

CASE REPORT

ARCANOBACTERIUM PYOGENES ENDOCARDITIS: A CASE REPORT AND LITERATURE REVIEW

Supavit Chesdachai¹, Noppadol Larbcharoensub², Tharintorn Chansoon²,
Panas Chalermpanyakorn², Pitak Santanirand³, Darunee Chotiprasitsakul⁴,
Disya Ratanakorn⁵ and Sarana Boonbaichaiyapruk⁶

¹Medical Student, ²Division of Anatomical Pathology, ³Division of Microbiology,
Department of Pathology, ⁴Division of Infectious Disease, ⁵Division of Neurology,
⁶Division of Cardiology, Department of Medicine, Faculty of Medicine Ramathibodi
Hospital, Mahidol University, Bangkok, Thailand

Abstract. We report the case of a 64-year-old man with *Arcanobacterium pyogenes* endocarditis. The patient presented with dyspnea and asymmetrical progressive quadriparesis. A transthoracic echocardiogram revealed mobile vegetations on both leaflets of his mitral valve measuring 0.5 x 3 cm, thickening of the mitral valve with severe mitral regurgitation due to dehiscence of the papillary muscle to the posterior mitral leaflet. He also had aortic sclerosis with a vegetation measuring 0.5 x 1 cm causing aortic valve dehiscence and free flow aortic regurgitation. An initial hemoculture grew out pleomorphic, gram-positive, non-motile, anaerobic to microaerophilic bacilli. A diagnosis of infective endocarditis was made using modified Duke criteria. He was treated with intravenous ampicillin and gentamicin. Four days after admission, he developed acute respiratory failure and succumbed to the disease. A pre-mortem hemoculture and post-mortem heart valve culture grew *Arcanobacterium pyogenes*. Septic thromboemboli involving the brain, kidneys, lungs and spleen were documented. The patient also had ischemic vasculopathy with focal spinal arteriolitis and bilateral demyelination of the cervical corticospinal tracts. There are three published reports of human *A. pyogenes* endocarditis in the literature. Neurological involvement with ischemic spinal vasculopathy and demyelination has not been reported. We report the first autopsy proven case of *A. pyogenes* infective endocarditis with ischemic spinal vasculopathy. We review the clinicopathologic features of systemic *A. pyogenes* infection.

Keyword: *Arcanobacterium pyogenes*, endocarditis, ischemic spinal vasculopathy, clinicopathologic features

Correspondence: Noppadol Larbcharoensub,
Department of Pathology, Faculty of Medicine
Ramathibodi Hospital, Mahidol University, 270
Rama VI Road, Ratchathewi, Bangkok 10400,
Thailand.
Tel: +66 (0) 2354 7277; Fax: +66 (0) 2354 7266
E-mail: Noppadol_l@hotmail.com

INTRODUCTION

Arcanobacterium pyogenes is a pleomorphic, gram-positive, non-motile, anaerobic to microaerophilic bacillus, that is commensal on mucosal surfaces of cattle, sheep, swine and occasionally other

domestic animals (Lipsky *et al*, 1982; Yeruham *et al*, 2002). It was formerly known as *Corynebacterium pyogenes* and later as *Actinomyces pyogenes* (Plamondon *et al*, 2007). Since 1997, it has been known as *A. pyogenes* (Ramos *et al*, 1997). *A. pyogenes* is primarily an animal pathogen causing pyogenic infections in cattle, including wound infections, pneumonia, endocarditis, endometritis and mastitis (Meyer and Reboli, 2009). *A. pyogenes* infections have rarely been reported in humans and occur almost exclusively in a rural setting (Gahrn-Hansen and Frederiksen, 1992; Plamondon *et al*, 2007; Meyer and Reboli, 2009). There are two main well-defined clinical manifestations of *A. pyogenes* infection in humans. The most common is localized infection, characterized by localized pain, swelling and redness of the infected site, typically the extremities (Kotrajaras and Tagami, 1987). The most serious manifestation of *A. pyogenes* infection is systemic infection, including septicemia, where endocarditis has been reported (Jootar *et al*, 1978; Reddy *et al*, 1997; Plamondon *et al*, 2007). Although systemic infection is relatively uncommon, this type of *A. pyogenes* infection appears to be increasing in incidence. Endocarditis caused by *A. pyogenes* has high morbidity and mortality rates (Jootar *et al*, 1978; Reddy *et al*, 1997; Plamondon *et al*, 2007). There are three published reports of human *A. pyogenes* infective endocarditis (IE) in the literature (Table 1). However, neurological involvement with ischemic spinal vasculopathy and demyelination has not been reported. We report here the clinicopathological features and autopsy findings of a patient with *A. pyogenes* endocarditis and ischemic spinal vasculopathy.

