【 CASE REPORT 】

Fatal Neutropenic Enterocolitis Caused by *Stenotrophomonas maltophilia*: A Rare and Underrecognized Entity

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Abstract:

Although *Stenotrophomonas maltophilia* causes substantial morbidity and mortality in immunocompromised patients, it has not been described as a causal pathogen of neutropenic enterocolitis (NEC). We describe the first case of histologically-confirmed NEC caused by *S. maltophilia* accompanied by bacteremia and pneumonia after salvage chemotherapy for acute myeloid leukemia relapse following a second hematopoietic stem cell transplantation. *S. maltophilia* should be included as a pathogenic organism of NEC in severely immunocompromised patients to prevent a delayed diagnosis, which carries a high risk of inappropriate antimicrobial selection and fatal outcome.

Key words: *Stenotrophomonas maltophilia*, neutropenic enterocolitis (NEC), acute myeloid leukemia (AML), hematopoietic stem cell transplantation (HSCT)

Introduction

Stenotrophomonas maltophilia is isolated from various types of environments and occupies ecological niches both inside and outside of hospitals (1). Severely immunocompromised individuals, particularly recipients of hematopoietic stem cell transplantation (HSCT), are vulnerable populations at risk for *S. maltophilia* infections due to several predisposing factors, such as cytotoxic chemotherapy, radiotherapy, neutropenia, graft-versus-host disease (GVHD), immunosuppressive therapies, monoclonal antibodies, indwelling catheters, broad-spectrum antibiotics, prolonged hospitalization, critical care in the intensive-care unit, gastrointestinal colonization, and severe mucositis (2).

Bacteremia and fatal hemorrhagic pneumonia are well known manifestations in patients following HSCT (3). Endocarditis, mastoiditis, peritonitis, meningitis, soft tissue and wound infections, urinary tract infections, and ocular infections also have been reported as less common manifestations (2). However, gastroenteritis has been rarely reported, and the causal associations remain unclear (4, 5). In addition, *S. maltophilia* has not been described as a causal pathogen of neutropenic enterocolitis (NEC) (6, 7).

We herein report a fatal case of histologically-confirmed NEC caused by *S. maltophilia* accompanied by bacteremia and pneumonia after salvage chemotherapy for acute myeloid leukemia (AML) relapse following a second HSCT.

Case Report

A 28-year-old man with no remarkable medical history presented with gingival swelling and was subsequently diagnosed with AML [t(9;11)(p22;q23); MLLT3(AF9)-MLL] by bone marrow aspiration 25 months before this evaluation. Four months later, peripheral blood stem cell transplantation

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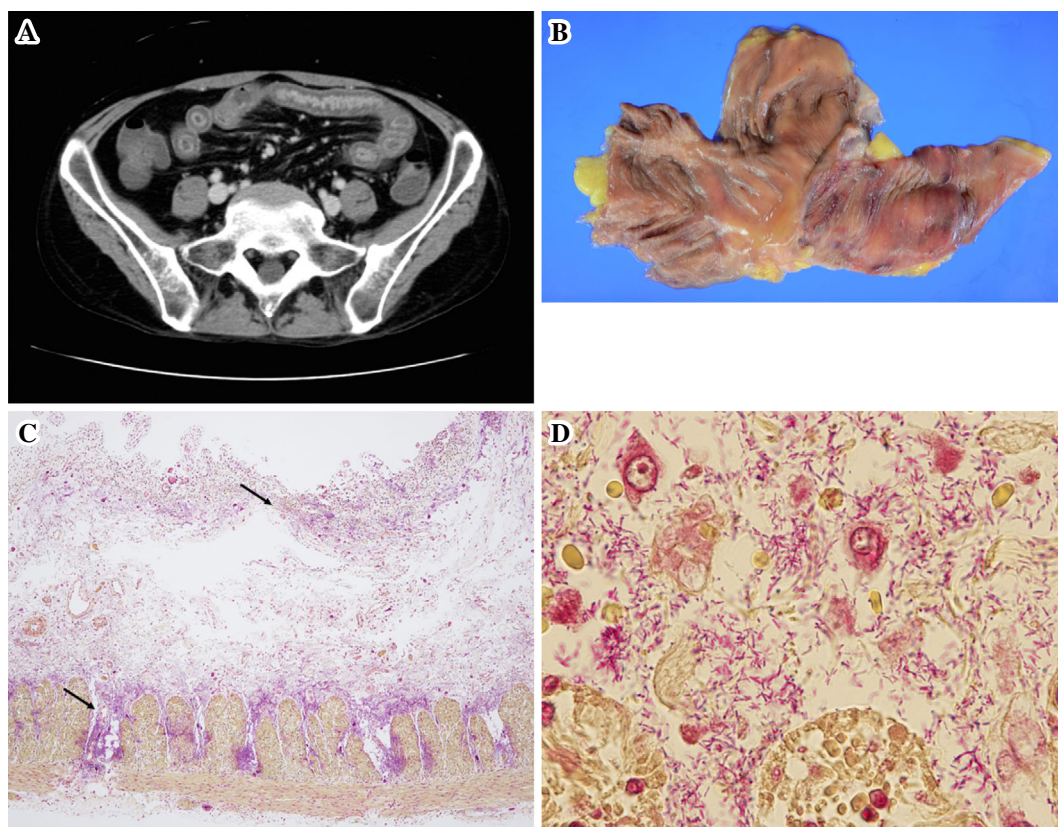
Figure 1. (A) Diffuse intestinal wall thickening was observed on CT. (B-D) Gross pathologic and histologic findings of neutropenic enterocolitis. (B) Erosion, patchy hemorrhaging, and edema were found throughout the lower intestinal tract, particularly in the terminal ileum. (C) low power and (D) highest power: Gram-negative bacilli (arrows) infiltrating all layers of the ileum were seen on a histologic examination.

