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ORIGINAL ARTICLE/ ARTÍCULO ORIGINAL

HISTOPATHOLOGICAL FEATURES OF *SCHISTOSOMA MANSONI* INFECTION IN *AKODON CURSOR* (RODENTIA: SIGMODONTINAE)

CARACTERÍSTICAS HISTOPATÓLOGICAS DE LA INFECCIÓN POR *SCHISTOSOMA MANSONI* EN *AKODON CURSOR* (RODENTIA: SIGMODONTINAE)

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Abstract

The Brazilian grass mouse *Akodon cursor* Winge, 1887 is notably susceptible to both natural and experimental infection by *Schistosoma mansoni* Sambon, 1907. This study was concerned with the histopathological features of the *S. mansoni* experimental infection. Laboratory-reared mice were infected with 150 cercariae (BH strain) by subcutaneous route and killed 9 weeks later. Samples of host tissues, including liver, spleen, intestine and pancreas were collected for histopathological examination. In this acute infection, tissue involvement was of variable intensity, although exudative granulomas predominated in all tissues observed. The cellular composition was predominated by lymphocytes, macrophages and eosinophils and fibroblasts, depending on the individual granuloma and its developmental stage. Our results showed that *A. cursor* may provide a useful model for studying the pathogenesis of schistosomiais mansoni in a wild rodent model.

Keywords: *Akodon cursor* – experimental infection – histopathology - *Schistosoma mansoni* - schistosomiasis mansoni.

Resumen

El ratón de hierba del Brasil *Akodon cursor* Winge, 1887 es especialmente susceptible a la infección natural y experimental por *Schistosoma mansoni* Sambon, 1907. Este estudio está referido a las características histopatológicas de la infección experimental por *S. mansoni*. Los ratones criados en laboratorio fueron infectados con 150 cercarias (cepa BH) por vía subcutánea y sacrificados nueve semanas más tarde. Las muestras de los tejidos del huésped, incluyendo el hígado, el bazo, el intestino y el páncreas se recogieron para su examen histopatológico. En esta infección aguda, la participación del tejido fue de intensidad variable, aunque granulomas exudativos predominaron en todos los tejidos observados. En la composición celular predominaron los linfocitos, macrófagos y eosinófilos y fibroblastos, según el granuloma individual y su etapa de desarrollo. Nuestros resultados mostraron que *A. cursor* puede proporcionar un modelo útil para estudiar la patogénesis de la schistosomiais mansoni en un modelo de roedor silvestre.

Palabras clave: *Akodon cursor* –histopatología – infección experimental – *Schistosoma mansoni* – schistosomiasis mansoni.

INTRODUCTION

Rural environments are of special interest to public health because of the transmission of several zoonoses from wildlife to humans (Rocha *et al*., 1988; Brandão-Filho *et al*., 2003; D'Andrea *et al*., 2007). Researches carried out in Brazil have demonstrated that some species of wild rodents are natural hosts for *Schistosoma mansoni* Sambon, 1907 (Rey, 1993), which is a drawback for schistosomiasis control programs (Peralta *et al*., 2009). Owing to the importance of this problem, wild rodents have been bred under controlled laboratory conditions for experimental purpose with *S. mansoni* (Souza *et al*., 1992; Maldonado Jr. *et al*., 1994; Ribeiro *et al*., 1998). Once such host-parasite interactions are better understood in the laboratory, it will be more feasible to extend the findings to infected hosts in nature.

The Brazilian grass mouse *Akodon cursor* Winge, 1887 (Rodentia: Sigmodontinae) possesses many qualities which would be highly desirable in a laboratory animal: it is capable of breeding successfully under simple conditions of management and displays good adaptation to laboratory facilities (Mello & Mathias, 1987). Previous studies demonstrated natural infection by *S. mansoni* (Coelho *et al*., 1979; Rodrigues-Silva *et al*., 1992), whereas develops experimental infection similar to that in white mice (Machado-Silva *et al*., 1991).

