ISSN 2618-1584 Vol. 6, Issue 11: 13-17, DOI: 10.25236/FMSR.2024.061103

Research on the Application Progress of Schistosomiasis Related Colorectal Cancer

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Abstract: *Schistosomiasis japonica is a parasitic disease that was once widespread in China, especially in the middle and lower reaches of the Yangtze River. Although it has been properly controlled in China, there are still some areas where schistosomiasis infection still exists. We found that schistosome eggs are not only prone to sedimentation in the liver, ultimately leading to cirrhosis, but also prone to the development of colorectal cancer. Therefore, this article will discuss the mechanism of action, diagnosis, and treatment prognosis of colorectal cancer related to schistosomiasis, summarize the latest research progress, and provide a basis for clinical treatment.*

Keywords: *Schistosomiasis; Colorectal cancer; Mechanism of action; Diagnosis; treat*

1. Introduction

Colorectal cancer (CRC) is a common digestive tract tumor worldwide, and most patients experience symptoms in the middle to late stages. Therefore, regular check ups are essential for populations with high-risk factors[1]. Previous studies have found that environmental and genetic factors can affect the occurrence of colorectal cancer. However, recent reports have found that some pathogens with carcinogenic potential can increase the risk of developing colorectal cancer. Although there is not yet a large amount of research to prove the association between the two, there are approximately 2.2 million new cases worldwide that can be attributed to pathogen infections, accounting for 15.4% of the total number of cancers. In China, this proportion is even higher, reaching 22%[2]. Schistosomiasis is a parasitic disease caused by trematodes, with a global infected population of about 200 million and an annual death toll of 28000 due to schistosomiasis. The main epidemic in our country is Schistosoma japonicum. Schistosoma japonicum is a hermaphrodite species, mainly transmitted through contact with infected water containing cercariae. The cercariae infect the host through the skin or oral mucosa, invade the host, mate and lay eggs, and produce eggs. The eggs deposit in the colon wall or liver, forming granulomas or fibrosis[3]. Schistosoma japonicum has been listed as a potentially carcinogenic human carcinogen (2B), and there is retrospective analysis showing a correlation between Schistosoma japonicum infection and colorectal cancer, but there is a lack of experimental data to support this[4]. This review will provide a reference for clinical practitioners in the treatment of schistosomiasis associated colorectal cancer (SACC) by elucidating its mechanism of action, diagnosis, and treatment.

2. Overview of Schistosomiasis

Schistosomiasis is one of the common infectious parasitic diseases in China, mainly prevalent in the middle and lower reaches of the Yangtze River in Hunan, Hubei, Yunnan, Jiangxi and other regions. The transmission mode of schistosomiasis is that the carrier excretes feces containing eggs and pollutes the water source, and humans and animals are infected with schistosomiasis through contact with the water source. Snails are the only intermediate host of Schistosoma japonicum, and the larvae invade the snail's body and multiply extensively to form daughter larvae, which then release cercariae. In the end, if the environment, temperature, and other conditions are suitable, the body will release cercariae, which will eventually invade the human body through the skin and become infected with Schistosoma. The cercariae will become larvae in the body, move to small veins and lymphatic vessels, and

ISSN 2618-1584 Vol. 6, Issue 11: 13-17, DOI: 10.25236/FMSR.2024.061103

eventually deposit in the hepatic portal vein and mesenteric blood vessels. A small number will be excreted through feces and continue to the next cycle[5].

