REGULAR ARTICLE

Schistosomiasis-Associated Pulmonary Arterial Hypertension

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Schistosomiasis is a major cause of group 1 pulmonary arterial hypertension (PAH) worldwide. Schistosomiasis results from a parasitic infection present in over 200 million individuals worldwide. Schistosomiasis-associated PAH was initially thought to be obstructive due to egg embolization but has a pulmonary vascular pathology like other forms of group 1 PAH and can be treated using conventional PAH therapies. Mechanisms that underlie the development of schistosomiasis-associated PAH include type 2 inflammation which triggers TGF-β signaling; importantly, TGF-β signaling is a pathway shared with other PAH etiologies. However, many things which are unknown about this disease remain, including if the lung vascular pathology results from egg embolization causing localized inflammation and vessel remodeling, or if this is a form of portopulmonary hypertension resulting from schistosomiasis liver disease.

SCHISTOSOMIASIS BACKGROUND

Schistosomiasis (bilharzia) is one of the etiologies of group 1 pulmonary arterial hypertension (PAH) per the current classification system,[1] although it is perhaps the least understood despite being one of the most common causes. Schistosomiasis is the clinical disease that results from infection with parasitic flatworms (nematodes) of the *Schistosoma* genus. Three *Schistosoma* species cause >95% of disease: *S. mansoni*, *S. haematobium*, and *S. japonicum*. Schistosomiasis is endemic in 51 countries worldwide, with about 90% of the disease burden in sub-Saharan Africa.[2]

Schistosoma have a mandatory 2-host lifecycle, with a snail intermediate host. Snail species are specific for each *Schistosoma* species. Infected snails release the cercariae lifeform of the parasite, which lives about 24 hours in fresh water. Humans are infected by exposure to contaminated water, with cercariae penetrating the skin within about 5 minutes, leaving behind a punctate rash (cercarial dermatitis). The parasite then migrates from the subcutaneous tissue to the systemic veins and then to the lungs, causing a hypersensitivity reaction (Katayama fever) characterized by fevers, cough, chest x-ray infiltrates, and eosinophilia: This syndrome may develop in travelers to endemic settings. After a few weeks, the parasites migrate to the target organ: In the case of *S. mansoni* and *japonicum*, this is the portal venous system; *S. haematobium* migrates to the bladder venous plexus. Here, the mature worms mate and release eggs, from several hundred up to 5000 per day for a *S. japonicum* worm pair. Most of the eggs erode through the intestinal or bladder wall to enter the feces or urine, where after excretion, they infect snails and complete the lifecycle. Eggs retained within the host cause inflammation and immunopathology. The worms have evolved many tactics for evading the host immune system[3] and can live for years or decades in the host while continually laying eggs.

CURRENT STATE OF SCHISTOSOMIASIS

Schistosomiasis is considered a neglected tropical disease. In 2019 (the most recent year worldwide figures are available), it was estimated 237 million individuals (about 3% of the global population) *required treatment*, i.e., were either actively infected or at high risk for infection with the parasite.[2] Of these, 105 million were treated. Praziquantel is the antihelminthic medication most used. It is effective against adult but not juvenile parasites; thus, acutely infected individuals need to receive 2 doses about 6 weeks apart. Praziquantel resistance can be induced in laboratory settings[4] but has not (yet) been reported clinically.

Substantial progress in schistosomiasis control has been made in recent years through public health efforts, including clean water, sanitation, and hygiene preventative measures and mass drug administration particularly of school age children in at-risk settings.[5] Unfortunately, the disease generally has highest prevalence in the regions which are most impoverished, often rural and with limited health care access, leading to concerns about substantial underestimates of the worldwide burden.[6] Environmental change with global warming is shifting the distribution of *Schistosoma* and its snail species, and public infrastructure projects such as dam construction for hydroelectric power or irrigation is changing the endemic territory.[7]

HISTORY OF SCHISTOSOMIASIS-ASSOCIATED PULMONARY HYPERTENSION

Schistosome eggs were initially reported in lung tissue in the 1880s[8] and then associated with pulmonary vascular disease in the 1930s in reports from Egypt.[9] In this era before the development of antihelminthics, autopsy specimens from individuals who died of schistosomal pulmonary hypertension (PH) often

