RESEARCH COMMUNICATION

Prevalence of Colorectal Cancer Associated with *Streptococcus bovis* among Inflammatory Bowel and Chronic Gastrointestinal Tract Disease Patients

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Abstract

Colorectal cancer (CRC) is the second most common cause of cancer mortality among men and women worldwide; the risk of its occurrence has been shown to be increased by chronic bacterial infections. A case control study was therefore carried out at Hospital Universiti Sains Malaysia (HUSM) to determine the incidence of colorectal cancer associated with *S. bovis* infection. A total of 166 stool specimens were collected from diseased patients and healthy individuals and *S. bovis* isolates were identified. Suspected colon tumor and cancer cases were diagnosed and confirmed. It was found that overall prevalence of *S. bovis* was 41 (24.7%) out of 166 cases studied. Some 41(48.6%) of these *S. bovis* isolates was found in patients with colonic polyps, adenocarcinomas, inflammatory bowel disease (IBD) and chronic gastrointestinal tract (GIT). It was also found that colorectal cancer incidence was 24.7%, adenocarinomas accounting for 51% with the highest incidence in the sigmoid part of the colon. Among the IBD and chronic GIT cases, ulcerative colitis featured in the majority of cases (41.4%). In conclusion, there is a high incidence of colorectal cancer associated with *S. bovis*.

Keywords: Colorectal cancer prevalence - *Streptococcus bovis* - inflammatory bowel disease

Introduction

Several species of bacteria have been linked to chronic infections of colon and have been shown to increase the risk of colon cancer by several microorganisms including *Escherichia coli* (Martin et al., 2004) and several Streptococci (Siegert and Overbosch, 1995). *Streptococcus bovis* is a normal inhabitant of the human gastrointestinal tract that might cause bacteremia, endocarditis and urinary infection (Bayliss et al., 1984). It is frequently associated with gastrointestinal lesions, especially carcinoma of the colon (Bayliss et al., 1984; Burns et al., 1985; Gold et al., 2004). Some studies validated earlier findings of association between colon cancer and *S. bovis* (Biarc et al., 2004; Gold et al., 2004). The incidence of *S. bovis* associated colon cancer has been determined as 18% to 62% of patients who presented with a *S. bovis* bacteremia (Zarkin et al., 1990). The first case reported on colonic cancer associated with *S. bovis* in Malaysia was in 2005 (Al-Jashamy et al., 2005). At present study, was undertaken to determine the prevalence of colorectal cancer associated with *S. bovis* among the patients with inflammatory bowel disease (IBD) and chronic gastrointestinal tract diseases (CGIT) and healthy individuals.

Materials and Methods

Case control study was performed on suspected patients who were admitted to GIT clinic unit/Hospital University Science malaysia (HUSM) from March 2007 until April 2008. The total number of stool specimens was 166, which met inclusive certain criteria of IBD, CRC and chronic GIT and exclusive of acute cases. A total of 70 stool specimens were collected from suspected patients that met the diseased criteria; these were considered as patient cases, while 96 healthy individuals were considered as control cases. Many other cases were excluded because they did not meet the study criteria.

All cases were studied and consecutively diagnosed and the data related to the cases was retrieved from the registry of pathology laboratory. The clinical details were obtained from the patients' clinical records at the medical record office of the hospital. All *S. bovis* isolates were identified in the microbiology laboratory department of USM.

All the suspected colon tumor and cancer cases were diagnosed and confirmed in the histopathology department of USM. The specimens were collected from both male and female patients, all of whom were aged 40 years or more.

