

CASE REPORT

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# *Schistosoma japonicum* infection associated with membranous nephropathy: a case report

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## Abstract

**Background:** Schistosomiasis is one of the most contagious parasitic diseases affecting humans; however, glomerular injury is a rare complication mainly described with *Schistosoma mansoni* infection. We report a case of membranous nephropathy associated with *Schistosoma japonicum* infection in a Chinese man.

**Case presentation:** A 51-year-old Chinese male with a long history of *S. japonicum* infection presented to the hospital with a slowly progressing severe lower limb edema and foaming urine for over 5 months. Serum *S. japonicum* antigen test was positive and immunohistochemistry showed that the glomeruli were positive for the antigens. The renal pathologic diagnosis was stage III membranous nephropathy. The patient was treated with glucocorticoid, praziquantel, and an angiotensin-converting enzyme inhibitor. The edema in both lower limbs disappeared within 2 weeks, but his renal function declined progressively and proteinuria persisted after 5 months of therapy.

**Conclusions:** Different classes of schistosomal glomerulopathy have completely different clinical manifestation and prognosis. Therefore, efforts should focus on alleviating symptoms, prevention, and early detection. *S. japonicum* associated with membranous nephropathy may show a good curative effect and prognosis. However, it is necessary to monitor the renal function in such patients.

**Keywords:** *Schistosoma japonicum*, Membranous nephropathy, Nephrotic syndrome

## Background

Schistosomiasis is one of the most infectious parasite illnesses that affects humans, killing 20,000 people per year [1, 2]. Glomerular damage is a very uncommon consequence associated with *Schistosoma* infections. The southern and eastern parts of China are endemic for schistosomiasis, while renal consequences are unusual. In China, schistosomiasis is endemic to the southern and eastern regions, but renal complications have rarely been reported. Three major species of *Schistosoma* affect ~ 200 million people: *Schistosoma hematobium* in Africa, *Schistosoma mansoni* in Africa and South America, and *Schistosoma japonicum* in the Far East [1].

Glomerular diseases had been well described in association with *S. mansoni* but exceptionally with other species [3]. Renal impairment is a severe form of schistosomiasis and the most common clinical presentation is nephrotic syndrome. According to the African Association of Nephrology (AFRAN), five classes of schistosomal glomerulopathy are recognized [4], and the most common histological finding is membranoproliferative glomerulonephritis (MPGN). The second most frequent histological type is focal segmental glomerulosclerosis [5]. The five classes do not include membranous nephropathy and only one case of *S. mansoni*, which caused membranous nephropathy, has been reported to date [6]. We report the first case of *S. japonicum* associated with membranous nephropathy in a Chinese man. We received written consent from the patient to publish the age, image findings, and pathologic pictures associated with this case report.

