

Schistosoma mansoni associated glomerulopathy with IgA mesangial deposits: case report

Glomerulopatia esquistossomótica com depósitos mesangiais de IgA: relato de caso

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ABSTRACT

Introduction: Renal involvement is a severe form of schistosomiasis and occurs in 10% to 15% of patients with the hepato-splenic form of the disease. Nephrotic syndrome is the most common clinical presentation. It is a complication caused by immune complexes (IC), it is rare to appear in the Brazilian context with an immunoglobulin A (IgA) deposits. When installed the renal injury by *Schistosoma mansoni*, classically presents as membranoproliferative glomerulonephritis (mesangiocapillary) with lobular accentuation. **Objective:** To report a case of schistosomiasis nephropathy that appeared 7 years after treatment of hepato-splenic schistosomiasis with histologic pattern of mesangial proliferative glomerulonephritis with IgA deposits in mesangium. Clinically developed with progressive decrease of proteinuria with angiotensin receptor blocker (ARB). **Method:** It was reported a case of a 36 years old patient, brown, with classical sintoms of nephrotic syndrome (proteinuria > 3.5 g/24h, hypoalbuminemia and hypercholesterolemia), however with hepato-splenic schistosomiasis history 7 years ago and portal hypertension. Patient underwent renal biopsy which showed IgA deposits in mesangial, being more intense than immunoglobulin G (IgG), accompanied by C1q and C3, with 4/13 glomeruli sclerotic, standard light mesangial glomerulonephritis renal injury with IgA deposits. Patient began taking ARB with progressive improvement in proteinuria. **Conclusion:** Patients with glomerulonephritis by schistosoma don't show improvement of disease progression with antiparasitic treatment. However the anti-proteinuric treatment can slow the progression of end stage kidney disease.

Keywords: angiotensin receptor antagonists; glomerulonephritis, IGA; *Schistosoma mansoni*.

RESUMO

Introdução: O acometimento renal é uma forma grave da esquistossomose e ocorre em 10% a 15% dos pacientes com a forma hepatoesplênica da doença. A síndrome nefrótica é a apresentação clínica mais comum. Trata-se de uma complicação causada por imunocomplexos (IC), sendo rara no contexto brasileiro apresentar-se com depósitos de imunoglobulina A (IgA). Quando instalada a lesão renal pelo *Schistosoma mansoni*, apresenta-se classicamente como glomerulonefrite membranoproliferativa (mesangiocapilar), com acentuação lobular. **Objetivo:** Relatar caso de glomerulopatia esquistossomótica que se apresentou 7 anos após tratamento de esquistossomose hepatoesplênica com padrão histológico de glomerulonefrite proliferativa mesangial com depósitos de IgA em mesângio. Clinicamente, evoluiu com diminuição progressiva de proteinúria com bloqueador do receptor de angiotensina (BRA). **Método:** Foi relatado caso de paciente com 36 anos, parda, com quadro clássico de síndrome nefrótica (proteinúria > 3,5 g/24h, hipoalbuminemia e hipercolesterolemia), no entanto, com histórico de esquistossomose hepatoesplênica há 7 anos e com hipertensão portal. Paciente foi submetida à biópsia renal, que apresentou depósitos de IgA em mesângio, sendo mais intensos que imunoglobulina G (IgG), acompanhados de C1q e C3, com 4/13 glomérulos esclerosados, padrão de lesão renal de glomerulopatia mesangial leve com depósitos de IgA. Paciente iniciou uso de BRA, com melhora progressiva da proteinúria. **Conclusão:** Pacientes com glomerulopatia por schistosoma não apresentam melhora da progressão da doença com tratamento antiparasitário. Entretanto, o tratamento antiproteinúrico pode retardar a progressão da doença renal crônica terminal.

Palavras-chave: antagonistas de receptores de angiotensina; glomerulonefrite por IGA; *Schistosoma mansoni*.

INTRODUCTION

Schistosomiasis is one of the most infectious-contagious parasitic diseases affecting humans.^{1,2} It is caused by worms of the genus *Schistosoma*, with freshwater snails of the genus *Biomphalaria* as intermediary hosts; and it may evolve from asymptomatic to extremely severe clinical forms.^{1,3} There are estimates of about 200 million people infected by the three major species of *Schistosoma* (*mansoni*, *haematobium* and *japonicum*).²

Renal impairment is a severe form of schistosomiasis and occurs in 10% to 15% of the patients with the hepatosplenic form, and the nephrotic syndrome (NS) is the most common clinical presentation. It is a complication caused by the deposition of immunocomplexes (IC);^{4,6} and mesangial deposits of immunoglobulin A (IgA)³ is rare in Brazil.