CASE REPORT

A 64-year-old man with underlying type 2 diabetes mellitus was admitted to

Ramathibodi Hospital, Bangkok, Thailand, in December 2011 with a one day history of dyspnea and asymmetrical progressive quadriparesis. In October 2011, he had a two-week history of high grade fever, paraparesis and weight loss. He went to the hospital and on physical examination in October was noted to have proximal muscle weakness of all extremities with left sided muscular atrophy, hyperreflexia and increased muscle tone of both lower extremities. His left foot was swollen and tender and he was given the diagnosis of cellulitis and treated with oral dicloxacillin 500 mg every 6 hours for ten days. Magnetic resonance imaging (MRI) of the cervical spine was planned. He was lost to follow-up because of the Thai floods that hindered transportation.

In December 2011, he developed dyspnea on exertion along with fever. He had a temperature of 38°C, a respiratory rate of 28/min, a pulse rate of 160/min, and a blood pressure of 85/50 mmHg.

Physical examination revealed a grade 4/6 pansystolic murmur at the right upper parasternal border radiating to the apex with a left ventricular heave. Both lungs were clear to auscultation. The cellulitis of his left foot had resolved. No lymphadenopathy was detected. The neurological finding was the same as on the first visit. He had no conjunctival hemorrhages, Janeway's lesions, Osler's nodes, or splinter hemorrhages. Ophthalmoscopic examination revealed no Roth's spot. A provisional diagnosis was infective endocarditis.

He was intubated and initially treated with intravenous ceftriaxone. Relevant laboratory investigations included: a hemoglobin of 6.8 g/dl, a hematocrit of 23%, a mean corpuscular volume of 55 fl, a white blood cell count of 22,710 per mm³ with 94% neutrophils, 4% lymphocytes and 2% monocytes. Hemoglobin electrophoresis

Table 1
Literature review of patients with *A. pyogenes* systemic infection.

Reference	Year	Number of cases	Age	Sex	Type of infection	Underlying disease	Treatment	Outcomes
Jootar <i>et al</i> ,	1978	1	20	F	Acute endocarditis	Not known.	Penicillin, gentamicin.	Died
Gahrn-Hansen and Frederiksen	1992	2	42	F	Abdominal abscess	Cervical carcinoma.	Surgery, penicillin, sulfonamide.	Cured
Drancourt <i>et al</i> ,	1993	2	68	M	Sigmoiditis, cystitis	Diverticulitis.	Penicillin.	Cured
			82	M	Subcutaneous lumbar abscess	None.	Surgery, ampicillin.	Cured
			56	M	Infected foot ulcer, bacteremia	Diabetes mellitus.	Surgery, cefotaxime, ofloxacin, metronidazole, amoxicillin/clavulanic acid.	Cured
Reddy <i>et al</i> ,	1997	1	64	M	Subacute endocarditis	Aortic stenosis.	Cefotaxime, gentamicin, amantadine, ceftriaxone, vancomycin, ampicillin, penicillin.	Died
Nicholson <i>et al</i> ,	1998	1	46	M	Septic arthritis	Diabetes mellitus.	Cloxacillin, penicillin, ampicillin, rifampicin.	Cured
Hermida Amejeiras <i>et al</i> ,	2004	1	81	M	Pneumonia	None.	Cefotaxime, clarithromycin.	Cured
Ide <i>et al</i> ,	2006	1	56	M	Spondylodiscitis	CVA, OA knees, hypercholesterolemia.	Penicillin, clindamycin.	Cured
Plamondon <i>et al</i> ,	2007	1	57	M	Acute endocarditis	Diabetes mellitus, cirrhosis.	Piperacillin/Tazobactam, Vancomycin, penicillin.	Died
Levy <i>et al</i> ,	2009	1	27	M	Otitis media, sepsis	None.	Cefepime, ampicillin, gentamicin.	Cured
Present case	2014	1	64	M	Acute endocarditis	Diabetes mellitus.	Ampicillin, gentamicin.	Died