Key Words—pulmonary hypertension, schistosomiasis, TGF-beta
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Disclosure: The authors have no relevant personal financial relationships to disclose.

demonstrated huge numbers (>100/section) of intravascular parasite eggs in addition to remodeled vessels with thickened media and intimal layers.[10] Based on this histopathology, at the time, schistosomal PH was ascribed to potentially be a combination of an embolic or obstructive disease and vascular remodeling. The first PH World Symposium (Geneva, 1973) categorized schistosomiasis-PH as embolic (group 3, at the time).[11] The second World Symposium (Evian, 1998) categorized schistosomiasis-PH as "directly affecting the pulmonary vasculature" (group 5),[12] and the third World Symposium (Venice, 2003) categorized it under embolic obstructive disease (group 4).[13]

At the Dana Point symposium (2008), the classification of schistosomiasis-PH was changed to an etiology of group 1 PAH,[14] and it has remained in group 1 subsequently. The rationale for assigning schistosomiasis to group 1 is multifactorial. Schistosomiasis-PAH (hereafter abbreviated SchPAH) patients often have a similar clinical presentation to idiopathic PAH (IPAH). The characteristic pulmonary vascular lesions found in IPAH are also present in SchPAH, including plexiform lesions.[15] These pulmonary vascular lesions are still present in modern autopsy series after the widespread use of praziquantel, but no significant eggs are present.[16] Evidence of shared underlying pathobiology exists, including altered TGF-β family signaling (see below). SchPAH patients also benefit from treatment with conventional PAH therapies, although these data are from smaller and generally retrospective series (see below).

PREVALENCE

Some of the eggs laid by worms that make their homes in the portal veins (all species other than *S. haematobium*) embolize into the prehepatic sinusoids, causing preportal fibrosis termed hepatointestinal schistosomiasis (HSS). HSS causes portal hypertension, like that seen in portopulmonary hypertension (PPHTN), and it is thought that HSS substantially increases the risk of developing SchPAH potentially as a form of PPHTN. *S. mansoni* is the species most clearly associated with SchPAH, and it has been estimated that approximately 5%–10% of those with chronic *S. mansoni* infection develop HSS.[17–19] On histopathology, it was observed that about 24% of individuals with HSS had evidence of pulmonary vascular disease.[20] By echocardiography, it was estimated that 11% of those with HSS had SchPAH.[21] By right heart catheterization (RHC), one study found that 21% of those with HSS had a mean pulmonary artery pressure (mPAP) > 20 mm Hg (the revised threshold), and 4 (12%) had a mPAP > 25mm Hg (the prior threshold), all with a normal wedge pressure.[22] Another study identified 18% of those with HSS had the suggestion of PH on echocardiography, of whom 5% were ultimately found to have SchPAH on RHC (using the mPAP ≥ 25 mm Hg threshold).[23] Overall, about 5%–10% of those with HSS may develop SchPAH, depending on the specific population, diagnostic test, and threshold. If 5% of those with schistosomiasis develop HSS and 5% of those develop PAH, that is 0.25% prevalence among all those with schistosomiasis, making this an uncommon complication of chronic disease. However, this also equates to a SchPAH prevalence of about 500,000 individuals, or about 64 per million worldwide, making it a relatively common cause of group 1 PAH.

DIAGNOSIS OF SCHPAH

The diagnostic criteria for SchPAH are not well established. Generally, the following 4 criteria are used:

1. PAH, by RHC using standard criteria.
2. At least 1 of the following:
   a. exposure to an endemic region for schistosomiasis,
   b. history of previous treatment for schistosomiasis, or
   c. history of or presence of *Schistosoma* eggs on stool examination or on rectal biopsy.
3. Liver ultrasound consistent with SchHSD, including left lobe enlargement and/or periportal fibrosis.
4. No evidence of other identified PH etiologies.

