

Strongyloides stercoralis – Associated Tip Variant Focal Segmental Glomerulosclerosis



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INTRODUCTION

Approximately 100 million people worldwide are infected with the intestinal nematode *Strongyloides stercoralis* (StrS). This roundworm is endemic in tropical and subtropical regions.^{1–4} StrS has an auto-infective cycle that allows it to survive and replicate in a human host for many years.⁴ StrS has 2 important life stages, namely, filarial and rhabditiform. In the filarial stage, StrS enters its human host percutaneously through feces-contaminated soil. In the rhabditiform stage, StrS lays eggs that hatch into larvae in the duodenum and are passed into the stool. Most patients with StrS infection remain asymptomatic. Although parasitic infections are known to be associated with immune complex-mediated glomerular lesions, StrS-associated glomerulopathy has not been well documented.

Nephrotic syndrome has rarely been associated with StrS infection.^{5–8} Minimal change disease is the most common glomerular disease reported in association with StrS infection. The pathophysiologic link between StrS infection and nephrotic syndrome is not well defined. As most primary podocytopathies, including minimal change disease and primary focal segmental glomerulosclerosis (FSGS), are thought to be mediated by circulating permeability or immune factors that act on the podocyte,⁹ the potential exists for infections to serve as immunologic triggers for these conditions. This scenario is reminiscent of the reported onset of minimal change disease following diverse immune stimuli such as viral infection, allergy, or immunizations. Tip variant is the histologic subtype of primary FSGS that most closely approximates minimal change disease with respect to its abrupt onset of nephrotic

syndrome, potential for relapse, low risk of progression to renal failure, and high rate of responsiveness to steroid therapy.^{10–12} Prognosis can be poor in patients with StrS infection and concomitant nephrotic syndrome if they are not treated appropriately,^{7,8} and early diagnosis and treatment of StrS infection improves outcomes. FSGS is a common cause of nephrotic syndrome in adults worldwide,^{13,14} but associations with helminthic infection are rare. We report the first case of tip variant FSGS associated with StrS and review the literature on StrS-associated nephrotic syndrome.

CASE REPORT

A 36-year-old Guatemalan man presented with sudden onset of anasarca and nephrotic syndrome. Laboratory data showed marked proteinuria (spot urine total protein to creatinine ratio, 10.6) and profound hypoalbuminemia (serum albumin, 0.4 g/dl). Serum creatinine was normal (0.5 mg/dl). The patient was admitted for workup and management of edema with i.v. diuretics. Past medical history included biopsy-documented tip variant FSGS at the age of 25 years that had responded to a 6-week course of corticosteroid therapy (Figure 1a and b). At the time of the first biopsy, there was no known history or symptoms of StrS infection, although specific testing for StrS was not performed. A repeat kidney biopsy performed during this hospitalization showed relapse of tip variant FSGS with severe podocyte foot process effacement (Figure 1c and d).

Kidney Biopsy Findings *Biopsy 1 (Performed in 2006)*

Of the 15 glomeruli sampled for light microscopy, 2 contained segmental cellular lesions of sclerosis with

