INTERNAL MEDICINE

□ CASE REPORT □

Methicillin-resistant *Staphylococcus aureus*-related Septic Pulmonary Embolism and Sacroiliitis Treated with Long-term Linezolid in a Patient with Adult-onset Still's Disease

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Abstract

We herein report the case of a 21-year-old woman with refractory adult-onset Still's disease who developed central venous catheter-related methicillin-resistant *Staphylococcus aureus* sepsis during aggressive immunosuppressive therapy. She subsequently experienced septic pulmonary embolism (SPE) and sacroiliitis during treatment with intravenous vancomycin and was successfully treated with long-term oral linezolid therapy. This case suggests that the occurrence of methicillin-resistant *Staphylococcus aureus* infection in immunosuppressive patients can trigger severe clinical manifestations such as SPE and septic sacroiliitis and that linezolid is suitable for treating such conditions.

Key words: adult-onset Still's disease, linezolid, septic pulmonary embolism, vancomycin

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Introduction

Adult-onset Still's disease (AOSD) is a systemic inflammatory disease characterized by recurrent fever, arthralgia, liver dysfunction and lymphadenomegaly. Although AOSD is usually responsive to steroids, the condition sometimes becomes resistant to treatment and requires aggressive immunosuppressive therapy. Therefore, some patients with AOSD become compromised hosts and are thus likely to suffer from opportunistic infections.

There is debate regarding the superiority of linezolid (LZD) over vancomycin (VCM) for the treatment of nosocomial pneumonia (1, 2). The appropriate treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infection in patients under aggressive immunosuppressive therapy has not been established. There are currently no reports of AOSD complicated by severe bacterial infection during the use of immunosuppressive therapy.

We herein report the case of a 21-year-old woman with AOSD who developed septic pulmonary embolism (SPE) and sacroiliitis under VCM treatment and was successfully treated with LZD.

Case Report

A 21-year-old woman was admitted to our hospital with pyrexia, oral ulcers and cervical lymphadenomegaly on the left neck in mid February 2012. She had a three-month history of recurrent fever, lymphadenitis and seizures. The re-

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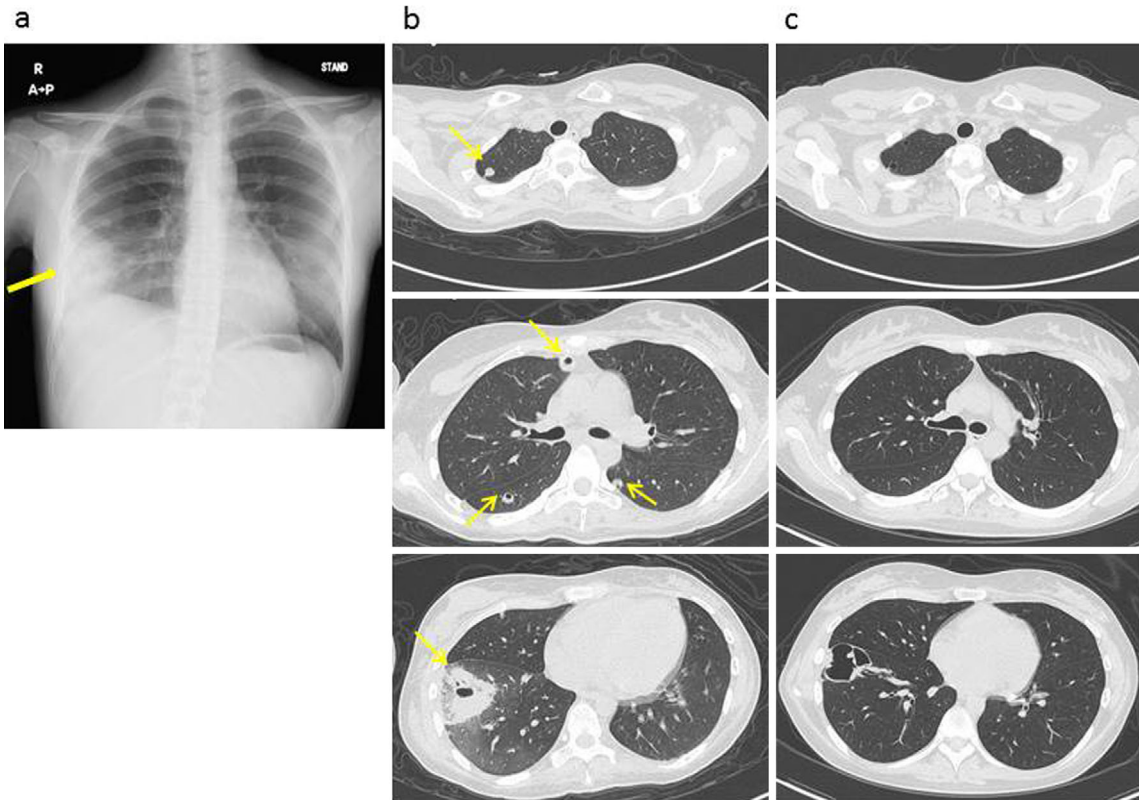