Schistosomiasis is a zoonotic parasitic disease. In the early stages of infection, non-specific symptoms such as fever, chills, diarrhea, and bloody stools may occur. In the later stages, complications such as splenomegaly, esophageal and gastric varices, and abdominal fluid accumulation may occur, and in severe cases, death may even occur[6]. We found that most patients infected with schistosomiasis did not seek medical attention in a timely manner in the early stages, mainly because the symptoms were mild and difficult to take seriously in the early stages, and when there were many complications in the later stages, the treatment options for patients were limited. Therefore, early diagnosis of schistosomiasis is crucial. At present, we have found many laboratory tests for diagnosing schistosomiasis, such as blood routine, pulmonary X-ray, and ultrasound examination. The blood routine of most patients infected with schistosomiasis shows elevated levels of eosinophils and white blood cells. Secondly, if the combined improved Kato method and fecal incubation test are used, it will improve the diagnostic rate of schistosomiasis[7]. MEDEIROS[8] et al. analyzed patients infected with schistosomiasis and found that over half of them exhibited pulmonary imaging changes, with 60.6% showing miliary opacities and 6.7% showing blurry lung shadows. These pulmonary manifestations generally disappear on their own after 3-6 months. Secondly, we can also use serological methods to detect rates, mainly including indirect immunofluorescence tests and immunochromatographic techniques. In recent years, due to the advancement of science and technology, target gene detection for schistosomiasis is being further studied, and many highly sensitive and specific detection methods have emerged, such as polymerase chain reaction, gene chip technology, etc. Through the above laboratory methods and related cutting-edge technologies, early diagnosis of schistosomiasis has become possible, which is conducive to improving the overall survival and quality of life of patients.

3. Overview of colorectal cancer

Colorectal cancer (CRC) is one of the most common malignant tumors in the world, with high incidence rate and mortality. In recent years, due to the accelerated trend of population aging in China, its incidence rate has increased. Therefore, we should actively seek effective treatment methods for colorectal cancer. Fang[9] et al. found that 58.1% of cases with colorectal cancer were over 60 years old, indicating that age is an independent risk factor for colorectal cancer. Therefore, we recommend that patients in the 50-70 age group should undergo regular follow-up examinations for tumor markers and gastrointestinal endoscopy to screen for colorectal tumors. Secondly, the 5-year survival rate for stage I colorectal cancer patients is 91%, while the 5-year survival rates for stage IV and locally advanced patients are 14% and 72%, respectively[10]. Therefore, actively seeking early diagnostic methods for colorectal cancer has become a current research hotspot.

Although treatment options for colorectal cancer have emerged with the development of science and technology, the mortality rate of advanced colorectal cancer patients remains high. At present, the main treatment methods for colorectal cancer are surgery, radiotherapy, chemotherapy, immunotherapy, or targeted therapy. The NICHE-3[11] clinical trial found that after combining LAG-3 inhibitors with nivolumab, 79% of patients achieved pathological complete remission, and the incidence of adverse reactions was low. For MSS/pMMR type colorectal cancer, the CAPAbility 01[12] study combined treatment with sildenafil (a histone deacetylase inhibitor) and sintilimab, dividing patients into two groups: one group received bevacizumab in addition to the above, and the other group did not. The experiment found that the addition of bevacizumab significantly improved the pathological remission rate in the experimental group, with a median survival period of 7.3 months, which was significantly longer than the control group's 1.5 months[13]. There have been many new advances in targeted therapy for colorectal cancer recently. The above treatment methods provide new ideas for clinical workers to treat colorectal cancer, thereby effectively improving the survival rate of patients.

4. Schistosomiasis related colorectal cancer

Data shows that the incidence rate of colorectal cancer in schistosomiasis endemic areas is higher than that in non endemic areas in China. Xiao Ran[14] et al. analyzed 120 patients with colorectal cancer and divided them into two groups: 60 patients with concurrent schistosomiasis infection and 60 patients with single colorectal cancer. The tumor marker CEA concentration was detected in both groups of patients, and the histological classification of the two groups was compared and analyzed for differences. Research has found that patients infected with schistosomiasis have significantly higher

