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World Journal of Clinical Cases

Thrice Monthly Volume 9 Number 23 August 16, 2021

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 9 Number 23 August 16, 2021

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 9 Number 23 August 16, 2021

Contents

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MINIREVIEWS

Novel mechanism of hepatobiliary system damage and immunoglobulin G4 elevation caused by *Clonorchis sinensis* infection

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Abstract

Clonorchis sinensis infection is still a major public health problem. It is estimated that more than 15 million people worldwide are infected, especially in Northeast China, Taiwan, South Korea, and North Vietnam. The detection of *Clonorchis sinensis* eggs in feces and bile is still the only gold standard for the diagnosis of *Clonorchis sinensis* infection, and new detection methods are needed to improve the detection rate. After *Clonorchis sinensis* invades the human body, it mainly parasitizes the hepatobiliary tract. Therefore, it is closely related to hepatobiliary diseases such as cholangitis, bile duct stones, liver fibrosis, and cholangiocarcinoma. The increase in immunoglobulin G4 (IgG4) caused by *Clonorchis sinensis* infection is rare and there are few reports about the relevant mechanism. It may be related to the inflammatory factors interleukin (IL)-4, IL-10, and IL-13 produced by human phagocytes, T cells, B cells, and other immune cells in the process of resisting the invasion of *Clonorchis sinensis*. However, this finding still needs further clarification and confirmation. This article reviews the epidemiology, clinical manifestations, serology, imaging, pathogenic mechanism, and control measures of *Clonorchis sinensis* infection to help establish the diagnostic process for *Clonorchis sinensis*. We report novel mechanisms of IgG4 elevation due to *Clonorchis sinensis* infection to provide more experience and a theoretical basis for clinical diagnosis and treatment of this infection.

Key Words: Liver damage; Bile duct damage; Hepatobiliary system destruction; *Clonorchis sinensis* infection; Immunoglobulin G4; Clinical manifestations

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INTRODUCTION

Clonorchis sinensis is an important food-borne parasite and one of the common zoonotic parasites. It was first discovered in the bile duct of a Chinese craftsman in Kolkata, India in 1875[1]. At present, *Clonorchis sinensis* infection is still a major public health problem. It is estimated that more than 15 million people worldwide are infected, especially in Asian countries and regions, including China, Japan, South Korea, Taiwan, and Vietnam[2]. Because adult *Clonorchis sinensis* often parasitizes the host's hepatobiliary ducts, it often damages the liver and bile ducts through mechanical destruction and excretion and secretion of antigens[3], which can easily cause abnormal liver function, bile duct dilatation, cholecystitis, obstructive jaundice, and a series of hepatobiliary injury diseases[4]. Thus, *Clonorchis sinensis* is also called the liver fluke. If *Clonorchis sinensis* is not cleared in time, its long-term obstruction and inflammatory stimulation will induce gene changes[5], which will eventually lead to the occurrence of cholangiocarcinoma. The World Health Organization (WHO) International Agency for Research on Cancer has classified *Clonorchis sinensis* as a Class I carcinogen[6,7]. This article reports several novel mechanisms of immunoglobulin (Ig) G4 elevation due to *Clonorchis sinensis* infection and reviews the epidemiology and clinical manifestations of *Clonorchis sinensis* infection published in the past to provide more experience and a theoretical basis for clinical diagnosis and treatment of this infection.

LIFE HISTORY

Clonorchis sinensis is a typical hermaphrodite that is 10-25 mm long and 3-5 mm wide. The front part of its body is sharp, while the back part is obtuse, and its shape is similar to a sunflower seed[8]. Through the first intermediate host (freshwater snails) and the second intermediate host (freshwater fish or shrimp), it invades the ultimate host (humans and carnivorous mammals) after the stages of adult worm, egg, miracidium, sporocyst, rediae, cercaria, cysticercus, and metacercaria (Figure 1). The eggs produced by adults are excreted through feces and enter the water. They are swallowed by freshwater snails. In the digestive tract of the snails, the eggs hatch into miracidia. The miracidia pass through the intestinal wall and develop into sporocysts in the snails. Through asexual reproduction, sporocysts produce rediae. In the same way, the rediae produce cercaria, and the mature cercaria eventually escape from the snail body into the water, invade the muscles and other tissues of freshwater fish or shrimp in the water, and develop into mature cysticercus. After people eat freshwater fish or shrimp, under the action of gastric acid and pepsin, the larvae in the sac are activated. The larvae break through the sac in the duodenum and flow up through the bile to reach the intrahepatic bile duct. There have also been experiments indicating that the larvae can reach the intrahepatic bile duct through blood vessels or through the intestinal wall and finally inhabit in the bile duct of the host[9]. The survival of adults after positioning can rely on their secretion of immune regulatory products[10], such as the upregulated expression of the secreted protein *Clonorchis sinensis* acetoacetyl-CoA thiolase located in the vitellarium and subtegumental muscle layer of adult worms[11], thereby helping the worms sense the cholesterol environment and better survive in the bile duct. After a large number of *Clonorchis sinensis* individuals

