Original Article

Clinical Characteristics of Streptococcus Bovis Bacteremia in VGHKS

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Key Words
Streptococcus bovis;
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Purpose. Colon cancer is increasing in incidence and is the leading cause of cancer-related death worldwide. *S. bovis* bacteremia frequently occurs with colonic neoplasia. The aim of this study is to assess the clinical characteristics of patients with S. bovis bacteremia in VGHKS.
Methods. From January 2001 to December 2006, 68 patients hospitalized at Kaohsiung Veterans General Hospital had bacteremia caused by *S. bovis*. This retrospective clinical evaluation was carried out to evaluate the relationship of these patients with *S. bovis* bacteremia to the endocarditis, colonic neoplasia and bacteremia of hepatobiliary origin. Data was analyzed using the Student *t*-test for numberical variables and chi-squared for categorical variables. Differences were considered to be significant at $p < 0.05$.
Results. Of 68 isolates of *S. bovis*, 25 were biotype I and 43 were biotype II. We excluded 16 cases because of incomplete survey. The sex and age distributions of patients infected were not significantly different. *S. bovis* I bacteremia had a higher rate of endocarditis than *S. bovis* II (53.3% vs. 13.5%, respectively; p = 0.003). *S. bovis* I bacteremia also had a higher rate of colonic neoplasia (60.0% vs. 18.9%, respectively; p = 0.004). However, *S. bovis* I had a lower rate of hepatobiliary source (46.7% vs. 59.5%, respectively; p = 0.4).
Conclusion. Because *S. bovis* bacteremia is the high incidence of colonic neoplasia, especially biotype I, we should complete studies (e.g.: cardiac echo, colonoscopy, upper abdominal sonography or abdominal CT scan) as soon as possible.
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Colorectal cancer has a high incidence worldwide and is the third leading cause of cancer-related death in Taiwan.[1]

The principle treatment is curative resection. Prognosis and overall survival rates are highly dependent on the pathological stage of the cancer.[2] Therefore, early detection with early treatment is a standard rule.

Many reports point to a close linkage between *Streptococcus bovis* infection and tumors of the human colon. Initially, a paper by McCoy and Mason appeared in 1951 suggesting a relationship between colon cancer and enterococcal endocarditis.[3] The coincidence of *Streptococcus bovis* bacteremia and *S. bovis* endocarditis was noted in several subsequent publications and confirmed shortly thereafter.[4-8] *S. bovis* endocarditis is considered to warrant colonoscopy since most of these patients present with either colon carcinomas or premalignancies.[9-12]

Several groups studied its diversity and devised

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schemes to distinguish strains by biotype. *S. bovis* strains among humans are said to be biotype I (or typical) if, among other traits, they ferment mannitol and produce glucan. Biotype II (or variant) cannot ferment mannitol or produce glucan. Biotype II strains are further divided into type II/1 and type II/2 by the ability of the latter group to produce beta-galactosidase and beta-glucuronidase and ferment trehalose but not glycogen.[15,18]

S. bovis is a human pathogen associated with endocarditis, sepsis and meningitis.[13-19] Since the early 1980s, genetic and biochemical diversity among *S. bovis* has been noted.[15,17,18] We therefore collected and indentified 68 blood cultures of *S. bovis* from patients at Veterans General Hospital Kaohsiung. A chart review was then carried out to assess clinical characteristics of *S. bovis* bacteremia.

Materials and Methods

Chart review. From January 2001 to December 2006, 68 patients hospitalized at Veterans General Hospital Kaohsiung had bacteremia caused by *S. bovis*. We excluded 16 cases because of incomplete survey. Of these 52 patients, polymicrobial infection was 6 and concomitant infection was 7. Medical records were reviewed using a standardized protocol, using the criteria set out by Broome et al., to determine patient demographics, in-hospital mortality rates and the clinical significance of the blood isolates.[20] Retrospective clinical evaluation was carried out to evaluate colonic tumors, including adenocarcinomas and adenomas. Bacteremia of hepatobiliary origin was diagnosed if the patient had clinically evident cholecystitis, cholangitis or cirrhosis with portasystemic shunting at the time of bacteremia. Endocarditis was diagnosed using the criteria defined by Durack et al.,[21] if *S. bovis* were recovered from two blood cultures and there was either a compatible clinical syndrome (a new or changing cardiac murmur, evidence of peripheral embolism, or cutaneous manifestations of endocarditis) or histopathological confirmation of endocarditis at surgical examination.

