SCHISTOSOMIASIS: REVIEW OF AN IMMUNE COMPLEX DISEASE

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ABSTRACT

BACKGROUND: Morbidity due to human schistosomiasis is associated with host immune responses which result in immune based inflammation, granuloma formation and fibrotic lesions.

MATERIALS AND METHODS: This is a review of the literature on the immunology of schistosomiasis and the description of the immunopathogenesis of the disease. Relevant articles were retrieved using electronic search and hand search of published literature.

RESULTS: Host responses which include immune based inflammation, granuloma formation and fibrotic lesions are aimed at destroying schistosome ova lodged in the liver, intestinal and bladder walls, and other tissues. At the site of the infection, 'swimmers' itch is due to physical damage to the skin by proteases and other toxic substances secreted by cercaria. During intestinal Schistosomiasis, the parasitic ova are lodged in the liver provoking fibrogenesis, while during urinary schistosomiasis pathology is attributed to the formation of granuloma along the urinary tract, there is fibrosis which lead to strictures, calcification and urodynamic abnormalities. The classic descriptions of schistosomiasis-related morbidity focus on pathologies unique to schistosome infection: periportal fibrosis for intestinal schistosomiasis and bladder deformity and hydronephrosis for urogenital schistosomiasis.

CONCLUSION: This review provides some useful information concerning some aspects of the relationships between Schistosoma species and the human host.

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INTRODUCTION

Schistosomiasis is a cause of significant parasitic morbidity and mortality in endemic countries. It is also known as bilharziasis after Theodor Bilharz who discovered the causative agent in Egypt in 1851. The disease has a relatively low mortality but high morbidity; causing severe debilitating illness in millions of people. It is caused by an infection with *Schistosoma* species of helminthic flat worms known as flukes belonging to the class *Trematoda* of the phylum *Platyhelminthes* [1]. The parasite afflict at least 243 million people [2, 3]

Most infections are subclinical but may progress to chronic forms characterized by the presence of liver, intestinal and kidney involvement[4].

Schistosoma parasites display considerable biodiversity in habitat[5] there are two major forms of schistosomiasis: intestinal caused by four main species *S.mansoni, S.japonicum, S. mekongi, S. guineensis* and *S. intercalatum* while urogenital form of the disease is caused by *S. haematobium*[1,4]

METHODS

Information for this review were from the comprehensive search of titles related to the immunology of schistosomiasis using PUBMED and other bibliographic data bases between 1985 and 2016 using key words, immunology, immunopathogenesis, epidemiologic trends and pathology of schistosomiasis. Relevant websites such as that of the World Health Organization (WHO) were also searched.

LIFE CYCLE

Infection is initiated by the infectious cercariae which burrow into the skin, transform into schistosomulae and then enter the vasculature, migrate to the portal system where they cross the endothelium and basement membrane of the vein and traverse the intervening tissue, basement membrane and epithelium of the intestine (*S. mansoni, S. japonicum* and other associated species) or bladder (*S. haematobium*). Adult male and female worms mate and produce fertilized eggs in the veins of their human hosts where they live for an average of between 3-19 years, with longevity records that extend for several decades.[6,7]

After a period of about 5-7 weeks the parasite matures to egg producing worms[8] and excretion to the exterior begins, the eggs hatch in water releasing free living ciliated miracidium[9]; suitable snail hosts are then infected by cercariae where asexual reproduction occurs through mother and daughter sporocyst producing thousands of cercariae which are infectious for humans.

The worms live within the perivesical (*S. haematobium*) or mesenteric (*S.mansoni*; *S.japonicum* and others) venules; they digest erythrocytes obtaining energy by glucose metabolism.[10,11]

The clinical features of human schistosomiasis depend on the species, developmental stage, and site of infection in the body. It comprises three major syndromes: cercarial dermatitis, acute schistosomiasis or katayama fever and chronic fibro-obstructive disease[4]

Epidemiology

Schistosomiasis is an acute and chronic disease caused by parasitic worms of the genus *Schistosoma.*[1]

There are two major forms of schistosomiasis: intestinal and urogenital; two hosts are required for the parasite to complete its life cycle (a vertebrate and a snail host). Snails of the genera *Biomphalaria, Bulinus, Neotricula and Onchomelania* are the principal intermediate hosts for *S. mansoni, S. haematobium, S. mekongi* and *S.japonicum* respectively.[2,5]

The intermediate hosts are more abundant during dry season in the tropics when temperatures are as high as between 48^0-50^0C; and children often go to the streams to reduce the heat of the day and for recreation; [12] this exposes them to infection. People are infected during routine agricultural, domestic and recreational activities which expose them to infection.[13]

The disease is prevalent in tropical and subtropical areas especially poor communities without access to safe drinking water and adequate sanitation.[1]

Transmission occurs when infected people contaminate fresh water with their excreta or urine which contains the eggs of the parasite. The eggs hatch releasing miracidia which infect appropriate snail hosts to continue their life cycle. Asexual reproduction occurs with the emergence of infectious cercariae. Following skin penetration by cercariae, they migrate in the circulation to the liver, develop into male or female, pair up and home to appropriate habitats.

