# Pulmonary Vascular Diseases Secondary to Schistosomiasis

Ghazwan Butrous, MB, ChB, PhD School of Pharmacy University of Kent Canterbury, UK Schistosomiasis is the most common parasitic disease associated with pulmonary arterial hypertension (PAH). It induces remodeling via complex inflammatory processes produced by the parasite eggs. Changes in the pulmonary vasculature after *Schistosoma* infection are common, but may not always be associated with a clinical manifestation of PAH. Those patients who presented with PAH show clinical signs and symptoms that are not distinguishable from other forms of PAH.

Schistosomiasis (bilharziasis) is a major cause of pulmonary arterial hypertension (PAH) worldwide. It is estimated that more than 5 to 20 million people suffer from the clinical manifestation of PAH because of the *Schistosoma* parasite. The majority is in sub-Saharan Africa. Unfortunately, this cause of PAH is the least studied. Schistosomiasis remains one of the most prevalent parasitic infections in the world. An estimated 240 million people are affected. Africa is the main affected area, followed by the Eastern Mediterranean region, South America, and Western Pacific regions. The condition is not present in Europe or North America (Figure 1).<sup>1-3</sup> The disease is largely a rural problem, but urban foci can be found in many endemic areas.<sup>4</sup> Even though control programs have had reasonable success in many parts of the world, the number of people estimated to be infected or at risk for infection has not been reduced.<sup>5</sup> This is due at least in part to the fact that control is not universal because of econom-



Figure 1: Geographic distribution of schistosomiasis infection throughout the world. Bright red indicates severe endemic areas. Bubbles indicate factors that increase the infection rate and/or represent difficulties in control efforts.

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remodeling

ical and developmental projects and new irrigation programs that lead to a remarkable redistribution of schistosomiasis worldwide. Furthermore, there are reports of resistance to praziquantel, the mainstream medical treatment.<sup>6-9</sup>

The etiologic agents of schistosomiasis are blood flukes, which belong to the genus *Schistosoma* of the class of Trematoda of the phylum of Platyhelminthes (flatworms). The 3 most important species that affect humans are Schistosoma mansoni, Schistosoma japonicum, and Schistosoma haematobium. There are several other species of lesser importance, which infect humans in Africa and Asia. Schistosoma is a white-greyish, cylindrical organism approximately 1 to 1.5 cm in length. It can survive for up to 20 to 40 years within human hosts. Schistosoma has separate sexes living in the blood vessels in a continuous, monogamous embrace, which produce thin-shelled eggs when excreted in feces or urine.

# LIFE CYCLE

Understanding the Schistosoma life cycle (Figure 2) is essential for understanding the pathobiology of schistosomiasis and for disease control. Schistosoma eggs are excreted from the human host into a freshwater environment through urine or feces. When the eggs hatch, they release *miracidium*, which penetrates the freshwater snail intermediate host. They multiply asexually in the snail into a multicellular form called cercaria. The fork-tailed cercaria leaves the snail intermediate host provoked by daytime light onto the water or up to 72 hours seeking the skin of a suitable definitive host.<sup>10</sup> When they meet human skin or the skin of other mammalian hosts, the cercaria penetrate the skin by mechanical activity and via proteolytic enzymes. They travel via the venous or lymphatic vessels and migrate to the heart and lungs and then target their final organ location depending on the Schistosoma species (liver, bladder, or other organs). The females then start to produce hundreds to thousands of eggs per day.<sup>10</sup> Half the number of eggs produced are excreted with feces or urine, while the rest remain in the tissues.



Figure 2: *Schistosoma* life cycle. (1) Eggs; (2) *Miracidium*; (3) Intermediary freshwater snails; (4) *Cercaria*; (5) The path of the parasite after entering the venous system to the target organs.

## PATHOLOGICAL AND IMMUNOLOGICAL REACTIONS

Schistosoma eggs (with diverse antigens in their shells) are the main pathological agent. The host's immune reaction to egg antigens evokes the formation of granulomatous inflammation around parasite eggs. This is a cardinal feature of schistosomiasis, and the egg-associated pathology is central to the morbidity and mortality that occurs in infected humans. Granulomas are dynamic structures of clustered inflammatory cells, including epithelioid and multinucleated giant cells, macrophages, monocytes, and T cells in addition to eosinophils and mast cells, with the proportion of cells differing in different organs.<sup>11</sup> Activation of T cells in the granulomas (mainly CD4 and CD8 T cells) via both Th-1 and Th-2 responses are essential in the pathogenesis; this occurs predominantly via the release of inflammatory mediators like TNF- $\alpha$ , interferon- $\gamma$ , interleukin (IL)-4, IL-5, IL-10, IL-12, IL-13, IL-23, IL-17, and resistin-like molecule (RELM)-α.<sup>12,13</sup> Granulomas play an important role in destroying the ova; however, they also result in a fibrotic deposition in host tissue, which will cause the clinical manifestation of chronic schistosomiasis.14 The granuloma formation results in increased fibrosis and periportal collagen deposition,

which leads to a gradual obstruction of blood flow in the targeted organ.<sup>14</sup> For *S. mansoni*, for example, where the liver and spleen are the target organs, this will result in hepatosplenomegaly, liver fibrosis, and portal hypertension.

