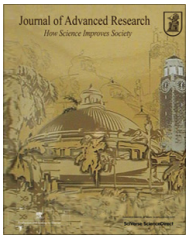
Journal of Advanced Research (2013) 4, 433–444

Cairo University

Journal of Advanced Research



REVIEW

Human Schistosomiasis: Clinical Perspective: Review

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Received 16 June 2012; revised 21 January 2013; accepted 24 January 2013
Available online 3 April 2013

KEYWORDS

Hepatointestinal schistosomiasis;
Urinary schistosomiasis;
Neuroschistosomiasis;
Schistosomal coinfection;
Treatment schistosomiasis

Abstract The clinical manifestations of schistosomiasis pass by acute, sub acute and chronic stages that mirror the immune response to infection. The later includes in succession innate, TH1 and TH2 adaptive stages, with an ultimate establishment of concomitant immunity. Some patients may also develop late complications, or suffer the sequelae of co-infection with other parasites, bacteria or viruses. Acute manifestations are species-independent; occur during the early stages of invasion and migration, where infection-naivety and the host's racial and genetic setting play a major role. Sub acute manifestations occur after maturity of the parasite and settlement in target organs. They are related to the formation of granulomata around eggs or dead worms, primarily in the lower urinary tract with *Schistosoma haematobium*, and the colon and rectum with *Schistosoma mansoni*, *Schistosoma japonicum*, *Schistosoma intercalatum* and *Schistosoma mekongi* infection. Secondary manifestations during this stage may occur in the kidneys, liver, lungs or other ectopic sites. Chronic morbidity is attributed to the healing of granulomata by fibrosis and calcification at the sites of oval entrapment, deposition of schistosomal antigen-antibody complexes in the renal glomeruli or the development of secondary amyloidosis. Malignancy may complicate the chronic lesions in the urinary bladder or colon. Co-infection with salmonella or hepatitis viruses B or C may confound the clinical picture of schistosomiasis, while the latter may have a negative impact on the course of other co-infections as malaria, leishmaniasis and HIV. Prevention of schistosomiasis is basically geared around education and periodic mass treatment, an effective vaccine being still experimental. Praziquantel is the drug of choice in the treatment of active infection by any species, with a cure rate of 80%. Other antischistosomal drugs include metrifonate for *S. haematobium*, oxamniquine for *S. mansoni* and Artemether and, possibly, Mirazid for both. Surgical treatment may be needed for fibrotic lesions.

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Peer review under responsibility of Cairo University.

Introduction

Genus schistosoma (Fig. 1, [1]) is a very well-preserved parasite across millions of years. DNA sequencing suggests that it had originated as a hippo parasite during the Cenozoic era [2]. Over so many decades, it must have been responsible for

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http://dx.doi.org/10.1016/j.jare.2013.01.005

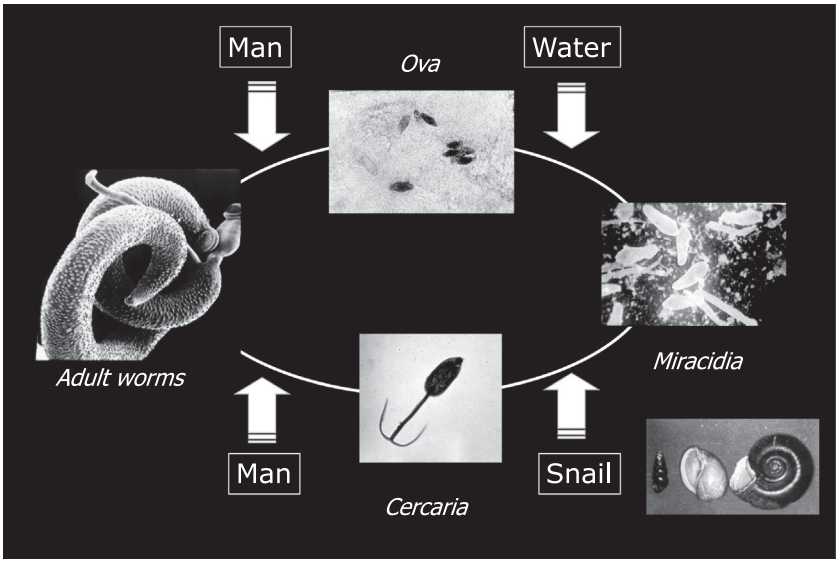

Fig. 1 Life cycle of schistosoma [1] (With permission).

morbidity and mortality of hundreds of million humans in underprivileged communities.

A few decades ago, the World Health Organization had started the implementation of schistosomiasis control programs in nations where the disease was endemic. The outcomes were variable, with complete eradication in certain countries like Japan, and actual increase in disease prevalence in others as certain areas in China [3]. The overall current global prevalence ranges 230–240 millions. (*See Barakat's article on Epidemiology of Schistosomiasis in Egypt in this issue of the Journal*).

Interestingly, despite the ready availability of inexpensive, effective single dose oral treatment, only 33.5 millions received treatment in 2010 [4]. This gap is partly attributed to the relatively low infection-related serious morbidity. While about 60% of infected patients are symptomatic, only 10% have serious disease urging them to seek medical advice. Disease-related mortality is low, amounting to only 200,000 (0.1% of infected patients) per annum, across the globe. Ninety percent of these are inhabitants of sub-Saharan Africa; hence the disease burden is disproportionately high in that part of the world.