Parasites represent an ecologically important stressor for hosts, which can leads to organ damage and changes on the physiology of hosts. The histopathological hallmark of the schistosomiasis mansoni infection is the development of granulomas around mature eggs, which are trapped in liver and intestines of immunological competent hosts (Cheever *et al*., 1998). Laboratory studies have shown that the hepatic granulomas of both *Nectomys squamipes* Brants, 1827 and *Calomys callosus* Renger, 1830 were composed of large and mature macrophages, often with abundant schistosomal pigment, eosinophilic granulocytes, lymphocytes and fibroblasts, characterizing an exudative-macrophage granuloma type, usually smaller than the equivalent granuloma type in mouse (Lenzi *et al*., 1995; Costa-Silva *et al*., 2002). Descriptions of pathological changes have not been systematized for *A.cursor-S.mansoni* experimental model. The aim of this study was further substantiate our knowledge about this relationship, which was assessed through histopathological parameters.

MATERIAL AND METHODS

Schistosomes and experimental hosts

The *S. mansoni* life cycle is maintained routinely during the past 40 years in *Biomphalaria glabrata* Say, 1818 snails and mice at the Laboratório de Malacologia (Instituto Oswaldo Cruz, Brasil) and prepared by exposing infected snails to light for 2 h to induce shedding of parasites (Freire *et al*., 2003). Eight laboratory-bred *A. cursor*, five-month-old, obtained from Laboratório de Biologia e Parasitologia de Mamíferos Silvestres Reservatórios (Instituto Oswaldo), were each subcutaneously inoculated with approximately 150 *Schistosoma mansoni* (BH strain) cercariae (Machado-Silva *et al*., 1991).

Husbandry

All mice were maintained under standard laboratory conditions. Mice were individually caged in polypropylene cages (40 x 33 cm) with stainless steel-screened covers. Animals fed conventional mice chow (Nuvilab CR1, Colombo, Paraná, Brazil) and water was *ad libitum*. The experiments reported here comply with the current laws regarding ethical procedures with investigated animals (Ellery, 1985). All animals procedures were approved by IBAMA (license number 02022.002062/01-04).

Histopathology and morphometry of S. mansoni granulomas

Infected mice were euthanized at day 63 after

infection by cervical dislocation. The liver, intestine, pancreas and spleen were removed. The tissues were processed routinely for histological preparation, embedded in paraffin, sectioned at 5 µm thickness, and stained with hematoxylin and eosin, Lennert's Giemsa, Silver, Masson's Trichrome and Picrosirius for collagen plus polarization microscopy (Lennert, 1978). Periovular reactions in the liver were classified according to Hsü *et al*. (1972) modified by Lenzi *et al*. (1998) in: pre-granulomatous stages: weakly reactive or non-reactive and exudative stages; granulomatous stages: exudative-productive, productive and involutional granulomas. The area, perimeter, major, and minor diameter of individual granulomas were measured by computed image analysis (Image Pro-Plus Media Cybernetics, US), as described previously (Costa-Silva *et al*., 2002).

Statistical analysis

Experimental data were compared by descriptive statistics or Kruskal-Wallis (Vieira, 1991). Measurements with p-values 0.05 were considered significantly different.

RESULTS

Liver

All mice infected with *S. mansoni* showed inflammatory infiltrates and peri-ovular lesions in the liver (Fig. 1A) in pre-granulomatous stage, characterized by exudative reaction (80%) and granulomatous stage characterized by exudative-productive reaction (15%) and productive reaction (5%) (Figs. 1B, 1C, 1D). Many granulomas contained two zones principally made up of epithelioid cells in the central region near the egg, surrounded by a peripheral zone consisting of numerous inflammatory cells, like pigmented and non pigmented macrophages, neutrophils, lymphocytes and plasma cells but predominantly of eosinophils (Figs. 1C, 1D). Two or more confluent granulomas were often present (Fig. 1E). Binucleate hepatocyte was seen around lesions (Figs. 1C, 1D). Focal necrosis was detected in the hepatic parenchyma (Figs. 1F).

The morphometric analysis of hepatic granulomas stained with haematoxilin-eosine was: area (496873485 µm²), major diameter (29913µm), minor diameter (2099 µm) and perimeter (83936 µm).