#### PATHOPHYSIOLOGY OF PULMONARY VASCULAR DISEASE DUE TO SCHISTOSOMIASIS

Pulmonary vascular pathology invariably precedes pulmonary hypertension (PH) development in schistosomiasis. The portal hypertension-induced venous shunts between the portal and systemic circulation facilitate the passage of Schistosoma eggs from the liver to the lungs.<sup>15-18</sup> Crosby et al<sup>19</sup> noticed that levels of bone morphogenetic protein receptor II (BMPR2) modify the pulmonary vascular response to chronic schistosomiasis. BMPR2+/- mice demonstrated dilatation of the hepatic central vein at baseline and post infection, compared with wild type, suggesting increased passage of eggs to the lungs. The eggs trapped in the lungs can induce isolated granulomas within the alveolar area.<sup>20</sup> In a study from our lab,<sup>21</sup> in mice infected with schistosomiasis, the liver was a target during infection and was enlarged more than 2-fold after infection. We noticed that 92% of the lungs harvested from these animals showed

evidence of granulomatous changes, secondary to egg deposition. However, the distribution of granulomatous lesions was heterogeneous. We also noticed remodeled pulmonary vessels in 46% of the lungs, but only near the granuloma. No remodeling was observed in the absence of granulomas, confirming the hypothesis that pulmonary vascular remodeling in PAH associated with schistosomiasis is caused by the local presence of granulomas. Others also observed a negative correlation between egg distance and degree of vascular remodeling.<sup>22</sup> Thus density and distribution of egg deposition within the lung can influence the degree of remodeling and subsequently the development of pulmonary vascular disease and clinical manifestation of PAH.<sup>21,23</sup> Histopathology of schistosomiasis-associated vascular diseases is similar to that of other forms of PAH, including occurrence of plexiform lesions.<sup>24,25</sup> However, some unique features were observed in autopsy specimens. For example, a dark pigment is commonly seen adjacent to vascular lesions. The etiology of this pigment is not known, but may represent either debris left from the parasite or remnants of the host response. Whole ova surrounded by granulomatous inflammation are rarely seen.26

The pathology of the remodeling process likely is inflammatory in nature.<sup>27</sup> In our lab, we noticed a significant increase in the number of mast cells (toluidine blue+), CD3+ cells, CD14+ cells, CD68+ cells, and CD15+ cells in Schistosoma-infected tissues compared with untreated healthy controls. Others also noticed an increase in the density of dendritic CD83+ cells.<sup>28</sup> These observations suggest that these cells may contribute to the pathophysiology of Schistosoma-induced pulmonary vascular remodeling.<sup>29</sup> This is not surprising, as it is well documented that multiple inflammatory mediators induce pulmonary vascular remodeling in a variety of PH models.<sup>30,31</sup> For example, IL-6 and IL-13 induce migration of pulmonary smooth muscle cells, thus contributing to pulmonary vascular remodeling.<sup>23,32-34</sup> Transforming growth factor (TGF)-β signaling seems to be particularly important in driving vascular remodeling.<sup>23,33</sup> It was also noticed that there is an

increase in RELM- $\alpha$  expression within pulmonary granulomas of schistosomiasis-infected mice, similar to that seen in hypoxia models of PH, thus implicating this molecule as a mediator of the remodeling process.<sup>33</sup> Other cytokines and mediators may also play a role.

## THE PREVALENCE OF PH SECONDARY TO SCHISTOSOMIASIS

The exact prevalence of pulmonary vascular disease caused by Schistosoma infection is not known. The presence of Schistosoma eggs in the lungs of African natives was described as early as 1885.<sup>35</sup> After that, several reports emerged from Egypt in the first half of the 20th century describing pathological and clinical manifestations of pulmonary vascular diseases secondary to infection by both S. mansoni and S. haematobium.36 In the second half of the 20th century, reports of many small series appeared in the literature, this time mainly from Brazil and occasionally a few cases from Africa, and more recently from China. In these studies, the prevalence ranged from 7.7% to 33%.<sup>37-40</sup>

