

## Predictors of conservative treatment for pyogenic spondylitis

Fumitaka Kugimiya<sup>1)</sup>, Shigeyuki Muraki<sup>2)</sup>, Daisuke Nagakura<sup>1)</sup>, Hidemasa Umekoji<sup>1)</sup>, Hiromi Oda<sup>1)</sup> and Keisuke Takahashi<sup>1)</sup>

1) Department of Orthopaedic Surgery, Saitama Medical University, Saitama, Japan

2) Department of Joint Disease Research, 22 Century Medical and Research Center, Faculty of Medicine, University of Tokyo, Tokyo, Japan

### Abstract:

**Introduction:** Although initial treatments for pyogenic spondylitis include conservative approaches such as rest and antibiotics, some cases are refractory to conservative therapy. The objective of this study was to clarify the predictors for achievement of C-reactive protein (CRP) normalization in pyogenic spondylitis by conservative therapy.

**Methods:** In the present study, we enrolled 83 patients (51 men and 32 women) with conservatively treated pyogenic spondylitis from 2006 to 2015. Multiple logistic regression analysis was used to examine the association of achievement of CRP normalization with the number of infected vertebrae, bacterial strain, blood data, and the expansion of abscess to the epidural space by using functional magnetic resonance imaging.

**Results:** We found significant differences in the subjects with and without achievement of CRP normalization with respect to age, the number of affected vertebrae, ratio of resistant pathogenic bacteria, ratio of expansion of abscess to the epidural space, and blood data such as Hb, ALB, eGFR, Cr, and ALP levels.

After adjustment for age and sex, the number of infected vertebral bodies, resistant bacteria, expansion of abscess to the epidural space, and Hb level showed significant associations with the normalization of CRP. In addition, we used multiple logistic regression analysis with age, sex, number of infected vertebral bodies, resistant bacteria, expansion of abscess to the epidural space, and serum Hb level as explanatory variables. We found that expansion of the abscess to the epidural and paravertebral spaces was significantly associated with the normalization of CRP level.

**Conclusions:** The number of infected vertebral bodies, resistant strains of pathogenic bacteria, expansion of abscess to the epidural and paravertebral spaces, and serum Hb level predicts the prognosis of patients with pyogenic spondylitis. Particularly, expansion of abscess to the epidural and paravertebral spaces was strongly associated with the achievement of CRP normalization.

### Keywords:

pyogenic spondylitis, conservative therapy, epidural abscess, paravertebral abscess

Spine Surg Relat Res 2017; 1(3): 135-139  
dx.doi.org/10.22603/ssrr.1.2017-0009

### Introduction

Pyogenic spondylitis is uncommon: the incidence has been reported to be between 0.2 and 2 cases per 100,000 per annum. However, there is evidence suggesting that the incidence is rising, possibly related to the improved life expectancy of patients with chronic diseases<sup>1-7)</sup>. The recent improvement of radiological, antimicrobial, and surgical techniques dramatically diminished the morbidity and mortality of pyogenic spondylitis. Nevertheless, the disease remains a neurological and life threatening condition<sup>8,9)</sup>.

Pyogenic spondylitis arises from haematogenous spread of

bacteria at the endplate and subchondral bone of the vertebrae<sup>10)</sup>. The abscess invades directly from the subchondral lesion to the intervertebral disk (avascular in adult) and the infection extends into the epidural and paravertebral spaces. Since the same segmental artery supplies both lower area of the upper vertebrae and upper area of the lower vertebrae, pyogenic spondylitis usually involves two adjacent vertebrae. In the lumbar spine, the valveless structure of Batson's venous plexus contributes to early seeding of microorganisms at the subchondral bone where the bacteria are shortly and directly transported from pelvic organs<sup>11,12)</sup>.

Initial treatments for pyogenic spondylitis include conser-

vative approaches such as antibiotic therapy and immobilization of affected spine segment; however, some cases are refractory to conservative therapy. Therefore, it is worthwhile to review the patients for the most appropriated surgical timing by outcome. The objective of this study was to clarify the predictors for achievement of C-reactive protein (CRP) normalization in pyogenic spondylitis by conservative treatment.

