Schistosomiasis: Overview of the History, Biology, Clinicopathology, and Laboratory Diagnosis

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Abstract

Schistosomiasis, a disease caused by small parasitic blood flukes, has afflicted humankind for thousands of years. It affects approximately 200 million people worldwide and is the cause of significant morbidity. Diagnosis used to rest on finding the characteristic eggs in stool or urine samples; however, techniques based on the detection of antibodies and schistosomal antigens have become more popular in recent years and are continuing to increase in both sensitivity and specificity. Molecular biology techniques, such as PCR, are also being applied to schistosomal genome research and methods of detection.

Introduction

Schistosomiasis is a major disease affecting approximately 200 million people worldwide with an estimated 650 million people at risk for infection. It is endemic in 76 countries and territories, although it is estimated that 85% of the people infected are on the African continent (1).

The term schistosomiasis refers to a disorder caused by infection with a parasitic fluke that lives inside the blood vessels of its host and belongs to the genus Schistosoma. The genus contains many species that infect animals, and some are parasitic in humans. There are three species of major medical importance: S. haematobium, S. mansoni, and S. japonicum.

Schistosomiasis has affected humankind since antiquity (2). The eggs of S. haematobium have been found in the kidneys from two Egyptian mummies dating back to the time of the 20th Dynasty (1250 to 1000 BC) (3). In China, the eggs of S. japonicum have been found in a preserved corpse dating back to the Han Dynasty (206 BC to 220 AD) (4). In France, S. mansoni eggs were recovered from material in an ancient latrine, which was dated to 1450 to 1550 AD (5).

With such a long association with humans, schistosomiasis undoubtedly played a role in shaping human history. The disease has been attributed to many different events, including the death of Alexander the Great (6), the death of King Herod the Great (7), part of the reason for the fall of ancient Jericho to Joshua and the Israelites (8), and part of the reason why the newly formed Chinese communist army did not invade Taiwan in the late 1940s (9).

History

The German pathologist Theodore Maximilian Bilharz (1825 to 1862) was the first to describe the symptoms of schistosomiasis in Japan. He was a practitioner of Chinese medicine who studied a local disease of the villagers who worked in the rice fields in the Katayama region of Japan. Yama means mountain and refers to an isolated hill in the middle of surrounding low-lying wet rice fields. The villagers who worked in them developed a rash on their legs, followed by fever, diarrhea, and bloody stools. Even today, these early acute symptoms are still known as Katayama fever. Many of his patients eventually became emaciated, developed ascites and leg edema, and then died. Dr. Fujii suspected that something in the water was causing the
disease and wrote about the illness, hoping that a cause could be found through the analytical methods of “Western medicine” (10).

It was not until 1904 that the causative agent of Katayama fever was found and described by Fujiro Katsurada, a pathologist at Okayama Medical College in Japan. He found the worm in the portal vein of an infected cat and proposed the name *S. japonicum* to distinguish it from *S. haematobium*.

In 1907, a third species of *Schistosoma* was found and described by Luigi Westenra Sambon (1865 to 1931) of the London School of Tropical Medicine. He named the species *S. mansoni* in honor of Patrick Manson (1824 to 1922), considered by many to be the father of tropical medicine.

**Classification**

The taxonomic classification of the schistosomes is given in Table 1. Schistosomes belong to the phylum *Platyhelminthes* (flat worms). The flat worms can be divided up into three classes: *Turbellaria* (planarians), *Cestoda* (tapeworms), and *Trematoda* (flukes). All trematodes are parasites, and there are several medically important species that affect humans. The flukes have flattened, leaf-like bodies and one or more suckers, from which they feed. The schistosomes are placed in the subclass called *Digenea*. *Digenea* are characterized by an alternation of generations in their life cycle. This means that when an egg hatches, it produces a larval form that eventually reproduces asexually. The offspring resulting from this asexual reproduction mature into adults that must reproduce sexually. Thus, the reproduction behavior alters with each successive generation.

There are several orders of trematodes. Many of them are divided by the morphology of their cercariae, a stage in the life cycle. The order *Echinostomatida* has cercariae with simple tails and includes the species *Fasciola hepatica*, a liver fluke of humans and domestic animals. Members of the order *Plagiordrilliidae* have cercariae with unforked tails that lack excretory vessels. This order includes the species *Paragonimus westermani*, a lung fluke in humans and carnivores. The order *Opisthorchiidae* includes genera that have cercariae with unforked tails and excretory vessels and includes the species *Heterophyes heterophyes* and *Opisthorchis sinensis*, parasitic flukes of the small intestines and bile ducts, respectively. The order *Strigeidae*, to which schistosomes belong, have cercariae with forked tails.