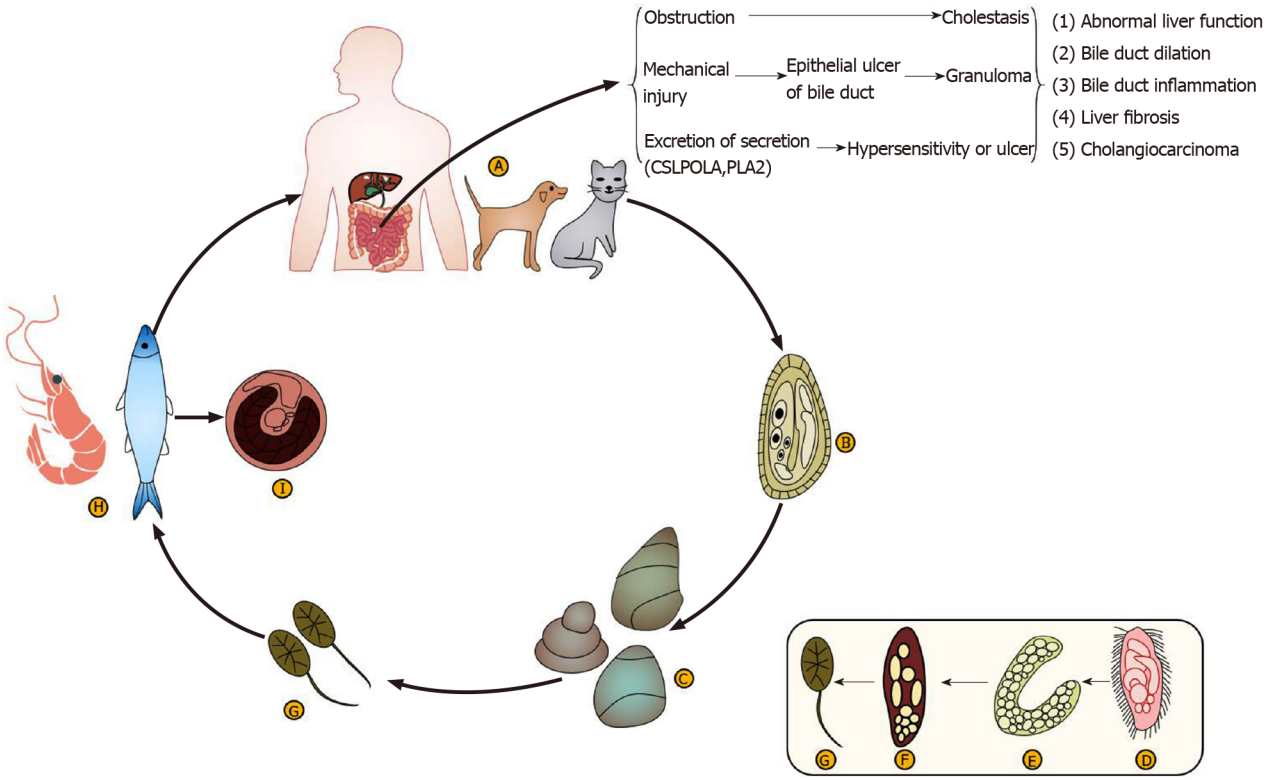

Figure 1 The life history of *Clonorchis sinensis*. A: Ultimate host; B: Egg; C: The first intermediate host; D: Miracidium; E: Sporocyst; F: Rediae; G: Cercaria; H: The second intermediate host; I: Cysticercus.

colonize and survive, they cause bile duct obstruction and bile stasis, inducing inflammation, secondary liver function abnormalities, and cholecystitis. If *Clonorchis sinensis* survives longer, it may even cause liver fibrosis or cholangiocarcinoma. This is due to the excretions, secretions, and other metabolites produced during the parasitic process of the parasite[12], which can promote the proliferation of bile duct epithelial cells and inhibit cell apoptosis. It stimulates the expression of profibrotic genes in hepatic stellate cells[13,14], upregulates proto-oncogenes, inhibits the expression of tumor suppressor genes, induces the production of free radicals, changes the state of the extracellular matrix, and promotes tumor cell metastasis[15]. A meta-analysis showed that the relative risk of liver fluke infection was 4.8, which is the strongest risk factor for cholangiocarcinoma[16].

EPIDEMIOLOGY

Types of endemic areas

Clonorchiasis infection is mainly prevalent in northeastern China, Taiwan of the China, southern South Korea, northern Vietnam, and eastern Russia[17,18]. There are occasional reports of related infections in other parts of the world, but due to the rarity of such infections, there are no systematic epidemiological reports. China is the main country affected by *Clonorchis sinensis*. In 2016, the third survey report on the status of important human parasitic diseases in China showed that *Clonorchis sinensis* was detected in 6226 out of 305081 people, and the infection rate was 2.04%. A total of 89.37% of infected people are distributed in the northeast and in Guangdong and Guangxi provinces[19]. Compared with other places in China, the prevalence rate is as much as 5-10 times higher. This is because there are many rivers in these areas, which are rich in freshwater fish such as river fish, and it is more common to eat freshwater fish. The infection rate in Taiwan is between 0.4% and 1.0%[1], with infections mainly occurring in Miaoli in northern Miaoli, Sun Moon Lake in the middle area, and Menong in the south[20]. The seventh national survey on the infection rate of intestinal parasites in South Korea in 2004 showed that the infection rate of *Clonorchis sinensis* was 2.4%, and there were approximately 1.17 million infected people[21]. The epidemic area was mainly the southern river basin, especially the Nakdong and

Yeongsan watersheds, and the average infection rate of *Clonorchis sinensis* among residents was 8.4%[22]. Since 2005, the Korean Centers for Disease Control have been treating infected people nationwide, especially in endemic areas. As a result, the national infection rate was reduced to 1.9% in the eighth survey of Korea in 2012[23]. The WHO estimated in 2004 that approximately 1 million people in Vietnam were infected with *Clonorchis sinensis*. The disease is mainly prevalent in northern Vietnam, with a prevalence ranging from 0.2% to 40.1%[24,25], but a national sample survey has not been conducted, and most surveys are small and unsampled[25].

Source of infection and route of transmission

Freshwater fish are the main transmission route of *Clonorchis sinensis* infection. Most human clonorchiasis infections occur due to eating fish parasitized by *Clonorchis sinensis*. The intensity of the infection is proportional to the cumulative number of freshwater fish consumed in a lifetime. The habit of eating raw fish increases the risk of infection with *Clonorchis sinensis* by 53 times[24]. A meta-analysis[26] showed that the comprehensive prevalence of *Clonorchis sinensis* in Southeast Asian fishes was 30.5%, of which China constituted 35.1%, Korea constituted 29.7%, and Vietnam constituted 8.4%. A meta-analysis in China[27] showed that 15 species of freshwater fishes have an average infection rate of 16.97%, with carp having the highest infection rate (40.74%). Among the 3221 freshwater fish examined in Northeast China, the overall prevalence of *Clonorchis sinensis* infection is 19.96%[28]. *Clonorchis sinensis* cercariae are common in river fishes in South Korea[29-31], and the average infection rate of *Clonorchis sinensis* is 8.4%[22], with the highest infection rate in the Nakdong River Basin of 11.7%. In 2016, a small survey in northern Vietnam found that 69.7% of fish were infected with *Clonorchis sinensis*, and the prevalence and intensity were significantly higher than those in 2010[32,33].

