

## Schistosomiasis: a case of severe infection with fatal outcome

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### ABSTRACT

Schistosomiasis is one of the most common parasitic diseases, still considered of public health significance. Acute schistosomiasis is of difficult diagnosis and therefore has been overlooked, misdiagnosed, underestimated and underreported in endemic areas. The delay between the exposure to contaminated water and the initial symptoms may explain this challenging diagnosis. Acute schistosomiasis is frequently reported in non-immune individuals while reinfection cases occurring in endemic areas is scarcely documented. The later usually shows a benign course but fatal cases do exist. The authors report a case of a young female patient, in the late puerperium, with a three-month history of weight loss, intermittent fever, cough, thoracic and abdominal pain and increased abdominal girth. Physical examination showed a tachycardia, tachypnea and hypotension. Laboratory tests showed a mild anemia, eosinophilia, and a slightly elevation of liver enzymes. Thorax and abdominal multidetector computed tomography evidenced a diffuse and bilateral pulmonary micronodules and peritoneal and intestinal wall thickening. The patient progressed rapidly to hepatic insufficiency, and death after respiratory insufficiency. An autopsy was performed and the findings were compatible with acute Schistosomiasis in a patient previously exposed to *Schistosoma mansoni*.

**Keywords:** Schistosomiasis; Hepatic insufficiency; Respiratory insufficiency; Autopsy.

### CASE REPORT

A 25-year-old female patient sought medical attention complaining of a three-month history of weight loss, intermittent fever, nonproductive cough, thoracic pain, abdominal pain and increased abdominal girth, nausea and vomiting. She presented syncope on the day she was admitted

in the hospital. Symptoms had begun two weeks after her third deliver. Her past obstetrics history comprised three gestations without pre natal care all of them were uneventful. She denied any other comorbidity, allergy, smoking, alcoholism, prior blood transfusion or similar cases in her family.

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She lived in a Brazil's northeastern state that is well known for high prevalence of schistosomiasis. Physical examination demonstrated tachycardia with pulse rate of 100 beats per minute, blood pressure of 90 × 60 mmHg, tachypnea with 25 respiratory movements per minute, temperature 37 °C, oxygen saturation of 96% at room air. Cardiac and pulmonary examinations were unremarkable while the abdominal exam showed signals of small ascites. Gynecological examination ruled out any abnormality and the transvaginal ultrasound was normal except for a presence of a small myoma. The initial laboratory tests are shown in Table 1.

The multi detector computed tomography (CT) of thorax and abdomen are shown in Figures 1-3.

The patient progressed, on the day after admission, with worsening of the abdominal pain, nausea and vomiting and respiratory distress. Besides the stability of hemodynamic parameters, the cutaneous perfusion got worse and serum lactate level rose.

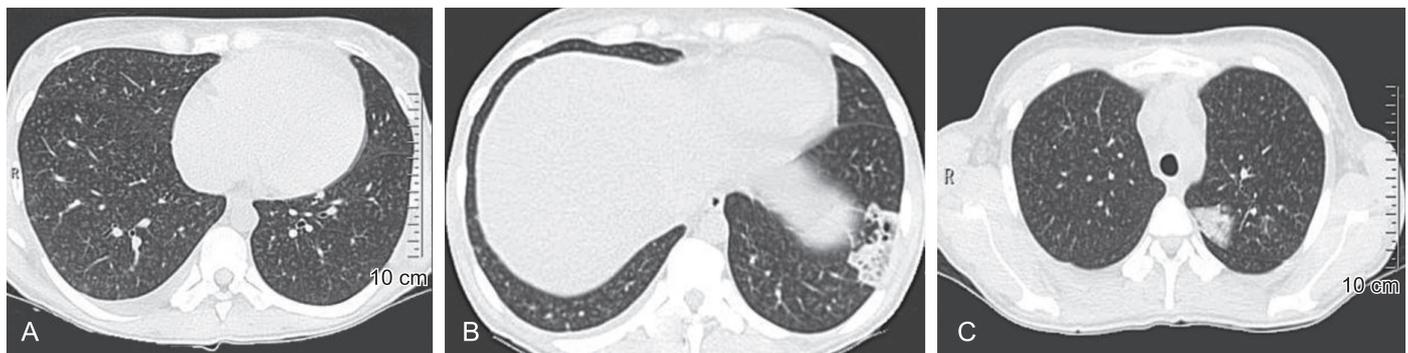
Table 2 shows the liver enzymes and prothrombine time evolution. She was referred to the Intensive Care Unit because of her clinical instability and respiratory insufficiency, where she presented cardiac arrest after vomiting and probable aspiration of gastric content.

Serologies for HIV and Hepatitis virus B and C were negative.

