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ORIGINAL ARTICLE

Associated factors in *Streptococcus bovis* bacteremia and colorectal cancer

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Abstract Reports suggest that between 25% and 80% of patients with *Streptococcus bovis/gallolyticus* bacteremia have concomitant colorectal tumors. This retrospective study was aimed to identify associations between clinical characteristics and a finding of colorectal neoplasm in patients with *S. bovis* bacteremia who had colonoscopy examination. We retrospectively reviewed the records of patients with *S. bovis* bacteremia from Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan, between January 2004 and January 2014. Clinical data including age, sex, comorbidities, blood culture, and colonoscopy findings were collected and their relationship to a finding of colorectal cancer was examined. A total of 107 patients with *S. bovis* bacteremia were identified, of whom 49 (72% male; age 65 ± 12 years) were investigated with colonoscopy; 15 of these patients (30.6%) had colorectal adenocarcinoma. Female sex ($p = 0.014$) and a history of noncolorectal malignancy ($p = 0.004$) were associated with a finding of colorectal adenocarcinoma. There were no associations with age, percentage of blood cultures, or the presence of diabetes mellitus, chronic liver disease, heart disease, or

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end-stage renal disease. Our results show that *S. bovis* bacteremia is associated with the presence of colorectal adenocarcinoma, especially in female patients, and concomitant existence of other malignancies.

Introduction

Group D streptococci, including enterococci and two non-enterococcal species—*Streptococcus bovis* and *Streptococcus equinus*—are part of the normal bowel flora of humans and animals [1]. Klein et al. [2] observed an association between *S. bovis* bacteremia and colorectal cancer in the early 1970s. It was also reported that *S. bovis* bacteremia was associated with other bowel disorders including colonic adenomas [3—5]. There are two *S. bovis* biotypes (I and II), with biotype I having the ability to ferment mannitol, a characteristic feature used for differentiating it from biotype II. The prevalence of colorectal neoplasm in patients infected with *S. bovis* biotype II is substantially lower than that observed for biotype I [6]. In 2003, Schlegel et al. [7] proposed a taxonomy that classified the bacteria into subspecies: *Streptococcus gallolyticus* subsp. *gallolyticus*, *Streptococcus infantarius* subsp. *infantarius*, *S. infantarius* subsp. *coli*, *S. gallolyticus* subsp. *pasteurianus*, and *S. gallolyticus* subsp. *macedonicus*, *S. bovis* (previously named *S. bovis* biotype I). These bacteria synthesize proteins and polysaccharides to assemble the capsular sheath, collagen-binding proteins, and three types of pili, all of which enable them to be highly efficient in causing bacteremia, endocarditis, and colorectal cancer [8]. Despite several reports confirming that between 25% and 80% of patients with *S. bovis* bacteremia have colorectal cancer [9—11], only limited information is available as to whether any clinical characteristics of bacteremic patients are specifically associated with this finding. Therefore, the aim of our study was to examine the clinical associations of colorectal adenocarcinoma in patients with *S. bovis* bacteremia.

Methods

This retrospective chart review study was approved by both the Institutional Review Board and Ethics Committee of Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan. The Ethics Committee waived the requirement for informed consent. All patients had provided written informed consent before undergoing colonoscopy.

From database records dating between January 2004 and January 2014, 107 patients with *S. bovis* bacteremia were identified, and the following data were extracted: age, sex, comorbidities [diabetes mellitus, liver cirrhosis, heart disease, end-stage renal disease (ESRD), malignancy], history of related infections (meningitis, arthritis, or endocarditis), percentage of blood cultures that were positive, blood tests [C-reactive protein, hemoglobin (Hb), hematocrit (Hct), and carcinoembryonic antigen (CEA)], and colonoscopy findings (polyp size, location, and histopathology). Comorbid heart disease was defined as heart failure, valvular heart disease, or endocarditis. Patients with incomplete clinical data or an incomplete colonoscopic examination were excluded.