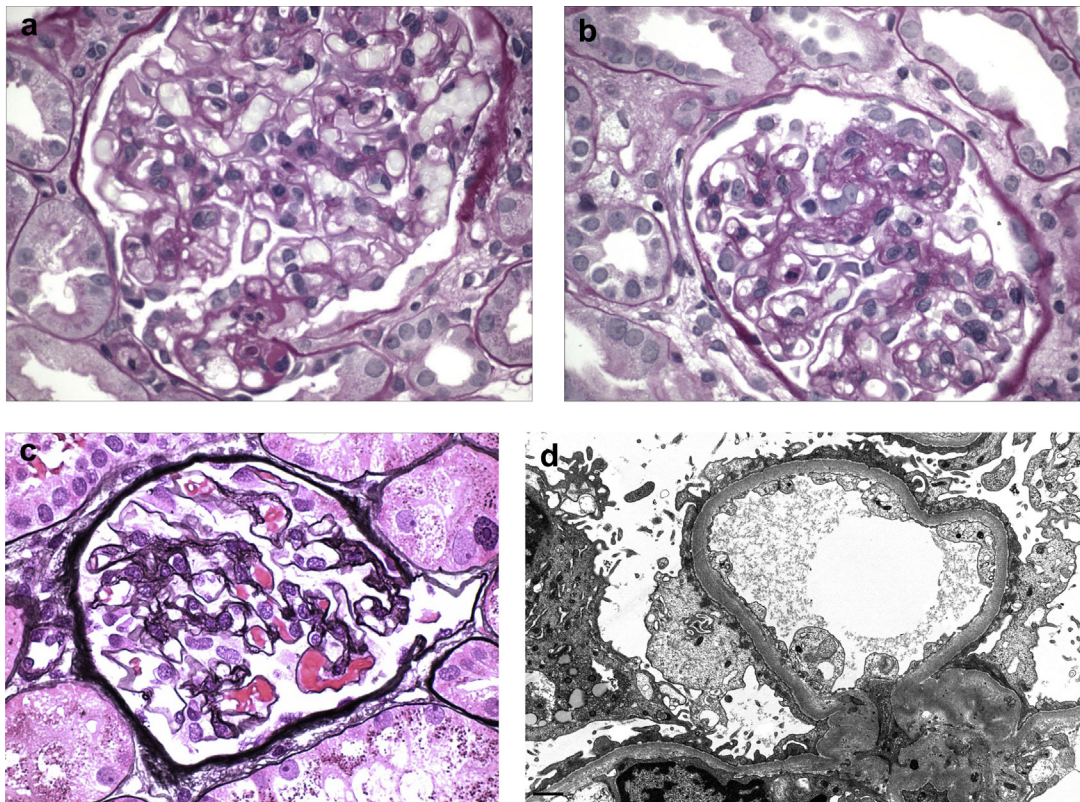


Figure 1. (a,b) Kidney biopsy 1 (performed in 2006). Light microscopy showing tip variant focal segmental glomerulosclerosis (FSGS), with a cellular segmental lesion containing endocapillary foam cells that protrudes into the tubular pole and forms an adhesion to the tubular orifice, consistent with a tip lesion (hematoxylin and eosin, original magnification $\times 600$) (a). Another glomerulus contains a segmental cellular lesion of sclerosis with hypertrophy of the overlying podocytes (hematoxylin and eosin, original magnification $\times 600$) (b). (c,d) Kidney biopsy 2 (performed in 2015). Light microscopy showing a small synechia (adhesion) between the peripheral glomerular tuft and Bowman capsule at the origin of the tubular pole, forming a tip lesion (Jones methenamine silver, original magnification $\times 400$). By electron microscopy, there is diffuse foot process effacement with microvillous transformation of the podocyte cytoplasm. The glomerular basement membrane is unremarkable and no electron-dense deposits are identified (electron micrograph, original magnification $\times 10,000$).

endocapillary hypercellularity, including mononuclear cells and foam cells, with swelling of the overlying podocytes. One of these lesions had an adhesion to the tubular pole, forming a tip lesion. The remaining glomeruli were histologically unremarkable. There was focal mild acute tubular injury. No significant tubular atrophy or interstitial fibrosis was identified. Vessels were unremarkable. Immunofluorescence staining was negative for all immune reactants (including IgG, IgM, IgA, C3, C1q, fibrinogen, albumin K and λ light chains) in the 6 glomeruli studied. Electron microscopy (3 glomeruli sampled) revealed diffuse effacement of podocyte foot processes involving 95% of the total glomerular capillary surface area. The glomerular basement membranes were unremarkable. No electron dense deposits were identified.

Biopsy 2 (Performed in 2015)

Among the 12 glomeruli sampled for light microscopy, 2 were globally sclerotic. Three glomeruli contained segmental small adhesions between the tuft and the tubular outlet, forming small tip lesions. The remaining

7 glomeruli were histologically unremarkable. The tubulointerstitial compartment was well preserved, with no evidence of tubular atrophy or interstitial fibrosis. There was minimal arteriolar hyalinosis. Immunofluorescence (5 glomeruli studied) revealed 1+ segmental mesangial positivity for IgM only. By electron microscopy (7 glomeruli sampled), extensive foot process effacement involved 90% to 95% of the total glomerular capillary surface area associated with microvillous transformation of the podocyte cytoplasm. No glomerular basement membrane abnormalities or electron-dense deposits were detected.

