

Cryptococcosis as a cause of nephrotic syndrome? A case report and review of the literature



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ARTICLE INFO

Keywords:

Cryptococcus neoformans
Primary cutaneous cryptococcosis
Cryptococemia
Psoriasis
Tinea
Nephrotic syndrome
Focal segmental glomerulosclerosis
Misdiagnosis

ABSTRACT

We present a case of a 74 years old male with cutaneous cryptococcosis of the right forearm. *Cryptococcus neoformans* var. *neoformans* was cultivated from the skin and from the bloodstream. He was diagnosed with nephrotic syndrome (focal segmental glomerulosclerosis) 21 months prior to admission, which was steroid-dependent. He was treated with prednisone and cyclosporine A. Concurrently with his renal disease he was also diagnosed as having disseminated severe tinea mannum, tinea corporis and tinea cruris; onychomycosis, skin eczema and psoriasis. After a prolonged course of anti-fungal therapy, his skin lesions as well as his nephrotic syndrome recovered completely. Follow up after 7 months without any anti-fungal or immunosuppression showed no skin or renal recurrence. We assume that the renal disease was related to the pre-existing cutaneous cryptococcosis, aggravated by immunosuppression, and discuss the close association between cutaneous cryptococcosis and nephrotic syndrome, as well as similar case reports in the literature.

Introduction

Cryptococcus neoformans and *Cryptococcus gattii* are important opportunistic fungal infections, commonly causing meningitis and pneumonia among immunocompromised hosts, but also among immunocompetent patients. The infection spectrum is wide and includes virtually any organ. Skin infection is common among patients with disseminated disease and fungemia, but primary cutaneous cryptococcosis (PCC) may also occur, typically among immunocompetent hosts commonly resulting from a direct inoculation of the skin. Cutaneous cryptococcosis may appear as almost any type of skin lesion and may pose a diagnostic challenge.

We describe a patient who had a misdiagnosed, disseminated and long-standing cryptococcal skin infection, which after a minor skin trauma developed PCC. He was also immunosuppressed due to nephrotic syndrome (NS) and its related drug therapy. We discuss the association and even the possible causality between cutaneous cryptococcosis and NS, and review the current literature and similar case reports.

Case description

A 74 year-old, HIV negative patient was admitted to the hospital due to right forearm cellulitis after an abrasion several days earlier. His past medical history included NS diagnosed 21 months prior to admission, with renal biopsy showing diffuse podocyte effacement and glomerular tuft collapse compatible with focal segmental glomerulosclerosis (FSGS). He was steroid-dependent and at admission he was on his third course of prednisone tapering (35 mg/day). Cyclosporine A (CSA) was added four weeks earlier. He also had dilated cardiomyopathy and was under warfarin treatment. Concurrently with NS, he was also diagnosed as having disseminated severe tinea mannum, corporis and cruris, onychomycosis, skin eczema and psoriasis.

On admission he was febrile and dyspneic and had cellulitis with pus-draining sinuses on the right forearm resembling bacterial infection (Fig. 1), and ipsilateral tender axillary lymphadenopathy. He also had multiple psoriatic-like, round superficial lesions on the limbs and trunk (Figs. 2 and 3) and thick and scaly skin on both palms. There were no neurological signs or symptoms. After two days of antimicrobial treatment, blood and wound cultures came back positive for yeast identified as *Cryptococcus neoformans* var. *neoformans*.

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Fig. 1. Cryptococcal cellulitis, right forearm.



Fig. 2. Abdominal cutaneous lesions diagnosed as psoriasis.

He was transferred to the intensive care unit (ICU) and treated with liposomal amphotericin B (LAMB) (3 mg/Kg) and intravenous fluconazole (400 mg/day). Prednisone dosage was reduced to 30 mg/day and CSA was continued. Whole body CT revealed only mild bilateral pulmonary ground glass opacities. Cerebrospinal fluid (CSF) was without cells, normal glucose and protein levels and culture negative. Cryptococcal antigen was negative from the CSF, and weakly positive (1:10) from the blood. *C. neoformans* was

further cultivated from the blood again four days after admission.