Parasitization per se is relatively harmless. Its only clinical manifestations are terminal dysuria, hematuria and occasionally dysentery. Almost all other clinical features of schistosomiasis are caused, directly or indirectly, by the host's immune response to different stages of the parasite's life cycle in the body. Yet this immune response is a double-faced coin, being

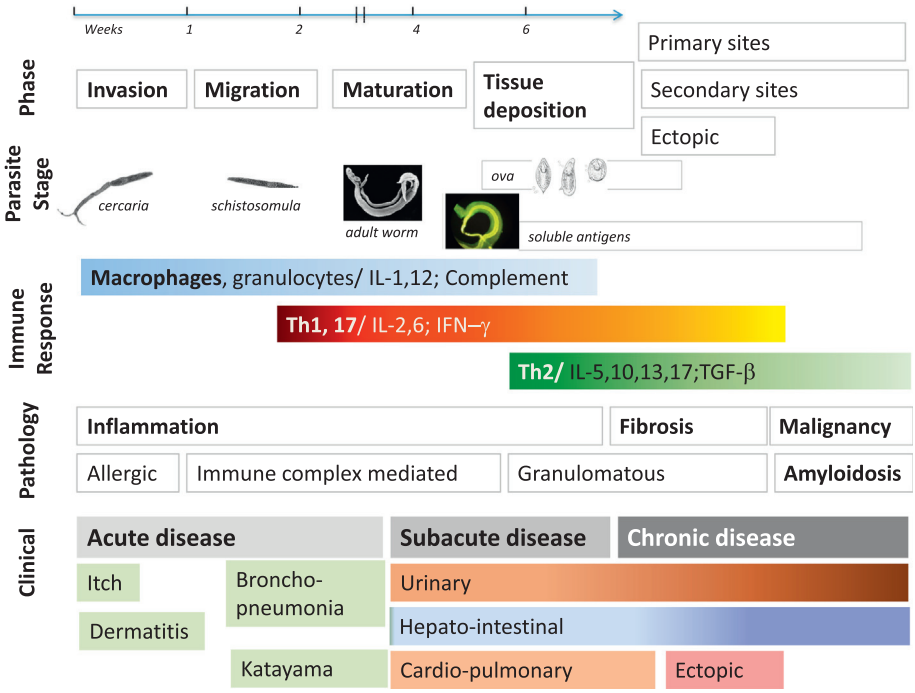

Fig. 2 Broad correlations of schistosomiasis clinical profiles with the progression of the parasite's life cycle *in vivo*, host immune response, and respective pathological lesions.

also crucial for containing the infection, avoiding its dissemination and reducing its pathogenicity. T-cell deficient nude mice experimentally infected with schistosomes die rapidly with massive cercarial tissue invasion [5]. But even competent mammalian immunity fails to completely eradicate schistosomal infection. It can only establish a host-parasite balanced interrelationship that keeps both alive, with reduced parasite's fertility, limited patient morbidity and resistance to re-infection. This status is often referred to as "concomitant immunity".

Therefore, it is not unexpected that the clinical profile of schistosomiasis mirrors the progression of the host's immune response to the process of parasite's maturation (Fig. 2). This concept is very well displayed in the typical clinical syndromes in schistosomiasis, which may be classified under the convenient broad titles acute, sub acute and chronic manifestations, late complications, and the composite sequelae of co-infection with other biological agents including parasites, bacteria and different viri.

Acute manifestations

These coincide with the invasion and migration stages of the parasite's life cycle, during which the immune response is initially innate, confounded a few days later by a TH1-dominant adaptive response. They may occur with any schistosomal species, most prominently *Schistosoma japonicum*. Most reported cases are infection-naïve expatriates, though super infection in previously infected subjects may also lead to pulmonary or systemic acute manifestations [6]. Four acute presentations are recognized:

Swimmer's itch

This is a local inflammatory, hardly visible wheel at the site of cercarial penetration, composed of edema, dilated capillaries and a few cells, attributed to the local release of monokines. The duration and severity of this reaction depend on the length of schistosomular stay in the dermis. Therefore, the lesion is most pronounced in infections with non-human-pathogenic species of the parasite, whose schistosomulae cannot migrate. An Arthus skin reaction has been occasionally described in expatriates acquiring infection in endemic areas.

Cercarial dermatitis

A temporary itchy maculopapular skin eruption, comprising discrete, 1 cm to 3 cm erythematous raised macules, may develop at the site of percutaneous penetration by schistosomal cercariae. Although pathogenetically similar to the "swimmers itch", this visible reaction develops in sensitized people when they are re-infected by schistosomal species that do not colonize in humans [7].

Bronchopneumonia

Bronchial hyper-reactivity with radiologically demonstrable pulmonary infiltrates may occur during the migration of schistosomulae through the pulmonary capillaries [8]. It is attributed to monokines and the TH1 cytokines that start to confound the immune response. It may also occur with superinfection in previously infected people [6]. Rebound epidemics have been reported in Chinese endemic communities exposed to floods [9].

Katayama syndrome

This is a delayed hypersensitivity reaction that may occur 4–8 weeks after infection, coinciding with worm maturity [6]. The supervening immune response profile is TH1 dominated. The syndrome is characterized by fever, arthralgia and vasculitic skin eruption. Eosinophila and high serum IgM are typical. Cryoglobulinemia has occasionally been described. Most patients recover spontaneously after 2–10 weeks, but some develop persistent and more serious disease with weight loss, dyspnoea, and diarrhoea, diffuse abdominal pain, toxaemia, hepatosplenomegaly and widespread rash. It can evolve rapidly to hepatic fibrosis, splenomegaly and portal hypertension [10].

Sub acute manifestations

The early clinical manifestations of established schistosomal infection are dominated by sub acute inflammatory lesions in certain organs, attributed to a supervening TH1 pro-inflammatory immune reaction, in concert with a building up TH2 response. The lesions are species- and organ-specific and depend on the provocative antigens, whether locally released from deposited eggs [11] or circulating upon regurgitation of adult worm gut juices [12]. The former lead to a granulomatous, predominantly cell-mediated inflammation in affected organs, while the latter lead to predominantly antibody-mediated glomerulonephritis.

Granulomatous lesions

Since the main target of the parasite is to expel its ova to the external environment in order to maintain species survival, the worms lay their eggs as near as possible to the exterior; the urinary bladder in *Schistosoma haematobium* infection and the distal colon and rectum in *Schistosoma mansoni*, *S. japonicum*, *Schistosoma intercalatum* and *Schistosoma mekongi* infections. These sites, therefore, are those of the earliest and worst pathology, hence the term "primary targets". These lesions spell over into "secondary targets" by different mechanisms. The upper urinary tract may be involved as a result of obstruction or reflux at the uretero-vesical junctions. The liver is usually involved as a result of drifting ova with the portal blood stream. The lungs may be a secondary target as ova are driven with the blood circulation, having reached the vena cava through even the normal porto-systemic anastomoses. Occasionally, ova may also reach ectopic sites as the brain, spinal cord, genital organs, skin or eyes, always through respective venous anastomoses with the inferior vena cava. Schistosomal granlomata are formed around deposited ova in all these sites, leading to a succession of sub acute and chronic lesions and clinical manifestations.

