Investigations of Hospitalized Cases of Pyogenic Vertebral Osteomyelitis

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Abstract
Pyogenic vertebral osteomyelitis is difficult to diagnose and treat. The duration of antibiotic therapy, the administration of treatment, and several other factors regarding pyogenic vertebral osteomyelitis remain controversial. The aim of this investigation was to examine its diagnosis and treatment and consider possible solutions. This was a retrospective study of 11 cases of hospitalized patients with pyogenic vertebral osteomyelitis, including their diagnosis, treatment, and other factors. The diagnosis of vertebral osteomyelitis was confirmed with the combination of imaging and biological evidence. The Erythrocyte Sedimentation Rate (ESR) level served as an index to determine the duration of therapy. The duration from symptom onset to diagnosis was 3–63 (median 10) days. Rate of positive blood cultures were obtained in 8 cases (72.7%). The most frequent comorbidity was infective endocarditis in 4 cases (36.6%). Affected vertebrae were lumber spine in 9 cases (81.8%) and multiple level involvement in 8 cases (72.7%). The mean duration of antibiotic therapy was 69.6 ± 17.9 days, with no recurrence. Patients diagnosed with pyogenic vertebral osteomyelitis require careful examination for infective endocarditis. Lumber level and multiple level involvement were more frequent than had previously been reported. Based on our experience, C-reactive Protein (CRP) is more useful than ESR as an index to evaluate the clinical response to therapy and may help determine the duration of treatment. It is important for general physicians to monitor vertebral osteomyelitis properly and provide an appropriate diagnosis and treatment.

Key words
pyogenic vertebral osteomyelitis, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)

Introduction
Infection of the intervertebral disc and the adjacent vertebrae, variably referred to as spondylodiscitis, disk-space infection, and vertebral osteomyelitis, all with or without associated epidural or iliopsoas abscess, is hematogenous in origin in most cases1. Vertebral osteomyelitis is a rare infectious disease that causes back pain. Diagnosis and treatment of vertebral osteomyelitis is difficult, and the duration of antibiotic therapy and comorbid disease is controversial2–4. There are few studies about the validity of C-reactive protein (CRP) or Erythrocyte Sedimentation Rate (ESR) to determine the duration of therapy. The details of this decision will be addressed in the future.

But to provide a more precise assessment and diagnosis, we added imaging and biological examinations. In this article, we investigated the accuracy of our di-

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agnosis and treatment. The aim of this investigation was to examine the diagnosis and treatment of vertebral osteomyelitis and consider possible solutions.

Materials and Methods

We studied 11 cases of vertebral osteomyelitis (6 male, 5 female). All patients were hospitalized at the Division of General Internal Medicine, St. Marianna University Hospital, from January 2012 to December 2013. St. Marianna University Hospital is a core medical facility of Eastern Kanagawa Prefecture, Japan. The diagnosis of vertebral osteomyelitis was confirmed with the combination of imaging and biological evidence. Imaging evidence included computed tomography and/or magnetic resonance imaging. Biological evidence included cultures from bone or disc biopsy, or sustained bacteremia. We defined the appearance of initial symptoms as back pain or a fever higher than 37.5 centigrade. Pathogenic bacterium was identified by blood culture, abscess, or intervertebral disc biopsy. Affected vertebrae were identified by imaging study (computed tomography or magnetic resonance imaging). More than three vertebrae were identified as poly-affected cases. Intravenous antimicrobial agents were chosen according to the type of microorganism and its susceptibility. The duration of antibiotic therapy was determined by measuring ESR once a week; antibiotic therapy ended once ESR became stable. We investigated the following items: the time period between the onset of initial symptoms and diagnosis, initial symptoms, the presence or absence of antibiotic therapy before inspection, pathogenic bacterium, the identification source of pathogenic bacterium, the duration of antibiotic therapy, the presence or absence of surgical operation, underlying illness, complication, the level and number of affected vertebrae, administered antimicrobial agents, and the recurrence of osteomyelitis. We also investigated the relationship between preceding load of antibiotics and identification of pathogenic bacteria. Significant differences between these groups were determined using Fisher’s direct probability (2 tailed). The difference was significant at <0.05. Statistical analysis was performed using Excel 2003 (Microsoft, Seattle, WA) with the add-in software Statcel 3rd ed.