The order *Strigeidae* includes several families. Schistosomes belong to the family *Schistosomatidae*, which includes those species that have separate sexes and whose adult forms live in the host’s circulatory system, hence the term “blood flukes.” Schistosomes also belong to the subfamily *Schistosomatinae*, which includes those species with a well-developed gynecophoral canal extending to the posterior end of the body. The gynecophoral (Gr: gyn, female; phoros, to carry) canal is a deep groove in the body of the male worm into which the female inserts herself. There she remains for life in ongoing copulation while the male carries her about.

The subfamily *Schistosomatinae* includes many genera. The genus *Schistosoma* (Gr: schisto, cleft; soma, body) includes approximately 19 species that have historically been divided into different groups centering around *S. haematobium*, *S. mansoni*, *S. japonicum*, and *S. indicum*, as shown in Table 2.

This grouping reflects similarities in egg morphology and the genera of intermediate snail hosts. While there are multiple species that are capable of infecting humans, the most important species worldwide are *S. haematobium*, *S. mansoni*, and *S. japonicum*.

**Epidemiology**

*S. mansoni* is found in the Nile delta, Madagascar, Brazil, Venezuela, Surinam, the Caribbean islands, and Puerto Rico. *S. japonicum* is found in China, South-
east Asia, and the Philippines. While S. japonicum used to be endemic in several areas of Japan, major eradication efforts during the 20th century have been very successful. The last human case of a new schistosomal infection in Japan was reported in 1977 (10). S. haematobium is found in many parts of Africa and Madagascar and in parts of the Middle East, including Iraq, Iran, and Saudi Arabia.

**Life Cycle**

The life cycle of the schistosome is complex and begins when eggs are released into freshwater through feces or urine. In the water, the eggs hatch, releasing free-swimming, ciliated miracidia. The miracidia are able to find, penetrate, and infect a snail host. Different species of schistosomes prefer different species of snails. S. mansoni prefers snails of the genus Biomphalaria, while S. haematobium and S. japonicum prefer snails of the genera Bulinus and Oncomelania, respectively.

Inside the snail, the miracidia develop into free-swimming forms called cercariae. While this transformation can take 4 to 6 weeks, one miracidium can develop into numerous cercariae. When fully developed, the fork-tailed cercariae leave the snail at a rate of 1,500 per day for up to 18 days. The cercariae leave the snail during daylight hours and are remarkably attracted to light. They have only a short time to find a host; otherwise, they will die within 1 day. An unfortunate host might be someone standing in the water to bathe or wash clothes, or a child out for a swim. Once the cercariae penetrate the skin, they lose their tails and differentiate into larval forms, called schistosomulae. Studies have shown that the schistosomulae of S. mansoni can produce cytokines that suppress human immunoregulatory cells, including T lymphocytes (11). After a set time, the schistosomulae begin to migrate through the skin and eventually gain access to the human host’s lymphatic system and begin to travel.

The schistosomulae first reach the lung in about 4 days, remain there for 3 to 8 days, and then migrate to the liver. Only those worms that reach the portal system of the liver mature into adults. The estimated lifetime of an individual worm is between 10 and 20 years. In the liver, male and female worms pair up. Both sexes are required for viable egg production. The female, being smaller than the male, inserts herself into the gynecophoral canal of the male. Once paired, the worms migrate to particular sites favored by the different species: S. mansoni to the mesenteric venules of the large bowel and rectum, S. japonicum to the mesenteric veins of the small intestine, and S. haematobium to the perivesical venous plexus surrounding the bladder. Safe in their favored sites, the worms begin to lay eggs.

The egg production rate of mature schistosomes can be prodigious. S. haematobium is able to lay eggs at a rate of 100 to 200 per day, S. mansoni around 400 per day, and S. japonicum around 2,000 per day. Electron microscopy shows that the eggs, which continue to grow and develop in the host’s tissue, are covered with multiple tiny spurs called microbarbs, which allow the eggs to cling to the vascular endothelium. The eggs also have very tiny pores. These pores are able to secrete antigens, as well as enzymes, which aid in the passage of the egg through the host’s tissues (12). The characteristic spine is thought to also help the egg work its way through tissue. Eventually, the eggs enter the lumen of the excretory organs. More than 50% of the eggs do not make it into the fecal or urinary stream and become entrapped in adjacent tissues or get carried away by the circulatory or lymphatic system and can become lodged in virtually any organ in the body (13).

