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PATHOLOGICAL CHANGES DUE TO MASSIVE SCHISTOSOMAL INFECTION IN MAN

(A CASE PRESENTATION)

Zilton A. ANDRADE, Sonia G. ANDRADE and Myron SUSIN

SUMMARY

A 13 year-old boy with a massive infection due to *Schistosoma mansoni* presented with portal hypertension and chronic *Cor pulmonale*, following extensive vascular destruction caused by disseminated egg granulomas in the liver and lungs. Besides pipe-stem fibrosis of the liver, splenomegaly, pulmonary arteritis and hypertrophy of the right side of the heart, post-mortem studies showed disseminated egg granulomas in several organs, including central nervous system and heart. There were numerous nodules in the peritoneal cavity (a pseudo-neoplastic lesion) and a membranous glomerulonephritis. The occurrence of this latter lesion strongly suggests that it could also be related to schistosomal infection, since recent investigations have indicated a cause-effect relationship between schistosomiasis and glomerulonephritis.

INTRODUCTION

A 13 year-old boy with a massive infection by *Schistosoma mansoni*, presented with a spectrum of changes which included pipe stem fibrosis of the liver, splenomegaly, pseudo-neoplastic peritoneal lesions, schistosomal pulmonary arteritis with chronic *Cor pulmonale*, and membranous glomerulonephritis. Although one or more of these changes may occur following a heavy infection with schistosomes, this appears to be the first time that all of them occurred together in a single patient. A similar picture has been described in the chimpanzee massively infected with *S. japonicum* [8]. This report describes the pathologic features and discusses the possible pathogenetic mechanisms of the several lesions found, especially those in the kidney which only recently have been recognized as an important manifestation of schistosomiasis [2, 4, 13].

CASE REPORT

A.B.B., a 13 year old male from a highly endemic area of schistosomiasis in the State of Bahia, Brazil, was admitted with dyspnea and anasarca of four months duration. One year previously he developed abdominal pain in the right upper quadrant associated with dark watery stools, abdominal distention, and episodes of seizures. On admission he was a dyspneic, poorly nourished, chronically ill boy with an apparent age of 8 years. He weighed 27 kilos and measured 1,15 m; temperature 37.2°C, pulse rate 120, respiration 36, and blood pressure 110/60 mm Hg. No cyanosis was present. Rales were heard throughout all lung fields. There was a systolic murmur heard in the fourth left intercostal space and a high pitched pulmonic second sound was present. Jugular veins were turgid. The abdomen was distended and prominent collateral veins were present.

Departamento de Patologia, Universidade da Bahia. Faculdade de Medicina, Salvador, Bahia, Brazil and Cornell University Medical College, New York, N.Y. — U.S.A.

The liver was enlarged, 5,5 cm below the right costal margin and 9 cm below the xiphoid process. The spleen was 5 cm below the left costal margin. Firm, irregular nodules were palpable through the anterior abdominal wall. Peripheral lymph nodes were not enlarged. A chest X-rays showed increased pulmonary vascular markings in the central as well as in the peripheral lung fields. The cardiac shadow was enlarged, and the ECG consistent with right ventricular hypertrophy. There was proteinuria, hyaline and granular casts and a few red and white blood cells in the urine. BUN was 40 mg% and the CO_2 was 20 mEq/l. Total serum protein was 9.7 g%, with 1.8 g% albumin and 7.9 g% globulins. Total white cell count was 12,000 with 60% neutrophils, 22% eosinophils, 15% lymphocytes and 3% monocytes. Repeated blood cultures were negative for pyogenic organisms and for *Salmonella*. The Widal reaction was also negative. *Schistosoma mansoni* eggs were present in large numbers in the stools. The patient remained hospitalized for three months receiving the usual treatment for cardiac failure when dyspnea and edema regressed partially. Specific treatment for schistosomiasis was not attempted. The patient's condition deteriorated rapidly and he died following an episode of convulsions, cyanosis and shock.

MATERIAL AND METHODS

A complete necropsy was performed six hours *post mortem*. For light microscopy, blocks of formalin-fixed tissues from all organs were embedded in paraffin. Sections were stained with Hematoxylin and Eosin. In some instances the following stains were also used: periodic acid Schiff (PAS), Weigert-van Gieson, Azan, Periodic acid methenamine silver (PAMS) and silver reticulum impregnation. Kidney sections were cut at 5 and 2 micra. For electron microscopy formalin-fixed tissue was washed in phosphate buffer, fixed in osmium tetroxide, and embedded in Araldite. The blocks were then sectioned on a Porter Blum MT-2 microtome with glass and diamond knives, stained with uranyl acetate and lead citrate, and examined in a Siemens Elmiskop 1 electron microscope.

