Subacute Infective Endocarditis Caused by *Corynebacterium diphtheriae* : A Case Report

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Abstract

The authors report an 11-year-old boy with septicemia and subacute infective endocarditis due to toxigenic-*Corynebacterium diphtheriae*. The patient had underlying congenital heart disease and incomplete immunization. He presented with fever, epistaxis and congestive heart failure. He received high-dose penicillin therapy and diphtheria antitoxin with clinical improvement. While he was receiving a high dose of penicillin for 1 month he developed a generalized tonic clonic seizure. A computerized tomogram revealed intracerebral and ventricular hemorrhage. Craniotomy with blood clot removal and ventriculostomy drainage were done. He died 2 days later from brain death and cardiovascular failure.

Key word : *Corynebacterium Diphtheriae*, Endocarditis

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Corynebacterium diphtheriae is an organism of toxin induced classic diptheria that is commonly manifested by a localized inflammatory lesion, usually in the upper respiratory tract or in the skin. Invasive disease due to *C. diphtheriae*, first described by Howard in 1893, is a rare event[1]. Endocarditis caused by

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this organism is also rare. Forty eight cases of endocarditis have been reported since 1950, mainly on nontoxigenic *C. diphtheriae*(2). Widespread immunization probably explains the reduction of cases and toxigenic strains isolated. The authors report a case of fatal mitral-valve endocarditis due to toxigenic strain of *C. diphtheriae* who died from ruptured mycotic aneurysm despite high dose penicillin therapy and diphtheria antitoxin.

CASE REPORT

An 11-year-old boy presented with fever, dyspnea and cough for 2 months. On the 7th day of illness he was admitted to a provincial hospital. Physical examination showed his weight to be 28.5 kg, body temperature 38°C, respiratory rate 30/min, heart rate 120/min and blood pressure 90/60 mmHg. Heart examination showed a pan systolic murmur grade IV at the left parasternal border. Chest examination was normal as was the remaining physical examination. Initial laboratory tests revealed a hemoglobin of 8 g/dl, hematocrit of 24 per cent, white blood count of 17,300/mm^3 (82% polymorphonuclear cells, 10% lymphocytes, 8% monocytes) and a platelet count of 358,000/mm^3, reticulocyte count of 1.4 per cent, G6PD was normal and hemoglobin typing was A_2A. Urine analysis showed a specific gravity of 1.017, pH5, blood 2+, Wbc 2-3/high power field (HPF), Rbc 10-15/HPF and epithelium 1-2/HPF. Blood chemistry was normal. A chest roentgenogram (CXR) revealed cardiomegaly without infiltration. His physician suspected congestive heart failure and infective endocarditis. He improved symptomatically after intravenous penicillin G 300,000 u/kg/day, gentamicin, diuretic, oral lanoxin and blood transfusion. Hematocrit was raised to 30 per cent after transfusion. He was afebrile within 1 day and discharged within 1 week with the diagnosis of congenital heart disease, congestive heart failure and respiratory tract infection with home medication of amoxycillin, diuretic and lanoxin. He was lost to follow-up after discharge from the hospital. Two of 3 specimens of his blood culture identified gram-positive bacilli and were sent for further identification at the National Institute of Health, Thai Ministry of Public Health. It grew toxin producing *Corynbacterium diphtheriae*. The patient returned to the provincial hospital 1 month later with afebrile and dyspnea (functional class II) and was referred to our hospital for evaluation of echocardiogram which showed a small perimembranous ventricular septal defect (VSD) with membranous aneurysm, mild to moderate mitral valve regurgitation and no vegetation. The physician gave lanoxin and supportive treatment. He was lost to follow-up again. Three days preceding his admission to hospital, he developed a high grade fever, epistaxis, nausea, vomiting, dyspnea and bloody urine. He had been sick since the initial visit and complained of fatigue and poor appetite. His past history was significant in that his immunization was incomplete and there were immigrants from Myanmar and Cambodia staying near his home. Physical examination showed his weight to be 27.7 kg, body temperature 38.3°C, respiratory rate 32/min, heart rate 120/min and blood pressure 105/65 mmHg. There were blood clots in both nostrils, heart examination showed a pan systolic murmur grade IV at the left lower parasternal border. The liver was palpated 2 cm below the costal margin with a 14 cm span. There were no petichiae of the skin, subungual area, conjunctiva or retina. No Osler nodes, Janeway lesions or other skin lesions were present. The rest of the physical examination including examination of the throat and chest were normal. Initial laboratory tests revealed a hemoglobin of 8 g/dl, hematocrit of 23 per cent, white blood count of 14,300/mm^3 (84% polymorphonuclear cells, 5% lymphocytes, 11% monocytes) and a platelet count of 171,000 /mm^3. Urine analysis showed a specific gravity of 1.020, pH 6.5, protein 3+, ketone 2+, blood 4+, Wbc 3-5/HPF, Rbc 15-20/HPF and epithelium 0-1/HPF. Blood chemistry showed BUN/Cr 32.4/1.42 mg/dl, and liver function tests were normal except for hypoalbuminemia 2.6 g/dl. A chest roentgenogram revealed cardiomegaly with increased perihilar marking and no localized infiltration. Erythrocyte sedimentation rate (ESR) was 140 mm/hour, echocardiogram revealed small VSD, vegetation at the anterior mitral valve leaflet and mitral valve prolapsed with regurgitation, there was left atrial and left ventricular enlargement. Packed red cell transfusion, diuretic, lanoxin and dopamine 5 micrograms/kg/minute were given including salt and water restriction to support congestive heart failure. He was put on intravenous penicillin G 400,000 u/kg/day. One of 3 blood cultures grew Corynbacterium species 3 days after admission. The authors sent a specimen to the National Institute of Health for further identification and it confirmed the same result of the blood culture which was seen 6 weeks previously, that grew toxin