**Clinicopathologic Correlations**

**Acute stages**

Soon after the cercariae penetrate the skin, the patient can experience a pruritic, papular rash called schistosome or cercarial dermatitis. This stage usually resolves spontaneously. Swimmers can develop this rash, called “swimmer’s itch,” due to penetration of the skin by cercariae that normally infect birds or other animals. Fortunately, many of these cercariae cannot complete their life cycle in humans and die.

After the onset of egg laying by the mature worms, which is approximately 4 to 13 weeks after skin penetration by the cercariae, patients who have never been exposed to schistosomiasis may develop an acute reaction (Katayama fever). Katayama fever is characterized by fever spiking in the afternoon, urticaria, malaise, and diarrhea. Examination shows eosinophilia, diffuse lymphadenopathy, and hepatosplenomegaly. As the person’s immune system adapts, these symptoms resolve over a period of 2 to 8 weeks (14).

**Chronic stages**

The eggs that remain entrapped in the host tissues continue to secrete antigens that incite an inflammatory granulomatous immune response. The resulting granulomas can be a hundred times the size of the egg. Over time, the granulomas are replaced by dense fibrosis that obstructs blood flow and leads to problems in normal organ function. Since the worms reside in different body sites, clinical symptoms vary with the species of the infecting worm, the total worm burden, and the patient’s state of health at the time of infection. Several well-known major syndromes have been described.

**Gastrointestinal complications**

Generally, these complications are caused by S. mansoni. The wall of the distal colon becomes damaged as the eggs either pass through or become lodged in the tissue. The resulting inflammatory response can cause focal ulcers or inflammatory polyps (15). In later stages, this can lead to dense fibrosis. The area of the involved bowel can be continuous or segmental in distribution. Clinically, the patient can develop diarrhea, abdominal pain, and colitis or bowel obstruction. Schistosomal colitis has been postulated as a predisposing factor for the development of colorectal cancer, although a definitive association is as yet unproven (16). Increased numbers of eggs also tend to accumulate in the appendix and can cause appendicitis.

**Hepatosplenic complications**

Many eggs are carried off by the portal circulation to the liver, where they incite a granulomatous response. The granulomas eventually become walled off with dense layers of fibrous tissue. In some patients, this process is extensive, leading to dense white fibrosis affecting portal tracts throughout the liver with fibrous septa linking the portal tracts together. The hepatic acini remain relatively unaffected. This process has been termed Symmers’ or
pipestem fibrosis. The fibrosis obstructs the portal veins and, over time, leads to portal hypertension with the resulting complications of esophageal varices and splenomegaly.

Cardiopulmonary complications

These complications usually develop in patients with severe hepatosplenic schistosomiasis and are caused by the portosystemic shunting of blood directly back to the heart. The eggs carried in the shunted blood become lodged in the small pulmonary arterioles. Just as in the liver, they form granulomas that block the pulmonary circulation and cause pulmonary hypertension, leading to right ventricular strain and, eventually, cor pulmonale and cardiovascular collapse.

Genitourinary complications

Eggs lodging in the wall of the bladder induce a mixed inflammatory infiltrate around the egg. The overlying bladder epithelium can become hyperplastic and develop sessile and pedunculated polyps (17). Often, adult worms and multiple eggs can be found at the base of the polyps. The polyps can erode and ulcerate and cause hematuria, which is a clinical symptom of infection.

Other changes, such as cystitis cystica, cystitis glandularis, and squamous and intestinal metaplasia, can also be seen. Over time, the eggs and granulomas calcify, causing a gritty appearance to the bladder wall, sometimes called a sandy patch. In extensive infections, the calcification can be severe, causing a dense, white ring visible on X-ray imaging. Long-standing and severe infections are associated with the development of urothelial carcinoma (Fig. 1).

