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Outcome of culture-negative pyogenic vertebral osteomyelitis: Comparison with microbiologically confirmed pyogenic vertebral osteomyelitis

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ABSTRACT

Objectives: Although pyogenic vertebral osteomyelitis (PVO) with no identified microorganism is treated empirically, the clinical outcome is not well understood.
Methods: We conducted a retrospective review of patients with PVO at a tertiary-care hospital from 2000 through 2012. The study compared clinical features and outcomes of microbiologically confirmed (M-PVO) with clinically diagnosed PVO (C-PVO).
Results: Of 151 patients with PVO, 75 (49.7%) had M-PVO. Compared to patients with M-PVO, patients with C-PVO had fewer underlying medical conditions. In addition, they presented less frequently with fever, high acute-phase reactants levels, and paraspinal abscess. The rate of treatment failure tended to be lower in the C-PVO group [9.2% (7/76) vs. 17.3% (13/75); $p = 0.157$]. The overall relapse rate was 6.6% and did not differ significantly between groups; notably this rate was higher in patients who received antibiotics for ≤ 6 weeks [18.8% (3/16)] and ≤ 8 weeks [12.1% (4/33)]. The independent risk factors for treatment failure were higher CRP levels [odds ratio (OR) = 1.087; 95% confidence interval (CI): 1.025–1.153; $p = 0.005$] and fever $\geq 37.8^{\circ}$C (OR = 8.556; 95% CI: 2.273–32.207; $p = 0.002$).
Conclusions: Patients with C-PVO had less systemic inflammatory response and a more favorable outcome compared to M-PVO. Prolonged antibiotic therapy, for at least 8 weeks, might be required for C-PVO, as well as for M-PVO until better outcomes are assured.

Introduction

The identification of microorganisms is necessary to guide appropriate antibiotic therapy for pyogenic vertebral osteomyelitis (PVO). Due to the low frequency of positive blood cultures, a computed tomography (CT)-guided bone biopsy or a surgical biopsy is often required to identify pathogens [1,2]. Despite exhaustive efforts, the causative microorganisms are often not identified microbiologically. A recent study reported an increasing incidence of PVO with no microbiologic diagnosis [3]. PVO with unidentified pathogen is empirically treated with antibiotics. A few studies have investigated the clinical outcome of culture-negative PVO [3,4]. However, the effectiveness of empirical antibiotic therapy has not been well established.

We conducted a retrospective study to evaluate clinical features and outcomes of PVO with unknown pathogens compared to those of PVO with identified microorganisms.

Methods

Study population, design, and data collection

A retrospective study was performed at Samsung Medical Center, a 1950-bed tertiary-care university hospital in South Korea. We reviewed the medical records of all patients diagnosed with

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PVO from January 2000 through December 2012. Patients older than 18 years were included in the study if they were diagnosed with a first episode of PVO. Patients who underwent spinal surgery or had prior spinal instrumentations were excluded because PVO after spinal surgery is usually caused by more resistant pathogens and instrumentations are frequently associated with treatment failure without a removal. Patients with PVO caused by *Mycobacterium tuberculosis*, brucellosis, and fungus were also excluded. Abstracted data included demographics, comorbidities, clinical presentations, vital signs, laboratory tests, radiologic findings, diagnostic procedures, microbiology, medical and surgical treatment, and outcome. History of perivertebral procedures, including epidural injection and acupuncture of the back, was also reviewed.

Definitions

The diagnostic criteria for PVO were a clinical illness compatible with vertebral infection and evidence of spinal structure involvement on conventional radiologic images, such as radiographs, CT, or magnetic resonance image (MRI) [5]. According to the isolated microorganisms, patients were classified into 2 groups, clinically diagnosed PVO (C-PVO) and microbiologically confirmed PVO (M-PVO) [6]. C-PVO was defined as a patient with clinical features and radiological findings compatible with PVO but without an identified microorganism [4,7]. A patient with PVO was considered to have M-PVO if microorganisms were isolated from any of following specimens: the blood, the involved vertebra, the intervertebral disk space, or a paravertebral or epidural abscess. The microbiological diagnosis was established through blood samples or vertebral tissue obtained by CT-guided percutaneous needle aspiration and/or biopsy or by open biopsy. Antimicrobial therapies were not standardized; they were selected by treating physicians. Therapeutic antibiotics for M-PVO were defined as appropriate antibiotics if the isolated microorganisms were susceptible to them based on in vitro susceptibility tests.