Susceptible population

Investigations conducted in various places found that the infection rate with *Clonorchis sinensis* was higher in males than in females. In some areas, male infections were 2-3.6 times higher than female infections, which may be related to the different eating habits of men and women. In some areas, it was found that the number of men who have the habit of eating raw fish is three times that of women, and compared with women, men prefer to eat fish and have more social activities and eating opportunities[34-36]. With increasing age, the infection rates in both men and women increase, and infection exists in all age groups, with the highest infection rate in the age group of 50 to 59. In addition, the infection rate in rural areas is significantly higher than that in urban areas. These characteristics can be reflected in the currently reported 11 cases of *Clonorchis sinensis*-infected patients (Table 1)[37-46]. The average age of the infected patients was 47.27 years old, of which 72.73% were over 40 years old, with men accounting for 4/5 of the total number, and the medical history shows that most patients had the habit of eating freshwater fish raw.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The incubation period of clonorchiasis is 1-2 mo, and patients may have different clinical manifestations. People with mild infections are often asymptomatic, and only eggs are found in the feces. Those with severe infections often start slowly, with dull pain and fullness in the upper right abdomen, nausea and vomiting, anorexia, fever, mild diarrhea, liver pain, liver swelling, major manifestations, and symptoms such as dizziness, insomnia, fatigue, lack of energy, palpitations, memory loss, and other neurasthenia. Pain in the right upper abdomen is the most common manifestation. Among the 11 cases reported, seven showed pain in the upper abdomen, accounting for 63.64%. The reason was that the parasites parasitized the bile ducts, causing the obstruction of the excretion of bile and other digestive substances, and the gallbladder strengthened and contracted, causing a series of symptoms of the digestive tract. When too many eggs accumulate, the bile duct will be blocked, leading to cholestasis and jaundice. In one-time consumption of food containing a large amount of *Clonorchis sinensis* metacercariae causing acute onset, the first symptoms consist of upper abdominal pain, a fever of up to 39 °C, and yellow urine, which are often accompanied by diarrhea, followed by hepatomegaly. Left hepatomegaly was predominant, and shock occurred.

Table 1 Review of case reports of *Clonorchis sinensis*

Country	Ref.	Age	Sex	Food	History
China	Wang *et al*[37], 2019	52	Male	Freshwater fish	None
China	Hao *et al*[38], 2016	48	Male	None	None
China	Liu *et al*[39], 2019	49	Male	Freshwater fish	-
China	Liu *et al*[39], 2019	40	Female	Freshwater fish	-
South Korea	Oh *et al*[40], 2014	68	Male	Freshwater fish	Gastric cancer and inguinal hernia
South Korea	Choi *et al*[41], 2015	53	Male	Freshwater fish	Chronic hepatitis B
South Korea	Lee *et al*[42], 2003	54	Male	Freshwater fish	None
South Korea	Lim *et al*[43], 2011	26	Male	Freshwater fish	-
Japan	Fujiya *et al*[44], 2016	60	Male	None	-
United States	Papachristou *et al* [45], 2005	35	Male	None	-
China	Bian *et al*[46], 2001	35	Female	None	-
Symptom(s)	**Ultrasound**	**CT**	**MRCP**	**ERCP**	**Pathology**
Severe abdominal pain in the right upper abdomen, acute shock	-	Cholecystitis, stone-like material in the gallbladder	Cholecystitis, stone-like material in the gallbladder	-	-
Jaundice	-	Cholecystitis, mild dilation of the intrahepatic duct	Cholecystitis, mild dilation of the intrahepatic duct	-	Liver biopsy: Eosinophil infiltration, obvious bile duct hyperplasia, liver cell degeneration, bile duct capillary blockage, chronic G3S1 hepatitis
Severe abdominal pain in the right upper abdomen	-	-	Bile duct stones, obvious spread of intrahepatic ducts	-	-
Jaundice, Severe abdominal pain	-	Bile duct obstruction, dilatation of the intrahepatic bile duct, bile duct stones, gallbladder stones	-	-	-
Fever, Severe abdominal pain in the right upper abdomen	-	Gallbladder dilation, thickening of the wall, fluid around the gallbladder, mild dilation of the extrahepatic bile duct	Gallbladder dilation, fluid around the gallbladder, mild dilation of the extrahepatic bile duct	-	Pathological examination of the gallbladder: Severe inflammatory mucosa and parasite eggs
Blood in stool, abdominal pain	-	A 4.3 cm heterogeneous solid and cystic mass in the distal pancreas	Multiple cystic tumors in the tail of the pancreas	-	-
Erythema rash	Mild splenomegaly	-	-	-	Lung biopsy: Microscopic examination of lung tissue shows infiltration of eosinophils
Anorexia, fatigue and weight loss	-	Mild dilation of intrahepatic bile duct	Slight dilation of bile ducts with irregular wall and depression	Edema and bulging of the duodenal papilla	Pathological examination of the duodenal papilla: Chronic active inflammation with many eosinophils in the mucosal layer
Jaundice, abdominal pain	-	Gallstone in the common bile duct, gallbladder stone, thrombus in the main hilar branch of the hilum, completely occluded in the left hilar branch	-	-	-
Darkened urine, fatigue, weight loss	-	Soft tissue masses in the hilum, dilation of intrahepatic and	-	Irregular dilation of intrahepatic	-