(PBSCT) from an human leukocyte antigen (HLA)-identical sibling was performed during the first hematological remission. The conditioning regimen consisted of busulfan (12.8 mg/kg) and cyclophosphamide (Cy) (120 mg/kg). For GVHD prophylaxis, cyclosporine A (CsA) and short-term methotrexate were prescribed. Although he developed grade I acute GVHD, methylprednisolone (mPSL) (1 mg/kg) was effective and gradually tapered. CsA was discontinued for 6 months after PBSCT without flare-up of acute GVHD.

Seven months after the first PBSCT, the patient suffered from molecular relapse of AML. As bridging therapies toward a second HSCT, 2 cycles of azacitidine (35 mg/m^2 for 7 days) plus gemtuzumab ozogamicin (3 mg/m^2 for 1 day) (8) and 2 courses of donor lymphocyte infusion (total CD3+ cells: 1.1×10^7/kg and 1.9×10^7/kg) were administered. He achieved molecular complete remission a second time, and a second bone marrow transplantation from an HLA-identical unrelated donor was performed 13 months after the first PBSCT. The conditioning regimen comprised Cy (120 mg/kg) and total body irradiation (1,200 cGy). For GVHD prophylaxis, tacrolimus and short-term methotrexate were prescribed. Although he developed skin and gut GVHD as well as cytomegalovirus enterocolitis, he was discharged 3 months after the second HSCT. The patient then developed bronchiolitis obliterans on day 147 after the second HSCT.

His lung function did not improve despite high-dose pulse mPSL therapy (1 g/day for 3 days) and mycophenolate mofetil.

One year after the second HSCT, hematological relapse of AML was confirmed, and the patient was admitted to the hospital for salvage chemotherapy. On admission, he presented with recurrent pneumonia and watery diarrhea with concurrent maculopapular skin rash. An infiltrative shadow in the inferior lobe of the left lung was detected by computed tomography (CT); however, intestinal edema was not observed at this time. Meropenem and vancomycin were initially prescribed, and his pulmonary symptoms resolved. Salvage chemotherapy consisting of mitoxantrone (36 mg/m^2), etoposide (480 mg/m^2), and intermediate-dose cytarabine (6 g/m^2) was also administered on hospitalization days 4-9 (9).

