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IMMUNE RESPONSE IN SCHISTOSOMIASIS MANSONIQUE

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Abstract - Introduction: Schistosomiasis is a disease caused by Schistosoma Mansoni, a flatworm that needs two hosts to perpetuate the cycle. This way, it is capable of generating a large inflammatory response in the body, leading to dangerous signs and symptoms that can evolve into a chronic phase or even the death of the infected patient. In this sense, this systematic review aims to understand the way in which the immune system reacts against the disease, and the associated clinical manifestations. Method: A bibliographic review of the "google academic" and "virtual health library" databases was carried out using 18 literatures in the construction of the article. **Discussion:** The pathology caused by Schistosoma Mansoni is mainly characterized by a sequence of chronic lesions formed around the vessels. Throughout the parasite's cycle, due to morphological changes, the lesions tend to worsen, mainly because they are associated with evasion mechanisms against the host's immune system, such as the release of proteases and the formation of immune complexes. Therefore, it is crucial to understand the epidemiology and pathogenesis of the parasite, to better understand the risk factors, mechanism of action, and harm to the host. Conclusion: Given the analyzes carried out, it was possible to observe that schistosomiasis has a very specific epidemiology, affecting mainly regions with low socioeconomic conditions, and together with this context, it was analyzed that having knowledge about the parasite cycle is of great importance to recognize the hosts, stage of the disease and associated clinical manifestations. Thus, it was confirmed that trying to reduce risk zones is essential, but while this is not possible, it is up to health professionals to recognize the signs and symptoms of the disease, to start treatment as soon as possible and have a better prognosis for the infected patient.

Keywords: Schistosomiasis; host-parasite interactions; evasion of the immune response; antigens; epidemiology.

INTRODUCTION

Schistosomiasis, a disease caused by *Schistossoma*, more specifically the species: *S. Mansoni*, arrived in Brazil along with the slave trade from Africa. Since then, it has adapted to the environment thanks to favorable environmental conditions and the presence of its respective intermediate and definitive hosts, snails of the genus Biomphalaria and humans (1). During the history of S. Mansoni in Brazil, it is worth highlighting two important points: the year 1910, in which it was described for the first time in the country by the doctor Pirajá da Silva, and the 1950s, when it was recognized as a disease of the masses and is highlighted as a public health problem (2). This disease is still very present in the Brazilian reality, which recorded a total of 423,117 cases from 2009 to 2019 and with more than 1.5 million people living in endemic areas (3).

Schistosoma is a flatworm that needs two hosts to perpetuate its development cycle. After fertilization of the eggs in the mesenteric venous plexus, the female migrates against the bloodstream and lays eggs in the small vessels of the intestine, undergoing the maturation process for 6 to 7 days (4). Through proteolytic enzymes and the pressure of the eggs arranged in rows, the mature eggs, called "miracids", possessing cilia which allow better movement in the aquatic environment, promote the passage of the capillary to the intestinal lumen where they are eliminated together with the feces (1).

Outside the organism, the eggs continue their development in the intermediate host, the Biomphalaria snails. The entry of the miracidia into the mollusc is facilitated by enzymes released by the terebratorium, a

structure that takes on the shape of a suction cup (1). In this entry process, the miracidium loses its cilia and other structures, releasing the germ cells (sporocyst) for the development of the cercariae (1) (4). Approximately 3 to 5 weeks later, the cercariae, larval stage, are released into the water through vesicles in the snail's integument until they find their definitive host (4). In humans, the cercariae enter the organism through the skin and mucosa through the use of suction cups, resulting in schistosomula, until they reach the circulation and reach the portal system, finishing the maturation process as an adult worm and starting a new cycle (1).

The main countries where schistosomiasis is considered endemic are Africa and Brazil, mainly in the northeast and southeast states (3). Therefore, the transmission of the disease is mainly linked to low socioeconomic status and poor sewage conditions (5). As a result of the biological cycle of Schistosoma, people at greatest risk of contamination are those who are exposed to water contaminated with surroundings, for example, streams where washerwomen work (1).

The symptoms caused by schistosomiasis are, initially, transient skin irritations caused by the entry of the larva into the body. The manifestations that occur during the acute phase of the disease are generic, such as weight loss, diarrhea, general malaise, vomiting, and are not always exuberant, which makes early diagnosis difficult (4). Evolving into the chronic phase, which presents itself in a polymorphic manner, the symptoms are divided into digestive, pulmonary vascular disorders, ectopic lesions, among others, as Schistosomes can travel throughout the body causing different reactions (4). Thus, the objective of this article is to contemplate the role of the immunological reaction in the formation of the pathology of the disease, since the appearance of these symptoms and the evolution of the disease are mainly determined by the quantity of infecting parasites and the organism's reaction to their evasion mechanisms (4).

