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Review

The chronic enteropathogenic disease schistosomiasis

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SUMMARY

Schistosomiasis is a chronic enteropathogenic disease caused by blood flukes of the genus *Schistosoma*. The disease afflicts approximately 240 million individuals globally, causing approximately 70 million disability-adjusted life years lost. Chronic infections with morbidity and mortality occur as a result of granuloma formation in the intestine, liver, or in the case of *Schistosoma haematobium*, the bladder. Various methods are utilized to diagnose and evaluate liver fibrosis due to schistosomiasis. Liver biopsy is still considered the gold standard, but it is invasive. Diagnostic imaging has proven to be an invaluable method in assessing hepatic morbidity in the hospital setting, but has practical limitations in the field. The potential of non-invasive biological markers, serum antibodies, cytokines, and circulating host microRNAs to diagnose hepatic fibrosis is presently undergoing evaluation. This review provides an update on the recent advances made with respect to gastrointestinal disease associated with chronic schistosomiasis.

1. Introduction

Schistosomiasis (bilharzia) is a chronic enteropathogenic disease caused by blood flukes of the genus *Schistosoma*.[1] It affects approximately 240 million people and is considered the third most devastating tropical disease in Africa, South America, the Caribbean, the Middle East, and Asia.[2–4] More than 78 countries are affected, and nearly 800 million people are at risk of infection.[3,4] Of the five species that infect humans, *Schistosoma mansoni*, *Schistosoma haematobium*, and *Schistosoma japonicum* cause the most morbidity.[3,5] The disease burden due to these three species is estimated to be as high as 29 million disability-adjusted life years (DALYs).[6]

The lifecycles of the five schistosome species are similar and involve a snail intermediate host (Figure 1). Chronic infections with all *Schistosoma* species, with the exception of *S. haematobium*, can cause significant morbidity and mortality as a result of granuloma formation in the intestine and liver.[7] However, cases of liver[8] and intestinal disease[9] from *S. haematobium* have also been reported. This review emphasizes the pathogenesis of the intestinal and hepatosplenic forms of the disease – the major causes of morbidity in schistosomiasis mansoni and japonica. The evaluation of hepatic fibrosis with diagnostic imaging and the performance of different direct serum biomarkers and potential use of circulating microRNAs (miRNAs) for disease staging and predicting the risk of hepatic fibrosis are also discussed.

2. Chronic schistosomiasis

2.1. Intestinal disease

One of the common manifestations of the chronic form of this enteropathogenic disease is intestinal schistosomiasis. The infection is caused by *S. mansoni*, *S. japonicum*, *S. mekongi*, and *S.*

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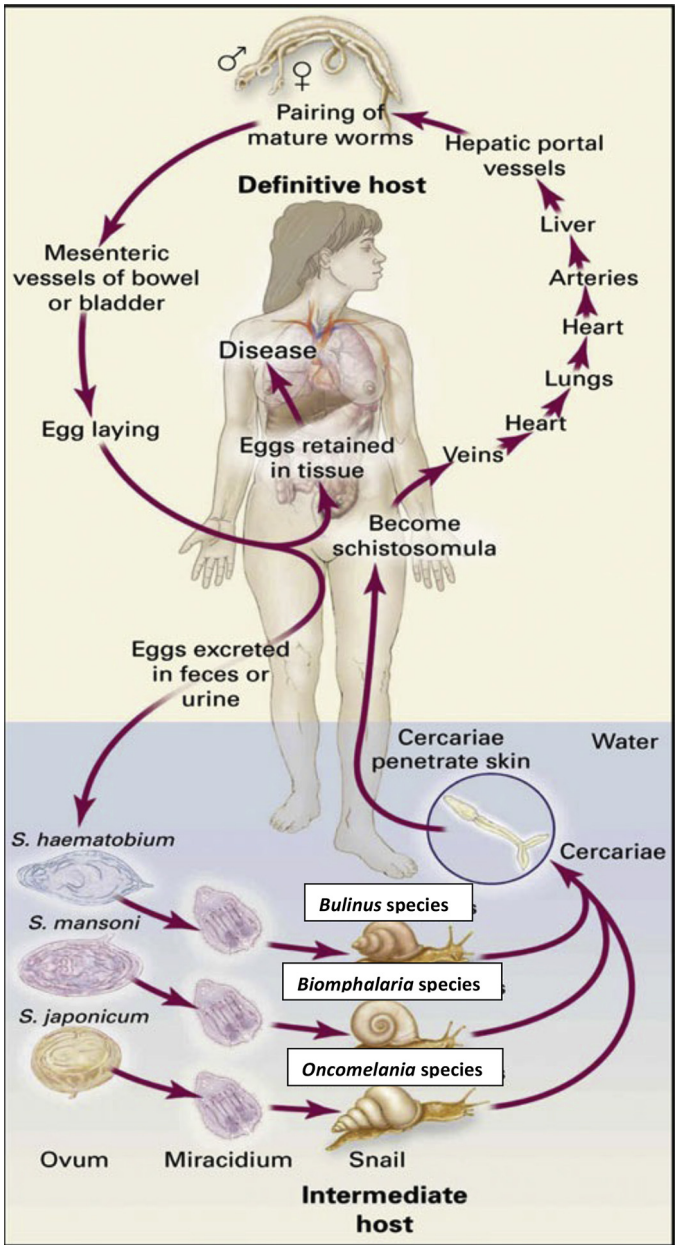