Clinical Follow-up

A detailed history revealed that the patient had recently traveled to El Salvador and subsequently suffered episodic abdominal pain and diarrhea with peripheral eosinophilia of 3.5 K/ μ l (41%). His stool ova and parasite smear confirmed the presence of StrS larvae, and the result of a serologic test for StrS antibody was positive. Serologic testing for hepatitis B surface antigen, hepatitis C antibody, antinuclear

antibody, antineutrophilic cytoplasmic antibodies, anti-glomerular basement membrane antibody, and HIV antibody were all negative. Serum complement C3 and C4 levels were normal. Serum immunofixation showed no evidence of monoclonal gammopathy. A kidney sonogram revealed normal-sized kidneys. Conservative management with lisinopril, atorvastatin, and diuretics was initiated, with no improvement in edema and with worsening of renal function. Ivermectin 12 mg daily for a total of 7 days was initiated to treat the parasitic infection. No immunosuppressive therapy was given to avoid the risk of exacerbating infection. One month after ivermectin therapy, edema improved, and within 2 months, the nephrotic syndrome resolved. Figure 2 summarizes the changes in laboratory findings over time following initiation of antihelminthic treatment. By 18 months following anti-Strs therapy, the patient was in complete remission of nephrotic syndrome, without resorting to glucocorticoid therapy.

DISCUSSION

Glomerular diseases associated with StrS have rarely been reported. A total of 18 cases of StrS-associated nephrotic syndrome have been reported in the literature^{5–8,15–27} and are summarized in Table 1.

Minimal change disease is the most common glomerular disease, reported in 8 patients with StrS infection.^{17–20,22,24,26,27} Most of these patients received corticosteroid treatment. To the best of our knowledge only 1 case of StrS-associated FSGS has been reported in the literature. The latter patient received both corticosteroid and antihelminthic therapy.¹⁵ In 7 of the 18 cases a kidney biopsy finding was not reported, but all case patients had nephrotic syndrome on presentation.^{7,16,21,26} In these case reports, there were poor outcomes associated with steroid use, including death in 7 patients from diverse causes. Corticosteroid

treatment in such cases can predispose to the development of hyperinfection syndrome (systemic dissemination of infection) and worsening sepsis, possibly by steroid-induced suppression of eosinophil and lymphocyte activation.²⁸

In 4 previously reported cases, nephrotic syndrome improved after treatment of StrS infection with anti-helminthic drugs alone, suggesting a direct causal relationship between this infectious agent and the glomerular injury,^{7,18,22,25} similar to the treatment response observed in our case. Because cases of podocytopathy associated with infection lack glomerular immune-type deposits, it is likely that the pathogenesis relates to immunologic activation and production of 1 or more circulating “permeability factors” that induce podocyte injury. Given his predisposition to podocytopathy before documented Strs infection, the recent development of parasitic infection was likely the precipitating immune stimulus, possibly via production of a circulating cytokine or other factor with podocyte dysregulatory potential. We opted to treat the StrS infection while avoiding steroid therapy to minimize the risk of aggravating StrS infection. All previous reported cases reviewed here (Table 1) demonstrate the importance of detecting underlying StrS infection in patients with nephrotic syndrome, because steroid therapy can promote hyperinfection, disseminated strongyloidiasis, and death.

Interestingly, an unrelated antihelminthic agent, levamisole, has been used as a nontoxic alternative to steroids in patients with minimal change disease who lack helminthic infection.^{29,30} Although its mechanism of action is unknown, the ability of this agent to induce remission of primary nephrotic syndrome suggests the potential for direct podocyte effects. Thus we cannot exclude the possibility that ivermectin also exerts direct effects on the podocyte that are independent of its antimicrobial effect.

Parasitic glomerulopathies have also been identified in patients infected with malaria, schistosomiasis, filariasis, kala-azar, trypanosomiasis, toxoplasmosis, and echinococcosis.²⁸ The clinical manifestations vary in these different infectious settings, ranging from mild abnormalities on urinalysis, to subnephrotic proteinuria or nephrotic syndrome, to acute kidney injury. Nephrotic syndrome as a result of parasitic glomerulopathy has been reported only in malaria, schistosomiasis, filariasis, and cysticercosis.²⁸ Most of the associated glomerulopathies are immune complex mediated, including membranous and membranoproliferative patterns of injury. Recovery after successful treatment of these parasites has been reported in patients with falciparum malarial nephropathy, schistosomal