F : M, female : male; CVA, cerebrovascular accident; OA, osteoarthritis.

revealed he had homozygous hemoglobin E. An arterial blood gas showed a wide gap metabolic acidosis with a pH of 7.176, a pCO₂ of 15.9 mmHg and a HCO₃⁻ 5.9 mmol/l. His blood urea nitrogen level was 58 mg/dl and serum creatinine level was 2.6 mg/dl. Microscopic hematuria was detected. He was seronegative for human immunodeficiency virus (HIV). Gram stain of the organism obtained with the hemoculture showed non-spore forming, gram-positive, pleomorphic bacilli with an irregular shape. Blood agar showed white round colonies with a large β-hemolysis zone. The organism was negative on the catalase test. Standard biochemical bacteriological testing confirmed *Arcanobacterium pyogenes* with the negative reverse CAMP test, the ability to produce acid from xylose, to hydrolyze gelatin and a positive β-glucuronidase test. An API Coryne Kit (bioMerieux, Marcy l'Etoile, France) revealed *A. pyogenes*.

A transthoracic echocardiogram revealed mobile vegetations on both mitral leaflets, measuring 0.5 x 3 cm and thickening of the mitral valve with severe mitral regurgitation due to dehiscence of the papillary muscle to the posterior mitral leaflet. He also had aortic sclerosis with a vegetation measuring 0.5 x 1 cm causing aortic valve dehiscence and free flow aortic regurgitation. Pulmonary hypertension was present. A diagnosis of infective endocarditis was made using modified Duke criteria. He was treated with intravenous ampicillin and gentamicin. Four days after admission, he developed acute respiratory failure and then succumbed to the disease. An autopsy was performed. His social history revealed he lived in Bangkok and had run a restaurant. The patient had no previous history of intravenous drug use, animal contacts or recent travel history.

Autopsy revealed endocarditis, involving the mitral and aortic valves with a ruptured papillary muscle to the posterior leaflet and a valve ring abscess (Fig 1). Hemoculture and heart valve culture revealed *Arcanobacterium pyogenes*. Systemic septic thromboemboli involving the brain, kidneys, lungs and spleen were documented. He had ischemic vasculopathy with focal spinal arteriolitis and demyelination of bilateral cervical corticospinal tracts. Demyelination of the anterior and posterior spinocerebellar tracts was also detected (Fig 2).

DISCUSSION

Systemic *A. pyogenes* is an uncommon bacterial infection in humans with a variety of clinical manifestations. It represents a challenge in diagnosis, treatment and clinical outcomes. Information regarding its clinical features is scanty. Only 12 cases have been reported in the literature since 1978, consisting mainly of single cases or small series case reports (Table 1). Patient ages range from 20 to 82 years with a mean age of 55 years. The male to female ratio is 5 to 1. Several forms of systemic *A. pyogenes* infections have been reported: endocarditis, septicemia, arthritis, pneumonia and multiple abscesses located in the subcutaneous tissue and abdomen have been reported (Table 1). Systemic *A. pyogenes* infection may present as otalgia, headache, malaise, abdominal pain, neuropathy, alteration of consciousness and fever. The duration of these symptoms may vary from an hour to a month. Most patients had symptoms, signs, and laboratory findings consistent with bacterial septicemia. Diabetes mellitus is the most common associated underlying disease occurring in 33% (Drancourt *et al*, 1993; Nicholson *et al*, 1998; Plamondon *et al*, 2007). A high index of suspicion is needed to diagnose

