Recurrent *Stenotrophomonas maltophilia* Bacteremia after Iliac Crest Bone Graft Harvest

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Abstract

We describe a rare case of recurrent *Stenotrophomonas maltophilia* bacteremia in a previously healthy 45-year-old man. The infection was caused by osteomyelitis at the site of an iliac crest bone graft harvest. A genetic analysis using enterobacterial repetitive intergenic consensus polymerase chain reaction (ERIC-PCR) revealed that the blood isolates and pathogens obtained from the surgical wound were identical. Initial treatment with levofloxacin and cefazopran was ineffective, but the patient's infection was successfully treated by long-term administration of latamoxef and trimethoprim-sulfamethoxazole. The present case suggests that attention should be given to the possibility of *S. maltophilia* infection in any situations.

Key words: enterobacterial repetitive intergenic consensus (ERIC)-PCR, latamoxef (LMOX), nosocomial infection, *Stenotrophomonas maltophilia*, surgical site infection, osteomyelitis

(Intern Med 53: 1693-1698, 2014)

(DOI: 10.2169/internalmedicine.53.1995)

Introduction

Stenotrophomonas maltophilia is an opportunistic pathogen of increasing importance. This gram-negative aerobic bacillus is not a highly virulent pathogen, but it is a multi-resistant waterborne organism that ubiquitously inhabits our living environment (1). *S. maltophilia* has been isolated from several in-hospital sources (2), and cross-infections of the organism between patients or transmission by healthcare workers has been reported (3). A previous large-scale worldwide study showed that *S. maltophilia* was the third most frequently isolated nonfermentative bacterium after *Pseudomonas aeruginosa* and *Acinetobacter* spp. (4).

Although a variety of infections associated with *S. maltophilia* have been reported, the organism has rarely affected the musculoskeletal system (5). Only a few cases of surgical site infection (SSI) after orthopedic surgery (6-8), trauma (9), or osteomyelitis (10-13) have been described in

previous reports. We herein describe a case of recurrent *S. maltophilia* bacteremia caused by right ilium osteomyelitis secondary to iliac crest bone graft harvest.

Case Report

A previously healthy 45-year-old man who had undergone corrective osteotomy on his right clavicle for thoracic outlet syndrome five months before subsequently received reconstructive surgery to treat nonunion of his right clavicle with an autogenous right iliac crest bone graft harvest (day 0). Two weeks after the operation, the surgical site of the right ilium was found to be infected with methicillin-sensitive *Staphylococcus aureus* (MSSA), and oral antibiotic therapy (cefdinir, a third-generation cephalosporin) was initiated. However, the infection was uncontrollable, and a re-operation for irrigation and debridement (I&D) against the harvesting site was performed on day 51.

Even after the re-operation, discharge of bloody exudate

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Received for publication October 24, 2013; Accepted for publication January 27, 2014

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Figure 1. Pelvis MRI. A, B: T2-weighted images on day 69. C, D: Contrast-enhanced T1-weighted image on day 111. Fluid retention and inflammatory changes in soft tissues were observed around the harvesting site and extending to the lateral side of the great trochanter. Bone marrow edema was apparent at the right ilium (arrows). The hypointense materials on the lateral side of the right ilium are the cement.

Table. Antimicrobial Susceptibility Testing of *Stenotrophomonas maltophilia*

Antibiotics	MIC (μg/mL)
Imipenem	>16
Meropenem	4
Biapenem	>16
Doripenem	16
Piperacillin/Tazobactam	>64
Ceftazidime	>16
Cefepime	4
Cefozopran	4
Aztreonam	>16
Gentamycin	>16
Tobramycin	>32
Amikacin	>32
Minocycline	≤0.5
Ciprofloxacin	4
Levofloxacin	1
Tosufloxacin	1
Colistin	8
Polimixin-B	1
Rifampicin	8
Latamoxef	1
Trimethoprim/Sulfamethoxazole	0.125/2.375

MIC: minimum inhibitory concentration (μg/mL)

continued, and both *S. maltophilia* and MSSA were isolated from the wound culture. Although administration of levofloxacin (LVFX) was initiated, his inflammatory state deteriorated. Fluid retention around the harvesting site and bone marrow edema of the right ilium, suggestive of wound infection, were confirmed by magnetic resonance imaging (MRI) on day 69 (Fig. 1A, B). Additionally, the patient's

blood culture became positive for *S. maltophilia*, even under administration of LVFX. The antimicrobial susceptibility testing results for *S. maltophilia* are shown in Table. According to the advice of an infectious disease specialist, treatment with ceftazopran (CZOP) and gentamicin in addition to LVFX was commenced, and the combination therapy was continued for 10 days. The treatment was changed to daptomycin (DAP) because methicillin-resistant *S. aureus* (MRSA) was newly detected from the wound culture. Five days later, *S. maltophilia* bacteremia recurred, and this time, *Acinetobacter baumannii* was simultaneously isolated from blood culture. The combination of LVFX and CZOP was re-administered, and a second I&D was performed on day 92. At that time, cement mixed with vancomycin and minocycline (MINO) was embedded in the surgical site.

