Bifidobacterium Bloodstream Infection in a Lymphoma Patient Undergoing Chemotherapy: A Case Study and Implications for Probiotic Use

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Conflict of interest: None declared

Patient: Female, 75-year-old
Final Diagnosis: Febrile neutropenia
Symptoms: Fever
Clinical Procedure: —
Specialty: Infectious Diseases

Objective: Unusual clinical course
Background: Fermenting bacilli producing lactic acid, including Bifidobacterium spp., are supposed to have low pathogenicity and no virulence for humans. Probiotics consisting of those fermenting bacilli can prevent and treat symptomatic gastrointestinal conditions, such as diarrhea. We use probiotics even in cancer patients, those who are immunocompromised, because a preferable effect to the intestinal commensal microbiome has been shown in a recent report. Some case reports warn of a rare risk of bloodstream infection caused by probiotics. However, complete prohibition of probiotic use in cancer patients abandons the benefits.

Case Report: A 75-year-old Japanese woman with malignant lymphoma was treated with immune-chemotherapy regimen consisting of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP). The patient had onset of febrile neutropenia during chemotherapy and had Bifidobacterium breve bloodstream infection on day 8 after the eighth R-CHOP treatment. She had usually eaten commercial yogurt every morning. This yogurt was produced from only Lactobacillus bulgaricus and Streptococcus thermophilus. It did not contain Bifidobacterium breve. The bloodstream infection in this case looked like it derived from her food; however, it was not associated with her habitual foods. The patient was treated with meropenem for 8 days and experienced complete remission of the bloodstream infection.

Conclusions: We speculate that fermenting bacilli can also be a source of bloodstream infection, not necessarily associated with probiotic strains, in cancer patients treated with chemotherapy. Additionally, we recommend that probiotics can alleviate alimentary tract symptoms in immunocompromised patients.

Keywords: Bacteremia • Bifidobacterium breve • Immunocompromised Host • Lymphoma • Probiotics

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Introduction

Probiotics are fermented organisms producing lactic acid, which promotes a favorable effect on the intestinal immune system. Clinical trials have demonstrated optimal outcomes with probiotics in cancer patients after chemotherapy [1]. While rare infectious complications associated with probiotics are infrequently reported, a pessimistic study suggests avoiding probiotics in immunocompromised hosts to prevent low-frequency bloodstream infections (BSI) caused by low pathogenic virulence pathogens. However, probiotic-induced BSI is rare, and BSI from other low-virulence organisms occurs in immunocompromised patients, even without probiotics [2]. Despite these considerations, the overall positive impact of probiotics in patients with cancer remains significant.

Bifidobacterium spp., including *Bifidobacterium breve*, ferment intestinal microorganisms that comprise the human microbiome. *Bifidobacterium* spp. are nonvirulent anaerobic gram-positive rods that live in the gut of healthy people. When these bacteria establish a pathogenic infection in humans, the host is immunocompromised, and the infection is opportunistic [2]. According to many case reports, *Bifidobacterium* bacteremia is a rare opportunistic infection caused by underlying diseases, all of which are severe or chronic gastrointestinal diseases [3], with the occasional immune-compromised condition [4]. In our clinical oncology experience, BSIs caused by commensal bacteria are opportunistic in immunocompromised hosts, such as patients undergoing chemotherapy [3].

