Spontaneous Pyogenic Spondylitis and Possible Infective Endocarditis Caused by Aggregatibacter actinomycetemcomitans

Naoko Yukihira¹, Hiroshi Hori², Takeshi Yamashita², Ai Kawamura², Takahiko Fukuchi² and Hitoshi Sugawara²

Abstract:
Aggregatibacter actinomycetemcomitans, an etiological agent associated with periodontitis, endocarditis, and other infections, has rarely been implicated in spondylitis. A 70-year-old man with aortic valve replacement presented with a 4-month history of lower back pain and was diagnosed with spondylitis. Prolonged incubation of blood cultures and a biopsy yielded A. actinomycetemcomitans. Concurrent infective endocarditis (IE) was probable considering the infectious organism and the patients’ prosthetic valve. The patient was treated with ceftriaxone and recovered well. Pyogenic spondylitis with possible concurrent IE may be caused by A. actinomycetemcomitans. Extended incubation and repeated cultures should be considered if Haemophilus spp., Aggregatibacter spp., Cardiobacterium spp, Eikenella spp, and Kingella spp. (HACEK) infection is suspected.

Key words: Aggregatibacter actinomycetemcomitans, pyogenic spondylitis, infective endocarditis

(Intern Med 60: 1621-1625, 2021)
(DOI: 10.2169/internalmedicine.5103-20)

Introduction
Aggregatibacter actinomycetemcomitans belongs to the HACEK (Haemophilus spp., Aggregatibacter spp, Cardiobacterium spp, Eikenella spp, and Kingella spp.) group of bacteria, which are commensal microbiota that colonize the oral-pharyngeal region in humans. The pathobiont A. actinomycetemcomitans has been implicated in periodontitis, endocarditis, and other infections (1); however, its association with pyogenic spondylitis has rarely been reported.

We herein report a rare case in which A. actinomycetemcomitans infection developed concurrently with pyogenic spondylitis and possible infective endocarditis (IE), as diagnosed by the modified Duke Criteria (2).

Case Report
A 70-year-old man with a history of aortic regurgitation that had been treated with aortic valve replacement at 62 years old presented to the emergency department with lower back pain. He had a four-month history of pain prior to presentation. Previously, he had visited another hospital and been treated with analgesics, which provided mild, short-term symptomatic relief. In the absence of a specific diagnosis, the patient continued to experience pain in the proceeding months but was not marked by a fever, chills, or night sweats. Three weeks before admission, he was brought to our hospital by ambulance with recurring back pain, treated with diclofenac, and discharged. However, the patient was readmitted to our hospital as the chronic pain increased in severity and he became unable to walk or stand.

Upon presentation, the patient was alert, and his vital signs were as follows: temperature of 35.8°C, blood pressure of 107/69 mmHg, regular heart rate of 70 beats/min, and respiratory rate of 16 breaths/min. A physical examination revealed anemic conjunctiva, periodontitis, mechanical valve sounds, systolic murmur at apex, and L4-L5 tenderness. No
skin lesions or neurological symptoms were noted. Extensive periodontitis was confirmed by a dentist. Laboratory tests showed a white blood cell (WBC) count of 11,190/μL with 84% neutrophils, hemoglobin concentration of 8.0 g/dL, C-reactive protein (CRP) of 12.3 mg/dL, and an erythrocyte sedimentation rate (ESR) of 134 mm/h. Other results are shown in Table 1. His chest X-ray and electrocardiogram findings were unremarkable.

Computed tomography (CT) of his lumbar spine showed L5 end plate erosion (Fig. 1). No abscess formation was detected. Magnetic resonance imaging (MRI) revealed T1-weighted low-intensity and T2-weighted high-intensity regions at the L4-L5 disc (Fig. 2A, B). This region showed a high signal intensity on short tau inversion recovery (STIR) imaging (Fig. 2C). The radiographic findings were suggestive of spondylitis of the L4-L5 spinal segment, and a CT-guided needle biopsy was performed on hospital day 5. Empiric antibiotic therapy with ceftriaxone (2 g intravenously daily) and vancomycin (target trough level of 15 to 20 μg/mL) was administered after the biopsy.

