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Immunopathological aspects of schistosomiasis-associated pulmonary arterial hypertension

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Summary *Objectives:* Pulmonary hypertension is a lethal complication of chronic hepatosplenic schistosomiasis. Little is known of the underlying (immuno-)histopathological characteristics of lung vasculopathy.
Methods: We characterized vasculopathy and inflammation in lung tissue of 10 patients with *Schistosomiasis*-associated PH (SCH-PH) in comparison to 22 idiopathic pulmonary arterial hypertension (IPAH) patients and 10 normal controls. SCH-PH cases were younger than controls.
Results: Plexiform lesions and/or angiomatoid lesions were found in 10/10 SCH-PH, and 19/22 IPAH patients (χ^2 $p = 0.22$). Lung granulomas with *Schistosoma* eggs were found in 2/10 of SCH-PH cases. PAH cases had increased peri-arterial density of CD3+ T cells, chymase+ and tryptase+ mast cells when compared to controls ($p \leq 0.047$). SCH-PH showed increased density of CD4+ cells when compared to controls ($p = 0.025$), paralleled by an increased density of dendritic CD83+ cells when compared to both controls and IPAH patients ($p \leq 0.022$).
Conclusion: Both SCH-PH and IPAH feature plexogenic arteriopathy and increased periarterial T cell and mast cell density. SCH-PH and IPAH differ only with respect to the density of

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dendritic CD83+ cells. These findings imply ongoing antigenic stimulation in SCH-PH, yet a pattern of pulmonary vasculopathy similar to IPAH, suggestive of a final common pathway in their pathogenesis of PAH.

Introduction

Schistosomiasis (bilharzia), particularly the hepatosplenic form, is complicated by pulmonary arterial hypertension (PH) in up to 10% of cases.[1–3] Despite the success of sanitary measures and antiparasitic treatment over the last 40 years in Brazil,[4] it is likely to still be among the leading causes of pulmonary hypertension in this area.[2,5]

In the chronic phase of *Schistosoma mansoni* infection, mature helminths have settled in the enteric vascular bed to produce eggs that either pass through the vessel wall into the intestinal lumen to be shed with faeces, or are washed into the portal circulation. These eggs elicit a fierce granulomatous inflammatory response that causes ulceration of the intestines, and pipestem fibrosis (Symmer's fibrosis) of the portal vascular tract. The latter may lead to portal hypertension, which, in turn, allows eggs to reach the pulmonary circulation via the collateral circulation.[6–8]

Similar to the portal tract, *Schistosoma* eggs embolizing the pulmonary arteries may result in scarring and occlusion of vessels.[6,7,9,10] Such lesions form the predominant pattern of pulmonary vasculopathy in schistosomiasis-associated pulmonary hypertension (SCH-PH), as originally described by Chaves in the 1960's.[6–8] Hence, the disease was formerly considered to be mainly a thrombo-embolic type of pulmonary hypertension.[11]

The onset of SCH-PH is mostly in adulthood, similar to idiopathic PAH (IPAH).[5] This indicates that the lag time between acute infection, usually in early childhood, and the development of pulmonary hypertension might be over 20 years.[12] Once pulmonary hypertension has established in schistosomiasis patients, antiparasitic therapy (e.g. praziquantel) is believed to have no effect on disease progression (reviewed in Ref. 13). This indicates that the disease has become self-perpetuating, similar to IPAH. Preliminary evidence suggests that an IPAH targeted therapy may be effective in SCH-PH.[12,14] Historic reports of SCH-PH series suggest that the disease may bare similarities to IPAH with respect to the histopathological features of pulmonary vasculopathy.[6–8,15] However, formal quantitative comparison has, as yet, not been performed.

In this study, we hypothesized that, beside vascular lesions related to *Schistosoma*-egg emboli and its inflammatory response, pulmonary vascular remodeling similar to IPAH takes place in SCH-PH. We tested this hypothesis by comparing the histo- and immunopathological features of pulmonary vasculopathy in autopsy/biopsy/explant specimens in SCH-PH patients to IPAH patients and normal controls.

Patients and methods

This study was approved by the Institutional Review Boards of the São Paulo University Medical School and VU medical center, Amsterdam.

Study population

Cases with the autopsy diagnosis of *Schistosoma*-associated pulmonary hypertension or IPAH were retrieved from the files of the Department of Pathology of the São Paulo University Medical School (USP), São Paulo, Brazil, during the period of 1993–2006. In addition, nine cases were retrieved from the pulmonary hypertension biobank at the department of pathology of the VU Medical Center, Amsterdam, The Netherlands (seven autopsy cases, one explanted lung, one surgical lung biopsy). These cases were previously published in comparative histopathological studies of systemic sclerosis-associated PAH and IPAH.[16,17]

A group of controls, *i.e.*, patients from the São Paulo area without a history of pulmonary diseases, all non-smokers who died of acute cardiovascular disease ($n = 9$) or acute pancreatic disease ($n = 1$) and had normal lungs at autopsy were used in the quantitative analysis of the inflammatory infiltrate (Table 1).

We reviewed case records including autopsy reports to confirm the diagnosis of pulmonary hypertension, defined as the presence of a systolic pulmonary artery pressure higher than 40 mmHg assessed by echocardiogram when present, and presence/absence of schistosomiasis, and excluded cases with other known causes of pulmonary hypertension, extensive bronchopneumonia, diffuse alveolar damage, pulmonary hemorrhage, or lung cancer. For the cases that met the above mentioned criteria, the following clinical parameters were assessed: age, sex, clinical and functional data related to pulmonary hypertension diagnosis (clinical signs of right heart failure, electrocardiogram, systolic and mean pulmonary artery pressure as estimated by transthoracic doppler echocardiogram and/or as measured by right heart catheterization) and clinical data related to schistosomiasis diagnosis (history of infection, active infection in rectal mucosa biopsy or stool analysis). In addition, chronic schistosomiasis diagnosis was confirmed by liver and spleen histological assessment at autopsy. Clinical charts of PAH treatment regimens were incompletely available. Treatment

Table 1 Summarized case characteristics. SCH-PH = Schistosomiasis associated pulmonary hypertension. IPAH = idiopathic pulmonary arterial hypertension. M = male, F = female.

Group	Sex	Age (years) (mean ± SD)
SCH-PH ($n = 10$)	2M/8F	32.8 ± 7.1
IPAH ($n = 22$)	8M/14F	42.9 ± 14.6
Controls ($n = 10$)	4M/6F	52.6 ± 5.8*

*Age distribution differed among the groups ($p = 0.002$, one way ANOVA). SCH-PH cases were younger than controls ($p < 0.001$).