## Materials and Methods

This study included 83 patients (51 men and 32 women) aged 23-83 years who were admitted to a single institution with pyogenic spondylitis from 2006 to 2015. Patients who had undergone emergency surgery for pyogenic spondylitis on admission were excluded. The follow-up period ranged from 1.0 to 8.7 years. To diagnose pyogenic spondylitis, we examined blood test, physical, neurological, and radiological findings in the present study. Specifically, patients complained of neck or back pain at the medical interview. Fever and elevation of CRP in laboratory test was present in many cases. For radiological examination, we relied on magnetic resonance imaging (MRI): Pyogenic spondylitis presents a signal decrease in T1-weighted sequences and a signal increase in T2-weighted sequences in the anterolateral vertebral body near endplate at the early stage. Taking these factors into consideration, we diagnosed pyogenic spondylitis.

We defined CRP normalization (NC) as a CRP level decrease to <0.25 mg/dl. The blood data analysis included the following measurements: white blood cell (WBC), hemoglobin (Hb), albumin (ALB), glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), gamma GTP, blood urea nitrogen (BUN), creatinine (Cr), uric acid (UA), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), estimated glomerular filtration rate (eGFR), triglyceride (TG), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), inorganic phosphorus (IP), and hemoglobin A1c (HbA1c) levels.

Since microbiological diagnosis is essential to enable targeted antibiotic treatment, all patients underwent blood culture to identify pathogenic bacteria. On radiological examinations, magnetic resonance images were classified into five categories (stage I-V)<sup>13</sup>. Stage I-III abscesses describe contained lesions within the posterior longitudinal ligament, while stage IV and V describe extended epidural or paravertebral lesions.

As for conservative therapy, antibiotic therapy that is sensitive for pathogenic bacteria is one of the essential treatments of pyogenic spondylitis. We initially used first generation cephalosporin aiming at common infective organisms, such as staphylococcus and streptococcus. For patients who did not respond to first generation cephalosporin and were infected with unknown bacteria, we used antibiotics targeted to methicillin-resistant staphylococcus aureus.

## Statistical analysis

Unpaired t-test was used to compare continuous values, and chi-square test was used to compare categorical values between NC and non-NC groups. Multiple logistic regression analysis after adjustment for age and BMI was performed to determine the association of age, gender, number of affected vertebrae, expansion of abscess, serum Alb level, eGFR, serum Hb level and resistant pathogenic bacteria with achievement of NC. In addition, to examine the variables independently associated with the normalization of CRP level, we used multiple logistic regression analysis with age, sex, number of infected vertebral bodies, resistant bacteria, expansion of abscess to the epidural and paravertebral spaces, and serum Hb level as explanatory variables. P values less than 0.05 were deemed to be statistically significant. All analyses were performed using JMP, version 11.0 (SAS Institute Inc., Cary, NC, USA).

## Results

A total of 83 patients with pyogenic spondylitis were treated between 2006 and 2015. Of these, 47 (57%) patients achieved NC by conservative therapy (NC group) and 36 (43%) patients did not achieve NC by conservative therapy (non-NC group). We investigated the level of paralysis using Frankel classification. In the NC group, there were 2 patients of Frankel B, 3 patients of Frankel C, 12 patients of Frankel D and 30 patients of Frankel E. In the non-NC group, there were 1 patient of Frankel A, 5 patients of Frankel C, 9 patients of Frankel D and 21 patients of Frankel E. The average of duration of CRP normalization in NC group was 45.1 days. Among the 36 patients in the non-NC group, 14 patients underwent surgery to control infection and/or stabilize spine after failure of conservative treatment.

Table 1 shows characteristics and complications in patients from the NC and the non-NC group. Patients in the NC group were younger than those in the non-NC group. There was no significant difference in the average period from the onset to admission between the NC and non-NC group. The average number of infected vertebrae was 1.90 in NC group and 2.60 in non-NC group. There was significant difference between two groups by using unpaired t-test.

Of the 83 patients, 81% had complications: 25 patients had diabetes, 22 patients had high blood pressure, 16 patients had heart disease, 9 patients had urinary tract disease, 7 patients had collagen disease, 5 patients had dialysis, 5 patients had malignant tumors, 4 patients had hepatic dysfunction, 3 patients had high uric acid.

