

RESEARCH ARTICLE

Schistosomiasis Combined with Colorectal Carcinoma Diagnosed Based on Endoscopic Findings and Clinicopathological Characteristics: A Report on 32 Cases

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Abstract

Aims and Background: To improve understanding of the relationship between schistosome-related enteropathy and colorectal carcinoma with particular focus on endoscopic findings and clinicopathological characteristics of colonic schistosomiasis. **Materials and Methods:** All cases of intestinal schistosomiasis diagnosed at West China Hospital, Chengdu, China, between October 2006 and October 2012 were included in this study. A total of 179 cases of colonic schistosomiasis diagnosed through colonoscopy and pathological examinations were collected for analysis and the demographics, symptoms, endoscopic findings and clinicopathological characteristics were retrospectively evaluated. **Results:** Of the 179 colonic schistosomiasis patients, 32 combined with colorectal cancer (CRC) were found, between the ages of 44 and 85 years (24 males, 75%). These 32 lesions were classified as 12 endophytic/ulcerative (37.5%), 10 exophytic/fungating (31.2%), 4 annular (12.5%), 3 giant polypus (9.4%), and 3 IIc (superficial depressed type) (9.4%). The segments of rectum and sigmoid colon were involved in 19 patients (59.4%) and 6 patients (18.8%), respectively. The histopathologic types were classified as follows: 30 well-differentiated adenocarcinomas, one mucinous adenocarcinoma and one poorly differentiated adenocarcinoma. The pathological findings suggest colorectal malignancy with deposited schistosome ova. **Conclusions:** Chronic schistosomal infestation has a probable etiological role in promoting genesis of colorectal neoplasms.

Keywords: Colonoscopy - pathological examination - colorectal carcinoma - schistosomiasis

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Introduction

Cancer is a major public health problem and the leading cause of death worldwide. Colorectal cancer is the second most commonly diagnosed cancer in females and the third in males, with over 1.2 million newly diagnosed cases and 608,700 deaths estimated to have occurred in 2008. Studies have shown that modifiable risk factors associated with colorectal cancer include: smoking, physical inactivity, obesity, red and processed meat consumption and excessive alcohol consumption (Jemal et al., 2011). And the estimated total of infection-attributed malignancies accounts for over 15% of malignancies worldwide. Recent advances in the fields of epidemiology, molecular biology and infectious diseases have led to significant revelations in clarifying the role of infective agents in colorectal carcinogenesis (Khurana et al., 2005).

Schistosomiasis ranks second only to malaria among the parasitic diseases in the world. The three main disease-causing species infecting humans are *S. haematobium*, *S. mansoni* and *S. japonicum*. The highest incidence

rates are found in economically developing countries in Africa, the Arabian peninsula, South America and Asia. It is estimated that 779 million people were at risk of schistosomiasis and 207 million people were infected in 2003 worldwide (Engels et al., 2002). Schistosomiasis japonica is a zoonotic disease endemic in China. Approximately 65 million individuals in China are at risk of infection and 325,824 cases were diagnosed as schistosomiasis in 2010 (Lei et al., 2011). Haematobium infection has been considered as a definitive cause of urinary bladder cancer with an associated 5-fold risk. Clinical and epidemiological studies in China and Japan support a probable role of *S. mansoni* infection as one of the risk factors in hepatocellular carcinoma (HCC) formation (Palumbo et al., 2007). However, the evidence supporting the role of *S. japonicum* in colorectal carcinogenesis is limited. In this study, research was conducted retrospectively based on endoscopic findings and clinicopathological characteristics in order to identify that schistosomiasis is a probable risk factor associated with the development of colorectal cancer.

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Materials and Methods

Patient Selection

In this study, retrospective analysis was conducted in 179 cases in patients (age 17 to 87 years old; 60.3% men; mean age, 60.1 years) diagnosed with intestinal schistosomiasis based on colonoscopy and pathology at West China Hospital between October 2006 and October 2012. All cases were initially diagnosed as schistosomal infection. Altered bowel habits, rectal bleeding, obstruction, abdominal pain and diarrhea were the main indications for colonoscopy.

