Original Article

Multicenter Study of the Clinical Presentation of *Staphylococcus lugdunensis* Bacteremia in Japan

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SUMMARY: *Staphylococcus lugdunensis* (SL) is a bacterium with a highly pathogenicity than most other coagulase-negative *Staphylococcus* spp. (CoNS). In Japan, data on this pathogen are sparse, and the current prevalence of SL bacteremia is unknown. Therefore, we investigated the prevalence of SL in blood culture specimens in a prospective multicenter study across 5 facilities. A total of 3,284 patients had positive blood cultures, and 2,478 patients had bacteremia. Among the patients with bacteremia, 7 patients (0.28%) had SL bacteremia. A total of 281 patients had CoNS bacteremia, with SL accounting for 2.49% of these cases. Of the 7 patients with SL bacteremia, 1 patient (14.3%) had infective endocarditis, and 1 patient (14.3%) died within 30 days. In this study, SL resulted in the development of bacteremia in select patients. Clinicians in Japan should be aware of the prevalence of SL and the complications of SL bacteremia.

INTRODUCTION

Staphylococcus lugdunensis (SL) is a species of coagulase-negative *Staphylococcus* spp. (CoNS). SL and *Staphylococcus aureus* (SA) are known for having a higher pathogenicity than other CoNS (1). Previous reports have demonstrated that SL can cause infective endocarditis (IE), catheter-related bloodstream infections, and skin and soft tissue infections (2–4); however, there have been only 4 reports on SL infections in Japan (5–8). Three additional reports have described the detection rates of SL in specimens of unknown clinical status (9–11). The lack of case reports on SL infections in Japan may be because Japan has lower prevalence rates of SL infections than other countries. Alternatively, the microbiological investigation and detection of SL may not be a priority in Japan.

The prevalence of culture specimen-confirmed SL

in CoNS cases was reported to be 0.8% in South Korea (3 of 358 cases, identified from urine, secretions, and abscesses) (12), 0.7% in China (5 of 670 cases, identified from secretions and blood) (13), and 2.8–7.3% in the United States (14 of 499 cases, identified from wounds, urine, and blood; 42 of 576 cases, identified from abscesses and soft tissue) (14,15). Three studies in Japan from the 1990s showed that the prevalence of SL among all CoNS-positive culture specimens ranged from 1.3% to 5.2% (9–11). In surveillance data from the United States, Canada, Latin America, and Europe, SL accounted for 0.3% of bloodstream infections (16). There have been no reports on the incidence of SL bacteremia in Japan; therefore, the true incidence of SL bacteremia in Japan is currently unknown.

To determine the current state of SL bacteremia in Japan, we investigated the prevalence of SL in blood culture specimens across multiple institutions.

MATERIALS AND METHODS

A prospective multicenter observational study was conducted between October 2012 and September 2013 at the Tokyo Women's Medical University Hospital (Tokyo), Center Hospital of the National Center for Global Health and Medicine (Tokyo), Kameda Medical Center (Chiba), Shizuoka Cancer Center (Shizuoka), and

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Toranomon Hospital (Tokyo). Data on positive blood culture results were collected. SL was identified using an automated system (MicroScan WalkAway; Siemens Healthcare, Erlangen, Germany) at all institutions.

Baseline characteristics were collected, including age, sex, date of admission, specimen collection site, healthcare-associated or community-associated infection, and underlying diseases. In addition, the date of a positive blood culture result, infective species, disease diagnosis, presence or absence of a catheter-related bloodstream infection, and prognosis were also evaluated.

Patients with blood culture-positive for SA or other CoNS were used as a comparative control group. Hospital-acquired infections were defined as cases with positive blood cultures using samples collected more than 48 h after the time of admission. Cases with positive blood cultures, using samples collected within 48 h of admission or collected in an outpatient department were defined as community-acquired infections. However, the following cases were defined as healthcare-associated infections: patients who received intravenous therapy, wound treatment, tube feeding, or nursing care at home within the last 30 days; patients who received hemodialysis or intravenous chemotherapy within the last 30 days; patients with a history of hospitalization at an acute-phase hospital for ≥ 2 days within the last 90 days; or patients who lived in a nursing home or long-term care facility. The remaining infections were defined as community-acquired infections (17).

Infectious disease specialists determined whether a case was bacteremia or a contamination of the blood culture; they also assessed the origin of bacteremia for each case. Patients with positive blood culture results were followed for 30 days, and their clinical outcomes were evaluated.

For statistical analyses, continuous variables were tested using the Mann–Whitney *U* test with Bonferroni correction for multiple comparisons. Categorical variables were tested with Fisher's exact test with Bonferroni correction for multiple comparisons. In general, two-sided testing was performed at a significance level of 0.05. However, for Bonferroni corrections, we used a significance level of 0.017. Statistical analyses were performed using R 3.0.2 software.