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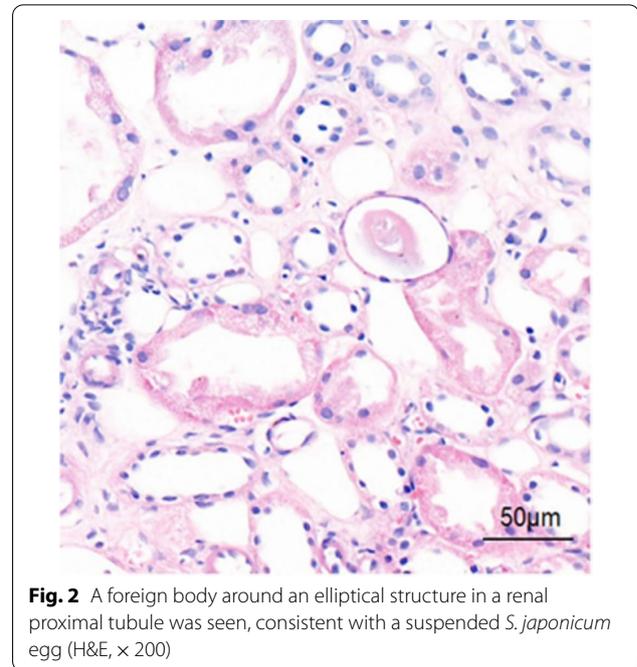
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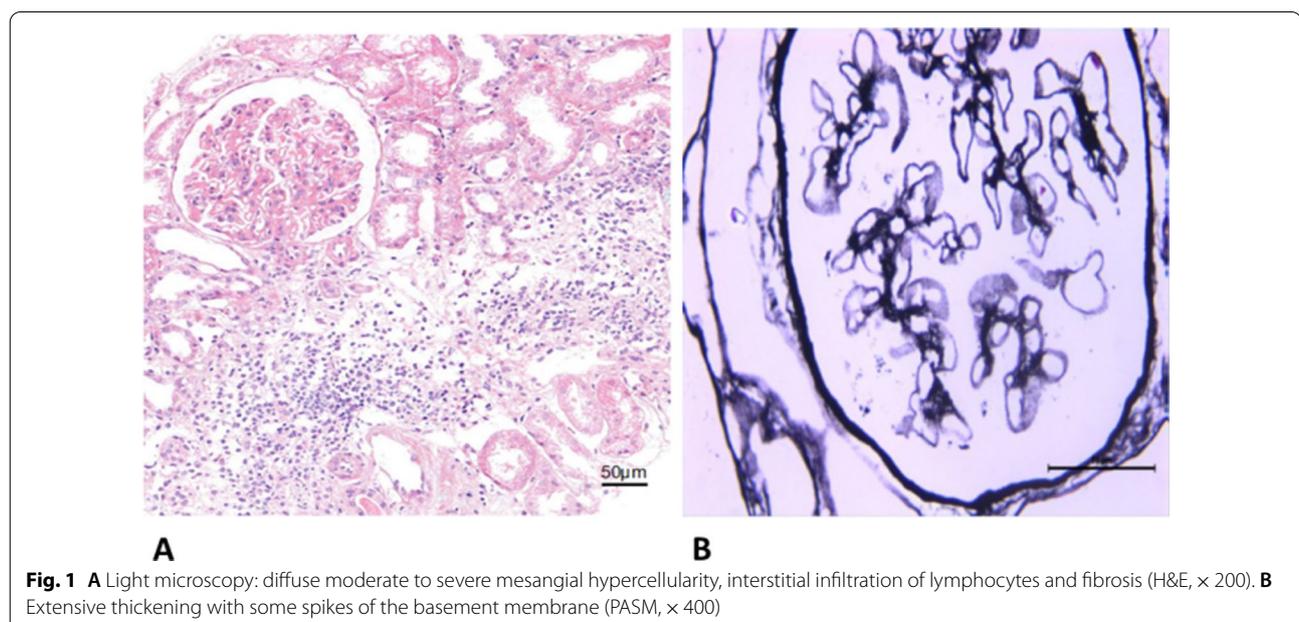
### Case presentation

A 51-year-old Chinese male presenting with slowly progressing severe lower limb edema and foaming urine for over 5 months was admitted to Xiangya Hospital. The patient was diagnosed with *S. japonicum* infection in 2000 due to Schistosomiasis eggs found in his feces. The patient had no personal or family history of renal disease. Physical examination at current hospital admission revealed severe edema of the lower extremities. Laboratory tests revealed creatinine, 92  $\mu\text{mol/l}$ ; glomerular filtration rate, 98.59 ml/min; white blood cell count,  $18.13 \times 10^9/\text{l}$ ; eosinophil count,  $10.09 \times 10^9/\text{l}$ ; albumin, 27.50 g/l; triglycerides, 1.65 mmol/l; total cholesterol, 9.98 mmol/l; 24 h proteinuria, 2388.44 mg/24 h. Autoantibody detection and serologic test results were negative for hepatitis B, hepatitis C, and HIV, but positive for *Schistosoma* antibody. Anti-nuclear antibodies include anti-Sm, anti-Ro, anti-La, anti-RNP, and anti-dsDNA antibodies were negative. Serum complement levels were normal. Abdominal B type ultrasonography revealed splenomegaly, diffuse lesion in the liver parenchyma; left kidney, 103  $\times$  54 mm; and right kidney, 97  $\times$  43 mm. Anti-phospholipase A2 receptor antibodies were detected at 48.13 RU/ml. Light microscopy examination for renal biopsy sample revealed diffuse moderate to severe mesangial hypercellularity, extensive thickening with some spikes of the basement membrane, interstitial infiltration of lymphocytes, and fibrosis (Fig. 1). A foreign body around an elliptical structure in the renal proximal tubule was noted, consistent with the findings