Next, we examined the distribution of affected vertebrae. We found that infected vertebrae were predominant on the lumbar spine (Fig. 1). We also examined the laboratory data upon admission. We found significant differences between NC and non-NC groups in the blood data such as Hb (12.0 vs. 10.6), ALB (3.12 vs. 2.85), eGFR (91.2 vs. 71.8), ALP (369.3 vs. 290.1) and Cr (0.9 vs. 1.9) levels by using un-

paired t-test (Table 2). We next examined the population of pathogenic bacteria found in our patients with pyogenic spondylitis (Table 3). Pathogenic bacteria were MSSA (13 patients), MRSA (21 patients), others (5 patients), and unknown (44 patients). The ratio of MRSA in the NC group was significantly higher than that in the non-NC group.

To examine the expansion of the infection, we used magnetic resonance images of the spine. As mentioned above, data were classified into two categories; stage I-III and stage IV-V. At stage I-III, abscesses existed in the posterior longi-

tudinal ligament, while at stage IV and V, abscesses expanded to epidural or paravertebral lesions. The ratio of expansion of abscess to the epidural and paravertebral spaces in the non-NC group was significantly higher than that in the NC group.

After adjustment for age and sex, the number of infected vertebral bodies, resistant bacteria, expansion of abscess to the epidural and paravertebral spaces, and Hb level showed significant associations with the NC (Table 4). To examine the variables independently associated with the NC level, we used multiple logistic regression analysis with age, sex, number of infected vertebral bodies, resistant bacteria, expansion of abscess to the epidural and paravertebral spaces, and serum Hb level as explanatory variables. We found that expansion of the abscess to the epidural and paravertebral spaces and serum Hb level were independently associated with the normalization of CRP level (Table 5).

**Table 1.** Characteristics and Complications in Patients with and without NC.

	NC group	non-NC group	P value
Age (average, yr)	62.5	68.6	0.0270
Men / Women	34/13	17/19	0.0198
Period from onset to admission (days)	65.2	55.3	0.1840
Number of affected vertebrae	1.90	2.60	0.0092
<i>Complications</i>			
Diabetes mellitus	13 (28%)	12 (33%)	0.5766
Hypertension	11 (23%)	11 (30%)	0.4644
Heart disease	7 (11%)	11 (30%)	0.0862
Urologic disease	5 (11%)	4 (11%)	0.9453
Hemodialysis	0 (0%)	5 (14%)	0.0084
Collagen disease	2 (4%)	5 (14%)	0.1175
Malignant tumor	2 (4%)	3 (8%)	0.4390
Liver disease	2 (4%)	2 (6%)	0.7840
Hyperuricemia	2 (4%)	1 (3%)	0.7208

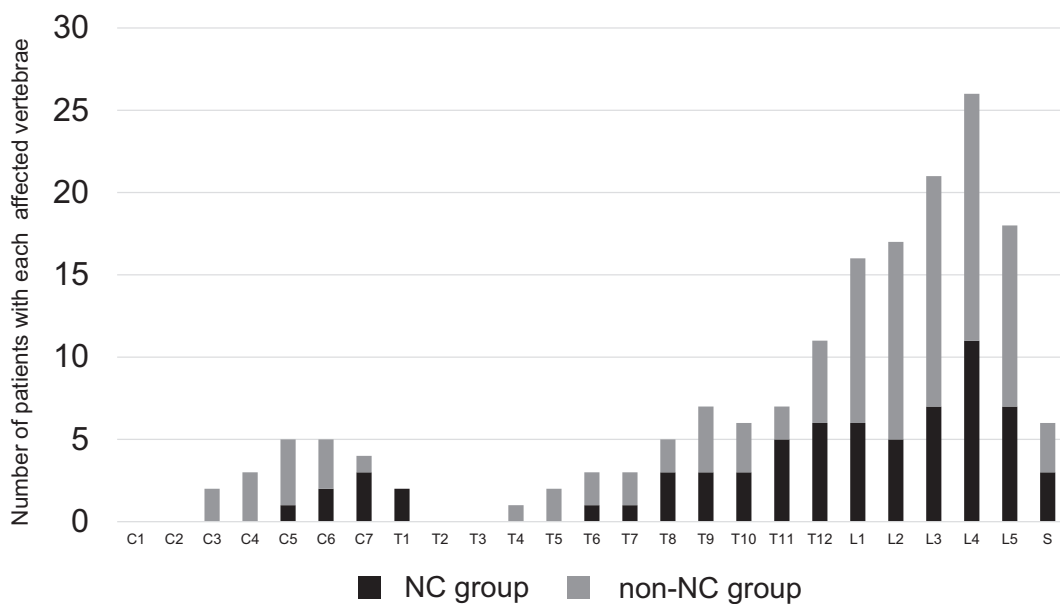
Non paired Students' t test was used to compare continuous values, and chi square test was used to compare categorical values between NC and non-NC groups.