The clinical course after the second re-operation was relatively good, and the patient's inflammatory status improved. However, *S. maltophilia* and *A. baumannii* were again isolated from blood culture after stopping the combination therapy. At that time, the case was referred to us. We performed gallium scintigraphy, which only showed positive uptake at the harvest site, and whole body contrast-enhanced computed tomography (CT) was negative for any other infectious sites. The findings from contrast-enhanced MRI were compatible with wound infection and osteomyelitis of the harvest site (Fig. 1C, D). Based on these results, we made a definitive diagnosis of osteomyelitis caused by *S. maltophilia* following iliac crest bone graft harvest, and a new combination therapy of latamoxef (LMOX, 1 g/8 h), mero-

Figure 2. The patient's clinical course. CEZ: cefazolin, CFDN: cefdinir, CRP: C-reactive protein, CZOP: cefozopran, DAP: daptomycin, GM: gentamicin, LMOX: latamoxef, LVFX: levofloxacin, LZD: linezolid, MEPM: meropenem, MRSA: methicillin-resistant *Staphylococcus aureus*, MSSA: methicillin-sensitive *S. aureus*, TMP-SMX: trimethoprim-sulfamethoxazole. The day of iliac crest bone harvesting was set as day 0. Positive results for *S. maltophilia* bacteremia were obtained three times throughout the patient's course. His blood culture results became negative after initiating combination therapy that included LMOX. Central venous catheters or arterial lines were not inserted during the course. There were no physical or laboratory findings that were suggestive of infective endocarditis.

penem and DAP was initiated. The patient's condition improved, and a third I&D and removal of the antibiotic-impregnated cement was performed on day 129.

The last combination therapy was continued for four weeks, and the patient was prescribed oral trimethoprim-sulfamethoxazole (TMP-SMX, T: 10 mg/kg) and discharged. He was treated for approximately three months in total without any recurrence. The patient's clinical course is summarized in Fig. 2.

Bacterial analysis

The occurrence of *S. maltophilia*-related wound infection or osteomyelitis is extremely rare, and we conducted an investigation to determine whether the strains obtained from blood and wound samples were genetically identical. Furthermore, environmental surveillance of the patient's surroundings, including the bathroom, was performed on day 120.

Isolates were obtained from four of the 10 sampling sites, including two sites of the sink and two sites of the shower drain. Enterobacterial repetitive intergenic consensus

(ERIC)-PCR was performed to genotype the isolates. After DNA was extracted from both the clinical and environmental isolates, amplification reactions using a primer (5'-AAG TAA GTG ACT GGG GTG AGC G-3') were performed according to a previous report (14). The results showed the amplicon patterns to be identical in the blood and wound samples, but they were different from all environmental isolates (Fig. 3).

Discussion

S. maltophilia infections are increasingly being recognized as a cause of severe nosocomial infections, particularly in immunocompromised patients (15). *S. maltophilia* exhibits resistance to a broad array of antibiotics (5), and the mortality rates of *S. maltophilia* bacteremia range from 14 to 69% (16, 17).

According to a previous epidemiological study, more than 90% of patients with *S. maltophilia* infection had underlying diseases (14). Such predisposing risk factors include malignancy (18), the presence of indwelling de-

Figure 3. Enterobacterial repetitive intergenic consensus (ERIC) PCR. M: size marker, 1: first blood culture, 2: second blood culture, 3: third blood culture, 4: wound, 5: shower drain one, 6: shower drain two, 7: sink one, 8: sink two, 9: negative control. PCR was performed according to a previously reported method: one cycle for three min at 94°C, two cycles of 45 seconds at 94°C, one min at 30°C, and one min at 72°C, and 44 cycles of 30 seconds at 94°C, 30 seconds at 55°C, and one min at 72°C, with a final extension for four min at 72°C (14). The PCR products were analyzed by electrophoresis on an agarose 1.5% w/v gel. All of the strains from the three blood cultures (lanes 1 to 3) and wound sample (lane 4) were identical. These clinical strains were different from the tested environmental strains (lanes 5 to 8).

vices (18, 19), chronic respiratory disease, immunocompromised status (18), the use of broad-spectrum antibiotics (19, 20), long-term hospitalization (mean duration of hospitalization before isolation reported to be approximately one month) (14), intensive care unit (ICU) stay (21), and the breakdown of mucocutaneous defence barriers (14). The present patient had a prolonged hospitalization and breakdown of mucocutaneous defense barriers due to repeated operations. However, because our patient was immunocompetent; was not an ICU patient; and was free from malignancy, indwelling devices, and previous broad-spectrum antibiotics, the patient was considered to be at relatively low risk for *S. maltophilia* infection. Even though, the possibility of *S. maltophilia* infection should have been considered when the organism was first detected from the wound culture (day 63).

