



Case report

First case of minimal change nephrotic syndrome resolving with antifungal therapy for isolated pleural cryptococcal infection



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ABSTRACT

We report the case of a 71-year-old male with poorly controlled diabetes mellitus who presented with lower extremity edema and acute renal failure. He was diagnosed with nephrotic syndrome secondary to minimal change disease (MCD). Treatment with steroids was withheld due to concern for hyperglycemia in the context of his poorly controlled diabetes mellitus. A week after discharge, he was subsequently re-hospitalized four times within a month with pleural effusions, dyspnea, and fever. Work up revealed isolated pleural cryptococcosis, demonstrated on two separate admissions. There was neither evidence of disseminated disease nor immunocompromising condition. Immunosuppression was not initiated for the treatment of MCD in the setting of poorly controlled diabetes and active infection. After six months of treatment with fluconazole 400 mg/day, the nephrotic syndrome, renal failure, and cryptococcal pleuritis resolved. This case is the first to our knowledge of isolated pleural cryptococcosis associated with nephrotic syndrome. The patient's course lends further support to the hypothesis that there may be causal relationship between cryptococcosis and nephrotic syndrome.

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Introduction

Human cryptococcosis is typically caused by two major pathogens, *Cryptococcus neoformans* and *Cryptococcus gattii* [1]. Most cryptococcal infections occur in immunocompromised patients such as those with human immunodeficiency virus (HIV), malignancies, solid organ transplants, and diabetes mellitus [1]. Cryptococcal infections have also been described in patients with nephrotic syndrome [2–11], which is not unexpected given that these patients are often immunocompromised. However, there have also been a few reports [2,5–8] of cryptococcal infections associated with nephrotic syndrome in which antifungal treatment resolved both the cryptococcosis and proteinuria, suggesting that cryptococcosis was causative of nephrotic syndrome in these cases. Here we report the first case of isolated pleural cryptococcosis associated with nephrotic syndrome in which the renal disease resolved with treatment of cryptococcal infection.

Case report

Admission #1: A 71-year-old Caucasian male veteran and retired timber logger with a past medical history of hypertension, poorly controlled, insulin dependent type 2 diabetes mellitus, and diabetic peripheral neuropathy presented to the emergency department (ED) with complaints of lower extremity swelling. On exam, he was anasarctic and admission lab work revealed hyponatremia, a serum creatinine of 1.0 mg/dL with new-onset high grade proteinuria (12.7 g/24 h) and a serum albumin of 2.2 g/dL. He was diagnosed with nephrotic syndrome and underwent diuresis, however his course was complicated by acute kidney injury resulting in a peak serum creatinine of 3.5 mg/dL. Subsequent renal biopsy revealed mild acute tubular necrosis with hyaline nephrosclerosis and extensive podocyte effacement with preserved glomerular structure on electron microscopy indicative of minimal change disease (Fig. 1). He was discharged on diuretics but did not receive steroids due to the patient's concerns about the potential side-effects.

Admission #2: The patient re-presented one week after discharge with exertional dyspnea and orthopnea and was found to have a new right pleural effusion. Upon pleural drainage and