The biopsy specimen subsequently yielded A. actinomycetemcomitans, which was also isolated from blood cultures obtained on admission and hospital day 5 (Fig. 3). Blood cultures required a prolonged incubation period of four days to more than one week before growth was detected and several more days to identify the organism. The culture of the biopsy specimen was positive on hospital day 13, and the organism was identified on hospital day 15. Antibiotic monotherapy was changed to ceftriaxone (2 g intravenously daily) based on an antimicrobial susceptibility test (Table 2). Since A. actinomycetemcomitans often causes endocarditis, transesophageal echocardiography (TEE) was performed, and neither vegetation nor destruction of valves were detected. Head MRI did not reveal findings suggestive of infectious lesions or a cerebral infarction. We also considered positron emission tomography (PET)-CT for the prosthetic valve endocarditis assessment but did not ultimately perform it because it was not covered by insurance.

Antibiotic therapy was continued for eight weeks after a negative blood culture was confirmed. This was in accordance with pyogenic spondylitis and IE treatment guidelines, which recommend six to eight weeks of antibiotic therapy (3-7). The patient responded well to treatment, and his

Table 1. Laboratory Data on Admission.

| CBC        | Chemistry          | Urinalysis |
|------------|--------------------|------------|
| WBC 11,190 μL | TP 7.7 g/dL | SG 1.020 |
| Neut 84.0 %  | Alb 2.8 g/dL | pH 5.5 |
| Lym 9.0 %    | AST 15 IU/L | Prot +/- |
| Mono 6.0 %   | ALT 16 IU/L | Glu - |
| Eosi 0.0 %   | LDH 192 IU/L | Uro +/- |
| Baso 1.0 %   | BUN 27 mg/dL | Bil - |
| RBC 270 *10^6/μL | Cr 1.05 mg/dL | Ket - |
| Hb 8.0 g/dL  | Na 136 mEq/L | Bld 2+ |
| Ht 24.2 %    | K 4.6 mEq/L | WBC - |
| MCV 89.6 fL  | Cl 106 mEq/L | |
| MCH 29.6 pg  | CRP 12.3 mg/dL | |
| PLT 43.1 *10^9/μL | ESR 134 mm/h | |

Alb: albumin, ALT: alanine aminotransferase, AST: aspartate aminotransferase, Baso: basophil, Bil: bilirubin, Bld: blood, BUN: blood urea nitrogen, CBC: complete blood count, Cl: chlorine, Cr: creatinine, CRP: C-reactive protein, Eosi: eosinophil, ESR: erythrocyte sedimentation rate, Glu: glucose, Hb: hemoglobin, Ht: hematocrit, K: potassium, Ket: ketone, LDH: lactate dehydrogenase, Lym: lymphocyte, MCH: mean corpuscular hemoglobin, MCV: mean corpuscular volume, Mono: monocyte, Na: sodium, Neut: neutrophil, PLT: platelet, Prot: protein, RBC: red blood cell, SG: specific gravity, TP: total protein, Uro: urobilinogen, WBC: white blood cell

Figure 1. A CT image of the lumbar spine shows an irregular erosion of the superior end plate of the L5 vertebra (arrow) and a possible fluid collection in the intervening L4/L5 disc space. Abscess formation is not detected. CT: computed tomography.
lower back pain was resolved. The CRP levels (0.09 mg/dL) and ESR (40 mm/h) were markedly reduced after 5 weeks of antibiotic therapy. The patient was transferred to another hospital to continue antibiotic therapy and rehabilitation after 63 days of admission. There was no evidence of infection or pain recurrence in the 12-month follow-up period.

