Pulmonary vascular disease associated with parasitic infection —the role of schistosomiasis

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Abstract

Parasitic diseases have been known to cause pulmonary vascular lesions. Schistosomiasis is the most common parasitic disease associated with pulmonary arterial hypertension, although other trematodes have been implicated. Systematic evaluation of and interest in this problem have been rekindled because of the current availability of pulmonary arterial hypertension treatment.

Keywords

Parasitic disease; pulmonary arterial hypertension; review; schistosomiasis

Schistosomiasis

Schistosomiasis (or bilharzia, bilharziosis or snail fever) is a parasitic disease caused by trematode flatworms of the genus *Schistosoma*. The parasites were first identified in 1851 by Theodor Bilharz, a German pathologist working in Egypt.

There are 24 species of *Schistosoma*, and they can be split into four distinct groups on the basis of the compatibility of species with particular snail host genera and geographical distribution, as well as common egg morphologies. Among these species, six cause disease in humans, with the three main species being *Schistosoma mansoni*, *Schistosoma japonicum* and *Schistosoma haematobium* [1]. Some species also infect wild animals and domestic stock (e.g. *S. japonicum*), and others are primarily veterinary pathogens (*Schistosoma bovis*, *Schistosoma mattheii* and *Schistosoma curassoni*) [2].

There is currently no vaccine available, and primary treatment for human schistosomiasis is the drug praziquantel, which is usually effective in a single dose. However, praziquantel does not prevent re-infection, is inactive against juvenile schistosomes and has only a limited effect on already developed liver and spleen lesions. Praziquantel is also limited by the emergence of schistosome phenotypes that are resistant to this drug [3]. Alternative treatments include oxamniquine [4,5].

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In this review, we will concentrate on pulmonary and inflammatory manifestations caused by *Schistosoma* infection, even though the lung is a mandatory step in the parasite cycle. These manifestations can be acute or chronic, depending on the phase of the cycle. Morbidity resulting from chronic manifestations is particularly severe and should be prevented whenever possible.

Life cycle of schistosomes

Schistosomes have a vertebrate–invertebrate life cycle, in which humans are a definitive host. The first step in the cycle is infection of a freshwater snail by the miracidium, a small, free-living larva that swims and penetrates specific snail inter-mediate hosts within 1–24 h. In the snail, miracidia transform into the next larval stage, cercariae, which subsequently emerge from the snail. The cercariae remain swimming in fresh water using a whip-like tail (for a maximum of 48 h) at speeds of about 4 m/h, and can penetrate the skin of people working or bathing in the infected water in 3–5 min. Cercariae have the ability to attach to human skin and, through secretion of enzymes, break down skin proteins and invade the new host. After penetration, they may remain in the skin for 1–2 days. After infecting humans, cercariae shed their tails and become schistosomula, which migrate in the venous circulation, pass through the lungs, and home to their target organ, where they mature and unite. A pair of worms, male and female, attaches to the superior mesenteric veins (*S. mansoni*), the inferior mesenteric and superior haemorrhoidal veins (*S. japonicum*) or the vesical plexus and veins draining the ureters (*S. haematobium*). About 4–6 weeks after infection, schistosomes begin to produce eggs, and this continues for the parasite's entire lifespan, usually 3–5 years (about 300 eggs per day for *S. mansoni* and up to 3000 eggs per day for *S. japonicum*). Eggs are excreted in the faeces (*S. mansoni* and *S. japonicum*) or urine (*S. haematobium*). Under optimal conditions, the eggs hatch within 30 min, releasing miracidia. Nevertheless, many of the eggs remain within the host, resulting in focal granulomatous reactions. Eggs laid by *S. mansoni* and *S. japonicum* remain in the tissues within the hepatic portal system, resulting in pre-hepatic fibrosis and portal hypertension.

Chronic portal hypertension can result in the opening of portocaval shunts, allowing eggs to migrate from the portal system to the pulmonary parenchyma. Within the lungs, the eggs induce an immune response, which similarly results in severe granulomas. However, a unique pathology of pulmonary arterial vascular remodelling is also manifested, resulting in clinical pulmonary arterial hypertension (PAH) [1,6–8].