Statistical analysis. Numerical variable, including mean age, was compared using of the Student *t*-test; categorical variables, including gender, endocarditis, colonic lesions, hepatobiliary origin, other malignancy, and number of patient who died during hospitalization were compared using chi-squared. Differences were considered significant at $p < 0.05$.

Results

Patient demographics and clinical characteristics are shown in Table 1. Of the 52 isolates of S. bovis that caused bacteremia, 15 were biotype I and 37 were biotype II. The sex and age distributions of patients infected were not significantly different (Table 1). Two infants had bacteremia from biotype II related to sepsis, one of which was a 4-month-old patient with a case of sepsis and meningitis. The other was 17-month-old patient with colon perforation and sepsis. They were significantly younger than those with bacteremia caused by *S. bovis.*

Of the 15 type I patients, eight had bacterial endocarditis in contrast to 5 of 37 patients (13.5%) with clinically significant bacteremia due to *S. bovis* type II (p = 0.003, Table 1).

Of the 15 type I patients, nine had associated malignant or premalignant colonic lesions. This association was significantly higher than that for patients with bacteremia caused by *S. bovis* type II (7 of 37 patients, 18.9%, Table 1; p = 0.004). We analyzed the malignant or premalignant colonic lesions with bacteremia caused by *S. bovis* type I and type II on

Table 1. Demographic and clinical characteristics of patients with biotype I and II of *S. bovis* isolated from blood cultures

	Type I (%)	Type II (%)	Total	*p* value
No. of patients	15 (28.8)	37 (71.2)	52	
Mean age	66 ± 13	61.9 ± 19.8	63.1 ± 18.1	0.474*
Gender-Female	5 (33.3)	11 (29.7)	16 (31.0)	0.799**
Endocarditis	8 (53.3)	5 (13.5)	13 (25.0)	0.003**
Colonic lesions	9 (60.0)	7 (18.9)	16 (30.8)	0.004**
Hepatobiliary origin	7 (46.7)	22 (59.5)	29 (78.4)	0.4**
Other malignancy	8 (53.3)	11 (29.7)	19 (36.5)	0.109**
No.of P't died during H.	2 (13.3)	11 (29.7)	13 (25.0)	0.216**

* Student *t*-test.
** chi-squared test.

Table 2.

S. bovis II bacteremia from a hepatobiliary source had a higher frequency (22/37, 59.5%) than *S. bovis* I (7/15, 46.7%), but no clinical significance (Table 1).

The rate of noncolonic malignancy (e.g.: lung cancer, esophageal cancer, gastric cancer, HCC, pancreatic cancer, ovarian cancer, and malignant lymphoma) was higher in patients with bacteremia caused by *S. bovis* I (8/15, 53.3%) than in patients with *S. bovis* II (11/37, 29.7%), but this was not clinically significant (Table 1).

Mortality rates during this hospitalization were higher in patients with *S. bovis* II (11/37, 29.7%) than *S. boivs* I (2/15, 13.3%), but this was also not clinically significant (Table 1).

Discussion

In our study, *S. bovis* I bacteremia had clinical significance in infective endocarditis and colon tumor in contrast to *S. bovis* II bacteremia. These results are compatible with studies done by Ruoff and Corredoira (Table 3).[17,22] *S. bovis* II bacteremia from a hepatobiliary source had a higher frequency than *S. bovis* I, but this was not significant. However, chronic hepatitis with liver cirrhoisis and hepatoma rate are higher in Taiwan than in Western countries. Due to the fact that *S. bovis* I bacteremia from a hepatobiliary source in Taiwan has a higher rate than in Western countries, our study shows *S. bovis* II bacteremia from a hepatobiliary source to have a higher frequency than *S. bovis* I, but this is not significant (Table 3).

The striking association between bacteremia caused by *S. bovis* type I and both colonic neoplasia and infective endocarditis, compared with bacteremia caused by type II, suggests the possibility of specific bacterium-host cell interactions involving S. bovis biotype I organisms. Such a specific interaction could involve, for example, selective adherence of the biotype to surface receptors on neoplastic colonic cells or cardiac endothelium. Further studies will be needed to address the possibility of such specific interactions directly.[17]

Besides, Ellmerich et al., suggested an active role of *S. bovis* in the promotion of intestinal carcinogenesis. Adult rats injected with azoxymethane (15 mg/kg body weight) once per week for 2 weeks and subsequently received either injections with *S. bovis* bacteria or wall-extracted antigens twice weekly. They observed progression of preneoplastic lesions through the increased formation of hyperproliferative aberrant colonic crypts, enhanced the expression of proliferation markers and increased production of IL-8 in the colonic mucosa.[23]