Outcome and follow-up

Outcomes were categorized as treatment success or treatment failure. Treatment success was defined as survival and absence of signs of infection at the end of the therapy, regardless of persistence of clinically significant residual disability such as neurologic bladder, motor weakness or paralysis, or pain [8]. The criteria for treatment failure were (i) "death", either caused by or associated with PVO; (ii) "recrudescence," re-aggravation of clinical signs, symptoms, and high acute-phase reactants such as erythrocyte segmentation rate (ESR) or C-reactive protein (CRP), following initial improvement, or isolation of the same microorganisms in new samples during the treatment; and (iii) "relapse," reappearance of clinical symptoms and a vertebral lesion meeting the diagnostic criteria for PVO after the completion of the treatment [3,5].

Statistical analysis

The Student *t*-test and the Mann–Whitney test were used to compare continuous variables. For categorical variables, the χ^2 and the Fisher exact tests were performed. All *p*-values were 2-tailed, and $p < 0.05$ was considered to be statistically significant. The cumulative rate of treatment failure-free survival was estimated by the Kaplan–Meier method. The equality of treatment failure between groups was tested with the log-rank test. A stepwise logistic regression analysis was used to control for potential confounding. Variables with $p < 0.1$ in the univariate analysis were included in the multivariate analyses to control for confounding and identify independent risk factors. Data were analyzed using the SPSS version 21.0 (SPSS Inc., Chicago, IL).

Results

Demographics and clinical characteristics

A total of 270 patients with a diagnosis of vertebral osteomyelitis were identified during the study period. A total of 119 patients were excluded because of postoperative PVO ($n = 39$), prior spinal instrument ($n = 42$), tuberculosis ($n = 37$), and brucellosis ($n = 1$). A total of 151 patients were included in this study, 75 (49.7%) had M-PVO. The comparisons of demographics and clinical characteristics of the M-PVO and C-PVO groups are described in Table 1. Compared to the M-PVO group, the C-PVO group had less frequently coexisting medical conditions. A history of perivertebral procedures and prior antibiotic exposure were more common in the C-PVO group. The body temperature, ESR, and CRP were significantly lower in C-PVO group. Paraspinal abscesses were observed significantly more often in the patients with M-PVO.

Causative microorganisms

Bacteremia was detected in 42 (35.9%) of 117 patients and in 56% (42/75) of the M-PVO group. Cultures of specimens obtained by CT-guided percutaneous needle aspiration and/or biopsy were positive in 21 (18.9%) of 111 patients. Open biopsies were performed in 15 patients and were positive in 4 (26.7%). Five patients were not evaluated by either blood or bone culture. For 8 patients with negative cultures obtained by CT-guided percutaneous approaches, subsequent cultures by open biopsy were positive in 2 (25%) cases. Causative microorganisms are listed in Table 2. Among the patients with M-PVO, the most common pathogen was *Staphylococcus aureus* [42.7% (32/75)], followed by *Streptococcus* spp. [18.7% (14/75)] and *Escherichia coli* [17.3% (13/75)]. Among the 32 cases caused by *S. aureus,* 14 (43.8%) were methicillin-resistant *S. aureus* (MRSA). The following predisposing extra-vertebral infections were found in 31 (20.5%) patients: 10 urinary tract infections, 8 infective endocarditis, 7 skin and soft tissue infections, 3 intra-abdominal infections, 2 central-line associated bloodstream infections, and 1 meningitis.

Treatment

Among the 151 patients, 110 (72.8%) received more than 8 weeks of antibiotics. Total duration of antibiotic therapy was similar in the 2 groups [mean $\pm$ standard deviation (SD), M-PVO vs. C-PVO, 109.6 $\pm$ 89.0 vs. 101.9 $\pm$ 67.1 days, respectively; $p = 0.548$]. However, patients with C-PVO were treated with a shorter duration of parenteral antibiotics than were patients with M-PVO (mean $\pm$ SD, 34.7 $\pm$ 17.7 and 47 $\pm$ 28.6 days, respectively; $p = 0.002$). The regimens of therapeutic antibiotics were not different between the M-PVO and C-PVO groups (Table 3). Most patients received parenteral antibiotics; however, 7 (4.7%) patients were initially treated with oral antibiotic agents. The most commonly administered parenteral antibiotics were first-generation cephalosporins, which were selected more frequently for the C-PVO group [52.6% (40/76) vs. 25.3% (19/75); $p = 0.001$]. Surgical treatment, abscess drainage in 24 patients and spinal cord decompression in 7 patients, was performed in 31 (20.5%) patients, and the frequency of surgery did not significantly differ between the 2 groups [M-PVO vs. C-PVO, 24% (18/75) vs. 17.1% (13/76), respectively; $p = 0.320$].