When the renal lesion is installed, the predominant histological finding is membranoproliferative glomerulonephritis (MPGN) (mesangiocapillary), with lobular accentuation. The second most frequent histological type is focal segmental glomerulosclerosis (FSGS).^{1,4,5,7}

The prognosis of renal injury caused by schistosomiasis does not change with the proposed therapeutic regimens (schistosomicides alone or associated with immunosuppressants). The kidney damage is progressive and the disease evolves to chronic end-stage renal disease (ESRD).^{1,4,6}

CASE PRESENTATION

A 36-year-old patient being followed at the gastroenterology clinic due to hepatosplenic schistosomiasis. She was submitted to a splenectomy in 2007. For about 6 months she had had proteinuria upon routine examinations. In 2015, she developed classic NS (proteinuria > 3.5 g/24h, hypoalbuminemia, dyslipidemia and edema) associated with systemic arterial hypertension (SAH), without hematuria, without renal dysfunction (Chart 1).

The patient had a normal physical examination, no comorbidities and no family history of ESRD.

Laboratory tests showed high levels of aminotransferases, normal complements, non-reactive anti-nuclear factor, negative viral serology (hepatitis B, hepatitis C and HIV), portal hypertension, non-alcoholic hepatitis (NASH) with advanced fibrosis and confirmation by Fibroscan, duodenal ulcer, varicose veins of the esophagus.

She was treated with losartan and atenolol, yielding a significant reduction of proteinuria - to subnephrotic levels (a renal biopsy was ordered), as shown in Figures 1 to 3.

We concluded that the presence of IgA deposits, being more intense than immunoglobulin G (IgG), together with C1q and C3, could correspond to a secondary IgA nephropathy, with 4/13 sclerosed glomeruli, mild hyaline arteriolesclerosis and moderate intimal fibroelastic thickening of the interlobular artery. Since there are C1q deposits, another possibility would be systemic lupus erythematosus (SLE), which was discarded because the patient did not meet other clinical and/or serological criteria. She also had mild focal tubular atrophy associated with mild interstitial fibrosis, and mild subintimal fibrosis in small gauge arteries.

With this lesion pattern shown in the biopsies (ML, IF and ME), it can be inferred that this is a case of schistosomal glomerulopathy with mesangial deposits of IgA.

DISCUSSION

Schistosoma glomerulopathy has six classes, according to Barsoum⁸ and Johnson⁹: Class I - mesangial proliferative glomerulonephritis, microhematuria and subnephrotic proteinuria; Class II - diffuse exudative glomerulonephritis, acute NS and toxemia; Class III - membranoproliferative glomerulonephritis, hepatosplenomegaly, NS, SAH and kidney failure; Class IV - Segmental and focal glomerulosclerosis, hepatosplenomegaly, NS, SAH, kidney failure; Class V - amyloidosis, hepatosplenomegaly, NS, SAH, kidney failure; Class VI - cryoglobulinemic glomerulonephritis (associated with the hepatitis C virus), hepatosplenomegaly, NS, purpura, vasculitis, arthritis, SAH, renal failure. According to the patient's biopsy, she had class I histology and class III symptomatology.

In a Brazilian study, carried out by Rodrigues *et al.*,² in patients with *S. mansoni*, they found that 12.7% of 63 patients had glomerular involvement, with mesangial lesion in all samples (electrodense deposits in the mesangium). In an immunofluorescence study, there were 85% with immunoglobulin deposits, IgG in 50%, immunoglobulin M (IgM) in 63% and IgA in 38%. The Complement 3 (C3) fraction was identified in 75%, and C1q in two samples.

