

[CASE REPORT]

Cellulitis Complicated with Bacteremia Due to *Sphingobacterium* Species: A Report of Two Cases and a Literature Review

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Abstract:

Sphingobacterium species rarely cause human infection. We herein report two cases of cellulitis complicated with bacteremia due to this genus. The patients, both in their 70s and receiving corticosteroid therapy for their underlying diseases, had antecedent skin injuries in their affected limbs. The patients' symptoms improved promptly and completely with the administration of cefazolin, which did not inhibit the growth of isolated organisms at a concentration of 4 µg/mL.

Key words: *Sphingobacterium*, cellulitis, bloodstream infection

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Introduction

The genus *Sphingobacterium*, first described by Yabuuchi et al. in 1983 (1), is a group of aerobic, glucose-non-fermentative, Gram-negative bacilli. The genus includes organisms classified originally as flavobacteria but distinguished afterwards from the group owing to the presence of a large amount of sphingophospholipids in the cell membrane (2). To date, approximately 50 species have been recognized as belonging to this genus (3), many of which have been detected in both hospital and natural environments and various clinical materials (4-7). However, the isolation of these species as a cause of human invasive infection has rarely been reported (8, 9).

We herein report two cases of cellulitis complicated with bacteremia due to *Sphingobacterium* species.

Case Reports

Case 1

A 74-year-old Japanese man was admitted because of pain in his right hand since the previous day. He had been hospitalized for the treatment of exacerbated chronic obstructive pulmonary disease 1 month before, for which prednisolone (12.5 mg/day), ambroxol, and the inhalants tiotropium bromide and budesonide/formoterol fumarate had been prescribed at the last visit to the outpatient department. Linaagliptin and self-injected insulin were also being administered for type 2 diabetes mellitus. He had been applying povidone-iodine sugar ointment to the dorsum of the right hand because a spontaneous skin tear had appeared one week before.

On admission, he had clear consciousness, an axillary temperature of 38.6°C, a pulse rate of 80 beats per minute, and a blood pressure of 123/75 mmHg. The dorsum of the right hand and forearm up to the level above the elbow showed swelling, pain, warmth, and redness. A non-purulent

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blister approximately 5 cm in diameter was present on the right dorsum as well as the forearm. No tenderness was detected in the axillary regions. Blood tests showed leukocytosis (11,550/ μ L, neutrophils: 70.5%), hyperglycemia (hemoglobin A1c: 8.1%), and elevated levels of serum C-reactive protein (5.54 mg/dL) and procalcitonin (12.36 ng/mL). Cefazolin (2 g/day) for 14 days and oral cefaclor (750 mg/day) for 7 more days thereafter were prescribed. His pyrexia subsided the next day, and the inflammatory signs in the affected limb improved within a few days. Relapse did not occur in the following two years.

Case 2

A 72-year-old Japanese woman who had been hospitalized to receive transsphenoidal surgery for the removal of a pituitary gland tumor abruptly developed pyrexia and vomiting on the day of hospitalization. She was receiving methylprednisolone (4 mg/day) and dipyridamole for chronic nephritis, valsartan for hypertension, pravastatin for hyperlipidemia, esomeprazole and rebamipide for peptic esophagitis, allopurinol for hyperuricemia, and mirabegron for an overactive bladder. At the onset, she complained of pain, swelling, warmth, and redness in the right lower leg; she had clear consciousness, an axillary temperature of 39.2°C, a pulse rate of 115 beats per minute, and a blood pressure of 118/64 mmHg.

A physical examination revealed a scar approximately 1 cm in length on the inside of the affected lower leg, where she had been injured with sewing scissors 2 days earlier, reporting feeling discomfort afterwards. Tinea pedis on the affected side of her foot was also present. No medical devices, including intravenous catheters, had been installed. Blood tests showed leukocytosis (16,370/ μ L, neutrophils: 87.4%) and an elevated level of serum C-reactive protein (2.25 mg/dL). The whole-blood glucose level was 116 mg/dL. Cefazolin (3 g/day) was prescribed for 7 days. Her pyrexia subsided the next day, and the inflammatory signs in the leg improved within several days. She was temporarily discharged on day 10 and re-admitted on day 30 for surgery, which was performed uneventfully. Relapse did not occur during the following six months.

Microbiological examinations

In both cases, two sets of blood culture were obtained before the administration of antibiotics. Two and one aerobic culture bottles yielded Gram-negative bacilli, named strain 1513 in Case 1 and strain 1761 in Case 2, respectively. Both strains produced small, non-hemolytic, smooth colonies with a pale-yellow pigment on sheep blood agar broth (Nippon Becton Dickinson, Fukushima, Japan) after aerobic incubation at 35°C for 24 hours. They did not grow anaerobically on Anaero Columbia Agar with RSB (Nippon Becton Dickinson), had catalase and oxidase activities, and did not ferment carbohydrates in triple sugar iron slant agar broth (Eiken Kagaku, Nogi, Japan). The MicroScan WalkAway 96 plus instrument (Dade Behring, Tokyo, Japan) identified

both organisms as *Chryseobacterium indologenes*. In contrast, only strain 1761 was identifiable with the Vitek[®] 2 GN ID Card (bioMérieux, Marcy-l'Étoile, France) as *Sphingobacterium thalpophilum*.