Results

The mean age was 69 ± 13 (mean ± SD) years old. The period between the onset of initial symptoms and diagnosis was 3–63 (median 10) days. The initial symptoms were back pain in 7 cases (63.6%) and fever in 4 cases (36.6%). Five cases (45.5%) had already been treated by antibiotics before diagnosis and 3 (60%) of these 5 cases were unable to identify a pathogenic bacterium. Previous administration of antimicrobial agents plays a large factor in the inability to identify pathogenic microorganisms (p=0.048). Pathogenic bacterium were identified as methicillin-sensitive Staphylococcus aureus (MSSA): 3 cases (27.2%), Staphylococcus epidermidis: 1 case (9.1%), Streptococcus agalactiae: 1 case (9.1%), Streptococcus oralis: 1 case (9.1%), Escherichia coli: 1 case (9.1%), Klebsiella pneumoniae: 1 case (9.1%), Unknown: 3 cases (27.2%). There were 8 cases (72.7%) of identifiable pathogenic bacterium detected in blood culture. Four cases (50.0%) were detected in abscess, and 7 cases (63.6%) were detected in tissue. Microbiological diagnosis was established in 8 (72.7%) cases. The mean duration of antibiotic therapy was 69.6 ± 17.9 days. The value of CRP at the end of treatment was 0.20 ± 0.32 mg/dL. The value of ESR at the end of treatment was 44.2 ± 23.5 mm/hr. Two cases (18.2%) necessitated surgical treatment after initiation of antibiotic therapy. Details of surgical therapy were fenestration and irrigation for epidural abscess and drainage for iliopsoas abscesses. Underlying illnesses were diabetes mellitus: 4 cases (36.6%), hepatic cell cancer: 1 case (9.1%), and lumbar disk herniation: 1 case (9.1%). Comorbid illnesses were infective endocarditis: 4 cases (36.6%) and endophthalmitis: 1 case (9.1%). Complications were epidural abscess: 1 case (9.1%) and deep venous thrombosis: 1 case (9.1%). The level of affected vertebrae was the cervical spine: 2 cases (18.2%), thoracic spine: 2 cases (18.2%), lumber spine: 9 cases (81.8%), and sacral spine: 2 cases (18.2%). The mean number of affected vertebrae was 2.7 ± 1.4. Eight cases (72.7%) of 11 cases were poly-affected (more than 3 vertebrae affected). Intravenous antimicrobial agents were Cephazolin (CEZ): 3 cases (27.2%), Penicillin G (PCG): 2 cases (18.2%), Cefotiam (CTM): 1 case (9.1%), Ceftriaxone (CTRX): 1 case (9.1%), Ampicillin (ABPC): 1 case (9.1%), Meropenem (MEPM): 1 case (9.1%), Teicoplanin (TEIC): 1 case (9.1%), and none: 1 case (9.1%). There was no recurrence of osteomyelitis.

Discussion

Early diagnosis of vertebral osteomyelitis is difficult. The median duration of our study to the diagnosis was 10 days. In one large investigation, only
28% of the episodes were diagnosed within the first month of onset of initial symptoms\(^5\). However, diagnostic delay is an independent risk factor for adverse outcomes\(^5\)\(^6\). There is often a considerable delay between the onset of symptoms and diagnosis (a range of 42 to 59 days in five studies\(^2\)\(^-\)\(^10\)). The reported median of the total duration to the diagnosis was 19 days\(^6\). In one study, the initial misdiagnosis rate was 34% with an average delayed diagnosis time of 2.6 months\(^11\). The initial symptoms were back pain in 7 cases (63.6%) and fever in 4 cases (36.6%). Back pain is the most common initial symptom of vertebral osteomyelitis; in the analysis of 14 case series, back pain was reported in 86% of the cases\(^12\). Fever is not invariably present (reported frequency, 35% to 60%)\(^12\)\(^13\). The differential diagnosis of back pain in a febrile patient is broad, including pyelonephritis, pancreatitis, and many other causes (e.g., viral infection syndrome). In the absence of fever, back pain may be attributed to multiple other causes. For patients with back pain and fever, some guidelines recommend MRI should be the first diagnosis imaging step\(^14\)\(^-\)\(^16\).

