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RESEARCH ARTICLE

Insights on the Pathophysiology of the Progression to Decompensated Hepato-Splenic Schistosomiasis

Bernardo Times de Carvalho*[1]

[1]Hospital Oswaldo Cruz

*b.timesc@gmail.com

ABSTRACT

Hepato-splenic schistosomiasis is the most important etiology of non-cirrhotic portal hypertension. It represents a particular type of chronic liver disease, which presents unique characteristics that differentiate it from those found in cirrhosis. The relative preservation of liver parenchyma despite portal fibrosis was thought to yield a more benign course of hepato-splenic schistosomiasis in terms of synthetic dysfunction and late decompensations. However, a wide range of immunologic and vascular modifications is responsible for an otherwise progressive liver disease resulting in decompensated condition frequently undistinguished from hepatic cirrhosis. A predominant Th2 immune response type, in which a fibrogenic profile of cytokines and interleukins such as IL-13, provides an immune-inflammatory background that favors fibrosis and its progression. Intra-hepatic vascular changes with portal vein branch derangement and abnormal vascular proliferation also contribute to continued disarray of the liver architecture resulting in decompensated disease frequently undistinguished from hepatic cirrhosis. This article will review immunologic and pathophysiological aspects of hepato-splenic schistosomiasis that might explain disease progression and severity.

Keywords: Schistosomiasis, portal hypertension, hepatosplenic schistosomiasis.

Introduction

Schistosomiasis is one of the most common causes of noncirrhotic portal hypertension worldwide. Of the three main Schistosoma species, *S. japonicum* and *S. mansoni* are known to cause liver disease[1]. It is considered an endemic infection in 78 countries in Africa, Asia, and Central and South America in places with poor sanitation. Although there is no specific global survey for schistosomiasis, it is estimated that about 200 million people are infected with Schistosoma in Africa, Asia, and South America, 20 million with severe disease, and other 600 million people are at risk of being infected[2–4]. Unlike liver cirrhosis, hepatosplenic schistosomiasis (HSS) has no gross loss of hepatocytes or nodular regeneration. Additionally, portal hypertension due to HSS has an important splenic venous hyper flow component contributing to the remaining preserved underlying hepatic function, and hepatic encephalopathy, ascites, and liver failure are uncommon [5]. Patients with hepatic schistosomiasis usually tolerate episodes of acute variceal bleeding better than patients with cirrhosis because of their preserved liver function.

It was believed that advanced cases of HSS hepatic decompensation with hypoalbuminemia and chronic ascites tended to occur only in patients with coexisting liver diseases such as chronic viral hepatitis B or C virus infection[6–8]. These coexisting liver diseases have been found to aggravate the course of hepatic schistosomiasis, changing its natural history [9]. However, evidence and evolving knowledge of pathophysiology have shown that HSS is a progressive liver disease with significant chances of developing decompensation with all the classical complications of cirrhosis, including hepatocarcinoma, especially with a long-term disease [10–13].

This brief review aims to discuss particularities of HSS in terms of pathophysiology, histopathologic findings, and immunologic events that would explain how HSS would progress to decompensated disease and which are the risk factors associated. In conjunction, it would help the medical community to elaborate clinical strategies better treat and follow those patients with HSS.

Immunologic aspects of Hepato-splenic Schistosomiasis

The human infection occurs when schistosomal cercariae enter the body through the skin. Adult worms eventually find their way to inhabit tributaries of the inferior (*Schistosoma mansoni*) or superior (*Schistosoma japonicum*) mesenteric veins, producing hundreds to thousands of eggs per day for several years before the end of their lifespan [14]. Some eggs pass through the intestinal mucosa and are excreted in the feces to continue their life cycle. About one-third of them falls back into mesenteric circulation towards the liver and impact in small portal branches, causing partial obstruction to portal blood flow [15]. *S. japonicum* can produce far more eggs than *S. mansoni* and thus causes more severe liver disease.

Soluble antigens produced by the larva inside the egg stimulate an immune reaction cascade that culminates in forming a peri-ovular granuloma. Although granuloma formation benefits the host by blocking the hepatotoxic effects of antigens released from parasite eggs, this process may lead to fibrosis with excessive accumulation of collagen and other extracellular matrix proteins in the periportal space [16]. Indeed, T-cell-deprived, nude, severe combined immunodeficiency disease or egg-tolerized mice die earlier than comparably infected immunologically intact mice because they cannot mount a protective granulomatous response. Widespread hepatic damage induced by toxic egg products contributes to the decreased survival of infected immunocompromised mice [17]. Presumably, the chronic detrimental effects associated with granulomas (fibrosis, portal hypertension) represents a better alternative, for the host and parasite, than that of the host dying soon after parasite egg production.