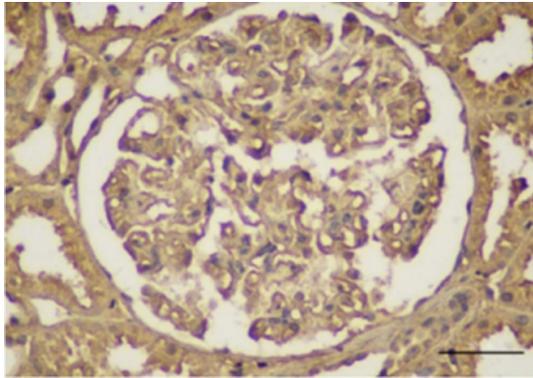


**Fig. 2** A foreign body around an elliptical structure in a renal proximal tubule was seen, consistent with a suspended *S. japonicum* egg (H&E,  $\times 200$ )

of a suspended *S. japonicum* egg (Fig. 2). Immunohistochemically, the glomeruli were positive for *S. japonicum* antigens (tested by polyclonal antibodies derived from the sera of mice infected with *S. japonicum*) (Fig. 3). Immunofluorescence showed granular deposits of IgG, IgM, IgA, C3, C1q, kappa, and lambda in the glomerular capillary loop. The final pathologic diagnosis was stage III membranous nephropathy (Fig. 4). The treatment of



**Fig. 1** **A** Light microscopy: diffuse moderate to severe mesangial hypercellularity, interstitial infiltration of lymphocytes and fibrosis (H&E,  $\times 200$ ). **B** Extensive thickening with some spikes of the basement membrane (PASM,  $\times 400$ )



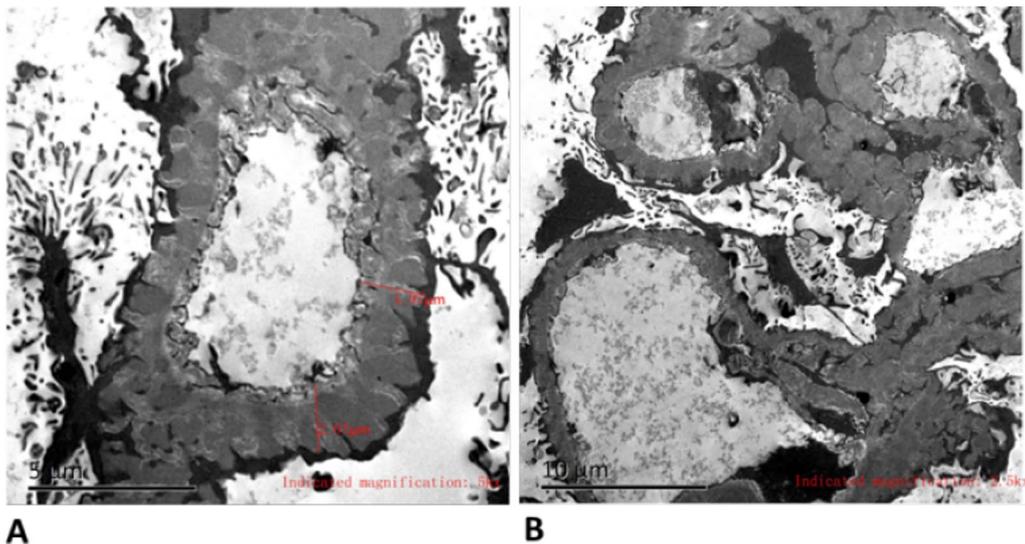
**Fig. 3** Immunohistochemical finding. *S. japonicum* antigen in the renal glomeruli and tubules was positive. Recognized by polyclonal antibodies IgG in sera of mice at 60 day post-infected ( $\times 400$ )

the patient was started with oral glucocorticoid (prednisone, 25 mg/day), praziquantel (60 mg/kg), an angiotensin-converting enzyme inhibitor (ACEI, 0.15 g/day) and ZhiLing capsula (0.75 g, thrice daily) with supportive therapy (salt-free diet, Etamsylate, vitamin K1). After 7 days of treatment, the patient was discharged from hospital. The patient was put on continuous oral ACEI (0.15 g/day) and Compound  $\alpha$ -Ketoacid Tablets (2.52 g, thrice daily) at home for 5 months, the edema in both lower limbs disappeared within 2 weeks, but the renal function declined progressively and proteinuria persisted after 5 months of therapy (Table 1).