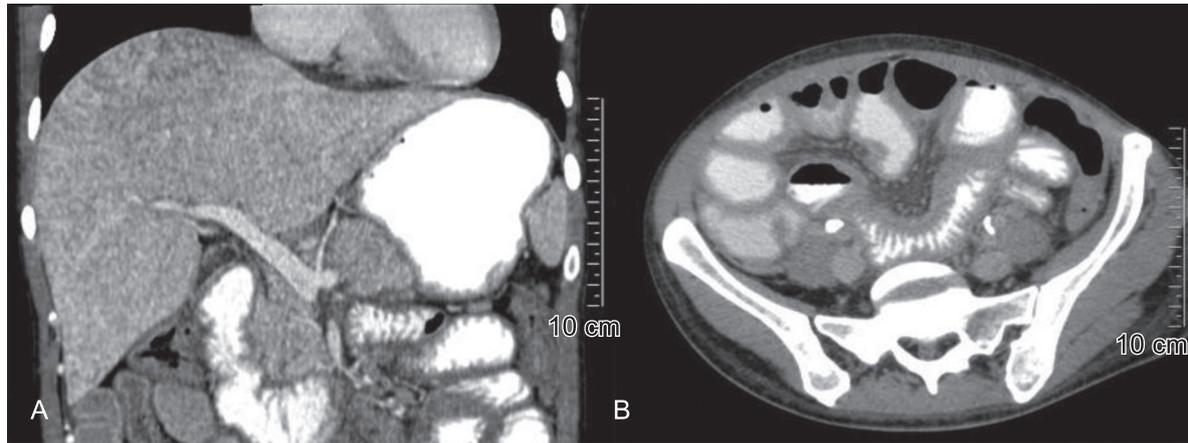
**Table 1 – Laboratory tests**

	12,4/36,3%	RV		RV
Hemoglobin	10,4	12,3-15,3 g%	Potassium	4,1
Hematocrit	32	36,0-45,0 %	Sodium	139
Leucocytes	6100	4,4-11,3 10 <sup>3</sup> /mm <sup>3</sup>	ALT	40
Segmented	61	45-70 %	AST	48
Eosinophils	10	1-4 %	AF	229
Basophils	1	0-2,5 %	γGT	62
Linfocytes	23	18-40 %	Total Bilirubin	0,4
Monocytes	5	2-9 %	Albumin	2,8
Platelets	314	150-40010 <sup>3</sup> /mm <sup>3</sup>	Globulin	5,1
BUN	10	5-25 mg.dL <sup>-1</sup>	PT (INR)	1,93
Creatinine	0,6	0,4-1,3 mg.dL <sup>-1</sup>	Glucose	91
CRP	10	<5 mg.L <sup>-1</sup>	Amilase	34

AF = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotranspharese, BUN = blood urea nitrogen CRP = C reactive protein, γGT = gama-glutamyltransferase, INR = international normalized ratio, PT = Prothrombine time.



**Figure 1 – MDCT of the thorax – axial images of the lung base (A and B), and the pulmonary apex (C). Note disseminated, bilateral non-calcified micro nodules with centro lobular distribution. The images B and C show wedge-shaped opacities with reversed halo sign, most evident in C compatible with pulmonary infarction.**



**Figure 2** – MDCT of the abdomen, obtained after oral and intravenous contrast media. In **A** a reformatted coronal image showing an heterogeneous enhancement of the hepatic parenchyma mainly at the periphery of the hepatic right lobe. Note patent portal vein of normal caliber, and lack of hepatosplenomegaly. In **B** – axial image – note the thickening of the intestinal wall.



**Figure 3** – MDCT of the abdomen, reformatted image, obtained after oral and intravenous contrast media. Note slightly enlarged mesenteric lymph nodes, thickening of the intestinal wall and presence of mild ascites.

An autopsy was performed.

The abdominal and thoracic cavities were opened, revealing a mild serous ascites and bowel distension. The visceral peritoneum showed a whitish diffuse thickening throughout the gastrointestinal tract from the stomach to the colon. (Figure 4).

**Table 2** – Evolution of liver enzymes and coagulation test

	2 <sup>nd</sup> day	3 <sup>rd</sup> day	RV
ALT	436	811	9-36 U.L <sup>-1</sup>
AST	10096	1946	10-31 U.L <sup>-1</sup>
TP (INR)	2,86	3,07	1

ALT = alanine aminotransferase, AST = aspartate aminotransferase, INR = international normalized ratio, PT = Prothrombine time.

The longitudinal sectioning of the small and large intestines showed some swollen and slightly congested patchy areas of the mucous membrane. The microscopic examination evidenced the presence of uncountable, embryonated and occasionally calcified eggs of *Schistosoma mansoni* within the wall (most prominent in the submucosal layer) and serosa of the gastrointestinal tract. Granulomatous reaction with eosinophilic infiltration surrounded the eggs. These granulomas, of miliary distribution, showed necrotic-exudative and productive patterns, but few of them showed an advanced fibrotic stage. There were also observed numerous viable and dead worms in the lumen of veins, especially in the subserosal layer and occasionally in the submucosa (Figures 5 and 6). On the distal submucosal layer of the esophagus it was found embryonated eggs. No evidence of esophageal varicose veins was depicted.

The liver weighted 1547.0 g (reference value: 1100.0-1450.0 g). On sectioning it showed a winy appearance with thickening of the larger portal tracts, featuring the Symmers fibrosis.

Multiple whitish granules scattered randomly in the parenchyma were present, more evident in the left lobe (Figure 7).

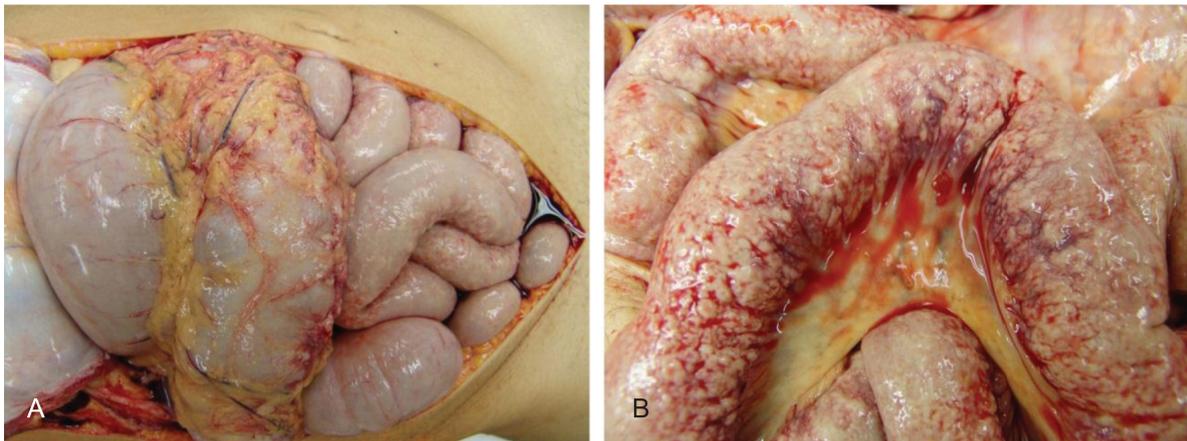
Microscopically, there were fibrous expansion of portal spaces in the pipe-stem pattern fibrosis with granulomatous reaction, at different stages of immunomodulation with eosinophilic infiltration, surrounding embryonated and occasionally calcified eggs in the conjunctive stroma or portal vessels, as well as in the hepatic lobule. In the hepatic lobule there were also extensive areas of sinusoidal congestion and hepatocyte necrosis, especially in zones 3 and 2, with areas of microvesicular steatosis (Figure 8).

