



Original Article

Invasive Infections of *Aggregatibacter (Actinobacillus) Actinomycetemcomitans*

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BACKGROUND/PURPOSE: *Aggregatibacter (Actinobacillus) actinomycetemcomitans*, part of the normal flora of the mouth, is frequently found in human periodontal cultures and is an important pathogen causing various invasive infections, particularly infective endocarditis. In this study, we describe the clinical course and outcome of patients with *A. actinomycetemcomitans* infection.

METHODS: All patients suffering invasive *A. actinomycetemcomitans* infections at the National Taiwan University Hospital from January 1985 to December 2004 were included in this study. Relevant data regarding clinical presentation, antimicrobial treatment and outcome of these patients were analyzed.

RESULTS: During the study period, there were 11 patients with invasive *A. actinomycetemcomitans* infections, including eight patients with infective endocarditis, one with osteonecrosis and two with pneumonia and chest wall lesions. Among the patients with infective endocarditis, four had prosthetic valve replacement, four suffered from rheumatic heart disease and one had undergone surgical repair of ventricular septal defect. Lesions in the oral cavity were the probable portals of entry of the microorganism, and included carious teeth, periodontitis or radiotherapy of the ear–nose–throat field, and were noted in nine patients. Transthoracic echocardiography and/or transesophageal echocardiography were performed

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on the patients with probable infective endocarditis but growth was demonstrated in only four of these patients. Blood culture yielded *A. actinomycetemcomitans* after prolonged incubation. Three isolates were resistant to penicillin and two of these were also resistant to ampicillin.

CONCLUSION: The diagnosis of invasive *A. actinomycetemcomitans* infection was delayed due to the indolent clinical course, non-specific presentation and slow growth of the organism. Antibiotic therapy using amoxicillin/clavulanic acid, ampicillin, ampicillin/sulbactam, ceftriaxone, clindamycin, cefotaxime, or levofloxacin was successful in all patients. None of the patients demonstrated recurrence of infection 2–36 months following treatment.

KEYWORDS: *Aggregatibacter (Actinobacillus) actinomycetemcomitans*, invasive infection, Taiwan

Introduction

Aggregatibacter (Actinobacillus) actinomycetemcomitans is a slow-growing, capnophilic Gram-negative coccobacillus, first described by Klinger in 1912.¹ The species was so named for its close association with the ray fungus *Actinomyces israelii*.¹ The first human case was described by Thjotta and Sydnes in 1951.² Endocarditis caused by this organism was first reported by Vallee and Gaillard in 1953.³ In 1962 King and Tatum reported 32 well-documented *A. actinomycetemcomitans* infections, and 23 of these patients had endocarditis.⁴ In 1959, Heinrich and Pulverer demonstrated that *A. actinomycetemcomitans* was part of the normal mouth flora.⁵ It is commonly found in human periodontal cultures and its pathogenic role in periodontitis is well established.⁶ *A. actinomycetemcomitans* is a member of the HACEK group of bacteria together with *Haemophilus influenzae*, *H. parainfluenzae*, *H. aphrophilus*, *H. paraphrophilus*, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella kingae*. They are all small Gram-negative bacteria, frequent colonizers of the oral cavity, slow growing and capnophilic although these bacteria are not phylogenetically related. Guntheroth in 1984 and Roberts in 1999 described that dental infection, dental treatments, or general dental hygiene procedures may be the portal of entry for these bacteria.^{7,8}

All HACEK microorganisms cause 3% of all cases of infective endocarditis (IE) and among them, *A. actinomycetemcomitans* is the most frequently involved.⁹ This species is easily isolated, although it requires a prolonged incubation time. Blood cultures were positive in 90% of cases of *A. actinomycetemcomitans* infection when incubated for longer than 8 days.⁹ According to a review by Paturol et al, these microbes were found in only 55.5% of patients who received

echocardiography.¹⁰ Previous studies have uncovered several characteristics of IE caused by *A. actinomycetemcomitans* including intermittent fever, weight loss, peripheral signs of endocarditis, anemia and microscopic hematuria.^{6,9,10} Besides IE, the pathogen may cause soft tissue abscess, periodontitis, chest wall destruction and infection of other rare sites.^{11–13} This report describes 11 cases of invasive *A. actinomycetemcomitans* infection which were treated at National Taiwan University Hospital from January 1985 to December 2004.