		extrahepatic ducts, ascites		and extrahepatic ducts	
Upper abdominal discomfort, nausea, anorexia	Cholecystitis, common bile duct obstruction	-	-	-	-
EO	**IgE**	**ALT (U/L)**	**TBIL**	**Diagnosis**	**Treatment**
15.1%	-	-	230.3 μmol/ L	Laparotomy, bile	Praziquantel
50%	-	211.9	229.7 μmol/ L	Stool	Praziquantel
6.50%	-	236	128.8 μmol/ L	Common bile duct exploration by laparoscopy	Albendazole
15.40%	-	399	129.2 μmol/ L	Common bile duct exploration by laparoscopy	Albendazole
-	-	94	2.8 mg/dL	Laparotomy, gallbladder	Praziquantel
-	-	27		Laparotomy, pancreas	
35%	1020 IL/ML	-		Stool	Praziquantel
18.30%	-	248	11.3 mg/dL	Bile	Praziquantel
154/μL	-	171		Bile	Praziquantel
4%	-	135	4.0 mg/dL	Biliary biopsy	Praziquantel
-	-	-	-	Biliary biopsy	Praziquantel

CT: Computed tomography; MRCP: Magnetic resonance cholangiopancreatography; ERCP: Endoscopic retrograde cholangiopancreatography; IgE: Immunoglobulin E; ALT: Alanine aminotransferase; TBIL: Total bilirubin.

Clonorchis sinensis infection most commonly presents an increased eosinophil count or proportion in laboratory examinations. Long-term parasitism may cause liver damage, especially the increase in alkaline phosphatase and gamma-glutamyl transferase, which are indicators of cholestasis. Computed tomography (CT) is a commonly used imaging examination method for clonorchiasis infection. It is characterized by diffuse dilation of intrahepatic bile ducts, and the small, dilated bile ducts under the capsule have similar diameters and are mainly distributed in the periphery of the liver[47]. The size of the adult worm is similar to the diameter of the secondary bile duct of the liver, meaning that it can directly block the terminal bile duct and cause its distal expansion, and secondary inflammation will also cause secondary bile duct dilation. Magnetic resonance cholangiopancreatography (MRCP) is more advantageous in displaying biliary diseases and has the highest diagnostic accuracy for complications caused by *Clonorchis sinensis* infection. Whether through laboratory or imaging tests, the diagnosis is not specific. The gold standard for the diagnosis of *Clonorchis sinensis* infection is to find *Clonorchis sinensis* eggs in feces or bile by the smear method. However, the eggs are small and similar in shape and size to some other trematode eggs[48], so it is easy to miss diagnoses and infer misdiagnoses. Immunological testing can also be used to detect patients infected with *Clonorchis sinensis*, but the sensitivity and specificity are affected by the selected antigen and the degree of infection and it cannot be used as a basis for diagnosis[49]. In addition, PCR molecular detection method development and serological explorations of *Clonorchis sinensis* infection-specific proteins are also ongoing. Recombinant Cs1 is located in a granular structure around the abdominal sucker, with a high sensitivity (94.3%) and specificity (94.4%)[50,51].

CLONORCHIS SINENSIS AND IGG4

Immunoglobulins refer to animal proteins with antibody activity, including five major classes: IgG, IgA, IgM, IgD, and IgE[52]. Among them, IgG is the main component of human serum immunoglobulins, accounting for approximately 70%-75% of the total immunoglobulins[53]. IgG4 is one of the four subclasses of IgG. It is produced by

plasma cells and has the lowest content in serum, accounting for approximately 5% of the total IgG[54]. Unlike other IgG subclasses, the binding of IgG4 to the C1q protein complex is negligible and cannot activate the classical complement pathway. In addition, the unique half-antibody exchange reaction of IgG4, which is also known as Fab arm exchange, separates the heavy chains and recombines them randomly, resulting in a mixed population of IgG4 molecules with random pairs of heavy and light chains[55]. This process causes the majority of IgG4 molecules in circulation to be composed of two different Fab arms, making them "bispecific" for a given antigen[56]. IgG4 is mainly induced by interleukin (IL)-4 and IL-13 secreted by subtype 2 follicular helper T (Tfh) cells and IL-10 produced by CD4+CD25+Foxp3+ regulatory T cells.

T cells and their cytokines play an important role in the increase of IgG4 and the conversion of IgG4 classes[57]. Type 1 helper cells (Th1) produce IL-2 and tumor necrosis factor-α to induce the inflammatory response, and type 2 helper cells (Th2) produce IL-4, IL-5, and IL-13 to counteract the microbicidal effect mediated by Th1. In terms of IgG4-related disease (IgG4-RD), the major disease with elevated IgG4, many studies have found the shift from Th1/Th2 balance to Th2 contributes to the pathogenesis of IgG4-RD. This is closely related to the cytokines produced by Th2. IL-4 and IL-10 are considered to be the main inducers of IgG4-type switching in naive B lymphocytes[58]. It has been proved that the class switch to IgG4 is caused by co-stimulation with IL-4 and IL-10. In addition to T helper lymphocytes, IL-4 is also derived from eosinophils, basophils, and mast cells. In eosinophils and mast cells, IL-4 exists in the form of particle-related peptides, which can be released quickly in allergic inflammatory reactions. IL-4 stimulates major histocompatibility complex (MHC) class II molecules, B7, CD40, surface IgM, and low-affinity IgE receptor expressed by B cells, thus promoting the antigen presentation ability of B cells. IL-4 induces the isotype conversion of immunoglobulin from IgM to IgE. Through cell experiments, it was found that IL-4 can significantly increase the contents of IgG and IgG4 in IgG4-RD. The level of IL-4 was directly proportional to the value of IgG4[59]. IL-10 is an important regulator of immune response, which directly affects antigen-presenting cells by down-regulating the expression of MHC class II and costimulatory molecules on the surface of macrophages and monocytes. IL-10 reduces the conversion to IgE induced by IL-4, and increases the conversion to IgG4[60]. IL-13 is also responsible for the production of IgG4 and IgE by B cells, which drive the deposition of the extracellular matrix through activated fibroblasts. At present, the specific mechanism of the relationship between cytokines and IgG4-RD is not clear, probably because the inflammatory environment constructed by cytokines is a key step in the pathogenesis of IgG4-RD.