The pancreas weighted 193.0 g (reference value = 60.0-135.0 g) and presented a whitish thickening of the anterior surface. On sectioning it showed the usual lobulated parenchyma. On

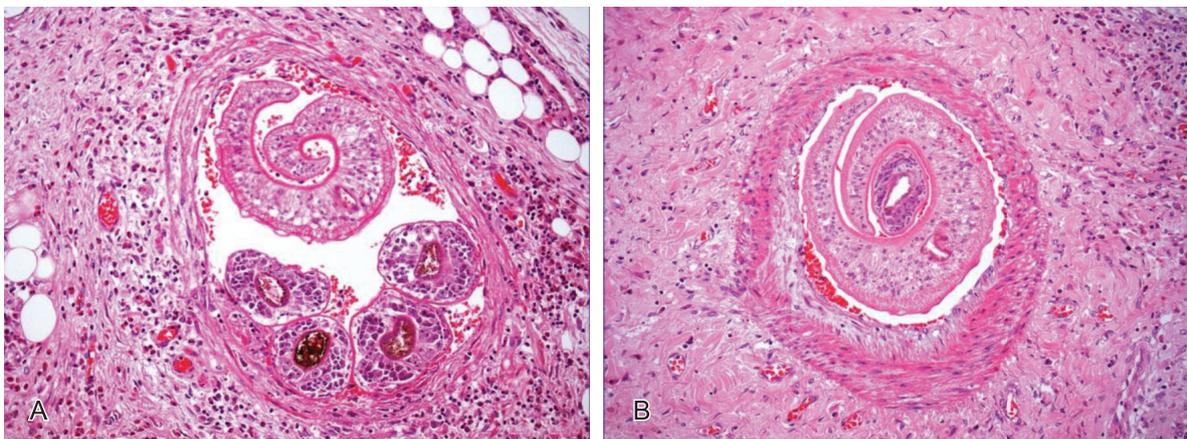
microscopy, it was observed countless embryonated eggs entrapped in the pancreatic parenchyma, some of them surrounded by granulomatous reaction exhibiting a necrotic-exudative pattern with eosinophil (Figures 9 and 10).

The spleen weighted 170.0 g (reference value = 112.0 g); the capsule was smooth and the parenchyma was homogeneous and winy, on sectioning. The microscopy showed white pulp reactive hyperplasia and red pulp congestion with no evidence of congestive spleen sclerosis (Figures 9 and 10).

In the thoracic cavity effusions were not observed. Both lungs were enlarged, right lung weighted 610.0 g and left lung weighted 498.0 g (reference value RL = 360.0-57.0 g and LL = 325.0-480.0 g) and showed countless whitish nodules measuring up to 0.2 cm scattered



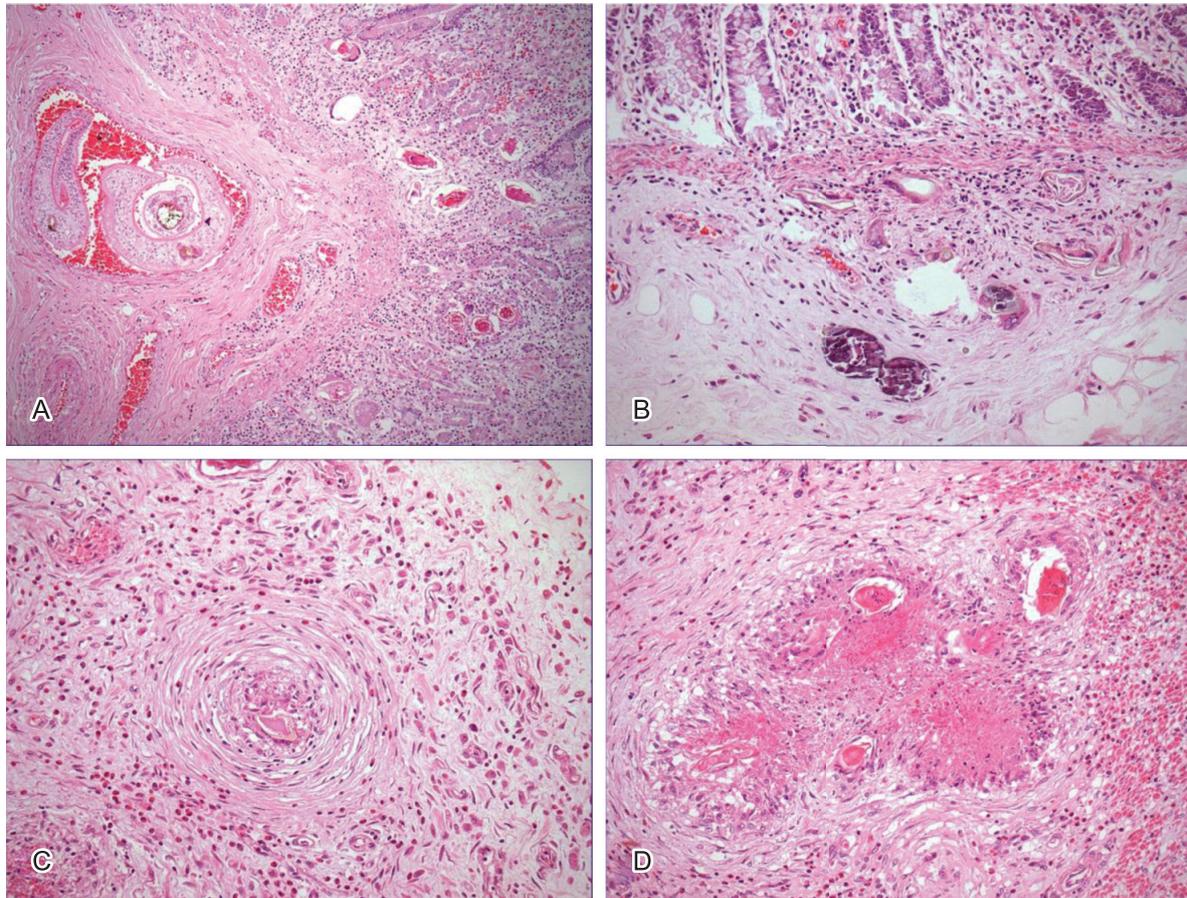
**Figure 4 – A-** Panoramic picture of the abdominal cavity showing distended bowel segments covered by a whitish and thick serosa and mild ascites. **B-** Detail of small bowel surface serosa showing the whitish granular thickness.



