

Retrospective Study

Comparison of non-schistosomal rectosigmoid cancer and schistosomal rectosigmoid cancer

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Abstract

AIM: To compare the clinicopathological features of patients with non-schistosomal rectosigmoid cancer and schistosomal rectosigmoid cancer.

METHODS: All the patients with rectosigmoid carcinoma who underwent laparoscopic radical surgical resection in the Shanghai Minimally Invasive Surgical Center at Ruijin Hospital affiliated to Shanghai Jiao-Tong University between October 2009 and October 2013 were included in this study. Twenty-six cases of colonic schistosomiasis diagnosed through colonoscopy and pathological examinations were collected. Symptoms, endoscopic findings and clinicopathological characteristics were evaluated retrospectively.

RESULTS: There were no significant differences between patients with and without schistosomiasis in gender, age, CEA, CA19-9, preoperative biopsy findings or postoperative pathology. Patients with rectosigmoid schistosomiasis had a significantly higher CA-125 level and a larger proportion of these patients were at an early tumor stage ($P = 0.003$). Various morphological characteristics of schistosomiasis combined with rectosigmoid cancer could be found by colonoscopic examination: 46% were fungating mass polyps, 23% were congestive and ulcerative polyps, 23% were cauliflower-like masses, 8% were annular masses. Only 27% of the patients were diagnosed with rectal carcinoma preoperatively after the biopsy. Computed tomography (CT) scans showed thickened intestinal walls combined with linear and tram-track calcifications in 26 patients.

CONCLUSION: Rectosigmoid carcinoma combined with schistosomiasis is associated with higher CA-125 values and early tumor stages. CA-125 and CT scans have a reasonable sensitivity for the accurate diagnosis.

Key words: Schistosomiasis; Rectosigmoid cancer; Colonoscopy; Biomarker; Diagnosis

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Core tip: The association between schistosomiasis and colorectal malignancy has long been suggested in the literature. This study aimed to improve our understanding of the relationship between *Schistosoma japonicum*-related enteropathy and rectosigmoid carcinoma, with a particular focus on laboratory examination, endoscopic findings and clinicopathological characteristics of rectosigmoid schistosomiasis.

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INTRODUCTION

Human schistosomiasis is a prevalent parasitic disease caused by trematode flukes of the genus *Schistosoma*, of which *Schistosoma mansoni*, *Schistosoma japonicum* (*S. japonicum*) and *Schistosoma haematobium* are the three major species. By conservative estimates, at least 230 million people worldwide are infected with *Schistosoma* spp, and it is important to acknowledge that schistosomiasis is now becoming a cause for concern in Europe, especially in southern Europe, because of

climate change as well as infected travelers who return from endemic areas^[1]. A number of epidemiological data has suggested a close etiological relationship between colorectal cancer and schistosomiasis, especially *S. japonica*^[2,3]. The microenvironmental changes and inflammation may form a causal link between schistosome chronic infection and colorectal carcinogenesis^[4,5]. However, as the symptoms of colonic schistosomiasis are nonspecific and may mimic other gastrointestinal problems, this condition could be under diagnosed^[6], and there is little relevant clinical data in the medical literature, mostly limited to case reports^[7-9]. On the other hand, in some schistosome-endemic areas, colonic schistosomiasis can be correctly diagnosed while colorectal cancer may be missed, especially when CEA or CA19-9 levels are within the normal range.

Detailed knowledge about schistosomiasis is necessary to improve the accuracy of clinical diagnosis. At present, colorectal neoplasia associated with schistosoma has only been reported on few occasions.

This research was conducted retrospectively, based on the recent data of schistosomal rectosigmoid cancer, including surgical findings and clinicopathological characteristics, to find a sensitive biomarker that might improve the accuracy of clinical diagnosis, and discuss the probable etiological role of chronic schistosomal infestation in rectosigmoid cancer.