NC, CRP normalization.

### Discussion

In the present study, we examined predictors of success in conservative treatment for pyogenic spondylitis, and found that the number of infected vertebral bodies, resistant bacteria, expansion of abscess to the epidural and paravertebral spaces, and Hb level showed significant associations with the NC. Expansion of abscess to the epidural and paravertebral spaces and serum Hb level were strong predictors for the achievement of NC.

Formerly, pyogenic spondylitis was considered to be a rare disease, however the incidence is likely to increase due to compromised hosts such as an aged population, patient with diabetes mellitus, and patients with renal failure and connective tissue disease using steroid and immunosuppressive drugs. Additionally, the improvement of diagnosis accu-



**Figure 1.** Distribution of the affected vertebrae in patients with and without NC. NC: normalization of CRP

**Table 2.** Laboratory Data in Patients with and without NC.

	NC group	non-NC group	P value
WBC ( $\mu$ L)	10329	11378	0.218
NEUT (%)	73.9	76.7	0.157
LYM (%)	18.1	15.6	0.125
Hb (g/dL)	12.0	10.6	0.0023
ALB (g/dL)	3.12	2.85	0.035
GOT (U/L)	30.9	31.0	0.489
GPT (U/L)	33.9	28.7	0.289
$\gamma$ -GPT (U/L)	65.9	50.5	0.210
ALP (mU/mL)	369.3	290.1	0.030
LDH (U/L)	207.0	229.6	0.109
eGFR (ml/min)	91.2	71.8	0.029
BUN (mg/dL)	18.5	24.4	0.052
Cr (mg/dL)	0.9	1.9	0.016
UA (mg/dL)	5.2	5.9	0.310
TC (mg/dL)	163.5	183.9	0.256
TG (mg/dL)	152	131	0.284
LDL (U/L)	94.1	85.2	0.292
HDL (U/L)	45.2	42.8	0.422
HbA1c (%NGSP)	7.0	6.1	0.240
IP (mEq/L)	5.2	3.2	0.091

WBC, white blood cell; NEUT, neutrophil; LYM, lymphocyte; Hb, hemoglobin; ALB, albumin; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic pyruvic transaminase;  $\gamma$ -GPT,  $\gamma$ -glutamyltransferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, hemoglobin A1c; IP, Inorganic phosphorus

**Table 3.** Pathogenic Bacteria and Radiological Findings in Patients with and without NC.

	NC group	non-NC group	
<b>Bacteria</b>			
MSSA	7 (14.8%)	6 (16.7%)	0.0005
MRSA	5 (10.6%)	16 (44.4%)	
Others	2 (4.3%)	3 (8.3%)	
Unknown	33 (70.3%)	11 (30.6%)	
<b>MRI</b>			
I, II, III	34 (72.4%)	11 (29.7%)	0.0043
IV, V	13 (27.6%)	25 (70.3%)	

Chi square test was used to determine differences between NC and non-NC group. NC, CRP normalization; MSSA, methicillin-sensitive staphylococcus aureus; MRSA, methicillin-resistant staphylococcus aureus

racy of pyogenic spondylitis by medical staff and aided by the increased availability of MRI in hospitals may contribute to apparent the increase in prevalence of the disease. The diagnosis of pyogenic spondylitis at the first medical examination is considered to be difficult. In the literature, the average period from first symptom to diagnosis has been reported between two and six months<sup>14</sup>. In our study the period from the onset to admission was 65.2 days in the NC

**Table 4.** Factors Associated with Achievement of CRP Normalization.

	OR	95% CI	P value
Age	1.03	0.998-1.07	0.0638
Women (vs. Men)	1.92	0.77-4.90	0.1624
Number of affected vertebrae (3 or more vs 2)	5.61	1.60-26.5	0.0059
Expansion of abscess (MRI Grade IV, V vs I, II, III)	4.20	1.63-11.5	0.0026
ALB	0.53	0.23-1.15	0.1116
eGFR	0.99	0.98-1.001	0.0751
Hb (1g/dl decrease)	1.31	1.04-1.69	0.0206
Resistant pathogenic bacteria	7.70	1.97-42.4	0.0023

OR was calculated by using multiple logistic regression analysis after adjustment for age and BMI. OR, odds ratio; CI, confidence interval; ALB, albumin; eGFR, estimated glomerular filtration rate; Hb, hemoglobin

**Table 5.** Independent Association of Number of Affected Vertebrae, Expansion of Abscess, Serum Hb Level and Resistant Pathogenic Bacteria with Achievement of CRP Normalization.

