

# Antibiotic-Induced Increase in Inflammatory Markers in Cured Infectious Spondylitis : Two Case Reports

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Conservative therapy with appropriate antibiotics is essential for most patients with infectious spondylitis. Although most antibiotics do not cause problems if used properly and serious side effects are rare, side effects can occur with any class of drugs and adverse reactions of antibiotics can range from mild allergic reactions to serious and fulminant adverse events. These side effects are also extremely variable from patient to patient and from antibiotic to antibiotic. A side effect of antibiotics may paradoxically increase inflammatory marker levels. Here, the author presents two cases of antibiotic-induced increase in inflammatory markers in cured infectious spondylitis. The patients were successfully treated after stopping the antibiotic therapy. The differential diagnosis between antibiotic side effects and infection should be considered very carefully because the treatment is completely different. Although the exact mechanisms underlying successful treatment without antibiotics are unclear, we should consider the side effects of antibiotics when following inflammatory markers during treatment of infectious spondylitis.

**Key Words :** Antibiotics · Spondylitis · Inflammation · Infection.

## INTRODUCTION

In addition to clinical symptoms and signs, radiologic and laboratory investigation is commonly used to support the diagnosis and assessment of an inflammatory process<sup>7)</sup>. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level are useful for screening and assessment in the diagnosis and treatment of infectious spondylitis. Compared to the ESR, CRP is a more sensitive and specific acute phase reactant and is more responsive to changes in the course of infection<sup>6,13)</sup>. However, an elevation in CRP and/or ESR should not be taken as pathognomonic for infection<sup>7)</sup>.

Conservative therapy with appropriate antibiotics is essential for most patients with infectious spondylitis<sup>13)</sup>. With resolution of infectious spondylitis, the CRP and ESR levels should decrease<sup>6,7)</sup>. If these inflammatory markers remain consistently elevated despite use of intravenous (IV) antibiotics, a repeat radiological study should be considered to look for any infectious lesions that may require a longer course of IV therapy<sup>5,13)</sup>. However, side effects can occur with any class of drugs and adverse reactions of antibiotics can range from mild allergic reactions to serious and fulminant adverse events. These side effects are also extremely variable from patient to patient and from antibiotic to antibiotic<sup>7)</sup>. A side effect of antibiotics is a

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paradoxical increase in inflammatory marker levels despite cure of infection. The author presents two cases of antibiotic-induced increase in inflammatory markers in cured infectious spondylitis. The patients were successfully treated after stopping the antibiotic therapy.