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Table 1. Distribution of Colorectal Cancer Among the Patients

Lesion Location	Tabular Adenomas	Tubovillous Adenomas	Villous Adenomas	Colonic Adenocarcinomas	Total/ %
Ascending	1	1	1	4	7 (17.0)
Transverse	-	1	-	2	3 (7.3)
Descending	-	1	-	-	1 (2.4)
Sigmoid	4	4	4	12	24 (58.5)
Rectum	1	1	1	3	6 (14.6)
Total	6 (14.0)	8 (17.5)	6 (14.0)	21 (51.0)	41

Table 2. Distribution of Inflammatory Bowel Disease and Chronic Gastrointestinal Tract Disease Among the Patients

Lesion Location	Ulcerative colitis	Crohn's Disease	Chronic GIT	Total/ %
Small intestine	-	3	2	5 (17.24)
Ascending	5	-	-	5 (17.24)
Transverse	2	-	-	2 (6.9)
Descending	2	2	-	4 (13.8)
Sigmoid	3	1	-	4 (13.80)
Rectum	-	-	6	6 (20.7)
Stomach	-	-	3	3 (10.3)
Total	12 (41.4)	6 (20.6)	11 (37.9)	29

Results

The case control study showed that the overall prevalence of *S. bovis* was 41 (24.7%) out of 166. Meanwhile, the number of *S. bovis* isolated from patients was 34 (48.6%) out of 70 cases, 19 (46.3%) had *S. bovis* isolate out of 41 patients who were diagnosed with colonic polyps and adenocarcinomas. Whereas 15 (51.7%) had *S. bovis* strains isolated out of 29 patients who were diagnosed with IBD and chronic GTI. 36 out of 70 stool specimens showed negative isolations of *S. bovis*. Seven (7.3) out of 96 health individuals specimens showed positive culture.

The total number of colorectal cancer cases was 41 (24.7%) out of 166 cases in different locations of the large intestine. Colonic adenocarcinomas formed the majority 21 (51%) of these cases, and the highest incidence 24 (58.5%) was in the sigmoid part of the colon (Table 1). This study shows the incidence of IBD and chronic GIT was 29 (17.5%) out of 166 cases, the incidence of IBD being the highest-18 (62.0%). Ulcerative colitis (UC) formed the majority cases-12 (41.4%) out of IBD cases with the majority of incidence being in the ascending colon (Table 2). There were no significant differences in the incidences between age groups and sex.

Discussion

The results of this study show that the overall prevalence of *S. bovis* associated with IBD, CRC and chronic GIT diseases was 24.7%. Streptococcus bovis was isolated from 46.3% of patients diagnosed with colonic polyps and colonic adenocarcinomas, and 51.7% of patients diagnosed with IBD and chronic GTI. The result also shows that 7.3% of fecal specimens in health cases were positive of *S. bovis* isolations. This result was consistent with previous work by Alazmi et al., (2006) who reported that *S. bovis* was isolated in 5-16% of fecal specimens in normal adults. In the early study, *S. bovis* caused about 24% of all streptococcal infection of endocarditis. There are some reports confirming the presence of *S. bovis* bacteraemia and endcarditis with various forms of gastrointestinal diseases, such as inflammatory bowel diseases (IBD) and colonic cancer (Teitelbaum and Triantafyllopoulou, 2006; Andrea et al., 2008). As early as 1951, McCoy and Mason (1951) suggested a relationship between colonic carcinoma and the presence of infectious endocarditis due to *S. bovis*.

Our results interestingly show that the incidence of colorectal cancer was 24.7%. Also colonic adenocarinomas was the majority (51%) among CRC cases; and the common site for the occurrence of carcinoma (58.5%) was in the sigmoid. This result disagrees with MGIR (2009) that showed the common sites for the occurrence of carcinoma to be the rectum 45.56 %, recto-sigmoid 18.53 % and sigmoid colon 13.13%. The results of our study show the incidence of IBD and chronic GIT to be 17.5% with UC (41.4%) forming the majority of cases among IBD. The main incidence was in the ascending colon. Colorectal cancer is characterized by uncontrolled growth of neoplastic cells developing in the lower segment of the digestive tract, with the potential to invade and spread to other sites. CRC is the highest second carcinoma incidence among females after breast cancer and the third highest in incidence among males, after prostate cancer and lung cancer (Hermann et al., 2010). Colorectal cancer is the third commonest cause of cancer deaths in Malaysia. Data from the Ministry of Health of Malaysia confirms an increase in CRC admission rates from 8.1% in 1987 to 11.9% in 1995, 13.2% (NCR, 2006). Recently, 56.37% carcinomas of colon were detected (MGIR, 2009). The results of this study show that the incidence of CRC was 24.7%. This low rate of incidence is not consistent with MGIR (2009). This could be due to the low number of cases studied and that this study was carried out in one hospital.