Methods

Bacterial isolates and antimicrobial susceptibility testing

All the isolates of *A. actinomycetemcomitans* were Gram-negative coccobacilli with positive catalase reactions. These isolates were identified at a species level by both conventional biochemical methods and using the *Neisseria-Haemophilus* Identification (NHI) card (Vitek, Biomérieux, Las Halles, France). Antimicrobial susceptibility of these isolates for penicillin, ampicillin, amoxicillin-clavulanate, ampicillin-sulbactam, ceftriaxone and clindamycin were determined by the disk diffusion method using Hueller-Hinton agar supplemented with 5% sheep blood, at 5% CO₂ for 2 days in accordance with the guidelines recommended by the Clinical and Laboratory Standards Institute.^{14,15}

Patients

Invasive infection due to *A. actinomycetemcomitans* was defined as isolation of the organism from a normally sterile body site. A total of 11 patients with invasive *A. actinomycetemcomitans* infections were identified from January 1985 to December 2004. These patients were treated at National

Taiwan University Hospital, a university-affiliated hospital with a 2,000 bed capacity located in northern Taiwan. Data on demographic characteristics, underlying disease, recent hospitalization in the 3 months prior to presentation, clinical manifestations of the patients, antimicrobial therapy and outcome were retrospectively analyzed.

Definitions

All included patients fulfilled the modified Duke criteria for definite or possible IE, as proposed by Li et al.¹⁶ Renal dysfunction was defined as a serum creatinine level greater than 1.5 mg/dL (133 μM), and liver dysfunction as elevation of liver enzymes by more than twice the upper limit of normal (aspartate aminotransferase >74 U/L, alanine aminotransferase >82 U/L). Neurological complications included cerebral emboli or ischemic stroke, mycotic aneurysm with or without cerebral hemorrhage, and cerebral abscess. Renal complications included acute renal failure, defined as an increase of serum creatinine by more than 0.5 mg/dL (44 μM) upon admission, or glomerulonephritis. Embolic complications included splenic infarct or abscess, coronary embolism with myocardial infarction, pulmonary embolism and peripheral limb embolization, but cerebral embolization was not included. Cardiac complications included new atrioventricular conduction block, intracardiac abscess and heart failure.

Results

Eleven patients with invasive infections due to *A. actinomycetemcomitans*, including five previously reported cases,^{13,17} were identified in our hospital from 1985 to 2004 (Table). Eight of these patients had *A. actinomycetemcomitans* endocarditis. One patient had osteonecrosis and the other two patients presented with pneumonia and chest wall mass lesions.

Among the eight patients with *A. actinomycetemcomitans* endocarditis, there were five men and three women with a mean age of 46 years. Four had rheumatic heart disease (3 had prosthetic valve replacement and 1 had a ventricular septal defect post prosthetic valve replacement). The most common presenting symptoms were fever (8/8) and cough (6/8), and the duration of symptoms before diagnosis varied from 2 weeks to 9 months. Hematuria was noted in five patients and anemia in seven patients. Only one patient

had leukocytosis. Transthoracic echocardiography (TTE) and/or transesophageal echocardiography (TEE) were performed on the patients with probable IE but bacteria were demonstrated in only four of these patients (3 in mitral valves and 1 in aortic valve). Two mitral valve lesions were detected by both TTE and TEE (Patients 8 and 9) and one mitral (Patient 2) and one aortic valve (Patient 10) lesion was demonstrated by TTE (TEE was not done in these 2 patients). Blood culture was positive from the 7th day to the 6th week of incubation. Three isolates were resistant to penicillin and two of were resistant to ampicillin. All isolates were susceptible to amoxicillin-clavulanate, ampicillin-sulbactam, ceftriaxone and clindamycin. Diagnosis was delayed due to the indolent clinical course, nonspecific presentation and the slow growth of the organism.

Both patients with pneumonia and chest wall mass lesions due to *A. actinomycetemcomitans* (Patients 6 and 11) had dental problems and one (Patient 6) had an atrial septal defect type II post patch repair 18 years ago. The TTE showed no bacterial growth in both cases. Patient 5 had *A. actinomycetemcomitans* infection in the left mandibular osteoradionecrosis (ORN) with skin fistula formation. She had a history of nasopharyngeal carcinoma post-radiotherapy in 1988. In December 2002, pain and swelling was found at the left periauricular area. Incision and drainage was done and the pus yielded *A. actinomycetemcomitans*. She received clindamycin for 1 week and hyperbaric oxygen therapy 40 times over 2 months. The lesions healed and no recurrence was noted until recently.

All patients responded to treatments and were cured after intravenous or oral antibiotic therapy, which included amoxicillin/clavulanic acid (18.2%), ampicillin (9.1%), ampicillin/sulbactam (9.1%), gentamicin (18.2%), ceftriaxone (27.3%), clindamycin (9.1%), cefotaxime (9.1%) and levofloxacin (9.1%). All patients were free of evidence of recurrence throughout the follow up periods ranging from 2 to 24 months.