## CASE REPORT

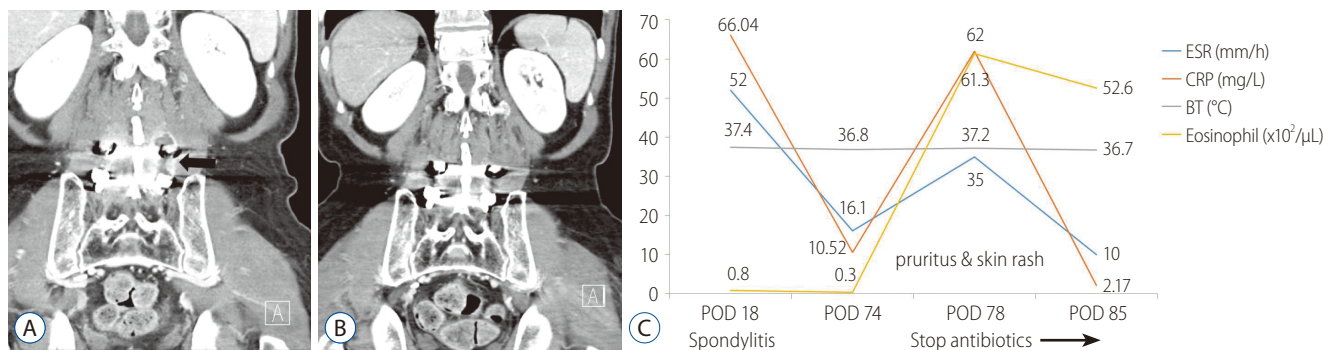
### Case 1

A 67-year-old man was admitted with pain and numbness in the thighs, buttocks, and calves, precipitated by walking. Magnetic resonance imaging (MRI) revealed spinal stenosis at L4/5 with hypertrophy of the ligamentum flavum. He underwent mini-open posterior lumbar interbody fusion with percutaneous screw fixation and was discharged on the 9th postoperative day (POD). However, he returned to our hospital because he experienced severe lower back pain and fever on the 18th POD. Laboratory investigation revealed ESR of 52 mm/h (normal range, 0–20), CRP concentration of 66.04 mg/L (normal range, 0–5), white blood cell (WBC) count of 11600/μL (normal range, 4000–10000/μL), neutrophil count of 9270/μL (normal range, 1500–7500/μL), and eosinophil count of 80/μL (normal range, 40–500/μL). Lumbar contrast-enhanced computed tomography (CT) revealed postoperative infection with abscess formation along the screw heads and rods (Fig. 1A). We performed aspiration and irrigation of the abscess under local anesthesia. *Staphylococcus caprae* was cultured from the abscess, and IV vancomycin was started based on the result of antimicrobial sensitivity testing. We continued IV antibiotics

therapy for 2 months, following which the ESR gradually decreased to 16.1 mm/h and the CRP to 10.52 mg/L. All other laboratory investigations also were normal. The inflammatory markers subsequently increased rapidly, with an ESR of 45 mm/h and CRP of 62 mg/L, although his severe lower back pain was relieved. Eosinophil count has also markedly increased to 6130/μL. Lumbar enhanced CT showed nearly complete disappearance of the abscess (Fig. 1B). At that time, the patient complained of whole-body pruritus and skin rash. We suspected an adverse effect and drug eruption and stopped the antibiotic. One week later, his laboratory tests had rapidly returned to normal with an ESR of 10 mm/h and CRP of 2.17 mg/L and his skin symptoms completely disappeared. Eosinophil count was still increased to 5260 and normalized after 3 weeks (Fig. 1C).

### Case 2

An 82-year-old man was transferred from another hospital for further evaluation and treatment. Approximately 4 months before transfer, he underwent several lumbar epidural blocks for low back pain. One month after these procedures, his low back pain worsened and developed a fever. Laboratory investigations revealed an increased WBC count of 13700/μL, ESR of 93 mm/h, and CRP of 51.0 mg/L. Lumbar MRI at another hospital suggested infectious spondylitis at L4 and L5 (Fig. 2A). He underwent IV antibiotic therapy with moxifloxacin and cefixime. During 2 months of IV antibiotic therapy, low back pain was relieved and the fever and inflammatory markers steadily decreased. The inflammatory markers subsequently increased rapidly, and additional IV antibiotic therapy



**Fig. 1.** Case 1. A : Lumbar coronal contrast-enhanced CT showing postoperative infection with abscess formation along the screw heads and rods (black arrow) before antibiotics therapy. B : CT obtained after antibiotic therapy for 2 months showing complete disappearance of abscess. C : The course of inflammatory markers with ESR and CRP, BT, and eosinophil. ESR : erythrocyte sedimentation rate, CRP : C-reactive protein, BT : body temperature, POD : postoperative day, CT : computed tomography.

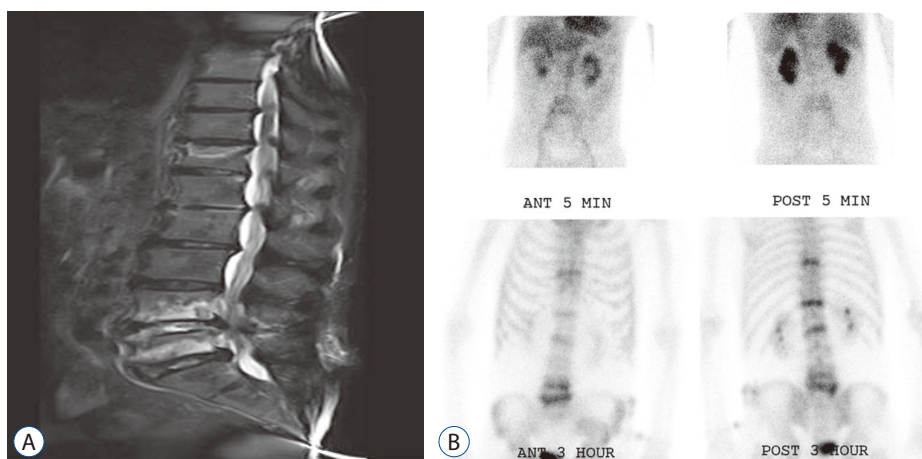
for suspected relapse of infectious spondylitis was recommended. However, the patient's family rejected the recommendation and requested a transfer to the university hospital. Laboratory investigation on admission to our hospital revealed a ESR 41 mm/h, CRP of 27.15 mg/L, WBC count of 9400/ $\mu$ L, neutrophil count of 6400/ $\mu$ L, and eosinophil count of 170/ $\mu$ L. A three-phase bone scan with Tc-99m 2,3-dicarboxypropane-1,1-diphosphonate was compatible with active spondylodiscitis at L4 and L5 (Fig. 2B). We suspected an adverse drug effect and recommended stopping antibiotic therapy because he had abdominal pain with diarrhea, the inflammatory markers were not extremely elevated, the pain was not manageable, and there was no fever. We advised his family that we would perform isolation and microbial culture and resume antibiotic therapy if the inflammatory markers increased after stopping the antibiotics. Two weeks after stopping the antibiotics, the all laboratory tests returned to normal. His pain resolved and he was discharged 2 weeks after admission.