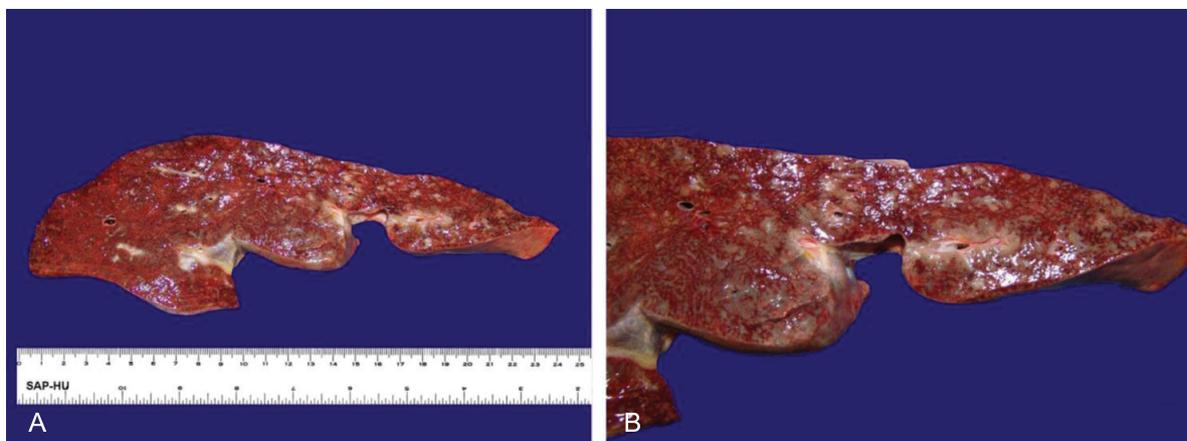
**Figure 5 – Photomicrography (HE-400x) - A and B-** Viable adult *S. mansoni* worms within vessel lumen.

throughout the lung parenchyma and pleural surface. In the left upper pulmonary lobe there was a cavitated lesion measuring 3.0 cm. In the base

of the right lung, a grayish triangular area of firm consistency was detected resembling a pulmonary infarction (Figure 11).



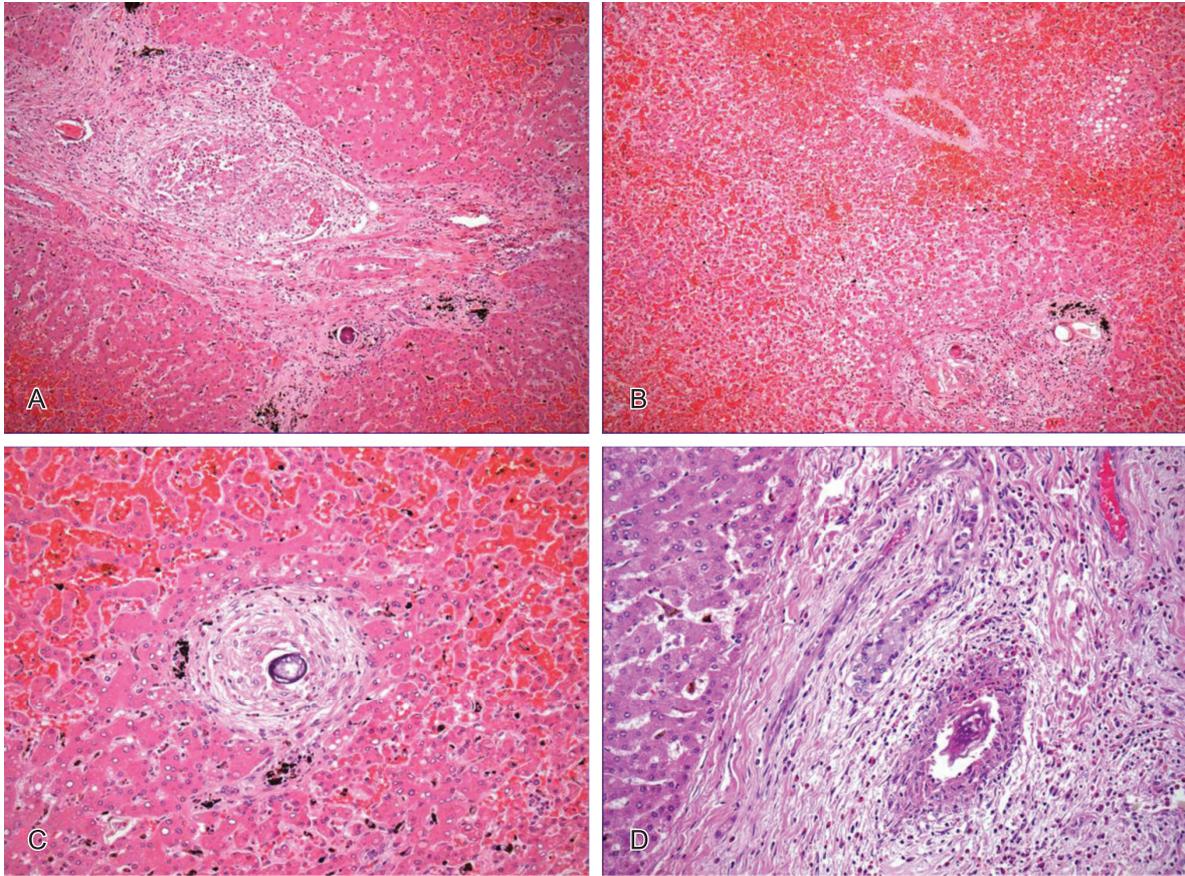
**Figure 6** – Photomicrography - **A-** (HE-100x) Gastric wall presenting viable *S. mansoni* adult worms within a venous vessel of the submucosa and presence of numerous eggs in the lamina propria of the mucosal layer; **B-** (HE-400x) Presence of calcified eggs within the large intestine submucosal layer; **C-** (HE-200x) Scar fibrotic granuloma surrounding egg debris within the large intestine subserosa; **D-** (HE-200x) Necrotic-exudative pattern granuloma involving viable eggs within the large intestine subserosal layer.