MATERIALS AND METHODS

Patient selection and diagnoses

In this study, retrospective analysis was conducted for 26 consecutive cases in patients diagnosed with rectosigmoid carcinoma combined with colonic schistosomiasis between 01-10-2009 and 01-11-2013, who underwent surgical resection at the Shanghai Minimally Invasive Surgical Center of Ruijin Hospital, which is affiliated to Shanghai Jiao-Tong University. Those patients were admitted to hospital because of liquid or pasty diarrhea, abdominal pain, pain on colon palpation or hematochezia. Colonoscopies were performed in the outpatient service of our department 1-14 d before hospitalization. Two to three biopsies were obtained and sent to the department of pathology. CT scans, magnetic resonance imaging and laboratory examinations were performed in the outpatient service or on the first day of hospitalization. Patients who were diagnosed with rectosigmoid carcinoma in the same time period without schistosomiasis were selected as a control group. After surgical resection, all specimens were reviewed histopathologically, and the pathological TNM stages were determined according to the classification established by the American Joint Committee on Cancer (AJCC, 7th edition). The gold standard for diagnosis of schistosomiasis depends on finding ova by microscopy in the colon, rectum or stool.

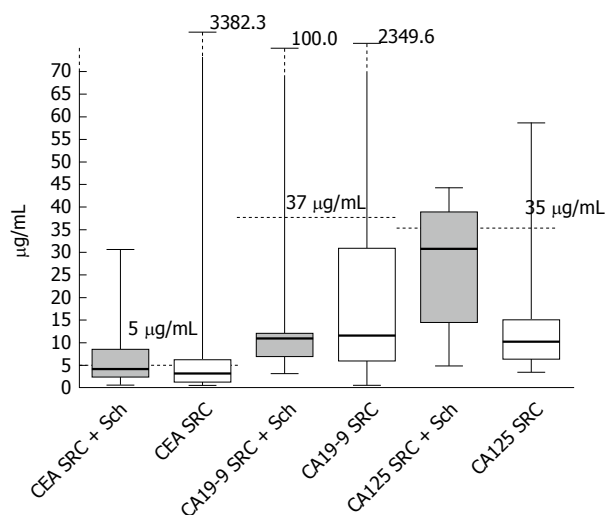


Figure 1 Quantities of CEA, CA19-9 and CA125 in the peripheral blood of patients who had rectosigmoid carcinoma with or without schistosomiasis. Dotted lines define the normal values. SRC: Rectosigmoid carcinoma; Sch: Schistosomiasis.

Examination and data collection

Abdominal ultrasonography, laboratory profiles, urine and stool tests were acquired after being admitted to hospital. Data on clinicopathological characteristics and treatments were collected routinely from the hospital records by trained registrars.

Statistical analysis

Analyses were performed using Stat View 5.0 for Windows (SAS Institute Inc., Cary, NC, United States). The χ^2 test or Fisher's exact test were applied to analyze the categorical variables. The results were subjected to a nonparametric Mann-Whitney *U* test. A Student's *t*-test was also used to analyze the intragroup differences. $P < 0.05$ was regarded as statistically significant. The statistical methods of this study were reviewed by Yi-Fei Zhang from the Institute for Stroke and Dementia Research Hospital of the University of Munich.

RESULTS

Clinical characteristics

In this study, 26 patients were diagnosed with sigmoid or rectal carcinoma combined with rectosigmoid schistosomiasis. Of these patients, 69.2% were male, while 31% out of the patients were female. 12 patients (46%) had elevated CEA values ($> 5 \mu\text{g/mL}$) and 47% patients (7/15) had abnormal CA-125 values ($> 35 \text{ U/mL}$). The distribution of these biomarkers is shown in Figure 1. It worth noting that only 1 patient (9%, 1/11) in this series had an abnormal CA19-9 value ($> 37.0 \text{ U/mL}$). In addition, there were no significant differences in gender, age, CEA value, CA19-9 value or findings from preoperative biopsy when these two groups were compared, based on characteristics and colonoscopic findings. Instead, patients with rectosigmoid schistosomiasis had significantly higher