Primary targets

Lower urinary

S. haematobium infection typically involves the bladder, lower ureters, seminal vesicles, and, less frequently, the vas deferens,

prostate, and the female genital system. The adult worms live in the peri-vesical venous plexus, to which they had migrated earlier on via the porto-systemic anastomosis at the level of the third lumbar vertebra. The females travel to the bladder wall driven by the oxygen gradient generated by its urinary content. There they lay their eggs with the terminal spikes directed towards the bladder lumen, to facilitate extrusion during detrusor contraction. Eggs that fail in getting their freedom remain trapped in the bladder wall; it is these, which cause the pathological lesions by releasing their antigens and provoking granuloma formation (Fig. 3, [13]).

Granulomata coalesce to form tubercles, nodules or masses that often ulcerate. The surrounding mucosa is hyperemic. The sub mucosa and muscle layers are also involved in the inflammatory process.

The characteristic clinical presentation is terminal hematuria, usually associated with increased frequency of micturition and dysuria. In endemic areas, hematuria is the red flag of schistosomiasis in children aged 5–10 years, sometimes confused with menstruation in girls and even a coming of age in boys. Typically, blood is first seen in the terminal urine, but in severe cases the whole urine sample can be dark colored. In a large cross sectional study on an un-treated African population infected with *S. haematobium*, microhematuria was reported in 41–100%, gross hematuria in 0–97% [14].

Colorectal

This region is targeted in *S. mansoni*, *S. japonicum*, *S. mekongi* and *S. intercalatum* infections. Adult worms live in the portal vein and its tributaries, notably the inferior mesenteric vein, to which they migrate against the blood stream after prior maturation in the hepatic sinusoids. The worms choose the portal rather than the systemic veins owing to the former's higher content of oxygen and nutrients. Like with *S. haematobium*, the females travel further against the blood stream towards the distal colon and rectum, driven by an oxygen gradient, to lay their eggs seeking freedom.

All segments of the colon may be affected, yet the rectum, sigmoid and descending colon, the domain of the inferior mesenteric vein, are the main site of pathology in over 90% of cases [15].

Egg deposition in the sub mucosa leads to granuloma formation, congestion, edema and polyp formation (Fig. 4, [16]) and ulceration. These may lead to abdominal cramping, diarrhea which may be bloody, and dysentery. The diagnosis is made by finding schistosoma ova in stools, rectal scrapings, or rectal snips (Fig. 5, [17]). Proctocolonoscopic examination helps to establish the diagnosis, exclude similar lesions including ulcerative and amebic colitis, and to categorize the histopathological patterns.

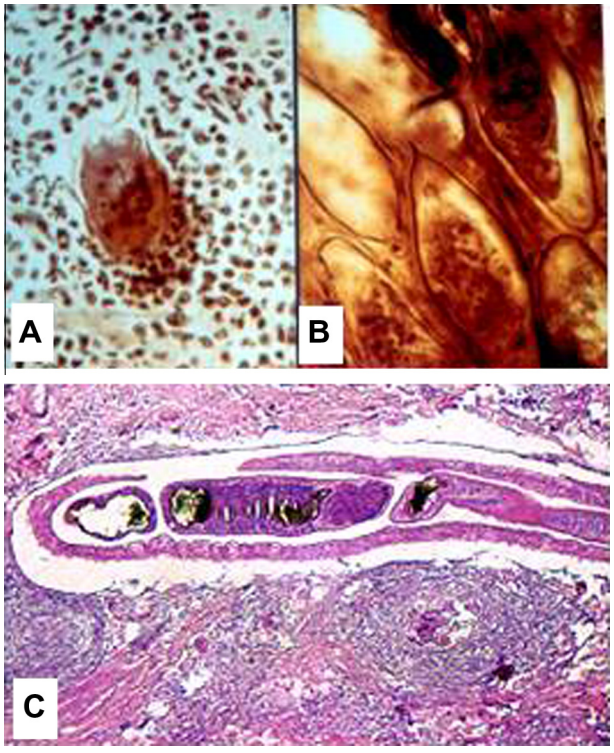

Fig. 3 Basic histopathological lesion in schistosomiasis. (A) Active *S. mansoni* granuloma. Note the central deformed ovum with a lateral spike and the surrounding mononuclear and few polymorphonuclear cells. (B) Sheet of live *S. haematobium* cells. (C) Multiple granulomata around *S. haematobium* worms and egg debris. Note the intact female worm and a coronal section in a male worm in a bladder venule, and the surrounding mononuclear cellular reaction and fibrotic granulomata [13] (With permission).

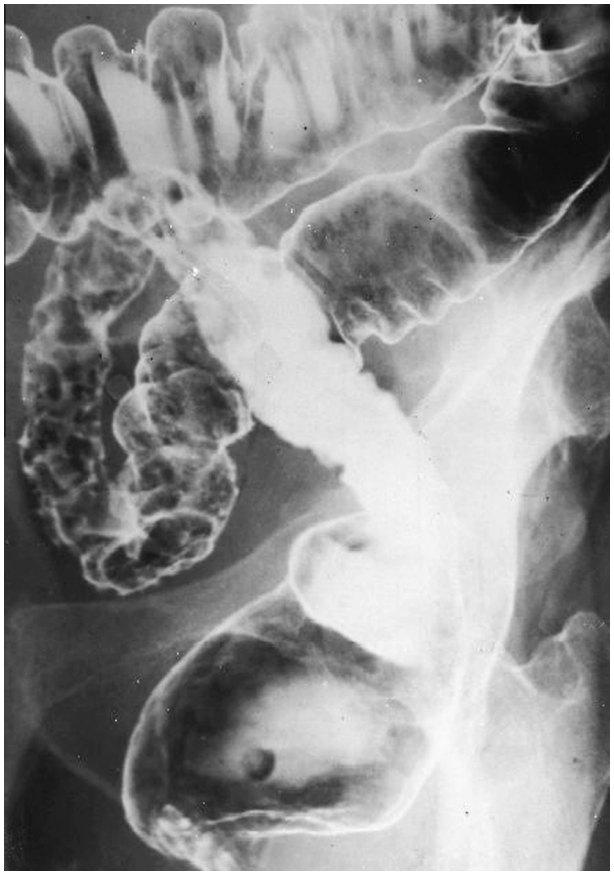

Fig. 4 Schistosomal intestinal polyposis. Extensive granulomas and polyposis of the sigmoid colon and rectum in a Brazilian patient with *Schistosomiasis mansoni* [16].