The elevation of IgG4 can be seen in a variety of diseases. The most common is IgG4-RD. IgG4-RD is a chronic, systemic, and autoinflammatory disease. The main clinical features of the disease are swelling, fibrosis, and sclerosis of the affected organs. The patient's serum IgG4 level is significantly increased, and a large number of lymphocytes in the affected tissues and organs form germinal centers, with especially prominent IgG4-positive plasma cell infiltration[61]. Elevated IgG4 can also occur in a variety of malignant tumors[62] and hepatitis, even closely related to severity[63].

However, elevated IgG4 is seen not only in the abovementioned diseases; allergic diseases, parasitic infections, bacterial infections, *etc.* can also cause IgG4 elevations. However, these diseases are often overlooked, especially parasitic infections, because parasitic infections that cause elevated IgG4 cases are not common and are often misdiagnosed as IgG4-RD. Saeki *et al*[64] reported two cases of paragonimiasis infection. The serum IgG4 level of the patients was elevated, and the IgG4-positive plasma cells in the lung lesions were densely infiltrated. Baird *et al*[65] also reported the case of a male patient with pulmonary schistosomiasis infection that caused a significant increase in serum IgG4 levels, which was considered to be related to IgG4-related lung diseases. However, lung biopsy revealed pulmonary schistosomiasis. Therefore, for patients with elevated IgG4, attention should be given to parasitic infections. However, there is currently little exploration about the increase in IgG4 caused by *Clonorchis sinensis* infection. Hong *et al*[66] found that *Clonorchis sinensis* infection mainly induces the production of IgG and IgE through SDS-PAGE and immunoblotting, but IgM and IgA were less affected. They further explored the serum IgG subclasses induced by *Clonorchis sinensis* infection. The study found that among the subclasses of antibodies, IgG3 antibodies are the least common, IgG1 and IgG2 antibodies are not specific, IgG4 antibodies are prominent and specific, and the positive rates of IgG and IgG4 antibodies are directly related to the intensity of infection. Our unpublished cases of two patients with elevated IgG4 due to infection with *Clonorchis sinensis* lived in Shenyang, Northeast China. Liver function enzyme indexes of a 41-year-old woman and another 68-year-old man were all increased. IgG4

was significantly increased to 14.5 g/L and 7.69 g/L (normal value: 0.03-2.01 g/L). Abdominal CT and MRCP showed diffuse dilation of the bile duct and a full pancreas (Figure 2). The pathological results of the woman's liver biopsy revealed a large amount of eosinophil infiltration and IgG4 infiltration (Figure 3). We performed a parasite examination of the patient's feces and detected eggs of *Clonorchis sinensis* under a microscope (Figure 4). The flow diagram of diagnosis is shown in Figure 5. Although the molecular mechanism of *Clonorchis sinensis* in causing the increase in IgG4 has not been elucidated in detail, it may be related to the inflammatory factors produced in the process of the human immune system resisting the invasion of the parasite (Figure 6).

First, *Clonorchis sinensis* infection induces an innate immune response. Multiple pattern recognition receptors on the surface of dendritic cells and macrophages can recognize the pathogen-related molecular patterns of the parasite and directly swallow and kill *Clonorchis sinensis*. For example, *Clonorchis sinensis* crude antigen can stimulate macrophages to produce the anti-inflammatory cytokine IL-10 through the ERK pathway[67]. The types of pattern recognition receptors include Toll-like receptors (TLRs), scavenger receptors, and complement receptors. TLRs play an indispensable role in the immune response to parasite infections[68]. A study found that[69] the expression of the TLR2 gene and protein increased after *Clonorchis sinensis* infection of the liver in mice, and blocking the TLR2 signaling pathway induced a downregulation of the proportion of Th2 in CD4+ T cells in mice infected with *Clonorchis sinensis*. Since the production of IgG4 is mainly controlled by Th2, the TLRs signaling pathway may have certain significance in the formation of IgG4.

Second, after some parasites break through innate immunity, the adaptive immune system takes effect. The activation of T helper cells play an important role in the occurrence of the host immune response after *Clonorchis sinensis* infection. T helper cells are activated after binding to *Clonorchis sinensis* antigens and secrete IL-2 to promote T cell proliferation, mainly including Th1 and Th2. Th1 mainly secrete IL-2, IL-12, interferon (IFN), *etc*., activating phagocytes, NK cells, and others to directly kill *Clonorchis sinensis*. Chung *et al*[70] confirmed that the *Clonorchis sinensis* coat protein rCsTegu21.6 stimulated T cell-specific antibody production and cytokine production of IL-2, IL-4, and IFN-γ in murine dendritic cells and T cell secretion. Th2 mainly produce IL-4, IL-5, IL-6, IL-10, IL-13, and other cytokines to promote the maturation of B cells, produce antibodies, and regulate humoral immunity. IL-4, IL-10, and IL-13 can all promote the expression of IgG4. Studies have shown that with the prolonged time of *Clonorchis sinensis* infection in BALB/c mice, spleen cells were cultured *in vitro* after infection for 2-4 wk. The secretion of the Th2 cytokines IL-10 and IL-5 increased, while the secretion of the Th1 cytokines IFN-γ and IL-2 decreased[71]. Therefore, IgG4 may increase during the immune response caused by *Clonorchis sinensis* infection. B cells mainly secrete IgE antibodies. B cells and eosinophils play an extremely important role in the immune response to *Clonorchis sinensis* infection[72]. After *Clonorchis sinensis* infection, Th2 cytokines can promote the production of IgE antibodies and subgroup conversion, and IL-5 can promote the development and activation of eosinophils. After the IgE antibodies bind to *Clonorchis sinensis*, they bind to the IgE receptor on the surface of eosinophils to promote cell activation, induce the production of bactericidal proteins and cytokines (IL-4, IL-5, and IL-13), and kill the parasites[73]. IgE antibodies can also bind to *Clonorchis sinensis* antigens to promote the release of histamine and other biologically active substances from mast cells, promote intestinal peristalsis, and facilitate the elimination of parasites. Therefore, *Clonorchis sinensis* infection can cause IgE antibodies and eosinophils to increase. The inflammatory factors released by eosinophils are also beneficial to the production of IgG4.