Table 1 Patient characteristics and colonoscopic findings *n* (%) or mean \pm SD

	With schistosomiasis (<i>n</i> = 26)	Without schistosomiasis (<i>n</i> = 34)	<i>P</i> value
Gender male/female	18/8	22/12	
Age (yr)	60.7 \pm 10.6	63 \pm 8.7	0.6100
CEA	4.2 \pm 8.8	82.9 \pm 428.1	0.3800
CA19-9	10.9 \pm 306.5	35.1 \pm 65.1	0.1300
CA-125	27.4 \pm 3.3	12.7 \pm 10.0	0.0001
Preoperative biopsy			
Carcinoma	7 (26.9)	16 (47.1)	
Hyperplastic polyps	5 (19.2)	8 (23.5)	
Villous adenoma	3 (11.5)	1 (2.9)	
Tubular adenoma	3 (11.5)	1 (2.9)	0.3400
Others	8 (30.7)	8 (23.5)	
Morphology			
Congestive, Ulcerative	6 (23.1)	13 (38.2)	
Fungating mass	12 (46.2)	8 (23.5)	0.1600
Cauliflower-like mass	6 (23.1)	6 (17.6)	
Annular	2 (7.6)	7 (20.6)	
Tumor stage			
I	16 (61.5)	6 (17.6)	
II	6 (23.1)	10 (29.4)	0.0030
III	4 (15.4)	17 (50)	
IV	0	1 (2.9)	
Differentiation			
Well	16 (61.5)	15 (44.1)	
Moderate	7 (26.9)	16 (47.1)	0.4000
Poor	3 (11.5)	3 (8.8)	
Postoperative pathology			
Adenocarcinoma	16 (61.5)	30 (88.2)	
Signet-ring cell carcinoma	7 (7.7)	0	0.1300
Mucinous adenocarcinoma	3 (30.8)	4 (11.8)	

CA-125 values than those without ($P = 0.0001$) (Table 1). 85% of the patients who were diagnosed with sigmoid or rectal carcinoma combined with rectosigmoid schistosomiasis were at early tumor stages (stage I or stage II), compared to 47% of patients without schistosomiasis ($P = 0.003$).

Endoscopic examination

Various morphological characteristics of schistosomiasis combined with rectosigmoid cancer were found in colonoscopic examinations (Figure 2). The fungating mass polyp was the major morphological type, being present in around 46% of all 26 patients. For the remaining patients, six (23%) had congestive and ulcerative polyps, six (23%) had cauliflower-like masses and two (8%) were annular type. Preoperative rectosigmoid biopsy provides an efficient but insensitive way of visualizing eggs, especially for those with low worm burdens. In this study, only seven patients (27%) were diagnosed with rectosigmoid carcinoma preoperatively; 19% of the biopsies showed hyperplastic polyps, and 8% and 23% revealed intraepithelial neoplastic changes (Table 1).

