Case Report

Nephrotic Syndrome Secondary to Strongyloidiasis: A Common Infection with an Uncommon Presentation

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Disseminated strongyloidiasis has often been linked with the use of immunosuppressants in patients with nephrotic syndrome. Nephrotic syndrome secondary to *Strongyloides stercoralis* infection, however, is a rare entity. Here, we present a case of nephrotic syndrome possibly caused by underlying *S. stercoralis* infection in a patient who received steroid therapy in a preceding asthmatic attack. Literature on associated sporadic reports is reviewed. [*Hong Kong J Nephrol* 2008;10(1):37–41]

Key words: nephrotic syndrome, *Strongyloides stercoralis*, strongyloidiasis

在腎病症候群患者間，擴散性擬圓蟲病通常與免疫抑制劑的使用有關；然而，*Strongyloides stercoralis* 感染後出現的腎病症候群卻相當罕見。本個案是一位氣喘患者，曾接受類固醇療程並於其後出現 *S. stercoralis* 感染及可能因此而起的腎病症候群。本文亦對相關的文獻報告作出回顧。

Introduction

Strongyloidiasis is a common parasitic infection estimated to affect more than 70 million people worldwide. It is endemic in tropical and subtropical countries including Southeast Asia, Sub-Saharan Africa, South America and Eastern Europe, with prevalence rates reported to be as high as 30% [1,2]. Most infected patients are asymptomatic or exhibit mild gastrointestinal symptoms only. Its association with nephrotic syndrome is usually in the context of disseminated infection secondary to the use of immunosuppressants [3–7]. However, strongyloidiasis as a cause of nephrotic syndrome has seldom been reported [8–10].

Case Report

A 77-year-old woman was admitted to Queen Mary Hospital for worsening bilateral ankle swelling of 1 month's duration in March 2007. She was born in the rural area of Xinhui, Guangdong in southern China and immigrated to Hong Kong at the age of 12. She did not smoke or drink and had no known allergy. Her medical history included hypertension diagnosed 5 years previously, which was being controlled with nifedipine SR 20 mg twice daily and indapamide 2.5 mg daily, and bronchial asthma since childhood. Her only major asthma attack in recent years was 4 months previously, which had been stabilized with a 3-week course of high-dose prednisolone.

On physical examination, she was afebrile, had a blood pressure of 134/65 mmHg and a heart rate of 82 beats per minute. She had bilateral lower limb pitting edema up to the mid shin, and purpuric rash over the buttock and thighs. Her cardiovascular, respiratory, abdominal and neurologic examinations were otherwise unremarkable.

Chest radiograph showed clear lung fields with a normal cardiothoracic ratio. Her electrocardiogram was in sinus rhythm with no evidence of ischemia. Laboratory investigations revealed mildly raised serum creatinine of 146 μmol/L, blood urea of 12.8 mmol/L, and serum bicarbonate, sodium and potassium of 21, 140 and 3.3 mmol/L, respectively. She had normal

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clotting profile and liver function tests except for marked hypoalbuminemia of 13 g/L. Her 24-hour urinary protein excretion was in the nephrotic range of 12.61 g/day. She also had hyperlipidemia with fasting cholesterol of 8.2 mmol/L (low-density lipoprotein, 6.0 mmol/L; high-density lipoprotein, 0.93 mmol/L) and triglycerides of 2.7 mmol/L. Her complete blood picture showed leukocytosis of 10.60×10^9/L with eosinophilia of 3.50×10^9/L. Her hemoglobin level was 13.3 g/dL and platelet count was 236×10^9/L (Table 1).

Further work-up for her newly diagnosed nephrotic syndrome was carried out. Doppler ultrasound scan showed normal-sized kidneys with no renal vein thrombosis. Her fasting blood glucose was 4.9 mmol/L. Immunologic tests were inconclusive, with the only abnormalities being a raised antinuclear antibody titer of 1/720, C-reactive protein of 0.78 mg/dL, and immunoglobulin A level of 634 mg/dL. Her antineutrophil cytoplasmic antibody was negative and her C3 and C4 levels were normal. Malignancy

Table 1. Comparison of the patient's laboratory findings at presentation and follow-up