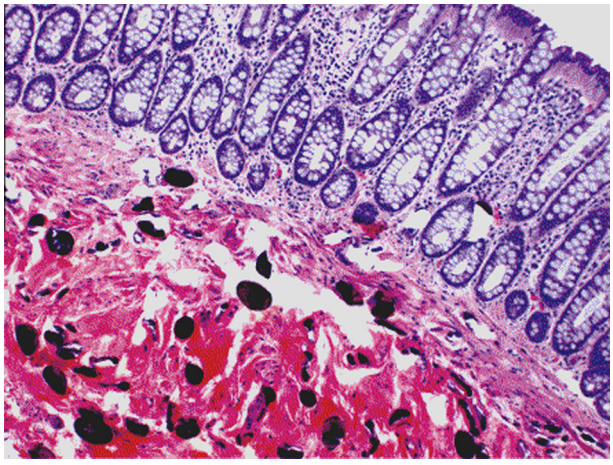

Fig. 5 Calcified schistosomal ova in a rectai biopsy. Normal mucosa overlying sub mucosal layer containing numerous calcified *Schistosoma japonicum* eggs [17].

Secondary targets

Kidneys

The kidneys are rare sites of asymptomatic ectopic granuloma formation. On the other hand, early back pressure due to lower urinary pathology may occur. Radiologically visible lesions in the upper urinary tract were observed in up to 62% of cases in a large series from sub-Saharan Africa. Kidneys function was preserved in most cases [14]. These changes are attributed to oedema of the uretero-vesical junctions, which are close to the area of heaviest oviposition, the trigone. They are spontaneously reversible upon resolution of the inflammatory oedema.

Back pressure changes may persist if the lower ureters are involved in the pathological process, with the formation of granulomata. These are often located in the lower third, and rarely cross beyond the middle. (*See Barsoum's article on Urinary schistosomiasis in this issue of the Journal*).

Liver

Although schistosomulae of all species grow and mature in the hepatic sinusoids, mature worms soon leave the liver as they prefer living and copulating in the more spacious, better oxygenated portal vein. Yet, the organ is notoriously involved later on, as ova are driven by the blood stream to settle in the portal tracts. This is inevitable in the majority of patients with *S. mansoni*, *S. japonicum*, *S. intercalatum* and *S. mekongi* infection. It may also be involved with *S. haematobium* infection as a consequence of the escape of ectopic ova into the portal venous system. Initially, the liver is mildly to moderately enlarged and tender. Unless the disease is complicated by concomitant viral infection (usually HCV or HBV), or associated non-alcoholic steatohepatitis (NASH), tests of hepatocellular function are not significantly affected at this stage. A few weeks to months later, the spleen is also enlarged due to the lymphoid hyperplasia featuring the host's immune response. (*See Elbaz and Esmat's article on Hepatic and Intestinal Schistosomiasis, in this issue of the Journal*).

Ectopic lesions

Organs affected by ectopic granulomata include the central nervous system, genital organs, skin and eyes.

Central nervous system

Ectopic ova gain access to the central nervous system through the anastomosis in between the lumbar veins, which are tributaries of the inferior vena cava, and the internal vertebral venous plexus. They may deposit and provoke granuloma formation in the adjacent spinal cord [18], or travel cephalad during coughing or straining, and impinge into the brain tissue. The small size of *S. japonicum* eggs facilitates their journey towards the brain, hence the preference of this species in cerebral schistosomiasis, including the cortex, subcortical white matter, basal ganglia, and internal capsule. On the other hand, myelopathy of the lumbosacral region is more commonly reported with *S. mansoni* and *S. haematobium* infection [19].

Neuroschistosomiasis is the most severe clinical syndrome associated with schistosomal infection. It includes signs and symptoms of increased intracranial pressure, myelopathy, and radiculopathy. The lesions can evolve to irreversible glial scars if left untreated. Complications of cerebral disease include encephalopathy with headache, visual impairment, delirium, seizures, motor deficit, and ataxia. Spinal symptoms comprise lumbar pain, lower limb radicular pain, muscle weakness, sensory loss, and bladder dysfunction.

Genital

Genital schistosomiasis, due to eggs of *S. haematobium* in the reproductive organs, is quite common but mostly occult in some endemic areas and a regular finding in travellers. Lesions of the ovaries and the fallopian tubes can lead to infertility. In men, hemospermia is a common symptom. The epididymis, testicles, spermatic cord, and prostate can be affected. [20,21]. Symptoms in female patients include hypertrophic and ulcerative lesions of the vulva, vagina, and cervix, which might facilitate sexual transmission of infections. Therefore, women with urinary/genital schistosomiasis are at an increased risk of acquiring HIV infection [22] (see later).

Skin

Skin involvement is rare. The most common sites are genital, where nodular lesions develop in the skin of the scrotum, penis, and vulva. They are usually asymptomatic, being non-tender, non-itchy, and non-ulcerative. Very rarely, similar lesions have been reported to occur around the umbilicus and overlying the scapulae and shoulders.

Eyes

Nodular lesions have also been described in the palpebral conjunctiva in patients with extensive *S. haematobium* disease. However, no effects on the eyeball have been reported.

Sub acute immune-complex mediated disease

Proliferative glomerulonephritis, with schistosomal antigen deposits, has been identified as a manifestation of early *S. haematobium* infection. A unique study was conducted on the inhabitants of an Egyptian village before and after *S. haematobium* was introduced as a consequence of changing the method of agricultural irrigation from seasonal to perennial. Transient proteinuria, hematuria and hypertension were noticed in infected subjects, and renal biopsy showed mesangial proliferation and infiltration with transit pro-inflammatory blood cells. Spontaneous recovery occurred in all patients, but follow

up-biopsy was not reported [23]. Sporadic cases of *S. haematobium*-associated glomerulonephritis have been described later [24].

Similar glomerular lesions were also described with *S. mansoni* infections, though in less dramatic scenarios. In contrast to the haematobium-associated lesions they seem to persist and progress to other forms of glomerulonephritis as described later.