ISSN 2618-1584 Vol. 6, Issue 11: 13-17, DOI: 10.25236/FMSR.2024.061103

levels of CEA in stage I and II colorectal cancer compared to uninfected patients, while there is no significant difference in CEA levels between stage III and IV patients. This indicates that schistosomiasis infection has a significant impact on the early stages of colorectal cancer. SCANUT[15] et al. validated the correlation between schistosomiasis infection and colorectal cancer by comparing the clinical and pathological characteristics of patients with schistosomiasis and non schistosomiasis colorectal cancer. Firstly, 351 patients with colorectal cancer were collected, and survival curves were plotted using the K-M method. Univariate and multivariate Cox proportional hazards models were used to determine the previous association between the two. Research has found that patients with chronic schistosomiasis and colorectal cancer are generally older than those without schistosomiasis. The K-M method analysis shows a significant correlation between schistosomiasis and overall survival. After statistical analysis, it was found that gender, TNM stage, and schistosomiasis infection are independent predictive factors for colorectal cancer.

4.1 Study on the Mechanism of Action of Schistosomiasis Related Colorectal Cancer

The development of schistosomiasis related colorectal cancer is a complex process involving multiple mechanisms of action. We have summarized the following mechanisms of action based on existing researches. Chronic inflammation plays a crucial role in the initiation of SACC, mainly because it can cause colorectal epithelial hyperplasia and adenomatous changes, making the colorectal epithelium susceptible to genotoxic substances, thereby promoting the growth of potential malignant lesions caused by exogenous carcinogens[16]. We also found that activated macrophages are associated with the production of genotoxic mediators, such as reactive oxygen species, reactive nitrogen, etc., which can cause DNA mutations and breaks, leading to the occurrence of tumors. Previous studies have found the presence of inducible nitric oxide synthase (iNOS) in Schistosoma japonicum. Relevant experiments have shown that iNOS can produce high concentrations of NO to participate in P53 gene mutations and tumor angiogenesis, thereby playing a role in the occurrence and development of tumors [17-18]. In addition, it has been found that schistosomiasis can also induce host cell escape and accelerate tumor growth by downregulating immune surveillance and anti-tumor immunity. Schistosoma antigens promote the accumulation of marrow-derived suppressor cells (MDSCs) in lymphoid organs and tumor microenvironments by activating the JAK/STAT3 signaling pathway. However, studies have shown that MDSCs can promote angiogenesis as well as tumor invasion and metastasis [19]. LIU W[20] et al. detected the protein expression of hMSH2 and hMSH1 in SACC patients through immunohistochemistry and other experiments, and ultimately found that the lack of hMSH2 and hMLH1 proteins can affect the development of SACC, and microsatellite instability may be involved in its malignant transformation process. Yang Xiuhong[21] et al. collected pathological tissue samples from 95 colorectal patients with schistosomiasis deposition for detection of ALDH1 gene expression. They ultimately found that low expression of ALDH1 gene could inhibit cell proliferation and promote cell apoptosis. A study detected the gene expression of tumor tissue samples from 60 SACC patients through immunohistochemistry, and found that cytochrome P450 II E1 (CYP II E1) was highly expressed and associated with the pathological classification of SACC patients, indicating that it may have an impact on the occurrence of SACC.

4.2 Colonoscopy and Laboratory Characteristics of Schistosomiasis Related Colorectal Cancer

Zhang Bin[22] et al. analyzed the endoscopic manifestations and case characteristics of 179 cases of colorectal schistosomiasis. There were a total of 32 patients with schistosomiasis complicated with colorectal cancer, aged 44-85 years, including 24 males. Ultimately, it was found that among the 32 SACC patients, there were 12 cases of endogenous/ulcerative (37.5%), 10 cases of exogenous/fungal (31.2%), 4 cases of annular lesions (12.5%), 3 cases of giant polyps (9.4%), and 3 cases of superficial depressed type (9.4%). Yang Jianghua[23] et al. collected 341 patients with postoperative pathological diagnosis of colorectal cancer, including 101 cases of schistosomiasis related colorectal cancer. Relevant statistical analysis was conducted on their imaging, and it was finally found that 87 patients showed linear calcification on CT imaging, 92 patients showed obvious thickening of the intestinal wall, and 9 patients showed obvious masses. WU W[24] et al. investigated the effect of transforming growth factor - α (TGF - α) serum concentration on SACC patients by collecting 48 SACC patients. By comparing the changes in TGF - α concentration before and after surgery, it was found that the TGF - α concentration in SACC patients was higher than that in schistosomiasis patients without colorectal cancer. The above indicates that TGF - α may become an indicator for evaluating the malignancy of colorectal cancer patients. YI Z[25] et al. collected 187 cases of schistosomiasis related colorectal patients, analyzed their clinical pathology and laboratory results, and found that among SACC patients,