**Discussion**

This report indicated that a patient with the insidious onset of back pain and a history of heart valve replacement and extensive dental disease concurrently developed pyo-

---

**Figure 2.** MRI of the lumbar spine. (A) T1-weighted image shows decreased signal intensity in the L4 and L5 vertebral bodies (arrows) and loss of end plate definition (arrow head). (B) T2-weighted image demonstrates increased signal in the L4/L5 interval disc space (arrow head). (C) Short tau inversion recovery image shows increased signal in the intervertebral disc space (arrow head) and adjacent L4 and L5 vertebral bodies (arrows). MRI: magnetic resonance imaging

**Figure 3.** Clinical course of the patient. Blood cultures were obtained on admission and hospital day 5, both of which were positive, with the organism identified as *A. actinomycetemcomitans* after a prolonged incubation period. A biopsy performed on hospital day 5 also yielded the same result. A follow-up culture obtained on day 14 was confirmed negative, and antibiotic therapy was continued for another eight weeks. The WBC, CRP, and ESR values showed marked declines after the antibiotic therapy was started. CRP: C-reactive protein, CTRX: ceftriaxone, ESR: erythrocyte sedimentation rate, VCM: vancomycin, WBC: white blood cell, wk: week
genic spondylitis and possible IE caused by A. actinomyce- 
etemcomitans. Extended incubation and repeated blood cul-
tures led to the detection and identification of the pathogenic
organism.

Three important clinical issues were noted from the clini-
cal course of this patient: 1) A. actinomyce-temcomitans may
cause pyogenic spondylitis, 2) Concurrent IE may have been
present in this A. actinomyce-temcomitans-mediated spondyl-
itis case, and 3) Infection was caused by A. actinomyce-tem-
comitans.

First, to our knowledge, only five cases of pyogenic spon-
dylitis caused by A. actinomyce-temcomitans have been re-
ported (8-12) (Table 3). This limited number of reports may
suggest a low frequency of infections. However, there may
be some unrecognized A. actinomyce-temcomitans spondylitis
cases. A systematic review of 14 studies including 1,008 pa-
tients with pyogenic spondylitis reported that the yield of
blood culture was 30-78%, while a CT-guided needle biopsy
together with open biopsy provided a yield of 47-100%, and overall,
the causative organism of pyogenic spondylitis was un-
known in up to 33% of cases (13). Slow growth of A. acti-
omyce-temcomitans is observed in standard culture media,
and isolation requires prolonged incubation (8, 9, 11). Typi-
cally, only a small fraction of blood culture bottles in pa-
tients with HACEK-linked IE demonstrate growth, and the
HACEK group is often associated with culture-negative IE
cases (5). Furthermore, capsular material from this organism
has been thought to be a potent mediator of bone resor-
pation (14). This implies that A. actinomyce-temcomitans can
cause bone infection in the setting of bacteremia. Thus,
there may be latent A. actinomyce-temcomitans spondylitis
cases considering the fastidious character and virulence of
the pathogen.

Second, concurrent IE may be present in patients with
pyogenic spondylitis caused by A. actinomyce-temcomitans.
In general, vertebral spondylitis is a complication of bactere-
emia, and associated endocarditis is seen in some patients. A
retrospective review including 91 cases of vertebral spon-
dylitis identified 28 patients (31%) with IE (15). Although
none of the five previously described cases of pyogenic
spondylitis due to A. actinomyce-temcomitans had an IE
complication (8-12), bacteremia caused by a HACEK organ-
ism is highly suggestive of IE. In addition, A. actinomyce-
comitans is most commonly involved in IE compared
to the rest of the HACEK group (16, 17). Although TEE
detected no apparent vegetation, IE was “possible” in this pa-
tient because the blood culture yielded A. actinomyce-
comitans, and the patient had a prosthetic valve, which satis-
fies one major (blood cultures) and one minor (predisposing
heart condition) modified Duke criterion (2). Furthermore,
the patient had two of the risk factors for A. actinomyce-
comitans endocarditis: a history of valve damage or valve
replacement surgery and dental disease (17). An evaluation
for concurrent IE is warranted even though the duration of
therapy for pyogenic spondylitis is adequate for the treat-
ment of IE in most cases (3-7). Patients with IE require ad-
ttional follow-up evaluations for valvular disease as well as
 prophylactic antibiotics for the prevention of subsequent IE.