Figure 1. Diagnostic chest imaging. a: A chest X-ray obtained on the 25th day after admission revealed a nodular shadow in the right lower lung field. b: Chest CT performed on the 25th day after admission revealed multiple nodular shadows in both lung fields, compatible with a diagnosis of SPE. c: Chest CT performed after four weeks of treatment with LZD.

sults of laboratory tests performed on admission revealed an elevated C-reacted protein (CRP) level, liver dysfunction and a positive direct Coombs test. Chest computed tomography (CT) revealed mild pericardial effusion and pleuritis.

The patient was diagnosed with AOSD based on the presence of pyrexia, arthralgia, a skin rash, lymphadenomegaly and liver dysfunction, meeting three of the four major criteria and two of the four minor criteria for the classification of AOSD proposed by Yamaguchi et al. (3). We also suspected a diagnosis of systemic lupus erythematosus (SLE). However, the titer of ANA was <×20 and disease-specific antibodies for SLE were negative. Furthermore, no characteristic organ complications, such as nephritis and neuropsychiatric symptoms, were found, a finding not compatible with the diagnosis of SLE. Because the bone marrow puncture findings on admission suggested the presence of hemophagocytic syndrome, we initiated treatment with plasma exchange and steroid pulse therapy (methylprednisolone 1 g/day for three days) followed by 50 mg/day of prednisolone after inserting a double-lumen catheter into the right internal jugular vein. The patient's pyrexia persisted after the first course of steroid pulse therapy, and we therefore reinstituted treatment with steroid pulse therapy along with intravenous immunoglobulin and oral cyclosporine (CsA), which was partially effective. We continued the immunosuppressive therapy with prednisolone combined with CsA. Meanwhile, we removed the internal jugular double lumen central venous catheter on the 16th day after admission, as additional plasma exchange was deemed unnecessary. However, the patient's low-grade fever and elevated CRP level persisted. Although no abscess formation was detected around the catheter, we suspected a central venous catheter-related infection, and MRSA was isolated from blood cultures obtained from the peripheral veins and central venous catheter. Transthoracic echocardiography revealed a preserved ejection fraction, with no signs of endocarditis. The serum procalcitonin level was slightly increased (0.243 ng/mL). We initiated treatment with intravenous VCM (1.0 g bid), and the patient's febrile condition gradually improved. Antimicrobial susceptibility testing revealed that the minimum inhibitory concentrations of VCM and LZD were ≤1 μg/mL and 1 μg/mL, respectively. Three days after the start of VCM treatment, the trough level of VCM was 5.30 μg/mL. Because the fever and elevated CRP level remained, we increased the dose of VCM to 1.0 g tid, after which the trough level of VCM increased to 9.24 μg/mL, and the serum CRP level declined. MRSA was not isolated from blood cultures performed after the administration of VCM. However, bloody sputum was detected, and a nodular shadow was noted on the right lung on a chest X-ray (Fig. 1a). Chest CT revealed multiple nodular shadows in both lung fields, compatible with the findings of SPE (Fig. 1b). At the same time, the patient developed right hip pain, and magnetic resonance imaging (MRI) of the pelvis revealed a high intensity area

