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Infectious Spondylodiscitis by Uncommon Pathogens: A Pitfall of Empirical Antibiotics

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Objective: The goal of this study is to evaluate the prevalence of spondylodiscitis (SD) caused by uncommon pathogens and review the efficacy of the treatment strategy including the coverage by usual empirical broad-spectrum antibiotic therapy.
Methods: Ninety-nine consecutive patients diagnosed and treated for infectious SD between January 2007 to May 2015 were reviewed retrospectively. The prevalence of uncommon SD, predisposing factors, antibiotics sensitivity, and clinical outcome were analyzed in comparison with that of common SD.
Results: Among 99 patients, 68 patients were culture positive. Out of 68 patients with positive culture results, 54 of them (79.4%) were common pathogen and 14 (20.6%) were uncommon pathogen. Postoperative SDs were significantly prevalent in uncommon SD (42.9%) than common SD (27.8%). Recurrence rate was higher in uncommon pathogen SD (14.3%) than common SD group (2.3%), and it showed statistically significant difference (p=0.025). Empirical antibiotics of vancomycin and 3rd or 4th generation cephalosporin covered 100% of nontuberculous common SD and 14.3% of uncommon SD.
Conclusion: In our study, the prevalence of uncommon SD was relatively high uncommon (20.5% of culture positive SD and 14.1% of total cases) and the coverage rate of empirical antibiotics for them were only 14.3%. In particular, the possibility of SD with fun gal, polymicrobial, or multiple drug resistant organism should be considered in SD unresponsive to broad spectrum antibiotics therapy.

Key Words: Spondylodiscitis · Pathogens · Antibiotics

INTRODUCTION

Infectious spondylodiscitis (SD) is an infection of intervertebral discs and adjacent vertebral bodies[7,10]. Various organisms including bacteria, tuberculosis, fungi, and parasites can cause SD[7]. In the past, tuberculosis infection was the major cause of spinal infections[5,7,10,15]. However, nowadays, the majority of spinal infections are bacterial monomicrobial[5,7,9,15]. *Staphylococcus aureus, Escherichia coli, Proteus, Klebsiella, Pseudomonas aeruginosa,* Coagulase negative *Staphylococcus,* streptococci, enterococci, and *Mycobacterium tuberculosis* were discussed as common pathogens in majority of literatures[3,5,6,9,11,13-15,18,20]. Empirical antibiotics have been used to focus on these common pathogens. Unfortunately, uncommon pathogens could be unresponsive to these empirical antibiotics resulting in treatment failure.

There are case reports on spinal infections cause by individual uncommon pathogens, but large studies encompass uncommon pathogens are rare. The goal of this study is to evaluate the prevalence of SD by uncommon pathogens and the efficacy of treatment strategy including empirical broad-spectrum antibiotics therapy in comparison with common SD.

MATERIALS AND METHODS

Ninety-nine consecutive patients treated for infectious SD in a single tertiary hospital from January 2007 to May 2015 were reviewed retrospectively. The diagnosis of infectious spondylitis was based on presentation of clinical symptoms, laboratory abnormalities (white blood cell counts, C-reactive protein, erythrocyte sedimentation rate), radiographic abnormalities, microbiological results and pathologic findings.

S. aureus, E. coli, Proteus, Klebsiella, P. aeruginosa, Coagulase negative *Staphylococcus,* streptococci, enterococci, and *M. tuberculosis* were discussed as common pathogens in majority of literatures[3,5,6,9,11,13-15,18,20]. We defined uncommon pathogens as every pathogen except the common pathogens mentioned above, that includes rare bacterial, fungal, and parasitic organisms.

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Patient demographics, predisposing factors such as systemic illness and previous history of spinal procedure or surgery, etiological organisms and its sensitivity to empirical antibiotics, and clinical outcome including mortality, hospitalization day, cure rate, recurrence, and need for reconstructive surgery were analyzed to compare uncommon SD group with common SD group. Statistical analyses were performed using IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA). The p-values were generated using Mann-Whitney test and p-values less than 0.05 were considered significant.