## DISCUSSION

Infectious spondylitis is defined as an infection of one or more components of the spine by a specific organism<sup>7</sup>. Most patients with infective spondylitis can be treated conservatively with antibiotics<sup>5,6</sup>. Because the clinical symptoms vary widely in the early stages, it is difficult to differentiate infectious spondylitis from other diseases, resulting in delayed diagnosis or misdiagnosis. The onset of symptoms is commonly

insidious, with spinal pain being the most common presenting complaint. Although more than 90% of cases are pyogenic<sup>6,9</sup>, fever is typically not present and occurs in less than 20% of patients<sup>6,13</sup>.

The WBC count, ESR, and CRP are indicators of inflammation in patients with infectious spondylitis. The WBC count is elevated in 40–66% of patients, and is not particularly useful in making a diagnosis of infectious spondylitis<sup>13</sup>. The ESR is a sensitive indicator of infectious spondylitis, and is positive in 76–81% of patients at the time of diagnosis, with levels ranging from 43–87 mm/h in pyogenic spondylitis<sup>4,13</sup>. Elevation of ESR is correlated with the inflammatory response but is not specific for infection. The ESR is often significantly affected by many factors other than the acute phase reaction<sup>7</sup>, including the plasma albumin level; the size, shape, and number of red blood cells; and non-acute phase reaction proteins, in particular normal and abnormal immunoglobulins. The lack of specificity of the ESR means the test is more likely to be falsely positive than the CRP. Moreover, the slow response of ESR to the acute phase reaction leads to false negatives early in an inflammatory process<sup>8</sup>. Despite the nonspecific nature of an elevation in the ESR, this test provides additional data regarding the possible presence of infection and some information on the response to treatment. CRP is a useful marker of the acute phase reaction as it responds quickly to the inflammatory process<sup>7,11</sup>. It is an acute phase protein synthesized by hepatocytes. Although CRP activation of complement increases inflammation and tissue damage, it also has some anti-inflammatory activity, and acts as a promoter and down-regulator of inflammation<sup>11</sup>. CRP is elevated in 90% or



**Fig. 2.** Case 2. A : Sagittal fat-suppressed T2-weighted image showing infectious spondylitis at L4 and L5. B : A three-phase bone scan shows active spondylodiscitis at L4 and L5.

more of patients with spinal infection, but is more specific than ESR and normalizes postoperatively or after appropriate treatment of an infectious process, more rapidly than the ESR<sup>7,11</sup>). A majority of patients with infective spondylitis can be treated without surgery. Although the optimal duration is not well defined, several studies recommend 6–8 weeks of IV antibiotics and others recommend only 4 weeks<sup>5,6,13</sup>). Insufficient IV antibiotic therapy for less than 4 weeks may result in a high recurrence rate. Some authors advise use of IV antibiotics until the CRP is normal<sup>6</sup>).