CT presentation

Abdominal CT enhanced dynamic scans (CTA) demon-

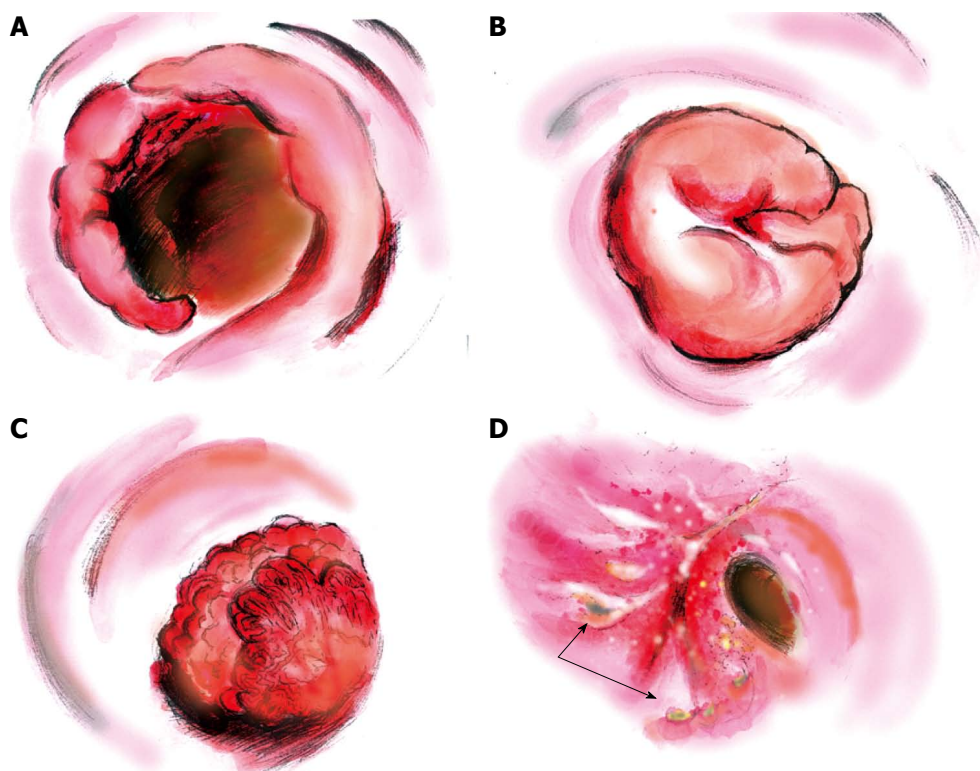


Figure 2 Endoscopic findings showing different morphological characteristics of schistosomiasis combined with rectal cancer. A: Annular; B: Fungating mass; C: Cauliflower-like mass; D: Congestive, ulcerative (black arrow).

strated evenly thickened intestinal walls combined with linear and tram-track calcifications in 26 patients, with (8%) or without (92%) perirectal fatty infiltration, the rectal lumen were locally narrowed in the primary lesions. Calcified ova could be found in 22 patients (85%). No significant lymphadenopathy was demonstrated. For those who had intestinal stenosis and for whom colonoscopic examinations were not recommended, virtual colonoscopy and virtual dissection were used to assess the condition and situation (Figure 3B-D).

Laparoscopic surgical finding and pathology characters

Irregular thickening of the intestinal wall was found in 25 patients (96%) during operations or postoperative sample assessments. Most of the patients were at Stage I (62%), and 23% and 15% were at Stage II and Stage III, respectively. In 18 patients (69%), schistosomal ova were only found in the submucosal layer; in 19% the ova had infiltrated muscularis propria, and serosal infiltrations were found in 12% of the patients. In 8% of the patients, schistosomal ova could be found infiltrating into the surrounding lymph nodes postoperatively. In 21 patients (81%), schistosomal ova could be found inside the tumor, while ova from the remaining 19% of patients were found in the adjacent tissues (Figure 4). Considering the pathological profiles, the largest percentage had well differentiated tumors and adenocarcinoma observed in postoperative pathological examination.

The information on signet-ring cell carcinomas (8%) and mucinous adenocarcinomas (31%) were also included in the present study (Table 2).

DISCUSSION

Schistosomal rectal cancer: better or worse prognosis?

Although schistosomiasis has been controlled in endemic regions^[10] in the tropics and subtropics, previous *S. japonicum* infection might lead to complications, such as chronic intestinal schistosomiasis and hepatosplenic schistosomiasis, and this condition is significantly associated with both liver cancer and colorectal cancer^[11]. Schistosome infection may have a negative effect on the prognosis of colorectal cancer^[12]; it has been reported that the five-year survival rate was 45.6% out of 430 cases complicated with schistosomiasis, which was significantly lower than in those without schistosomiasis (50.9% out of 2717)^[13]. In the present study, schistosomal rectosigmoid cancer seemed to be related to early tumor stage, possibly because schistosomiasis-related intestinal damages are mainly granuloma and fibrosis resulting from schistosomal ova deposition, especially in the large intestine^[14-16]. Continuous epithelial proliferation adjacent to a chronic schistosomal ulcer and polyp formation, which lead to more obvious symptoms, might encourage the patients to seek a medical examination earlier. Wang *et al*^[17] analyzed 30 patients with schistosomal rectal cancer and showed that schistosomiasis ($P = 0.026$)