producing *Corynbacterium diphtheriae*. The isolate was not biotyped and sensitive to penicillin and ampicillin. Diphtheria antitoxin 80,000 u/kg/day was given intravenously. His temperature declined gradually and he was afebrile within 8 days. On the 10th day of admission he developed epistaxis from both nostrils. Hematocrit dropped to 22 per cent. Packed red cell was transfused and the hematocrit rose to 27 per cent. Laboratory test showed a normal platelet count and coagulogram. The ear, nose and throat (ENT) department was consulted for anterior packing. After the bleeding was controlled, the left and right nasal cavity were evaluated and bleeding was found from the floor of the nasal septum without a white patch or mass. Bleeding was stopped by coagulation of trichloro acetic acid (TCA) at the left nasal septum and floor. Bacteriologic studies of the nose and throat revealed *S. aureus* and Acinetobacter spp. No diphtheria was identified. He improved symptomatically gradually. One month after admission he developed headache, vomiting, a generalized tonic clonic convulsion and required mechanical ventilation and mannitol intravenously to decrease the intracranial pressure and marked deterioration of his mental status. A computerized tomogram (CT) of the brain showed a right frontoparietal hemorrhage 5 x 3 cm in size, intraventricular hemorrhage, hydrocephalus and diffuse brain edema. An emergency craniotomy with blood removal and ventriculostomy drainge was done. Findings on operation were bloody CSF, sub cortical hematoma at the right frontoparietal area and no definite abnormal vessel was seen. After operation he developed pneumonia and urinary tract infection and died 2 days later from brain death and circulatory failure. Heart blood culture revealed no growth. Lung biopsy showed focal atelectasis and interstitial infiltration of alveoli. Liver biopsy showed mild fatty change and vascular congestion.