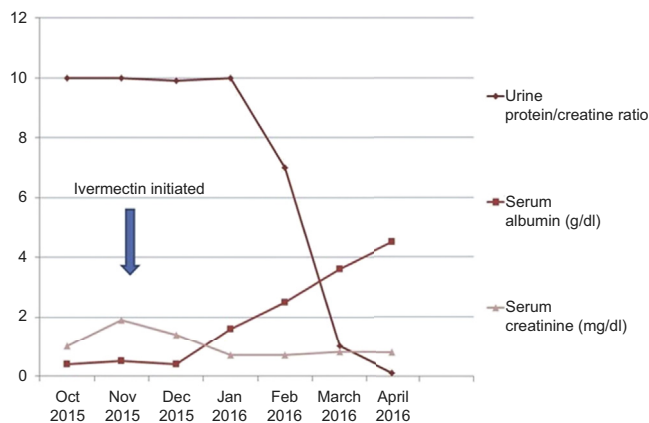


Figure 2. Time course of nephrotic syndrome response in relation to antihelminthic therapy.

Table 1. Literature review: *Strongyloides stercoralis*–associated nephrotic syndrome: clinical features, treatment, and renal and patient outcomes in reported cases

Reference	Age (yr)	Sex	Kidney biopsy findings	Corticosteroid used	Treatment	Renal remission	Patient outcome
Willis et al. 1966 ¹⁵	26	M	FSGS	Yes	Dithiazinone and thialbendazole	No	Survived
Willis et al. 1966 ¹⁵	22	M	Glomerulonephritis, (type not specified)	Yes	Dithiazinone and thialbendazole	no	Survived
Cruz et al. 1966 ¹⁶	22	M	NB	Yes	Thialbendazole	No	Died
Cruz et al. 1966 ¹⁶	10	F	NB	Yes	Thialbendazole	No	Died
Cruz et al. 1966 ¹⁶	34	F	NB	Yes	Thialbendazole	No	Died
Cruz et al. 1966 ¹⁶	5	M	NB	Yes	Thialbendazole	No	Died
Wong et al. 1998 ¹⁷	42	F	MCD	Yes	Thiabendazole, abendazole	Yes	Survived
Mori et al. 1998 ¹⁸	62	M	MCD	No	Ivermectin	Yes	Survived
Yee et al. 1999 ¹⁹	55	M	MCD	Yes	Thiabendazole	Yes	Survived
Morimoto et al. 2002 ²⁰	60	F	MCD	Yes	None	No	Died
Mitsunga et al. 2003 ²¹	75	M	NB	Yes	Ivermectin	Yes	Survived
Seet et al. 2005 ⁷	51	M	NB	No	Ivermectin	Yes	Survived
Hsieh et al. 2006 ²²	72	M	MCD	No	Ivermectin	Yes	Survived
Sathe et al. 2006 ²³	38	F	MPGN	Yes	None	No	Died
Lam et al. 2006 ²⁴	55	M	MCD	Yes	Thialbendazole	Yes	Survived
Chan et al. 2008 ²⁵	77	F	NB	No	Albendazole	Yes	Survived
Miyazaki et al. 2010 ²⁶	69	M	MCD	Yes	Ivermectin	Yes	Died
Li Cavoli et al. 2011 ²⁷	25	M	MCD	Yes	Albendazole	Yes	Survived
Current case	36	M	FSGS	No	Ivermectin	Yes	Survived

F, female; FSGS, focal segmental glomerulosclerosis; M, male; MCD, minimal change disease; MPGN, membranoproliferative glomerulonephritis; NB, no biopsy.

glomerulopathies, and cysticercosis-related nephrotic syndrome.²⁸

In conclusion, we believe that StrS infection in our patient acted as an immunologic trigger for relapse of nephrotic syndrome due to tip variant FSGS. Supportive evidence includes the close temporal association of explosive nephrotic syndrome with active StrS infection and the complete resolution of nephrotic syndrome following antihelminthic treatment alone. The nature of the circulating “permeability factor” that mediates podocytopathy secondary to StrS is unknown. Steroid therapy is usually first-line therapy for primary podocytopathies.³¹ Our case illustrates the importance of identifying potential infectious pathogens that can be specifically targeted with antimicrobial therapy while avoiding the risks of immunosuppression.

DISCLOSURE

All the authors declared no competing interests.

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