Practically, however, some major issues with these criteria exist. Foremost, RHC is not widely available in the areas where schistosomiasis is most endemic. The requirement for prior schistosomiasis exposure or infection is subject to recall bias and does not establish a clear causal relationship between prior infection and subsequent PAH development. The requirement for liver disease misses cases from *S. haematobium* or those that may occur in the absence of liver disease. Lastly, often, limited resources are available for a systematic evaluation for other PH etiologies in endemic settings.

In developed settings such as PH clinics in the United States, the diagnosis of SchPAH is sometimes considered among patients being evaluated who have a history of schistosomiasis or who have previously lived in endemic settings. If uncertainty in exposure history exists, serologic testing can be performed, although some serologic tests have species specificity. Serologic testing is less useful if the individual is known to come from a very high prevalence region, as it is almost certain to be positive.

Individuals may have active infection even if they have not been in an endemic area for many years, due to the long-lived nature of the parasite. Suggestive signs and symptoms include eosinophilia and blood in the urine (*S. haematobium*) or stool (other *Schistosoma* species), which can be screened by ova and parasite examination. It should be noted that microscopy has a relatively low sensitivity, particularly for low intensity disease. If there is concern for active infection, praziquantel can be administered: It is relatively safe, and a single dose is usually effective. One concern for side effects is if there are neurologic symptoms which may have resulted from egg embolization to the spine or brain (a condition called neuroschistosomiasis): Individuals with concern for this should be pretreated with steroids to avoid excessive inflammation.[24] If concern for HSS exists, abdominal ultrasound can be used to screen for periportal fibrosis; if periportal fibrosis is not present (and *S. mansoni* or *japonicum* are suspected, based on geography), SchPAH is less likely.

PROGNOSIS AND RESPONSE TO THERAPY

The clinical course of SchPAH may be more benign than IPAH or PH associated with connective tissue diseases,[25] even in the absence of specific PAH treatment.[26] Treatment-naïve SchPAH patients have been reported to have overall survival rates at 1, 2, and 3 years of 95%, 95%, and 86%, respectively,[26] although a more recent series from an endemic setting reported 1-, 3-, and 5-year survival estimates of 92%, 75%, and 51%, respectively,[27] figures closer to the prognosis in IPAH. A recent systematic review that included 18 studies concluded that SchPAH has a better prognosis than IPAH,[28] despite presenting with initially similar hemodynamics, although it should be cautioned that many of these patients were studied in nonendemic settings.

Patients with SchPAH should be treated as those with any other form of group 1 PAH. This conclusion is based on reports from clinicians in endemic settings and published case series and open-label studies, but SchPAH has generally not been included in prospective clinical trials of PAH therapeutics to date. Authors of one study compared survival between historical SchPAH patients (before PAH medications were available) and SchPAH patients receiving provider-selected medications and found that the newer, treated series had significantly better survival.[29] Authors of another study reported that sildenafil improved clinical and cardiac magnetic resonance imaging parameters in 7 SchPAH patients, including an improved 6-minute walk distance from an average of 114 to 335 m ($P < 0.0001$), and an improved right ventricular ejection fraction from an average of 33% to 43% ($P < 0.004$).[30] The same group reported 13 patients with SchPAH treated with sildenafil for 6 months had improved World Health Organization functional class ($P < 0.001$), the 6-minute walk distance improved from 121 to 394 m ($P < 0.0001$), and the average pulmonary artery systolic pressure on echocardiography decreased from 97 to 80 mm Hg, without significant adverse events.[31]