Schistosoma-associated glomerular lesions are significantly modified by concomitant infections. Best known is co-infection with salmonella species, which lead to an exudative glomerulonephritis with sub acute onset of the nephrotic syndrome [25]. More recently, the impact of viral infections, particularly HCV, was recognized as a cause of accelerated glomerular pathology, fibrinoid necrosis and crescent formation [26]. (*See Barsoum's article on Urinary Schistosomiasis, in this issue of the Journal*).

Chronic manifestations

Chronicity in schistosomiasis requires switching of the immune response from a predominantly TH1 pro-inflammatory into a TH2 modulatory profile (Fig. 2). This takes place gradually over several weeks; coinciding with egg deposition, as a result of humoral mediators of parasitic as well as host origin. Inflammatory cells are gradually abolished, being replaced by fibroblasts. Granulomas shrink and may calcify. The pattern of glomerular pathology is changed with more matrix deposition and sclerosis.

Morbidity in schistosomiasis is notoriously much more aggressive upon healing than with active pathology. Therefore, the most serious manifestations of the disease occur many years after infection. They include four categories, namely fibrotic lesions, glomerulonephritis, amyloidosis and malignancy.

Fibrotic lesions

Urinary

Healed schistosomal granulomas are associated with patchy or confluent fibrosis and calcification. This often interrupts the muscular layer of the bladder and ureteric walls, leading to motor abnormalities of bladder function or disruption of the internal vesical or ureterovesical sphincter mechanisms. Diffuse fibrosis may lead to cicatricial contraction in critical sites including the ureter, ureterovesical junction or urethra leading to respective obstructive manifestations, upstream backpressure and ascending infection (Fig. 6, [27]). (*See Barsoum's article on Urinary Schistosomiasis, in this issue of the Journal*).

Hepato-intestinal

Chronic colonic manifestations are categorized into "chronic sub mucosal colitis", and "chronic active sub mucosal colitis". The former is characterized by sub mucosal scarring amidst calcified ova, and may lead to strictures in the left colon or rectum. Active sub mucosal colitis also exhibits signs of active granulomatous inflammation around live ova, with the formation of polyps or nodules. Neoplastic changes were reported in up to one third, with frank malignant changes in 17.4% of Chinese patients referred for colonoscopy [15], but this obviously constitutes a positive selection bias.

Chronic schistosomal colitis is often silent. Some patients may complain of recurrent vague abdominal symptoms, infra-umbilical pain, flatulence or disturbances of bowel habits. Chronic diarrhea or rectal bleeding may mimic ulcerative colitis. An occasional patient may develop a left pericolic mass that may be clinically confused with diverticular disease or malignancy, but the differential diagnosis can be readily resolved by colonoscopy or radio-imaging.

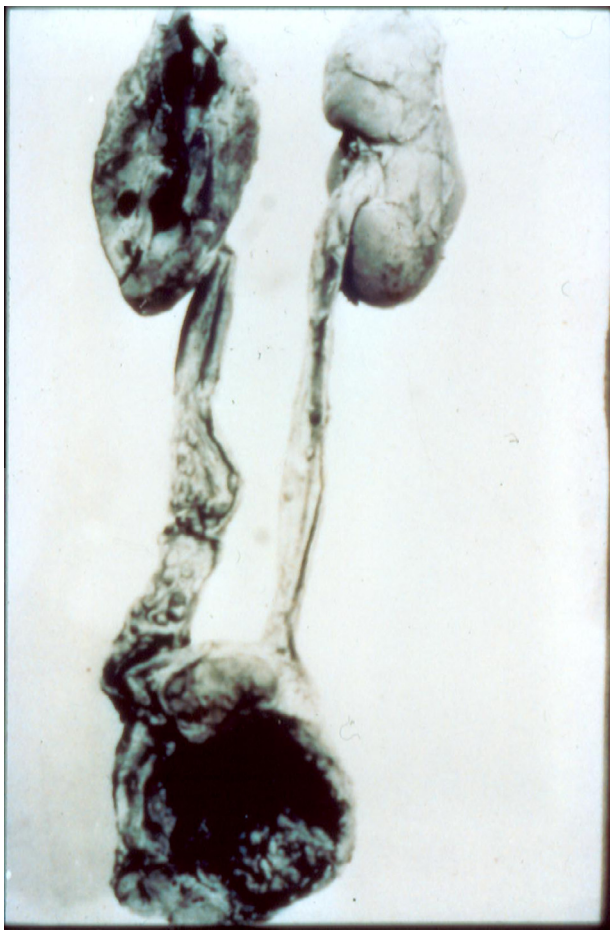

Fig. 6 Advanced urinary schistosomiasis. Post-mortem specimen showing dirty thickening of the bladder wall with a neoplastic growth; dilated right ureter and ureterovesical junction with multiple nodular lesions (ureteritis cystica), bilateral renal scarring with dilated right pelvicalyceal system [27] (With permission).

Chronic hepatic schistosomiasis is far more serious. It affects immunogenetically predisposed young and middle-aged adults [28]. Its severity correlates with the intensity of infection [29]. Histologically, the hepatocytes are spared and the lobular architecture is preserved. The fibrotic, thickened portal tracts appear as "pipe stems" which confer a characteristic histopathological as well as ultrasonographic appearance (Fig. 7). Eventually the liver shrinks, with typical pre-sinusoidal portal hypertension, which manifests by splenomegaly, portosystemic collaterals, and ascites. (*See Elbaz and Esmat's article on Hepatic and Intestinal Schistosomiasis, in this issue of the Journal*).

Cardio-pulmonary

S. haematobium ova may be carried to the right cardiac chambers from the perivesical venous plexus via the inferior vena cava, while *S. mansoni* or *S. japonicum* ova gain access across portosystemic shunts. They usually stop short of the peri-alve-

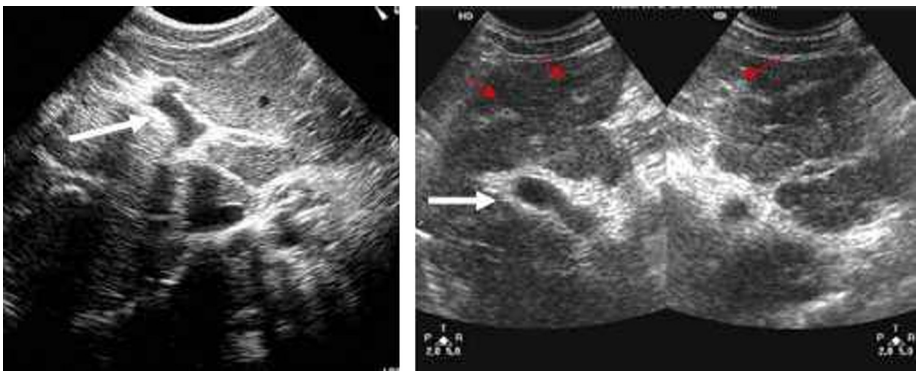

Fig. 7 Schistosomal "pipestem fibrosis". Ultrasonographic images in hepatic schistosomiasis. Note the central periportal fibrosis (white arrow) and fibrosis on the periphery of the liver (red arrows) in a patient with advanced hepatosplenic schistosomiasis [30] (With permission).