Homology analyses of the 16S ribosomal RNA sequences with the Basic Local Alignment Search Tool demonstrated the sequence of strain 1513 (1451 base pairs including 15 undeterminable ones; DDBJ Accession Number: LC436857) to be closest to those of *Sphingobacterium siyangense* SY1^T (sequence accession number: EU046272.1; identity: 98.2%) and *Sphingobacterium cladoxiae* No.6^T (FJ868219.1; 98.1%). Strain 1513 grew at 42°C and did not produce acid from cellobiose, glucose, maltose, mannose, or sucrose in an assay with ID32E (bioMérieux), which was compatible with the characteristics of *S. siyangense* (10). The 16S ribosomal RNA sequence of strain 1761 (1450 base pairs including 2 undeterminable ones; DDBJ Accession Number: LC436858) was closest to that of *Sphingobacterium multivorum* NBRC 14947^T (AB680717.1; 97.4%). Minimum inhibitory concentrations, measured using the DryPlate (Eiken Kagaku) and interpreted according to the description of the Clinical and Laboratory Standards Institute (11), indicated both organisms to be susceptible to cefotaxime (4 μ g/mL), ceftazidime (4 μ g/mL), cefepime (\leq 2 μ g/mL), imipenem (1 μ g/mL), ciprofloxacin (0.25 μ g/mL), and trimethoprim-sulfamethoxazole (\leq 0.25/4.75 μ g/mL) and resistant to aztreonam, gentamicin, and amikacin. Cefazolin did not inhibit the growth of either organism at a concentration of 4 μ g/mL.

Discussion

In the present two cases, both patients showed typical manifestations of cellulitis, including swelling, pain, warmth, and redness of the affected limbs (12), without abscess formation and no evident signs or symptoms of infection in other organs. In addition, blood culture detected only *Sphingobacterium* species in the patients' bloodstream. These findings clearly indicate that these patients developed non-purulent cellulitis complicated with bacteremia due to *Sphingobacteria*.

The patients in the present cases were in their 70s and receiving corticosteroid therapy for their underlying diseases. These factors may have impaired the patients' immunity, causing the infection with uncommon organisms. In addition, the patients had antecedent skin disruptions in their affected limbs, through which the causative organisms may have entered. In case 1, the patient self-administered povidone-iodine sugar ointment to a spontaneous skin tear on the hand that had appeared one week before the onset of infection, suggesting that the wound had been contaminated with materials containing the causative organism during self-treatment. In case 2, the organism was more likely to have entered through an injury incurred with sewing scissors than through the minor cracks associated with tinea pedis on the affected side of the foot, as the event occurred two days before the onset and the patient continued to feel discomfort at

Table. Summary of Skin and Soft Tissue Infections Due to *Sphingobacterium* species.

| Case | Age/ sex | Underlying disease | Organism | Diagnosis (site of infection) | Treatment | Outcome | Reference |
|------|-------------|--|------------------------|----------------------------------|--|---------------------------|--------------|
| 1 | 72/M | Parkinson disease, chronic venous stasis, onychomycosis, intertriginous cracking of toes, walking barefoot in backyard | <i>S. spiritivorum</i> | Cellulitis (R leg) | CEZ+ABPC/SBT, CFPX | Complete recovery | [13] |
| 2 | 84/M | Refractory anemia | <i>S. mizutai?</i> | Cellulitis (R leg) | AMPC/CVA | Complete recovery | [14] |
| 3 | 64/F | Corticosteroid for rheumatoid arthritis, morbid obesity, diabetes mellitus, dog scratch | <i>S. multivorum</i> | Necrotizing fasciitis (R leg) | AMPC/ CVA+CLDM+GM, extensive debridement | Recovery without sequelae | [17] |
| 4 | 89/M | Parkinson disease, hypothyroidism, chronic kidney disease, fall in nursing home | <i>S. spiritivorum</i> | Cellulitis (R leg) | PIPC/TAZ, AMPC/ CVA | Complete recovery | [15] |
| 5 | 80/M | COPD, chronic heart failure, pacemaker, tinea pedis | <i>S. spiritivorum</i> | Cellulitis (L leg) | CEZ, MEPM, LVFX | Complete recovery | [9] |
| 6 | 86/M | Pacemaker, biological aortic valve prosthesis, scratch by rooster | <i>S. hotanense</i> | Cellulitis (R arm) | AMPC/CVA | Complete recovery | [16] |
| 7 | 74/M | Corticosteroid for organizing pneumonia, COPD, diabetes mellitus | <i>S. siyangense</i> | Cellulitis (R arm) | CEZ, CCL | Complete recovery | Present case |
| 8 | 72/F | Corticosteroid for chronic nephritis, pituitary gland tumor, injury with sawing scissors, tinea pedis | <i>S. multivorum</i> | Cellulitis (R leg) | CEZ | Complete recovery | Present case |