Colonoscopy and Pathological Examination

Colonoscopies, after bowel preparation with Sodium Phosphates Oral Solutions, were performed by experienced colonoscopists using endoscopy equipment (Olympus CF260). Unless the patient refused sedation or a contraindication existed, sedation was usually induced with Sufentanil, propofol and midazolam. If lesions were detected, biopsies were obtained and fixed in 10% buffered formalin, embedded in paraffin and stained with hematoxylin and eosin. All procedures were performed without serious complications. The slides were interpreted by expert gastrointestinal pathologists under a light microscope (Olympus, Tokyo, Japan). The initial macroscopic diagnosis was made by the colonoscopists according to World Health Organization (WHO) classifications (Stanley et al., 2000) and Japanese Group Classification (JGC) (Japanese Society for Cancer of the Colon and Rectum, 2009) and the final diagnosis was confirmed histopathologically.

Data Collection and Ethics

The patients' age, sex, endoscopy findings and clinicopathological characteristics were evaluated retrospectively. Signed informed consent was obtained from all participating patients. The study protocol was approved by the ethics committee of the West China Hospital, Sichuan University.

Results

Clinical and Endoscopic Features

All data was derived from 179 patients. The characteristics of the study population are as shown in Table 1 and Table 2. The caecal intubation rate was 81.0% (145/179 patients) in this series. The most common endoscopic findings were lesions comprising mainly polyps in 56 patients (31.3%), acute colitis in 37 patients (20.7%), chronic colitis in 14 patients (7.8%), exophytic/fungating in 21 patients (11.7%), endophytic/ulcerative in 30 patients (16.8%), annular in 4 patients (2.2%) and ulceration in 17 patients (9.5%). Acute colitis was characterized by edematous or friable mucosa and erosions, visible submucosal blood vessels, scattered petechial hemorrhage and mucosa with ulcerations. Confused vascular net, pale intestinal mucosa with elevated or flat yellow nodules, even enteric cavity stricture could be observed in chronic colitis patients by colonoscopy. Three IIc (superficial depressed type) patients

Table 1. Endoscopic Findings of the 179 Schistosomiasis Patients

Types of endoscopic findings	Subjects (%)	Subjects with cancer (%)
Polyps	56 (31.3)	3 (9.4)
Acute colitis	37 (20.7)	—
Chronic colitis	14 (7.8)	3 (9.4)
Exophytic/Fungating	21 (11.7)	10 (31.2)
Endophytic/Ulcerative	30 (16.8)	12 (37.5)
Annular	4 (2.2)	4 (12.5)
Ulceration	17 (9.5)	—
Total	179 (100.0)	32 (100.0)

Table 2. Characteristics of the Study Population

Variable	No. of patients (%)	
	Subjects without cancer (n = 147)	Subjects with cancer (n = 32)
Sex		
Male	84 (57.1)	24 (75.0)
Female	63 (42.9)	8 (25.0)
Age		
Mean age (y)	58.1	64.9
17-40 y	21 (14.3)	—
41-60 y	66 (44.9)	12 (37.5)
61-87 y	60 (40.8)	20 (62.5)
Main indication of colonoscopy		
Abdominal pain	126 (85.7)	4 (12.5)
Changes in bowel habits	99 (67.3)	15 (46.8)
Diarrhea	26 (17.7)	3 (9.4)
Obstruction	32 (21.8)	9 (28.1)
Rectal Bleeding	25 (17.0)	14 (43.8)
Location of affected colon		
Cecum	1 (0.7)	1 (3.1)
Ascending colon	9 (6.1)	3 (9.4)
Transverse colon	5 (3.4)	2 (6.2)
Descending colon	3 (2.0)	1 (3.1)
Sigmoid colon	37 (25.2)	6 (18.8)
Rectum	81 (55.1)	19 (59.4)
Multiple locations	11 (7.5)	—
Pathological findings		
Inflammatory lesions	103 (70.1)	—
Colorectal carcinoma	—	32 (100)
Inflammatory polyps	7 (4.8)	—
Hyperplastic polyps	8 (5.4)	—
Tubular-villous adenoma	8 (5.4)	—
Villous adenoma	6 (4.1)	—
Tubular adenoma	7 (4.8)	—
Indefinite neoplastic lesion	8 (5.4)	—

were misdiagnosed as chronic colitis based on endoscopic findings.