All *S. bovis* isolates were identified by Gram stain as Gram-positive lactic acid bacteria growing as pairs or chains of cocci, and subsequent analysis with matrix-assisted laser desorption/ionization time-of-flight mass spectrometry in the Microbiology Laboratory of Kaohsiung Chang Gung Memorial Hospital. The number of blood cultures yielding *S. bovis* for each patient was expressed as a percentage of the total number of cultures analyzed. Colonoscopies were performed using an Olympus CF Q260 or H260 video colonoscope (Olympus Optical Co., Ltd, Tokyo, Japan), with recording of all videos for subsequent review. The diagnosis of colorectal adenocarcinoma including carcinoma *in situ* was confirmed by the histopathological examination of either colonoscopic biopsy specimens or the resected specimen. Additional colorectal neoplasms were defined as tubular adenoma, villous adenoma, tubulovillous adenoma, and serrated adenoma after histopathological examination.

Statistical analyses

All data were collected and analyzed using Microsoft Excel 2003 (Microsoft Corporation, Redmond, WA, USA) and IBM SPSS statistics version 22 (IBM, Armonk, NY, USA). We divided the patients into the following two groups: (1) *S. bovis* bacteremia without colon cancer and (2) *S. bovis* bacteremia with colon cancer, according to the histopathological diagnosis of colorectal adenocarcinoma, and examined differences in proportions for each variable using Chi-square test, with $p < 0.05$ taken to indicate statistical significance. Univariate and multivariate logistic regression analyses were performed to examine relationships between the clinical characteristics and the finding of colorectal adenocarcinoma. Data are reported as mean ± standard deviation.

Results

In this study, 107 patients with *S. bovis* bacteremia were identified, among which 14 patients (28.6%) were female. The mean age of the study patients was 65 ± 12 years. Among the 107 patients with *S. bovis* bacteremia, 28 (26.2%) concomitantly had cirrhosis, 10 (9.3%) had gallstones, 11 (10.2%) had acute cholecystitis, two (1.9%) had

acute pancreatitis, and 16 (15.0%) had esophageal varices. Twenty-four patients (22.4%) had peptic ulcer disease.

Of the 107 patients, 49 had a record of complete clinical data and colonoscopy. Among these 49 patients, 15 (30.7%) were found to have a colorectal adenocarcinoma. Full colonoscopic examination was not performed due to the following reasons: inadequate bowel preparation, patient refusal to the examination, unstable hemodynamic status, and/or critical condition, which was not appropriate to the procedure. Among the 49 patients who received colonoscopy, 35 (71.4%) patients had a total of 36 colorectal neoplasms [tubular adenoma: 15 (41.2%); tubulovillous adenoma: 6 (16.7%); villous adenoma: 0 (0%); adenocarcinoma: 15 (41.2%)] and six hyperplastic polyps.

In the noncolorectal adenocarcinoma group ($n = 34$), there was male predominance (27/34; 79.4%) with a mean age of 68.7 $\pm$ 13.9 years. Documented comorbidities in this group included 10 (29.4%) cases with other malignancies, 14 (41.2%) with liver cirrhosis, 11 (32.4%) with diabetes mellitus, 28 (82.4%) with heart disease, 12 (35.2%) with ESRD, and one (2.9%) with arthritis. The colonoscopy findings were as follows: 17 patients had one polyp, two patients had two polyps, and one patient had three polyps. A total of 15 (44.1%) patients had at least one polyp equal to or larger than 1 cm; in five patients (11.7%), the polyps were $<$ 1 cm and 14 patients did not have a polyp.

In the colorectal adenocarcinoma group ($n = 15$), there was only a slight male predominance (8/15; 53.5%) and the mean age was 68.9 $\pm$ 9.1 years. Documented comorbidities in this group included 10 (66.7%) cases with other malignancy, two (13.3%) cases with liver cirrhosis, six (40.0%) cases with diabetes mellitus, nine (60.0%) cases with heart disease, three (20.0%) cases with ESRD, and none with arthritis; 12 patients had only one neoplasm and three patients had two neoplasms. The mean size of the tumor was 4.2 $\pm$ 3.8 cm, with the majority located at the rectum (1 at cecum/2 at ascending colon/1 at transverse colon/1 at descending colon/2 at sigmoid colon/8 at rectum) and staged as Stage II [3 intraepithelial carcinomas, 6 Stage II (4 Stage IIa and 2 Stage IIb), 2 Stage IIIb, and 4 Stage IV] with moderate differentiation (1 well differentiated/8 moderately differentiated/6 unknown).