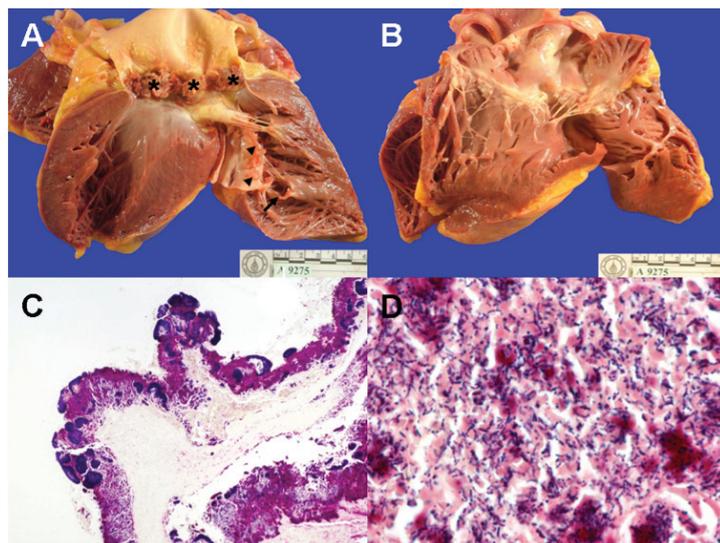


Fig 1—Multiple vegetations on aortic valves (asterisk), mitral valve leaflet (arrowhead) and ruptured chordae tendineae (arrow) (A). The tricuspid valve was intact (B). Acute inflammatory cells and multiple bacterial organisms on the endocardial surface of the aortic valve (C, x40). Gram stain showing pleomorphic gram-positive bacilli (D, x1,000).

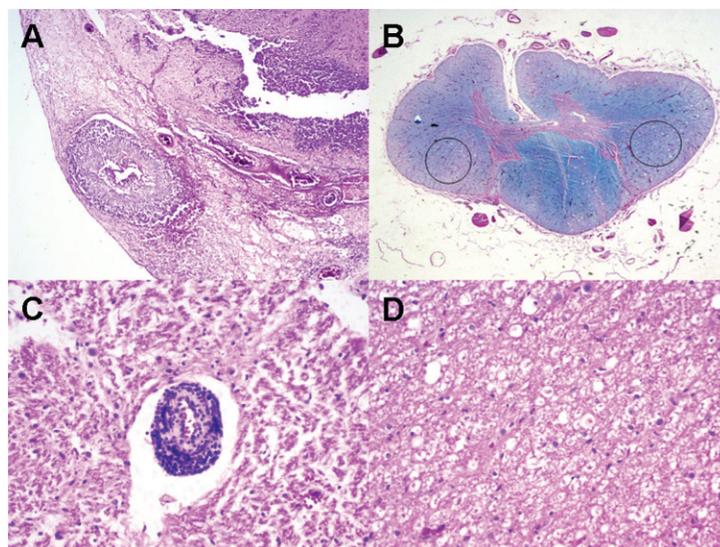


Fig 2—A section of the brain showing a brain abscess with meningitis (A, x40). A section of the spinal cord showing focal loss of myelinated fibers (decreased staining) in bilateral corticospinal tracts without degeneration of anterior horn cells (B, x100). Focal spinal arteriolitis (C, x200) and vacuolar myelopathy (D, x200) are seen.

this disease, but it should be considered in a patient with a history of animal contacts. A case of fatal endocarditis in a patient with no animal contacts has been reported (Plamondon *et al*, 2007). In our case, the patient had no history of animal contacts.

Endocarditis is a serious infection characterized by colonization or invasion of the heart valves or the mural endocardium by a microbe. This leads to the formation of vegetations composed of thrombotic debris and organisms, often associated with destruction of the underlying cardiac tissues (Halder and O’Gara, 2011). The diagnosis of bacterial endocarditis is made using modified Duke criteria, and is confirmed by demonstration of the organism with tissue reaction on the valvular leaflets. Endocarditis is most frequently caused by bacteria. *Streptococcus viridans* is the most common causative organism (Halder and O’Gara, 2011). *A. pyogenes* infection is an uncommon cause of endocarditis. There are three reported cases of endocarditis caused by *A. pyogenes* in the literature: one with subacute and two with acute infection (Jootar *et al*, 1978; Reddy *et al*, 1997; Plamondon *et al*, 2007). The patient we report here had acute endocarditis.