Spleen

Histologic examination of the spleen showed several isolated eggs with viable miracidiae, but without yet any inflammatory reaction or with weak reaction (Fig 2A). The organ was less afflicted by schistosomal infection than the liver.

Intestine

Mucosa showed intestinal crypts and villi covered with absortive epithelial cells with some globet cells secreting mucus. A normal limit was presented in the intestinal mucosa that was not involved by the presence of granulomas. The same occur with villus, crypts and glands (Fig. 2B).

A diffuse inflammatory infiltrate of eosinophils and mononuclear cells, mainly lymphocytes, was seen at the mucosa and submucosa layers, but egg granulomas were most frequently seen in the submucosa (Figs. 2B, 2C).

Intestine presented a clear predominance of exudative, exudative-productive stage granulomas and productive granulomas, as well as several isolated eggs with viable miracidium, but without any inflammatory reaction. Granulomas around eggs containing well-preserved miracidium showed an acute inflammatory reaction, with predominance of polymorphonuclear cells, including eosinophils, and sometimes, macrophages. The inflammatory reaction was of the chronic type, with macrophages, fibroblasts and collagen deposition in varying amounts around empty eggshells or eggs containing degenerated miracidia (Figs 2B, 2C, 2D).

Pancreas

Granulomas were in general large, exudative, or initial exudative-productive, and a few in productive reactive stage. The cellular composition of the granulomas of all mice was predominated by lymphocytes, macrophages and eosinophils and

fibroblasts depending on the individual granuloma and its developmental stage (Fig. 2E, 2F). Inflamatory infiltrate rich in eosinophilis in the interlobular septa were seen (Fig. 2E). Confluent granulomas were observed (Fig. 2F).