Epidemiology

Schistosomiasis affects over 200 million people worldwide, resulting in more than 250 000 deaths and up to 4.5 million disability-adjusted years lost annually [9–15]. The chronic morbidity of schistosomiasis includes anaemia, fatigue, undernutrition and chronic pain. Schistosomiasis is endemic in 74 countries, including throughout Africa, Brazil, the Middle East and Southeast Asia. Schistosomiasis is the third most common parasitic disease worldwide after malaria and amoebiasis.

Cercariae are found in fresh water in endemic regions, resulting in human infection in the context of daily activities, including farming, walking, bathing and swimming. Despite the

availability of antihelminthic agents such as praziquantel, endemic areas can have case-prevalence rates in excess of 50%. Treated individuals are re-infected upon re-exposure, making the disease difficult to completely eradicate. Socio-economic development projects such as the construction of dams, natural disasters, including flooding, and poor sanitary conditions all combine to result in high prevalence rates within underdeveloped and developing regions [16].

Of all people infected with *Schistosoma* worldwide, approximately 10% of those chronically infected with *S. mansoni* develop hepatosplenic disease, resulting in pre-portal fibrosis and portocaval shunting, including oesophageal varicies [17]. Approximately 10–20% of those with hepatosplenic disease, or 2–5 million people worldwide, develop PAH, a progressive and fatal illness [18]. This high prevalence makes schistosomiasis one of the most common causes of PAH worldwide [19], resulting in considerable mortality and morbidity, although the precise disease burden is unknown.

Clinical manifestations of Schistosoma infection

Patients initially infected with *Schistosoma* develop a maculo-papular rash at the site of parasite penetration within hours of infection [20]. This reaction lasts for several days and then spontaneously resolves as the cercariae transform into schistosomula and move into the systemic venous system. The rash, also called cercarial dermatitis, occurs more commonly in people infected for the first time than in chronically infected and re-infected individuals.

As the parasite embolizes through the systemic venous circulation to the pulmonary arterioles, it causes a generalized inflammatory response in the host, termed Katayama fever. This self-limiting syndrome is characterized by fevers, chills, shortness of breath and a dry cough [21]. Physical examination may reveal tender hepatomegaly and splenomegaly [20]. Chest radiographs may show a patchy alveolar infiltrate. Laboratory studies reveal peripheral eosinophilia. Katayama fever begins 2–12 weeks after primary infection, and can last for several weeks, before spontaneous resolution as the parasite passes through the lungs and migrates through the systemic arterial circulation to its target organ.

The symptoms of chronic *Schistosoma* infection depend on the specific parasite and the severity of disease. Patients with intestinal *S. mansoni* or *S. japonicum* infection can have abdominal pain, diarrhoea and iron-deficiency anaemia, with the resulting constitutional symptoms including weight loss, undernutrition and chronic fatigue. Patients with hepatosplenic disease have the symptoms of intestinal *Schistosoma* infection plus the symptoms resulting from pre-portal fibrosis and portal hypertension, including splenomegaly and the formation of oesophageal and haemorrhoidal varicies with resultant bleeding (potentially massive and fatal). However, because the disease remains pre-portal, cirrhosis does not generally result. Patients with chronic *S. haematobium* infection have symptoms resulting from chronic inflammation of the venous plexus around the bladder, including haematuria, fibrosis with ureteral obstruction and nephrolithiasis, and squamous cell carcinoma of the transitional epithelium of the bladder [22].

In patients with chronic *Schistosoma* infection, eggs can embolize throughout the body, with focal granulomatous reactions and symptoms that depend on the precise location of

deposition. One of the most sensitive locations is the central nervous system, with the consequence of focal or generalized tonic–clonic seizures or focal neurological deficits [20,23].