Recently, more carefully controlled methodological studies were conducted in patients with hepatosplenic schistosomiasis and liver fibrosis in Brazil, and results determined that 7.7% to 10.7% of patients were diagnosed with PH.<sup>38,39,46</sup> It is, however, difficult to estimate the real prevalence of pulmonary vascular diseases worldwide, as this depends on many factors such as the geographical distribution, the public health status, differences in antigenicity and immune responses, and progress of the pathological changes. It is suggested from our experimental observations that the changes in the pulmonary vasculature after Schistosoma infection are far more common, but may not always be associated with significant increases in pulmonary vascular resistance or full clinical manifestations of PAH.<sup>21</sup>

### CLINICAL PRESENTATION OF SCHISTOSOMIASIS-INDUCED PAH

The pulmonary involvement of schistosomiasis can be as early as the first exposure to infection. Acute schistosomiasis (Katayama syndrome) is common



Figure 3: A chest radiograph of a 52-yearold man with schistosomiasis-associated pulmonary arterial hypertension, resulting in right ventricular hypertrophy and a dilated pulmonary trunk. Reproduced with permission from Safwat T. Bilharzial pulmonary hypertension with aneurysmal pulmonary artery dilatation. *PVRI Rev.* 2009;1:139.

in those infected with any Schistosoma species for the first time. Thus, this is commonly seen in nonimmune travelers or immigrants to Schistosoma-endemic regions.<sup>3,41,42</sup> The early symptoms of acute schistosomiasis are usually nonspecific symptoms such as nocturnal fever, cough, dyspnea, myalgia, headache, and abdominal tenderness with eosinophilia, and lymphadenopathy. The condition can be resolved without morbid consequences. On the other hand, chronic pulmonary disease is more common in endemic areas, but may not always produce any clinical symptoms. It is usually after repeated infections with a high antigenicity load of eggs that severe remodeling of the vessels produces PH with a significant increase in the pulmonary vascular resistance and consequently right heart failure.<sup>21</sup> These patients generally present with signs and symptoms that are not distinguishable from other forms of PAH, such as dyspnea on exertion, anemia, fatigue, weakness, cough, dizziness, fainting, and exercise intolerance. Physical examination may reveal a prominent pulmonic component of the second heart sound and right ventricular heave and digital clubbing. Radiographs may reveal cardiomegaly, particularly dilatation of the right ventricle and right atrium, and enlarged pulmonary trunk and arteries, with pruning of the distal vasculature. It was demonstrated that pulmonary artery enlargement is more pronounced in schistosomiasis-induced PAH than another form of PAH, suggesting that this is a more distinct feature of schistosomiasis-induced PAH (Figure 3).<sup>43-45</sup> Electrocardiography may show right ventricular hypertrophy or strain and right atrial enlargement, and may also reveal a right bundle branch block. Echocardiography may demonstrate right ventricular dilatation, potentially compressing the left ventricle with septal bowing, usually accompanied by right atrial dilation, tricuspid valve regurgitation, and an increased pressure gradient across the tricuspid valve as well as dilatation of the main pulmonary artery.

To assess causality, it is important to rule out other causes of PH. Patients in endemic areas should be suspect to have schistosomiasis as the cause of PH if they exhibit signs of prehepatic portal hypertension.<sup>9</sup> We do not yet have biomarkers or serological tests to help in the diagnosis.<sup>46</sup> It is, however, essential to perform right heart catheterization in order to provide a direct measurement of the mean pulmonary arterial pressure and to assess right ventricular function and pulmonary artery wedge pressure (PAWP). It is worth mentioning that about 13% of patients will also have compromised left ventricular function with an increase in PAWP.47 In addition, acute vasodilator challenge may be performed, but only a small number of patients exhibit a significant vasodilator response.48

#### TREATMENT OF SCHISTOSOMIASIS-INDUCED PAH

There are no clinical trials to confirm the application of any of the currently approved therapies for other types of PAH in schistosomiasis-PAH. Our current evidence is mainly observational from various centers all over the world. It has been conventional in many centers to treat these patients with the current modalities such as phosphodiesterase-5 inhibitors or endothelin receptor antagonists.<sup>49,50</sup> Treatment with an anthelmintic drug, such as praziquantel is warranted in cases of active schistosomiasis. This helps reduce the antigenic load, thus reducing the granulomata and probably preventing further deterioration.<sup>22</sup> Interventions aimed at targeting

inflammation, such as corticosteroids, may be useful, but it is uncertain whether they have any significant effect on the pulmonary vascular pathology. The prognosis of this condition has not been systematically studied. Initial small observations showed a more benign clinical course than in cases of idiopathic PAH.<sup>48</sup>

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