Case Report

Primary Actinomycotic Endocarditis: A Case Report and Literature Review

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Primary actinomycotic endocarditis is extremely rare. The author reported a case who suffered from endocarditis due to Actinomyces georgiae which the portal of entry for the organism could not be determined. The author also reviewed the literature which described similar conditions. In addition, to the author's knowledge, there have been no reported cases of actinomyces georgiae endocarditis. Thus, this is the first report in the world. Clinical features of this rare condition are indistinguishable from other bacterial endocarditis. Actinomyces spp. is usually susceptible to a wide range of antibiotics, and endocarditis caused by this genus needs a prolonged course of antimicrobial treatment. However, the optimal duration of therapy is still unknown. Prognosis is good with early detection and proper management.

Keywords: *Actinomycosis, Actinomyces, Actinomycotic endocarditis, Actinomyces georgiae*

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Actinomyces species infection is generally limited to a cervicofacial, thoracic, abdomino-pelvic or cerebral region[1,2]. Infection caused by *Actinomyces* species with involvement of the heart is rare. Most of these cases, which predominantly affect the pericardium, are due to local extension of adjacent intrathoracic infection. Endocardial involvement is usually secondary to myocardial and pericardial infectious process[3,4]. Primary actinomycotic endocarditis is extremely rare. The author reported a case who suffered from endocarditis due to *A. georgiae* in which the portal of entry for the organism could not be determined. The author also reviewed the literature which described the similar conditions. In addition, to the author's knowledge, there have been no reported cases of *Actinomyces georgiae* endocarditis. Thus, this is the first report in the world.

Case Report

A 46-year-old, farmer, male who lived in Nan province of Thailand had no history of valvular heart disease. First, he was transferred from a district hospital to Nan hospital on 29th January 2007 because of abnormal heart sound with mild dyspnea. Auscultation revealed pansystolic murmur grade 3/6 at the apical area. A transthoracic two-dimensional echocardiogram demonstrated mild mitral regurgitation and mitral valve prolapse. He was treated with enarapril 2.5 mg/day. Thereafter, on 20th February 2007 he revisited Nan Hospital because he had a prolonged fever without any localized symptoms. He also had shortness of breath during exertion. He denied recent dental procedures or intravenous drug abuse. He denied heavy alcohol drinking, smoking and steroid use. He was admitted to the hospital on 6th March 2007.

Physical examination revealed oral temperatures between 38-38.5°C, pulses between 90-110/minute, respiratory rates between 18-20/minute, and blood pressures between 90/50-110/70 mmHg. There were no subconjunctival hemorrhage and petechial spots. His teeth and gums were in good condition. Cardiac examination showed shifting apical impulse to the 6th intercostal space, lateral to mid-clavicular line, and a pansystolic murmur grade 4/6, best heard at the apex. There were no cutaneous petechiae, purpurae, Janeway lesions, Osler's nodes, nor clubbing fingers. Neurological examination was normal.

On admission to the hospital, complete blood count analysis showed white blood cell count of 14,900/μL (86.7% neutrophils, 5.6% lymphocytes, 5.5% monocytes, and 2.2% eosinophils), hemoglobin of 8.7

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g/dL, and platelet count of 285,000/μL. Urine examination revealed red cells of 5-10 cells/high-power field, and white cells of 2-3 cells/high-power field. Blood chemistry results were unremarkable. Chest radiography showed a cardiomegaly with diffuse pulmonary congestion. An electrocardiogram showed sinus tachycardia. Five sets of blood cultures were performed, 1 day after admission. Three of them grew Gram-positive bacilli with small branchings, after 72 hours of incubation, which were likely to be *Actinomyces* species based on the morphology (Fig. 1). Additionally, the two sets of blood culture yielded gram-positive bacilli were dispatched to the National Institute of Health (NIH) for species identification. Enzymatic reactions showed negative to both catalase and urease reactions. Sugar fermentations identified positive results for glucose, rhamnnose and trehalose, otherwise negative result for raffinose. The biochemical tests were compatible with *Actinomyces georgiae*. Repeated echocardiogram, following 2-days admission, revealed mobile vegetations at both mitral valve leaflets and severe mitral regurgitation worsen than the previous result (Fig. 2).