Each patient was treated with various antibiotics, but we assumed that they were treated with vancomycin and 3rd or 4th generation cephalosporin for the empirical antibiotics before identification of organism, which are one of the most broad spectrum antibiotics, in the analysis of the empirical antibiotics treatment efficacy. Patients with tuberculosis spondylitis (with either microbiological or radiological confirmation) were excluded from antibiotics efficacy analysis, because they tend to have unique clinical, radiological features to differentiate them from pyogenic infections, relatively sensitive diagnostic tools including acid fast stains and reverse transcription-polymerase chain reaction, and require entirely different medications[7,9,15,17,20]. Patients were treated for various periods of time, however, clinical improvements, normalization of inflammatory marker, improvement on imaging follow-up were required for cessation of treatment.

RESULTS

1. Patient Demographics and Risk Factors

Of 99 patients who fulfilled inclusion criteria, 55 (55.6%) were male and 44 (44.4%) were female with a mean age of 60.8 years. There were 68 cases with positive culture results, 54 of them (79.4%) were common pathogen and 14 (20.6%) were uncommon pathogen. Thirty (55.6%) were male and the mean age was 61.3 years in the common pathogen group. Ten (71.4%) were male and the mean age was 60.1 years in the uncommon pathogen group.

Systemic illness including diabetes, hepatic failure, Cushing syndrome, renal failure, heart failure in common pathogen group, and uncommon pathogen group were noted in 15 (55.6 %) and 5 cases (33.3%), respectively. There was no statistically significant difference (p=0.559). Twenty-seven (50%) of common pathogen group and 7 (50%) of uncommon pathogen group had history of previous spinal invasive procedures adjacent to the lesion such as acupuncture, epidural blocks, spinal anesthesia, skin grafts, catheter insertions. History of previous spinal surgery was much higher in uncommon SD group (42.9 %) than in common SD group (27.8%), and it was statistically significant (p=0.009) (Table 1).

2. Etiologic Organism

Among 99 patients, 64 had open and 35 had percutaneous (fluoroscopic or ultrasound guided) biopsies. The causative organism was confirmed by in 68 cases (68.6%). Culture positive rates for open and percutaneous procedures were 78.1% (50 of 64) and 51.4% (18 of 35), respectively.

There were 14 cases (20.5% of culture positive SD and 14.1% of total cases) of SD caused by uncommon pathogens. Microorganisms were: *Abiotrophia defectica, Acinectobacter baumanni, Bacteroides fragilis, Haemophilus parainfluenza* with *Corynebacterium afermentans, Porphyromonas gingivalis, Serratia marcescens,* 3 cases of *Candida* with coinfected bacterial infection, 2 *Candida* species, 3 *Aspergillus* infections (Table 2).

Table 1. Comparison of demographics, predisposing factors, and clinical outcome in patients with common SD and uncommon SD

Variable	Common	Uncommon	p-value
No. of the patients	54	14	
Mean age (yr)	60.3	60.1	
Male sex	30 (55.6)	10 (71.4)	
Systemic illness	15 (27.8)	5 (33.3)	0.559
Previous spinal procedure	27 (50)	7 (50)	0.060
Previous spinal surgery	15 (27.8)	6 (42.9)	0.009
Mortality	2 (2.3)	1 (7)	0.072
Mean hospitalization day	107	68.4	0.324
Cure	52 (92.6)	13 (92.9)	0.699
Sensitivity to empirical antibiotics*	35/35 (100)	2/14 (14.3)	0.000
Recurrence	2 (2.3)	2 (14.3)	0.025
Need for reconstruction	9 (35.2)	2 (14.3)	0.134

Values are presented as number (%) unless otherwise indicated.
SD, spondylodiscitis.
*Tuberculous SD were excluded.

Of 54 cases with common SD (79.4% of culture positive SD and 54.5% of total cases), 33 were bacterial monomicrobial, 2 were bacterial polymicrobial, 19 were tuberculous.

3. Treatment and Outcome

The cure rate of common and uncommon SD group was 96.3 % and 92.9%, respectively. Two patients in common SD group died of aggravated pneumonia and hepatic failure, and one patient in uncommon SD group died of sepsis. The mean duration of hospitalization was 107 days and 68.4 days for common and uncommon pathogen group. Statistical analysis showed no significant difference in mortality, cure rate and duration of hospitalization between the 2 groups ($p>0.05$) (Table 1).