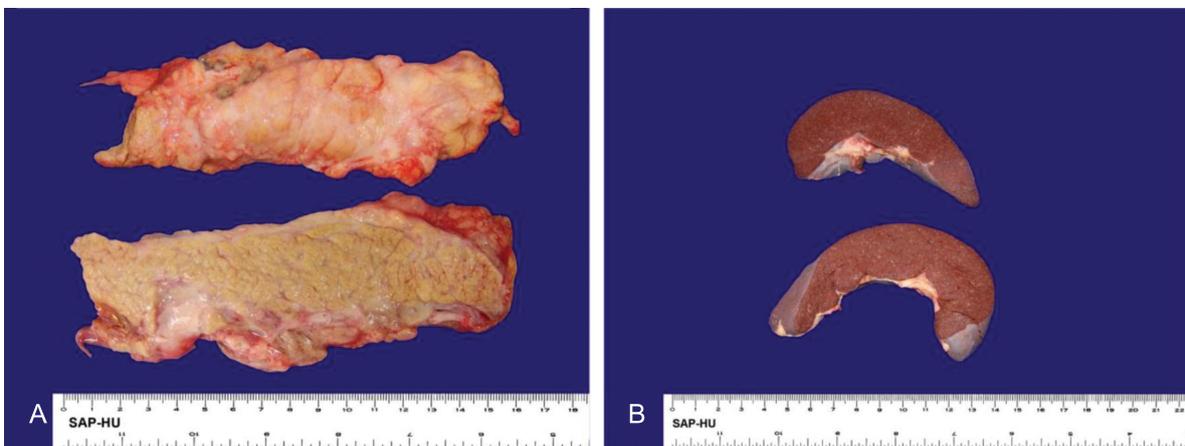
**Figure 7** – **A-** Gross examination of the liver showing waxy hepatic parenchyma presenting multiple whitish micro nodules. Note the fibrous thickness of portal space; **B-** Detail of the whitish fibrous thickening of the portal space, characterizing the presence of *Symmers* fibrosis.

The microscopic examination showed a necrotic-exudative granulomatous reaction with eosinophil surrounding embryonated eggs of *S. mansoni* within peribronchial artery branches and adjacent alveolar parenchyma. There were

still observed the presence of numerous viable and dead worms within the vascular lumen, sometimes eliciting necrotic-exudative granulomatous reaction, eosinophilia, and ischemic necrosis of the adjacent parenchyma. It was also identified



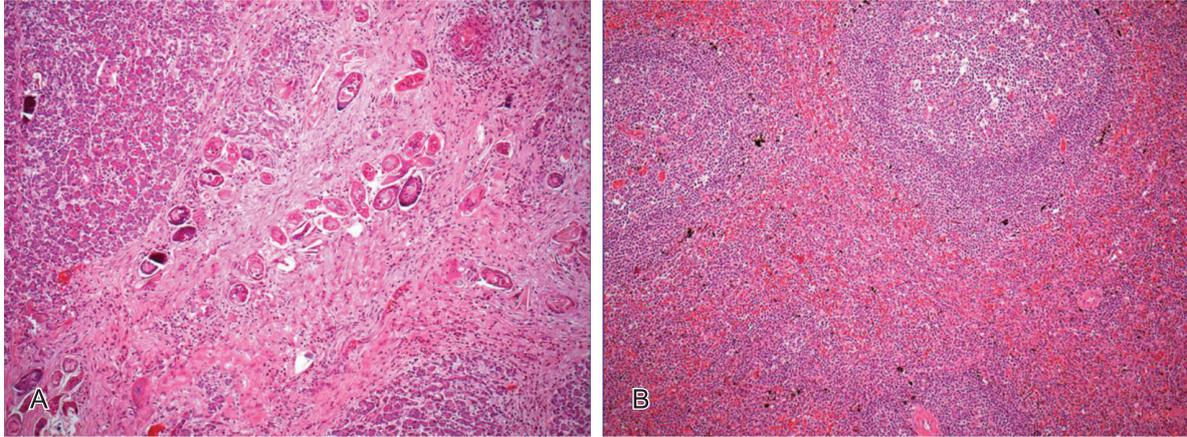
**Figure 8** – Photomicrography - **A** (HE-100x) Portal space presenting a necrotic exudative granuloma with eosinophils besides the presence of a calcified egg and Symmers fibrosis; **B** (HE-100x) Hepatic parenchyma presenting passive congestion with hepatocyte necrosis in zones 2 and 3; **C** (HE-400x) Presence of a scar granuloma with concentric fibrosis involving a calcified egg within the hepatic parenchyma; **D** (HE-400x) Presence of necrotic-exudative pattern granuloma surrounding a viable egg within the portal space. Note the presence of blackened schistosome pigment deposition in all these photomicrographies.