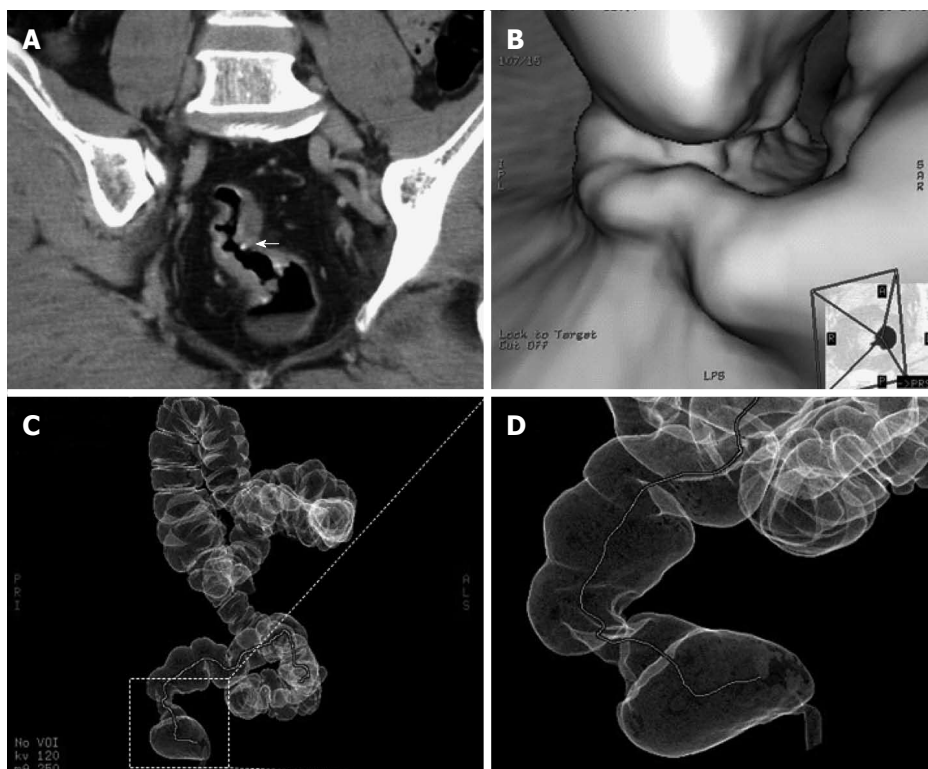


Figure 3 Computed tomography presentation. A: Computed tomography (CT) scan showing curvilinear calcification in the rectosigmoid colon and calcified, conglomerate nodules (arrow) protruding from the wall of the rectosigmoid colon; B: Lobulated polypus in the rectum; C, D: CTVC enables three-dimensional view of walls of the colon as a result of reconstruction of multislice CT images. The colorectal stenosis is showed in the area surrounding by dotted lines. CTVC: CT virtual colonoscopy.