Case Report

A 75-year-old Japanese woman with malignant lymphoma (diffuse large B-cell lymphoma) was treated with the rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) regimen. A large mass was found on her left cervical lymph node. Malignant lymphoma had a poor risk status in the revised international prognostic index (IPI) and a high intermediate risk in the NCCN-IPI. She achieved complete remission after 8 courses of R-CHOP. The dosage of the CHOP regimen was adjusted with a 50% reduction in the first cycle, followed by a 20% reduction in the second cycle, and full dose administration after the third cycle. The dose modification was due to the patient’s general condition. At the last course of chemotherapy, she developed febrile neutropenia (white blood cell count of 1900/µL and neutrophil count of 87/µL) with mild diarrhea on day 8 after the eighth R-CHOP, despite of the use of pegfilgrastim 3.6 mg. This febrile episode marked the patient’s initial occurrence of febrile neutropenia. She was admitted to the hospital for treatment of febrile neutropenia. Blood culture at the onset of febrile neutropenia revealed bacteremia caused by *B. breve*. BSI caused by *B. breve* was diagnosed, and she was given meropenem 1.0 g/day for 8 days (until day 16) as an empirical treatment. However, the drug sensitivity indicated that meropenem was resistant to the detected organism, *B. breve*. The drug sensitivity results for isolated *B. breve* are shown in Table 1. The patient did not use anti-acid medication. She was not given probiotics; however, she preferred to eat commercial yogurt (Meiji Bulgaria Yogurt, Meiji Corporation, Ltd., Tokyo) every morning until admission. This yogurt is produced from only *Lactobacillus bulgaricus* and *Streptococcus thermophilus*. It does not contain *B. breve* (according to official information). We concluded that she was not infected by food yogurt. We speculated that isolated *B. breve* was derived from the patient’s commensal bacterial flora. Her neutropenia had completely recovered, reaching 2148/mL on day 12. Her febrile status was reduced to the normal range on day 13. Her infectious condition fully resolved following the recovery from neutropenia. However, despite an 8-day course of meropenem, the effectiveness of antimicrobial treatment remained uncertain. This uncertainty stemmed from the in vitro drug sensitivity test, which indicated resistance of isolated *B. breve* to meropenem (Table 1).

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<tr>
<th>Antimicrobial drug</th>
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<td>ABPC</td>
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<td>ABPC/SBT</td>
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Table 1. The drug sensitivity results for isolated *B. breve* in this case.

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Discussion

In our field, hematological malignancies, including malignant lymphoma, require several months of constitutive chemoinmunotherapy with the R-CHOP regimen. In these cases, probiotics, such as fermenting bacilli that produce lactic acid, can sometimes be a suspicious preparation drug, causing probiotic-associated BSI [6]. In some cases, probiotics have been used to identify genetic isolates derived from blood cultures and organisms [7]. In other cases, clinical isolates from blood had identically different phenotypes from probiotic strains, using molecular methods [8]. Thus, the consistency or association between probiotic treatment and BSI is not well established. In another view, a neutropenic diet devoid of raw food was not linked to an increased risk of infections and mortality [9,10]. These fermenting bacteria are found in the human gastrointestinal tract. Although microorganisms in the gastrointestinal tract are less pathogenic than bacteria, almost all of them are antimicrobial-resistant. We believe that even if 2 isolates of BSI and probiotics are identified as the same species, this does not always imply that the BSI originated from probiotics. In the present case, B. breve BSI was not caused by probiotics contained in the patients’ diet.

As demonstrated in this case, probiotics, including food and pharmaceutical lactic acid bacteria preparations, do not always cause lactate-producing bacteria translocation in the alimentary tract. In our case, one of the commensal nonvirulent bacteria, B. breve, caused BSI, a potentially severe infection. We considered that the isolation of B. breve in this case was true bacterial BSI. In our speculation, other causative agents of this serious infection derived from commensal bacteria should be recognized as an opportunistic infection other than B. breve. Therefore, it is necessary to support cases in which rare indigeneous bacteria with little risk cause febrile neutropenia in a patient with cancer, even without probiotics. Some clinical evidence suggests that probiotics can help reduce clinical symptoms and infections [11,12]. Furthermore, synbiotics can improve intestinal barrier function [13]. Even in recipients of hematopoietic stem cell transplantation, the use of probiotic formations did not affect the incidence of BSI caused by probiotic organisms [14].

Conclusions

We observed that fermenting bacilli, including Bifidobacterium spp., can also be a source of BSI, not necessarily associated with probiotic strains, in cancer patients undergoing chemotherapy. We advocate that probiotics should not always be prohibited in immunocompromised patients.

Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study protocol was approved by the institute’s committee on human research.

References: