Original Article

Anaerobic gram-negative rod bacteremia as a marker of gastrointestinal cancer in Japanese patients: a single-center retrospective study

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Background: Gram-negative rod (GNR) bacteremia has been suggested as a clinical marker of occult cancer; however, no studies are available in this regard in the Japanese population. Here, we investigated the risk factors for gastrointestinal cancer with GNR bacteremia.

Methods: Patients with GNR bacteremia admitted to St. Luke's International Hospital between January 2011 and July 2021 were included. The clinical data of patients with and without cancer, 1 year before and after GNR bacteremia diagnosis, were compared. Univariate analysis was performed using χ^2 and Fisher's exact tests for categorical variables and the Mann-Whitney *U* test for continuous variables, while multivariable analysis was performed using logistic regression analysis, and a P of <0.05 was considered statistically significant.

Results: Of 2,296 GNR bacteremia-positive patients, 96 were associated with gastrointestinal cancer, and univariate analysis showed significant differences between the gastrointestinal cancer and comparison groups in terms of mean body mass index (BMI; 20.5 *vs.* 21.8 kg/m^2), *Enterobacterales* detection (64.6% *vs.* 81.3%), and anaerobic GNR detection (24.0% *vs.* 8.5%). Thirty-five (36%) and 61 (64%) patients had upper and lower gastrointestinal cancer, respectively. There were 23 patients with anaerobic GNR bacteremia related to 24 strains (upper and lower gastrointestinal cancer, 5 and 18 cases, respectively). Multivariate analysis identified anaerobic GNR [odds ratio, 3.440; 95% confidence interval (CI): 2.085–5.675, P<0.001] as a significant risk factor for cancer.

Conclusions: Anaerobic GNR in blood cultures may be a risk factor for gastrointestinal cancer. Therefore, it is necessary consider cancer workup, such as endoscopy, for patients with anaerobic GNR bacteremia.

Keywords: Occult cancer; blood culture; gram-negative rod (GNR); anaerobic gram-negative rod (anaerobic GNR); gastrointestinal cancer

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Introduction

Background

Blood culture is a clinically useful tool for detecting bacteremia and fungemia, which are associated with high mortality rates (1). Urinary tract infections are the most common source of gram-negative rod (GNR) bacteremia, followed by gastrointestinal infections (2,3). The associations between *Streptococcal* endocarditis, *Streptococcus gallolyticus* (*S. gallolyticus*) bacteremia, and cancer were first reported over 50 years ago (4,5). Further, a meta-analysis showed the existence of an association between *S. gallolyticus* and colorectal cancer (6). Another study also showed that GNR bacteremia is a clinical marker of occult cancer (7).

Rationale and knowledge gap

However, to the best of our knowledge, no study has examined the association between gastrointestinal cancer and GNR bacteremia in the Japanese population.

Objective

Thus, we aimed to investigate risk factors for gastrointestinal malignancies in Japanese patients with GNR bacteremia. We present this article in accordance with the STROBE reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-23-126/rc).

Highlight box

Key findings

- Gram-negative rod (GNR) bacteremia was reported as a clinical marker of gastrointestinal cancer. We should consider the gastric fiber or colon fiber.

What is known and what is new?

- Bacteremia caused by *Streptococcus gallolyticus* is known to be a marker of colon cancer.
- GNR bacteremia has been reported as a potential marker for gastrointestinal cancer in some studies; however, its prevalence in the Japanese population was previously unknown. This study has revealed the presence of this marker in a Japanese cohort.

What is the implication, and what should change now?

- We performed the retrospective cohort study to investigate risk factors for gastrointestinal malignancies in Japanese patients with GNR bacteremia. We should consider the gastric fiber or colon fiber for the occult GNR bacteremia. Further investigation of the prospective study is needed.

Methods

Study design and setting

This single-center retrospective cohort study was conducted at St. Luke's International Hospital, a 520-bed teaching hospital in Tokyo, Japan.

Patient consent statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of St. Luke's International Hospital in Tokyo, Japan (approval number 21-J021) and individual consent for this retrospective analysis was waived.

Inclusion and exclusion criteria

Adult patients (age ≥18 years) who were diagnosed as GNR-positive (>1 set) between January 2011 and July 2021 were included. The eligible patients were identified from the hospital's electronic database. To control for confounding factors, patients with cancer diagnosis before or after GNR bacteremia-positive blood culture detection within 1 year were included. As daily clinical tests, microbial identification and antimicrobial susceptibility testing were performed using a MALDI Biotyper (Bruker Daltonik, Bremen, Germany) and MicroScan WalkAway 96 Plus with Neg ID panels (Beckman Coulter, Brea, CA, USA).