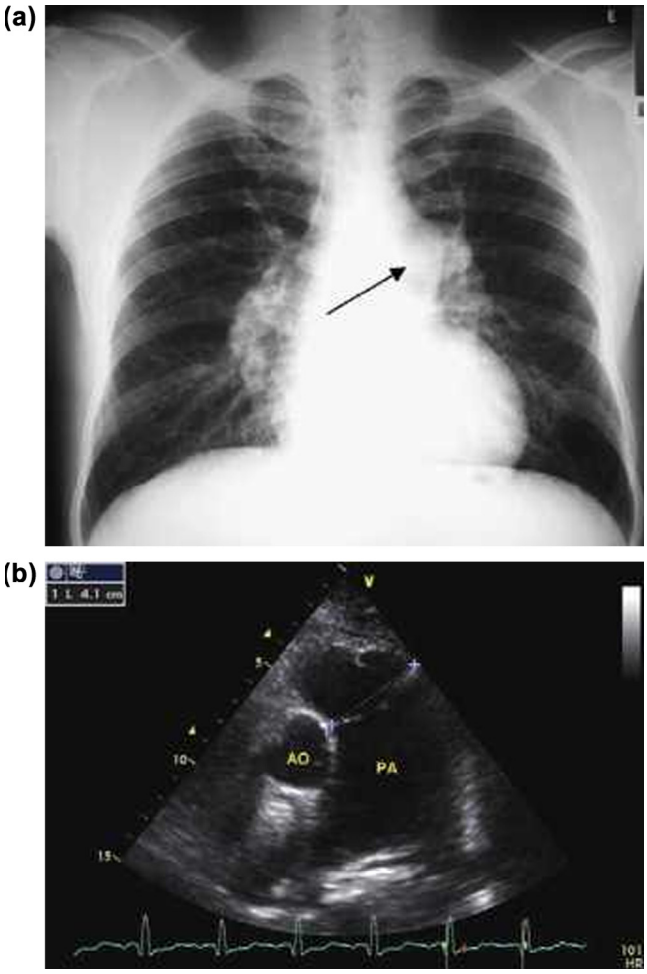

Fig. 8 "Bilharzial" cor pulmonale. (a) Chest X-ray showing signs of pulmonary hypertension (prominent fourth arc – arrow). (b) Ecocardiography in a patient with cor pulmonale in schistosomiasis mansoni: PA = trunk of the pulmonary artery; AO = aorta. In normal people the diameter of the aorta is greater than the trunk of the pulmonary artery. The relation here is inverted (note the diameter between the blue crosses) [30] (With permission).

olar shunts where they lead to granuloma formation and also provoke immune-mediated endothelial proliferation in both pre-and post-alveolar capillaries (Fig. 8, [30,31]).

Obstructive pulmonary hypertension is the morbid physiological expression of these lesions. This is usually asymptomatic, or may be associated with shortness of breath. Cyanosis is unusual since the obstruction is proximal to the level of pre-alveolar shunts; but may occur if peri-bronchial arteriovenous shunts are opened. Clinical examination shows the typical signs of pulmonary dilatation and hypertension. Right ventricular failure, with severe tricuspid incompetence are terminal events.

Owing to the gradually progressive nature of the disease, pulmonary artery dilatation may reach massive dimensions as seen in radiological examination, associated with pulmonary oligemia and right ventricular dilatation and hypertrophy.

Although, at autopsy, *S. haematobium* eggs are found in the lungs twice as frequently as *S. mansoni* ova, the incidence of cor pulmonale in patients with urinary schistosomiasis is much lower compared to the 7.7–18.5% reported in those with hepatosplenic schistosomiasis [32]. It is unclear if *S. haematobium* pulmonary disease is too mild to draw the patient's or physician's attention, or is simply under-reported, considering the selective predominance of haematobiasis in sub-Saharan Africa, where reporting is exceptional. It is noteworthy, though, that the antigenicity of *S. haematobium* is definitely less intense than that of other schistosomal species, which may have a bearing on this observation, as well as on incidence of glomerulonephritis (*See Barsoum's article on Urinary Schistosomiasis, in this issue of the Journal*).

A restrictive pattern of right ventricular dysfunction was observed in some of these patients. Endo-myocardial biopsy showed considerable subendocardial fibrosis, which is thought to represent a diffuse form of the cellular response to schistosomiasis. The specificity of this lesion has yet to be confirmed.

Chronic glomerulonephritis

Further to the early glomerular pathology described under sub acute manifestations, glomerular lesions may progress into mesangiocapillary, focal segmental sclerosis and global sclerosis in 15% of patients with hepato-intestinal schistosomiasis [33]. This issue is addressed in detail in the article on Urinary schistosomiasis in this issue of the Journal.

Amyloidosis

Secondary amyloidosis can be induced by experimental infection with *S. mansoni* and *S. japonicum* in mice [34] and rabbits [35], and with *S. haematobium* in hamsters [36]. It has also been reported in patients with long-standing infection with *S. mansoni*, *S. haematobium*, or both [37]. Co-infection with HCV seems to favor amyloidogenesis due to complex immunological interactions [26]. The lesions were usually restricted to the kidneys, and were associated with the conventional schistosoma-associated glomerular and interstitial lesions. It is believed that schistosoma-associated amyloidosis results from an imbalance in-between the formation and uptake of AA protein by the monocytes and hepatocytes. While synthesis is up-regulated by IL-6, re-uptake is down-regulated by IL-10. The abundance of these particular cytokines in established infection [38] may add up to critically increase the level of circulating Serum A protein in schistosomiasis [39]. Selective deposition in the glomeruli is presumably related to the abundance of amyloidophilic proteoglycans as decorin and biglycan [40].