As in many other studies\(^6\)\(^8\)\(^13\), \(S.\) \(aureus\) was the most frequent isolated microorganism. As the metillin-resistant \(Staphylococcus aureus\) (MRSA) increases, the relative importance of MRSA as a cause of vertebral osteomyelitis simultaneously increases. However, MRSA was not identified in our study, possibly because most of our patients were not affected after surgical intervention.

In a systematic review, positive blood cultures were reported in 58% of cases (range across studies, 30 to 78%)\(^13\). In our facilities, positive blood cultures rate were obtained 72.7%, higher than the reported average. Combined with tissue biopsy, microbiological diagnosis was finally established in 72.7% cases, provided that the patient did not receive antimicrobial therapy before microbiological diagnosis was established. To provide a sure diagnosis, we actively added examinations other than blood cultures, except in the case of all blood culture bottles being positive. If vertebral osteomyelitis is suspected after imaging is performed, and blood cultures do not show sure growth of microorganisms, a biopsy is generally warranted.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Gender</th>
<th>Underlying Illness, Complication</th>
<th>Duration of Antibiotic Therapy</th>
<th>Level of Affected Vertebrae</th>
<th>Number of Affected Vertebrae</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>M</td>
<td>DM</td>
<td>83</td>
<td>C5–7, L5/S1</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>83</td>
<td>F</td>
<td>EO, IE</td>
<td>56</td>
<td>Th12/L1</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>76</td>
<td>F</td>
<td>DVT</td>
<td>70</td>
<td>L3/4</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>F</td>
<td>IE</td>
<td>55</td>
<td>L3/4</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>83</td>
<td>F</td>
<td>DM</td>
<td>66</td>
<td>L2–4</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>69</td>
<td>M</td>
<td>DM</td>
<td>87</td>
<td>C7/Th1, Th10/11, L1/2</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>66</td>
<td>F</td>
<td>IE</td>
<td>110</td>
<td>S1/2</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>59</td>
<td>M</td>
<td>LDH</td>
<td>72</td>
<td>L4/5</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>76</td>
<td>M</td>
<td>HCC, HCV</td>
<td>55</td>
<td>L1/2</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>71</td>
<td>F</td>
<td>Sepsis</td>
<td>70</td>
<td>L2–4</td>
<td>3</td>
</tr>
<tr>
<td>11</td>
<td>38</td>
<td>M</td>
<td>None</td>
<td>42</td>
<td>L4/5</td>
<td>2</td>
</tr>
</tbody>
</table>

M: male, F: female

Table 1. Patient Characteristics

Table 2. Frequency of Affected Level with Vertebral Osteomyelitis

<table>
<thead>
<tr>
<th>Affected level</th>
<th>Total number of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>2 (18.2%)</td>
</tr>
<tr>
<td>Thoracic</td>
<td>2 (18.2%)</td>
</tr>
<tr>
<td>Lumber</td>
<td>9 (81.8%)</td>
</tr>
<tr>
<td>Sacral</td>
<td>2 (18.2%)</td>
</tr>
</tbody>
</table>
A culture of a biopsy specimen has a higher overall diagnostic yield than does a blood culture (77%; range across studies 47 to 100%) \(^{13}\). An antibiotic-free interval of 1 to 2 weeks would allow a higher microorganism diagnostic yield.

It is thought to be good to treat patients with negative cultures despite repeat biopsies, based on organisms that most likely to cause infection. An appropriate empiric regimen consists of vancomycin, plus one of the following: cefotaxime, ceftazidime, ceftriaxone, cefepime, or ciprofloxacin. If such empiric therapy does not result in objective clinical improvement in three to four weeks, a third percutaneous biopsy should be performed.