Genetics, experimental and epidemiological data suggested that the CRC develop from the complex interactions between inherited susceptibility and environmental factors. The current hypothesis is that adenomatous polyps and some pathogenic bacteria are the precursors of the vast majority of colorectal

cancers (Mager, 2006; Yang and Pei, 2006). Sigmoid adenocarcinomas develop in patients' sufferings from endocarditis due to organisms identified as *S. bovis*. Importantly, many reports have suggested a potential relationship between increased fecal carrier levels of *S. bovis* and human gastrointestinal disease, IBD and primarily colonic cancer evidence suggesting a trend for the highest fecal carriage rate of *S. bovis* in adult patients with IBD (Teitelbaum and Triantafyllopoulou, 2006; Yang and Pei, 2006).

An association between *S. bovis* and CRC neoplasia has been recognized since the first reports of *S. bovis* endocarditis related to CRC in 1974. Bacteria have been linked to cancer by two mechanisms: chronic inflammation and production of carcinogenic metabolites by intestinal microflora. These have been reported to have an action on the carcinogenesis of colon cancer (Schlegel et al., 2003; Gold et al., 2004; Tafe and Ruoff, 2007).

The reason for this association has not been elucidated. One theory is that colonic neoplasia specifically allows for the overgrowth or translocation of *S. bovis* and that *S. bovis* is in fact causative of neoplasia itself (Yang and Pei, 2006; Tafe and Ruoff, 2007). Some authors thought that alteration in local conditions and disruptions of capillary channels at the site of neoplasm allow *S. bovis* to proliferate and gain entry into the blood stream. Local actions of cytokines or chemical mediators able to promote vasodilatation and the enhancement of capillary permeability may support bacterial adherence to various cells. It has also been speculated that *S. bovis* produce a carcinogen that induces intestinal cancer (Ellmerich et al., 2000; Tafe and Ruoff, 2007).

As mentioned earlier, there is a correlation between the incidence of *S. bovis* and colon cancer. *S. bovis* is occasionally present as human colonic flora, and it has been reported that fecal carriage of the bacteria is increased among colon cancer patients. Various studies have shown that 25% to 80% of patients with *S. bovis* also had colorectal adenomatous polyps, aberrant crypt foci and extracolonic malignancy (Gold et al., 2004).

In view of the potential involvement of *S. bovis* in intestinal carcinogenesis, experimental study has been carried out to determine the effects of *S. bovis* on preneoplastic histopathological changes in the intestinal tract of rats treated with the carcinogen in azoxymethane (AOM). From the study, it has been found that changes in mucosal polyamines and the expression of proliferating cell nuclear antigen (PCNA), might indicate a hyperproliferative state in the colonic mucosa in laboratory animals that interfere with AOM and *S. bovis* (Ellmerich et al., 2000; Al-Jashamy et al., 2009).

The bacterial association was also significant. For example, convincing evidence has linked Helicobacter pylori with both gastric cancer and mucosa-associated lymphoid tissue lymphoma. However, other species associated with cancer include *S. bovis* (colon cancer), Salmonella typi (gallbladder cancer), and Chlamydia pneumoniea (lung cancer). Important mechanisms by which bacterial agents may induce carcinogenesis were chronic infection, immune evasion and immune suppression (Mager, 2006). It has been demonstrated that

S. bovis or its wall extracted antigens (WEA) were able to promote carcinogenesis in rats (Gold et al., 2004). In conclusion; while the incidence of CRC is increasing in our local setting, there is a high incidence of colorectal cancer associated with *S. bovis*.

Acknowledgments

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