Schistosomiasis-associated PAH

PAH is one of the pulmonary manifestations in schistosomiasis, particularly in its hepatosplenic presentation. Portal hypertension almost invariably precedes PAH in schistosomiasis, establishing venous shunts between the portal and systemic circulation, allowing the passage of schistosome eggs from the liver to the lungs [24]. In one recent series of 65 patients, the incidence of PAH (pulmonary artery systolic pressure >40 mmHg) in patients with hepatosplenic disease referred to a gastroenterology clinic was 18.5% on echocardiography, and PAH was confirmed in 7.7% by right heart catheterization [25] (Loureiro *et al.*, American Heart Association, 2004, Abstract No. 2659, pp. III-572). Other reports from two pulmonary referral centres in Brazil demonstrated that, among all the patients, 30% had symptoms of PAH associated with schistosomiasis [26]. Analysis of chest radiographs revealed that among 115 schistosomiasis patients, 84 had radiographs compatible with cardiopulmonary abnormalities, including 11 suggestive of PAH [27]. Portopulmonary hypertension and PAH associated with schistosomiasis have also been described in Africa [28].

Patients who develop schistosomiasis-associated PAH have the signs and symptoms of this condition, primarily resulting from progressive right heart failure. Initial symptoms include dyspnoea, fatigue and exercise intolerance. As the disease progresses, patients can experience chest pain from right ventricular angina and syncope caused by from depressed cardiac output and low systolic blood pressure. Physical examination may reveal a prominent pulmonic component second heart sound (P2), right ventricular heave and digital clubbing. Patients with frank right heart failure manifest cyanosis and peripheral oedema or anasarca. 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 (Fig. 1). Electrocardiography typically shows right ventricular hypertrophy or strain and right atrial enlargement, and may also reveal a right bundle branch block. Echocardiography demonstrates 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. Finally, right heart catheterization (when available) is used to confirm the diagnosis of PAH in the absence of an elevated pulmonary artery occlusion pressure.

Specific prognostic data from patients with schistosomiasis-associated PAH arelacking, but the prognosis is probably similar to that with other forms of PAH, including idiopathic PAH (IPAH). Patients with untreated IPAH usually die within 3–5 years after initial presentation, the lifespan being <1 year in those with severe symptoms [29]. It is of note that patients with varical bleeding as a consequence of schistosomiasis portal hypertension who receive surgical portocaval shunt therapy can have poor short-term outcomes, because of the development of PAH [30].

Histopathology of schistosomiasis-associated PAH

The pulmonary histopathology of schistosomiasis-associated PAH has similarities to and differences from other forms of PAH that are more common in the developed world, most classically IPAH. The pathology of IPAH includes focal alterations in all layers of the arterial vasculature, including the intima, media and adventitia. However, the precise distribution of lesions is not known, as both abnormal and normal vasculature are often seen concurrently even in the same specimen. Examples of vascular lesions seen at autopsy in a patient who died of schistosomiasis-associated PAH are shown in Fig. 2.

There are four types of intimal lesion: concentric thickening, eccentric thickening, plexiform, and dilated or angiomatoid [31]. Lesions with concentric thickening have an onion skin appearance, with multiple layers. Eccentric lesions may result from old or chronic thrombus that has become largely incorporated into the vessel wall. Plexiform lesions are focal proliferations of endothelial cells resulting in focal tortuous passages. Dilated or angiomatous lesions may be located downstream of plexiform lesions resulting from the focal turbulence in blood flow.

The vascular media can be thickened in association with or in locations distinct from the endothelial lesions. Most severe forms of PAH, including that associated with schistosomiasis, are probably inflammatory in nature [32], with an inflammatory infiltrate often being seen around the adventitia of affected vasculature. Remarkably, there is evidence that this infiltrate, and potentially many of the cells forming the vascular media and intimal lesions, are derived from the circulatory system [33,34].

Most of the molecular studies on PAH have been performed in IPAH and connective tissue disease-associated PAH. Many of the pathological lesions manifest as an imbalance between the proliferation and death of vascular cell elements [35]. Elements of abnormal cell proliferation include clonality, loss of tumour suppression, and germline mutations in familial disease, specifically in the bone morphogenic protein receptor type 2 (BMPR-2). Pathological endothelial cells also display resistance to normal cell death through apoptosis [36]. Remarkably, these characteristics are all highly suggestive of neoplasia [37–39]. It is unclear at this time what the roles of BMPR-2, clonality and dysregulated proliferation are in schistosomiasis-associated PAH.