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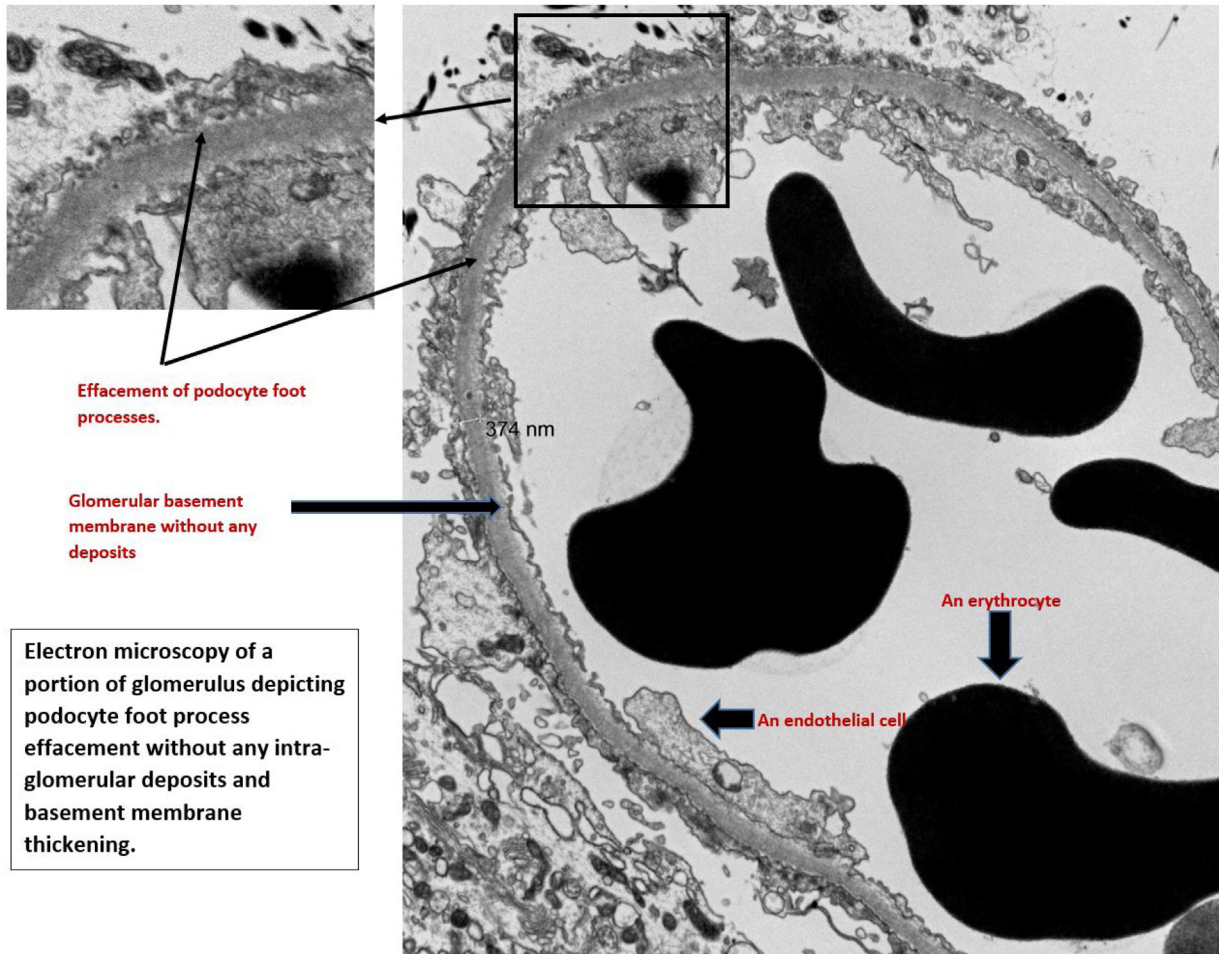


Fig. 1. Renal biopsy demonstrating minimal change disease. Electron microscopy of a portion of glomerulus depicting podocyte foot process effacement without any intra-glomerular deposits and basement membrane thickening.

increased diuretic dose, his dyspnea resolved and he was again discharged.

Admission #3: One week later, his dyspnea worsened with orthopnea and paroxysmal dyspnea as well as a low-grade fever, therefore he was admitted again for the third time in one month. On examination, he was found to have a low-grade fever (100.4 °F) with decreased breath sounds over the right lower hemi-thorax

and anasarca with 3+ bilateral pretibial pitting edema. Laboratory results were remarkable for normocytic anemia (hemoglobin 11.4 g/dL; normal range 13.5–18 g/dL, HbA1c 13%), resolving acute kidney injury (serum creatinine of 1.5 mg/dL) and spot urine protein to creatinine ratio of 5.9 g/day. A contrast-enhanced computed tomography (CT) of the chest showed bilateral pleural effusions, right greater than left side (Fig. 2), and transthoracic

