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Blood culture-negative infective endocarditis with thalassemia and neurological complication: A dangerous combination

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Abstract

Background: Infective endocarditis (IE) is a life-threatening systemic disease that mostly affects people with valvular heart disease, prosthetic valves, or intracardiac devices. Infective endocarditis is a dangerous cardiac involvement in thalassemia patients. Thus, a multidisciplinary approach is important to provide efficient and effective therapy.

Case presentation: A 31-year-old man came to our tertiary referral hospital complaining of right-side paralysis of his body and slurred speech. Vital signs were normal. There were grade III/VI systolic murmurs from chest examination in midclavicular line intercostal space V sinistra. Head CT scan without contrast showed an embolic event. Peripheral blood smear showed iron deficiency anemia. Further electrophoresis hemoglobin (Hb) examination showed HbE-pathy. Echocardiography showed vegetations on the anterior and posterior mitral leaflet, leading to severe mitral regurgitation (MR). Blood culture examinations showed no bacterial growth. The patient was then diagnosed with severe MR due to possible IE, acute stroke infarction, and HbE thalassemia. The patient was treated with optimal medical therapy because he refused surgery. After six months of follow up, patients were found dead at his house

Conclusions: Thalassemia is a risk factor for infective endocarditis. Both are a dangerous combination, and early recognition should be made carefully to prevent worse outcome.

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1. Introduction

Infective endocarditis (IE) is a life-threatening systemic disease that mostly affects people with valvular heart disease, prosthetic valves, or intracardiac devices [1]. Nearly 90% of patients present with fever. IE should be suspected when finding patients with fever and embolic phenomena [2]. IE can also occur with negative blood cultures, or so-called blood cultures negative infective endocarditis (BCNIE). BCNIE is described as IE without microorganisms growing on the usual blood culture method. BCNIE can occur in 31% of all IE cases and often becomes a dilemma for determining further diagnostics and therapy [2]. Serological tests for certain types of bacteria and specific polymerase chain reactions (PCR) are needed in this case. A scoring system

like Duke criteria is also commonly used to help IE diagnosis.

Thalassemia is linked to certain morphological changes in the heart valve that allow it to become easily infected. The presence of IE in thalassemia patients is rarely found, but some do present with worse outcomes [3]. Early recognition should be made carefully, and a multidisciplinary approach is needed.

2. Case Presentation

A 31-year-old man came to a tertiary referral hospital complaining that his right side was paralyzed and he had slurred speech. For the past three month, he had abdominal pain and intermittent fever without taking any medication. There was no history of diabetes, hypertension, or previous smoking.

Blood pressure examination showed 100/70 mmHg, pulse 82 beats/minute, respiratory rate 20 breaths/minute with an O2 saturation of 100% free oxygen, temperature 38oC. He appeared to be anemic, and a grade III/VI systolic murmur was heard from chest examination at midclavicular line intercostal space V sinistra. During hospitalization, he progressively complained of shortness of breath, and there were rough wet rales and wheezing in 2/3 of bilateral lung fields. During abdominal examination, we found a palpable spleen examination of Schaffner 2 (palpable halfway between the umbilicus and costal margin) and Hacket 3 (expands toward umbilicus). There were neither palpable liver nor ascites. The extremities were warm and dry.

The ECG examination was normal. Chest X-ray showed cardiomegaly with left ventricle enlargement and infiltrate at the lung bilateral. The abdominal ultrasound found splenomegaly, and other organs were normal **(Figure 1A).** The head CT scan without contrast showed infarction at the left corona radiata **(Figure 1B)**. The laboratory findings showed anemia, leukocytosis, hematuria, and urinary tract infection **(Table 1).**

Peripheral blood smear showed anemia with iron deficiency and electrophoresis hemoglobin (Hb) examination showed HbE pathy **(Figure 1C)**. Blood cultures taken twice showed no bacterial growth. Sputum culture showed bacterial growth of Klebsiella pneumonia (Extended-spectrum beta-lactamases/ESBL+) .