An initial therapy with penicillin G sodium of 18 million units/day and enalapril was given, and the patient's temperature gradually subsided within 6 days. However, fever relapsed after 14-days penicillin therapy, but symptoms of the patient were stable. Following echocardiogram showed no local complications. Ceftriaxone 2 g/day was substituted for penicillin. The fever decreased and did not exist. Total course of antimicrobial treatment was 28 days in Nan Hospital. The patient had mild dyspnea on exertion, chest radiography still showed a cardiomegaly. Thereafter, the patient was referred to a tertiary medical center – Maharaj Nakorn Chiangmai Hospital in Chiang Mai province, for proper management. Finally, he received conservative treatment with ampicillin 12 g/day for six weeks, then switched to amoxicillin 4 g/day for 6 months. The follow-up blood cultures, taken on 4th May 2007 (after 1-month therapy), were negative. The patient looked well, had a better functional class (functional class II) and resumed his activities later, even though he had a severe mitral regurgitation persistently. Besides, he has also been following up on his illness with a cardiologist of Maharaj Nakorn Chiangmai Hospital, mitral valve surgery was due to be held on 25th February 2008.

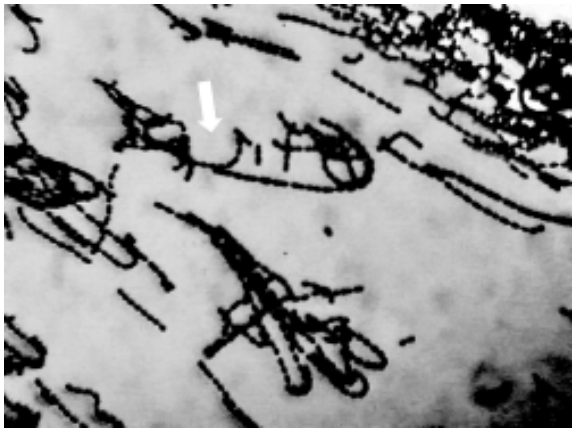

Fig. 1 Blood cultures yielded Gram-positive bacilli with small branchings after 72 hour of incubation which were likely to be an *Actinomyces* species

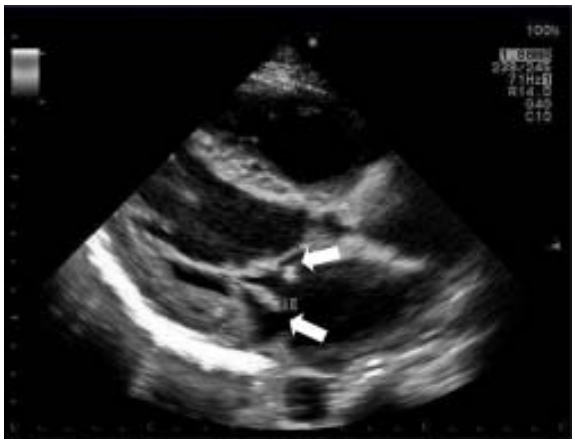

Fig. 2 The echocardiogram revealed mobile vegetations at both mitral valve leaflets

Discussion

Human actinomycosis was first described in 1878 by Israel[5]. Six *Actinomyces* species may cause disease in humans including *A.israelii*, *A.naeslundii*, *A.odontolyticus*, *A. viscosus*, *A.meyeri* and *A.gerencseriae*[5]. There are a few case reports of primary actinomycotic endocarditis in the literature. Actinomycotic endocarditis with undetermined portal of entry was first identified in 1939, then these rare conditions were sporadically reported which were mostly caused by *A.israelii*, *A.viscosus*, *A.bovis*, and *A.meyeri*[2,3]. To the author's knowledge, there have been no case reports of primary actinomycotic endocarditis caused by *A.georgiae*.

A.georgiae was initially identified in 1990 by Johnson et al[6]. It is a human periodontal flora. Moreover, there was a study that demonstrated bacteremia from *A. georgiae* following surgical dental extraction[7].

Actinomyces species is a Gram-positive, non-spore forming, facultative anaerobic branching filamentous bacilli. It is classified as a low virulent pathogen. At least 17 other cases of primary actinomycotic endocarditis have been reported in literature[2-4,8-12] (Table 1). Most of the patients presented as subacute to chronic endocarditis and involved the native heart valves. The data extracted from Table 1 revealed that the infection of this organism involved the mitral valve (41%), aortic valve (30%), combination of both (23%), and tricuspid valve in only one case[10]. Contributory risk factors for endocarditis included periodontal disease corresponding to pre-exisitng valvular heart disease[2]. This condition affected males more than females; the ratio of 2.4:1. The majority of the patients had no history of dental procedure. None exhibited the classic signs of endocarditis such as splinter hemorrhages, Roth spots, or Janeway lesions, despite the prolonged course of symptoms. Fifty-three percent of patients were complicated by systemic embolisation, for example, CNS emboli, GI emboli, and renal emboli with a preponderance of the central nervous system.