PATHOLOGIC FINDINGS

The cadaver was that of a pale, undernourished, cyanotic edematous boy. He appeared 3 to 4 years younger than his stated age, 13 years. The main pathologic findings appear in Table I. The liver showed schistosomal portal fibrosis (Fig. 1 B).

The peritoneal cavity contained several nodules that on first inspection appeared as a nodular disseminated peritoneal malignancy (Fig. 1 A). There were 500 ml of straw-color fluid within the peritoneal cavity. Blood vessels were markedly dilated and congested. Some of the vessels on the liver surface and over the larger nodules were varicose. Within the portal vein several pairs of adult worms could be easily collected. Sections of adult worms were also seen microscopically in the spleen, liver, intestines, and in the peritoneal nodules.

Microscopically, lesions caused by the schistosome eggs were numerous in several organs. The abdominal nodules showed a tremendous accumulation of eggs, some of them calcified. Around the eggs there were several stages of inflammatory reaction: accumulation of polymorphonuclear cells, especially eosinophils (pseudo-abscesses), granulomatous formation, non-specific chronic inflammation and fibrosis.

In the kidney all glomeruli showed a diffuse membranous thickening, forming the classical pattern of "membranous glomerulonephritis" or "membranous glomerulopathy" (Fig. 1 D). However, in some glomeruli a slight to moderate mesangial expansion with mesangial cells proliferation could be disclosed. Special staining methods revealed silver-positive "spikes" (Fig. 1 C) and Azan-positive "deposits" on the epithelial aspect of the glomerular capillary walls. Although electron microscopy was performed on ordinary formalin fixed autopsy tissue, it showed well preserved electron-dense deposits along the epithelial side of the glomerular basement membrane (Fig. 2). All the other cellular details were lost in those sections.

DISCUSSION

The case here reported represents an example of a massive infection with *Schistosoma*

TABLE I

Pathological changes found in a patient with massive schistosomal infection

Organs	Weight (g)	Gross Description	Microspical Findings	*S. mansoni* eggs	Anatomical diagnosis
Heart	200	Rt. ventricular hypertrophy (1 cm in thickness)	Muscular hypertrophy (right ventricle)	+	Chronic *Cor pulmonale*
Lungs	(*)	Disseminated whitish nodules (0,5 to 1 cm) in parenchyma. Arterial thickening.	Egg granulomas in alveolar tissue, arterial walls. Vascular narrowing and occlusion.	+++	Schistosomal pulmonary arteritis
Liver	1,000	"Pipe-stem" portal fibrosis. Congestion.	Granulomatous inflammation. Portal vein occlusion. Portal fibrosis, septal fibrosis. Parenchyma mantains lobular architecture.	++	Schistosomal portal fibrosis (Symmers' clay pipe-stem fibrosis)
Spleen	200	Firm and congested.	Reticulo-endothelial hyperplasia. Congestion. Worms present in splenic veins.	+	Mild "congestive" splenomegaly
Intestines	—	Tumor nodules (1 to 15 cm) on peritonel surface, epiplon, mesentery, intestinal submucosa, and mesenteric lymph nodes.	Numerous mature, disintegrating and calcified eggs surrounded by granulomatous inflammation and extensive fibrosis.	++++	Pseudo-neoplastic abdominal schistosomiasis
Kidneys	350	Swollen and pale, with smooth surface. Good cortico-medullary markings.	Membranous thickening of glomerular capillary walls. Tubules, vessels and interstitium well preserved. A few egg granulomas.	+	Membranous glomerulopathy
Brain	1,200	Congestion and edema of leptomeninges.	Several eggs found in "crushed" preparations. Egg granulomas, focal vasculatis, and peri-vascular haemorrhage.	++	Cerebral schistosomal granulomas