The pathology of schistosomiasis-associated PAH is unique, in that a dark pigment is commonly seen adjacent to vascular lesions (see example in Fig. 2d). The aetiology 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.

Schistosomiasis, inflammation and PAH

The pathology associated with schistosomiasis is mostly attributed to the intense granulomatous inflammation and subsequent fibrosis induced by parasite eggs that become trapped in host organs.

The primary response is caused by migrating parasites in the circulatory system, and shows characteristics of a type 1 T-cell response (Th1)—production of proinflammatory cytokines

such as interleukin (IL)-1 [6,7,40], IL-12 [41–44], inter-feron-γ (INF-γ) [6,45], transforming growth factor-β (TGF-β) [42,46] and tumour necrosis factor-α (TNF-α) [7,41]. They may modulate the release of chemokines such as CXCL2, CXCL5, CXCL9, CXCL10, CXCL11, CXCL22, CCL3, CCL7, CX3CR1, RANTES and lymphotactin (XCL1) [2].

The secondary response is caused by schistosome eggs and egg-derived antigens, which are potent and independent inducers of the type 2 T-cell response (Th2). Transition to the Th2 response occurs approximately 8 weeks post-transfection, and is characterized by secretion of IL-4 [2,43,47], IL-5 [48], IL-10 [49,50] and IL-13 [45,51,52].

Although Th2-mediated pathology is ultimately detrimental to the host, it is also clear that granulomas serve an important host-protective function during infection. In chronically infected hosts, schistosome eggs provide a chronic antigenic stimulus for the immune response [52]. If these antigens are not sequestered or neutralized effectively, they may damage host tissues, the liver being particu larly sensitive [52–54]. CD4$^+$ T-cells are essential for granuloma formation, and early studies examining the respective roles of Th1-associated and Th2-associated cytokines showed that the granulomatous response evolves from an early Th1-type to a sustained and dominant Th2-type cytokine response [55–57]. Granuloma formation therefore occurs in an environment that is initially proinflammatory and type 1-like, but switches rapidly to one that is predominantly type 2-like.

Interestingly, recent reports have suggested that inflammation plays an important role in pulmonary hypertension. T-cells, B-cells, mast cells, macrophages and dendritic cells, as well as inflammatory cytokines and chemokines, were identified in the lungs of patients with PAH, in remodelled small pulmonary arteries including plexiform lesions. Several cytokines, as well as receptors, are reported to be increased in PAH patients [58–62], and cytokine antagonist therapy has been tested with the experimental monocrotaline model of PAH, including antagonists to IL-1 [63], RANTES [64], CCL2 [65] and CX3CR1 [66].

Little is known about the direct effects of *Schistosoma* infection on the pulmonary vasculature, and more studies need to be performed. A recent publication correlated cytokines with pulmonary remodelling, and provided some new insights on the topic [59]. Interestingly, some of the cytokines were seen to be increased in a time-dependent manner, in parallel with vascular changes and plexiform lesion formation, whereas right ventricular hypertrophy was not observed. Moreover, a significant positive correlation between the number of muscularized small peripheral vessels and the lung egg burden was reported [59].

As inflammation is the main feature of *Schistosoma* infection and plays a role in the pulmonary vasculature as well, correlation of different cytokines with schistomiasis and PAH is characterized below.

IL-1, a profibrotic cytokine secreted by monocytes and macrophages, is released in the early stages of *Schistosoma* infection [40]. On the other hand, an IL-1 antagonist was shown to lower pulmonary artery pressure in acute respiratory distress syndrome associated with PAH in a piglet model [67], whereas an IL-1 receptor antagonist reduced pulmonary artery pressure and right heart hypertrophy in monocrotaline-treated rats [63].