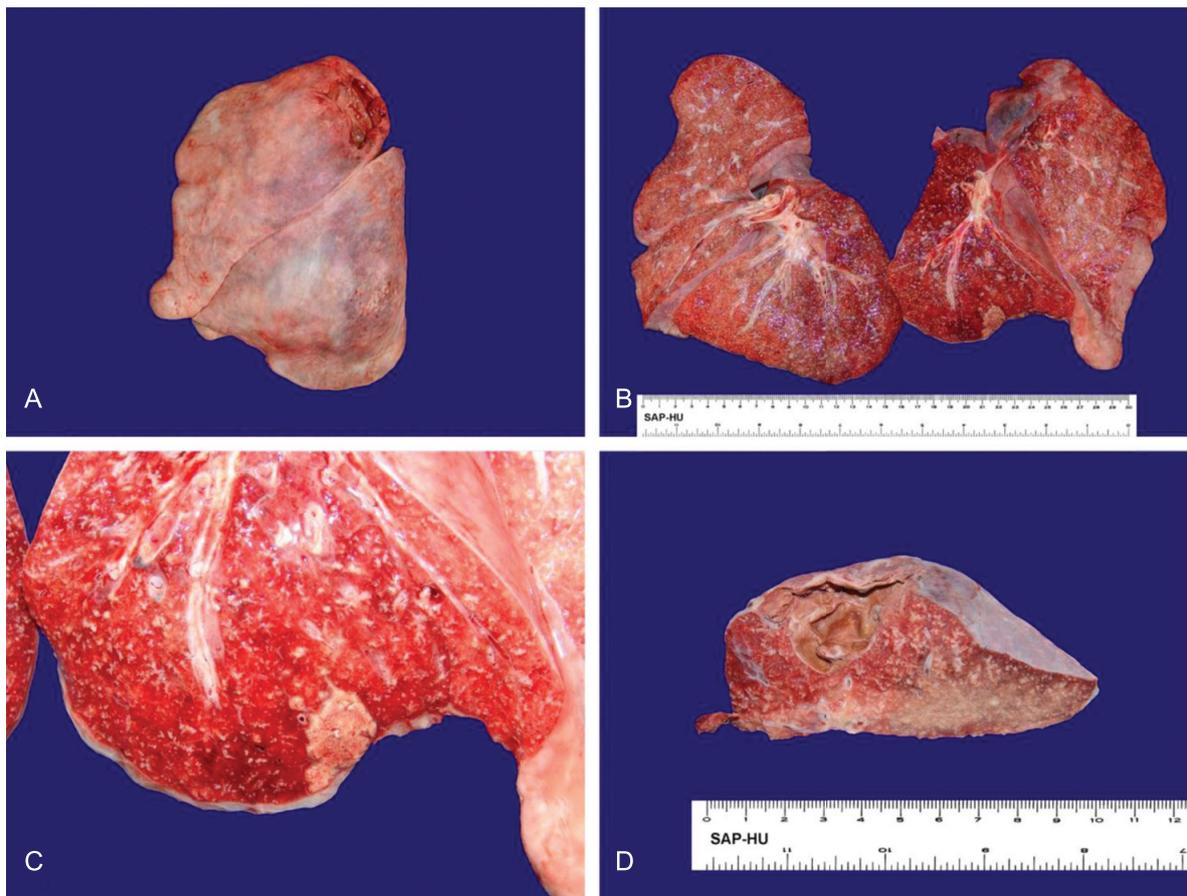
**Figure 9** – **A**- Gross examination of the pancreas showing whitish thickening of the anterior surface, preserved parenchyma lobulation on sectioning and lack of steatonecrosis; **B**- Gross examination of the spleen showing a homogeneous winy parenchyma on sectioning surface.

a dead worm within a segmental bronchus accompanied by the similar histologic feature of the acute Loeffler's syndrome. On the wall of the left upper lobe cavity lesion it was identified the presence of countless embryonated eggs (Figure 12).

Lymphadenomegaly was found in the mesenteric, peripancreatic, along the curvature of the stomach, pulmonary hilum and peritracheal lymph node chains. Many of these lymph nodes entrapped schistosome eggs surrounded by granulomatous reaction.



**Figure 10** – Photomicrography (HE-200x) – **A**- Numerous viable eggs of *S. mansoni* within the pancreatic parenchyma; **B**- Splenic parenchyma showing white pulp reactive lymphoid hyperplasia.



**Figure 11** – **A**- Panoramic picture of the left lung showing a cavitory lesion in the apex of the superior lobe; **B**- Panoramic picture of right lung sectioning surface showing multiple whitish nodules and the presence of a triangular whitish area corresponding a inferior lobe infarction; **C**- Detail of the right inferior pulmonary lobe showing multiples tiny whitish nodules, measuring up to 0,1 cm and a triangular infarction area; **D**- Sectioning surface of the left superior pulmonary lobe showing an apical cavitory lesion.