## Discussion and conclusion

This is the first case report of membranous nephropathy associated with *S. japonicum* infection in a Chinese man.

Schistosoma infection may be underdiagnosed in endemic areas with high schistosomiasis prevalence due to a lack of comprehensive screening. Furthermore, in 10–15% of patients with *S. mansoni* infection, glomerular damage related to schistosomiasis has been documented, with MPGN being the most frequent histological type [7–9]. Direct deposition of schistosomal antigens causes glomerular damage in most cases. Moreover, immune complex (IC) deposition is the main mechanism underlying the different forms of schistosomal glomerulonephritis [10], which is associated with IC deposition in the sub-endothelial, sub-epithelial, and mesangial regions of the glomerulus, together with IgA aggregates and parasite antigens, as shown in the glomeruli of both experimental animals and people with membranoproliferative and mesangioproliferative glomerulonephritis [11]. Schistosomal glomerulopathy is a distinct disease entity, which has been identified with experimental [12], epidemiologic [13], post-mortem [14], and clinical evidence [4]. The AFRAN endorsed a clinicopathologic classification for schistosomal glomerulopathy in 1992, wherein 5 classes of schistosomal glomerulopathy were recognized. Class I is mesangial proliferative glomerulonephritis. Class II is an exudative glomerulonephritis; patients with this form are concomitantly infected by *Salmonella* and *Schistosoma* [4]. Class III is MPGN usually reported in Caucasian individuals, and Class IV is a focal proliferative/sclerosing lesion typically seen in African-origin



**Fig. 4** Electron microscopy. **A** Glomerulus had mild mesangial hyperplasia and thickened basement membrane ( $\times 5000$ ). **B** Electron density was deposited in the subepithelium and basement membrane of the glomerulus ( $\times 2500$ )

**Table 1** Progression of the tests between March and July 2018

Tests/dates	Reference values	03.05.18	03.21.18	05.31.18	06.08.18	07.03.18	07.30.18
White blood cells ( $\times 10^9/l$ )	3.5–9.5	18.13	13.51	10.7	8.9	12.5	13.5
Platelet count (fL)	123–350	256	247	233	208	169	215
Eosinophils count ( $\times 10^9/l$ )	0.02–0.52	10.09	1.72	1	0.8	1.1	0.1
Eosinophils (%)	0.4–8.0	55.7	12.8	9.7	8.5	9	0.1
Hemoglobin vale (g/l)	130–175	149	129	129	119	119	110
Urea (mg/dl)	3.10–8.00	4.4	6.67	4.89	6.38	8.78	14.71
Creatinine ( $\mu\text{mol/l}$ )	41–111	92	98.3	114	105.4	121	140.8
Alumin (g/l)	40–55	27.5	27.77	36.5	35.7	37.3	37.7
Triglycerides (mmol/l)	< 1.70	1.65	6.67	1.35	1.31		
Total cholesterol (mmol/l)	< 5.18	9.98	9.97	6.97	6.86		

Search for abnormal elements/sediment in the urine		Positive (++++)	Positive (++++)	Positive (++)	Positive (++++)	Positive (+)
Proteins						
Red blood cells	0–5	55	7	7	19	2
Urine volume/24 h l	L	1.8		1.5		
Microalbuminuria (mg/24 h)	0–30	3599		1332		
24 h proteinuria (mg/24 h)	< 150	3588.4		1710.62		

individuals. Class V is renal amyloidosis of the AA type. Recently, The inclusion of Class VI to the AFRAN classification of schistosomal glomerulopathy has been recommended. Class VI is cryoglobulinemic glomerulonephritis associated with the hepatitis C virus infection.