Endocarditis caused by *A. pyogenes* may not meet modified Duke criteria and may arise insidiously. *A. pyogenes* is cultured on sheep blood agar under carbon dioxide enrichment (Meyer and Reboli, 2009). Colonies are weakly hemolytic at 24 hours and become strongly hemolytic at 48 hours (Meyer and Reboli, 2009). A negative reverse CAMP test, the ability to produce acid from xylose and to hydrolyse gelatin and a positive β -glucuronidase test clearly differentiate *A. pyogenes* from other closely related species (Kavitha *et al*, 2010). *A. pyogenes* may be misidentified as *A. haemolyticum*, which gives similar results with conventional biochemical tests (Gaharn-Hansen and Frederiksen, 1992). The authors hypothesize *A. pyogenes* is probably under-recognized. Patient with *A. pyogenes* endocarditis have high mortality and complication rates (Jootar *et al*, 1978; Reddy *et al*, 1997; Plamondon *et al*, 2007).

A. pyogenes is part of the normal flora in domestic animals. *A. pyogenes* may become pathogenic in humans, as in this case. *A. pyogenes* typically directly invades the subcutaneous tissue and spreads hematogenously to multiple organs (Meyer and Reboli, 2009). Endocarditis with secondary septic emboli may occur. The histopathology of infected sites includes minimal inflammation, marked suppurative inflammatory infiltration, abscess formation, and necrosis, depended on the underlying immunologic status of the patients and virulence of the pathogen (Kotrajaras and Tagami, 1987). Using a Gram stain, the organism may be detected in areas of suppurative inflammation.

Neurological complications occur in about 25% of patients with endocarditis (Heiro *et al*, 2000). The majority of neurological complications are due to emboli (Heiro *et al*, 2000). Both septic and non-septic emboli may cause ischemic neuropa-

thy (Heiro *et al*, 2000). Septic emboli may also cause hemorrhagic stroke through direct vascular necrosis or mycotic aneurysm (Heiro *et al*, 2000). The development of demyelination probably represents a continuum of processes whose outcome depends on host defense factors, timing and appropriateness of antibiotic therapy and virulence of the infected organism (Heiro *et al*, 2000). The postulated pathogenesis of myelopathy caused by ischemic spinal vasculopathy with demyelination include hematogenous seeding of bacteria during septicemia or septic emboli due to endocarditis and immunologic phenomenon. Antibodies to heterologous protein and bacterial antigen forming immune complexes can be found in the serum and in vascular lesions (Kotrajaras and Tagami, 1987). We stress the importance of histopathological studying spinal cord specimens to diagnose ischemic spinal vasculopathy. Clinical and pathological correlations are essential.

The diagnosis is often delayed and systemic emboli frequently complicate infection (Jootar *et al*, 1978; Reddy *et al*, 1997; Plamondon *et al*, 2007). Recent diagnostic tools including 16S rDNA sequencing provide the opportunity to detect the pathogen. A rapid molecular-based diagnostic method is also an adjunctive tool. Prompt identification of the infective organism permits prompt antibiotic treatment. It is crucial to make an early definitive diagnosis and identification of the pathogen.

A. pyogenes is susceptible to most antibiotics, including penicillin, cephalosporin, macrolide, tetracycline and aminoglycoside (Meyer and Raboli, 2009). Patients should be treated initially with penicillin, ampicillin and gentamicin (Meyer and Reboli, 2010). Continuing antibiotics throughout the entire course of therapy is no longer the standard. Intravenous cephalosporin

is recommended as alternative treatment of systemic *A. pyogenes* infection (Meyer and Raboli, 2009). However, no patient has been successfully treated for *A. pyogenes* endocarditis (Jootar *et al*, 1978; Reddy *et al*, 1997; Plamondon *et al*, 2007).