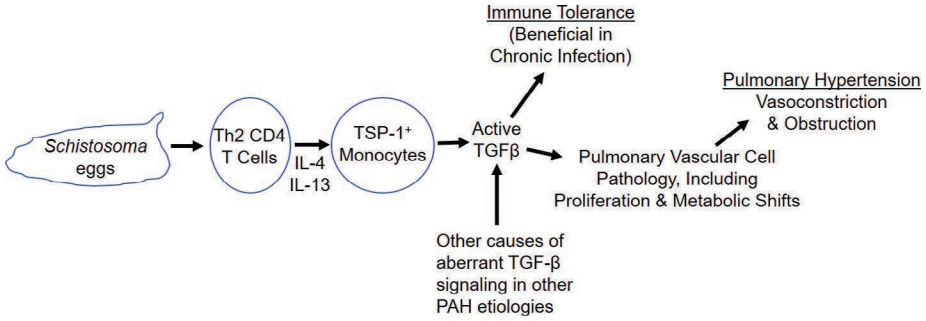

Figure: TGF-β signaling may function as a local immunosuppressant, benefiting the host with chronic schistosomiasis, but TGF-β signaling can also cause pathology in the pulmonary vascular cells resulting in pulmonary hypertension. Embolization of *Schistosoma* eggs to the lungs causes a type 2 immune reaction including the activation of CD4 T cells to a Th2 phenotype, resulting in the secretion of cytokines IL-4 and IL-13. This immune activation causes recruitment of classical monocytes which express the protein thrombospondin-1 (TSP-1), which has the functional ability to activate TGF-β. TGF-β causes a localized immune tolerance, which may be beneficial in the setting of a long-lived infection in which the host cannot effectively eradicate the parasite, through limiting the amount of tissue destruction. TGF-β also causes a pathology among the pulmonary vascular endothelial and smooth muscle cells, including excessive proliferation and changes in cellular metabolism, resulting in vasoconstriction and occlusion of the vasculature, and pulmonary hypertension. TGF-β signaling is a key step shared with other pulmonary arterial hypertension etiologies.

One major limitation in treating SchPAH worldwide is medication availability in endemic settings. In many countries, only PDE5 inhibitors are widely available; in some settings, there is access to endothelin receptor antagonists but only rarely prostacyclin analogues or other medications. Lung transplantation is also generally not available; occasionally atrial septostomy is performed as a rescue procedure. Otherwise, nonvasodilator therapies such as controlling volume status and pulmonary rehabilitation are similarly effective.

SCHISTOSOMIASIS-PH PATHOBIOLOGY: TYPE 2 INFLAMMATION TRIGGERS TGF-B ACTIVATION

Our current concept of schistosomiasis-PH is that the host immune system inadvertently causes the pulmonary vascular disease. *Schistosoma* parasites have evolved mechanisms to evade the host immune system, leading to very long-lived infections. In this setting, the host immune system needs to adapt to the infection without causing excessive tissue destruction in trying to kill the parasite. TGF-β is a classically immunosuppressive cytokine, and the host immune system may use TGF-β signaling as a counterregulatory mechanism to check the immune response to the parasite. Unfortunately, TGF-β also induces pulmonary vascular pathology, which is a shared pathway with many PAH etiologies including familial disease (eg, BMPR2 mutations), IPAH,[32] scleroderma-associated PAH[33] (Figure).

In mice, experimental PH can be induced by administering *Schistosoma* eggs directly to the lung vasculature. Modulating the egg dose to the lungs positively correlates to the PH phenotype, as was observed in $BMPR2^{+/-}$ mice having more liver disease, more egg embolization, and greater PH.[34] After embolization, the eggs induce a strong and localized type 2 immune reaction.[35] It is observed that remodeled vessels occur in proximity to the peri-egg granulomas,[36] suggesting the cytokines and immune cells responding to the eggs also cause the vascular disease.

Blocking type 2 immunity by using $IL\text{-}4^{-/-}IL\text{-}13^{-/-}$ mice suppressed the *Schistosoma*-PH phenotype.[35] More precisely, deleting IL-4 and IL-13 in CD4 T cells also suppresses the PH phenotype.[37] A key role of type 2 inflammation is the recruitment of circulating classical monocytes to the inflamed tissue. These monocytes express thrombospondin-1, which can locally activate TGF-β, and it has been observed that blocking monocyte recruitment or

thrombospondin-1 prevents *Schistosoma*-induced PH.[38]

Activation of TGF-β may benefit the host immune system through promoting regulatory immune mechanisms and acting as an immunosuppressant.[39] However, TGF-β is also toxic to the pulmonary vasculature: Among other effects, TGF-β induces proliferation of endothelial and smooth muscle cells,[40] including a metabolic shift of increased glycolysis which supports pathologic phenotypes.[41]

MAJOR OPEN QUESTIONS IN SCHISTOSOMIASIS-PH

Despite its relatively high prevalence, much is still unknown regarding SchPAH.