Table 1. A summary of 17 reported cases diagnosed primary actinomycotic endocarditis

Ref.	Age (year)	Sex	Allied cardiac diseases	Affected valve	Duration of illness	Organism	Therapy	Complications	Outcome[c]
2	38	M	None	Mitral	21 days	*A. viscosus*	Multiple[b]	Cutaneous emboli	Alive
2,3	37	M	None	Mitral	13 months	*Actinomyces sp.*	Sulfathiazole	Renal/GI emboli, CHF	Dead
	71	F	RHD	Aortic	2 months	*Actinomyces sp.*	None	Renal failure	Dead
3	24	M	None	Aortic, Mitral	35 days	*A. bovis*	None	CNS emboli, CHF	Dead
3	55	M	None	Aortic, Mitral	9 months	*Actinomyces sp.*	None	CNS/GI/renal emboli	Dead
3	39	M	Murmur	Mitral	42 days	*Actinomyces sp.*	Penicillin G	CNS emboli	Alive
3	43	F	RHD	Aortic, Mitral	2 months	*A. bovis*	Penicillin G	GI emboli	Alive
3	6	M	None	Mitral	6 days	*A. israelii*	Penicillin G	CHF	Dead
3	70	M	None	Mitral	5 months	*A. viscosus*	Penicillin G	CNS emboli, CHF	Alive
3	65	M	RHD	Aortic, Mitral	28 days	*A. israelii*	Penicillin G	None	Alive
4	55	F	None	Mitral	21 days	*A. meyeri*	Ampicillin/ sulbactam	None	Alive
8	64	M	AS	Aortic	49 days	*A. pyogenes*[a]	Multiple[b]	CNS emboli, CHF	Dead
9	81	M	None	Aortic	NA	*A. viscosus*	Ceftizoxime then ceftriaxone	None	Alive
10	40	F	IVDU, Previous IE	Tricuspid	16 days	*A. funkei*	Multiple[b]	Pulmonary emboli	Alive
11	43	F	Bicuspid AV	Aortic	60 days	*A. viscosus*	Multiple[b] and AVR	CHF	Alive
12	68	M	Bicuspid AV	Aortic	21 days	*A. neuii*	Multiple[b] and AVR	Paravalvular abscess	Alive
Present case	46	M	None	Mitral	36 days	*A. georgiae*	Multiple[b]	CHF	Alive

Ref = reference, M = male, F = female, RHD = rheumatic heart disease, AS = aortic stenosis, IVDU = intravenous drug user, IE = infective endocarditis, AV = aortic valve, AVR = aortic valve replacement, CNS = central nervous system, GI = gastrointestinal, CHF = congestive heart failure

[a] Currently reclassified into *Arcanobacterium pyogenes*

[b] At least 3 antimicrobial agents including penicillin, ampicillin, amoxicillin-clavulanate, cephalosporins, gentamicin, vancomycin, clindamycin, rifampicin or azithromycin were identified in the literature whether empirically, combined or subsequently used

[c] The overall mortality was 35.29%

Abnormal urinary sediment was identified in this case, possible owing to renal complications. However, there are no specific clinical features that differentiate actinomycotic endocarditis from other bacterial endocarditides.

A diagnosis of actinomycotic endocarditis depends on the identification of the organism from blood cultures, ranged from 2 to 7 days (median = 72 hours) for the incubation periods. The specimens should be collected with minimal exposure to oxygen and CO_2 enriched environments, yield may be improved by holding primary cultures for up to 4 weeks[11,13].

Species identification of *Actinomyces* requires special investigations, for instance, biochemical methods, gas-liquid chromatography, and analysis of nucleic acids. The clinical isolates, originated from the patient's blood culture, were proceeded to identify species by biochemical methods. Enzymatic reactions showed negative to both catalase and urease reactions. Sugar fermentations identified positive results for glucose, rhamnnose and trehalose, otherwise negative result for raffinose. The negative raffinose reaction can differentiate *A.georgiae* from *A.gerencseriae* which gives a positive raffinose test. The methods may pose major problems for clinical laboratories in terms of labor, time, and cost[14]. Gas-liquid chromatography is used for analysis of metabolic products[15]. Sophisticated novel methods, exemplified and amplified in 16S Ribosomal DNA restriction analysis, are able to identify the most problematic *Actinomyces* species. However, this method is available only in research centers[16]. Currently, some commercial test systems for rapid identification of *Actinomyces* such as the RapID ANA II system (Remel, Lenexa, Kans), the Rapid ID 32 A system (bioM□rieux), the RapID CB Plus system (Remel), and the BBL Crystal ANR ID system (Becton Dickinson) are widely used, but none of the commercial kits can identify *Actinomyces* strains correctly[17].