The ages of the 179 patients were divided into three age groups: 17–40 years old, 41–60 years old and 61–87 years old. Intestinal schistosomiasis and colonic schistosomiasis prevalence combined with CRC has been reported to vary with age and sex as this report shows a male and older age groups (>40 years) are predominant. Lesion locations were classified into 7 groups: cecum, ascending colon, and transverse colon (including the splenic flexure), descending colon, sigmoid colon, and rectum, multiple locations. The most commonly affected locations with CRC were the rectum (19, 59.4%) and sigmoid colon (6, 18.8%) as shown in Table 2.

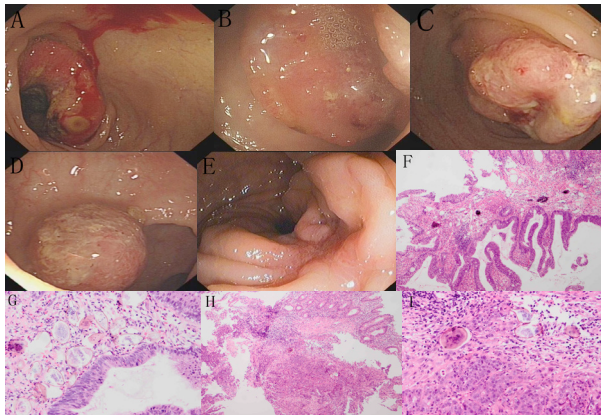


Figure 1. Figure 1 Endoscopic Findings and Pathology of Schistosomal Colonic Disease with Neoplastic Change. Photos A, B, C, D, and E show different morphologic characteristics of schistosomiasis combined with CRC: A: endophytic/ulcerative; B, C, and D: exophytic/fungating; E: Annular; F: Adenocarcinoma with deposited schistosomal ova (original magnification $\times 100$); G: Adenocarcinoma with deposited schistosomal ova (original magnification $\times 100$) at a different magnification (magnification $\times 400$ is shown in photo F); H: Villous adenoma accompanying high-grade intraepithelial neoplasias with schistosomal ova deposited in rectum (original magnification $\times 100$); I: Villous adenoma accompanying high-grade intraepithelial neoplasias with schistosomal ova deposited in rectum, at a different magnification (magnification $\times 400$)

Pathology Characteristics

Of the 179 colonic schistosomiasis patients, 32 cases (17.9%) (male = 24, 75%) age 44–85 years old were diagnosed as CRC. The pathological findings suggested colorectal malignancy with *S. japonicum* ova deposited in lamina propria. The histopathologic types of the 32 subjects were classified as follows: 30 (93.8%) well-differentiated adenocarcinomas, one (3.1%) mucinous adenocarcinoma, one (3.1%) poorly differentiated adenocarcinomas. The histopathologic types of the remaining 147 patients were classified as: 103 mucosal inflammatory lesions, seven inflammatory polyps, eight hyperplastic polyps, eight tubular-villous adenoma, six villous adenoma, and seven tubular adenoma (Table 2), eight indefinite neoplastic lesion. Of the 147 patients, two were diagnosed as canalicular adenoma with low-grade intraepithelial neoplasias; three canalicular adenoma with high-grade intraepithelial neoplasias; six tubular-villous adenoma with high-grade intraepithelial neoplasias, two villous adenoma with low-grade intraepithelial neoplasias, one tubular adenoma with low-grade intraepithelial neoplasias.

Discussion

It has been identified that multiple pathways are related to the evolvement of colorectal cancer (Jass, 2007). A few studies have shown that infectious origin is one of the possible factors involved (Khurana et al., 2005). Carcinogenesis associated with helminth infections such as schistosomiasis is a complex process, which may involve several different mechanisms, but chronic inflammation appears to play a central role (Vennervald and Polman, 2009). Schistosomiasis typically occurs

after the penetration of schistosome cercariae through the skin and the migration of the larvae within the body and oviposition. Chronic inflammation can generate nitrogen species and free radicals, which can damage and oxidize DNA and lead to genetic instabilities and chronic inflammatory lesions in chronic intestinal schistosomiasis may evolve into ova polyps, proliferative polyps, atypical epithelial hyperplasia and finally into neoplastic transformation (Vennervald and Polman, 2009; Zhang et al., 2012). There is limited evidence suggesting that *S. japonicum* is possibly carcinogenic to humans and leads to colorectal cancer. The relationship between schistosomiasis and CRC is also controversial. The results of the present study confirm that the history of schistosomiasis proves to be a possible risk factor for the development of colorectal neoplasias. One hundred and seventy-nine patients with colonic schistosomiasis participated in the present study, 32 cases (17.9%) were accompanied by colorectal cancer.