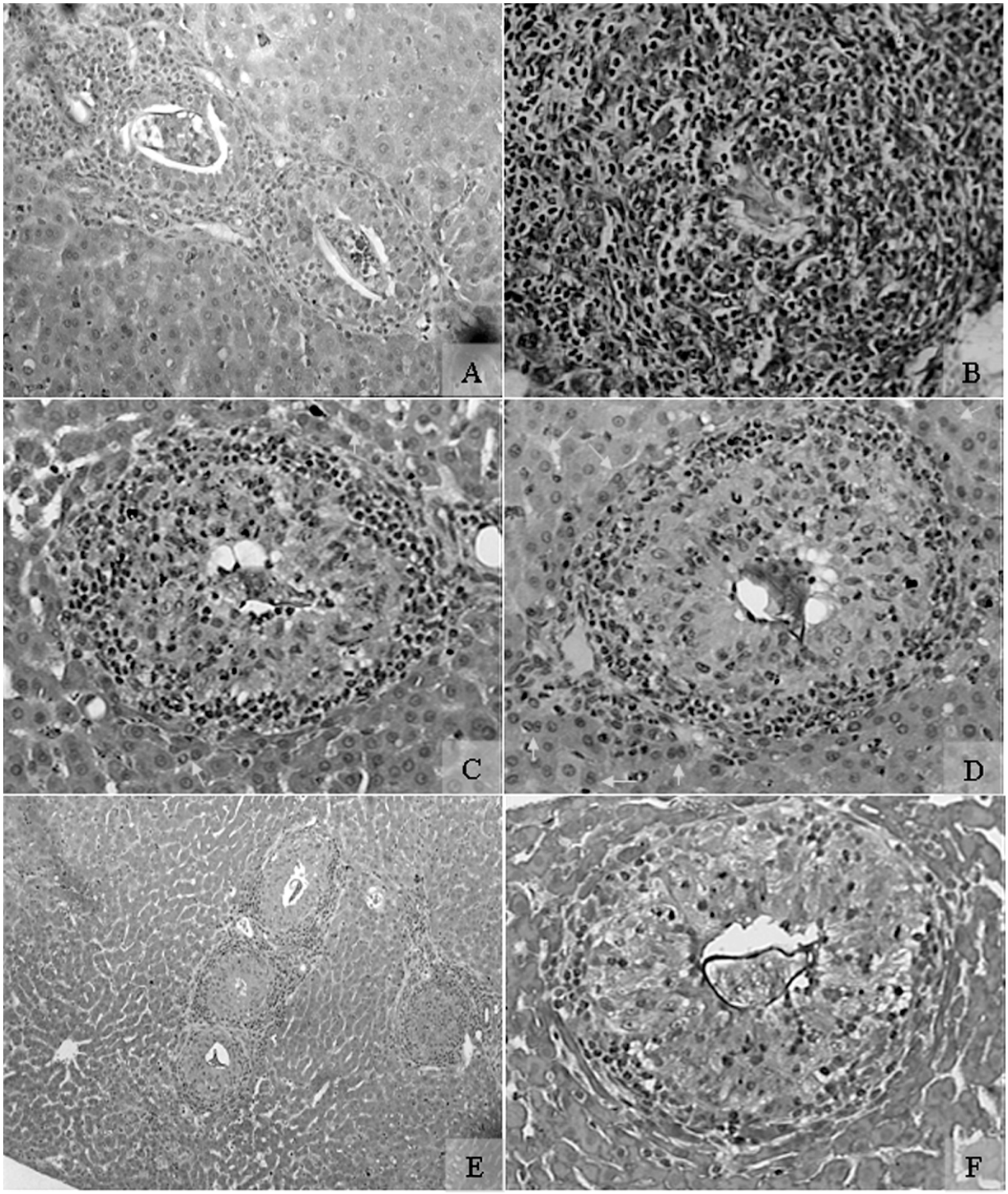

Figure 1. Hepatic infection with *Schistosoma mansoni* showing various stages of peri-ovular lesions. A: Initial pre-granulomatous reaction (H&E). B: exudative granuloma (Lennert's Giemsa). C: exudative-productive granuloma (H&E). D: productive granuloma (H&E). E: confluence between three granulomas (H&E). F: Focal necrosis in hepatic parenchyma (Masson's trichrome).