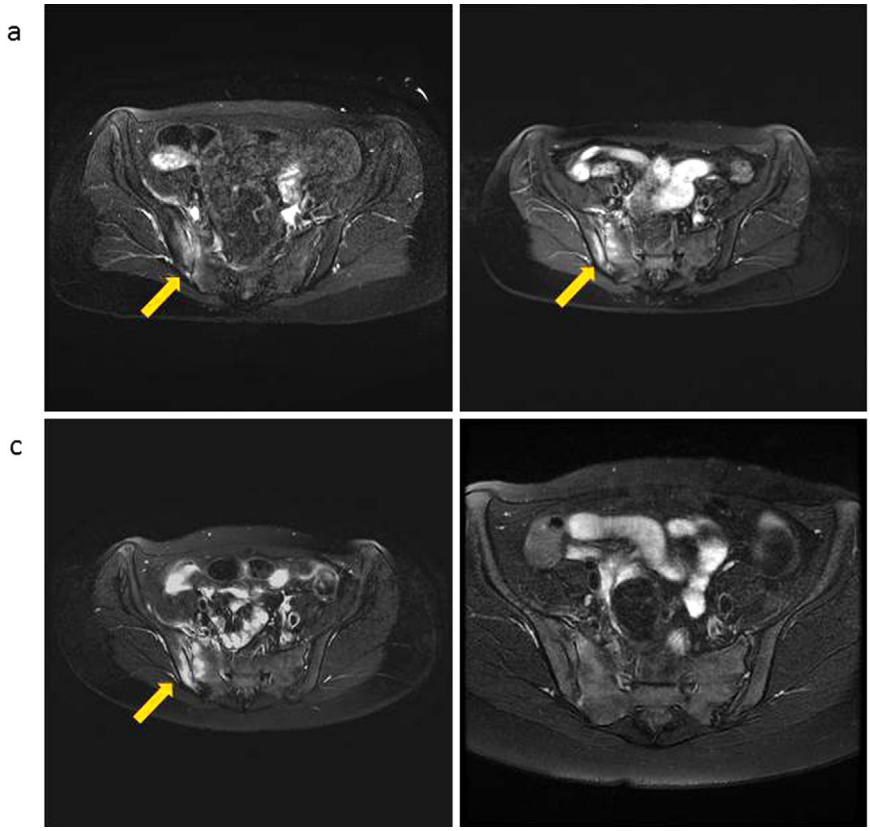

Figure 2. **Sacroiliac MRI findings. a: MRI of the pelvis revealed a high-intensity area in the right sacroiliac joint, compatible with the findings of sacroiliitis due to MRSA infection. b: MRI of the pelvis performed after four weeks of treatment with LZD. c: MRI of the pelvis after an additional four weeks of treatment (eight weeks in total) with LZD. d: MRI of the pelvis performed after a total of 14 weeks of LZD treatment.**

on short time inversion recovery (STIR) images in the right sacroiliac joint and posterior right iliac bone, compatible with the presence of synovitis around the right sacroiliac joint and osteomyelitis (Fig. 2a). As VCM appeared to be ineffective against the MRSA-associated SPE and sacroiliitis, we switched to oral LZD (1,200 mg/day). The nodular shadows in the lung field gradually disappeared. The administration of LZD was discontinued after four weeks due to improvements in the patient's hip pain, CRP level and CT findings (Fig. 1c).

Only four days after the termination of LZD, recurrence of the right hip pain associated with an increase in the CRP level was noted. MRSA was isolated from blood cultures. The CsA treatment was discontinued because the serum ferritin level, a disease activity marker of AOSD, normalized. Serum ferritin LZD therapy was again initiated and discontinued after four weeks due to improvements in the patient's hip pain, pyrexia and CRP level. However, a high-intensity area persisted in the right sacroiliac joint on MRI (Fig. 2b, c), and the hip pain again became exacerbated soon after the discontinuation of LZD. The serum ferritin level remained normalized. LZD was administered for a further six weeks and the dose of prednisolone was tapered gradually each week (Fig. 3), with improvements in both the hip pain and MRI findings (Fig. 2d). During the administration of LZD, progressive anemia was observed (the hemoglobin level dropped to 7.1 g/dL), which resolved after termination of the LZD therapy. In addition to anemia, the patient developed mild thrombocytopenia, from which she recovered upon termination of LZD (Fig. 3).

Discussion

Although many cases of AOSD are self-limiting or responsive to steroids, some patients develop a persistent fever with various visceral symptoms under aggressive immunosuppressive therapy. SPE is a medical condition in which an embolic blood clot leads to infarction in the pulmonary vasculature containing microorganisms that can induce a focal abscess. Cook et al. reported that three of 14 SPE cases were associated with an infected central venous catheter and that all patients were in an immunosuppressive state following the administration of aggressive immunosuppressive therapy, as in the present case (4). It is therefore necessary to recognize the possibility that patients with a central venous catheter who are treated with immunosuppressive drugs are at risk of SPE.

There are several bacteria capable of causing SPE, including MRSA, methicillin-sensitive *Staphylococcus aureus* (MSSA), *Streptococcus*, *Bacteroides* and *Fusobacterium* (5).