Malignancy

Schistosomiasis has been associated with the development of malignancy in the bladder [41], rectum [42] and lymphoid tissue [43]; the pathogenic link being most firmly established with the former. In addition, the association of hepatosplenic mansoniasis with hepatitis B or C viral infections increases the risk of liver malignancy and non-Hodgkin lymphomas many folds. It is presumable that the predominant TH2 dominated scenario in late schistosomiasis is largely responsible for increasing the susceptibility to oncogenic provocations.

Bladder

Chronic urinary schistosomiasis is epidemiologically associated with squamous cell bladder cancer in Egypt and other African foci. Nitrosamines, β-glucuronidase, and inflammatory gene damage have been identified as possible carcinogenic factors. Another explanation is that schistosomiasis lesions intensify the exposure of the bladder epithelium to mutagenetic substrates from tobacco or chemicals. (*See Khaled's article on Schistosomiasis and Cancer, in this issue of the Journal*).

Colorectal

Schistosomiasis is generally accepted as a risk factor for colorectal cancer in Asia, where the infective species is *S. japonicum*. Supportive reports are published from China [44], Japan [45] and others, though there are still some question marks about a true cause and effect relationship [46].

Lymphoma

A Burkitt's type of lymphocytic lymphoma associated with *S. mansoni* intestinal schistosomiasis was reported in a 14 year old Zairian girl, with suggestive evidence of a cause and effect relationship [43].

Co-infection

Attention has been drawn since the sixties of last century that schistosmiasis is often associated with other parasitic, bacterial or viral infections [47], many of which may be endemic in the same regions.

Parasitic infections

Co-infection with malaria and leishmaniasis has been well documented in experimental models as well as humans. In both cases, schistosomiasis modified the course of the associated infection, with little impact of the latter on schistosomal morbidity. It seems that the concomitant immunity established in between Schistosomes and their host interferes with the immune response to the superadded infection.

West African patients with chronic mansoniasis who acquire malaria are subject to severe disease with heavy parasitemia [48]. This does not occur in those with *S. haematobium* infection, who even seem to be protected [49]. The mechanism involved in this discrepancy remains unclear.

Reports from East Africa and South East Asia suggest that recovery from Kala Azar is delayed in patients with hepatosplenic schistosomiasis [50].

Co-infection of schistosoma and toxoplasma infection in mice has been associated with augmented hepatotoxicity yet without increase in tachyzoite counts. It was hypothesized that excessive release of TNF-α was responsible for this injury, indicating reactivation of earlier phases of immune response [51].

Schistosoma-filaria co-infection was reported from Egypt [52]. It was shown that the clinical course of either parasite is aggravated by prior infection with the other. Since the immune response to these worms is similar, it is understandable that concomitant immunity to either may induce relative tolerance to the other.

Bacterial infection

Schistosomiasis has been associated with several bacterial co-infections including Salmonella, tuberculosis, staphylococcus [47] and sexually transmitted diseases including Neisseria gonorrhea, Chlamydia trachomatis, Mycoplasma genitalium, and Trichomonas vaginalis [53].

The most established of these, with highest impact on morbidity is salmonellosis. This has been described with urinary schistosomiasis since the late fifties [54], as well as with hepato-intestinal schistosomiasis a decade later [55]. Acute appendicitis, cholecystitis, pyelonephritis and exudative glomerulonephritis have been documented with this association.

Viral infection

Several viral infections are notoriously associated with schistosomiasis owing to the favorable immunological environment caused by TH2 predominance [56]. These include Hepatitis B and C, HIV and human papilloma virus [57].

Hepatitis viruses

A few decades ago, Hepatitis B (HBV) infection was a main co-infective agent in hepato-intestinal schistosomiasis, infection being acquired during the intravenous administration of tartar emetic for the treatment of schistosomiasis. It used to confound the hepatic pathology by inducing hepatocellular

necrosis, architectural collapse and subsequent cirrhosis. HBV soon became recognized as a significant risk factor for the development of hepatoma in those patients.

With the rapid decline of HBV incidence during the past 2 decades, Hepatitis C virus (HCV) replaced HBV as a frequent co-infection in hepato-intestinal schistosomiasis. Infection might have also been acquired along with intravenous anti-schistosomal treatment, though other routes of infection remain unclear. HCV confounds hepatic pathology in a similar pattern as HBV, including a dramatic increase in the risk of hepatic malignancy (*See Elbaz and Esmat's article on Hepatic and intestinal schistosomiasis, in this issue of the Journal*). In addition, HCV confounds the glomerular lesions in hepatosplenic schistosomiasis by adding the elements of cryoglobulinemia and amyloidosis [26]. (*See Barsoum's article on Urinary Schistosomiasis, in this issue of the Journal*).

Human immunodeficiency virus

HIV is the most recent addition to the list of viral co-infection with schistosomiasis. Studies showed that up to 17% of HIV-infected patients from sub-Saharan Africa were seropositive for schistosomiasis [58]. It was shown that women and men with lower urinary schistosomiasis were at a significantly increased risk of acquiring, and subsequently transmitting HIV to their sexual partners. There are three main clinical patterns of schistosomiasis in such cases, namely gastrointestinal, disseminated and neurological. Gastrointestinal schistosomiasis is the most common and typically presents with weight loss, diarrhoea, abdominal pain and odynophagia [59].

Neuroschistosomiasis (NSS) should be included in the differential diagnosis in HIV-infected patients from endemic areas who display an acute encephalopathy. While CT scan and MRI are useful tools in the investigation of NSS, the definitive diagnosis is based on the direct identification of the eggs in tissue biopsy [60]. There are promising, yet currently less reliable serological methods including the detection of circulating adult worm and soluble egg antigens by using monoclonal or polyclonal antibodies [61].

Management

Prevention

A schistosomiasis control program typically includes two approaches: (a) Control of morbidity, aiming at reducing the number of severe form of the disease; and (b) Control of transmission, by interrupting the evolutive cycle of the parasite [62,63]. This includes sanitation and proper sewage control, as well as limiting access to infested fresh water and provision of safe water supply. Programs focused on eradication of snail species have been attempted. In general, this approach does not result in complete eradication and is difficult to sustain; repopulation by snails can occur very rapidly. Educational programs also have a role.