It has been previously reported that males proved to be an independent risk factor for the development of colorectal neoplasias (Regula et al., 2006). Additionally, men are more prone to schistosomal infection through contact with cercariae-infested waters during agricultural activities (Salim et al., 2010). In this study, schistosomiasis combined with CRC was more common in males than in females (M:F ratio, 3:1), which was in keeping with previous observations reported in studies performed elsewhere (Madbouly et al., 2007). Since Praziquantel has become the first choice of drug treatment, great advances have been made in the control of the disease through population-based chemotherapy (Gryseels et al., 2006). In support of this view, data from this study shows that schistosomiasis combined with or without CRC tends to occur mainly in patients who were older than 40 years. It has been reported that schistosomal colorectal cancer was notably shown to occur in younger age groups with a maximum age incidence of 6 to 16 years earlier than ordinary colorectal cancer (Salim et al., 2010). The mean age of schistosomiasis combined with CRC in this study is 64.9 years old. *Schistosoma* ova are mainly parasitized in the inferior mesenteric and portal vein when one is infected with *Schistosoma*. Most lesions occur due to deposition of *Schistosoma* ova and are situated mainly in the sigmoid colon and rectum (Cao et al., 2010). In this study, one (3.1%) case of schistosomiasis combined with colorectal carcinoma was located in the cecum, three (9.4%) in the ascending colon, two (6.2%) in the transverse colon, one (3.1%) in the descending colon, six (18.8%) in the sigmoid colon, 19 (59.4%) in the rectum, which parallels with the locations of intestinal schistosomiasis (Table 1).

The gross morphologic characteristics of schistosomiasis combined with CRC have not been systematically described during routine colonoscopy. Compared with the criteria outlined by WHO classifications (Stanley et al., 2000) and the Japanese Society for Cancer of the Colon and Rectum (Japanese Society for Cancer of the Colon and Rectum, 2009), our findings in individuals diagnosed as schistosomiasis combined with CRC were mainly 12 as endophytic/ulcerative (37.5%), 10 as exophytic/fungating (31.2%), 4 as annular

(12.5%), 3 as giant polypus (9.4%), 3 as IIC (superficial depressed type) (9.4%). The endoscopic findings of schistosomiasis combined with CRC was nonspecific. In this study, adenocarcinoma was the most frequent with well-differentiated differentiated tumors accounting for more than 93% of cases. Other histopathological tumors were one mucinous adenocarcinoma, one poorly differentiated adenocarcinomas, and 14 cases (7.8%) had complications of neoplastic change and precancerous lesion. Nevertheless, this finding is in disagreement with Madbouly who reported that mucinous histology is the main histopathological pattern of schistosomiasis combined with CRC (Madbouly et al., 2007). The association between *S japonicum* and ring cell carcinoma of the rectum, as well as rectal carcinoid tumour has also been proposed, although the reports in the literature are limited to case reports (Zanger et al., 2010; Canepa et al., 2012). And since rectal bleeding is one of the symptoms of colorectal neoplasia. Changes in bowel habits and rectal bleeding may be attributed to hemorrhages, ulcerations and enteric cavity strictures, etc. Therefore, it is recommended that the patients with symptoms such as rectal bleeding, change of bowel habits and anemia should undergo colonoscopies early.

In conclusion, a history of colonic schistosomiasis is a probable independent risk factor for the development of colorectal neoplasias and large prospective studies are warranted to verify this finding. Assuring the periodical administration of anthelmintics is essential in order to promote the control of schistosomiasis in endemic countries. Although the enzyme-linked immuno-sorbent assay (ELISA) technique has proven to be a rapid, sensitive and specific method for screening of *Schistosoma japonicum* infection (Deng et al., 2013), colonoscopies are still the gold-standard screening tool for those at high risk for CRC and colonoscopic removal of adenomatous polyps prevents death from colorectal cancer (Zauber et al., 2012). Endoscopic biopsies may be falsely negative, it is recommended from this study that individuals with a history of colonic schistosomiasis should undergo colonoscopy and pathological examinations regularly if necessary medical infrastructures are available.

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