IL-4 is one of the major Th2 cytokines that stimulates proliferation of activated B-cells and controls the release of other cytokines. Its important role was demonstrated in many studies in which IL-4 levels increased after infection [68–70]. Moreover, administration of IL-4 with schistosome eggs led to increased granuloma size, whereas anti-IL-4 treatment or IL-4 knockdown suppressed granuloma formation and hepatic fibrosis [43,47,51]. Concerning the lungs, the role of IL-4 role is mostly clearly shown for asthma [71,72]. The role of IL-4 in PAH is less clear, but IL-4 can potentiate pathogenic autoreactive B-cells, which are present in the plexiform lesions in some models and may produce anti-endothelial antibodies [73,74]. In a recent study, it was demonstrated that IL-4 levels increase in a time-dependent manner after *Schistosoma* infection in a murine model of PAH [59]. It was also reported that the severity of pulmonary arterial remodelling was correlated with the levels of IL-4 in bronchoalveolar lavage fluid [75].

IL-5 was reported to participate in the maturation of eosinophils and in tissue eosinophilia associated with *Schistosoma* infection [48]. It has been suggested that different variants of the *IL-5* gene region may modulate the immune response to *Schistosoma* infection [69]. With respect to PAH, the effect of IL-5 may be similar to that of IL-4, and the severity of pulmonary arterial remodelling correlates with the levels of IL-5 in bronchoalveolar lavage fluid in a murine model [75].

IL-6 acts as both a proinflammatory and an anti-inflamma-tory cytokine, and is secreted by T-cells and macrophages to stimulate the immune response. It was reported that *Schistosoma* infection induces IL-6 secretion *in vitro* in human and mouse lung microvascular endothelial cells, as well as *in vivo* in the pulmonary microvasculature in mice [76]. IL-6 correlates with the development and progression of pulmonary vascular remodelling [59], and has been shown to be proproliferative [77,78].

A major function of IL-10 is to limit and ultimately terminate inflammatory responses, effectively controlling immune responses and tolerance *in vivo*. The levels of IL-10 have been demonstrated to be elevated in schistosomiasis patientsand to be associated with the inhibition of fibrosis, owing to IL-10's antifibrotic and anti-inflammatory effects [50,53,68,70,79]. In mice infected with *Schistosoma*, IL-10 levels increase in a time-dependent manner, in parallel with vascular remodelling [59]. Additionally, when overexpressed, IL-10 signals via haem oxygenase-1. IL-10 has been reported to reduce mean pulmonary artery pressure and the remodelling effect of monocrotaline-induced PAH, as well to inhibit the proliferation of cultured human pulmonary artery smooth muscle cells (PASMCs) [80].

IL-13 is known to induce physiological changes in parasitized organs that eliminate the offending organisms or their products. IL-13 has been reported to be induced after *Schistosoma* infection [45,51,52,59,69], and several studies performed in mice using IL-13 suppression [81] and inhibition [82], demonstrated decreased inflammation after *Schistosoma* infection. In the lung, depletion of IL-13 significantly ameliorated pulmonary arterial muscularization in mice exposed to inhaled *Aspergillus* [75] and was reported to prevent emphysema and pulmonary inflammation. Moreover, IL-13 stimulates PASMC migration, which is probably significant in vascular remodelling [59].

The IFN-γ level is elevated after *Schistosoma* infection [68,68,70]. IFN-γ is associated with protection against fibrosis [79]. IFN-γ was reported to induce human PASMCs to release endothelin-1, which is a potent vasoconstrictor and comitogen for vascular smooth muscle [83]. IFN-γ produced at high levels in inflammation acts on endothelial cells to modulate the evolution of the inflammatory response and endothelial damage [84].