ABPC/SBT: ampicillin/sulbactam, AMPC/CVA: amoxicillin/clavulanic acid, CCL: cefaclor, CEZ: cefazolin, CLDM: clindamycin, COPD: chronic obstructive pulmonary disease, CFPX: ciprofloxacin, F: female, GM: gentamicin, LVFX: levofloxacin, L: left, M: male, MEPM: meropenem, PIPC/TAZ: piperacillin/tazobactam, R: right

the site of the injury. Unfortunately, we did not have a chance to confirm the sources of the causative organisms microbiologically in either case.

To our knowledge, six other cases of skin and soft tissue infection (SSTI) due to *Sphingobacterium* species, including five cases of cellulitis and one of necrotizing fasciitis, have been reported in the English literature (Table). The patients in the cellulitis cases demonstrated non-purulent lesions with positive blood culture findings (9, 13-16). In the patient with necrotizing fasciitis, the blood culture was negative, but the causative organism was detected in multiple surgical samples (17). All 6 patients were >60 years of age and, mostly, had multiple underlying diseases. Skin disorders possibly causing entry of the microorganisms included animal scratches (16, 17), dermatomycosis of the foot (9, 13), and skin tears after a fall (15). All of the patients with cellulitis improved promptly with antibiotic therapy only. The patient with necrotizing fasciitis, despite requiring management in an intensive-care unit and extensive and repeated debridement, also recovered without sequelae (17). The clinical courses of these previous and present cases show that *Sphingobacterium* species, while extremely rare, may be the underlying pathogens of SSTI in individuals in an immunosuppressive state and/or with predisposing factors. Furthermore, blood culture is an effective tool for the diagnosis, and antibiotic therapy is highly effective, especially in cases of cellulitis.

We first administered cefazolin for both patients in the present cases because the drug is recommended for the treat-

ment of moderate non-purulent cellulitis (18). The antibiotic therapy promptly resolved both patients' symptoms without relapse. Interestingly, the minimum inhibitory concentration of cefazolin against the isolated organisms was >4 µg/mL, indicating some degree of resistance according to the interpretative criteria for *Enterobacteriaceae* established by the Clinical and Laboratory Standards Institute (11). Cefazolin was solely used for the treatment of another patient with cellulitis due to *Sphingobacterium* species for the initial few days. In that case, the patient also recovered completely, although the antibiotic was switched to meropenem after the causative organisms were confirmed to be glucose non-fermenting Gram-negative bacilli (9). We therefore speculate that the clinical effectiveness of cefazolin noted in the present cases is not exceptional. The further accumulation of microbiological and clinical knowledge is necessary in order to clarify why the administration of cefazolin, considered ineffective on *Sphingobacterium* species *in vitro*, was effective in the present cases.

The homology analysis of the 16S ribosomal RNA sequence is now widely used for bacterial identification, especially in cases with unreliable results on conventional tests (19). We used this method to identify the organisms isolated in the present cases because automated identification systems did not yield confirmative results. The sequence of strain 1513, isolated in case 1, was almost completely homologous to those of *S. siyangense* and *S. clado-niae* (98.2% and 98.1% identity, respectively), although the biochemical features were compatible with those of *S. siyan-*

gense. Strain 1761, isolated in case 2, was closest to *S. multivorum*, but the identity between their sequences was slightly lower (97.4%). These low and ambiguous homology values (19) indicate that the analyses of the 16S ribosomal RNA sequences were insufficient for the precise classification of the organisms isolated in the present cases. In the last decade, a number of organisms, especially those from soil, sludge, plants, and food, have been recognized as new species of the genus *Sphingobacterium* (3), indicating that the taxonomy of the organisms in this genus is still being determined. The precise identification of *Sphingobacterium* species through more appropriate methods may reveal new findings concerning the epidemiology and pathogenesis of human infection with these organisms.

In conclusion, we encountered two cases of cellulitis complicated with bacteremia due to *Sphingobacteria*. Physicians should know that the organisms might be a true pathogen of skin and soft tissue infection in patients with an immunocompromised condition and/or predisposing factors. The clinical efficacy of cefazolin for *Sphingobacterium* infection, shown in the present cases, should be evaluated in further studies.

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

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