Finally, in addition to the above possible mechanisms, the excretion and secretion products of *Clonorchis sinensis* may play an important role. CsRNASET2 is a glycosylated T2 ribonuclease that exists in the excretion and secretion products of *Clonorchis sinensis*. Xu *et al*[74] immunized BALB/c mice with CsRNASET2 and found that the level of IL-4 expressed by the spleen cells of mice immunized with CsRNASET2 was elevated and that CsRNASET2 immunity triggered a Th2 immune response by promoting the synthesis of IL-4[74]. In addition, the excretion and secretion products of *Clonorchis sinensis* can highly express nitric oxide by activating the nuclear factor kappa B signaling pathway, which promotes Th1 to Th2 immune transformation[75].

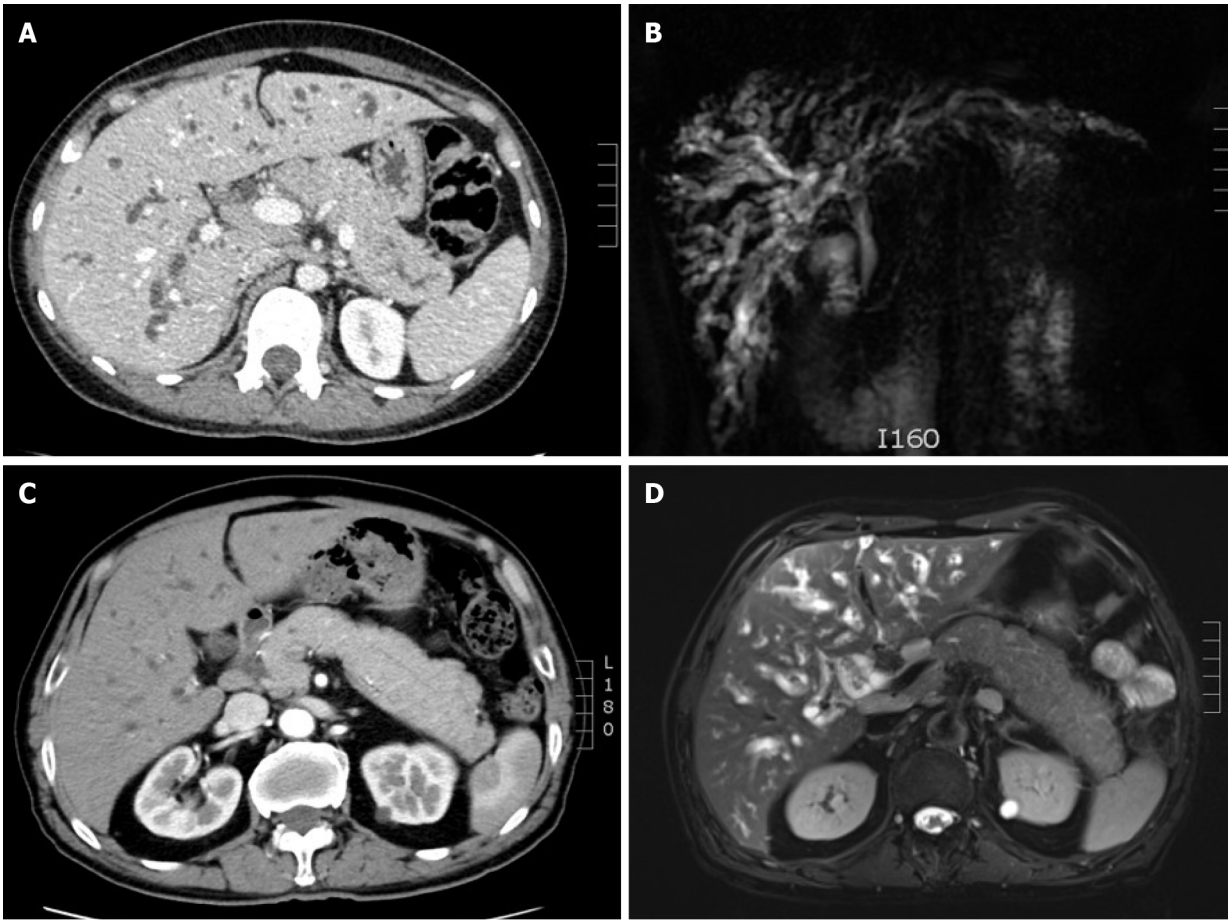

Figure 2 Images. A: Computed tomography (CT) image of a woman. The intrahepatic bile duct was diffusely dilated, the pancreas was full, the pancreatic duct in the tail of the body was slightly dilated, and multiple enlarged lymph nodes in the hilar and retroperitoneum were visible; B: Magnetic resonance cholangiopancreatography (MRCP) image of the woman. Intrahepatic bile ducts were dilated and had an uneven thickness, and the pancreas was full; C: CT image of a man. The intrahepatic bile duct was diffusely dilated, and the pancreas was full; D: MRCP image of the man. The intrahepatic and extrahepatic bile ducts and common bile ducts were dilated, and enlarged peripancreatic lymph nodes were visible.