TGF-β is a multifunctional cytokine that controls proliferation, cellular differentiation [85,86] and other functions in many cells. It is known to play a role in immunity [50,87], cancer [86,87], heart disease and fibrosis [86]. In schistosomiasis, TGF-β suppresses hepatic inflammation, whereas TGF-β blockade significantly increases the production ofIL-4, IL-6, IL_17, TNF-α and IFN-γ [46,50], as well as neutrophilia [50]. It has been reported that TGF-β levels are elevated in PAH patients [88]. Moreover, genetic mutations in members of the TGF-β receptor superfamily, mostly BMPR-2, are observed in patients with familial PAH and are associated with changes in the structure of the lung vasculature [89–93]. Additionally, TNF-α, IL-1β and IL-10 levels correlate with pulmonary vascular changes in *Schistoma*-infected mice [59].

Pulmonary Vascular Diseases Associated with Other Parasitic Diseases

Wuchereria bancrofti (Filaria) is a parasitic filarial nematode worm spread by mosquitoes. It largely affects areas across the broad equatorial belt (Africa, Turkey, India, Southeast Asia, Philippines, Oceanic Islands, Australia and parts of South America). If the *W. bacrofti* infection is left untreated, it can develop into a chronic disease called elephantiasis [94,95].

Filarial worms are known to cause PAH in animals, and it has been shown that this disease may also cause human PAH [96–99]. Many studies in dogs suggest that *Dirofilaria immitus* (heartworm) is the cause of pulmonary diseases, and its effect on pulmonary arterial pressure has been noted [100–103], as well as its effect on lesion formation [102]. It has also been demonstrated that chronic mild interstitial lung disease persists in tropical pulmonary eosinophilia [104]. *W. bancrofti* can also cause acute or refractory bronchial asthma [105]. Current therapy for filariasis includes treatment with albendazole, ivermectin, doxycline and diethylcarbamazine [106–110].

Clonorchis sinensis lives in the liver of humans, and is found mainly in the common bile duct and gall bladder, feeding on bile. *C. sinensis* is endemic in Japan, China, Taiwan and Southeast Asia. A few cases of PAH have been associated with this parasite [95].

Conclusions

Schistosomiasis is a common cause of PAH and a prototypical model for other inflammatory causes of PAH. The antihelminthic agent used for the treatment of schistosomiasis is praziquantel, but it appears to have little effect on patients with schistosomiasis-associated PAH after prolonged chronic infection [111]. The effects of more conventional PAH therapies on schistosomiasis have been very poorly investigated.

Phosphodiesterase (PDE) inhibitors are currently used to treat PAH [112–114], and the PDE5 inhibitors sildenafil and tadalafil are in clinical use [115–119]. PDE and its inhibitors

have been reported to affect schistosomes [120–122], which could also be a promising targets. Small studies have suggested that PDE5 inhibitors can be effective in treating schistosomiasis-associated PAH (Loureiro *et al.*, American Heart Association, 2004, Abstract No. 2659, pp. III-572) [123].

Recent reports have suggested that tyrosine kinase (TK) inhibitors could have anti-remodelling effects and also reverse the PAH changes [124–129]. Interestingly, effects of TKs on adult schistosomes have been reported, and some studies have suggested that TKs directly affect adult worms [130–133].

The pathogenic mechanism by which the combination of the parasite's effect on the host and the host's immune response to the parasite results in PAH remains largely unknown at this time. Further basic science and clinical research is necessary to determine elements of this process that could be amenable to future treatments for *Schistosoma* infection in general and schistoschomiasis-associated PAH specifically. In particular, agents directed at blocking or reversing inflammation caused by the parasite antigens and proliferation of vascular elements may be required for complete treatment of the disease.