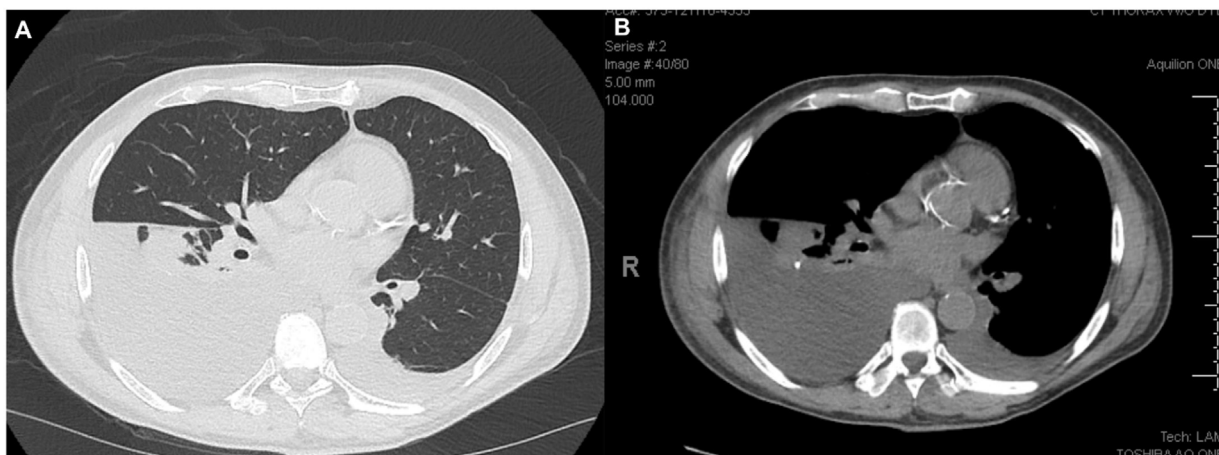


Fig. 2. CT chest demonstrating right greater than left pleural effusions. (A) Lung window. (B) Mediastinal window.

Table 1
Laboratory results from Admission 3.

Test	Result	Reference Range
Pleural Fluid Analysis		
Glucose	265 mg/dL	N/A
Total protein	1.1 g/dL	N/A
Albumin	0.7 g/dL	N/A
LDH	65 U/L	N/A
WBC	791 #/cmm	N/A
Lymphocytes	61 %	N/A
Granulocytes	16 %	N/A
Mononuclear cells	23 %	N/A
RBC	<2000 #/cmm	N/A
TB culture	No growth	N/A
Aerobic culture	<i>Cryptococcus neoformans</i>	N/A
Cytology	No malignancy	N/A
Serum LDH	133 units/L	100–190 units/L
Serum protein	4.5 g/dL	6.0–8.2 g/dL
Immunologic Workup		
IgG	378 mg/dL	652–1375 mg/dL
IgA	202 mg/dL	76–341 mg/dL
IgM	35 mg/dL	57–359 mg/dL
Total lymphocyte count	1855 cells/ μ L	850–3900 cells/ μ L
CD4 Absolute count	738 cells/ μ L	490–1740 cells/ μ L
CD4%	40	30–61
CD8, Absolute count	738 cells/ μ L	180–1170
CD8 %	36 %	12–42%
CD4/CD8	1.1	0.86–5.00
Total complement	56 U/mL	31–60 U/mL
HIV	Negative	N/A

echocardiography demonstrated moderate diastolic dysfunction but a normal ejection fraction and no structural heart disease. The pleural fluid analysis from his second admission revealed transudative effusion by Light's criteria [12], however pleural fluid cultures ultimately yielded *Cryptococcus neoformans* and the

patient was diagnosed with cryptococcal pleuritis without lung parenchymal involvement. Upon further questioning, he denied any exposure to bats, birds, feral animals or eucalyptus trees. During this admission, he underwent repeat thoracentesis as well as additional testing to assess for immunocompromising conditions (Table 1). At that time, he was found to be HIV negative with a lymphocyte-predominant effusion that was persistently transudative by Light's criteria; pleural fluid cultures again grew *Cryptococcus neoformans*. Lumbar puncture revealed normal cerebrospinal fluid with 1 WBC, normal glucose, normal protein, negative cultures, and India ink test was negative for *Cryptococcus*. His serum cryptococcal antigen and CSF cryptococcal antigen were also negative. He was treated with fluconazole 400 mg/day for pulmonary cryptococcosis per guidelines [13] without any evidence of dissemination or central nervous system involvement. He eventually defervesced and was discharged.

Admission #4: The patient was again hospitalized a week later with hypoglycemia due to accidental self-overdose of insulin. During that hospitalization, he had no fever and his exertional dyspnea had improved. However, he was found to have a persistent right pleural effusion and therefore underwent a third thoracentesis. Pleural fluid analysis was transudative by Light's criteria, but pleural fluid cultures were negative. He was discharged with a diabetes treatment regimen. He was continued on oral fluconazole 400 mg daily for treatment of cryptococcal pleural effusion.