Only 2 cases (14.3%) in uncommon SD group were covered by empirical antibiotics whereas every 35 cases (100%) of non-tuberculous cases of common SD group were covered by vancomycin and 3rd or 4th generation cephalosporin (Tables 1, 2).

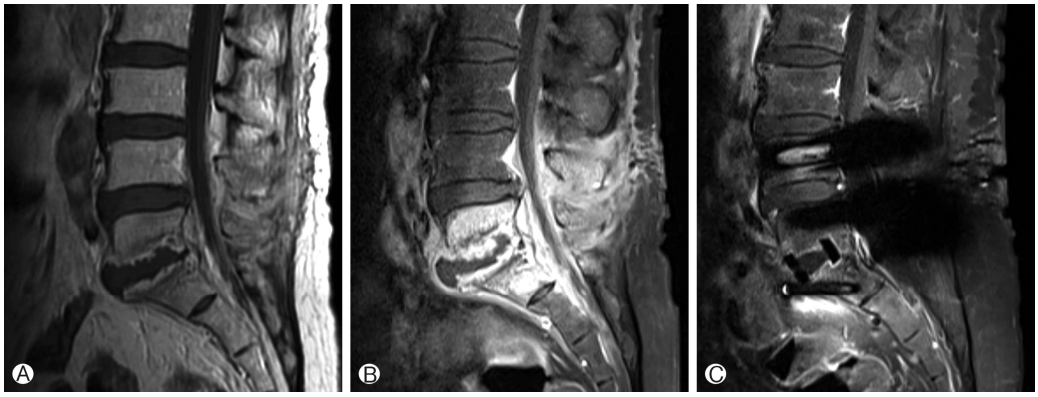

Fig. 1. (**A**) Enhanced T1 magnetic resonance image of lumbar spine at the time of diagnosis. (**B**) After 3 weeks treatment of empirical ceftriaxone and ciprofloxacin without biopsy, follow-up image showed aggravation of spondylitis. (**C**) Eighteen-month follow-up image after administration of fluconazole for *Aspergillus fumigatus*. Reconstructive fusion operation was performed and total control of infection was achieved.

Table 2. Summary of patients with uncommon pathogen

Case No.	Sex/ age	Etiological organism	Initial treatment	Treatment after culture	Systemic illness	HD	Outcome
1	F/43	*Abiotrophia defectica*	VAN	VAN	-	51	Cured
2	M/70	*Acinectobacter baumanni*	Meropenem	Levofloxacin	-	73	Cured
3	M/70	*Aspergillus* spp	VAN	Amp B	-	88	Cured
4	M/59	*Aspergillus* spp	Ampicillin/sulbactam	VOR	Pulmonary aspergillosis	91	Recurred
5	F/59	*Aspergillus fumigatus*	CFT + CPR	VOR	-	61	Cured
6	F/39	*Bacteroides fragilis*	Ceftazidime + netilmicin	MTZ	-	36	Cured
7	M/55	*Candida albicans*	Teicoplanin	FCZ	Neutropenia	36	Cured
8	M/67	*Candida glabrata*	VAN + CPR	AMP	Diabetes	75	Recurred
9	M/81	*Staphylococcus epidermidis + Staphylococcus capitis + Candida* spp	VAN + RFP + MTZ	VAN + FCZ	Skin fungal infection	85	Cured
10	M/74	*Enterococcus faecalis + Candida albicans*	CFT + CPR	VAN + FCZ + ceftaxidime	-	168	Cured
11	M/74	*Enterococcus faecium + Candida albicans*	VAN + CFT	VAN + CFT + FCZ	Renal cell carcinoma	20	Died of sepsis
12	M/61	*Haemophilus parainfluenzae + Corynebacterium afermentans*	VAN + cefepime	VAN + CFT	-	89	Cured
13	M/51	*Porphyromonas gingivalis*	VAN + CFT + MTZ	CFT + MTZ	-	35	Cured
14	M/47	*Serratia marcescens*	VAN + CFT	Meropenem	-	-	Cured

HD, hospitalization day; AMP, amphotericin B; CFT, ceftriaxone; CPR, ciprofloxacin; FCZ, fluconazole; RFP, rifampicin; MTZ, metronidazole; VAN, vancomycin; VOR, voriconazole.