What Is the True Prevalence of SchPAH? Does SchPAH Occur in Species Other than S. mansoni?

Most of the literature in this field is from nonendemic settings, and systematic screening in high prevalence regions is lacking. Most clinical data in SchPAH are from Brazil, where only *S. mansoni* is endemic, but less is known about the other species. Case reports have indicated that *S. japoniucm*[42] and *S. haematobium*[43] can cause PH, but it may be substantially less common with these other species. In a recent echo-based study from China (where only *S. japonicum* is endemic), authors found 0.005% of those with schistosomiasis had evidence of PH,[44] a rate ~100-fold lower than is anticipated based on *S. mansoni*-derived data (see calculations above). In a study comparing experimental *S. japonicum*-induced PH to *S. mansoni*-induced PH, authors found that *S. japonicum* could cause PH in mice, but the severity was significantly less than that caused by *S. mansoni*.[45] If these species-specific phenotype differences are real clinically, it is largely unknown why these differences may occur and what the potential phenotype from *S. haematobium* infection is.

What Is the Relationship between SchPAH and PPHTN? Is Schistosomiasis Liver Disease a Necessary Precursor?

It is thought that preportal liver fibrosis in HSS is important in the development of *S. mansoni*-induced SchPAH. HSS could directly cause PPHTN. However, the liver fibrosis and portal hypertension in HSS also causes egg embolism to the lungs through portocaval shunts, and in mice, more severe liver disease increases egg embolization and causes more severe experimental PH.[34] Mice which receive only experimental egg embolism to the lungs develop a PH phenotype without any liver disease.[38] Notably different than viral or alcoholic cirrhosis, SchHSD causes preportal fibrosis without significant hepatocellular injury. Case reports exist of *S. haematobium*-induced SchPAH[43] which causes urinary but not liver disease. Overall, it remains unclear if PPHTN underlies or contributes to clinical SchPAH or if SchPAH largely results from a specific pathobiology induced by egg embolization to the lungs causing localized inflammation and vascular disease.

Does Antihelminthic Therapy (Praziquantel) Benefit SchPAH Patients Who Have Active Infection?

In schistosomal liver disease, eradicating the parasite leads to at least partial reversal of the liver pathology.[46,47] In a mouse model of schistosomiasis coupled with portal hypertension induced by portal vein ligation, the pulmonary disease partially improved after praziquantel administration,[48] and authors of another study of parasite infection alone found more substantial reversal of pulmonary disease with praziquantel treatment.[49] However, SchPAH patients continue to die in the absence of active infection,[16] so it is unclear if praziquantel has clinical benefit in SchPAH. Some favor treating all SchPAH patients with praziquantel due to the severity of the disease and relatively low risk of harm.[50] It may be that the pulmonary disease reaches a point of no return, after which the pathology autonomously progresses even without infection.

Will Targeting the Immune System Be Beneficial to Those with SchPAH? Is There a Way to Block the Inflammation that Causes Pulmonary Vascular Disease without Inhibiting the Global Host Response to the Parasite for Those Susceptible to Reinfection?

In SchPH mouse models, blocking type 2 immunity prevents the schistosomiasis-PH phenotype.[36] However, it is unclear if targeting inflammation later in the disease course can effectively reverse established disease, potentially even after parasite eradication when presumably the type 2 inflammation is reduced. Furthermore, broadly blocking type 2 inflammation in individuals that live in endemic locations may result in more severe reinfection if that occurs. Specific immune responses may be driving the pulmonary vascular disease; if so, precisely targeting host drivers or even vaccinating or inducing immune tolerance against specific parasite factors may prevent or reverse the pulmonary vascular disease without inhibiting the response to the parasitic infection more broadly.

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