ISSN 2618-1584 Vol. 6, Issue 11: 13-17, DOI: 10.25236/FMSR.2024.061103

the incidence rate of men was significantly higher than that of women, with an average age of (64.79 ± 10.91) years. By comparing their laboratory results, it was found that the positive rate of fecal occult blood in SACC patients was significantly higher than that in patients with simple colorectal cancer. Secondly, the red blood cells and tumor markers (CEA, CA19-9) in the blood routine of SACC patients were significantly higher than normal values. Through the above research, we can find that in areas where schistosomiasis is prevalent, regular follow-up of gastrointestinal endoscopy is necessary for early diagnosis of colorectal cancer.

4.3 Treatment and Prognosis of Schistosomiasis Related Colorectal Cancer

At present, the main treatment for schistosomiasis is anti parasitic therapy, and quinolones are generally preferred due to their low side effects and high effectiveness. Early schistosomiasis can still be treated with surgery, but due to the susceptibility of schistosomiasis to complications such as thrombocytopenia, cirrhosis, and portal hypertension, surgery is more difficult. CHENG M[26] et al. conducted a retrospective analysis of patients with schistosomiasis infection undergoing surgical resection for colorectal cancer, evaluating the short-term efficacy of laparoscopic treatment for SACC patients. It is suggested that that patients undergoing laparoscopic surgery and those undergoing open surgery have similar rates of intraoperative and postoperative complications, with lower and similar average surgical blood loss. There is no difference in safety between the two. Secondly, it was found that the lymph node clearance rates of the two were also similar. However, this study only evaluated short-term efficacy, and further research is needed for long-term follow-up. There is a study that detected the levels of CD4+, CD8+T cells and C-reactive protein in the stroma and tumor of colorectal cancer patients through immunohistochemistry and other experiments. It was ultimately found that tumor infiltrating lymphocytes and C-reactive protein were not significantly correlated with schistosomiasis, and stromal CD4 and tumor CD8 were independent prognostic factors for SACC patients. Therefore, we can know that different subtypes of tumor infiltrating lymphocytes have different biological functions and prognostic value in the immune microenvironment of SACC patients. PAN W[27] et al. conducted a retrospective analysis of 354 colorectal cancer patients and found that in 50 of them, c-MYC gene amplification was found to be associated with age, tumor stage, and lymph node metastasis. This indicates that c-MYC amplification can be used as an indicator for predicting poor prognosis of SACC.

5. Summary and outlook

Although there is currently no conclusive data to prove a clear etiological link between schistosomiasis and colorectal cancer. However, extensive retrospective analysis and researches on related mechanisms of action have shown a correlation between the two. In clinical practice, studies have found that the incidence of liver cancer is higher in schistosomiasis endemic areas than in non endemic areas, and patients infected with schistosomiasis mainly die from liver cancer. Therefore, in areas where schistosomiasis is prevalent, attention should be paid not only to screening for colorectal cancer, but also to gastrointestinal tumors such as liver cancer. This review elaborates on the epidemiology, mechanism of action, diagnosis, treatment, and prognosis of patients with schistosomiasis related colorectal cancer, aiming to provide a basis for clinical practitioners to treat SACC.

Acknowledgments

Fund project number: 2023HC21.

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