(*) Lungs not weighed

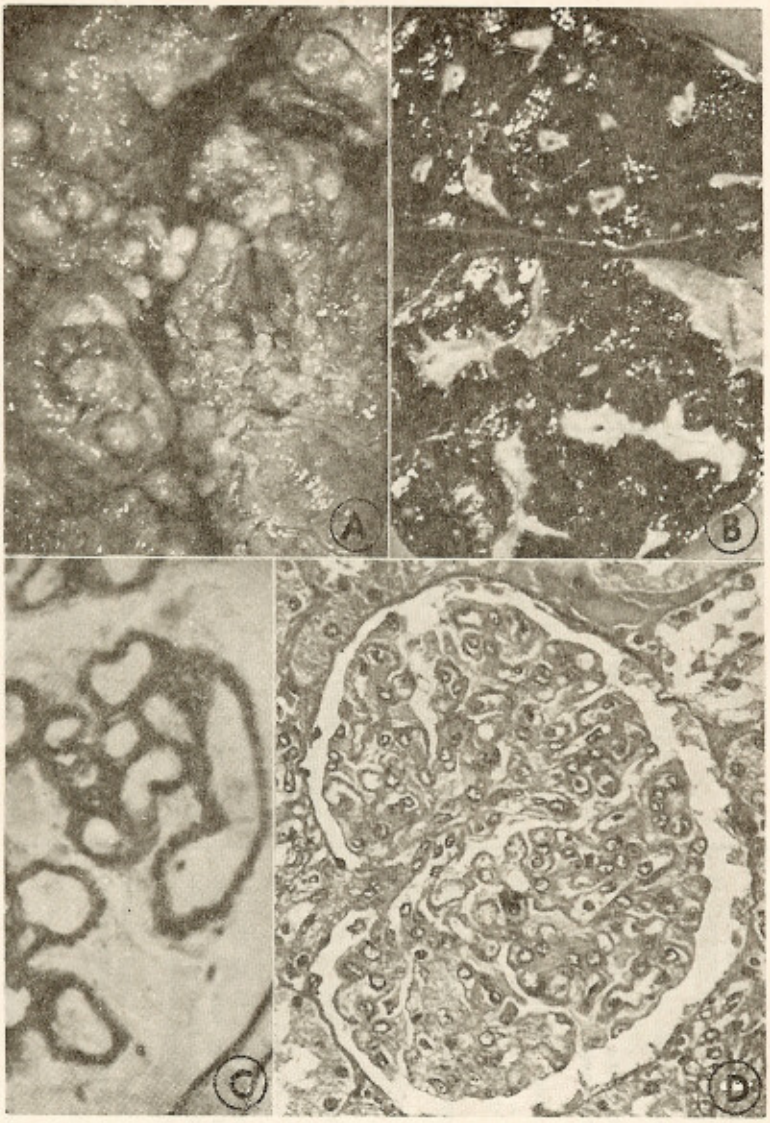

Fig. 1 — A) Several nodules disseminated on the peritoneal surface (Pseudo-neoplastic schistosomal lesions). B) Marked portal fibrosis, representing "pipe stem" fibrosis of the liver. C) Silver-positive "spikes" projecting from the capillary wall of the glomerulus. PAMS, 450 ×. D) Light photomicrograph of renal glomerulus showing diffuse, uniform thickening of the glomerular capillary wall, characteristic of membranous glomerulonephritis. PAS, 360 ×.

mansoni. Whether the child had one single massive infection or several repeated infections is not known. The importance of heavy infection to the development of portal vascular obstruction and portal fibrosis is evident. Numerous mature eggs were trapped within the portal spaces of the liver where they provoked an intense inflammatory reaction, with a severe vascular destruction and obstruction. Collateral circulation resulting from portal obstruction and hypertension diverted many eggs to the lungs. There they