Discussion

Patients 6 and 11 had *A. actinomycetemcomitans* pneumonia and chest wall infection, which was similar to a previously reported case.¹² Patient 6 had underlying cardiopathy and both Patients 6 and 11 had dental caries. Underlying cardiopathy in patients with *A. actinomycetemcomitans* infection

Table. Clinical and echocardiographic characteristics, therapy and outcome in 11 patients with invasive *Aggregatibacter (Actinobacillus) actinomycetemcomitans* infection, 1985–2004

Case	Age (yr)/sex	Year	Type of infection	Predisposing factors	Dental status	Duration of signs before diagnosis	Delay of collect blood culture	Blood culture	Valve	Echo-cardiography	Under-lying disease	Medical treatment	Surgical treatment	Duration of medical treatment (wk)	Outcome	Reference
1	67/F	2000	IE	RHD, prosthetic aortic valve	Caries periodontitis	9 mo	6 wk	3/3	-	TTE (-), TEE (-)	-	AMX/CLV	-	5	Recovered	
2	33/M	2002	IE	HOCMP	Caries	3 wk	2 wk	2/3	Mitral valve	TTE (+)	-	AMP, CTX	-	7	Recovered	
3	52/M	2001	IE	Trans-sphenoid adenomectomy	Caries periodontitis	3 wk	-	7/7	-	TTE (-), TEE (-)	-	CTX	-	4	Recovered	
4	58/M	2004	IE	RHD	Periodontitis	4 wk	-	2/2	-	TTE (-), TEE (-)	CHF	CFT LEV	-	5	Recovered	
5	35/F	2000	Left periauricular ORN	NPC, ORN	ORN	4 mo	2 wk	1/1	-	-	-	Clin	I & D	1	Recovered	
6	56/F	2004	Pneumonia with chest wall mass	ASD	Caries with retained root	2 wk	-	1/1	-	TTE (-)	-	AMP/STB AMX/CLV	Excision	4	Recovered	
7	51/F	1985	IE	MVP	-	1 mo	9 d	10/10	-	TTE (-)	-	PCN, GM	-	6	Recovered	[17]
8	42/F	1988	IE	RHD, prosthetic mitral valve	Caries	2 mo	7 d	3/3	Mitral valve	TTE (+), TEE (+)	-	CFM, TOB, ERT	-	5	Recovered	[17]
9	42/M	1989	IE	RHD, prosthetic mitral, aortic valves	Caries	2 mo	7 d	3/3	Mitral valve	TTE (+), TEE (+)	CHF, Renal infarction	CHL, GM, AZT	-	6	Recovered	[17]
10	26/M	1989	IE	VSD, prosthetic aortic valve	-	2 wk	4 d	6/6	Aortic valve	TTE (+)	-	PCN, GM, CTX, Clin	-	6	Recovered	[17]
11	67/M	1990	Pneumonia with chest wall and rib destruction	-	Marginal gingivitis	7 mo	-	-	-	TTE (-)	-	PCN, AMX	-	12	Recovered	[13]

AMP = ampicillin; AMX = amoxicillin; ASD = atrial septal defect; AZT = aztreonam; BC = blood culture; CFM = cefamandole; CFT = cefotaxime; CHF = congestive heart failure; CHL = chloramphenicol; Clin = clindamycin; CLV = clavulanic acid; CTX = ceftriaxone; GM = gentamicin; HOCMP = hypertrophic obstructive cardiomyopathy; I & D = incision and drainage; ERT = erythromycin; F = female; IE = infective endocarditis; LEV = levofloxacin; M = male; NPC = nasopharyngeal carcinoma; ORN = osteoradionecrosis; PCN = Penicillin; RHD = rheumatic heart disease; STB = sulbactam; TEE = transthoracic echocardiography; TTE = transthoracic echocardiography; TOB = tobramycin; VSD = ventricular septal defect.

was frequently found not only in patients with endocarditis but also in patients with other infection foci. Only a few pathogens cause concomitant infection of the lung and the soft tissue of the chest wall over the pneumonic area, these include *Actinomyces* and *Mycobacterium tuberculosis*. The infection may present with a diffuse alveolar-filling process, occasionally extending into the pleural space or chest wall. This disease pattern is easily misinterpreted as malignancy initially. In this study, we also reported a patient with left mandibular ORN (Patient 5) with skin fistula formation. The infection was treated successfully with oral clindamycin and hyperbaric oxygen therapy. Although mixed flora was reported in mandibular ORN, *A. actinomycetemcomitans* was frequently found.¹⁸ *A. actinomycetemcomitans* infection should be included as a differential etiology of mandibular ORN superimposed infection.