Schistosomiasis can also affect the ureters. The major lesions are incomplete ureteral stenosis, caused by the inflammatory response elicited by the eggs, and ureterolithiasis. These lesions are often symmetrical and are more frequently found in the interstitial ureters than in the more proximal portion (18). The most common proximal lesion is hydrourereter, which can be caused by distal obstruction or by direct egg deposition in the ureter walls, leading to loss of muscle action. If the obstruction goes unchecked, the end result can be hydronephrosis and renal failure. Kidney damage can also result from the direct deposition of the eggs in the renal parenchyma. Immune complexes containing soluble worm antigens also can deposit in the glomeruli, causing glomerulonephritis (19).

In females, S. haematobium eggs can be swept to the ovary. Schistosomiasis is the only common parasitic infestation of the ovary. Inflammation in the ovary later results in dense ovarian fibrosis. Clinically, this can result in oophoritis, abdominal pain, and infertility. The eggs can also involve the fallopian tube, uterus, and cervix causing cervical stenosis and vaginitis (20).

In males, eggs have been found in the seminal vesicles, epididymides, and testes. Involvement of the testis is rare, and the development of a painless mass in the testicle can be mistaken for testicular carcinoma and lead to orchidectomy. As the ultrasound appearance of testicular schistosomiasis is identical to that of testicular malignancy, schistosomiasis should be ruled out before orchidectomy, if there is any suspicion for exposure to the disease (21). Egg deposition in the prostate is not uncommon. There are several reports in the literature that speculate as to an association between schistosomal infestation of the prostate and prostatic adenocarcinoma; however, an association remains unproven (22,23).

Figure 1. Low-power view of the bladder. The left half shows squamous metaplasia of the mucosa while the right half shows invasive squamous cell carcinoma. Note the numerous small, darkly stained, calcified S. haematobium eggs and inflammatory cells in the lamina propria.

Figure 2. Higher-power view of S. haematobium eggs.
Central nervous system complications

Egg deposition in the spinal cord is more common in *S. haematobium* and *S. mansoni* infections. The resulting inflammation is more diffuse than the granulomatous lesions seen in other organs and results in a transverse myelitis-like syndrome. Egg deposition in the brain is more common in *S. japonicum* infections. The eggs and the resulting inflammatory response can cause a generalized encephalopathy. Many such cases were reported in American soldiers following World War II and the invasion of the Philippines.

Laboratory Diagnosis

Microscopic analysis

The diagnosis of a schistosomal infection can be made by detecting the presence of eggs in wet mounts of stool or urine samples. The morphology of the eggs is slightly different in the three species. *S. haematobium* eggs, similar in size to *S. mansoni* eggs, are 112 to 180 µm by 40 to 70 µm. They are oval and have a slender terminal spine. They can occasionally be found in urine CytoDyn preparations and cervical Papanicolaou (Pap) smears, often accompanied by numerous inflammatory cells. They stain a blue-mauve color with the Pap stain. They can also sometimes be seen in stool or rectal biopsy specimens, since the eggs disseminate widely in the body.

*S. mansoni* eggs, although smaller in size (116 to 180 µm by 45 to 58 µm), have a characteristic and prominent lateral (subterminal) spine that protrudes from the side of the egg near one end. The opposite end is slightly curved and pointed. If the material is unfixed and the egg is viable, the miracidium can sometimes be seen moving within the egg.

*S. japonicum* eggs are 75 to 90 µm by 60 to 68 µm and are oval to semi-spherical in shape. They possess a small, rounded, lateral (subterminal) spine, often located in a depression on the shell; this small spine can sometimes be very difficult to detect, especially in tissue sections.

Although there are several different methods available for preparing the wet mounts, the Kato-Katz method is usually recommended. In this technique, an aliquot of stool is smeared onto a glass slide through a plastic template. A coverslip, which is soaked in methylene blue and glycerin, is placed over the stool, and the slide is read. Another technique which requires no reagents, is the Teedle technique. In this method, after the stool is smeared onto a slide, the slide is overturned onto another clean slide and pressure is applied between the two to create a thin smear. The slide is then read. Studies comparing the two methods found little difference in sensitivity (24).

Patients with a light infection or one that has resolved are likely to have few, if any, eggs found in the stool or urine. If no eggs are found, rectal or bladder biopsy specimens are sometimes used to detect the presence of eggs. A fresh, unstained crush preparation can be made between two glass slides and easily and rapidly examined under the microscope. Eggs can also be observed in formalin-fixed, paraffin-embedded tissues. It is important not to make a species-specific diagnosis on the basis of only a few crushed or highly calcified eggs unless there is evidence of a clear-cut lateral or terminal spine.