The timing in the diagnosis of extracolonic malignancy was as follows: six of the 10 extracolonic cancers were diagnosed before *S. bovis* bacteremia, with a mean period of 18 months. The remaining four extracolonic cancers were, however, diagnosed only after *S. bovis* bacteremia, with a mean period of 6 months. Among the 10 extracolonic cancers, there were four hepatocellular carcinomas (2 Stage II, 1 Stage IIIc, and 1 Stage IV), two bladder cancers (1 Stage 0 and 1 Stage I papillary urothelial carcinoma), two renal cell carcinomas (1 Stage 0 squamous cell carcinoma and 1 Stage II clear cell carcinoma), one buccal cancer (Stage I squamous cell carcinoma), and one lung cancer (Stage IV small cell lung cancer).

Univariate analysis of categorical variables showed that sex ($p = 0.041$) and a history of other malignancies ($p = 0.014$) were significantly related to colon adenocarcinoma. The proportion of male patients in the colon cancer group (53.3%) was less than that in the noncancer group (79.4%). Ten of the 15 patients (66.7%) with colorectal cancer were found to have a history of other malignancies compared with only 10 of 34 patients (29.4%) in the noncolorectal cancer group. Comorbidity with liver cirrhosis, diabetes mellitus, heart disease, ESRD, and arthritis showed no relationship with colon adenocarcinoma in the univariate analysis (Table 1) nor were there any significant relationships with age, percentage of blood cultures that were positive, C-reactive protein, Hb, Hct, or CEA (Table 2).

Table 1 Univariate analysis for categorical variables associated with a finding of colorectal cancer in patients with *Streptococcus bovis* bacteremia.

Factor	*Streptococcus bovis* bacteremia without colon cancer	*Streptococcus bovis* bacteremia with colon cancer	*p*
Sex			0.041*
Female	7 (20.6)	7 (46.7)	
Male	27 (79.4)	8 (53.3)	
Other malignancies			0.014*
No	24 (70.6)	5 (33.3)	
Yes	10 (29.4)	10 (66.7)	
Liver cirrhosis			0.083
No	20 (58.8)	13 (86.7)	
Yes	14 (41.2)	2 (13.3)	
Diabetes			0.604
No	23 (67.6)	9 (60.0)	
Yes	11 (32.4)	6 (40.0)	
Heart disease			0.148
No	6 (17.6)	6 (40.0)	
Yes	28 (82.4)	9 (60.0)	
End-stage renal disease			0.336
No	22 (64.7)	12 (80.0)	
Yes	12 (35.3)	3 (20.0)	
Arthritis			>0.99
No	33 (97.1)	15 (100)	
Yes	1 (2.9)	0 (0)	

All data are presented as *n* (%).
* Mean significant difference.

Table 2 Univariate analysis for continuous variables associated with a finding of colorectal cancer in patients with *Streptococcus bovis* bacteremia.

Factor	*Streptococcus bovis* bacteremia without colon cancer	*Streptococcus bovis* bacteremia with colon cancer	*p*
Age (y)	68.7 $\pm$ 13.9	68.9 $\pm$ 9.1	0.954
Positive blood cultures (%)	79.35 $\pm$ 29.5	65.9 $\pm$ 35.3	0.183
C-reactive protein (mg/L)	83.9 $\pm$ 82.2	142.4 $\pm$ 120.6	0.252
Hemoglobin (g/dL)	10.5 $\pm$ 2.3	10.9 $\pm$ 2.7	0.610
Hematocrit (%)	31.8 $\pm$ 6.5	31.9 $\pm$ 7.1	0.933
Carcinoembryonic antigen (ng/mL)	27.6 $\pm$ 88.9	423.7 $\pm$ 1190.2	0.274

All data are presented as mean $\pm$ standard deviation.

Table 3 Binary logistic regression of predictors of colorectal cancer in patients with *Streptococcus bovis* bacteremia.

Factor	Comparison	OR (95% CI)	*p*
Sex	Male vs. female	0.101 (0.016–0.629)	0.014 *
Other malignancy	Yes vs. no	12.376 (2.207–69.402)	0.004 *
Endocarditis	Yes vs. no		0.236

CI = confidence interval; OR = odds ratio.
* Mean significant difference.

We further calculated the binary logistic regression of predictors of colon adenocarcinoma, which revealed that female sex ($p = 0.014$) and comorbidity with other malignancies ($p = 0.004$) were significantly associated with colorectal cancer. There was no correlation with age, percentage of blood cultures that were positive, liver cirrhosis, diabetes mellitus, heart disease (including endocarditis), ESRD, arthritis, or other blood tests (Table 3).