ACKNOWLEDGEMENTS

The authors thank the attending physicians for managing the reported case.

REFERENCES

- Drancourt M, Oules O, Bouche V, Peloux Y. Two cases of *Actinomyces pyogenes* infection in humans. *Eur J Clin Microbiol Infect Dis* 1993; 12: 55-7.
- Gahrn-Hansen B, Frederiksen W. Human infections with *Actinomyces pyogenes* (*Corynebacterium pyogenes*). *Diagn Microbiol Infect Dis* 1992; 15: 349-54.
- Halder SM, O'Gara P. Infective endocarditis. In: Fuster V, Walsh RA, Harrington RA, eds. *Hurst's the heart*. 13th ed. New York: McGrawHill, 2011: 1940-69.
- Heiro M, Nikoskelainen J, Engblom E, Kotilainen E, Marttila R, Kotilainen P. Neurologic manifestations of infective endocarditis: a 17-year experience in a teaching hospital in Finland. *Arch Intern Med* 2000; 160: 2781-7.
- Hermida Amejeiras A, Romero Jung P, Cabarcos Ortiz De Barrón A, Treviño Castallo M. One case of pneumonia with *Arcanobacterium pyogenes*. *An Med Interna* 2004; 21: 334-6.
- Ide L, Decostere A, Stuer A, *et al*. *Arcanobacterium pyogenes* spondylodiscitis in a veterinary surgeon: a plea for cooperation between medical and veterinary microbiologists in identification of causal agents of zoonotic infections. *Clin Microbiol Newsl* 2006; 28: 163-7.
- Jootar P, Gherunpong V, Saitanu K. *Corynebacterium pyogenes* endocarditis report of a case with necropsy and review of the literature. *J Med Assoc Thai* 1978; 61: 596-601.
- Kavitha K, Latha R, Udayashankar C, Jayanthi K, Oudeacoumar P. Three cases of *Arcanobacterium pyogenes* -associated soft tissue infection. *J Med Microbiol* 2010; 59: 736-9.
- Kotrajaras R, Tagami H. *Corynebacterium pyogenes*. Its pathogenic mechanism in epidemic leg ulcers in Thailand. *Int J Dermatol* 1987; 26: 45-50.
- Levy CE, Pedro RJ, Von Nowakowski A, Holanda LM, Brocchi M, Ramo MC. *Arcanobacterium pyogenes* sepsis in farmer, Brazil. *Emerg Infect Dis* 2009; 15: 1131-2.
- Lipsky BA, Goldberger AC, Tompkins LS, Plorde JJ. Infections caused by nondiphtheria corynebacteria. *Rev Infect Dis* 1982; 4: 1220-35.
- Meyer DK, Reboli AC. Other Coryneform bacteria and Rhodococci. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas and Bennett's principles and practice of infectious diseases*. 7th ed. Philadelphia: Saunders Elsevier, 2009: 2700-1.
- Nicholson P, Kiely P, Street J, Mahalingum K. Septic arthritis due to *Actinomyces pyogenes*. *Injury* 1998; 29: 640-2.
- Plamondon M, Martinez G, Raynal L, Touchette M, Valiquette L. A fatal case of *Arcanobacterium pyogenes* endocarditis in a man with no identified animal contact: case report and review of the literature. *Eur J Clin Microbiol Infect Dis* 2007; 26: 663-6.
- Ramos CP, Foster G, Collins MD. Phylogenetic analysis of the genus *Actinomyces* based on 16S rRNA gene sequences: description of *Arcanobacterium phocae* sp. nov., *Arcanobacterium bernardiae* comb. nov., and *Arcanobacterium pyogenes* comb. nov. *Int J Syst Bacteriol* 1997; 47: 46-53.
- Reddy I, Ferguson DA Jr, Sarubbi FA. Endocarditis due to *Actinomyces pyogenes*. *Clin Infect Dis* 1997; 25: 1476-7.
- Yeruham I, Orgad U, Avidar Y, Elad D. Pituitary abscess and high urea concentration as causes of neurological signs in a cow: A retrospective analysis and literature review. *Revue Méd Vét* 2002; 12: 829-31.