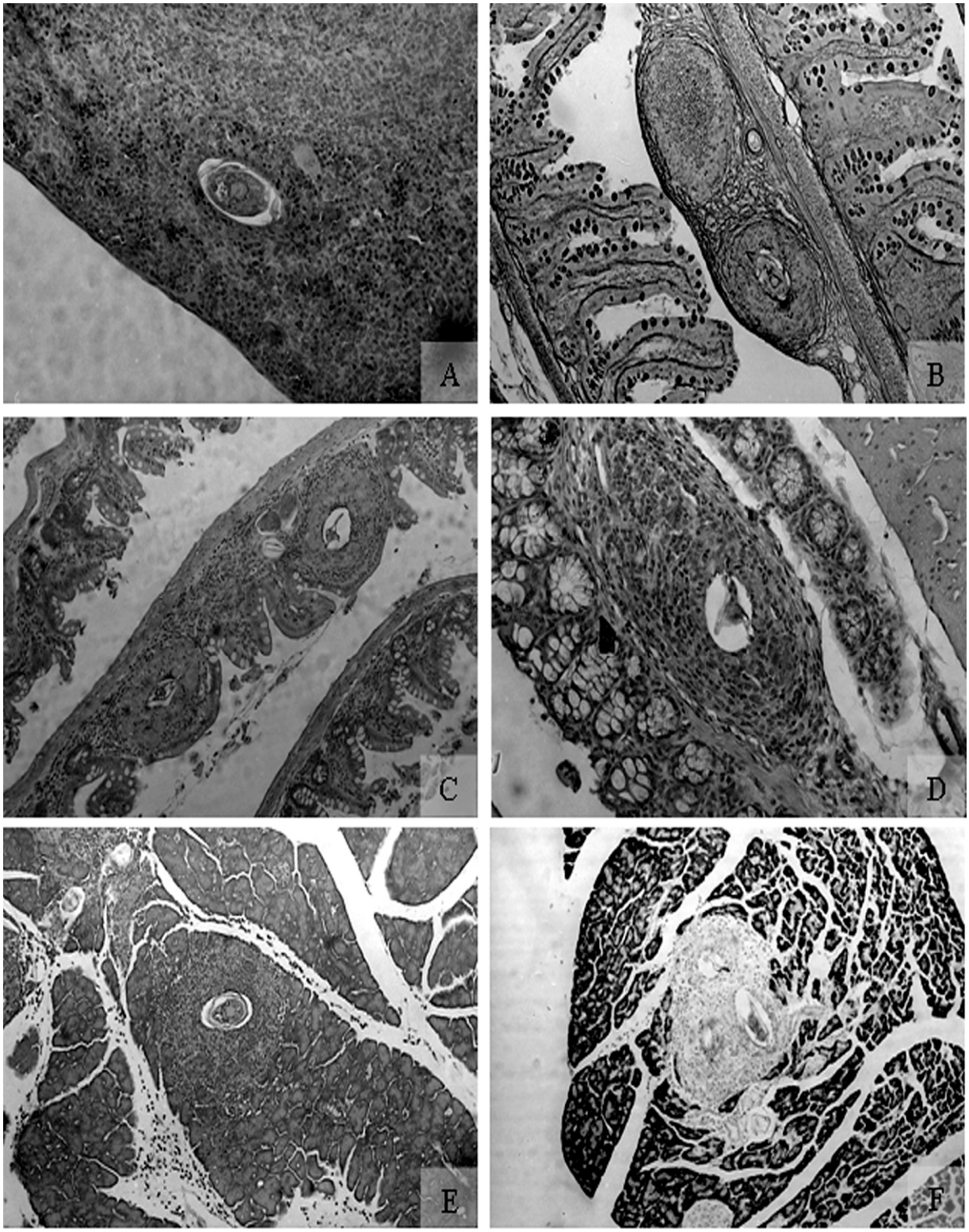

Figure 2. Photomicrographs of spleen (A), intestine (B, C, D) and pancreas (E, F) showing inflammatory and peri-ovular reaction. A. Spleen with isolated eggs and viable miracidiae without inflammatory reaction (H&E). B. Intestinal crypts and villi covered with absortive epithelial cells with some globet cells secreting mucus (Silver stain). C. A diffuse inflammatory infiltrate at the mucosa and submucosa layers. Egg granulomas were seen in the submucosa (H&E). D. Granuloma around egg containing well-preserved miracidium showing an acute inflammatory reaction (H&E). E. Granulomas in initial exudative-productive. Inflamatory infiltrate rich in eosinophilis in the interlobular septa were seen (H&E). F. Pancreas confluent granuloma (Masson's trichrome).

DISCUSSION

It is known that wild animals harbour many types of parasitic agents (Brandão-Filho *et al.*, 2003; D' Andrea *et al.*, 2007). Over the past several years, we have used laboratory-breeding colonies of wild rodents for parasitological purpose with *S. mansoni* (Souza *et al*., 1992; Maldonado Jr. *et al*., 1994; Ribeiro *et al*., 1998). However, descriptions of histopathological changes have not been systematized for *A. cursor*. However, rodent models may have their limitations in parasitological research due to host physiology, parasite size constraints and a relatively short host life span. In addition, rodents living in endemic areas may be infected with several cercariae load.

Egg production is responsible for both life cycle progression and host immunopathology during schistosomiasis, This is a dynamic process in which eggs exploit the host immune response for egg output (Doenhoff *et al*., 1986; Lenzi *et al*., 1987; Brindley, 2005), whereas infection elicits a robust cellular inflammation around mature egg within the host tissue (Andrade, 2009). Gut is the disposal site of mature eggs, whereas trapped eggs induce a gastrointestinal pathology (Chatterjee *et al*., 2001).

In this study, schistosome and granulomas lodged within the mucosa and submucosa of the small intestine, charactering a pre-granulomatous stage (Lenzi *et al*., 1998). This acute inflammatory phase facilitates the passage of the eggs through the intestinal wall (Lenzi *et al*., 1987), which might explains why *A. cursor* sheds a high number of fecal eggs (Machado-Silva *et al*., 1991). In *C. callosus* eggs were distributed along all layers of the intestine, whereas several intestinal nodules were localized at the interface between external muscular layer and intestinal serosa (Lenzi *et al*., 2002). Also, diffuse eosinophil infiltration in the mucosal lamina propria and predominance of macrophages in the granulomas has been reported (Lenzi *et al*., 1995). In this study, eosinophils and mononuclear cells, mainly lymphocytes, were seen at the mucosa and submucosa layers. In general, intestinal granulomas were similar to Swiss mice (Lenzi *et al*.,1987).