Paturel et al reviewed 102 cases of *A. actinomycetemcomitans* endocarditis and found that 73 patients were male and 29 were female.¹⁰ Fourteen of the female patients (50%) contracted the infection between the ages of 50 and 70 years, and 53% of men developed endocarditis between the ages of 40 and 60 years. The age range of our patients was 26–67 years, similar to the patients reported by Paturel et al. Of the 102 cases, 27 had prosthetic valves. In their study, intermittent fever was observed in all patients, and weight loss and peripheral signs of endocarditis were also common. Anemia and microscopic hematuria were frequent findings and our patients also presented with symptoms of fever, coughing and hematuria. According to Paturel et al the disease was insidious, with mean symptom duration of 13 weeks before diagnosis, as confirmed by blood cultures incubated for greater than 5 days. In our results, the duration of symptoms before diagnosis varied from 2 weeks to 9 months. Paturel et al also reported that the aortic valve was most commonly involved; however, in our study the mitral valve was more commonly involved. Complications occurred in 63% of patients from the study conducted by Paturel et al, with emboli being the most common, but no complications were evident in our patients.

The oral cavity is considered the most common portal of entry for *A. actinomycetemcomitans* infection. This microorganism is part of the normal oral flora and can be found in 25–30% of adults,^{19,20} and in 78% of the healthy Chinese population.²¹ *A. actinomycetemcomitans* is strongly

associated with periodontopathy, especially juvenile periodontitis, and can cause endocarditis, bacteremia and polymicrobial wound infections.⁹ In 1998, Storm et al²² reported that dental treatment procedures were not a risk factor for IE. The bacteria may gain entry to the vascular system through dental procedures, dental infections, daily oral hygiene procedures or mastication.^{7,8} Among the 102 patients reviewed by Paturel et al,¹⁰ 43 had dental disease including carious teeth, periodontitis or retained roots. In our study, 81.8% (9/11) had an underlying dental disease. The finding of a high prevalence rate of dental disease may have been due to the awareness of its relationship to *A. actinomycetemcomitans* infection, endocarditis, pneumonia and ORN with superimposed infection. A high colonization rate of *A. actinomycetemcomitans* in Taiwan may contribute to these infections.^{23,24}

The optimal antimicrobial therapy for invasive *A. actinomycetemcomitans* infection is not known. This organism usually has *in vitro* susceptibility to cephalosporin, aminoglycosides, fluoroquinolones and tetracycline. Susceptibility to ampicillin and penicillin G is variable. It is generally resistant to vancomycin, erythromycin and clindamycin.^{25–28} Though a fluoroquinolone showed superior effects against *A. actinomycetemcomitans* in a previous study,²⁸ intravenous ampicillin or amoxicillin with gentamicin should be the treatment of choice for *A. actinomycetemcomitans* infection.²⁹ According to the American Heart Association, the duration of treatment should be 4 weeks for native valve infection and 6 weeks for prosthetic valve endocarditis.²⁹ Surgical treatment should be reserved for treatment failure, persistent infection, or complications. Amoxicillin can be expected to be effective as endocarditis prophylaxis in patients harboring *A. actinomycetemcomitans* who have underlying cardiopathy and undergo dental procedures.³⁰

Analysis of this case series suggests that underlying dental disease and cardiopathy are risk factors for *A. actinomycetemcomitans* endocarditis. The relationship between the harboring of *A. actinomycetemcomitans* in the oral cavity and the development of invasive *A. actinomycetemcomitans* infection remains unclear. Due to the low incidence of *A. actinomycetemcomitans* infection, it is not easy to evaluate the efficacy of prophylactic antibiotics prior to dental treatment.³¹ The frequently insidious initial presentation of *A. actinomycetemcomitans* infection and delayed diagnosis

also complicates analysis of the need for prophylactic antibiotics. The delay in diagnosis is exaggerated by the slow growth of this organism. Brouqui et al reported the mean duration of blood culture before detection of growth was 7.1 days.²⁹ Thus, a longer incubation time should be requested for patients with prolonged constitutional symptoms, including fever, chills, malaise, anorexia and weight loss. Polymerase chain reaction amplification of universal bacterial loci and subsequent sequencing for identification of possible causal microorganisms may be helpful.³²

The clinical presentation of *A. actinomycetemcomitans* is usually insidious and the fastidious growth of the organism almost always leads to delayed microbiological diagnosis. In patients with underlying cardiopathy, or dental disease with a subacute or chronic illness, *A. actinomycetemcomitans* endocarditis should be considered. Diagnosis is based on blood cultures but a prolonged incubation period should be requested. Ampicillin or amoxicillin with gentamicin combination could be the therapy of choice, but isolation of the organism and *in vitro* drug sensitivity testing is very important to appropriate management. Prolonged treatment is required according to the clinical manifestations.

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