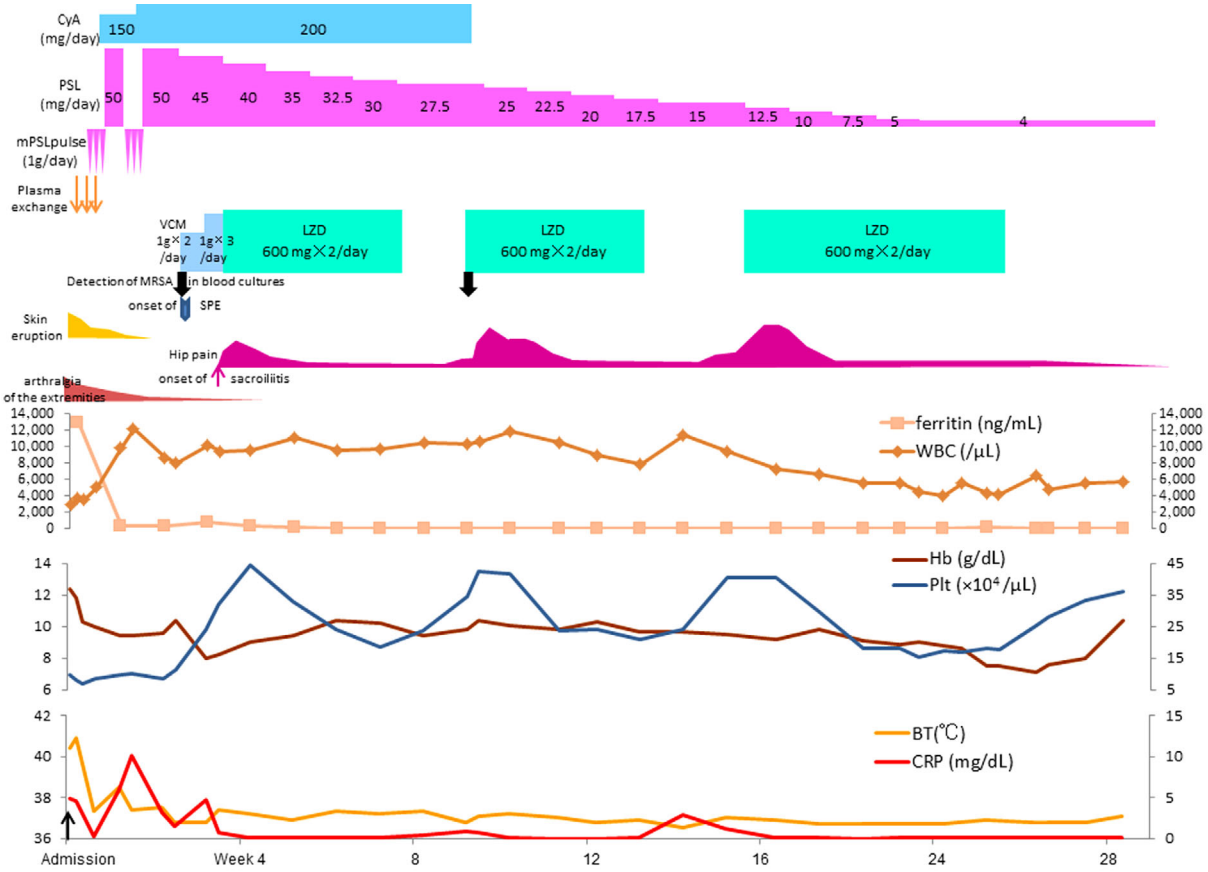

Figure 3. **Clinical course. BT: body temperature, CRP: C-reactive protein, CsA: cyclosporine A, CT: computed tomography, Hb: hemoglobin, LZD: linezolid, mPSL: methylprednisolone, MRI: magnetic resonance imaging, MRSA: methicillin-resistant *Staphylococcus aureus*, Plt: platelet count, PSL: prednisolone, SPE: septic pulmonary embolism, VCM: vancomycin**

MRSA-related SPE, especially in patients in a state of immunosuppression, is likely to manifest as pulmonary embolism and pneumothorax, both of which are life-threatening (6). Therefore, providing an early diagnosis and relevant treatment is necessary for treating MRSA-related SPE in such patients.