During salvage chemotherapy, his diarrhea worsened with the expansion of the maculopapular skin rash. Remarkable intestinal edema was observed on CT on day 10 of hospitalization (Fig. 1A). Laboratory data at the time were as follows: white blood cells 20/μL; hemoglobin 8.4 g/dL; platelets 12,000/μL; lactate dehydrogenase 228 U/L; and C-reactive protein 1.24 mg/dL. Neither *Clostridium difficile* toxins A/B nor glutamate dehydrogenase (GDH) was detected in a fecal sample. Based on the worsening skin rash,
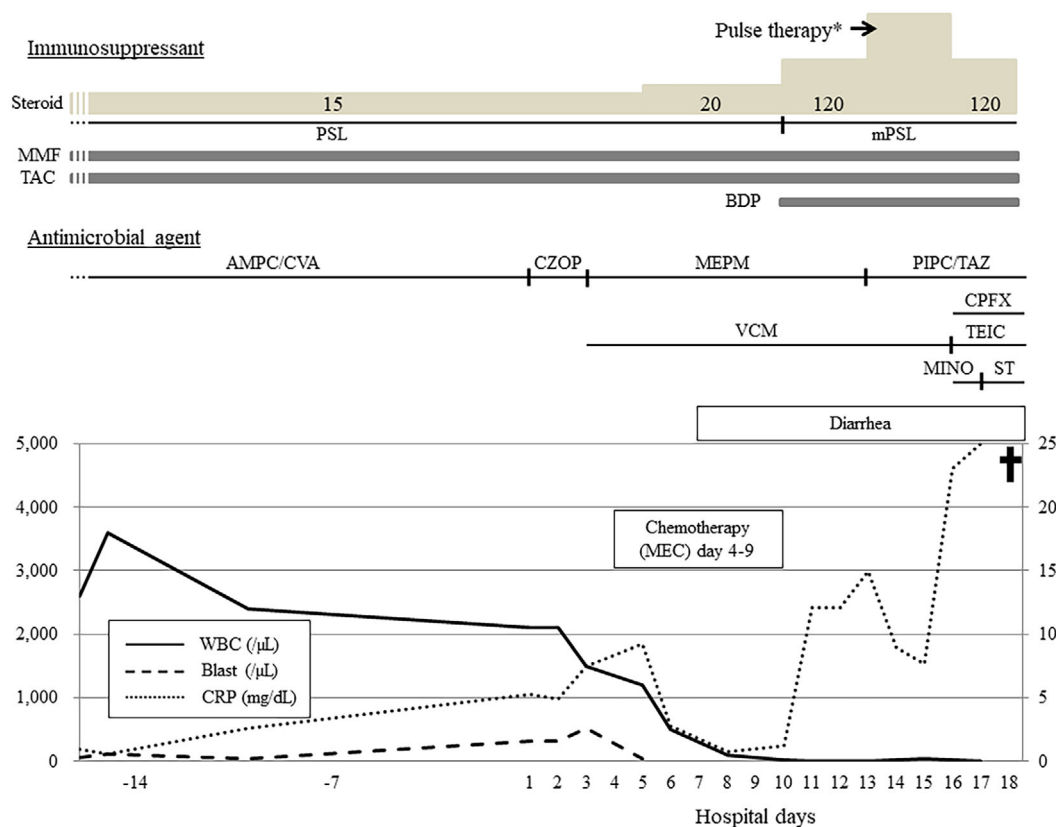
Figure 2.   Patient's clinical course. *Methylprednisolone was administered at 1,000 mg/day for 3 days. PSL: prednisolone, mPSL: methylprednisolone, MMF: mycophenolate mofetil, TAC: tacrolimus, BDP: beclomethasone dipropionate, AMPC/CVA: amoxicillin/clavulanate, CZOP: cefozopran, MEPM: meropenem, PIPC/TAZ: piperacillin/tazobactam, CPFX: ciprofloxacin, VCM: vancomycin, TEIC: teicoplanin, MINO: minocycline, ST: trimethoprim-sulfamethoxazole, MEC: mitoxantrone, etoposide, and cytarabine, WBC: white blood cell, CRP: C-reactive protein

recurrence of acute gut GVHD was suspected. On day 10 of hospitalization, mPSL was increased up to 120 mg/day, and beclomethasone dipropionate was prescribed at 8 mg/day. However, his diarrhea worsened, and steroid pulse therapy (mPSL 1 g/day for 3 days) was performed on days 13-15. Colonoscopy was not possible due to his poor general condition.

On day 16 of hospitalization, hemorrhagic diarrhea developed, and blood cultures became positive for Gram-negative bacilli. Minocycline and ciprofloxacin were additionally prescribed. The Gram-negative bacilli were identified as *S. maltophilia* the following day, and minocycline was changed to trimethoprim-sulfamethoxazole. Unfortunately, the patient died on day 18 of hospitalization because of the rapid progression of respiratory failure and hemodynamic instability, which was presumably caused by severe hemorrhagic enterocolitis and pneumonia with septic shock.

An autopsy revealed erosion and petechial hemorrhaging throughout the lower intestinal tract, particularly in the terminal ileum (Fig. 1B), and Gram-negative bacilli were found in all layers of the ileum (Fig. 1C and D). The proliferation of Gram-negative bacilli was predominantly observed in the proper muscular layer. We found no findings of apoptotic bodies, cytomegalovirus (CMV)-infected cells, or pseu-

domembranous colitis. These autopsy findings suggested that the cause of the patient's fatal diarrhea had been *S. maltophilia* hemorrhagic enterocolitis. Hemorrhagic pneumonia caused by *S. maltophilia* was also found in the inferior lobe of the left lung. The proliferation of Gram-negative bacilli was not observed in other organs. The clinical course of the patient is shown in Fig. 2.