Transparency Declaration

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FIG. 1.
A chest radiograph of a 52-year-old man with schistosomiasis-associated pulmonary arterial hypertension, resulting in right ventricular hypertrophy and a dilated pulmonary trunk. Reproduced with permission from Safwat, *PVRI Review* 2009; 1: 139 [134].
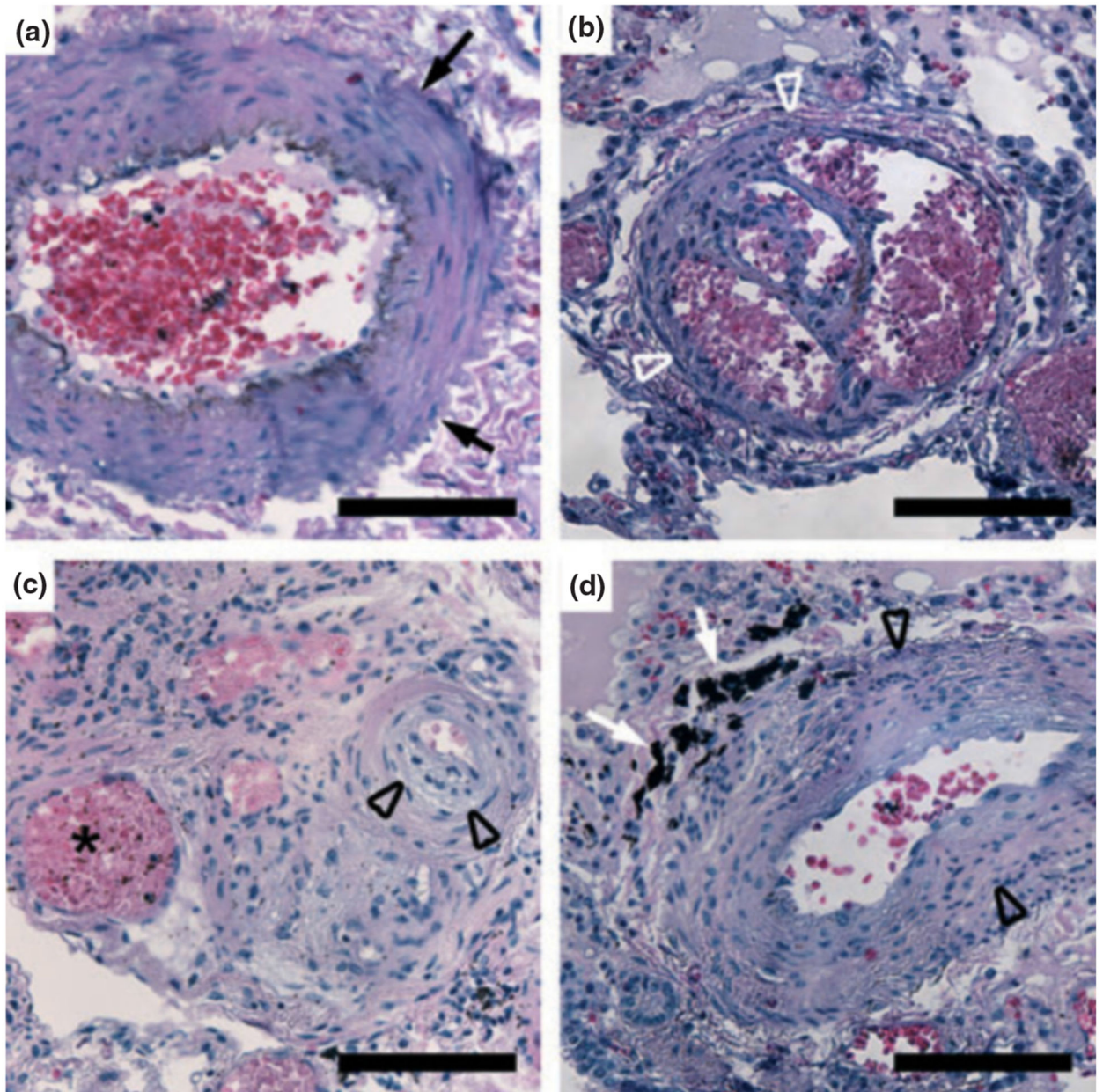
FIG. 2.

Representative pulmonary pathology from a patient who died of schistosomiasis-associated pulmonary arterial hypertension. (a) Medial hypertrophy (arrows). (b) Plexiform lesion (white arrowheads). (c) Eccentric intimal thickening (black arrowheads) and a dilated or angiomatoid lesion (star). (d) Pigment (white arrows) adjacent to intimal thickening (black arrowheads). All scale bars are 100 μm.