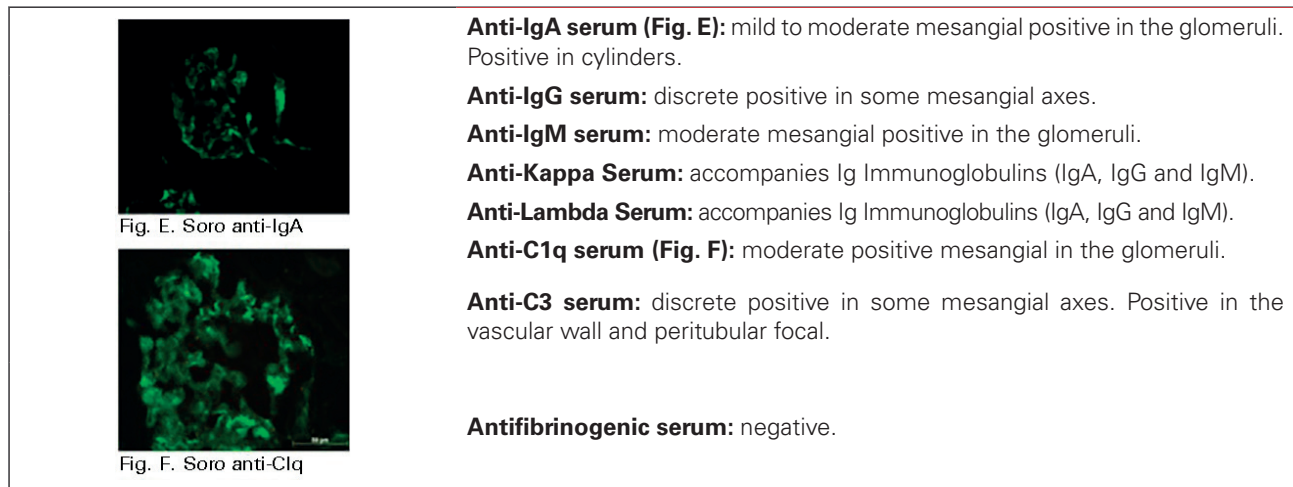
CHART 1 PROGRESSION OF THE TESTS BETWEEN AUGUST, 2013 AND NOVEMBER OF 2015

Tests/Dates	Reference values	08.16.13	03.20.14	27.03.15	24.08.15	28.09.15	14.10.15	23.11.15
Urea (mg/dl)	10.0 - 50.0	24.0	22.0	16.0	18,0	22,0	29,0	15,0
Creatinine (mg/dl)	0.70 - 1.20	0.58	0.54	0.64	0,68	0,65	0,78	0,74
Glutamic pyruvic transaminase (GPT)(U/L)	0 - 31	100	75	57	84	129		74
Glutamic oxalacetic transaminase (GOT)(U/L)	0 - 32	68	56	49	111	141		106
Triglycerides (mg/dl)	65 - 150	105	150	157	120	117		
Total cholesterol (mg/dl)	< 200	308	472	535	302	254		319
Albumin	3.5 - 5.0 g/dL			2.9	2,4			
Search for abnormal elements/sediments in the urine								
Proteins	Negative			Positive(++++)	Positive(+++)	Positivo(+++)	Positivo(+++)	Positivo(++)
Hemoglobin	Absent			Absent	Absent	Absent	Absent	Absent
Red blood cells	/field			0	0	0	3	rare
Leucocytes	/field			2	8	4	10	3
Proteinuria and microalbuminuria								
Urine volume/ 24h	mL			2000	2000	1960		1900
Microalbuminuria (mg/24h)	0.0 - 30.0				3620.8	3048.2		2039.5
24h proteinuria (mg/24h)	30 - 140			4372	2888	2760		1766

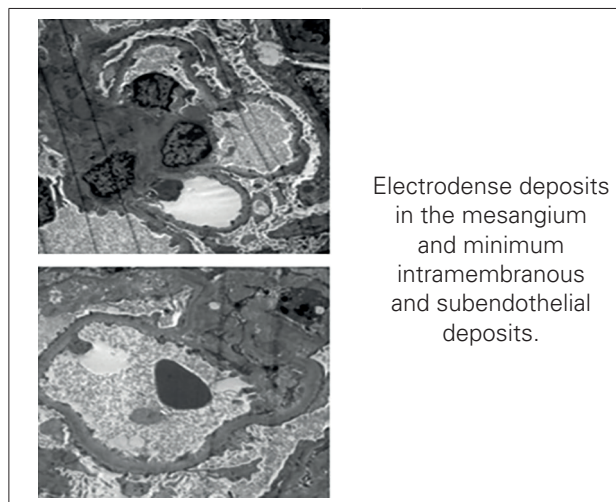
Source: Laboratory test results from the Base Hospital of the Federal District.

Figure 1. Light microscopy (LM).

Source: MEC Federal University of the Triângulo Mineiro (UFTM) - Department of Nephrology - Discipline of General Pathology - Uberaba, MG.

Figure 2. Immunofluorescence (IF).

Source: MEC Federal University of the Triângulo Mineiro (UFTM) - Department of Nephrology - Discipline of General Pathology - Uberaba, MG.

Figure 3. Electron microscopy.