Primarily, the eggs cause a moderate type 1 helper (Th1) immune response to its antigens. However, this usually evolves to a robust and dominant Th2 delayed cell-mediated hypersensitivity response with the recruitment of eosinophils, a granulomatous vascular disease characterized by presinusoidal pylephlebitis and thromboembolism subsequently replaced by progressive fibrosis[18–20]. The balance between Th1 and Th2-type cytokines influences the extent of the pathology and the development of fibrosis detectable inside the granulomas with the subsequent formation of marked portal and peri-lobular fibrosis [20]

The egg granulomata activate antigen-specific CD4 Th-1 and Th-2 cells, inducing the release of specific immunomodulating antifibrogenic (interleukin [IL]-12, interferon [IFN] gamma) and fibrogenic (tumor necrosis factor [TNF] α, IL-4, IL-10, IL-13, transforming growth factor [TGF] β1) cytokines, respectively [19,21]. Most importantly, it has been observed that IL-13, but not IL-4, is the primary type 2 cytokine driving type I and III collagen mRNA production and hepatic fibrosis in infected mice. In the context of the type 1/type 2 cytokine paradigm, data from mice and humans have categorized schistosomiasis as a predominantly type 2 disease [16].

As part of the Th2 immune response branch, some studies have emphasized macrophages' role in the fibrosis mechanism. Macrophages are functionally activated and polarized into either M1 or M2 phenotypes when responding to diverse stimuli. M1 macrophages are shown to be cytotoxic to schistosomula and also play a role in preventing hepatic fibrosis. However, schistosome eggs induce M2 macrophage-rich granulomas, in which M2 macrophages enhance Th2-biased responses and promote the granulomatous and fibrotic development in the liver during the chronic stage [22,23].

Schistosomal egg antigens also stimulate the production of reactive oxygen species (ROS), which contributes to further M2 macrophage differentiation and fibrosis formation [23]. This mechanism was tested *in vivo,* inhibiting ROS production in *S. japonicum* infected mice, which reduced M2 macrophages and Th2 cells, but at the same time increased M1 macrophage and Th1 cells, concomitantly with alleviation of granulomatous inflammation and hepatic fibrosis. These findings suggested ROS's previously unrecognized immunological role in enhancing M2 macrophage differentiation and Th2 responses, leading to immunopathological liver damage in hepatic schistosomiasis [24].

Since hepatic fibrosis results from the inflammation induced by eggs and worm products in the portal spaces, it has been thought that disease development depends on a patient's worm load. However, a wide variety of factors, other than parasite load, can significantly impact fibrosis formation and progression, for instance, duration of infection and host genetic profiles [21,25].

This vast and intricate cascade of immunologic and fibrotic events highlights the considerable importance of the host response. The particular course of the immune reaction, in terms of Th1/Th2 predominance, and the intensity of the response with the amount and pro-fibrotic and pro-inflammatory cytokines would help investigators predict which patients have higher chances of developing an unfavorable course of the disease. Some studies have proposed specific gene locus related to higher titles of IFN-γ and heavier liver fibrosis [21].

Vascular and hemodynamic aspects of Hepato-splenic Schistosomiasis

Added to fibrosis, angiogenesis is an essential step in the pathogenesis of schistosomal lesions. Some authors have suggested that liver fibrosis *per se* usually causes no problems in an organ with such considerable functional reserve as the liver unless the structure being supported by such fibrosis is damaged [26–28]. To them, the development of peri-ovular granuloma determines extensive damage to the hepatoportal vascular system, with inflammatory and fibrovascular reactions of the host, which are the major cause for the obstruction of portal venous flow instead of fibrosis itself. The relevance of liver fibrosis is related to the fact that these changes act as a support for abnormal vascularization. Therefore, intrahepatic vascular derangement, venous and arterial, caused by chronic liver insults are the main background for physiological changes [15,29].

In the formation of peri-ovular granuloma, there is a vascular proliferation that progressively affects the granuloma periphery as it grows by the appearance of fibrosis. When there is a fusion of granulomas, as occurs in periportal fibrosis of advanced disease, small blood vessels proliferate and exhibit a prominent aspect in intergranuloma tissue, assuming an angiomatoid feature. Despite this vascular proliferation, many portal veins are distorted, with thickening of the muscular layer and occluded [15,28,30,31].