	OR	95% CI	P value
Number of affected vertebrae (3 or more vs 2)	3.17	0.75-17.0	0.1183
Expansion of abscess (MRI Grade IV, V vs I, II, III)	3.40	1.17-10.7	0.0245
Hb (1g/dl decrease)	1.34	0.74-1.04	0.0232
Resistant pathogenic bacteria	4.34	0.96-26.0	0.0563

OR was calculated by using multiple logistic regression analysis with age, BMI, number of affected vertebrae, expansion of abscess, serum Hb level and resistant pathogenic bacteria. OR, odds ratio; CI, confidence interval; Hb, hemoglobin

group and 55.3 days in the non-NC group. In the meantime, pyogenic spondylitis progresses and exacerbation of the disease makes it difficult to cure. Generally speaking, chronic inflammation causes anemia, low concentration of ALB in the blood, and the abscess to expand to the next vertebrae and/or the epidural space. Although our study showed no significant difference between NC and non-NC groups in the period from the onset to admission, there was a significant difference between NC and non-NC groups in the number of affected vertebrae; blood levels of Hb, ALB, and ALP; and ratio of expansion of abscess to the epidural space. These data suggest that patients in the non-NC group might be in later stage of pyogenic spondylitis than those in NC group.

Conservative therapy, such as antibiotic treatment and spinal immobilization, leads to clinical success in approximately 75% of patients of pyogenic spondylitis. The remaining 25% of patients need further therapy including surgery<sup>15</sup>. Many of patients suffering from pyogenic spondylitis are compromised host. Therefore, rates of complications for surgery for pyogenic spondylitis are high. In the present study

of 83 patients, 81% had complications, such as diabetes, high blood pressure, heart disease, urinary tract disease, collagen disease, dialysis, malignant tumor, hepatic dysfunction. These complications may incline surgeons to hesitate to move from conservative therapy to surgery. Because a long period of conservative therapy may cause progression of the disease and extension of hospitalization period, it is useful to clarify the factors that determine the success of conservative therapy for pyogenic spondylitis.

Our study suggests that the expansion of the abscess to the epidural and paravertebral spaces revealed by using MRI was significantly associated with the NC level. MRI is one of the most important examination techniques to diagnose pyogenic spondylitis<sup>16,17</sup>. Regarding the diagnosis of the pyogenic spondylitis, it has been shown that the sensitivity was 96% and the specificity was 92% by using MRI<sup>18</sup>. Epidural abscess associated with pyogenic spondylitis can cause neurological symptoms<sup>19,20</sup> and an indication for emergency treatment<sup>21,22</sup>. Uchida et al. reported that stage III represented a threshold with a confined lesion within the segmental compartment, while stage IV and V represent multisegmentally extended lesions<sup>13</sup>. Although some patients can possibly be treated using conservative treatment, stage IV and V are indications for surgery. Yoshida also reported that almost 70% of stage IV and V patients underwent surgery<sup>23</sup>.

In conclusion, our study suggests that advanced age, women, the number of affected vertebrae, blood data such as low Hb, low ALB, low ALP, low eGFR, and high Cr levels, high ratio of resistant pathogenic bacteria, and high ratio of expansion of abscess to the epidural and paravertebral spaces are related with NC in pyogenic spondylitis patients. Especially, our results suggest that expansion of the abscess to the epidural and paravertebral spaces is significantly associated with the NC level.

Conflicts of Interest: No conflicts of interest and no financial support.