Schistosome eggs that do not successfully pass through the intestinal mucosa towards the lumen are usually carried by the portal vein blood flow to the liver, where they become trapped due to the insufficient diameter of the sinusoids (Pearce, 2005). This process leads to marked inflammation, tissue eosinophilia, collagen deposition, fibrous expansion of the portal spaces and intrahepatic portal-vein obstruction (Abath *et al*., 2006).

Early studies in mouse models demonstrated that the morphological aspects of hepatic granulomas vary among different hosts (Cheever *et al*., 1998) and time of infection (Andrade, 2009). This study and others (Andrade & Warren, 1964; Lenzi *et al*., 1995; Costa-Silva *et al*., 2002) demonstrated that hepatic granulomas were mainly exudative type, containing neutrophils, lymphocytes and plasma cells but predominantly eosinophils. In addition, hepatic granulomas of *C. callosus* and *N. squamipes* are smaller than granulomas from mice at the same time of infection (Lenzi *et al*., 1995; Costa-Silva *et al*., 2002). In our experimental design, the morphometric analysis of granulomas showed that they were smaller than mice (Costa-Silva *et al*., 2002).

In the present study, histologic examination of the spleen did not show important features in the severity of infection-induced pathology. Microscopically, well-preserved eggs were found without around inflammatory reaction or weakly reactive response. On the other hand, acutely infected mice showed splenomegaly with enlargement of the white pulp and splenic cords with increased cellularity (Andrade & Azevedo, 1987) and diffuse cellular hyperplasia in both the red and white pulps, accompanied with congestion of the splenic sinuses (Souza *et al*., 2009). In addition, there was a correlation between reactive spleen changes and liver alterations, during the acute phase of mice infection (Andrade & Azevedo, 1987). This statement was not herein confirmed because changes in the liver have not a repercussion on splenic architecture, which was normal in appearance. These results suggest that *A. cursor* develops distinct pathophysiological

alterations in the acute stage of infection, in which a role for immunoregulatory mechanisms in this process should be investigated.

Pancreatic involvement during murine schistosomiasis has also been reported. The early stage of the acute infection did not evoke histologic alteration, which was detected soon began egg oviposition. At this time of infection, pancreatic granulomas, minimum lobular atrophy and eosinophilic change in the ductal epithelium was observed (Lenzi *et al*., 1989). As infection progressed, intense lobular atrophy, interlobular and pseudocapsular inflammatory infiltrate and edema, periductal fibrosis and decrease in number of pancreatic islets were detected. Chronically-infected mice showed severe pancreatitis, including involvement of the endocrine pancreas (Lenzi *et al*., 1989). Previous studies showed that naturally-infected *N. squamipes* had a spectrum of morphological changes ranging from mild lesions to severe, which was characterized by granulomatous pancreatitis (Silva & Andrade, 1989).

In our investigation, pancreatic involvement was of variable intensity, predominating pre-granulomatous stages, which appears to be in disagreement with predominance of exudative-productive granulomas in mouse model (Lenzi *et al*., 1989). It has been suggested that the pathogenesis of pancreatic injury depends mainly on the embolization of eggs due to the changes within the portal system after adult worm maturation and egg oviposition (Lenzi *et al*., 1989). Interestingly, our earlier studies have shown that schistosome egg-laying in *A. cursor* increased between 6-8 weeks post-infection (Machado-Silva *et al*., 1991).

Additional studies are needed to extend our findings to chronic infection, where egg-induced granulomas cause extensive tissue scarring. The present data, taken together with previously reported (Machado-Silva *et al*., 1991) confirm that the Brazilian grass mouse may provide a useful model for studying the biology and pathogenesis of schistosomiasis mansoni.

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