Embolization of eggs and distal occlusion of portal branches causes an increase in intrahepatic portal venous pressure, which induces the formation of periportal collaterals in larger diameter vessels, allowing a diversion of the blood flow. With the continuing arrival of eggs, damage to larger caliber veins will occur, with the formation of granulomatous periportal inflammation, inter-granuloma fibrosis, and vascular occlusion, which, in turn, promotes portal hypertension, increasing splenomegaly and portosystemic collaterals [4,15,28]. Another mechanism involves soluble antigens secreted by the worm. These enable physiological changes in intrahepatic portal vasculature, characterized by an increased sensitivity of portal branches to vasoconstrictors such as serotonin and acetylcholine [32]. Coupled with the increased extracellular matrix, vascular contraction increases portal resistance.

Studies of vascularization in plastic models, obtained by injection in different vascular systems - portal vein, hepatic vein, and hepatic artery - of plastic substance with different colors could document the intrahepatic vascular changes in HSS [28,31]. Portal branches are reduced, and the less prominent of the three vascular sectors. Unlike cirrhosis, vascular changes in schistosomiasis affect larger portal branches, with considerable distortion and reduction of small peripheral ones [33]. Portal ramifications of medium and large calibers often have dilatation, tortuosity, and sudden diameter reduction without emitting the terminals rami, with a

network of thin newly formed vessels coming up of the main branches and anastomosing with each other [28,34].

The hepatic veins sector does not show any changes. But the hepatic artery sector shows considerable hyperplasia and hypertrophy with a denser and more tortuous vascular network, especially in the peri-biliary plexus [15,28,31,35,36]. These changes in the hepatic artery bed may be considered compensatory to decreased portal venous perfusion consequent to distortion of the portal venous system by occlusions or amputations of their branches [33]. An intense arterial network grows through venous anastomotic and distorted branches around the thick trunks of portal veins and fills the spaces that lack portal branches.

Thus, total hepatic blood flow remains unchanged. However, this increase in intra-hepatic arterial flow is responsible for a rise in sinusoidal pressure causing a more significant accumulation of collagen fibers within the Disse space. These changes determine the capillarization of hepatic sinusoids and impair the exchange surface between sinusoids and hepatocytes, contributing to episodes of bleeding and decompensated stage of HSS [4,28,31,37]. One of the main physiological disadvantages of hypertrophy of the hepatic artery sector is the hepatic parenchyma dependence on arterial flow. When there are episodes of massive gastrointestinal bleeding – a common complication of HSS – there is liver hypoperfusion because blood flow depends more on the mean arterial pressure. As a consequence of these ischemic insults, areas of hepatic necrosis appear and become focal peripheral post-necrotic scars with the formation of fibrotic septa, isolating nodules indistinguishable in appearance from cirrhosis [38].

Hepatosplenic patients with a history of significant bleeding episodes a few days before dying usually show focal areas of parenchymal necrosis, of variable extension, at necropsy, especially in sub-capsular regions of the liver. It is presumed that such sites would undergo post-necrotic scarring in case the patients survive, with nodular regeneration of the parenchyma delimited by fibrous bands and septa. Such focal "cirrhotic" areas are frequently seen in autopsy or biopsy specimens taken from patients with advanced schistosomiasis [31].

A study using angioscintigraphy to evaluate hepatic perfusion with findings similar to those described in cirrhotic patients [39]. It observed a rise of radioisotope uptake in the arterial phase of hepatic perfusion of patients with HSS. Thus, it is suggested that there is an increased arterial component in the total hepatic flow of the schistosomal liver, similar to what occurs in cirrhosis. This increase would be secondary to the impairment of intrahepatic portal flow caused by a vascular distortion of this sector due to fibro-cicatricial phenomena of schistosomal hepatopathy.

Dynamic studies in animal models also described changes in the arterial circulation of mice livers. Morgan et al. studied an HSS model in hamsters showing that, with the progression of liver disease, there was a significant decline in portal blood flow partially compensated by an increase in arterial flow [40]. Sarin et al., in a murine model of HSS using the radioactive microspheres technique, demonstrated that the decline in the portal flow of infected animals was 61% greater than in healthy animals and observed an increase of two times in arterial inflow of animals with HSS compared to controls [41].