Finally, the present patient’s clinical course suggested that
an extended incubation period and repeated sampling for
cultures would be required for the detection and identifica-
tion of A. actinomyce-temcomitans. In this patient, blood cul-
ture from the outpatient clinic was negative after seven days
of incubation. The second and third blood cultures were ob-
tained on admission and hospital day 5, respectively. The
third culture was positive for Gram-negative rods (GNRs)
after four-day incubation, while the second culture remained
negative at that point. We requested two-week incubation of

**Table 2. Susceptibility Test Results.**

| Antimicrobial agents | MIC (μg/mL) | Susceptibility |
|----------------------|------------|---------------|
| Ampicillin           | 1          | S             |
| Sulbactam/ampicillin | 1          | S             |
| Cefotaxime           | <0.25      | S             |
| Ceftriaxone          | <0.25      | S             |
| Meropenem            | <0.125     | S             |
| Clarithromycin       | 8          | S             |
| Levofloxacin         | <0.5       | S             |
| Sulfamethoxazole/trimethoprim | <10 | S         |

The identified organism was susceptible to all of the above listed antimicro-
bial agents. An “ID test HN20 rapid” panel and mass spectrometry were used
to identify the bacterial species. In addition, the MIC obtained by the broth
microdilution method and the CLSI (The Clinical & Laboratory Standards
Institute) M45 breakpoints were referred to in determining the susceptibility.
S: susceptible, MIC: minimum inhibitory concentration

**Table 3. Previously Reported Pyogenic A. actinomyce-temcomitans Spondylitis Cases.**

| Case | Age/Sex | Endocarditis | Complication | Treatment | Reference |
|------|---------|--------------|--------------|-----------|-----------|
| 1    | 45/M    | Evaluated but no evidence of IE | axillary abscess | ampicillin 6 weeks | 8         |
| 2    | 66/M    | Not mentioned | nil          | cefotaxime 2 weeks → amoxyllin 4 weeks | 9         |
| 3    | 65/M    | Not mentioned | nil          | antibiotic (detail unknown) 6 weeks | 10        |
| 4    | 72/M    | Evaluated but no evidence of IE | epidural abscess | debridement + ceftriaxone 6 weeks | 11        |
| 5    | 52/F    | Evaluated but no evidence of IE | nil          | ceftriaxone 4 weeks → levofloxacin 6 weeks | 12        |

F: female, M: male, IE: infective endocarditis
the second culture because the patient had a prosthetic heart valve and HACEK infection was possible. Later, the second culture proved positive for GNRs as well, requiring over a week of incubation time. The GNRs were subsequently identified as *A. actinomycetemcomitans*. Recent studies have shown that HACEK bacteria can be isolated using standard culture methods and media within a standard five-day incubation period (18, 19). However, our case required a longer incubation period and repeated cultures before growth was detected. A review of 102 IE cases also found that the mean duration to obtain a positive blood culture was 7.1 days, with a range of 1-15 days. Therefore, extended incubation and repeated blood cultures should be considered if a HACEK infection is suspected.

In conclusion, although the frequency is low, *A. actinomycetemcomitans* can cause pyogenic spondylitis and concur-rent IE. There may therefore be latent *A. actinomycetemcomitans*-mediated spondylitis cases. Patients with spondylitis, a history of heart valve disease and extensive dental disease, and for whom blood cultures remain negative might have infection caused by *A. actinomycetemcomitans*. Upon presentation of these signs, extended incubation and repeated blood cultures must be employed to de-tect and identify the pathogenic organism. Further research is needed to obtain a reliable estimate of the frequency of *A. actinomycetemcomitans* spondylitis and the coexistence of IE.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

This case was presented at the 31st International Congress of Antimicrobial Chemotherapy and 4th Gulf Congress of Clinical Microbiology and Infectious Diseases (31st ICC - 4th GCCMID 2019).