Antibiotics are used for the treatment and prevention of many infectious disorders and are thought to be safe when applied properly. However, like all drugs, they also show various adverse effects in some patient conditions<sup>17</sup>). Antibiotic complications can affect the hematologic, cardiac, respiratory, gastrointestinal, hepatobiliary, renal, genitourinary, rheumatologic, dermatologic, and neurologic systems, and can cause a drug fever<sup>17</sup>). Multiple antibiotics are associated with QT prolongation and may increase the risk of sudden cardiac arrest due to torsades de pointes<sup>10</sup>). Patients treated with antibiotics frequently experience diarrhea. Although *Clostridium difficile* infection is obviously of great concern, the majority of diarrhea cases will not be attributable to this infection. Nausea is frequently encountered and it is often difficult to identify a specific cause, although it should be noted that there are some antibiotics for which this is a very common side effect<sup>3</sup>). The most common dermatologic adverse reaction associated with antibiotic therapy is a drug-induced exanthem, or “drug rash.” Parenteral therapy with beta-lactams (penicillins and cephalosporins) is associated with drug-induced fever, as is therapy with several other antibiotics including sulfonamides<sup>15</sup>).

A research carried out at six pharmacovigilance centers in Korea reported that antibiotics including vancomycin were the most frequent causes of adverse reactions of drug, and that cutaneous symptoms were the most common manifestations in adverse reactions<sup>12</sup>). In this study, 3.1% of 1418 cases were associated with vancomycin. An et al.<sup>1</sup>) reported that the skin rashes associated with increased peripheral eosinophil, representing suspected immune-mediated delayed hypersensitivity reactions, are a common adverse reaction of vancomycin. Eosinophilia is considered when absolute eosinophil count exceeds 500/ $\mu$ L in peripheral blood. Peripheral eosinophilia can be caused by parasitic infections, allergy, drug reactions, leukemia, and non-hematologic malignancies<sup>14</sup>). The author

treated infectious spondylitis with vancomycin in case 1 patient. During the period of treatment with vancomycin, inflammatory markers decreased gradually. However, after 2 months, the inflammatory markers subsequently increased rapidly, and whole-body pruritus and skin rash were observed. Laboratory tests revealed significant eosinophilia. The author suspected that an adverse effect of allergic reaction of adverse drug effects.

Case 2 patient treated with moxifloxacin and cefixime had no eosinophilia or skin symptoms other than abdominal pain due to diarrhea. Antibiotic-associated diarrhea is defined as unexplained diarrhea association with antibiotic administration<sup>3</sup>). Although the frequency of antibiotics-associated diarrhea depends on the antibiotics, it occurs in approximately 5.2 to 6.2% of patients who are treated with moxifloxacin and 15 to 20% of those who receive cefixime<sup>2,3</sup>). A common first step is to identify cases of antibiotic-associated diarrhea that are due to *Clostridium difficile* infection, because this is the most common identifiable and treatable pathogen. The tests used for diagnosis depend on the type of laboratory investigations available. Enzyme immunoassays for detecting toxin A or toxins A and B are generally available<sup>3</sup>). In case 2, *Clostridium difficile* toxin was not detected. Only 10–20% of the stool specimens submitted for testing of *Clostridium difficile* toxins are reported as positive<sup>16</sup>). Antibiotic-associated diarrhea can also be caused by other enteric pathogens, direct effects of antibiotics on the intestinal mucosa, and the metabolic consequences of reduced concentrations of fecal flora. Many patients with enteric disease caused by antibiotics have a response to withdrawal of the inducing agent<sup>3,16</sup>). The author thought that a direct effect of antibiotics affected the digestive system has increased levels of inflammatory marker in case 2 patient. After stopping antibiotics, the inflammatory markers in both cases rapidly returned to normal.

## CONCLUSION

As with any medication, antibiotics can cause side effects. Most antibiotics do not cause problems if it used properly and serious side effects are rare. It is possible that the inflammation due to these antibiotic complications may result in a greater increase in the inflammatory markers. The differential diagnosis between antibiotic side effects and infection should

be considered very carefully because the treatment is completely different. We should identify the systemic symptoms of patient and closely monitor laboratory tests including complete blood counts for accurate detection of the side effects of antibiotics when following inflammatory markers during treatment of infectious spondylitis. The antibiotics cannot be effective and the inflammation may not be well controlled when the elevation of the inflammatory marker is accompanied by eosinophilia or diarrhea. Further observations are necessary to clarify the clinical and laboratory significance of this phenomenon.

## CONFLICTS OF INTEREST

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

## INFORMED CONSENT

Informed consent was obtained from all individual participants included in this study.

## AUTHOR CONTRIBUTIONS

Conceptualization : KSE

Data curation : KSE

Formal analysis : KSE

Funding acquisition : KSE

Methodology : KSE

Project administration : KSE

Visualization : KSE

Writing - original draft : KSE

Writing - review & editing : KSE

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