Source: MEC Federal University of the Triângulo Mineiro (UFTM) - Department of Nephrology - Discipline of General Pathology - Uberaba, MG. General Pathology Discipline. <http://www.uftm.edu.br/patge/> Federal University of the Triângulo Mineiro.

IgA deposits were seen in the renal tubules in all the cases, around the cylinders, and Kappa and Lambda in 75%. Electrodense deposits were found in the glomerular structures of three patients, all with type 1 MPGN. In summary, the sample showed: four patients with type 1 MPGN; one patient with mesangioproliferative segmental sclerosis and C3 deposits; one patient with mesangial deposits of IgA, C1q and C3, and one patient with segmental and mesangial sclerosis with of IgM, C3 and C1q deposits.²

Schistosomotic glomerulopathy occurs because of chronic infection by *Schistosoma mansoni*.^{1,6} According to the Department of Surveillance of Communicable Diseases of the Ministry of Health,¹ Dos Santos *et al.*¹⁰ and Nussenzveig *et al.*,³ when renal injury is established, the histological picture is usually one of mesangiocapillary glomerulonephritis.

The second type of glomerulopathy most found in these cases is FSGS; however, the relationship between FSGS and *Schistosoma* glomerulopathy has not yet been well established,^{3,8} and it is more associated with African descendants.

Our patient was positive for C1q, which according to Gusmão *et al.*,¹¹ has been strongly associated with renal involvement due to systemic lupus erythematosus (SLE), although she did not have all the criteria for SLE, according to the Brazilian Society of Rheumatology.¹²

The histological diagnosis of IgA nephropathy (IgAN) is direct, and it is defined by the presence of IgA-dominant or codominant immune deposits within the glomerulus, as shown by immunohistochemistry and immunofluorescence.^{13,14} The product of the activation of the classical complement pathway: C1q, is not typically found in IgA nephropathy.

According to the Oxford classification,¹³ the intensity of IgA immunopositivity should be more than traces, and its distribution is characteristically mesangial, with or without deposits in capillary loops. IgG and IgM may be positive, but not at a greater intensity than IgA.

According to Barsoum *et al.*,¹⁵ IgA may be a late mediator of glomerular injury in these cases. The dominance of mesangial IgA deposits in the Egyptian context is common, suggesting significant glomerular pathogenicity by IgA, requiring a factor of comorbidity with concomitant exposure to schistosomal antigens.

In the studies by Brito *et al.*,⁷ only one of its cases with membranous GN presented IgA (+), IgG (++) , IgM (+) and C3 in the glomerulus, which, according to Nussenzveig *et al.*,³ suggests that IgA deposits in schistosomal glomerulopathy are rare in Brazil due to geographic factors, when compared to the findings of Barsoum *et al.*¹⁵

The glomerular deposits of IgA that have been found in patients with portal hypertension in the hepatosplenic form of schistosomiasis can be considered as a factor of progression of renal disease, and are explained by the dysfunction in immunoglobulin clearance of by Kupffer cells.¹⁴

The importance of IgA in the pathogenesis of this nephropathy is unknown, and studies are needed to redefine the molecular structure of glomerular IgA deposits.¹⁴

Patients diagnosed with IgAN are treated with angiotensin converting enzyme inhibitors (ACEI) and/or ARB, and associations may be more effective when the patients have proteinuria ≥ 1 g/day, being hypertensive or not, with normal renal function and mild histological lesions;^{16,17} as it was the case in question, showing progressive proteinuria improvement.

CONCLUSION

Although global and national parameters present MPGN as the main histological lesion in *Schistosoma mansoni* infection with renal impairment,^{3,8,18} the case in question presents histology of a schistosomal GN with mesangial deposits of IgA.

The importance of IgA in the pathogenesis of this nephropathy is still unknown. Treatment with ARB resulted in improvements in proteinuria, contributing to retard the progression to ESRD.

Mesangial proliferative GN is the earliest and most frequent form, followed by MPGN, favoring the hypothesis of the mesangium as the initial target. The clinical presentation is variable, and glomerulopathy is asymptomatic in up to 35% of the patients. However, since the diagnosis is usually late, SN, SAH, and hypocomplementemia are common findings.^{7,19}

Considering the national frequency of the disorder, it is necessary to understand the different histological presentations of schistosomal glomerulopathy.^{3,18}

Patients with schistosomal glomerulopathy do not show improvements in terms of disease progression with antiparasitic treatment;^{8,10,20} however, treatment with antiproteinuric agents can delay the progression of ESRD.^{8,21}

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