However, as Tjalsma et al. showed that *S. bovis* antigen profiles could distinguish 11 out of 12 colon cancer patients from 8 control subjects, whereas antigen profiles derived from the gut bacterium *Escherichia coli* were not diagnostic for colon cancer.[24] Moreover, *S. bovis* antigen profiles were also detected in polyp patients, indicating that infection with this

Table 2. Malignant or premalignant colonic lesions with bacteremia caused by *S. bovis*

	Streptococcus bovis	
Colon tumor	Type I	Type II
Malignancy	3	1
Benign	5	5
No pathological proof	1	1

Table 3. Clinical characteristics of patients infected with *S. bovis* biotypes in comparison with the Kathryn study and the Corredoria study

	Ruoff (1989)				Corredoria (2005)				Our Study			
	Type I (%)	**Type II (%)**	**Total**	***p* value**	**Type I (%)**	**Type II (%)**	**Total**	***p* value**	**Type I (%)**	**Type II (%)**	**Total**	***p* value**
No. of patients	17 (50)	17 (50)	34		42 (68)	20 (32)	62		15 (28.8)	37 (71.2)	52	
Infective Endocarditis	**16 (94)**	**3 (18)**	**19**	**< 0.001**	**31 (74)**	**3 (15)**	**34 (55)**	**0.01**	**8 (53.3)**	**5 (13.5)**	**13 (25.0)**	**0.003**
Colonic Neoplasm	**12 (71)**	**3 (17)**	**15**	**< 0.01**	**24 (57)**	**3 (15)**	**27 (44)**	**0.005**	**9 (60.0)**	**7 (18.9)**	**16 (30.8)**	**0.004**
Hepatobiliary Origin	**0 (0)**	**9 (53)**	**9**	**< 0.001**	**2 (5)**	**10 (50)**	**12 (19)**	**0.0001**	**7 (46.7)**	**22 (59.5)**	**29 (78.4)**	**0.4**

bacterium does occur early during carcinogenesis. Highly accurate tandem mass spectrometry was used to identify one of the diagnostic antigens as a surface-exposed heparin-binding protein, which might be involved in attachment of *S. bovis* to tumor cells. Together, these findings corroborate the hypothesis that colonic lesions provide a specific niche for *S. bovis*, resulting in tumor-associated "silent" infections. These infections, however, only become apparent in colon cancer patients with a compromised immune system (bacteremia) or coincidental cardiac valve lesions (endocarditis).

Conclusion

Therefore, early detection of colon cancer, or identification of individuals at risk, is one of the great challenges in the battle against this disease. Due to *S. bovis* bacteremia is of the high incidence of colonic neoplasia, complete studies (e.g.: cardiac echo, colonoscopy, upper abdominal sonography or abdominal CT scan) should be done as soon as possible, especially biotype I, should indicate colonoscopy.

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原　著

從高雄榮總的經驗談 Streptococcus bovis 引起菌血症在臨床上表現的特色

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目的　大腸癌目前在世界上的發生率以及死亡率一直高居不下，而 *Streptococcus bovis* 引起的菌血症也是大腸腫瘤的危險因子之一，本篇目的是從高雄榮總的經驗談 *Streptococcus bovis* 引起的菌血症在臨床上表現的特色。

方法　本篇將高雄榮總從 2001 年至 2006 年，共 68 位因 *Streptococcus bovis* 引起菌血症的病人，其中 16 位病人並未完成檢查而排除，分析這 52 位病人得到心內膜炎、大腸腫瘤及肝膽源所引起的感染其之間的相關性。統計方法：數值資料用 T 檢定，類別資料用卡方檢定，當 $p < 0.05$ 時才有統計上的顯著差異。

結果　68 位因 *Streptococcus bovis* 引起菌血症的病人中：第一型佔 25 位、第二型佔 43 位；第一型比第二型更容易罹患心內膜炎 (分別是 53.3%、13.5%；$p = 0.003$)；第一型比第二型更容易罹患大腸腫瘤 (分別是 60.0%、18.9%；$p = 0.004$)；第一型比第二型較不容易罹患肝膽源引起的感染 (分別是 46.7%、59.5%；$p = 0.4$)。

結論　因 *Streptococcus bovis* 引起的菌血症是大腸腫瘤的危險因子之一，第一型比第二型更容易罹患大腸腫瘤，因此對這類的病人應儘快完成相關檢查 (如：心臟超音波、大腸鏡檢、上腹部超音波或腹部電腦斷層掃描)。

關鍵詞　Streptococcus bovis、大腸腫瘤、大腸癌。