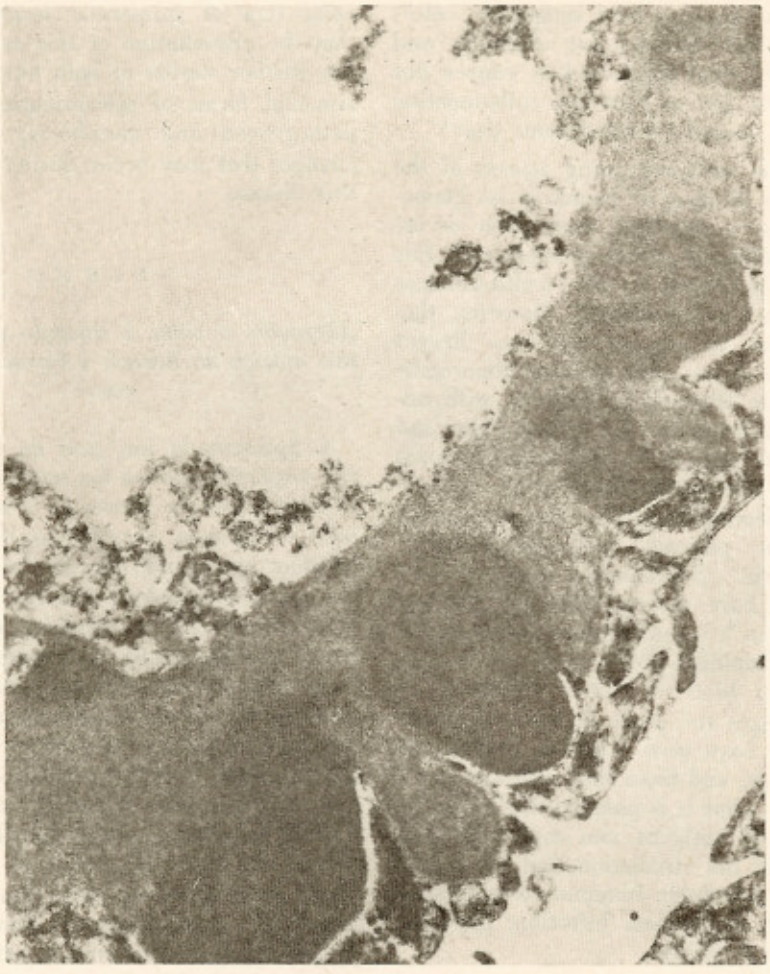

Fig. 2 — Human membranous glomerulonephritis in schistosomiasis. Electron micrograph of thickened glomerular capillary basement membrane with large, electron-dense, epimembranous deposits, separated by intervening spike-like projections of the basement membrane. The poor preservation of the cytoplasm is due to *post-mortem* autolytic changes. Magnification: 24.000 ×.

were responsible for disseminated arterial and arteriolar inflammation and obstruction which led to hypertension in the lesser circulation and hypertrophy of the right ventricle of the heart (*Cor pulmonale*). In this case the importance of massive egg embolization to the lungs in the pathogenesis of schistosomal *Cor pulmonale* was evident, which is in agreement with the findings obtained in previous studies with experimental [15] and human materials [1, 12].

An unusual finding in schistosomiasis was present in the abdominal cavity in the present case. A massive dissemination of egg granulomas had produced tumor-like nodules in the peritoneum, omentum, mesentery and mesenteric lymph nodes, that simulated a wide spread malignant neoplasm. This pseudo-neoplastic form of schistosomiasis is related to a massive deposition of eggs in relatively small areas [5]. The case provides an extraordinary demonstration of this process. This form of the disease is relatively

unknown and patients have undergone colectomies for such lesions that clinically and radiologically were diagnosed as cancer but actually were due to extensive inflammation and fibrosis caused by schistosome eggs [5].

One of the most intriguing aspects of the case was the finding of membranous glomerulonephritis, a relatively uncommon occurrence in childhood. It is possible that this lesion was unrelated to the schistosomiasis and developed independently. However, there is evidence to suggest otherwise. Recent studies have shown that urinary abnormalities are quite frequent in patients with advanced schistosomiasis [9], and lipoproteins and globulins are present in the urine of such patients [10]. Glomerular mesangial thickening [4] and glomerulonephritis [2] are frequently observed in patients with hepatosplenic schistosomiasis. *Schistosoma mansoni* and its products have several metabolic and somatic antigens [6, 7] and infected humans and experimental animals produce circulating antibodies [14] that bind to several structures in the mature eggs and adult worms [3]. Circulating antigens have been found in heavily infected animals, and these may also appear in the urine [11]. Thus it is possible that different proportions of antigens and antibodies can be present in the circulation and can reach the kidneys as soluble immune complexes in patients with *S. mansoni* infection, there by inducing renal disease.

Although schistosomal antigen has not been demonstrated in the kidney, both immunoglobulins (IgG and IgM) and complement (BlC) have been found within the mesangium as granular and linear deposits along the glomerular capillary basement membrane in patients with hepatosplenic schistosomiais [13]. In chimpanzees heavily infected with *S. japonicum*, glomerular lesions similar to those seen in humans have recently been demonstrated [8].

Although nearly every form of glomerulonephritis has been associated with schistosomiasis [2], this is the first time that we have seen membranous glomerulonephritis in a patient with severe schistosomiasis. Perhaps the heavy infection, with the continued release of antigen in a patient with a moderate level of cross-reacting antibody to schistosomal antigens was responsible for this particular type of glomerular lesions. We hope that the presentation of this case will stimulate further studies of both human and experimental forms of schistosomiasis, regarding pathogenesis and morphology of the renal changes that may occur during the course of this disease.

RESUMO

Alterações devidas à infecção esquistossomótica maciça no homem (Apresentação de um caso)

É apresentado um caso de intensa infecção esquistossomótica em menino de 13 anos. O paciente veio a falecer e o estudo *post-mortem* demonstrou granulomas ovulares disseminados em grande número por quase todos os órgãos, causando lesões vasculares obstrutivas. Havia fibrose hepática de tipo Symmers, esplenomegalia congestiva com hiperplasia reticular, arterite pulmonar e *Cor pulmonale*, extensa lesão pseudo-neoplásica envolvendo peritôneo, linfonodos mesentéricos, grande epíplon e mesentério, além de um processo de glomerulonefrite crônica membranosa (glomerulopatia membranosa). A ocorrência desta última lesão em um paciente que apresenta todo um espectro de lesões da esquistossomose grave, suscita o problema do relacionamento etiológico deste tipo de glomerulopatia com a esquistossomose.

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