Patients with negative culture results were treated with broad spectrum antibiotics except for 2 patients who showed typical magnetic resonance finding of tuberculosis spondylitis and treated with antituberculosis medication. All of 31 patients with negative microbiological results showed clinical improvement with the use of antibiotics.

Recurrence rate was higher in uncommon pathogen SD (14.3 %) than common SD group (2.3%), and it showed statistically significant difference (p=0.025). Reconstructive fusion operations were performed because of progressive deformity or intractable pain despite treatment for 19 (35.2%) in common SD group and 2 (14.3%) in uncommon SD group (Table 1).

4. Case Rresentation

A 59-year-old female (case number 5) with a history of discectomy 2 months before the symptom onset was transferred from local clinic with high fever and severe back pain. She was diagnosed with SD (Fig. 1A) and treated with empirical antibiotics treatment of ceftriaxone and ciprofloxacin for 3 weeks in local clinic without biopsy. Follow-up image shows aggrava- tion of the disease (Fig. 1B). Open biopsy was performed and *Aspergillus fumigatus* was identified. Intravenous voriconazole for 2 weeks and oral voriconazole for 9 months was administered. Reconstructive fusion operation was performed later. Eighteen-month follow-up image shows total control of the SD (Fig. 1C).

DISCUSSION

Infectious spondylitis is not a common disease, consisting 2%–7% of cases of osteomyelitis[2,3,5,7]. However, several studies have reported increased incidence possibly due to increasing average age, immunodeficiency, diabetes, drug abuse, various invasive procedure, spinal surgeries, and better diagnostic tools[2,3,5,7,10,12].

Tuberculous SD was believed to be the leading cause of spinal infection in developing countries including Korea[5,7,15]. In our study, *M. tuberculosis* was the single most common causative organism (27.9%). Then again, bacterial pyogenic infection all together (60.3%) showed almost 2 folds higher incidence and uncommon SD (20.6%) had at least a half incidence. With the greater use of immunosuppressants, prolonged use of broad-spectrum antibiotics, indwelling catheters, and the higher prevalence of chronic debilitating diseases, the epidemiology and etiology appear to be changing[8,9,19]. It is also important that these once-rare pathogens can be resistant to antibiotics that are currently used[1,8].

Many reports and guidelines strongly recommend identification of the pathogen before the start of antibiotics treatment, except when the patient is in a septic condition[1,4,7,19]. Various procedures from simple blood culture, percutaneous biopsy, and excisional biopsy to even reconstructive instrumentation can be performed. However, in our study, only 54.9% of the patients who were transferred from other hospitals were treated with various IV antibiotics without an attempt to acquire microbiological identification of the causative organism. This seems inappropriate since a considerably high portion of SD is resistant to even the most broad-spectrum antibiotics we use. In addition, such treatment can decrease the sensitivity of culture[1,9].

In our study, uncommon SD was not-so-uncommon (20.5% of culture positive SD and 14.1% of total cases) within modern population, and only 14.3% of them were proved to be sensitive to vancomycin and 3rd or 4th generation cephalosporin. In addition, the ratio of presence of previous spinal surgery in uncommon SD is significantly higher than that of common SD (p=0.009), which is contrary to popular belief that etiology of postoperative infections is most likely one of skin microbiota. Positive ratio of recurrence was the only parameter with statistically significant difference between two groups in clinical outcome. Two cases (case numbers 4 and 8) recurred after cessation of parenteral antibiotics were both fungal infection (*Aspergillus and Candida*), which require much longer periods of treatment and recur more often. Sufficient duration of treatment and careful observation in follow-up periods are required for uncommon SD.

Physicians should always consider uncommon pathogens with multiple drug resistance, fungal organisms, and polymicrobial infections especially when treating patients with known risk factors or experiencing treatment failure or recurrence[1,6,16,19]. In addition, the importance of identification of the pathogen before the start of antibiotics treatment must be emphasized.

CONCLUSION

In our study, the prevalence of uncommon SD was relatively high uncommon (20.5% of culture positive SD and 14.1% of total cases) and the coverage rate of empirical antibiotics for them were only 14.3%. In particular, the possibility of uncommon pathogen with fungal, polymicrobial, or multiple drug resistant organism should be considered in especially when treating patients with known risk factors or experiencing treatment failure or recurrence.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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