More than half a century ago, during sputum testing for acid-fast bacteria, it was noted in areas of high endemicity that *S. mansoni* eggs, which occasionally showed up in the sputum, also stained red (25). In order to fully utilize this observation, the Ziehl-Neelsen stain was modified to optimize the staining of the eggs in paraffin sections, as well as in stool smears. *S. japonicum* eggs are also positive, while those of *S. haematobium* are negative. This useful feature can be used as an aid in distinguishing different species (26).

Antigen detection

Antigen detection methods have been shown to be more sensitive than direct examination for eggs. Many different methods have been developed to test for schistosomal antibodies. Some reference laboratories use a Falcon assay screening test, which is a specially designed kinetic-based enzyme-linked immunosorbent assay (ELISA) technique to rapidly screen sera. In this technique, tiny polystyrene beads are coated with schistosomal antigens. The beads are attached to 96 small sticks molded onto the lid of a microdilution plate so that, when the lid is in place, each bead fits into a different well on the plate. The wells are filled with patient sera, and the lid is put in place, allowing any antischistosomal antibody to adhere to the beads. After being washed, the wells are filled with an anti-human antibody-enzyme complex, and the lid is replaced to allow binding. The final step entails exposure of the beads to the enzyme’s substrate and absorbance measurements (27). Further confirmation of infection can be performed with an enzyme-linked immunoelectrotransfer blot. This technique uses antigen strips prepared from different species of schistosomes, so that a positive reaction indicates the species (28). Many other inventive techniques to measure anti-schistosomal antibodies have been developed. A recent report from China uses a quartz-crystal microbalance coated with an antigen from *S. japonicum* to detect the presence of antibodies in infected rabbit serum (29).

Antibody techniques suffer from several disadvantages. There is cross-reactivity with other helminthic infections. They are also unable to differentiate between active and old infections or assess the effects of chemotherapy, since antibodies persist for a long time. Antibodies cannot be correlated very well with worm burden or egg production rates and thus cannot provide reliable information on the intensity of the infection. The detection of worm antigens in the sera of infected patients would be able to differentiate an active from a chronic infection, as well as correlate with overall worm burden (30).

Antigen detection

In the late 1960s, it was shown that low levels of soluble schistosomal antigens could be found in an infected person’s blood by immunoelectrophoresis. There are two major circulating antigens, called the circulating anodic antigen (CAA) and the circulating cathodic antigen (CCA) (31). Both of these antigens come from the gut of the schistosome worm. By sensitizing sheep erythrocytes with mouse immunoglobulin M monoclonal anti-schistosomal antibodies, an indirect hemagglutination assay has been used to establish the levels of CAA and CCA in infected humans (32). ELISA tests using monoclonal antibodies to CAA have also been shown to have a high sensitivity, capable of detecting <1 ng of antigen/ml of serum (33). This ELISA technique has been applied to the detection of CAA in mummies and has been shown to detect the anti-
gen with high sensitivity in 3,200- to 5,000-year-old desiccated tissue (34). Tests with an ELISA using a different monoclonal antibody have shown that schistosomal antigens can be passed through the placenta, as well as in breast milk (35).

Molecular studies
In 1993, the World Health Organization initiated a parasite genome project for six parasites, including schistosomes. One of the goals was to catalog new parasite genes. To date, approximately 20 to 25% of the total schistosome genome has been discovered (36). Molecular diagnostic techniques have only relatively recently been applied to the detection of schistosomal infections. Species-specific probes have been developed that bind to a 640-bp segment of S. mansoni DNA (37). Using this probe, PCR has been used to detect S. mansoni DNA in human serum (38). Furthermore, this technique has been shown to be more sensitive than the Kato-Katz direct examination (39).

Treatment
While there are several different anti-schistosomal drugs available worldwide, praziquantel (Biltricide) is the drug of choice and is approved for use in the United States. It is a pyrazinoisouquinoline derivative that is able to cause increased muscular contractions in the worms, which detaches them from the host’s tissues. In higher concentrations, it damages the worm’s ability to adjust cation levels across its outer tegument. Praziquantel is effective against all of the species of schistosomes that infect humans.

Acknowledgements
I thank James Navin and Dr. Aliyah Rahemtullah for providing materials used in the preparation of this review.

References
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