METHODOLOGY

This article consists of a bibliographic review, in which 18 literatures were used during the production process. The databases consulted for this purpose were: Google Scholar, Virtual Health Library (VHL) in addition to data from the Ministry of Health. The keywords searched were: schistosomiasis; host-parasite interactions; evasion of the immune response; antigens; epidemiology verified using the DECS/MESH descriptors.

DISCUSSION

Schistosomiasis is mainly characterized by a sequence of chronic inflammatory lesions that form around blood vessels due to the presence of eggs or byproducts of the parasite, and occasionally, by dead adult worms (6). Throughout the phases of the evolutionary cycle of S. mansoni in different tissues, the parasite goes through notable morphological and biochemical changes, which function as an evasion strategy against the host's immune system (7). Each stage of this development triggers the activation of immunological mechanisms (7).

Schistosome cercariae also penetrate the body through mucous membranes (4), causing a skin infection that triggers an inflammatory response called cercarial dermatitis. This condition develops after repeated contact with cercariae (8). Symptoms of the disease manifest themselves through a skin rash characterized by spots, papules and vesicles, appearing between 12 and 24 hours after infection (9). In patients who manifest clinical symptoms of dermatitis, the parasites are destroyed soon after penetrating the skin, thus constituting a barrier for the organism (8). Playing a crucial

role in enhancing the inflammatory response, several immunocompetent helper cells act as sentinels in this area, being a vital source of cytokines and chemokines (10). IL-12 stands out, which plays a significant role in promoting the TH1-type immune response in the first 14 days (10).

In the stratum corneum, surviving cercariae go through an incubation period, transforming into immature forms of the parasite called schistosomula (11). These schistosomula are then released into the bloodstream (11). Migrating to the lungs in the first few days, they can subsequently be found in the blood vessels of the liver and the intrahepatic portal system, where they reach maturity to become adult parasites (4). The adult parasite, in turn, employs strategies to escape the liver's specific immune response, incorporating host antigens into its tegument, such as glycolipids from the ABO blood groups and products from MHC classes I and II (12). Interacting with the complement system and immunoglobulins, the secretion products released by the adult worm contain antigens that are deposited in the tissues (1). These antigens act as camouflage on the external surface of the parasite, having the ability to regenerate the damaged integument through the action of the complement system. These interactions trigger inflammatory reactions, resulting in damage to surrounding tissues (1).

There are also ectopic forms of schistosomiasis, which goes through processes different from those already mentioned, occurring when the presence of the parasitic element is located outside the portocaval system, with neuroschistosomiasis being important, which is the most frequent and most serious form. It is believed that there are three ways in which eggs can find their way to the central nervous system: their dissemination through the arterial network, migration through arteriovenous connections and deposition of eggs there. (4).

S. mansoni can be considered a helminth extremely adapted to humans, having developed several escape mechanisms, including: attachment of antigens from the vertebrate host to the plasma membrane itself to hinder recognition, production and release of proteases, production of immune complexes and occurrence of fibrosis (4).

The laying of adult worms occurs approximately 30 days after their arrival in the portal circulation, and a few days later, eggs are already found in the feces (11). Within the scope of the inflammatory process triggered by Schistosoma mansoni, the characteristic lesion induces a granulomatous response around the eggs. (13). The antigens, predominantly released by the internal membrane of the mature egg, known as the Von Lichtenberg envelope, will trigger both a humoral and cellular immune response to form the granuloma (1). The response is mediated by CD4+ T cells, and granulomas consist of collagen and cells, including lymphocytes, macrophages, and eosinophils (13).

Antigens from S. mansoni eggs trigger, in subsequent phases, a modification in the host's initial response pattern, originally characterized as Th1 type and mediated by CD4+ T lymphocytes (12). This transition to a predominantly Th2 response is facilitated by the presence of IL-10. The Th2 response manifests itself in the production of several cytokines, such as IL-4, IL-5, IL-10 and IL-13 (12). Although IL-13 is associated with fibrogenic stimulation and plays a role in the progression of lesions and disease, a balanced immune response between Th2 and Th1 types results in granulomas with less fibrosis (12).