There is no sex predilection to infection both sexes are equally susceptible to schistosomiasis; different local, cultural and social practices may predispose either sex to higher infection.

Immunopathogenesis

The mechanism of pathogenicity of *Schistosoma* is attributable to the antigenic secretions of the parasites which perturbs the immune system of the host; including type I and type IV hypersensitivity reactions.[14]

Life cycle stages of the parasite express several antigens that the host immune system confront [15, 16] the challenges posed stimulate humoral and cellular responses. The life cycle stages which express antigens include juvenile worms, adult worm and egg: penetrating cercariae, migrating schistosomulae, adult worm and eggs produced by the adult worm.[15,16]

There is an overriding differential pattern in the host's immune responses against worm-derived antigens when compared to egg derived antigen.[17] This is seen as early high

level responses to soluble egg antigen (SEA) that decreases as infection becomes chronic.[18, 19, 20]

However responses to soluble worm antigen preparations (SWAP) rises early in the course of infection and continues to be expressed throughout the chronic stage of infection.[21]

During infection with any *Schistosoma* species, chronic disease is the result of the ongoing host response to accumulating tissue-trapped eggs.

In, *S. mansoni* and *S. japonicum* infections, the liver is the principal site that is affected because, many of the eggs are carried by the blood into this organ and the sinusoids are too narrow for the eggs to traverse. This is a dead end for the eggs which eventually die within the tissue. Symmers' fibrosis of the liver which may result in portal hypertension and congestive splenomegaly is the most severe form of intestinal schistosomiasis.[22]

During *S. haematobium* infection, the passage of eggs across the bladder wall causes damage to the organ. The $CD4^+$ T response that is induce by egg antigens orchestrates the development of granulomatous lesions which are composed of collagen fibers and cells which include macrophages, eosinophils and $CD4^+$T cells around individual eggs.[23]

In intestinal schistosomiasis, eggs swept back to the liver in the portal circulation lead to chronic inflammation and fibrosis of the portal triad; eventually resulting in cirrhosis, portal hypertension, splenomegaly and bleeding esophageal varices.[1]

In genitourinary infections, the bladder, lower ureters, seminal vesicles are often involved, less frequently involved are: the vas deferens, prostate and female genital system.[14]

The initial lesions are mucosal granulomas which coalesce to form tubercles, nodules or masses which usually ulcerate. The characteristic clinical presentation is terminal hematuria, usually associated with increased frequency of micturition and dysuria[1]; recurrent bacterial urinary tract infection, obstruction of ureters with the development of hydroureter and hydronephrosis and ultimately renal failure. The bladder mucosa appears pale with granular patches known as 'sandy patches' which are characteristic of healed schistosomiasis.[14]

Schistosoma granuloma is the typical 'unit' of the cellular immune response to schistosomal infecton[14] It is composed of different blood and tissue cells being recruited by specific chemo-attractants and serving specific function and; although this is cellular in nature, the role of antibodies and complement has been documented in experimental models for decades.[24]

Local tissue injury resulting from passage of parasite eggs through the walls of the intestine to the bowel lumen is associated with abdominal pain and bloody stool in intestinal schistosomiasis and; the passage of parasite eggs through the urinary bladder wall, to the bladder lumen resulting in bloody urine in genito-urinary schistosomiasis.[1]

Circulating immune complexes have been reported to be involved in the pathogenesis of human schistosomiasis).[25] Granular basement membrane deposits, immunoglobulin, compliments and parasite antigens have been demonstrated in the renal glomeruli of patients with chronic schistosomiasis.[24]

Chronic schistosomiasis is the consequence of parasite eggs trapped in tissues, with resulting granulomatous reaction to the eggs.[1]

Schistosoma parasites flourish in the human host despite the development of a pronounced immune response. This suggests that the immune response is incapable of preventing primary infection and; resistance to superinfection takes years to develop.[26] It has been observed that the development of acquired immunity to human schistosomiasis is extremely slow;[27,28] due to the following hypotheses: i) that dying worms are the main source of protective antigen which is delayed by the long parasite lifespan;[29] ii) exposure to certain threshold level of antigen is required before protective response is stimulated.[30]

Despite the long time to taken to develop some degree of protective immunity, it rarely results in sterile immunity.[27]

In acute schistosomiasis, after initial infection with *S.mansoni*, *S.japonicum* or *S. haematobium*, a serious illness accompanied by high fever (Katayama fever) may be seen.

This is due to the release of soluble parasite antigen into the circulation as the worms mature and begins to release eggs.[1]

Katayama fever is commonly associated with S.japonicum infection and is probably due to larger number of eggs released by the species. The onset of symptoms is about 20-40 days after exposure. This fever is less common in *S.mansoni* and rare with *S. haematobium*

CONCLUSION

This review is summary of the immunology of schistosomiasis which reflects the pathogenesis of the disease in humans. Host immune responses to the various developmental stages of the parasite produce cell mediated responses, granulomatous reaction and fibrosis.

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