Investigation	At presentation (03/2007)	At follow-up (05/2007)
Complete blood picture		
White cell count	10.60×10^9/L	6.40×10^9/L
Neutrophil	4.00×10^9/L	3.30×10^9/L
Lymphocyte	2.30×10^9/L	2.30×10^9/L
Eosinophil	3.50×10^9/L	0.30×10^9/L
Hemoglobin	13.3 g/dL	11.4 g/dL
Platelet	236×10^9/L	276×10^9/L
Renal function tests		
Sodium	140 mmol/L	146 mmol/L
Potassium	3.3 mmol/L	3.6 mmol/L
Urea	12.8 mmol/L	4.9 mmol/L
Creatinine	146 μmol/L	83 μmol/L
Liver function tests		
Total bilirubin	3 μmol/L	9 μmol/L
Alkaline phosphatase	163 U/L	107 U/L
Alanine aminotransferase	8 U/L	5 U/L
Aspartate aminotransferase	18 U/L	20 U/L
Albumin	13 g/L	40 g/L
Immunology		
Antinuclear antibody titer	1/720	1/720
Antineutrophil cytoplasmic Ab	Negative	Negative
Immunoglobulin G	1,190 mg/dL	897 mg/dL
Immunoglobulin A	634 mg/dL	296 mg/dL
Immunoglobulin M	134 mg/dL	73 mg/dL
C-reactive protein	0.78 mg/dL	< 0.35 mg/dL
C3/C4	89/34 mg/dL	
Tumor markers		
Alpha-fetoprotein	2 ng/mL	
Carcinoembryonic antigen	2.9 ng/mL	2.2 ng/mL
CA15.3	37 U/mL	20 U/mL
Microbiology		
Hepatitis B surface antigen	Negative	
Hepatitis B surface antibody	Positive	
Urine culture	No growth	No growth
Stool ova and cyst	*S. stercoralis* rhabditiform larvae	No ova or cyst detected
24-hr urinary protein excretion	12.61 g/d	0.15 g/d

screening was unremarkable apart from a mildly elevated CA15.3 level of 37 U/mL. A mammogram and positron emission tomography scan were thus performed, with neither showing any evidence of an underlying malignancy. Urine for microscopy was unremarkable and culture yielded no growth. She was immune to hepatitis B with positive hepatitis B surface antibody. Investigation for the eosinophilia, however, showed that the patient suffered from *Strongyloides* infestation with *S. stercoralis* larvae being found in stool.

As the patient was not keen for renal biopsy and in view of previous sporadic reports of remission of nephrotic syndrome after anthelmintics in patients suffering from strongyloidiasis [6–8,10], she was treated with a 10-day course of albendazole. After completion of the course of albendazole, the patient gradually showed symptomatic improvement with resolution of lower limb edema and purpuric rash over the following 2–3 months. Subsequent 24-hour urinary protein measurements taken 2 months after treatment confirmed significant decrease in proteinuria to 0.15 g/day (Figure). Serum albumin level had risen to 40 g/L and serum creatinine level had decreased to 83 μmol/L (Table 1). Eosinophil count, C-reactive protein and CA15.3 levels were also normalized. Repeated stool samples were negative for *S. stercoralis*. She remained well and stable at follow-up 5 months after presentation.

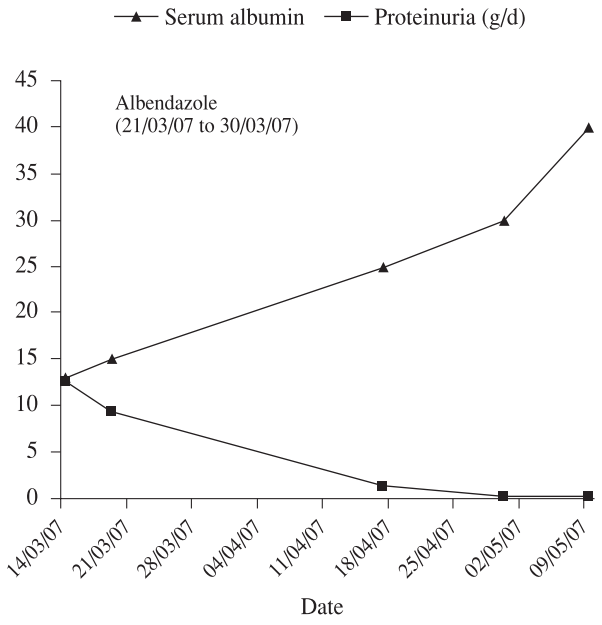

Figure. Serial trend in serum albumin and proteinuria levels.

Discussion

Nephrotic syndrome secondary to parasitic infections has previously been associated with malaria, schistosomiasis and filariasis. However, cases due to strongyloidiasis have rarely been reported. We describe a patient who developed nephrotic syndrome with *S. stercoralis* larvae detected in stool after recent use of steroid for an asthma attack. She subsequently achieved complete remission clinically and biochemically after treatment with albendazole. The absence of other identifiable causes, the presence of steroid as a precipitating factor, the time course of development and resolution strongly suggested that this case was a rare manifestation of strongyloidiasis presenting as nephrotic syndrome.