Penicillin was the initial therapy for this case. High doses of penicillin are recommended for penetration of the fibrotic vascular vegetative lesions, but the optimal duration of therapy is unknown[3]. Nevertheless, the long duration of treatment is preferable. *Actinomyces* species appear to be susceptible to a wide range of beta-lactam antibiotics which should be regarded as agents of first choice. However, early studies have indicated that lots of patients responded insufficiently or not at all to penicillin G and have led to the suggestion of prolonged high-dose therapy[18]. Patients allergic to penicillin may be treated with tetracycline, clindamycin, or cephalosporins. Some studies have demonstrated that tetracycline was less active and had poor performance[19]. After the 14-day therapy, penicillin was changed for ceftriaxone because the patient suffered a relapse of fever. However, MICs were not evaluated on account of an unavailable test in Nan Hospital, the disc diffusion method for susceptibility test, which was the limitation of the present study, was performed instead. The third-generation cephalosporins are the alternative treatment, though the necessary duration of treatment is inconclusive.

The indications for surgical intervention in infective endocarditis comprise refractory cardiac failure, persistent sepsis caused by a removable focus or a valvular ring or myocardial abscess, and persistent life-threatening embolisation[20]. In many case reports, most of survivals were administered merely by a prolonged antimicrobial therapy without requiring surgical intervention. The follow-up echocardiography to detect any residual vegetations is impractical; however, it is used for evaluation of the severity of endocarditic valve that required valve replacement surgery. Long-term outcome of this patient was not completely studied because the patient followed up on his illness with a physician at Maharaj Nakorn Chiang Mai Hospital. This was another limitation of the present study. Only three case reports including the presented patient, a valve replacement was carried out as a result of worsening regurgitant valve. With several innovations of investigation and treatment, the overall mortality associated with primary actinomycotic endocarditis was amerio-lated, from 50% to 35%. All patients to whom antimicrobial agents did not apply were dead inevitably. Missed diagnosis and ineffective antibiotics are the major causes of death. The prognosis is good with early detection and appropriate antimicrobial therapy.

Conclusion

Endocarditis caused by *Actinomyces* species in the absence of any recognizable focus of infection is extremely rare and should be considered in case of culture-negative endocarditis. The clinical features of this condition are indistinguishable from other bacterial endocarditides. Diagnosis of *Actinomyces* species can be difficult, special identification methods may be necessary. Meanwhile, the organism is susceptible to a wide range of antibiotics, optimal drug choices; duration of therapy is not definite.

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เยื่อบุลิ้นหัวใจอักเสบจากการติดเชื้อ Actinomyces sp.รายงานผู้ป่วย 1 รายและทบทวนวรรณกรรม

อนุภพ จิตต์เมือง

เยื่อบุลิ้นหัวใจอักเสบจากการติดเชื้อ Actinomyces species พบน้อยมาก รายงานนี้นำเสนอผู้ป่วย 1 ราย ที่เกิดเยื่อบุลิ้นหัวใจอักเสบจากเชื้อ Actinomyces georgiae ซึ่งไม่พบตำแหน่งของการติดเชื้อนี้ที่บริเวณอื่น ๆ ของร่างกายนำมาก่อน และทบทวนวรรณกรรมที่เกี่ยวข้อง รายงานนี้จัดเป็นรายงานแรกของโลกที่พบการติดเชื้อ Actinomyces georgiae ที่เยื่อบุลิ้นหัวใจ ลักษณะทางคลินิกของโรคนี้ไม่สามารถแยกได้จากโรคเยื่อบุลิ้นหัวใจอักเสบจากเชื้อแบคทีเรียชนิดอื่น ๆ Actinomyces species ตอบสนองดีต่อยาปฏิชีวนะหลายขนาน เยื่อบุลิ้นหัวใจอักเสบจากเชื้อชนิดนี้ต้องให้การรักษาด้วยยาปฏิชีวนะเป็นระยะเวลานานซึ่งระยะเวลาที่เหมาะสมยังไม่ทราบแน่ชัด การพยากรณ์โรคของภาวะนี้ดีถ้าวินิจฉัยอย่างรวดเร็วและรักษาอย่างเหมาะสม