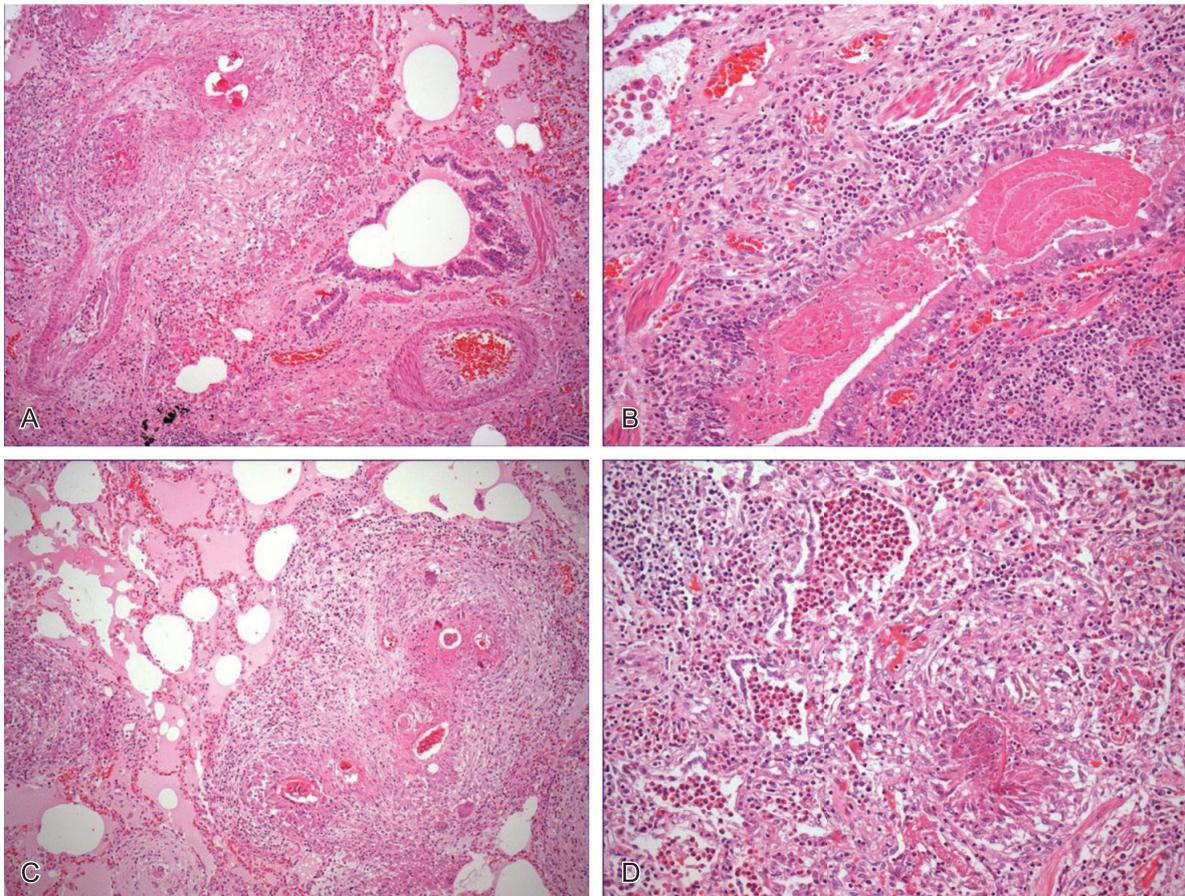
No other significant gross or microscopic findings were detected.

## DISCUSSION

Schistosomiasis is one of the most common parasitic diseases, still considered of public health significance, affecting around 207 million people in tropical and subtropical areas of the globe.<sup>1,2</sup> In Brazil, the disease ranks higher in prevalence than HIV/AIDS. The clinical manifestations can be divided into three major stages. The first stage occurs after skin penetration by the cercariae and manifests as a pruritic rash. The second stage usually occurs weeks after infection during maturation of the adult fluke and the third or chronic stage appears months to years after infection and results from granuloma formation around the schistosome eggs entrapped in many tissues. Acute schistosomiasis (AS) has been overlooked, misdiagnosed, underestimated and underreported in endemic areas. Among

the non-immune individuals, risk groups are well known, including military recruits, some religious congregations, rural tourists and recreational water sports practitioners.<sup>3</sup>

We report a fatal outcome case of postpartum young woman, coming from an endemic area for schistosomiasis, with signs of massive reinfection developing clinical symptoms of AS. AS or Katayama syndrome (KS) (formerly called Katayama fever) occurs as an early clinical manifestation of infection with *Schistosoma* species in non-immune individuals or after heavy reinfection with schistosome cercariae in endemic areas.<sup>3-5</sup> The disease is usually acquired after the exposure to contaminated water. A contact as brief as 1-5 minutes may be enough to allow transcutaneous penetration by cercariae.<sup>6</sup> KS caused by *S. mansoni* is rarely reported among chronically exposed population, probably because of in-utero sensitization or because an adaptive immune response protects from developing an acute toxic condition<sup>7</sup> or even because these



**Figure 12** – Photomicrography - **A** (HE – 100X) Peribronchial arterial vessel showing endarteritis and granulomatous reaction surrounding viable eggs of *S. mansoni*; **B** (HE – 400X) Presence of dead worms, with coagulative necrosis, within the lumen of a small bronchus; **C** (HE – 100X) Lung parenchyma exhibiting the presence of necrotic-exudative granulomas surrounding viable eggs and alveolar edema; **D** (HE – 400X) Lung parenchyma exhibiting the presence of exudative granuloma with intense infiltration of eosinophils.

cases simply go unrecognized.<sup>4,8</sup> In Brazil, there were only two cases described in the literature.<sup>9-12</sup>

The KS occurs due to a systemic hypersensitivity reaction against the larvae (schistosomules), adult schistosome organisms and early oviposition by adult worms occurring within 14-60 days after the infection.<sup>3,5,13,14</sup> In many cases, the acute phase of infection courses without symptoms.<sup>4</sup> Incubation periods ranging from 1 to 12 weeks have been reported.<sup>6</sup> The severity of symptoms varies according to the infecting species, the cercarial burden and immune response to the released parasites antigens. Rocha et al., showed a statistic significance correlation between the levels of IgE and IgG and the intensity of the infection estimated by the number of eggs in the feces.<sup>6,15</sup>

Disease onset is usually sudden, presenting high grade fever, chills, headache, fatigue, myalgia, malaise, facial and lower limbs edema, urticaria, non-productive cough (occasionally bronchospasm), eosinophilia and patchy pulmonary infiltrates on chest radiography. Abdominal symptoms may develop within a few weeks due to the migration of juvenile worms and oviposition by the mature ones. Most patients recover after 2-10 weeks, whereas some develop serious disease with weight loss, dyspnea, chest pain, diarrhea, diffuse abdominal pain, splenomegaly, hepatomegaly with elevation of hepatic enzymes, restrictive respiratory insufficiency and generalized rash.<sup>4,7,16</sup> The central nervous system involvement of AS may occur as meningoencephalitis or myelitis.<sup>17</sup>

The clinical picture presented by our patient was very similar to the signs and symptoms described above. Advanced chronic schistosomiasis was not clinically identified, not even the computed tomography could show signs of hepatic fibrosis or portal hypertension.