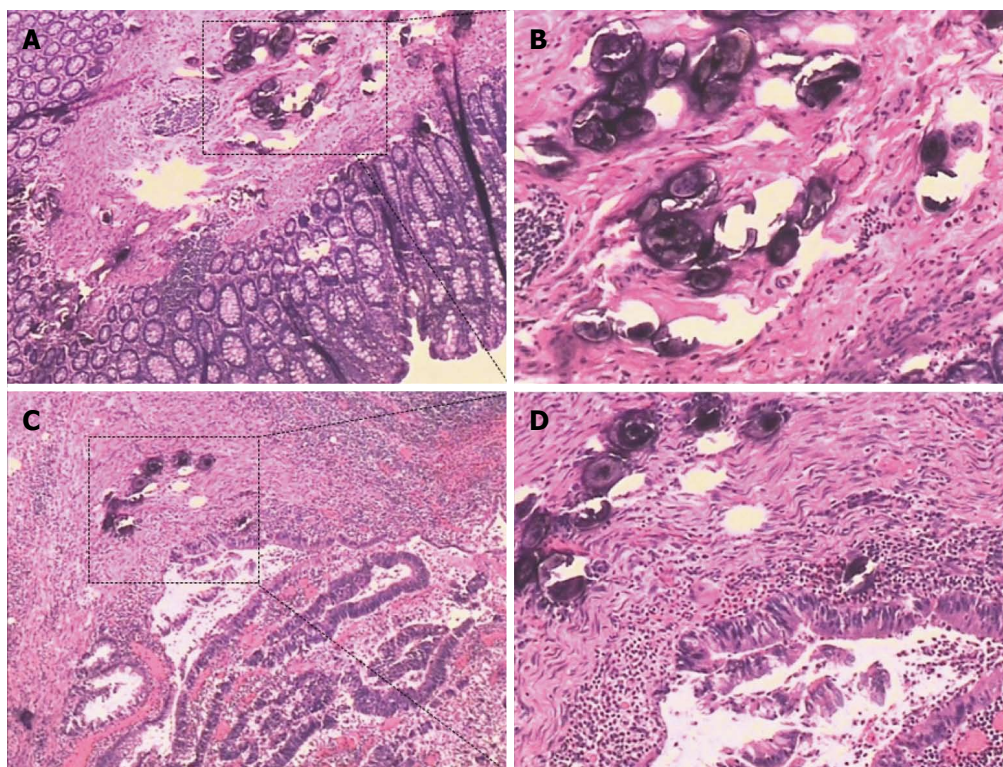


Figure 4 Pathological features of schistosomiasis-associated rectal adenocarcinoma. A, B: Schistosomiasis ova in tumor adjacent tissues. C, D: Schistosomiasis ova in tumor tissues.

Table 2 Laparoscopic surgery findings and pathological characteristics *n* (%)

	Male, <i>n</i>	Female, <i>n</i>	Total
Schistosomal ova position			
Submucosa infiltration	12	6	18 (69.2)
Muscularis propria	4	1	5 (19.2)
Serosal infiltration	2	1	3 (11.5)
Infiltration in the sLNs	1	1	2
Intra-tumor tissue	14	7	21 (80.8)
Para-tumor tissue	4	1	5 (19.2)
Calcification ova (CT)	15	7	22 (84.6)
Irregular thickening of the intestinal wall	17	8	25 (96.2)
Rough serosal surface	2	1	3 (11.5)

CT: Computed tomography; sLNs: Surrounding lymph nodes.

was statistically significantly correlated with overall survival (OS). Schistosomiasis was an independent prognostic factor for worse DFS and OS in multivariate analysis^[17].

Sensitivity of biomarker examinations

In cases of intestinal cancer associated with schistosomiasis, the location of the cancer was predominately the rectum^[18], followed by the sigmoid colon, and then the other parts of the colon, while small intestinal cancer with a relatively lower distribution of *S. japonicum* eggs is quite rare^[4,19]. Fan *et al.*^[20] analyzed 285 pathological specimens with colorectal cancer from surgical operations in an endemic area for schistosomiasis and found that cancer in the rectum and sigmoid colon accounted for 44% and 27% in the 220 cases of cancer combined with schistosomiasis, respectively. In those patients without schistosomiasis, the comparative figure was 23% and 18%, respectively, with a significant difference^[20]. Peripheral blood tumor marker IL-2, TNF-2 and CEA might be elevated in those patients^[21]. Yu *et al.*^[22] divided schistosomal egg induced polyps into three types: fibrous type, mixed type and epithelial proliferative type; CEA and PNA receptors were present in 18/20 (90%) and 6/18 of epithelial proliferative type, respectively. In the present study, 46% and 47% patients had elevated CEA or CA-125, whilst few patients had abnormal CA19-9. On the other hand, after statistical analysis, schistosomal rectosigmoid carcinoma was only associated with a higher CA-125 level.

Is colonoscopy specific?

Colonoscopy provides valuable information for the diagnosis of colonic schistosomiasis^[23]. Liu *et al.*^[3] systematically described morphological types of schistosomal colorectal cancer (endophytic/ulcerative, exophytic/fungating, annular, giant polyp and Iic), and found that the ulcerative type were the most common cases. However, in this study, which focused on rectosigmoid cancers, fungating masses seemed form the majority of the cases. The endoscopic findings of

schistosomal rectosigmoid cancer were non-specific.

Considering the diagnoses of carcinoma, only 27% of the patients were diagnosed with rectal carcinomas preoperatively, 19% of the biopsies showed hyperplastic polyps, and 8% and 23% revealed low or high grade intraepithelial neoplastic changes, respectively. Considering the diagnosis of colonic schistosomiasis: if schistosoma ova are not observed in biopsies, the near-normal crypts with excess mucus and diffuse or focal infiltration of eosinophilic granulocytes may be highly suggestive of colonic schistosomiasis^[24]. Therefore, multisite biopsies are recommended to improve the accuracy of diagnosis. Ye *et al.*^[25] analyzed clinical and endoscopic manifestations for 96 patients, and found that epidemiological investigations and colonoscopic examinations combined with multi-block and multi-site biopsies may improve the rate of correct diagnosis of intestinal schistosomiasis.