A distinctive characteristic of *S. stercoralis* is its ability to survive and replicate inside the human host while producing minimal symptoms for decades after infection. In symptomatic patients, the most common findings are fever and gastrointestinal upset [3,11]. In disseminated cases, the nematode can virtually affect every organ with the most prominent manifestations being gastrointestinal and pulmonary [3,12]. Dermatologic lesions are variable, with the most characteristic being larva currens, a serpiginous urticarial eruption, in chronic strongyloidiasis; and widespread petechiae and purpura in the disseminated form as observed in our patient [13,14]. Renal failure secondary to disseminated infection and superimposed bacterial infections are occasionally encountered, whereas nephrotic syndrome are uncommonly seen.

An extensive review of the medical literature identified only three other sporadic case reports of strongyloidiasis-induced nephrotic syndrome (Table 2) [8–10]. In 1998, Wong et al reported a case of a middle-aged woman who presented with nephrotic syndrome that was resistant to steroid and cyclophosphamide [8]. Subsequently she developed disseminated strongyloidiasis and was treated with thiabendazole. Interestingly, after treatment with the anthelmintic, the patient achieved clinical remission and remained free of recurrence.

Yee et al reported a similar case in 1999 [9]. Hsieh et al described a patient who suffered from strongyloidiasis-induced nephrotic syndrome without preceding immunosuppressive therapy in 2006 [10]. As in our case, the patients described in these cases all achieved clinical and biochemical remission after the underlying *Strongyloides* infection was treated.

A number of interesting observations can be made from further analysis of this series of case reports. First, almost all of the patients described have had a history of steroid use. As in our patient, the major risk factor for severe strongyloidiasis is the use of steroid and immunosuppressive drugs [15,16]. Other risk factors

Table 2. Reports in the literature of strongyloidiasis-induced nephrotic syndrome

Author	Sex/Age (yr)	Steroid use	Eosinophilia	Renal biopsy	Treatment	Outcome
Wong et al, 1998 [8]	F/42	Yes	Yes	Minimal change disease	Thiabendazole, albendazole	Remission
Yee et al, 1999 [9]	M/55	Yes	No	Minimal change disease	Thiabendazole	Remission
Hsieh et al, 2006 [10]	M/72	No	Yes	Minimal change disease	Ivermectin	Remission
Present case	F/77	Yes	Yes	Not available	Albendazole	Remission

include advanced age, chronic illnesses, malignancies (especially hematologic), and human T cell leukemia virus type 1 infection (HTLV-1) [17].

Another common finding among the reported cases is the presence of peripheral eosinophilia. This is of clinical interest in two ways. It prompts the physician to make an early diagnosis, especially among nephrotic patients from an endemic area and in whom risk factors are present. Second, it has been advocated, along with enzyme-linked immunosorbent assay (ELISA), as a useful laboratory marker of treatment success for *Strongyloides* infection [18]. ELISA has emerged as a reliable serodiagnostic tool for strongyloidiasis, with a high sensitivity of 94–97% and specificity of 95% [19, 20].

Besides peripheral eosinophilia, renal biopsy findings are also similar among the reported cases. Interestingly, all of them yielded minimal change disease as the underlying renal histopathology, with two of them showing positive immunofluorescence for C3. It is postulated that T lymphocytes play a crucial role in the development of strongyloidiasis-associated minimal change disease. While the pathogenesis of minimal change disease has long been linked with the action of abnormal T cell response [21–23], the association between hyperinfection with *S. stercoralis* and HTLV-1 has also been well recognized [17,24]. Further studies are necessary to confirm this hypothesis.

In terms of treatment response, the reported cases have also demonstrated an important point. Treatment with steroid caused clinical exacerbation whereas remissions were only possible after the institution of anthelmintics including albendazole, thiabendazole and ivermectin. Clinical improvement was evident on an average of 1–2 months after the use of anthelmintics. Based on these findings and the treatment success in our patient, we advocate that in cases of nephrotic syndrome where renal biopsy is contraindicated or when it is refused by the patient, empirical steroid therapy should only be instituted with caution after underlying parasitic infections have been excluded in order to prevent the possibly disastrous outcome of disseminated disease.

In conclusion, we have reported a case of nephrotic syndrome that was likely to have been caused by *S. stercoralis* infection. Previous case reports have identified minimal change nephropathy as the common underlying histopathology. We advocate establishing diagnosis early on by adopting a high index of clinical suspicion, especially among those patients who come from endemic areas, who have identifiable precipitating factors and peripheral eosinophilia. As we become more aware of the possible causal relationship between the two entities, more cases are likely to be identified in the future. This will in turn help us to gain more knowledge on the pathogenesis, histopathologic characteristics and treatment approaches of this distinctive clinical syndrome. The fatal outcome of disseminated strongyloidiasis secondary to injudicious use of immunosuppressive therapy can thus be avoided and complete remission may then be achieved with appropriate anthelmintics.

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