After 14 days of combination therapy, the right forearm wound healed and oral fluconazole (400 mg/day) was given. He was discharged a week later but returned after five days with proximal muscle weakness and cramps and was re-admitted to the ICU. He had rhabdomyolysis (creatinine kinase (CK) 3358 IU/L), acute kidney injury (creatinine 4 mg/dL) and bilirubin (2 mg/dL) and hepatocellular liver enzymes elevation (GOT 160 IU/L, LDH 1063 IU/L).



Fig. 3. Left forearm cutaneous lesion diagnosed as tinea.

CSA toxicity was suspected and was discontinued, along with simvastatin. CSA blood level was 439 ng/mL (desired level 100–175 ng/mL). Considering drugs interactions, fluconazole dosage was reduced to 200 mg/day. The weakness and kidney function gradually improved but after two days, the right forearm primary lesion became more erythematous and nodular (Fig. 4). After two more days, a bulla within an existing skin hematoma appeared on the left forearm in an area of a preexisting peripheral venous access (Fig. 5). LAMB, together with 400 mg/day of fluconazole were readministered. A skin biopsy from the right forearm was sterile but histopathology showed granulomatous inflammation and PAS stain revealed yeast forms. Blood and repeated CSF cultures were negative. After 14 days, and clear clinical improvement, the treatment was switched to oral voriconazole. The prednisone dose was reduced to 2 mg/day and tapering was continued after discharge. During this hospitalization we noticed that all the ‘psoriatic’ skin lesions disappeared (Fig. 6), as well as his proteinuria.

Voriconazole was continued for seven months until the skin healed completely (Figs. 7–9). Follow up after another seven months showed no signs of fungal infection, any skin disease or nephrosis without any anti-fungal or immunosuppressive therapy.

Discussion

C. neoformans infection in this patient presented primarily as multiple chronic skin lesions that progressed to an invasive disease after immunosuppressive therapy. Both fungal infection and NS resolved completely with anti-fungal therapy.

The case is unique from two aspects: the difficulty and ambiguity of the exact diagnosis of PCC versus secondary skin infection, and chronic cryptococcal cutaneous infection as a probable cause of ‘idiopathic’ NS, both resolving with anti-fungal therapy. The possible clinical failure of fluconazole and its interaction with CSA and with statins are also important lessons from this case.

According to the French Cryptococcosis Study Group, PCC is defined as the traumatic inoculation of an unclothed skin with the fungi (typically *C. neoformans* var. *neoformans* (serotype D)), in the context of outdoor activity or of exposure to bird droppings, resulting in a local infection with no signs of systemic dissemination [1]. The presented case had indeed several of these features: traumatic lesion of an exposed