Approximately, 10–15% of patients with the hepatosplenic form of the disease have renal involvement. Individuals with hepatosplenic schistosomiasis have greater laboratory and clinical indicators of renal impairment than patients with other clinical forms of *S. mansoni* infection or non-infected controls [15]. Although the present case of membranous nephropathy caused by *S. japonicum* infection was rare, the mechanism of glomerular damage may have been comparable to that caused by *S. mansoni* infection. Between 2003 and 2009, the Renal Pathology Services at the Goncalo Moniz Research Centre-Fiocruz conducted a study that indicated a decrease in the number of reports of *S. mansoni* infection in biopsy specimens. Positive results for *S. mansoni* was reported for 24 out of 689 patients, and 4 out of the 24 had membranous glomerulonephritis. The prevalence of schistosomal glomerulopathy has decreased as a result of widespread treatment with oral medicines [16]. Compared with the study between 2003 and 2006, a study reported by Queiroz between 1970 and 1973 revealed that positive results for *S. mansoni* infection were reported for 38 out of 100 individuals, and 2 of these 38 had membranous glomerulonephritis [11]. So far, one case of membranous nephropathy associated

with *S. mansoni* infection has been reported by Neves et al. [6]; the renal biopsy results in this case supported the diagnosis of an organic renal lesion caused by *S. mansoni* infection.

Altogether, *S. japonicum* infection leading to membranous nephropathy appears to be unique and previously unreported. While anthelmintic and immunosuppressive drugs can relieve renal injury caused by schistosomiasis, the disease finally evolves to chronic end-stage renal disease (ESRD) [17]. Medical history, physical examination, laboratory examination, and renal pathology results in this report were consistent with a diagnosis of *S. japonicum* associated with membranous nephropathy. In this case, *S. japonicum* infection was induced by the patient's contact with infected water, as evidenced by the presence of Schistosomiasis eggs in the feces. Immunohistochemistry showed that the glomeruli were positive for parasitic antigens; treatment using praziquantel was effective. Moreover, since membranous nephropathy caused by other secondary factors was excluded, it can be inferred that the kidney injury was secondary to *S. japonicum* infection. Renal manifestations of glomerular disease caused by *S. mansoni* infection can range from asymptomatic albuminuria and normal renal function to chronic ESRD [7], although most patients have nephrotic syndrome and a plasma creatinine concentration between 88 and 176  $\mu\text{mol/l}$  [8]. In individuals with class I–II disease, complete recovery can occur spontaneously or

after therapy, while in cases with classes III–V, treatment with anthelmintic drugs and immunosuppressive agents is usually not effective to arrest the progression to ESRD. However, our patient's case differed from all the above classes. During the 10-month follow-up, his plasma creatinine level progressively increased between March 2018 and July 2018 and thereafter remained stagnant between 110 and 120  $\mu\text{mol/l}$  between July 2018 and December 2018; the proteinuria was persistent and showed no decline.

In summary, membranous nephropathy is a rare complication associated with *S. japonicum* infection. Following treatment with praziquantel, ACEI, and glucocorticoid, our patient's symptoms were rapidly resolved. However, the renal function declined progressively, creatinine and urea nitrogen levels increased, and proteinuria persisted. Therefore, efforts should be focused on alleviating symptoms, prevention, early detection, and treatment of *Schistosoma* infection among at-risk groups rather than eliminating urinary protein. Moreover, it is necessary to monitor the renal function in such cases.

Our research has several limitations, firstly, no attempt was made to give the patient the immunosuppressive therapy recommended for membranous nephropathy, such as rituximab, tacrolimus (FK506), because the patient did not have regular follow-up appointments. Secondly, it is not known whether the patient has progressed to end-stage renal disease because the follow-up period is not long enough.

#### Abbreviations

IC: Immune complexes; MPGN: Membranoproliferative glomerulonephritis; ESRD: End-stage renal disease; ACEI: Angiotensin converting enzyme inhibitors; AFRAN: African Association of Nephrology.

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#### Authors' contributions

ZNL wrote the manuscript. LJT, HLY, XCX, MXL and ZZP participated in the clinical care of the patient. ZNL and ZZP assisted in interpreting the results under clinical prospective. All authors assisted the results interpretation and manuscript revision. All authors read and approved the final manuscript.

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#### Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

#### Declarations

##### Ethics approval and consent to participate

Not applicable.

##### Consent for publication

Written informed consent was obtained from the patient. A copy of the consent form is available for review and can be provided on request.

#### Competing interests

The authors declare that they have no competing interests.

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