Study approvals were obtained from the ethical committees at each institution. This study was registered in the clinical trial database (UMIN000007935).

RESULTS

In total, 3,284 patients had a positive blood culture, and 2,478 patients were diagnosed with bacteremia after excluding contamination. Of those, 7 (0.28%) out of 2,478 patients had SL bacteremia. The rate of SL among patients with CoNS bacteremia was 2.49% (7/281). Methicillin-resistant SL was isolated in 3 of these cases (42.8%). Of the patient with SL bacteremia, 2 patients had community-acquired bacteremia and 1 patient had IE with a methicillin-resistant strain. The patient with IE died within 30 days (Table 1). Of the patients with hospital-acquired SL bacteremia, 75% had a catheter-related bloodstream infection.

Among the patients with blood culture-positive the rates of bacteremia with SA and other CoNS were 95.0% (287/305) and 36.3% (274/755), respectively. The rate of methicillin-resistant SA was 31.0% (89/287). The rates of intravascular device-associated infections in patients with SA- and other CoNS-positive blood cultures were 47.7% (137/287) and 86.5% (237/274), respectively. The rates of IE in patients with SA- and

Table 1. Characteristics and prognoses of the cases of bacteremia

		① SL	② SA	③ Other-CoNS	① – ②	① – ③
		No.	7	287	274	<i>p</i> -value
Characteristics	median age (range)		76.5 (68 – 86)	70.0 (0 – 97)	64.0 (0 – 100)	0.032
	women : men		4 : 3	85 : 202	87 : 187	0.12
			<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	
	Hospital-acquired		4 (57.1)	193 (67.2)	239 (87.2)	0.68
	Healthcare-associated		1 (14.3)	42 (14.6)	12 (4.4)	0.061
	Community-acquired		2 (28.6)	52 (18.1)	23 (8.4)	
	DM		3 (42.9)	81 (28.2)	35 (12.8)	0.41
	CKD		3 (42.9)	89 (31.0)	47 (17.2)	0.68
	CHF		1 (14.3)	44 (15.3)	21 (7.7)	1
	COPD		0 (0.0)	8 (2.8)	4 (1.5)	N/A
	Malignancy (blood)		0 (0.0)	21 (7.3)	81 (29.6)	N/A
	Malignancy (solid tumor)		0 (0.0)	81 (28.2)	76 (27.7)	0.20
	Steroid		1 (14.3)	31 (10.8)	45 (16.4)	0.56
Diagnosis	Intravascular device-associated infection		4 (57.1)	137 (47.7)	237 (86.5)	0.71
Complication	IE		1 (14.3)	16 (5.6)	2 (0.7)	0.34
Mortality	within 7 days		0 (0.0)	25 (8.7)	13 (4.7)	N/A
	within 30 days		1 (14.3)	57 (19.9)	36 (13.1)	1

SL, *Staphylococcus lugdunensis*; SA, *Staphylococcus aureus*; CoNS, coagulase-negative *Staphylococcus* spp.; DM, diabetes mellitus; CKD, chronic kidney disease; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; N/A, not applicable; IE, infective endocarditis.

other CoNS-positive blood cultures were 5.6% (16/287) and 0.7% (2/274), respectively. The mortality rates within 30 days in patients with SA- and other CoNS-positive blood cultures were 19.9% (57/287) and 13.1% (36/274), respectively.

DISCUSSION

We speculated that many SL bacteremia cases have been overlooked and the prevalence of SL infections has thus been underestimated, potentially leading to inadequate clinical care for these patients. In our study, SL bacteremia accounted for 0.28% of all bacteremia cases, which is comparable to surveillance data from the United States, Canada, Latin America, and Europe combined (0.3%) (16).

Reports from other countries have stated that data on SL infection prevalence are still lacking because it has been neglected in terms of the predisposition to having a lower risk. Compared with other CoNS infections, the risks of complications associated with SL, such as IE, has not been studied extensively (12,13). Although IE was observed in only one case in our study, further investigations may have disclosed additional complications. Consequently, it is important that clinicians consider the differences between SL and other CoNS infections in Japan.

Our study has several limitations. The first limitation involves the microbiological accuracy of bacterial identifications. In our study, the identification methods were autonomous for each study site, and none of the strains at any site was confirmed by molecular testing. Although reliability issues with the microbiological diagnoses may exist, it has been reported that SL identification is 94% accurate using conventional methods (9). Therefore, the results may not significantly differ after genetic analyses with molecular tests. Second, the statistical power of the tests was insufficient owing to the small number of SL cases. Although there were no significant differences in the detection of SL and other CoNS or SA, additional studies with larger sample sizes may lead to different results.

In conclusion, the prevalence of SL bacteremia was 0.28% across multiple institutions in Japan, which is similar to the prevalence rates reported for other countries. Japanese clinicians should be aware of the importance of SL and the complications of SL bacteremia.

Conflict of interest None to declare.

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