## References

- Grammatico L, Baron S, Rusch E, et al. Epidemiology of vertebral osteomyelitis (VO) in France: analysis of hospital-discharge data 2002-2003. *Epidemiol Infect.* 2007;136(5):653-60.
- Butler JS, Shelly MJ, Timlin M, et al. Nontuberculous pyogenic spinal infection in adults: a 12-year experience from a tertiary referral center. *Spine (Phila Pa 1976).* 2006;31(23):2695-700.
- Frangen TM, Kalicic T, Gottwald M, et al. Surgical management of spondylodiscitis. An analysis of 78 cases. *Unfallchirurg.* 2006; 109(9):743-53.
- Sampath P, Rigamonti D. Spinal epidural abscess: a review of epidemiology, diagnosis, and treatment. *J Spinal Disord.* 1999;12(2): 89-93
- Boszyk BM, Krause P, Bolay H, et al. Spinal epidural abscess following blunt pelvic trauma. *Eur Spine J.* 2000;9(1):80-4.
- Soehle M, Wallengang T. Spinal epidural abscesses: clinical manifestations, prognostic factors, and outcomes. *Neurosurgery.* 2002; 51(1):79-85.
- Korovessis P, Repantis T, Iliopoulos P, et al. Beneficial influence of titanium mesh cage on infection healing and spinal reconstruction in hematogenous septic spondylitis: a retrospective analysis of surgical outcome of twenty-five consecutive cases and review of literature. *Spine (Phila Pa 1976).* 2008;33(21):E759-67.
- Carragee EJ. Pyogenic vertebral osteomyelitis. *J Bone Joint Surg Am.* 1997;79(6):874-80.
- Deyo Ra, Nachemson A, Mirza SK. Spinal-fusion surgery - the case for restraint. *N Engl J Med.* 2004;350(7):722-6
- Kobayashi S, Baba H, Takeno K, et al. Fine structure of cartilage canal and vascular buds in the rabbit vertebral endplate. *J Neurosurg Spine.* 2008;9(1):96-103.
- de Winter F, van de Wiele C, Vogelaers D, et al. Fluorine-18 fluorodeoxyglucose-position emission tomography: a highly accurate imaging modality for the diagnosis of chronic musculoskeletal infections. *J Bone Joint Surg Am.* 2001;83-A(5):651-60.
- Emery SE, Chan DP, Woodward HR. Treatment of hematogenous pyogenic vertebral osteomyelitis with anterior debridement and primary bone grafting. *Spine (Phila Pa 1976).* 1989;14(3):284-91.
- Uchida K, Nakajima H, Yayama T, et al. Epidural abscess associated with pyogenic spondylodiscitis of the lumbar spine; evaluation of a new MRI staging classification and imaging findings as indicators of surgical management: a retrospective study of 37 patients. *Arch Orthop Trauma Surg.* 2010;130(2):111-8.
- Butler JS, Shelly MJ, Timlin M, et al. Nontuberculous pyogenic spinal infection in adults: a 12 year experience from a tertiary referral center. *Spine.* 2006;31(23):2695-700.
- McHenry MC, Easley KA, Locker GA. Vertebral osteomyelitis: long-term outcome for 253 patients from 7 Cleveland-area hospitals. *Clin Infect Dis.* 2002;34(10):1342-50.
- Ansari S, Ashraf AN, Moutaery KA. Spine infection: a review. *Neurosurg Q* 2011; 11(2) 112-23.
- Harada Y, Tokuda O, Matsunaga N. Magnetic resonance imaging characteristics of tuberculous spondylitis vs. pyogenic spondylitis. *Clin Imaging.* 2008;32(4):303-9.
- Modic MT, Feiglin DH, Piraino DW, et al: Vertebral osteomyelitis: assessment using MRI. *Radiology.* 1985;157(1):157-66.
- Baba H, Maezawa Y, Kokubo Y, et al. Rapidly progressing quadriplegia secondary to cervical pyogenic spondylitis in a patient with Klippel-Feil syndrome. *J Spinal Disord.* 1995;8(2):151-6.
- Yayama T, Uchida K, Kokubo Y, et al. Lumbar epidural abscess causing septic shock: case report. *J Orthop Sci.* 2003;8(1):109-11.
- Darouiche RO. Spinal epidural abscess. *N Engl J Med.* 2007;355 (19)2012-20.
- Euba G, Narváez JA, Nolla JM, et al. Long-term clinical and radiological magnetic resonance imaging outcome of abscess-associated spontaneous pyogenic vertebral osteomyelitis under conservative management. *Semin Arthritis Rheum.* 2008;38(1):28-40.
- Yoshida A, Nakajima H, Uchida K, et al. *Spine & Spinal Cord.* 2012;25(10):920-5. Japanese

Spine Surgery and Related Research is an Open Access article 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/>).