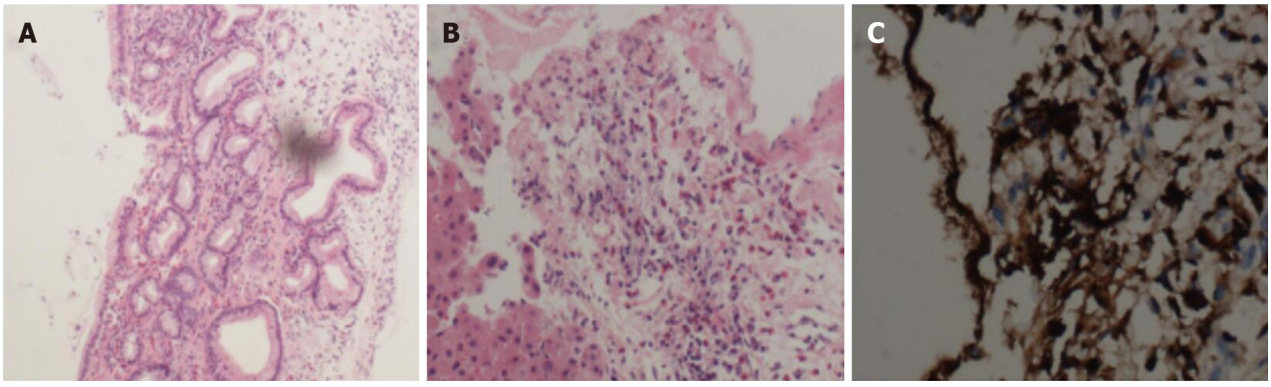

Figure 3 Pathological pictures. A: Massive bile duct hyperplasia; B: Eosinophils and plasma cells; C: Immunoglobulin G 4.

TREATMENT

The most effective treatment for clonorchiasis is praziquantel. According to the WHO recommendation, the dose is 25 mg/kg orally three times a day for 2 consecutive days [76]. This program has cured approximately 99% of infected patients. If the first treatment cannot completely cure the infection, nearly 100% of patients can undergo a second treatment[77]. Praziquantel also causes some adverse reactions, such as dizziness, headache, gastrointestinal pain, and nausea[2]. These side effects are mild and tolerable, but severe hypersensitivity reactions can also occur, including skin rash

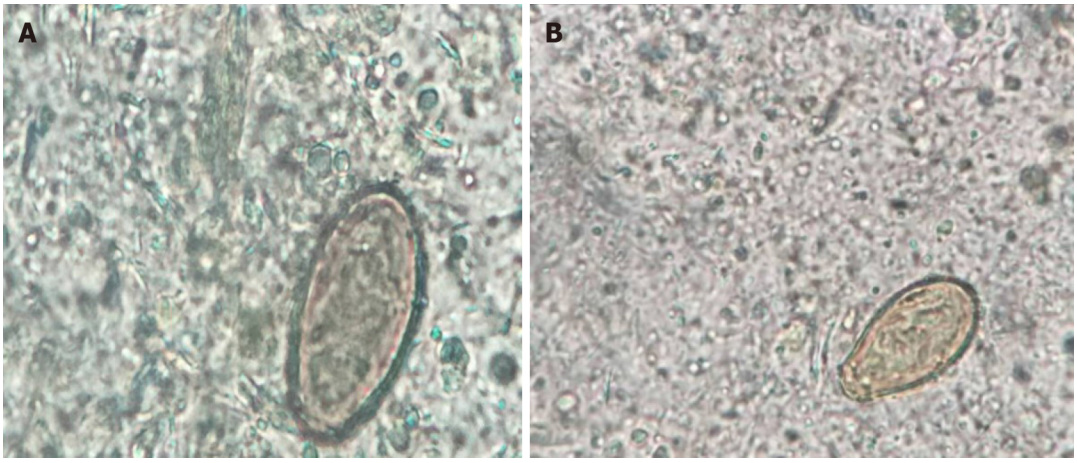

Figure 4 *Clonorchis sinensis* eggs in stool. A: Woman; B: Man.

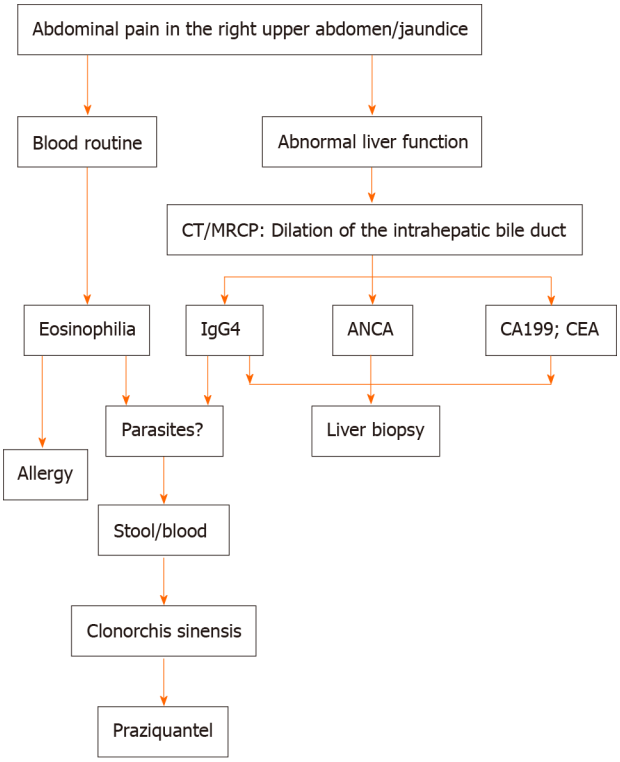

Figure 5 Flow diagram of diagnosis. IgG4: Immunoglobulin G 4; ANCA: Anti-neutrophil cytoplasmic antibody; CEA: Carcinoembryonic antigen; CT: Computed tomography; MRCP: Magnetic resonance cholangiopancreatography.