Figure 1. Schistosome lifecycle (Ross AG, McManus DP, Farrar J, Hunstman RJ, Gray DJ, Li YS, et al. Neuroschistosomiasis. J Neurol 2012; 259:22–32).

intercalatum.[10] Some cases of *S. haematobium* and *S. guineensis* infection have also been reported.[11,12] The pathology associated with intestinal schistosomiasis is due to egg deposition and granuloma formation, which eventually leads to acute then chronic schistosomal colitis and polyp formation.[13] Although areas in both the small and large intestine may be involved, most severe lesions are found in the large intestine. It is theorized that the adult worms have a tendency to inhabit the branches of the inferior mesenteric vein and superior hemorrhoidal vein; hence, more eggs are deposited in the large intestine, especially in the rectum, sigmoid, and descending colon.[14]

Ova are generally distributed in the loose submucosa of the large intestine and to a lesser extent in the subserosa. The muscularis mucosa subsequently becomes involved, and the underlying mucosa may either undergo hyperplastic changes or be denuded and form small superficial ulcers. When the submucosa becomes heavily thickened with fibrous tissue containing massive amounts of calcified eggs, atrophy of the overlying mucosa ensues and it acquires a granular dirty yellowish appearance.[15] Polyps, which are said to be the most common among the spectrum of intestinal lesions,[16] may result from an immune-mediated inflammatory process associated with continued egg deposition[17] and ova entrapment leading to a foreign body reaction with progressive inflammation and fibrosis. Schistosomal eggs are deposited in the superficial layers of the submucosa where reactive cellular debris and vascular granulation tissue accumulate. Eggs will then produce a cell-mediated inflammatory response with granuloma formation and necrosis. The subsequent healing of the necrotic foci will lead to the formation of fibrous connective tissue and hypertrophy of the muscularis mucosa. The fibrous connective tissue in the submucosa and the hypertrophied muscularis mucosa form a barrier to the ova transiting from the mesenteric veins to the gut lumen. The trapped ova then elicit further inflammation and fibrosis. This continuous process elevates the hypertrophied muscularis mucosa to form a nodule which is the earliest detectable polyp.[18]

Clinical manifestations of intestinal schistosomiasis include abdominal pain, altered bowel habits, and bloody stools.[5] Iron-deficiency anemia and eosinophilia are also present.[19] Polyposis from intestinal schistosomiasis does not appear to be related with colorectal carcinoma,[20,21] but a recent study has shown that a history of colonic schistosomiasis japonica is a probable independent risk factor for the development of colorectal neoplasias.[22]

Appendiceal schistosomiasis was first documented in 1909, and the most frequent species associated with this condition are *S. haematobium* and *S. mansoni*. In one case report, schistosomiasis haematobia presented as acute appendicitis in a 26-year-old Israeli male who developed symptoms 2 years after visiting Africa; tissue sections showed extensive inflammatory areas and fibrosed granulomas.[9] This rare condition was also reported recently in a 30-year-old male UK resident from Ghana; histological sections of his appendix revealed luminal pus associated with numerous *S. mansoni* egg masses transmurally and within the subserosal adipose tissue. The usual granulomatous response around the eggs was evident. Eggs in the submucosa produce an obstructive type of appendicitis, while serosal lesions produce inflammation and adhesion formation.[23]

In Saudi Arabia, an unusual case of disseminated peritoneal *S. japonicum* has also been reported in a 32-year-old Filipino female who presented with signs and symptoms of acute appendicitis. However, a right iliac fossa mass was also seen on diagnostic laparoscopy. Microscopic sections of both the appendiceal wall and the adherent omental mass showed suppurative inflammation and multiple foci of schistosomal ova highly indicative of the *S. japonicum* species. Interestingly, a granulomatous response was not seen in the sections examined.[24]

2.2. Hepatosplenic disease

Hepatic schistosomiasis represents the best known form of chronic disease with a wide range of clinical manifestations, and its pathogenesis is related to the host cellular immune response.[13] The mechanisms involved in granuloma formation and fibrosis have been documented extensively in experimental models and humans infected with *S. mansoni* and *S. japonicum*. Eggs trapped in the pre-sinusoidal portal venules secrete soluble egg antigens which are taken up by antigen-presenting cells such as macrophages.[25] Subsequently, antigen presentation stimulates Th1 cells (CD4+ T lymphocytes) to secrete interleukin (IL)-2, interferon gamma (IFN-γ), and tumor necrosis factors (TNF), which in turn drive a cell-mediated response and attract more immune cells around the ova. As the granuloma becomes more organized, the Th1 cells are gradually replaced by Th2 cells, which produce IL-4, IL-5, IL-10, and IL-13, completing granuloma maturation.[26]