We conducted 2D transthoracic echocardiography (TTE) that showed severe mitral regurgitation (MR) with anterior mitral leaflet (AML) flail, Carpentier type II **(Figure 2A).** The left atrium and left ventricle (LV) appeared dilated (LVIDd 7.4 cm) with normal LV systolic function (LV ejection fraction (LVEF) by Teich 68%). Segmental analysis showed normokinetic with eccentric LV hypertrophy. There were vegetations seen on the posterior mitral leaflet (PML) and AML. We confirmed TTE results with transesophageal echocardiography (TOE) examination, which also showed severe mitral regurgitation and vegetation on AML and PML valves **(Figure 2B).**

From the above examination, the patient was diagnosed with severe MR due to possible infective endocarditis complicated with pneumonia with ESBL+ bacteria, acute stroke infarction, and HbE thalassemia. The patient was treated according to the consensus plan of a multidisciplinary heart valve team, including a cardiologist, neurologist, pulmonologist, cardiovascular and thoracic surgeon, physiatric, and internist. He was treated with an injection of meropenem 1 gram three times daily within seven days (based on sputum culture antibiotic sensitivity result), furosemide 20mg once daily intravenous (i.v), CDP Choline 500 mg once daily i.v, Methylprednisolone 62,5 mg three times daily i.v, lisinopril 5mg once daily per oral (p.o), and paracetamol 500mg three times daily p.o and planned for urgent surgical procedure. Two weeks after medication, the patient showed an improvement from infection, diminished congestion, and was in recovery state from the acute phase of stroke. Follow-up of physical and radiographic examinations showed good results. However, the patient refused to undergo surgery. Then he was discharged with followed up every month in the outpatient care clinic. He was found dead at his house six months after discharge.

3. Discussion

Beta thalassemia syndrome is a hereditary blood group that causes a decrease or absence of beta-globin chain synthesis. The most common combination in beta thalassemia with abnormal Hb structure or Hb variation is HbE. It is often found in southeast Asia, where the number of carriers reaches 50% of the population, while in Indonesia, the prevalence of

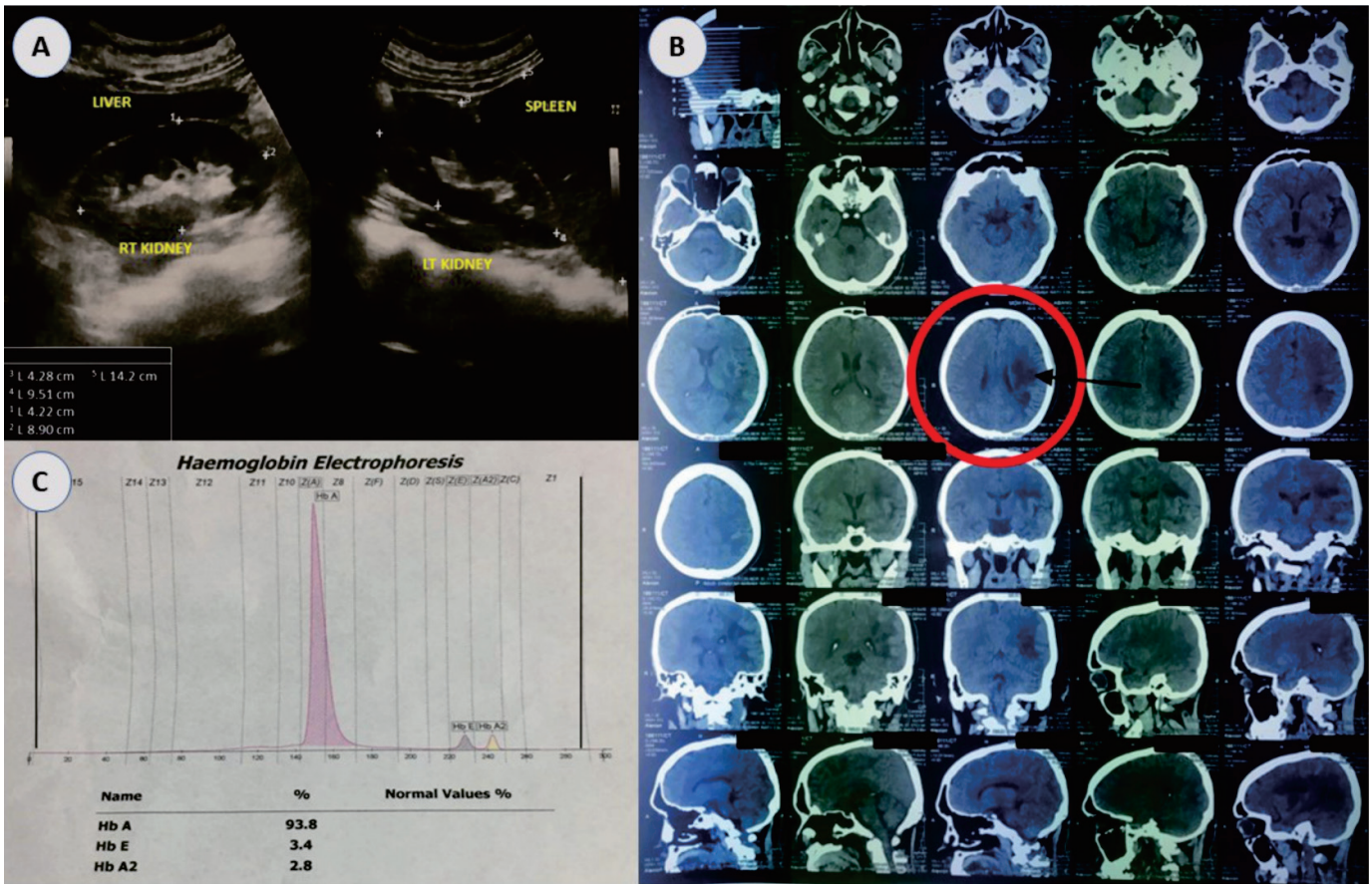

Figure 1. (A) Abdominal ultrasound examination; shows splenomegaly was found with a size of ± 14.2 cm, other organs were no abnormalities. (B) Head CT scan; shows the results showed hypodense lesions in the left corona radiata. There were no abnormalities with the conclusions of infarction at corona radiata as an embolic impression. (C) Haemoglobin Electrophoresis showed HbE-pathy

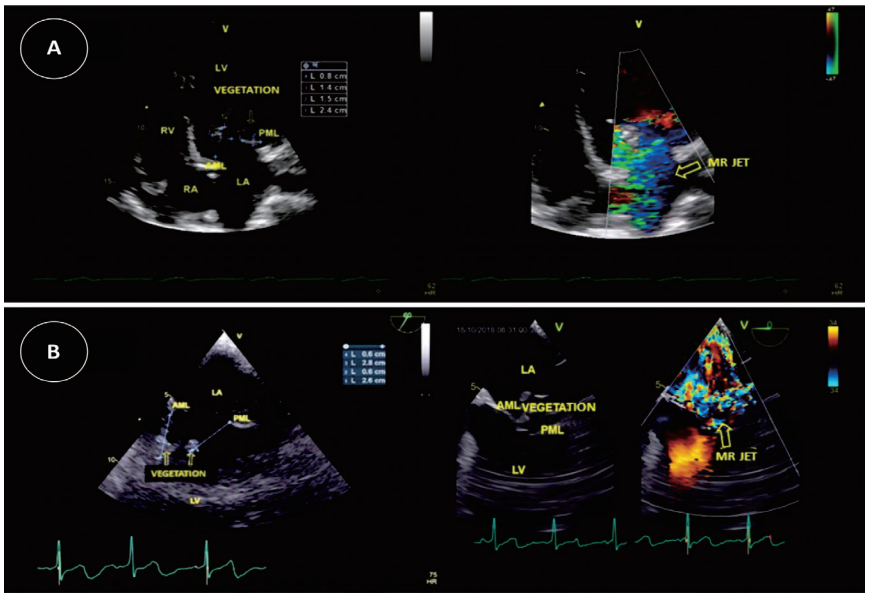

Figure 2. (A) Transthoracic echocardiography and (B) Transesophageal echocardiography showed vegetation appeared on AML valve and PML valve with intact septum intra-atrial

