemia, which can be adequately treated with antibiotics and anticoagulants, to severe ischemia requiring limb amputation.[2]

The embolic events are primarily found in the left side of the heart. In one study, septic embolism in IE occurred predominantly in patients with vegetation in the anterior leaflet than the posterior leaflet, suggesting fragmentation of the vegetation due to rapid and forceful leaflet movement during valve closure.[10] Large (>10 mm) and high mobility of the vegetation appear to be the most risk of septic embolism.[9,10]

The approaches for IE management are clinical stabilization, acquisition of blood cultures, and aggressive medical and/or surgical treatment. Antibiotics are given according to the identified microorganisms and their antibiotic sensitivity.[2] However, empiric antibiotic therapy should include staphylococci, streptococci, and enterococci. Appropriate antimicrobial administration can reduce the risk of embolization.[11] Embolic complications significantly reduce after completion of 2 weeks of antibiotic therapy.[11] Unfortunately, our patient developed septic embolism after antibiotic therapy with meropenem for more than two weeks. However, the antibiotic was continued in this present case because antimicrobial therapy is the cornerstone of IE presenting with septic embolism.[2]

In the treatment of IE patients, there is no evidence to support the initiation of anticoagulant and antiplatelet use. Patients with IE receiving anticoagulant may be at risk for embolic event than those who are not.[12] While, antiplatelet agents did not reduce the risk of embolism. In this present case, the patient had CLI before, so long-life aspirin was given. Anticoagulant was given due to ALI.

Surgery for embolism preventions in patients with IE is indicated in patient with persistent vegetation >10 mm after one or more embolic episode despite appropriate antibiotic therapy. Also, surgery may be considered in large vegetation >30 mm and no other indication for surgery.[9] In this case, we recommended the patient to undergo valve replacement surgery to avoid similar events in the future.

Patients with suspected septic embolism with unusual symptoms, usually neurologic, should undergo imaging. Location and type of emboli guide the treatment strategy. Once the clinical diagnosis of ALI due to septic emboli is established, treatment with unfractionated heparin should be given to prevent embolism/thrombus propagation and maintain the patency of the collateral vessels.[13] If a neurologic deficit occurs, immediate revascularization is mandatory. Amputation is often necessary to remove necrotic tissue.[2,13] The urgency of surgical treatment depend on the severity of the limb ischaemia. Limb ischaemia with neurological deficit needs urgent revascularization. Various technique can be used, including endovascular intervention, percutaneous catheter directed thrombolysis, surgical thromboembolectomy, bypass, or hybrid procedures.[13]

CONCLUSION

In IE patients with ALI, septic embolism should be considered a possible etiology. Dental examination should be included during the initial evaluation, as infection source control and appropriate antibiotic therapy are the cornerstones of septic emboli management.

AUTHORS' CONTRIBUTION

NSDLA and AS: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. RM, RAN, and MA: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

Conflict of interest: Authors declared no conflict of interest.

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REFERENCES

1. Yellapu V, Ackerman D, Longo S, Stawicki SP. Septic Embolism in Endocarditis: Anatomic and Pathophysiologic Considerations. In: Firstenberg MS, editor. Advanced Concepts in Endocarditis. Rijeka: IntechOpen; 2018. Available from: https://doi.org/10.5772/intechopen.76766
2. Elsaghir H, Al Khalili Y. Septic Emboli. [Updated 2022 Jul 21]. Treasure Island (FL): StatPearls Publishing. 2022 [cited 2022 Dec 21]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK549827/
3. Rudasill SE, Sanaiha Y, Mardock AL, Khoury H, Xing H, Antonios JW, et al. Clinical Outcomes of Infective Endocarditis in Injection Drug Users. J Am Coll Cardiol. 2019;73(5):559-70.
4. Del Giudice C, Vaia E, Liccardo D, Marzano F, Valletta A, Spagnuolo G, et al. Infective endocarditis: A focus on oral microbiota. Microorganisms. 2021;9(6):1-18.
5. Mahabadi AA, Mahmoud I, Dykun I, Totzeck M, Rath P-M, Ruhparwar A, et al. Diagnostic value of the modified Duke criteria in suspected infective endocarditis -The PRO-ENDOCARDITIS study. Int J Infect Dis. 2021;104:556-61.
6. Maaroufi A, Zahidi H, Abdulhakeem M, Arous S, Benouna EG, Drighil A, et al. Evolving trends in infective endocarditis over three decades in a developing country. Eur Heart J. 2021;42(Supplement_1).
7. Dhotre S, Jahagirdar V, Suryawanshi N, Davane M, Patil R, Nagoba B. Assessment of periodontitis and its role in viridans streptococcal bacteremia and infective endocarditis. Indian Heart J. 2018;70(2):225-32.
8. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Rwin JP, Gentile F, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021;143(5):E72-227.
9. Rajani R, Klein JL. Infective endocarditis: A contemporary update. Clin Med J R Coll Physicians London. 2020;20(1):31-5.
10. Hu W, Wang X, Su G. Infective endocarditis complicated by embolic events: Pathogenesis and predictors. Clin Cardiol. 2021;44(3):307-15.
11. Houard V, Porte L, Delon C, Carrié D, Delobel P, Galinier M, et al. Prognostic value of residual vegetation after antibiotic treatment for infective endocarditis: A retrospective cohort study. Int J Infect Dis. 2020;94:34-40.
12. Pathickal S, Park T, Sharma R. Clinical Outcomes Associated With the Use of Anticoagulant and Antiplatelet Agents in Patients Undergoing Treatment for Infective Endocarditis: A Pilot Study. Clin Ther. 2020;42(9):1828-38.
13. Björck M, Earnshaw JJ, Acosta S, Bastos Gonçalves F, Cochennec F, Debus ES, et al. Editor's Choice - European Society for Vascular Surgery (ESVS) 2020 Clinical Practice Guidelines on the Management of Acute Limb Ischaemia. Eur J Vasc Endovasc Surg. 2020;59(2):173-218.

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