Periodic mass treatment, which has become possible since the introduction of the effective and safe oral drug, Praziquantel [64], has also been very effective in China and Egypt. Adolescents have been primarily targeted in these programs, being the age group with the highest intensity of infection However, there are certain drawbacks of mass treatment strategies including logistic and financial issues, possible development of drug resistance, lack of resistance to re-infection and possible increase in the risk of hepatic disease with interrupted treatment. For these reasons, the search for an effective vaccine continues despite repeated disappointments with many attempts in the past.

Vaccines

Data from animal vaccination studies has yielded important information that shaped human vaccine-development strategies. It is clear that an immune status is achieved by the integration of humoral and cellular mechanisms, dominated by up-regulation of antigen-specific TH1and TH2 clones leading to a favorable IgE/IgG4 ratio [65].

It remains to identify the right target antigen. More than 10 antigens with strong potential as vaccines candidates were tried; most have been difficult to move forward [65]. The most eligible candidates are the schistosomular tegument membrane antigens Sm 23, SmTSP-2 and Sm29. Also eligible are egg antigens, targeting which would decrease parasite fecundity and egg viability. A potential strategic approach would involve multiple antigens together [66]. Proteomic and genomic studies [65] are underway for integrating these antigens into a master mix, hoping to raise the effectiveness of vaccination over the current 70% success rate.

Treatment of active lesions

Active lesions readily respond to antischistosomal chemotherapy. The drug of choice today is Praziquantel (PZQ), a pyrazinoisoquinoline derivative [67]. It is effective against all species of human pathogenic schistosomes with a cure rate of 80%. However, it cannot be used for chemoprophylaxis, since it is active only against mature worms. The recommended therapeutic dose is 40 mg/kg body weight as a single morning dose for *S. haematobium* and *S. mansoni*. For *S. japonicum*, the dose should be increased to 60 mg/kg body weight given in two divided doses on the same day. The same dose is used for *S. mekongi*, preferably divided into three doses given in the same day. The drug is safe, but a few side-effects have been reported including abdominal pains, headaches, dizziness, and skin rash. Resistance to PZQ in humans is still a rare occasion in *S. mansoni* and not reported in *S. haematobium*.

The organophosphorus preparation metrifonate is effective only against *S. haematobium* infections. The drug is safe and can be used in mass treatment. The recommended dose is 10 mg/kg body weight as a single dose, which may be repeated twice at fortnightly intervals in order to achieve a high cure rate.

Oxamniquine is a quinoline derivative (2-aminomethyl-tetrahydro-quinoline), which is effective against *S. mansoni* only infections. The recommended single-dose treatment is 20 mg/kg body weight.

Artemether, a derivative of the Chinese antimalarial Quyinghaosu alkaloids is a promising new agent that can effectively kill the invading cercariae, maturing schistosomulae as well as the mature adult worms by interfering with the parasite's glycolytic pathways [68]. It has been tried in *S. japonicum* – endemic areas in southern China to prevent new infections [69]; it was found to be active against other

human schistosomes and appears to be synergistic to PZQ in killing adult worms.

Mirazid is an herbal drug derived from myrrh (purified Commiphora molmol Engier) that was developed in Egypt. The drug was found to be safe with no serious side effects. However, its efficacy has been debated; some studies showed high efficacy in the treatment of schistosomiasis and fascioliasis [70] with a cure rate of 91.7%, whereas other authors have found it to have a much lower cure rate than PZQ in their studies [71]. Therefore, Botros and colleagues did not recommend mirazid as an agent to control schistosomiasis [72].

Adjuvant treatment with colchicine has been successful in reducing fibrosis in experimental murine schistosomiasis [73] and the development of amyloidosis in Syrian Hamsters [74]. It has been widely used in patients with hepatosplenic schistosomiasis, yet without conclusive therapeutic benefit.

Results of treatment

Anti-schistosomal chemotherapy leads to parasitological cure in 40–80% of cases, depending on the drug used, the parasite species and strains, the host's nutritional state, and other factors. Even without such a cure, the intensity of infection is significantly reduced [63]. The effectiveness of treatment can be tested by the progressive decline in the number of eggs excreted in urine and stools; to disappear within 3–4 months. Tissue biopsy from the bladder or rectal mucosa after effective treatment may still show trapped dead ova for many years. The titers of circulating gut and egg antigens rapidly decline with effective treatment. Persistence of the former after the disappearance of eggs from the excreta usually indicates the survival of sterile or single-sex worms. This outcome has the advantage of possibly conferring active immunity against re-infection, so much so that it is considered the aim of certain mass treatment programmes. Owing to the absence of ova, such a setting is certainly harmless from the point of view of granulomatous lesions. However, its effect on the development and propagation of immune-complex-mediated glomerular injury has not yet been elucidated.

The reversibility of established lesions after effective antischistosomal therapy depends on the species, the organ(s) affected, the duration of infection, and the degree of damage already sustained. Best results are achieved with early bladder lesions or back pressure in *S. haematobium* infections, early colonic or hepatic lesions in *S. mansoni* infections, or brain lesions in *S. japonicum* disease. Certain glomerular lesions confounded by concomitant infections may be reversible by dual therapy.

Treatment of fibrotic lesions

Many of the residual lesions need no surgical correction. Examples are colonic sub mucosal and pericolic fibrosis sparing motility, hepatosplenic schistosomiasis without portal hypertension, lower ureteric fibrosis without pelvicalyceal dilatation even when associated with mild to moderate reflux, and bladder fibrosis and calcification without significant urodynamic disturbances.

In certain instances, however, extreme degrees of portal hypertension may necessitate shunting operations and prominent oesophageal varices may require sclerotherapy. Lower urinary tract lesions are frequently treated by urological procedures that include percutaneous nephrostomies for the temporary relief of obstruction, endoscopic dilatation of stenosed ureters, subureteric silicone injection for the amelioration of reflux, ureterovesical implantation, ureteroplasty and cystoplasty, and the use of ileal loops for restoration of adequate urodynamic function.

Owing to the silence of cardiopulmomary lesions, the diagnosis is usually delayed beyond the point of any reversibility. Patients with schistosomal cor pulmonale tend to have progressive right ventricular failure, which is hardly affected by any treatment.

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