Study outcome

The patients were divided into two groups according to whether they were associated with gastrointestinal cancer within 1 year before or after GNR bacteremia detection. The diagnosis of cancer was based on our medical records, and the included patients were diagnosed with gastrointestinal cancer based on the results of endoscopy, imaging studies, and pathological analysis.

Statistical analysis

Univariate analysis was performed using χ^2 and Fisher's exact tests for categorical variables and the Mann-Whitney *U* test for continuous variables. A significance level of 0.05 was set for the univariate analysis of the variables to be included in multivariable analyses. Further, multivariable

Table 1 Baseline characteristics of patients with bacteremia resulting from gram-negative rod infection (n=2,296)

Characteristic	Value
Age (years), mean (SD)	72.4 (15.7)
Male sex, n (%)	1,236 (53.8)
Body mass index (kg/m^2), mean (SD)	21.7 (4.5)
Gastrointestinal cancer, n (%)	96 (4.2)
Heart failure, n (%)	264 (11.5)
Diabetes mellitus, n (%)	388 (16.9)
COPD, n (%)	38 (1.7)
Myocardial infarction, n (%)	90 (3.9)
Collagen disease, n (%)	34 (1.5)
Liver cirrhosis, n (%)	194 (8.4)
Chronic kidney disease, n (%)	273 (11.9)
Hemodialysis, n (%)	99 (4.3)
Cerebrovascular disease, n (%)	107 (4.7)
Hypertension, n (%)	535 (23.3)
Human immunodeficiency virus, n (%)	4 (0.2)
Immunosuppressant use, n (%)	67 (2.9)
Biologics use, n (%)	23 (1.0)
Steroid use within 90 days, n (%)	397 (17.3)
Enterobacterales, n (%)	1,851 (80.6)
Anaerobic GNR, n (%)	210 (9.1)

SD, standard deviation; COPD, chronic obstructive pulmonary disease; GNR, gram-negative rod.

logistic regression analyses were performed for each characteristic based on the bivariate analysis results. All analyses were performed using SPSS 19.0 J statistical software (IBM Japan, Tokyo, Japan).

Results

A total of 2,296 patients who tested GNR-positive based on blood culture analysis were included in the study. The patient characteristics are summarized in *Table 1*. The mean age and body mass index (BMI) of the patients were 72.4 [standard deviation (SD): 15.7] years and 21.7 (SD: 4.5) kg/m^2, respectively. Most of the GNR blood cultures (80.6%) were classified as *Enterobacterales*, whereas 9.1% was classified as anaerobic GNR.

Of the 2,296 patients, 96 (4.2%) were diagnosed with gastrointestinal cancer before or after 1 year of bacteremia onset. In univariate analysis, we analyzed age; sex; BMI; comorbidity; use of immunosuppressants, biologics, and steroids within the past 90 days; *Enterobacterales* detection; and anaerobic GNR detection.

In univariate analysis, the mean BMI (20.5 kg/m^2 for the cancer group *vs.* 21.8 kg/m^2 for the non-cancer group, P=0.006), blood culture positive for *Enterobacterales* (64.6% *vs.* 81.3%, P<0.01), and blood culture positive for anaerobic GNR (24.0% *vs.* 8.5%, P<0.01) were identified as significantly associated with gastrointestinal cancer (*Table 2*).

Among patients with gastrointestinal cancer, 35 (36%) and 61 (64%) patients had upper and lower gastrointestinal cancer, respectively (*Table 3*). The gastrointestinal cancer types were distributed as follows: sigmoid colon cancer, 21 patients (22%); rectal cancer, 21 patients (22%); colon cancer, 16 patients (17%); gastric cancer, 21 patients (22%); esophageal cancer, 6 patients (6%); papillary adenocarcinoma, 5 (5%); and others, 6 patients (6%). Further, anaerobic GNR bacteremia, including 24 strains, was observed in 23 patients with gastrointestinal cancer (upper gastrointestinal cancer, 5 patients; lower gastrointestinal cancer, 18 patients with a polymicrobial pattern observed in 1 patient). Furthermore, the strains included the *Bacteroides* spp. (n=19), *Fusobacterium* spp. (n=1), and *Prevotella* spp. (n=2). Details of the pathogens detected in patients with bacteremia are shown in *Table 3*.