Table 1. Laboratory results

Parameters	*Day 1*	*Day 4*	*Day 14*	*Urinalysis*
Leucocyte	13,32	19,14	16,67	Protein (esbach) 0,1 g/L
Hemoglobin	9,5	9,5	10,4	Protein excretion 0,15 g/day
Hematocrit	30,9	31,5	34,6	Erythrocyte 10,969/uL
Platelet	281	416	396	Leucocyte 149,1/uL
AST	36		32	Cast 2,94 /uL
ALT	33		72	Bacteria 327,9/uL
Albumin	2,4	3,4		
Ureum	24	27	31	Microscopic:
Creatinine	1,1	1,15	0,7	Erythrocyte >100
Natrium	130	143	137	Leukocyte 10-25
Kalium	3,9	4,4	3,8	Cylinder erythrocyte cast +
Chloride	89	99	96	Epithelial cell 0-1
BG	126			Bacteria +++
ANA test		11,3 (negative)		
C_3		27,4 (low)		
C_4		<6 (low)		
SI		20 (low)		
TIBC		165 (normal)		
Ferritin		400 (low)		
ASTO		52,86 (normal)		
ESR		87 (high)		

ALT = alanine aminotransferase; ANA test = antinuclear antibody test; AST = aspartate aminotransferase; ASTO = antistreptolysin; BG = Blood glucose; ESR = erythrocyte sedimentation rate; SI = serum iron; TIBC = total iron-binding capacity

Table 2. Review of thalassemia and heart surgery from literatures.

Author	*Disease*	*Surgery*	*Complication and Follow-up*
Raffa et al. [7]	AV endocarditis	AVR	Long term good result
Omoto et al. [8]	AR	AVR, mechanical	6 months
Darwazah et al. [9]	MVE, Gram-	MVR, mechanical	Early post-operative death
Botta et al. [4]	MVSI	MVR, mechanical	6 months
Farmakis et al. [10]	AS	AVR, mechanical	Prosthetic valve thrombosis; 16 months
Métras et al. [11]	MR	MVRep	–
deLeval et al. [12]	-	MVRs, biologic	Recurrent systemic emboli, reoperation; 1 to 4 years

AR = aortic regurgitation; AS = aortic stenosis; AVR = aortic valve replacement; MR = mitral regurgitation; MVE = mitral valve endocarditis; MVR = mitral valve replacement; MVRep = mitral valve repair; MVRs = mitral valve replacement(s); MVSI = mitral valve steno-insufficiency

beta thalassemia is 3,8% of the entire population [4]. Thalassemia intermedia can become asymptomatic and splenic enlargement is the consequence because of it major role in removing damaged red blood cells from the bloodstream [5]. In our case, it appeared that the patient was in form of mild HbE because Hb levels were found between 9-12 g/dl and without significant clinical problems. The presence of thalassemia alone could not contribute to heart failure and stroke. Thus, further workup was needed to ensure the diagnosis. The presence of mitral vegetation from echocardiography examination contributes to one major Duke Criteria for IE. Unfortunately, it was not supported by the presence of growth bacteria. So, BCNIE suspicion is cautiously overlooked since it can occur in 31% of all IE [2]. Cardiac involvement in thalassemia has various manifestation such as thickening of leaflets, leaflet calcification,,

and chorda tendineae rupture, causing the valve to become easily infected[6].

The management of IE consists of antibiotics administration and surgical intervention. The surgical option was made in case of heart failure and uncontrolled infection. Since the patient had good heart failure progression during hospitalization, the surgical option was made during the heart team discussion. There are only a few cases of surgical therapy in the thalassemic-IE patients described, of which a few were successful [7]. Heart valve surgery in thalasemia patients is also rarely reported **(Table. 2).** Hypercoagulation is a matter of caution in beta thalassemia [13], so choosing a bioprosthetic or a mechanical type of valve requires careful consideration [10]. However, the surgical intervention carries a high risk of prosthetic complications, including thrombosis and embolization, despite optimal anticoagulation management [10]. This marks poor outcome of IE patients among thalassemia population [9].

4. Conclusion

Thalassemia could be asymptomatic, but some have an increased risk of infective endocarditis. We reported, a man with suspicion of IE presents with a chief complaint of hemiparesis in combination with anemia. Examinations show blood culture-negative IE with embolic stroke infarction and positive electrophoresis of Thalassemia HbE. Both BCNIE and thalassemia are dangerous since both are asymptomatic and usually have a worse prognosis. The presence of embolic stroke drove our suspicion of this linked combination. Once the diagnosis was assessed, the multidisciplinary team should be gathered to discuss the best possible management option for the patient.

Declarations of interest

None.

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