There have been no investigations about the cause of negative cultures of pyogenic vertebral osteomyelitis. In our study, previous administration of antimicrobial agents played a large role in the inability to identify pathogenic microorganisms. In a study of 63 patients with blood culture negative infective endocarditis (IE) analysis, two-thirds of the 32 patients for whom no pathogen was identified had received antibiotics before blood was cultured.\(^{17}\) A total of 107 patients with a diagnosis of IE was studied retrospectively. Twenty patients (18.7%) with negative-culture endocarditis comprised the study population. The main reason for negative blood culture in bacteremia is administration of antibiotics before sample withdrawal 14 (70%) had received previous antibiotic therapy before blood was cultured.\(^{17}\) A total of 107 patients with a diagnosis of IE was studied retrospectively. Twenty patients (18.7%) with negative-culture endocarditis comprised the study population. The main reason for negative blood culture in bacteremia is administration of antibiotics before sample withdrawal 14 (70%) had received previous antibiotic therapy before blood was cultured.

The most frequent comorbidity was infective endocarditis. Endocarditis is diagnosed in up to a third of reported cases proving the necessity of careful examination for infective endocarditis under the existence of pyogenic vertebral osteomyelitis\(^ {19}\).

There are no data from controlled trials that suggest the optimal duration of therapy. The recommended duration ranges from 4 to 6 weeks to 3 months\(^ {5}\). In our facilities, the ESR level served as an index to determine the duration of therapy. The mean duration of antibiotic therapy was 69.6±17.9 days, with no resulting recurrence.

Increasing leukocyte counts do not have high sensitivity for the diagnosis of osteomyelitis\(^ {20,22}\). However, CRP and ESR are highly sensitive and have been reported in 98% and 100% of cases\(^ {21,23}\). In the case of continuously normal values of CRP or ESR, the diagnosis of pyogenic vertebral osteomyelitis may be ruled out\(^ {20}\). But our results could not show which marker is more correlated to a clinical response to therapy. There are reports that the value of CRP is more closely correlated with the clinical response to therapy than is the value of ESR. However, that is true in the case of post-operative spinal wound infections\(^ {23}\). The normal value range of ESR is likely affected by various factors such as age, gender, and race. Based on our experience, CRP is more useful than ESR as an index to evaluate the clinical response to therapy and may help to determine the duration of treatment period. Determining the duration of therapy remains a controversial but important matter.

Pyogenic hematogenous vertebral osteomyelitis can usually be treated with antibiotics alone. Surgery may be needed to drain an abscess, although drainage with CT or X-ray image-guided catheter is sufficient in many cases\(^ {20}\). Pyogenic vertebral osteomyelitis may be complicated by direct seeding in different compartments, resulting in paravertebral, epidural, or iliopsoas abscess. In one study, pyogenic vertebral osteomyelitis was complicated by paravertebral abscess in 26% of cases, epidural abscess in 17% of cases, and disk space abscess in 5% of cases. Neurologic complications were reported in 33–38% of the patients\(^ {20,25}\).

The most common site is the lumber spine (58%), followed by the thoracic spine (30%) and the cervical spine (11%)\(^ {12}\). Another study reports that the lumber and lumbar sacral involvement rate was 68%\(^ {20,25}\). Our study showed a more frequent occurrence of lumber spine. Even if there were no localized symptoms, we actively added whole spine imaging examinations to provide a sure diagnosis. Multiple level involvement can be rare, as it was reported in only one case\(^ {25}\). However, in our study, multiple level involvement was observed in 72.7% of cases of pyogenic vertebral osteomyelitis, more frequent than has been reported previously.

Pyogenic vertebral osteomyelitis is an important illness for learning more about diseases involving back pain and/or fever. We believe that accurate knowledge of the illness is a prerequisite for general physicians and management to provide an appropriate diagnosis and treatment.

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