VCM is a glycopeptide and the oldest anti-MRSA drug. VCM is used with dose adjustment according to the monitored peak, trough, or both, serum concentrations. The Japanese Society of Chemotherapy and the Japanese Society of Therapeutic Drug Monitoring jointly proposed recommendations for the use of anti-MRSA drugs in 2012. According to the recommendations, the VCM trough level should be maintained at 10-15 μg/mL initially, then increased to 15-20 μg/mL with caution, in patients with severe conditions (7). However, it has been reported that the tissue penetration of VCM is limited due to its large molecular weight. Deresinski reported that the concentration of VCM in lung epithelial fluid in patients under mechanical ventilation is less than 14% of the VCM serum concentration (8), which suggests that the administration of VCM is insufficient for treating severe pulmonary infection. In the present case, it cannot be denied that the dose of VCM was insufficient. This problem may not be solved by increasing the dose of VCM. Jeffres et al. reported that a greater VCM trough concentration (≥15 μg/mL) or area-under-the-curve concentration are not associated with improvements in the prognosis of patients with healthcare-associated pneumonia resulting from MRSA infection (9).

LZD an oxazolidinone antibiotic that is recognized to be effective for MRSA as well as vancomycin-resistant *Enterococci* and penicillin-resistant *Streptococcus pneumoniae* (10). LZD can be administered both intravenously and orally or enterally with 100% bioavailability. In addition, no dose adjustment is needed in cases of moderate renal or liver dysfunction (11). Therefore, LZD is useful for treating patients with severe MRSA infection. Yoshizawa et al. reported that treatment with LZD, but not VCM, significantly suppresses inflammatory cytokines in mouse MRSA pneumonia models (12). Honeybourne et al. reported good penetration of LZD into the bronchial mucosa, pulmonary macrophages and epithelial lining fluid in a study of 10 patients undergoing bronchoscopy (13). In the present case, the administration of VCM did not prevent the development of SPE, although the CRP level declined after the start of VCM therapy. We postulate that the effects of VCM on the patient's pulmonary infection were attenuated due to the drug's poor penetration. LZD, which exhibits good penetration into the lungs, is suitable for patients with severe MRSA infection who are at risk of developing SPE. Al-

though the present case was not complicated by heart valve infection (data not shown), the superiority of LZD over VCM has been reported in the setting of Gram-positive cocci-related heart valve endocarditis, a refractory bacterial infection that may coexist with SPE (14). Although LZD is well tolerated in most cases, adverse effects can appear, including bone marrow suppression. In a phase III trial, 2.4% of the patients treated with LZD developed thrombocytopenia. However, cytopenia due to LZD is usually reversible, as observed in this case (15).

Another striking feature of this case is that the patient developed sacroiliitis in addition to SPE. The main causative pathogen of pyogenic sacroiliitis is *Staphylococcus aureus*. Many cases of pyogenic sacroiliitis appear as secondary infections, and approximately 45% of cases of adult pyogenic sacroiliitis are complicated by concurrent infectious diseases, such as soft tissue infection, disseminated septic emboli or respiratory tract infection, as noted in the presented case. The treatment of pyogenic sacroiliitis often requires long-term antibiotic therapy (two to six weeks of intravenous antibiotics and two to three weeks of oral antibiotics). If antibiotic therapy is ineffective, surgical debridement is performed as a last resort (16). Although we did not perform puncture of the sacroiliac joint, we considered that the sacroiliitis was caused by MRSA infection based on the patient's clinical course and blood culture findings. To the best of our knowledge, there is no consensus regarding the treatment of sacroiliitis associated with MRSA infection. Surgery for sacroiliitis is highly invasive; therefore, we selected treatment with LZD. Another potent anti-MRSA drug is daptomycin. According to the guidelines proposed by the Infectious Diseases Society of America (IDSA), daptomycin, in addition to VCM and LZD, is a major therapeutic option for treating septic arthritis. Daptomycin is a lipopeptide antibiotic that exhibits good bactericidal activity and excellent tissue penetration. A point to note is that the activity of daptomycin is inhibited by surfactant in the lungs, and the use of daptomycin in cases of MRSA pneumonia is not covered by medical insurance in Japan. In the present case, the patient's sacroiliitis persisted following the improvement of the MRSA pneumonia (17). If LZD had been ineffective or its toxicity intolerable, daptomycin could have been used an alternative option, assuming that the patient's respiratory disease was well controlled.

In this study, we reported the case of a patient with AOSD complicated by SPE and sacroiliitis as a consequence of MRSA bacteremia. This case indicates that it is necessary to recognize the possibility that MRSA infection in immunosuppressive patients can trigger severe clinical manifestations, such as SPE and septic sacroiliitis. This case demonstrates that LZD is beneficial for the treatment of MRSA bacteremia in immunosuppressed patients.

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

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