The infection route in our case was unclear, and we performed an epidemiological investigation by ERIC-PCR. ERIC sequences are 126-base pair conserved motifs found in many species of enteric bacteria. The utility of ERIC-PCR for epidemiological surveillance of *S. maltophilia* has already been demonstrated. Although the results are typically less discriminatory than those of pulsed-field gel electrophoresis, ERIC-PCR has been proven to be a rapid and easy method for *S. maltophilia* genotyping and epidemiological studies with a lower cost (22-25). According to our results, the isolates from the blood and wound samples were identical but were different from those derived from the environmental specimens. Nevertheless, we still speculate that *S. maltophilia* infected the patient not hematogeneously, but during, for example, the operation, when taking a shower, or when receiving wound irrigation. The time difference be-

tween the occurrence of infection and environmental sampling might be a reason for the discordance of band patterns on ERIC-PCR.

Differentiation between colonization and infection may be difficult when *S. maltophilia* is isolated from a clinical specimen, especially with other bacteria. Sattler et al. reported that approximately 70% of *S. maltophilia* isolates from nonrespiratory sites were from polymicrobial cultures (26). In our patient, *S. maltophilia* was detected from the surgical wound site with MSSA and MRSA, and from blood samples that were positive for *A. baumannii*. Because *Staphylococcus* spp. are well-known pathogens of wound infections, the isolation of *S. maltophilia* was first considered as a contamination. Antibiotics against *S. maltophilia* were therefore administered for a relatively short time, resulting in recurrent *S. maltophilia* bacteremia. The complication of osteomyelitis at the surgical site remained unclear because bone marrow edema confirmed by MRI could be attributed to the bone graft harvesting. However, ERIC-PCR showed that the strains from the blood and wound samples were genetically identical. Given that osteomyelitis is a general cause of recurrent bacteremia, *S. maltophilia* was confirmed as a causal pathogen of osteomyelitis following iliac crest bone graft harvest.

Only a few cases of osteomyelitis due to *S. maltophilia* have been described in previous literatures (10-13). Landrum et al. reported a postoperative case of vertebral osteomyelitis (12), and German et al. described a community-acquired case of spondylodiscitis in an immunocompromised patient (13). Those patients were successfully treated with surgical debridement and long-term antibiotic administration.

TMP-SMX is currently considered the first-line treatment for *S. maltophilia* infection, although resistant strains have been reported to be increasing (27). The emergence of a resistant strain has been reported during treatment for *S. maltophilia* infection, and some investigators advocate the use of combination therapy for serious cases. TMP-SMX is the only known antimicrobial to which the emergence of resistance during therapy has not yet been reported (28). While Al-Jasser et al. insisted that a clinical advantage of combination therapy with other antimicrobials has not yet been clearly demonstrated (29), Muder et al. reported the superiority of combination therapy, mainly with TMP-SMX (30).

Tetracyclines, such as doxycycline or MINO, are considered to be second-line agents. Fluoroquinolones (FQs), cef-tazidime or ceftriaxone, and ticarcillin/clavulanate are also alternative options (4, 14, 31). Among them, FQs are pharmacokinetically recommended agents for treating osteomyelitis. Specifically, *in vitro* bactericidal activity of LVFX against *S. maltophilia* has been reported (32, 33). Landrum et al. described the clinical effectiveness of FQs for the treatment of osteomyelitis caused by *S. maltophilia* infection (12). A recent review article indicated the possible efficacy of moxifloxacin against a multi-drug resistant *S. maltophilia* strain (5). In our patient's early course, combination therapy comprised of LVFX and CZOP was chosen. How-

ever, there is no clinical evidence of better effectiveness of these drugs compared with TMP-SMX or tetracyclines. Administration of TMP-SMX or tetracyclines was avoided only because these drugs frequently have adverse effects. However, earlier administration of these drugs could prevent the recurrence of *S. maltophilia* bacteremia and avoid a longer treatment period.

LMOX, which first appeared on the market in 1981, has been reported to be effective against *S. maltophilia* *in vitro* (34, 35), but there has been little clinical experience of the drug for treating *S. maltophilia* infection. Understandably, there has been no report showing the efficacy of this drug against osteomyelitis caused by *S. maltophilia*. The results of the present case suggest that LMOX can be considered as an alternative drug for *S. maltophilia* infection. However, at present, we do not recommend administration of LMOX, especially for severe cases. For clinical use, more credible data on the effectiveness of LMOX against *S. maltophilia* infection are needed, and further investigation is warranted.

A. baumannii bacteremia was confirmed twice during the course. The organism often causes line-associated infection; however, the patient did not have an arterial or central line throughout the disease course, and peripheral venous lines were repeatedly exchanged every three to four days. Systemic investigation did not reveal any infectious foci other than the surgical site. *A. baumannii* bacteremia was therefore assumed to be derived from the surgical site infection. However, the organism was not detected in the specimen obtained from surgical site, and we remain unsure about the exact origin of the *A. baumannii* bacteremia.

In summary, we herein presented a case of recurrent *S. maltophilia* bacteremia following iliac crest bone graft harvesting. This highly resistant organism has the potential to cause infections with a high mortality rate. We need to consider this organism as a more clinically problematic pathogen in various situations.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

We appreciate the cooperation by the following members of the Department of Clinical Laboratory in Okayama University Hospital: Takumi Fujimori, Ayaka Kakehi, Koji Iio, Motoko Nose, and Toshiyuki Watanabe.

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