It was observed that the hepatic vein/hepatic artery oxygen gradient is reduced compared to that in normal subjects and cirrhosis. Additionally, studies demonstrated that sinusoidal hypertension in schistosomiasis, as measured by the occluded wedged hepatic vein pressure, is dependent on arterial hypertrophy [42,43]. During surgery for splenectomy, patients with the catheter inside the hepatic vein presented a marked reduction of the elevated hepatic vein pressure when the main trunk of the hepatic artery was digitally compressed. This exact procedure made in a patient without artery hypertrophy did not interfere with the sinusoidal pressure.

At the beginning of infection, the portal resistance is mainly presinusoidal. Hemodynamic studies in patients with hepatic schistosomiasis have demonstrated a hyperdynamic systemic and splanchnic circulation with normal hepatic venous pressure gradient (HVPG) and total hepatic blood flow [14,44,45]. However, as the fibrotic changes in the portal tracts progress, lobular distortion at the sinusoidal level occurs. This increases resistance to portal venous flow, as evidenced by an increased wedged hepatic venous pressure (WHVP) in advanced cases [46].

In the early stages, hepatic perfusion is usually normal or increased paradoxically because of the focal distribution of the inflammation, periportal neovascularization, and compensatory hepatic arterial hypertrophy and flow [47–49]. The hepatic venous pressure gradient is normal and does not reflect true splanchnic hemodynamics and disease severity [47]. With disease progression, compensatory changes become inadequate [33]. A high hepatic venous pressure gradient might suggest sinusoidal involvement or associated viral or alcoholic hepatitis.

Congestive splenomegaly results from an association of portal hypertension, lymphoid hyperplasia, or secondary hypersplenism. Portal hypertension long precedes any change in liver function, with the development of both intrahepatic and extrahepatic shunts [50]. Hemodynamic studies in schistosomal disease reveal a unique hyperdynamic circulatory syndrome characterized by increased cardiac index and decreased peripheral vascular resistance, splenic hyperflow, and reduced mesenteric blood flow, with a mild increase in portal flow compared with the total hepatic blood flow [26,34,51]. There is also elevated intrasplenic and portal venous pressure and a normal or slightly elevated sinusoidal pressure [47].

These vascular events, coupled with the immune and granulomatous response, suggest that HSS is a progressive disorder that could evolve into an advanced and decompensated liver disease, even without a concurrent liver condition. Moreover, the general concept that decompensated *pure* HSS was essentially linked to successive variceal bleeding or a reduction in the portal vein flow after a splenectomy indicated to treat portal hypertension and variceal bleeding[52] may need to be reconsidered. Evolving knowledge points to HSS as an evolutive disease *per se*, requiring time and propitious host background to advance.

Schistosomiasis and Hepatocellular Carcinoma

The association between schistosomiasis and hepatocellular carcinoma (HCC) has been evaluated over the last 40 years in both experimental and clinical studies. The association between *Schistosoma haematobium* and squamous cell carcinoma of the bladder is already well-established [53]. It is speculated that parasitic infections may play a role in carcinogenesis due to changes in the host's inflammatory response. Schistosomiasis has been associated with the development not only of HCC, but also colorectal cancer, prostate cancer and giant follicular lymphomas [54]. It is known that liver schistosomiasis likely potentiates hepatic injury when coinciding with hepatitis B virus and hepatitis C virus (HCV) infections [10,55]. However, some studies have directly linked chronic liver schistosomiasis with carcinogenic pathways related to the development of HCC in animal models [10,56].

Although in the majority of the studies, a concomitant liver disease (chronic viral hepatitis, non-alcoholic hepatitis, or alcoholic liver disease) was present or could not be excluded [11,57], a case series of 6 patients in Brazil demonstrated schistosomiasis to be the solely liver disease associated to HCC [13]. In this study, all six patients underwent liver transplantation, and their whole explanted liver could be analyzed for any concurrent liver disease. Hepatosplenic schistosomiasis was the only liver disease in all of them, however.

Nevertheless, the association between schistosomiasis and HCC is still a subject of debate, and further studies to better clarify this particular topic.

Conclusion

Hepatosplenic schistosomiasis is a neglected disease with high prevalence in African, Asian, and American countries. Considering the number of people affected by the disease and the fact that HSS is the most significant etiology of non-cirrhotic portal hypertension, dedication to its study is of utmost importance. This review discussed several meaningful aspects of HSS to set light on conflicting features of the disease that would change the way investigators and clinicians see it.

Conflict of Interest

The author declares no conflicts of interest.

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