Discussion

To our knowledge, the present case is the first histologically-confirmed case of fatal NEC caused by *S. maltophilia*. In severely immunocompromised hosts, especially HSCT recipients, NEC is a life-threatening complication (10). The mortality rate was found to be between 30% to 50% in a recent report, indicating that increasing awareness, early recognition, and appropriate interventions are critical for the management of NEC (11). The diagnostic criteria for NEC include a fever, neutropenia, bowel wall thickening >4 mm detected by ultrasonography or CT, gastrointestinal symptoms, and the exclusion of other possible diagnoses (6). Bacteremia is found in <50% of patients, with enteric organisms such as *Escherichia coli*, *Klebsiella* species, viridans group streptococci, *Enterococcus* species,

Pseudomonas aeruginosa, and anaerobes such as *Bacteroides* species and *Clostridium* species being isolated most frequently (6).

In our case, the appropriate exclusion of differential diagnoses was crucial for making a definitive diagnosis of NEC. While a wide variety of differential diagnoses are generally considered in HSCT recipients, acute GVHD, CMV infection, *C. difficile* infection, and drug toxicity are the most common causes of diarrhea (12). Several points should be noted. First, we found no clinical or pathological evidence of gut GVHD because the patient's digestive symptoms worsened despite increasing the dose of steroids, with no findings of apoptotic bodies associated with GVHD observed on an autopsy. Second, there was no pathological evidence of CMV colitis based on immunohistochemical staining of CMV-infected cells. Third, *C. difficile* infection was unlikely because *C. difficile* A/B toxins and GDH were both negative with no pathological evidence of pseudomembrane formation. Finally, our case met all of the criteria for NEC regarding the clinical, radiological, and histological features (6). We therefore believe that NEC caused by *S. maltophilia* is the most likely diagnosis based on the exclusion of the main differential diagnoses microbiologically and histologically, a consistent pathophysiological background at the onset, and the histological evidence of Gram-negative bacilli proliferation in the gut mucosa.

The pathogenesis of NEC is likely multifactorial, consisting of neutropenia itself, the destruction of the normal mucosa architecture due to cytotoxic chemotherapy and/or radiotherapy, possible coexistent leukemic or lymphomatous infiltrates, intramural hemorrhaging due to severe thrombocytopenia, and a shift in the microflora from normal commensals to more opportunistic organisms due to the exposure of antimicrobial agents (6, 13). Our case underwent salvage chemotherapy following a second HSCT, and systemic steroids and mycophenolate mofetil were administered simultaneously. Furthermore, hemorrhagic enterocolitis developed under the use of broad-spectrum antimicrobials at the onset of NEC. We believe that these findings are consistent with a background of NEC caused by *S. maltophilia*.

Although the causal association between NEC and pneumonia was inconclusive, NEC was considered to be the primary source of disseminated *S. maltophilia* infection based on the onset of hemorrhagic enterocolitis prior to pneumonia and the pathological findings of the intestine.

The pathogenicity of *S. maltophilia* against human intestinal tract has been controversial. In general, *S. maltophilia* is known to be a low-virulence non-fermenting Gram-negative bacillus that is unlikely to cause enterocolitis (1). *S. maltophilia* from feces was first reported in 1961 (14). One report showed that *S. maltophilia* was able to cause chronic enterocolitis via colonization of the small bowel in an immunocompetent adult (5). In cancer patients, several risk factors for intestinal colonization of *S. maltophilia* have been reported. Although previous authors showed that 9.5% of diarrheal patients were colonized with *S. maltophilia* in an on-

cology unit but did not assess the causal relationship between colonization and infection, they concluded that the gastrointestinal tract should be evaluated as a potential source of systemic *S. maltophilia* infection (15). In our patient, severe hemorrhagic enterocolitis with the proliferation of Gram-negative bacilli predominantly in the proper muscular layer was observed. *S. maltophilia* is known to produce extracellular enzymes, such as deoxyribonuclease, ribonuclease, fibrinolysin, lipases, hyaluronidase, protease, and elastase, which may contribute to the pathogenesis of *S. maltophilia* infection (1). Despite the limited data on *S. maltophilia* (16), a recent report also reviewed outer membrane vesicles of Gram-negative bacteria and the associated functions, including tissue invasion (17). These virulence factors may play a role in the pathogenesis of hemorrhagic enterocolitis due to *S. maltophilia* in addition to the aforementioned risk factors and severely immunosuppressive conditions.

In conclusion, we propose that *S. maltophilia* be considered as a potential causative agent of NEC in severely immunocompromised hosts to prevent a delayed diagnosis, which carries a high risk of inappropriate antimicrobial selection and a fatal outcome.

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

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