Follow Up: In outpatient follow-up three months later, his dyspnea and pleural effusions had fully resolved (Fig. 3). Furthermore, his proteinuria had resolved, his urine protein creatinine ratio was 184 mg/g creatinine, and his creatinine had returned to baseline (0.9 mg/dL) (Fig. 4). His diuretics were discontinued, and he completed a course of fluconazole 400 mg/day for a total of six months. At six-month follow-up, his chest radiography was clear



Fig. 3. Posterior Anterior chest x-ray demonstrating resolution of pleural effusions.

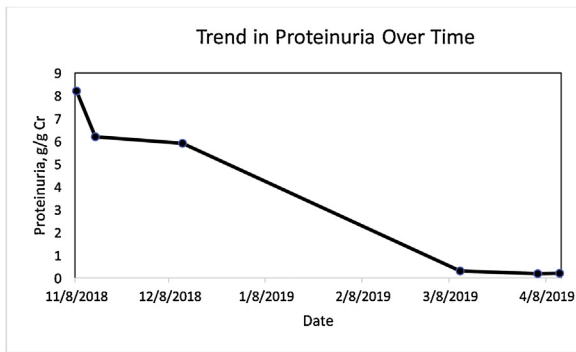


Fig. 4. Graph demonstrating trend in proteinuria.

without evidence of effusion, mass or abnormality and his nephrotic syndrome remained in remission.

Discussion

Cryptococcal pleuritis is a rare presentation of cryptococcosis. Only six cases [14–19] of localized cryptococcal pleural infections have been reported in the English literature to date. To our knowledge, this is the first case of isolated cryptococcal pleural infection with concurrent development of nephrotic syndrome.

Humans typically become infected with *Cryptococcus neoformans* following inhalation of the organism [1]. However, *Cryptococcus neoformans* is endemic, so the development of *Cryptococcal* infection following exposure to the organism usually depends upon the immune status of the patient and the inoculum size. Active disease commonly manifests in immunocompromised patients, many of whom have AIDS.

While our patient had no evidence of objective immunocompromise, the occurrence of cryptococcal pleuritis in our patient may indeed have been related to relative immunocompromise from poorly controlled diabetes mellitus and possibly minimal change disease. Indeed, several cases of cryptococcal infections in patients with nephrotic syndrome have been reported in the literature [2–5,7–11,20] (Table 2). Patients with nephrotic syndrome are predisposed to infection due to deficiencies in humoral immunity [21], decreased levels of complement pathway factors, and immunosuppressive therapy; cryptococcal infections are therefore unsurprising in this setting.

Conversely, given the timing of onset of proteinuria relative to pulmonary symptoms, and the abrupt resolution of renal disease with cryptococcal treatment, our case suggests that *Cryptococcus* is likely a cause of nephrotic syndrome. In support of our hypothesis, several investigators have reported improved or resolved nephrotic syndrome in patients with cryptococcosis after treatment with antifungal agents while immunosuppression for nephrotic syndrome was withheld or tapered given the infection [2,5–8]

Table 2
Case Reports of *Cryptococcus neoformans* with Concomitant Nephrotic Syndrome.

Author	Patient Demographics	Cryptococcosis Infection	Renal Diagnosis	Treatment	Outcome
Kubo, 1994 [14]	80F	Pulmonary parenchymal infiltrate	Physical/lab findings – immune complex glomerulonephritis	6 mo antifungals	Resolution of infection at 6 mo & dramatic renal improvement at 1 wk
Nakayama, 2005 [15]	68M Rheumatoid arthritis on low dose steroids, MTX	Pulmonary nodules	Biopsy – necrotizing glomerulonephritis with crescent	No steroids ~2 mo antifungals	Resolution of infection at 2 mo & renal improvement at 1 month
Ogami, 2005 [16]	26M	Primary cutaneous cryptococcosis	Biopsy – minimal change disease	No increased steroid use from baseline home dose	Resolution of infection at 3 mo & of renal improvement (unlisted timing)
Quadir, 2006 [17]	37M Farmer	Disseminated– cutaneous, bone marrow, meningitis	Biopsy – membranous glomerulonephritis	3 mo antifungals Steroids tapered Azathioprine stopped	Resolution of infection at 2 mo & renal improvement at ~1 mo
Giri, 2014 [18]	15F On 2 years of MMF and steroids for NS	Disseminated –cutaneous, pulmonary, meningitis, cryptococemia	Biopsy – focal segmental glomerulosclerosis	4 mo antifungals No steroids Long-term steroids (≥2 years)	Resolution of infection at 3 mo, peritoneal dialysis for 1 year
Suarez-Rivera, 2008 [19]	11F	Pulmonary & anterior mediastinal cryptococemia	Biopsy – crescentic glomerulonephritis	3 mo antifungals followed by fungal prophylaxis for ≥2 years Steroids (unclear duration)	Hemodialysis dependent at 18 mo
Ni, 2013 [20]	Hispanic 34M On 1 year of steroids for NS	Disseminated – cutaneous, probable meningitis	Biopsy – minimal change disease	Antifungals (unclear duration)	Death at day 6 of admission for cryptococcosis
Cohen, 2018 ²⁴	70M	Disseminated – cutaneous, cryptococemia	Biopsy – focal segmental glomerulosclerosis	2 days antifungals	Improvement of infection & renal findings at 1 mo
Chizinga, 2020	71M Retired logger	Pleuritis	Biopsy – minimal change disease	7 mo antifungals ~1 mo steroid taper 6 mo antifungals	Resolution of infection & renal findings at 3 mo