Granulomas go through three distinct phases during their development. Initially, there is a phase in which a zone of necrosis

forms around the egg, which is later surrounded by the deposition of eosinophilic material (1). Then, the repair phase of the necrotic area begins, and finally, the fibrosis phase occurs, resulting in the formation of a nodule (1). Currently, periportal fibrosis (PPF) stands out as the main global cause of morbidity and mortality, influenced by several factors (14). This granulomatous phenomenon, which culminates in the accumulation of fibrotic tissue, is a consequence of chronic liver damage associated with the accumulation of extracellular matrix elements (14). The subsequent development of presinusoidal intrahepatic portal hypertension emerges as part of this process (14). This complication, generally asymptomatic, manifests itself through signs and symptoms arising from underlying conditions.

Frequently observed, hypertrophy of the hepatic artery increases the vulnerability of the tissue to the drop in systemic pressure, resulting in ischemic focal necrosis and a decrease in the oxygen gradient between the hepatic artery and the portal vein (15). During infection, liver cells, Küpffer cells, sinusoids and lobules do not suffer directly from this process, but face the consequences of disturbances in portal circulation (12).

Three fundamental conditions linked to schistosomiasis include gastroesophageal varices, ascites and hypersplenism. Complications such as bleeding in the digestive tract, caused by the rupture of varicose veins in the esophagus, play a crucial role in the mortality rate associated with this disease. (16).

Schistosomiasis mansoni infection triggers a complex liver disease, evidenced by inflammatory lesions in the branches of the intrahepatic portal system and the formation of granulomas around worm residues and/or Schistosoma eggs (15). Initial lesions reveal inflammatory foci with a predominance of eosinophils over neutrophils. As the infection progresses, lymphocytic infiltrates in the portal vasculature and hepatocyte necrosis become more evident (17).

In the intermediate stage, the presence of focal endophlebitis stands out, devoid of centrilobular endophlebitis, together with a plasma cell infiltrate, zonal necrosis of hepatocytes and Radman bodies. In necrotic areas, the uniformly acidophilic hepatic cytoplasm and pyknotic nuclei are notable, in addition to the reduction of hepatic glycogen in these foci (17).

In advanced stages, cicatricial pseudotuberculosis develops, with emphasis on the presence of portal fibrous bridges and amyloidosis (17). The diagnosis of advanced schistosomiasis includes a characteristic liver involvement, described as a fibrous thickening in the portal spaces, radiating into a long, thin septal fibrosis (18). This microscopic lesion shows varying degrees of inflammation, destruction and obstruction in the infrahepatic portal branches, in addition to granulomas around the parasite eggs (18).

Investigations into hepatic granulomas in hamsters caused by S. mansoni indicate that these granulomas are recognized by the presence of epithelioid cells that harbor mature and degenerated eggs, configuring a type of granuloma associated with a diverse inflammatory response (17). Compared to other species of schistosome, the occurrence of neutrophils is less common, and a small central necrosis, the absence of the Hóeppli phenomenon, rare cases of peripheral bleeding and edema are observed. These characteristics highlight the complexity of the liver's reaction to Schistosoma mansoni infection. (17).

CONCLUSION

Through this work, it was possible to understand that schistosomiasis caused by Schistosoma, mainly of the species S. Mansoni, has an important history and epidemiology, as it adapts according to environments and hosts favorable for development, and in Brazil, it has a higher prevalence in the Southeast and Northeast regions as it is directly related to low socioeconomic conditions. Therefore, it is considered a public health problem and needs to be addressed.

Along with epidemiology, knowing the cycle is important, as this differentiates between definitive and intermediate hosts, understands the pathophysiology with the immune response presented by the host, and makes association with the clinical picture, its manifestations and main complications.

Symptoms have a lot to be studied, mainly to distinguish the acute (generic) from the chronic (more specific, such as digestive and vascular) symptoms and thus, associate them with better prognoses and potential treatments.

Thus, it was seen that it is extremely necessary to reduce risk zones and endemic regions in Brazil, in order to reduce the number of cases of the disease. While this future is distant, it is necessary that people, with emphasis on health professionals, have knowledge about the manifestations and dangers of the disease, so that infected patients receive the best possible treatment, aiming to prevent the chronicity of cases and achieve the well-being of everyone, especially those who have a low socioeconomic status and are at risk of infection on a daily basis.

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