Recent technological advances have significantly enhanced the role of imaging in the detection, characterization, and management of infectious diseases involving the large intestine. Lee *et al.*^[26] reported that CT demonstrated calcifications resembling tram tracks in the sigmoid colon and postulated that the tram-track appearance is noted only in the distal large intestine because this portion of the colon has a thicker, muscular layer than the proximal colon. Irregular thickening of the intestinal wall, soft tissue masses, multiple *S. japonicum* ova calcifications inside the tumor with obscured margins and multiple intestinal masses in some patients, are important CT features of CRC with schistosomiasis. Zhang *et al.*^[27] compared the CT presentation and pathological characteristics and found that the intestinal wall was irregularly thickened in 95% of the patients, with soft tissue masses in 5% patients. Linear, spotty and small patchy calcifications were seen in 104 (80%) patients, with 96 out of 130 patients having ill-defined margins^[27]. In support of this view, in our study, CT scan and CT virtual colonography have a reasonable sensitivity and specificity for detecting these lesions. CT allowed the visualization of evenly thickened intestinal wall combined with linear and tram-track calcifications in all 26 patients.

Recent studies have also thrown some light on the molecular events associated with schistosomal colorectal cancer. Ruan *et al.*^[28] found that the expressions of vascular growth factors including PD-ECGF and VEGF are higher in the colorectal carcinoma patients with schistosomiasis than in those without. Zalata *et al.*^[29] found that signet ring cell carcinoma and mucinous adenocarcinoma both exhibited intense c-myc expression compared with non-mucinous carcinoma ($P = 0.001$). When adjusting for *S. mansoni* infection, 58% of schistosomal colorectal cancer cases were Bcl-2 positive compared with only 33% of non-schistosomal colorectal cancers ($P = 0.046$). They also suggested that the genotoxic agents produced

endogenously through the course of *Schistosomiasis mansoni* infection may play a role in CRC- *Schistosoma mansoni* pathogenesis through the dysregulation of apoptosis by the alteration of the expression pattern of Bcl-2 protein^[29].

A recent study showed that the prognosis of patients with schistosomal rectal cancer is worse than those with non-schistosomal rectal cancer; therefore, a diagnosis of schistosomiasis might be necessary^[17]. In the present research, CA-125 levels and CT scans have a sufficient sensitivity to diagnose rectosigmoid carcinoma combined with schistosomiasis.

COMMENTS

Background

Colorectal cancer coexisting with schistosomiasis is a typical schistosomiasis-related intestinal damage, especially in the sigmoid colon and rectum.

Research frontiers

Epidemiological data have suggested that a close relationship exists between colorectal cancer and schistosomiasis, especially when infected with *Schistosoma japonicum*. However, there have been little available data regarding the role of *Schistosoma japonicum* in rectosigmoid carcinoma.

Innovations and breakthroughs

The authors compared the clinicopathological features of patients with non-schistosomal rectosigmoid cancer or schistosomal rectosigmoid cancer, and analyzed the laboratory examinations, endoscopic findings and clinicopathological characteristics between those two groups. There were no significant differences in CEA values, CA19-9 values or findings from preoperative biopsies. However, patients with rectosigmoid schistosomiasis had significantly higher CA-125 values.

Applications

According to this study, rectosigmoid carcinoma combined with schistosomiasis might be associated with higher CA-125 values and early stages; CA-125 and computed tomography (CT) scans have a sufficient sensitivity for accurate diagnosis.

Terminology

Endoscopy and CT scans contribute to the diagnosis of schistosomal rectosigmoid carcinoma, although they are nonspecific. A correct diagnosis of schistosomal rectosigmoid carcinoma can be established by endoscopy as well as CT scans in combination with its clinicopathological characteristics and laboratory tests (CA-125).

Peer-review

The manuscript written by Feng *et al* retrospectively evaluated the endoscopic findings and clinicopathological characteristics of schistosomal rectosigmoid cancer. The findings are important and provide novel information for the management of patients with rectosigmoid carcinoma, as well as schistosomiasis. However, there are some concerns that need to be addressed.

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