M – male, F – female, MTX – methotrexate, NS – nephrotic syndrome, MMF – mycophenolate mofetil, mo-months, wk-weeks, pulmonary-parenchymal lung involvement only.

(Table 2). And, while it remains possible that our patient's nephrotic syndrome simply spontaneously resolved, the rate of resolution we observed exceeded that reported in the literature for untreated minimal change disease. Black et al. [22] conducted the only randomized controlled trial in adult patients (N = 125) with nephrotic syndrome comparing treatment with prednisone versus no treatment. The study showed that among those with untreated minimal change disease, 100 % had persistent proteinuria at 1 months and spontaneous resolution of proteinuria (defined as <1 g/day) occurred in approximately 50 % by one year. In contrast, reported cases of nephrotic syndrome associated with cryptococcosis which responded to antifungal treatment observed an earlier and more dramatic decline in proteinuria, in line with clinical course of our patient. Kubo et al. [5] report of an 80-year-old female with pulmonary cryptococcosis associated with immune complex glomerulonephritis in which proteinuria resolved within a week of institution of anti-fungal treatment in the absence of treatment with steroids. Nakayama et al. [2] report of a 68-year-old female with pulmonary cryptococcosis with necrotizing glomerulonephritis on 5 mg of prednisone for rheumatoid arthritis in whom treatment with fluconazole resulted in a dramatic decline in proteinuria within a month of initiation of antibiotics. Similarly, the case reported by Cohen et al. [6] of primary cutaneous cryptococcosis and focal segmental glomerulosclerosis resulted in resolution of proteinuria within about a month of initiation of antifungal treatment. In our patient, proteinuria had completely resolved after three months following initiation of treatment of cryptococcosis with fluconazole. This early and dramatic decline in proteinuria argues against spontaneous resolution of minimal change disease but rather supports a response to antifungal therapy.

The mechanism by which cryptococcus may cause minimal change disease is unknown. However, it has long been postulated that humoral factors from T cells may be responsible for minimal change disease [23] by modifying podocyte shape and properties and provoking proteinuria under experimental conditions [23]. Such factors include IL-13, TNF- α , circulating cardiotrophin-like cytokine factor 1, hemopexin, radical oxygen species, and the soluble urokinase-type plasminogen activator receptor [23]. It is plausible that cryptococcal infection stimulates T cells to elaborate some or all of these factors to cause nephrotic syndrome and that treatment of the infection subsequently reduces these circulating factors to resolve the renal disease.

In conclusion, we present the first case of isolated cryptococcal pleuritis in the setting of nephrotic syndrome. Treatment with antifungal antibiotics resolved both cryptococcal pleuritis and nephrotic syndrome suggesting cryptococcal-induced nephrotic syndrome. Although uncommon, *Cryptococcus* infection should be considered in patients with nephrotic syndrome with the right risk factors as identification and treatment of *Cryptococcus* may lead to resolution of infection as well as resolution of renal failure and nephrotic syndrome without the need for steroid therapy.

Authorship statement

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in

the work to take public responsibility for the content, including participation in the patient care, analysis, writing, or revision of the manuscript.

Declaration of Competing Interest

No support/funding was provided for this manuscript and authors have no conflicts of interest to disclose.

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