In univariate analysis, while BMI was significantly associated with gastrointestinal cancer, the clinical relevance of this finding was deemed insignificant due to the minimal difference in BMI between the two groups. Consequently, in the multivariable analysis—which was adjusted for age, sex, *Enterobacterales* detection (*Table 4*), and anaerobic GNR detection (*Table 5*), only anaerobic GNR detection [odds ratio, 3.440; 95% confidence interval (CI): 2.085–5.675, P<0.01] were identified as significant risk factors for gastrointestinal cancer.

Discussion

In this study, anaerobic GNR bacteremia was identified as a factor associated with gastrointestinal cancer within 1 year before or after the onset of bacteremia in Japanese patients. Previous studies have shown an increased incidence of gastrointestinal cancer in patients with GNR bacteremia (7) as well as anaerobic GNR bacteremia (8). The association between bacteremia and gastrointestinal cancer suggests that the disruption of the normal mucosal barrier owing

Table 2 Univariate analysis of factors associated with the risk of gastrointestinal cancer

Characteristic	Cancer (n=96)	Non-cancer (n=2,200)	P value
Age (years), mean (SD)	73.8 (11.5)	72.3 (15.8)	0.23
Sex (male), n (%)	35 (36.5)	1,025 (46.6)	0.05
Body mass index (kg/m^2), mean (SD)	20.5 (4.0)	21.8 (4.5)	0.006
Heart failure, n (%)	8 (8.3)	256 (11.6)	0.32
Diabetes mellitus, n (%)	13 (13.5)	375 (17.0)	0.37
COPD, n (%)	3 (3.1)	35 (1.6)	0.21
Myocardial infarction, n (%)	5 (5.2)	85 (3.9)	0.42
Collagen disease, n (%)	0	34 (1.5)	0.40
Liver cirrhosis, n (%)	7 (7.3)	187 (8.5)	0.68
Chronic kidney disease, n (%)	7 (7.3)	266 (12.1)	0.16
Hemodialysis, n (%)	3 (3.1)	96 (4.4)	0.80
Cerebrovascular disease, n (%)	4 (4.2)	103 (4.7)	>0.99
Hypertension, n (%)	23 (24.0)	512 (23.3)	0.88
Human immunodeficiency virus, n (%)	0	4 (0.2)	>0.99
Immunosuppressant use, n (%)	0	67 (3.0)	0.11
bDMARDs use, n (%)	0	23 (1.0)	0.62
Steroid use within 90 days prior to GNR bacteremia, n (%)	16 (16.7)	381 (17.3)	0.08
Enterobacterales, n (%)	62 (64.6)	1,789 (81.3)	<0.01
Anaerobic GNR, n (%)	23 (24.0)	187 (8.5)	<0.01

SD, standard deviation; COPD, chronic obstructive pulmonary disease; bDMARD, biologic disease-modifying anti-rheumatic drug; GNR, gram-negative rod.

Table 3 Type of gastrointestinal cancer in all patients with gastrointestinal cancer with anaerobic gram-negative bacteremia

Type of cancer	All patients with cancer (n=96)	Number of pathogens detected in cancer patients with anaerobic GNR bacteremia
Sigmoid colon cancer	21 (22%)	*Bacteroides* spp. (n=2), *Bacteroides thetaiotaomicron* (n=1), *Bacteroides fragilis* (n=1), *Bacteroides ovatus* (n=1), *Bacteroides vulgatus* (n=1), *Prevotella intermedia* (n=1), *Fusobacterium* spp. (n=1)
Rectal cancer	21 (22%)	*Bacteroides fragilis* (n=3), *Bacteroides* spp. (n=2), unidentified anaerobic GNR (n=2)
Colon cancer	16 (17%)	*Bacteroides fragilis* (n=2), *Bacteroides vulgatus* (n=1), *Bacteroides* spp. (n=1)
Gastric cancer	21 (22%)	*Bacteroides fragilis* (n=1)
Esophageal cancer	6 (6%)	*Bacteroides thetaiotaomicron* (n=1), *Prevotella* spp. (n=1)
Papillary adenocarcinoma	5 (5%)	*Bacteroides fragilis* (n=1)
Other	6 (6%)	*Bacteroides fragilis* (n=1)

GNR, gram-negative rod.

