Case Report

Prosthetic Valve Endocarditis Caused by *Histoplasma Capsulatum*: The First Case Report in Thailand

Narisorn Lorchirachonkul MD*, Suporn Foongladda DVM, PhD**
Ruchira Ruangchira-urai,MD*** , Methee Chayakulkeeree MD, PhD*

** Division of Infectious Diseases and Tropical Medicine, Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand*
*** Department of Microbiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*
**** Department of Pathology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand*

The authors report a rare case of fungal endocarditis caused by Histoplasma capsulatum in an immunocompetent woman with mitral valve prosthesis. The patient presented with chronic fever and embolic phenomenon. Transthoracic and transesophageal echocardiography revealed a mobile mass attached to mitral prosthetic valve and her blood cultures were negative for both bacteria and fungi. The diagnosis was made by presence of budding yeasts in the histopathological findings of the vegetation and recovery of H. capsulatum from tissue culture of the excised vegetation. The patient was improved after a 6-week course of amphotericin B. Fungal endocarditis caused by Histoplama capsulatum is rare but should be considered as a possible causative organism in culture-negative endocarditis. To our knowledge, this is the first case report of H. capsulatum endocarditis in Thailand.

Keywords: *Histoplasma capsulatum, Endocarditis, Prosthetic valve endocarditis, Fungal endocarditis, Histoplasmosis*

J Med Assoc Thai 2013; 96 (Suppl. 2): S262-S265
Full text. e-Journal: *http://jmat.mat.or.th*

Fungal endocarditis is a rare manifestation of infective endocarditis. The most common pathogens causing fungal endocarditis include *Candida* spp. (~50%-80%) followed by *Aspergillus* spp. (~20%-25%). A thermally dimorphic fungus, *Histoplasma capsulatum*, is an uncommon cause of fungal endocarditis. Similar to endocarditis caused by other fungi, it is difficult to treat and usually has unfavorable outcomes. Due to the paucity of instances of *Histoplasma endocarditis*, this may cause delay in diagnosis and treatment as it may not be included in the differential diagnosis. The incidence of fungal endocarditis is increased in high-risk patients including those receiving broad-spectrum antibiotics or invasive interventions such as long-term central venous catheter or prosthetic heart valve replacement. The authors herein describe a case of prosthetic mitral valve endocarditis caused by *H. capsulatum* successfully treated with systemic antifungal agent and surgery.

Correspondence to:
Chayakulkeeree M, Division of Infectious Diseases and Tropical Medicine, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Prannok Road, Bangkok Noi, Bangkok 10700, Thailand.
Phone: 0-2419-9462, Fax: 0-2419-7783
E-mail: methee.cha@mahidol.ac.th

Case Report

A 58-year-old woman with a history of mitral valve regurgitation and previous native-valve endocarditis caused by a *viridians streptococcus*, underwent mitral valve replacement 6 years ago. Two months prior to admission, she had intermittent low grade fever, dyspnea on exertion and weight loss of three kilograms in a month. She took oral antibiotics for seven days without improvement. One month prior to admission, the patient developed petechiae on both legs. She has neither history of animal exposure nor recent traveling. Physical examination revealed temperature of 37.1°C, heart rate 74/min, blood pressure 84/43 mmHg and respiratory rate 18/min. She was conscious with no sign of poor tissue perfusion and no acute distress. Splinter hemorrhage was discovered at the third to the fifth digits of her left hand. The cardiovascular system showed normal valve click without cardiac murmur. Liver and spleen were not enlarged.

Complete blood count showed a white blood cell count of 3,150 cells/mm^3 with 61.2% neutrophils, 30.5% lymphocytes and 7.3% monocytes, hemoglobin

of 10.5 g/dl and platelet count of 181,000/mm^3. Anti-HIV was non-reactive. There were 10-20 non-dysmorphic red blood cells/HPF found in her urine examination. Renal function test was normal. Her chest radiograph showed mildly increased cardiothoracic ratio and a heart valve prosthesis. Transthoracic echocardiography (TTE) showed two vegetations size 1.5 x 1 cm and 0.5 cm. in diameter attached to mitral prosthetic valve. Three blood cultures, including one fungal culture were collected. The presumptive diagnosis was subacute bacterial endocarditis and ceftriaxone, cloxacillin and gentamicin were commenced. Multiple blood cultures were performed over the following seven days. All blood cultures were negative and cloxacillin was discontinued. Doxycycline was therefore added to cover other possible agents causing culture-negative endocarditis. After treatment for nineteen days, fever still persisted. Transesophageal echocardiography (TEE) was performed and demonstrated 2 large vegetations size, 2 x 0.9 cm and 1.1 x 0.7 cm attached to mitral prosthesis without paravalvular leakage or abscess. A cardiothoracic surgeon was consulted and ceftriaxone was switched to vancomicin for extended coverage to *Enterococcus spp.* and Methicillin-resistant *Staphylococcus aureus* (MRSA). While waiting for surgery, she developed right hemiparesthesia and computed tomography (CT) scan of the brain revealed hypodensity lesion at left frontoparietal region. She underwent mitral valve replacement in which the old prosthesis was removed and replaced by a new one (Perimount Magna No. 25). Direct microscopic examination of the vegetation by gram stain disclosed few budding yeasts. Histopathology of the vegetation showed necrotizing granulomatous reaction. Gomori's methenamine silver (GMS) stain demonstrated numerous budding yeasts (Fig. 1). Culture from the excised vegetation grew a thermally dimorphic fungus producing tuberculated macroconidia compatible with *H. capsulatum* (Fig. 2). All of the antibiotics were discontinued and intravenous amphotericin B (1 mg/kg/day) was initiated. Six weeks after surgery, amphotericin B was discontinued and itraconazole (400 mg/day) was commenced. The patient was improved without fever and she was discharged from the hospital with oral itraconazole. She is still doing well on one-month follow-up after discharge with oral anti-fungal agent.

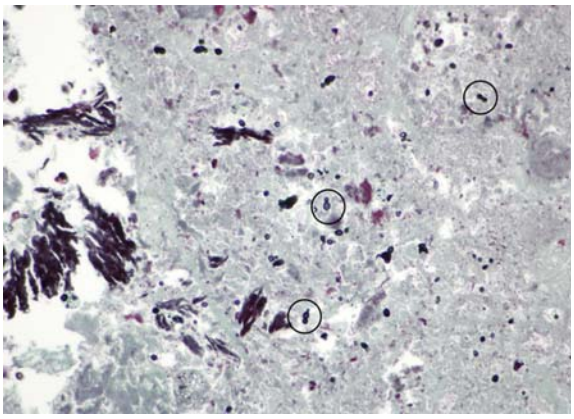

Fig. 1 Gomori'smethenamine silver (GMS) stain of the excised vegetation demonstrated numerous budding yeasts (circled)

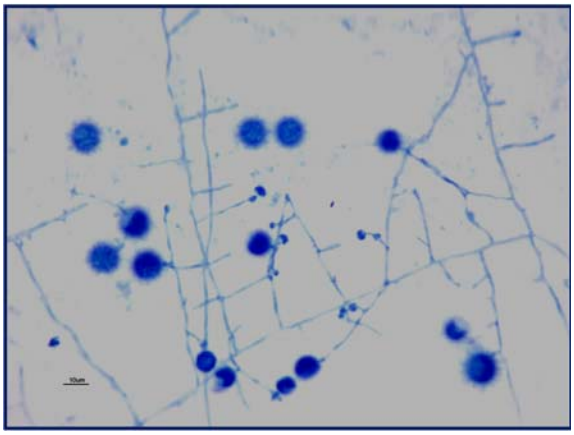

Fig. 2 Filamentous fungi with tuberculated macroconidia compatible with *H.capsulatum* isolated from the excised vegetation

Discussion

Prosthetic valve endocarditis occurs in approximately 10-15 percent of patients with infective endocarditis[1]. A recent study in 31 patients with blood culture-negative early prosthetic valve endocarditis revealed that fungus were the most common pathogens identified[2] and the most common fungal pathogen was *Candida spp.* followed by *Aspergillus spp.*[3,4]. In fact, *Candida albicans* is the most common species (30-40%) of fungal endocarditis[3,5]. *Histoplasma spp.* is responsible for approximately 6% of cases. In a review of 44 cases of infective endocarditis caused by *H. capsulatum* reported from 1943 to 2010, it is more common in male and the mean age at onset is 47.6 years[6]. The most common sites of involvement include aortic valve and mitral valve. More than 70 percent of cases occur in the setting of widely disseminated histoplasmosis[7]. *Histoplasma endocarditis* exhibits

high rate of systemic embolism (approximately 58%). Risk factors for *Histoplasma endocarditis* include prosthetic heart valve, cardiac abnormalities with repair, and prolonged venous catheter use.

Clinical presentations of *Histoplasma endocarditis* include fever (96%), heart murmur (76%), hepatomegaly or splenomegaly (48%), petechiae (35%), and/or major artery embolization (32-53%)[8], which is similar to our patient. The diagnosis of *Histoplasma endocarditis* is generally delayed for weeks or months because of consistently negative blood cultures. Echocardiography is useful to demonstrate vegetation and TEE (75-90%) is more sensitive than TTE (60%). Diagnostic tools for *H. capsulatum* infection include serology for anti-*Histoplasma* antibodies, culture, histopathology, and antigen detection. The standard serologic tests for anti-*Histoplasma* antibodies are the immunodiffusion (ID) test and the complement fixation (CF) test. However, these tests, as well as antigen detection, are not available in Thailand. *Histoplasma* endocarditis is an endovascular infection and therefore the antigen assay should be useful for the diagnosis, although it may give a negative result. Blood cultures are rarely positive in *Histoplasma* infection. Our patient was diagnosed *Histoplasma* endocarditis from histopathology and culture from the vegetation, from which *H. capsulatum* was isolated and identified.

Histoplasma endocarditis is a curable disease but it is uniformly fatal without appropriate and prompt treatment. Lipid formulation of amphotericin B (3 to 5 mg/kg/day) is recommended for both native and prosthetic valve endocarditis[9]. Parenteral amphotericin B with a mean cumulative dose of 3.4 g (range 1.3-7 g) has shown to improve survival to 73%[7]. Currently, there is no data for the use of novel antifungal agents or combination antifungal therapy for *Histoplasma* endocarditis. Although antifungal therapy in combination with valve replacement does not appear to improve cure rates, our case underwent surgery because of uncontrolled infection and the outcome was favorable.

In conclusion, *Histoplasma endocarditis* is a rare condition which is difficult to diagnose because blood cultures are rarely positive. It is therefore important to consider *H. capsulatum* as a potential cause of culture-negative endocarditis.

Acknowledgement

The authors wish to thank Dr. Nadthanan Pinchai for providing microscopic picture of tuberculated macroconidia from *H. capsulatum* isolated of this patient. The author Methee Chayakulkeeree is supported by Chalermphrakiat Grant, Faculty of Medicine Siriraj Hospital, Mahidol University.

Potential conflicts of interest

None.

References

1. Beynon RP, Bahl VK, Prendergast BD. Infective endocarditis. BMJ 2006; 333: 334-9.
2. Thuny F, Fournier PE, Casalta JP, Gouriet F, Lepidi H, Riberi A, et al. Investigation of blood culture-negative early prosthetic valve endocarditis reveals high prevalence of fungi. Heart 2010; 96: 743-7.
3. Pierrotti LC, Baddour LM. Fungal endocarditis, 1995-2000. Chest 2002; 122: 302-10.
4. Kossoff EH, Buescher ES, Karlowicz MG. Candidemia in a neonatal intensive care unit: trends during fifteen years and clinical features of 111 cases. Pediatr Infect Dis J 1998; 17: 504-8.
5. Millar BC, Jugo J, Moore JE. Fungal endocarditis in neonates and children. Pediatr Cardiol 2005; 26: 517-36.
6. Jinno S, Gripshover BM, Lemonovich TL, Anderson JM, Jacobs MR. Histoplasma capsulatum prosthetic valve endocarditis with negative fungal blood cultures and negative histoplasma antigen assay in an immunocompetent patient. J Clin Microbiol 2010; 48: 4664-6.
7. Bhatti S, Vilenski L, Tight R, Smego RA Jr. Histoplasma endocarditis: clinical and mycologic features and outcomes. J Infect 2005; 51: 2-9.
8. Blair T, Raymond L. Histoplasma capsulatum endocarditis. Chest 1981; 79: 620.
9. Varghese GM, Sobel JD. Fungal endocarditis. Curr Infect Dis Rep 2008; 10: 275-9.

การติดเชื้อที่ลิ้นหัวใจเทียมจากเชื้อราฮิสโตพลาสมาแคปซูลาตัม: รายงานผู้ป่วยรายแรกในประเทศไทย

นริสร หล่อจีระชุณห์กุล, ศุภร ฟุ้งลัดดา, รุจิรา เรืองจิระอุไร, เมธี ชยะกุลคีรี

ผู้นิพนธ์ได้รายงานโรคที่พบน้อยซึ่งเป็นผู้ป่วยภูมิคุ้มกันปกติมีการติดเชื้อราฮิสโตพลาสมาแคปซูลาตัมที่ลิ้นหัวใจเทียมไมตรัล ผู้ป่วยมีอาการไข้เรื้อรังและมีปรากฏการณ์เอ็มโบลิก (embolic phenomenon) ผลการตรวจด้วยคลื่นเสียงความถี่สูงผ่านผนังทรวงอก (Transthoracic echocardiography) และผ่านทางหลอดอาหาร (Thansesophageal echocardiography) พบก้อนเคลื่อนไหวได้ติดอยู่ที่ลิ้นหัวใจเทียมไมตรัล ผลการเพาะเชื้อจากเลือดไม่พบเชื้อแบคทีเรียหรือเชื้อรา ผู้ป่วยได้รับการวินิจฉัยโดยการตรวจพบเชื้อสา่ (yeast) จากการตรวจชิ้นเนื้อที่ตัดออกมาจากลิ้นหัวใจเทียม และการเพาะเชื้อจากชิ้นเนื้อดังกล่าว ขึ้นเชื้อราฮิสโตพลาสมาแคปซูลาตัม ผู้ป่วยมีอาการดีขึ้นหลังได้รับการรักษาด้วยยาต้านเชื้อราแอมโฟเทอริซินบีเป็นเวลา 6 สัปดาห์ โรคลิ้นหัวใจอักเสบจากเชื้อราฮิสโตพลาสมาแคปซูลาตัมพบได้น้อย แต่ควรคำนึงถึงว่าอาจเป็นเชื้อก่อโรคได้ในผู้ป่วยลิ้นหัวใจอักเสบที่เพาะเชื้อไม่ขึ้น รายงานนี้เป็นรายงานแรกของผู้ป่วยลิ้นหัวใจอักเสบจากเชื้อราฮิสโตพลาสมาแคปซูลาตัมในประเทศไทย