References

1. Wang CY, Wang HC, Li JM, et al. Invasive infections of *Aggregatibacter (Actinobacillus) actinomycetemcomitans*. J Microbiol Immunol Infect 43: 491-497, 2010.
2. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Am J Med 96: 200-209, 1994.
3. Berbari EF, Kanj SS, Kowalski TJ, et al. 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the di-agnosis and treatment of native vertebral osteomyelitis in adults. Clin Infect Dis 61: e26-e46, 2015.
4. Park KH, Cho OH, Lee JH, et al. Optimal duration of antibiotic therapy in patients with hematogenous vertebral osteomyelitis at low risk and high risk of recurrence. Clin Infect Dis 62: 1262-1269, 2016.
5. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications. A scientific statement for healthcare professionals from the American Heart Association. Circulation 132: 1435-1486, 2015.
6. Habib G, Lancellotti P, Antunes MJ, et al. ESC guidelines for the management of infective endocarditis. Eur Heart J 36: 3075-3123, 2015.
7. Nakatani S, Ashihara K, Izumi C, et al. Guidelines for prevention and treatment of infective endocarditis. Circ J 83: 1767-1809, 2019.
8. Muhle I, Rau J, Ruskin J. Vertebral osteomyelitis due to *Actinobacillus actinomycetemcomitans*. JAMA 241: 1824-1825, 1979.
9. Farrington M, Elykn SJ, Walker M, Warren RE. Vertebral osteo-myelitis due to coocobacilli of the HB group. Br Med J (Clin Res Ed) 287: 1658-1660, 1983.
10. Nashli M, Venkatalaksham AK, Unsworth PF, Muddu BN. Diskitis caused by *Actinobacillus actinomycetemcomitans*. Orthopedics 21: 714-716, 1998.
11. Patel SM, Mo JH, Walker MT, Adley B, Noskin GA. Epidural abscess and osteomyelitis due to *Actinobacillus actinomycetemcomi-танs*. Diagn Microbiol Infect Dis 50: 283-285, 2004.
12. Uno S, Horiuchi Y, Uchida T, et al. A successful antimicrobial therapeutic strategy for the discitis caused by *Aggregatibacter actinomycetemcomitans* under unknown drug susceptibility: a case report. J Infect Chemother 24: 849-851, 2018.
13. Mylona E, Samarkos M, Kakalou E, Fanourgikis P, Skoutelis A. Pyogenic vertebral osteomyelitis: a systematic review of clinical characteristics. Semin Arthritis Rheum 39: 10-17, 2009.
14. Wilson M, Kamin S, Harvey W. Bone resorbing activity of purified capsular material from *Actinobacillus actinomycetemcomitans*. J Periodontal Res 20: 484-491, 1985.
15. Pigrau C, Almirante B, Flores X, et al. Spontaneous pyogenic vertebral osteomyelitis and endocarditis: incidence, risk factors, and outcome. Am J Med 118: 1287.e17-1287.e24, 2005.
16. Das M, Badley AD, Cockerill FR, Steckelberg JM, Wilson WR. Infective endocarditis caused by HACEK microorganisms. Annu Rev Med 48: 25-33, 1997.
17. Patureau L, Casalta JP, Habib G, Nezri M, Raoul D. *Actinobacillus actinomycetemcomitans* endocarditis. Clin Microbiol Infect 10: 98-118, 2004.
18. Baron EJ, Scott JD, Tompkins LS. Prolonged incubation and ex-tensive subculturing do not increase recovery of clinically signifi-cant microorganisms from standard automated blood cultures. Clin Infect Dis 41: 1677-1680, 2005.
19. Petti CA, Bhally HS, Weinstein MP, et al. Utility of extended blood culture incubation for isolation of *Haemophilus, Actinoba-cillus, Cardiobacterium, Eikenella*, and *Kingella* Organisms: a ret-rospective multicenter evaluation. J Clin Microbiol 44: 257-259, 2006.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).