DISCUSSION

C. diphtheriae is an uncommon cause of bacteremia and endocarditis as only 48 cases have been recorded since 1950 and 32 of these have survived[2]. Of these, 18 cases occurred in children age below 15 years old. The cases reported before 1950 nearly all had invasive strains which were toxin-producing, whereas, the cases reported after 1950, had nontoxigenic strains of *C. diphtheriae* (41/48) which is more common than the toxin-producing strain (7/48)[2]. The last case of toxin-producing *C. diphtheriae* endocarditis was reported in 1996[3]. In addition to the presented patient 8 cases of toxin-producing *C. diphtheriae* have been reported since 1950 with 4 deaths. Of these, 3 were isolated from patients with no underly ing heart disease[3-5], 2 with rheumatic heart diseases [6,7], 2 with cyanotic heart diseases[8,9] and 1 with VSD. Four of the toxin-producing organisms were not biotyped, and of the remainder 2 were of biovar gravis, 1 biovar mitis and 1 biovar intermedius[2]. Full immunization against diphtheria may protect individuals from the toxic effects of *C. diphtheriae* but does not prevent invasion of the blood stream. Blood stream invasion is not related to the toxigenic character of the strain, and the mechanisms of pathogenicity of nontoxigenic strains of *C. diptheriae* are unknown[10]. Widespread immunization explains the reduction of case and toxigenic strains isolated. The presented patient had incomplete immunization that can explain why a toxigenic strain of *C. diphtheriae* was found again. The diagnosis of endocarditis was made in all cases by the isolation of the organism from the blood stream as well as a clinical presentation consistent with endocarditis. Mitral valve involvement in the presented patient is similar to another report that *C. diphtheriae* seem to have a predilection for left sided valves and tend to form large valvular vegetations, septic emboli and aneurysms that can explain the very high morbidity and mortality from *C. diphtheriae* endocarditis[2]. The presented patient died from intracranial hemorrhage that might have been cause by mycotic aneurysm rupture which can occur after symptomatical improvement and the blood culture was negative because the organism was seen on gram stain of resected material[2] and the blood vessel was destroyed from diphtheria toxin. The pitfalls of delayed diagnosis of endocarditis in this patient were because Corynebacterium spp isolated in blood cultures are often classified as contaminants and the organism is a rare cause of endocarditis which resulted in missing the opportunity to administer antibiotics from the beginning which may have produced a better outcome. Almost all patients who have survived were treated with a combination of intravenous penicillin and aminoglycoside[2]. There have been 4 reports of successful therapy using penicillin alone[10-13].

In conclusion, endocarditis caused by *C. diphtheriae* is uncommon. The presented case emphasize the importance of identifying Corynebacterium

isolates from sterile sites which are a potential cause of morbidity and mortality that should be carefully interpreted related to other clinical information. A combination of intravenous penicillin and aminoglycoside is recommended as the first line drugs for treatment of *C. diphtheriae* endocarditis.

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รายงานผู้ป่วยลิ้นหัวใจติดเชื้อรองเฉียบพลันจากเชื้อ *Corynebacterium diphtheriae*

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รายงานผู้ป่วยเด็กชายอายุ 11 ปีที่มาด้วยอาการติดเชื้อในกระแสเลือดและลิ้นหัวใจติดเชื้อรองเฉียบพลัน จากเชื้อ *Corynebacterium diphtheriae* ที่สร้างท็อกซิน ผู้ป่วยมีโรคหัวใจผิดปกติแต่กำเนิดเป็นโรคประจำตัวและได้รับวัคซีนไม่ครบตามเกณฑ์อายุ ครั้งนี้มาด้วยอาการไข้ เลือดกำเดาไหลและหัวใจล้มเหลว ได้รับการรักษาด้วยยาเพนนิซิลลินขนาดสูงและสารต้านท็อกซินต่อเชื้อ *diphtheria* จนอาการดีขึ้น ระหว่างที่ได้รับยาเพนนิซิลลินขนาดสูงมานาน 1 เดือน ผู้ป่วยเกิดอาการชักเกร็งกระตุกทั่วตัว ได้ทำเอ็กซเรย์คอมพิวเตอร์สมองพบว่ามีเลือดออกในสมองและช่องเวนตริเคิล ได้รับการผ่าตัดนำก้อนเลือดออกจากสมองและใส่สายระบายน้ำจากเวนตริเคิล แต่ผู้ป่วยเสียชีวิตอีก 2 วันต่อมาจากสมองตายและระบบการไหลเวียนของโลหิตล้มเหลว

คำสำคัญ : เชื้อ *Corynebacterium diphtheriae*, ลิ้นหัวใจติดเชื้อ

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