Table 4 Multivariable logistic regression analysis of factors associated with gastrointestinal cancer, adjusted for age, sex, and *Enterobacterales* detection

Variables	Odds ratio	95% CI	P value
Age	1.011	0.996–1.025	0.14
Sex (male: 0)	0.695	0.453–1.066	0.09
Enterobacterales	0.413	0.266–0.641	<0.01

CI, confidence interval.

Table 5 Multivariable logistic regression analysis of factors associated with gastrointestinal cancer, adjusted for age, sex, and anaerobic GNR detection

Variables	Odds ratio	95% CI	P value
Age	1.011	0.996–1.025	0.14
Sex (male: 0)	0.697	0.454–1.070	0.09
Anaerobic GNR	3.440	2.085–5.675	<0.01

GNR, gram-negative rod; CI, confidence interval.

to tumor growth may be a portal of entry for bloodstream infection (9). Further, it has been suggested that changes in intestinal microbiota composition, such as the proliferation of anaerobic bacteria, may activate immune response and induce genetic mutations that may contribute to colon cancer carcinogenesis (10). The results of our study may be consistent with both of these hypotheses, although it is still unclear whether there is a causal relationship between GNR bacteremia and gastrointestinal cancer. In a cohort study in Denmark, *S. gallolyticus*, *Clostridium septicum*, *Bacteroides ovatus*, *Bacteroides uniformis*, *Clostridium tertium*, *Fusobacterium* spp. (excluding *Fusobacterium necrophorum*), and gram-positive anaerobic cocci were found to be associated with colorectal cancer (11). Similarly, our study showed that *Bacteroides* were the most frequently observed anaerobes in patients with gastrointestinal cancer.

According to the registry of gastrointestinal cancer in Japan in 2021 (12), colon cancer has the highest prevalence rate, followed by stomach and rectal cancers. This is because the disruption of the gastrointestinal membrane is more common in the lower gastrointestinal tract than in the upper tract, and the portal of entry to bacteremia often results from membrane disruption in the lower gastrointestinal tract. Therefore, our results suggested that sigmoid colon and rectum cancer may be more frequently associated with GNR bacteremia.

This study has some limitations. First, it was a single-center, retrospective study. Both groups of patients were diagnosed with cancer retrospectively; thus, the diagnosis methods may not be identical and might not have been performed for patients in the non-cancer group, introducing a potential selection bias. Second, the number of GNR-positive blood culture samples was not considered. This could be a confounder given that the probability of obtaining a positive blood culture increases with the number of blood culture sets drawn; thus, the sensitivity of diagnosing cancer may increase. We only considered GNR, not anaerobic gram-positive cocci (GPC), which are also markers of colorectal cancer (6). In future, we intend to investigate the association between cancer and anaerobic GPC in the Japanese population. Third, the duration of follow-up of the patients with bacteremia was not identical due to the retrospective design of the study; hence, we may have missed some patients who developed cancer within 1 year before or after being diagnosed with GNR bacteremia.

In this study, we included data on cases of gastrointestinal cancer that occurred within 1 year of onset of bacteremia. Biomarkers are generally used to detect previously undiagnosed cancers. The aim of this retrospective study was to assess the efficacy of anaerobic GNR as a marker for gastrointestinal cancer, which required the collection of a substantial number of samples. Based on these results, we plan to conduct prospective studies in patients with anaerobic GNR bacteremia who have not been diagnosed with cancer, performing endoscopic examinations and other tests to confirm the validity of this method. Lastly, a previous study revealed a significant association between *Enterobacterales* bacteremia and gastrointestinal cancer (7). In this multivariate analysis, *Enterobacterales* acted as a protective factor against gastrointestinal cancer. However, we did not exclude urinary tract infection as a source of *Enterobacterales* bacteremia. Therefore, we consider that it cannot be concluded to be protective.

Conclusions

Bacteremia, due to anaerobic GNR infection, may be associated with an increased risk of gastrointestinal cancer in the Japanese population. Thus, gastroscopy or colonoscopy should be considered for these patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://cco.amegroups.com/article/view/10.21037/cco-23-126/rc

Data Sharing Statement: Available at https://cco.amegroups.com/article/view/10.21037/cco-23-126/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-23-126/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of St. Luke's International Hospital in Tokyo, Japan (approval number 21-J021) and individual consent for this retrospective analysis was waived.

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