or hives, difficulty breathing, and hypotensive shock[78]. Compared with praziquantel, albendazole has fewer side effects and is well tolerated and lower in price, along with being safe, convenient, and economical. It can be used as the first choice for general treatment of clonorchiasis in Guangdong and is applicable to all age groups [79]. Recently, it was discovered that tribendimidine has the same efficacy as praziquantel in the treatment of *Clonorchis sinensis* infections. Compared with praziquantel, it has fewer adverse effects and is being studied as a promising chemotherapy method[80-82]. However, Xiao *et al*[83] found that broad-spectrum anthelmintic mebendazole has potential for use against larvae (14 days old) and adults, according to oral administration at a single dose of 150 mg/kg in rats infected with *Clonorchis sinensis*. The single effective dose ranges of mebendazole and tribendimidine for clonorchiasis in rats are similar, but the window is wider, and the range of praziquantel is narrower. In addition, studies have found that *Clonorchis sinensis* does not easily survive under high concentrations of bile, so dopamine receptor antagonists that promote bile secretion and antipsychotics with dopaminergic antagonism (such as

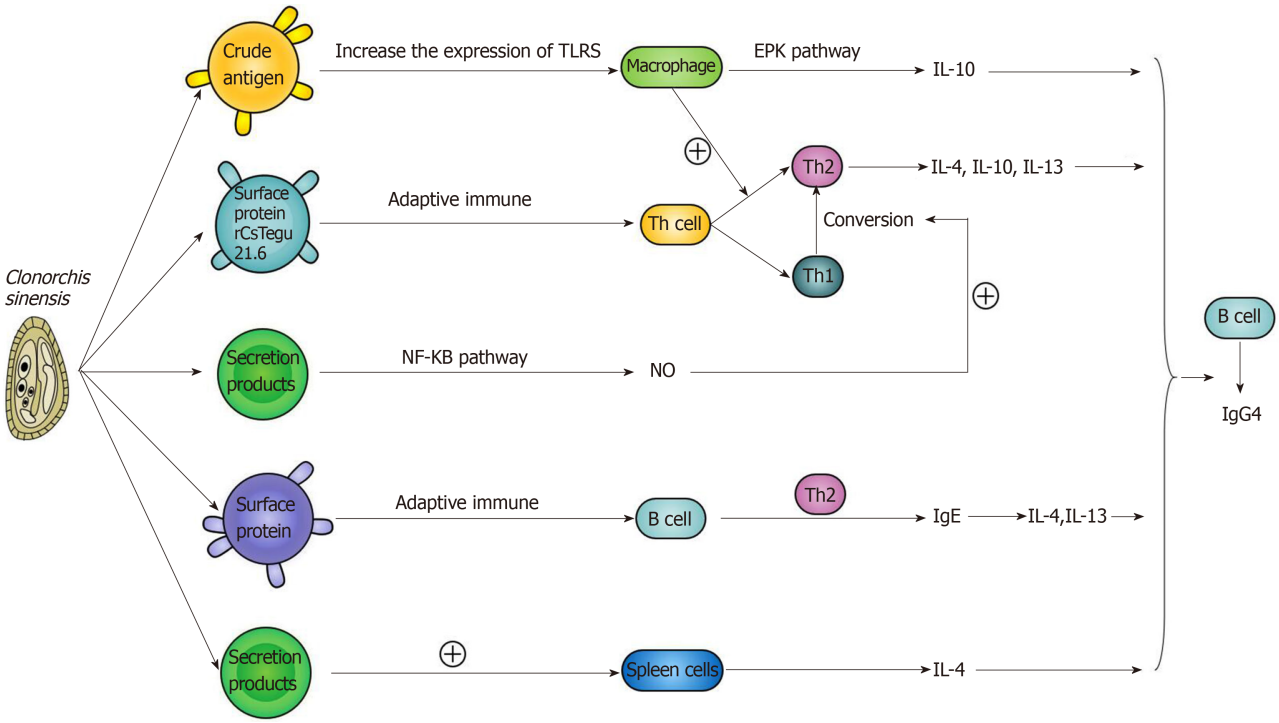

Figure 6 The related mechanisms between *Clonorchis sinensis* and immunoglobulin G4. TLRS: Toll-like receptors; EPK: Eukaryotic protein kinase; IL: Interleukin; IgE: Immunoglobulins E; NF-kB: Nuclear factor kappa B.

chlorpromazine, haloperidol, and clozapine) can also be considered as new anthelmintics. For complications such as upper cholangitis, which may require biliary drainage or surgery, cholecystitis may require cholecystectomy.

PREVENTION

Among strategies to prevent infectious diseases, vaccination is the most effective. However, there is still no effective vaccine to prevent the disease examined in this paper. Bai *et al*[84] found that vaccination with the CsAg17 protein and cDNA can reduce the pathological changes of the bile duct and liver and reduce the burden of worms through cellular and humoral immune responses. Therefore, the *CsAg17* gene and its products can be used as an effective candidate vaccine against *Clonorchis sinensis*, which furthers our understanding of the prevention and control of liver flukes, and more studies are needed to confirm this hypothesis in the future. Therefore, the current prevention strategy is mainly a comprehensive strategy of health education and health promotion, environmental reconstruction, and chemotherapy[81]. Health education should be carried out in endemic areas, people should consciously refrain from eating raw and undercooked shrimp, and dogs and cats should not be fed raw fish or raw fish offal. More attention should be paid to the safety of freshwater fish, the infection rate and distribution of freshwater fish should be investigated in endemic areas, and infected ponds should be monitored. In addition, sanitary toilets should be built with harmless treatments, manure management should be strengthened, and untreated feces should not be emptied into fishponds or water sources[18].

CONCLUSION

Due to the widespread distribution of intermediate hosts and human eating habits, *Clonorchis sinensis* infection is still common. The detection of *Clonorchis sinensis* eggs in feces and bile is still the only gold standard for the diagnosis of *Clonorchis sinensis* infection, and new detection methods are needed to improve the detection rate. There is an urgent need for effective and systematic prevention strategies to increase human awareness and prevent *Clonorchis sinensis* infection. In addition, the increase in IgG4

caused by *Clonorchis sinensis* infection is rare, which may be related to the inflammatory factors IL-4, IL-10, and IL-13 produced by human phagocytes, T cells, B cells, and other immune cells in the process of resisting the invasion of *Clonorchis sinensis*. However, this finding still needs further clarification and confirmation.

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