In the case reported here the hallmark pathological findings for the diagnosis of KS by reinfection of *S. mansoni*, on autopsy, were: the evolving pattern of granulomatous response, parasite load represented by the number of spread worms and eggs, the hepatic portal fibrosis with the typical pattern of Symmers fibrosis, and finally the absence of signs and findings of portal hypertension despite the hepatic portal fibrosis.

Regardless the anatomo clinical presentation of the disease, the most important lesion of schistosomiasis is the granulomatous inflammation

around the eggs. On gross examination the granulomas appear as tiny, whitish nodules, isolated or confluent, countless in the acute form of the disease, located mainly in the liver, small and large intestines and lungs. The number of the granulomas diminishes gradually with the chronicity of the disease.<sup>3,18</sup> Protein antigens derived from eggs and adult worms induce immune response mediated by Th1 and Th2 lymphocytes alternatively, according to the stage of infection (acute, chronic or delayed).<sup>18</sup>

The study of Jesus et al. showed that the Th1 response dominates the early phase of acute schistosomiasis when IFN- $\gamma$ , IL-2 and TNF- $\alpha$  are detected in high levels. This proinflammatory reaction is down regulated by the secretion of a series of cytokines as: IL-4, IL-5, IL-10 and IL-13, which are released when oviposition ensues. The Th2 cells produce protective eosinophil-rich granulomatous lesions around new deposited eggs, which in early phase show necrotic-exudative features. The absence of or inability to develop a Th2 response also contributes to maintaining the toxemic symptoms and a fatal outcome.<sup>3,7</sup> Proinflammatory cytokines and TNF- $\alpha$  detected in the serum of these patients may explain constitutional symptoms.<sup>7</sup>

The granulomatous reaction is a dynamic process. Initially, the granulomas are bulky, exhibits a necrotic-exudative pattern, with large numbers of macrophages, lymphocytes and eosinophils around the egg. This exudate progressively decreases, being replaced by fibrotic nodules.<sup>18</sup> Granulomas of the acute phase of the disease are all synchronic and show the necrotic-exsudative pattern, featuring the first oviposition.<sup>3,19</sup> The fibrotic granuloma appears from 150 days of the disease and as well as the calcified eggs characterizes the chronic phase of the disease. Another characteristic of chronic disease is the presence of non-synchronous granulomas indicating that the eggs appeared in successive periods.<sup>18,19</sup>

In the case reported here, it was observed a miliary spread of eggs with granulomas showing the necrotic-exudative pattern in all the affected organs. Fibrotic granulomas and calcified eggs were scarcely detected within the colon wall and the liver. The presence of Symmers fibrosis in the hepatic portal spaces also indicated the coexistence of the two forms of the disease simultaneously.

The Symmers fibrosis is described as the anatomopathologic hallmark of the chronic hepatosplenic form of schistosomiasis when portal

hypertension and its hemodynamic effects are present.<sup>18,19</sup> Patients from endemic areas may show changes similar to those described in liver Symmers fibrosis, but without splenomegaly or other evidence of portal hypertension. It is suggested that these patients are able to adapt to minimize hemodynamic portal hypertension. Such cases could represent the advanced hepatointestinal or pre-hepatosplenic stage.<sup>19</sup>

Pulmonary involvement may occur at all stages of infection. During the acute stage, the pulmonary lesions are due to larval pneumonitis or by granulomatous reaction elicited by the eggs deposited around pulmonary vessels, what also occurs in chronic infection.<sup>20</sup> The disproportion between the number of eggs and worms, the finding of granulomas and vascular lesions in different evolutive phases indicates that the eggs do not reach the lungs at the same time, but in successive periods during chronic infection.<sup>18</sup> Interestingly, in this case, we observed an acute miliary spread of schistosome eggs and embolization of numerous worms alive or dead within the lungs, eliciting exudative-necrotic granulomatous reaction with dense eosinophilic infiltration. There were also dead worm pneumonitis, with areas of pulmonary infarction and cavitations, with histologic findings similar to Loeffler's syndrome. Vascular lesions, such as vasculitis, endarteritis and necrosis secondary to embolized eggs and worms in small arteries and arterioles, were observed as well.

Eggs and worms embolism into the pulmonary vessels elicit granulomatous and fibrous response that leads to pulmonary hypertension in patients with chronic infection who have liver disease with portal hypertension.<sup>20</sup>

The patient presented here did not present findings or signs of portal hypertension and the pulmonary pathological findings were more compatible with the acute phase of the disease. We assume that the pulmonary hypertension developed in this case was due to the extension of pulmonary vascular involvement, which associated to the cardiovascular collapse, resulted in passive congestion and hepatic necrosis with consequent hepatic failure.

Pulmonary complications are correlated with scattered pulmonary nodules ranging in size from, 2 to 15 mm with ill-defined borders, observed on chest X-rays or computed tomography. Less common are the reticulonodular pattern. In some

cases the nodules are associated with a ground-glass halo while diffuse ground-glass pattern is also reported. Labertucci et al reported a case in which the nodules seemed to coalesce in some areas, thus simulating pulmonary condensation. These radiographic abnormalities point to interstitial pneumonitis. Micronodules disseminated in both lung fields have also been described in acute or chronic schistosomiasis. The miliary distribution of eggs, known to occur in this phase, may be sufficient to explain this presentation.<sup>16,21</sup> The radiographic abnormalities seem to be not correlated with respiratory symptoms, as they may be present even in the absence of the symptoms.<sup>6,22-25</sup>

Enormous effort has been made to control schistosomiasis in Brazil, but unfortunately it remains a public health problem. The recognition of acute schistosomiasis in populations from endemic and non-endemic areas with a prior infection history is still challenging. The AS has a wide spectrum of clinical manifestations, and may be fatal in severe forms.

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