Discussion

Bacteremia involving *S. bovis*, an organism usually found in the healthy gut, is known to be associated with colorectal neoplasia. One meta-analysis indicated a sevenfold increase in the risk of having a colorectal neoplasm in the presence of *S. bovis* septicemia [12]. Other studies have shown that up to 80% of patients with bacteremia caused by *S. bovis* biotype I (now called *S. gallolyticus* subsp. *gallolyticus*) have a colorectal neoplasm, a rate markedly greater than that noted in the general population [13,14]. By contrast, the prevalence of colorectal neoplasm in patients infected with *S. bovis* biotype II is significantly lower than the rate in patients infected with biotype I, and does not appear to be higher than the general population [6]. However, identification of *S. bovis* subtypes is not widely available, and is not a routine practice in our hospital. The growth of *S. bovis* in stool aspiration content or the existence of bacterial-specific antibody provides an alternative way to identify patients at increased risk of having colorectal neoplasia [15–17]. However, a few published reports have examined the clinical characteristics specifically associated with colorectal adenocarcinoma in patients with *S. bovis* bacteremia.

A recent meta-analysis of 20 published case series showed that 43% of patients with *S. bovis* bacteremia that was examined by colonoscopy had adenomas and 18% had carcinomas [14]. Our finding of colorectal neoplasm (adenoma and/or carcinoma) in 61.2% of patients and adenocarcinoma in 30.7% of patients accords very closely with these figures. In addition, we observed that female sex and comorbidity with noncolorectal malignancy were particularly associated with colorectal adenocarcinoma.

It is unclear why female sex should be a risk factor. It is established that the age-adjusted incidence of colonic adenomas and adenocarcinoma is higher in men than in women, possibly explained by the indirect tumor-promoting effects of testosterone [18]. Most case–control studies examining the association of *S. bovis* bacteremia with colorectal disease enrolled patients who were matched by sex and age [5,13], so the relationship we observed has not been apparent in the past.

Several studies have reported a link between *S. bovis* bacteremia and extracolonic malignancy. Previous researchers observed that 29% of such patients harbored tumors in the duodenum, gallbladder, pancreas, ovary, uterus, lung, or hematopoietic system [19,20], and some investigators have advocated more thorough investigation of the gastrointestinal tract than with colonoscopy alone [21,22]. In a Taiwanese study [23], 40% of *S. bovis* bacteremic patients had underlying malignancies, 21% had liver cirrhosis, and 24% had diabetes mellitus. A recent large prospective study spanning 20 years observed 22 cases of noncolorectal cancer among 133 bacteremic patients (17%) [24]. The malignancies observed in these studies included esophageal [21] and gastric carcinoma [3,25], gastric lymphoma, and pancreatic carcinoma.

It remains controversial as to whether *S. bovis* plays an etiological role in the development of colorectal tumors or is a consequence of the disease. Three mechanisms have been proposed. First, it has been suggested that a chronic inflammatory response to *S. bovis* could play a role in the malignant transformation of colonic mucosa. Antigens extracted from the cell wall of *S. bovis* are associated with overexpression of cyclooxygenase-2 and increased concentrations of interleukin-8 *in vitro*. These are frequently overexpressed in human colorectal cancers and can inhibit apoptosis, and stimulate proliferation and angiogenesis [26]. Second, *S. bovis* has a strong capacity—partly due to specific collagen- and heparan sulfate-binding proteins and pili—to form biofilms on collagen-rich surfaces, which *in vivo* are found on damaged heart valves as well as on precancerous sites with a displaced epithelium [27,28]. Third, *S. bovis* has the ability to increase vascular permeability and facilitate bacterial translocation into the portal circulation [29]. Moreover, the bacteria can then bypass the hepatic reticuloendothelial system and access the systemic circulation easily [30].

Our study has several limitations. First, it was conducted in a single center with a relatively small number of patients. Our analysis indicates that it would be worthwhile to collect further data from multiple centers to identify additional associations. Second, not all the patients with *S. bovis* bacteremia were examined with colonoscopy although the importance of colonoscopy screening in these patients had been emphasized in the previous studies. In conclusion, this study suggests that *S. bovis* bacteremia is associated with colorectal adenocarcinoma, especially in female patients, and concomitant existence of other malignancies.

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