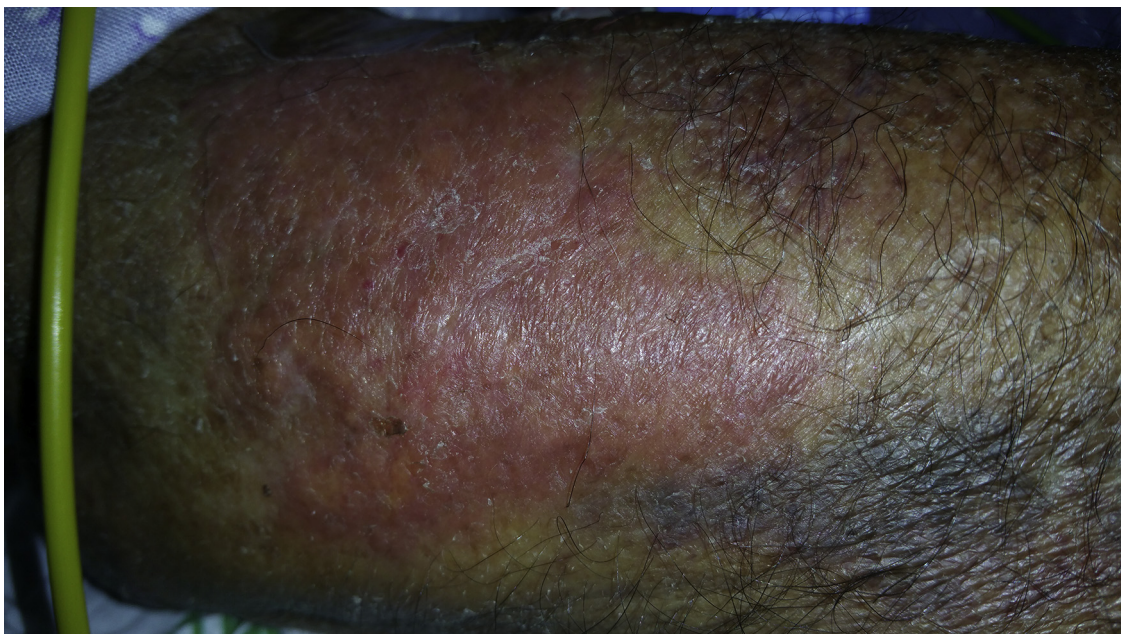


Fig. 4. Reactivation of cryptococcal cutaneous infection, right forearm.



Fig. 5. New lesion on left forearm.

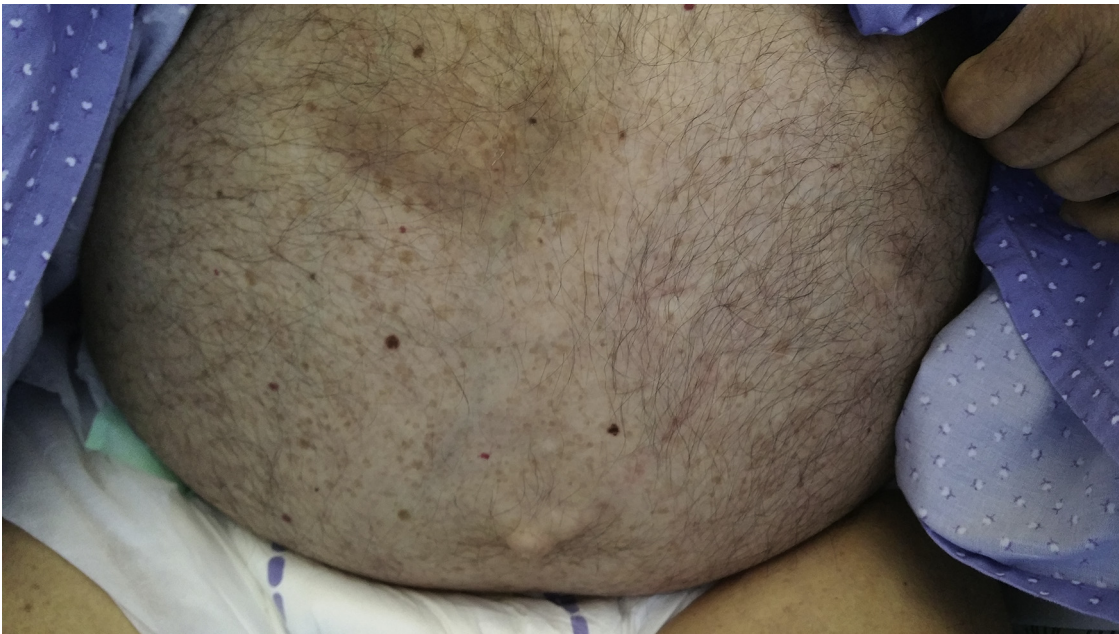


Fig. 6. Resolution of skin lesions on the abdomen.

site with primarily a locally confined skin area infection caused by the typical *C. neoformans* serotype. But, at the same time, this patient had also cryptococemia, and eventually another non-contiguous cutaneous cryptococcosis, resulting either from hematogenous spread or from another iatrogenic traumatic lesion of his previously heavily colonized skin. Clinical, laboratory and imaging studies did not support pulmonary or meningeal infection, and we assume that the fungemia was the result of the cellulitis, spreading to regional lymph nodes and then to the bloodstream. Considering the long-standing superficial skin

disease, diagnosed erroneously as psoriasis or dermatophytosis, it appears that the patient had chronic cryptococcal skin colonization awaiting for a skin injury to invade. Repeated prednisone courses and addition of CSA, could have facilitated the fragility of the skin and inability to resist systemic invasion. Hence, we believe that this patients' cryptococcal cellulitis represent PCC and not secondary cryptococcal skin infection. Given the low antigenemia titer, we also raise the possibility of blood culture contamination by the abundant cryptococcal skin colonization, which also support the diagnosis of PCC.



Fig. 7. – Left forearm lesion after 3 weeks.



Fig. 8. Left forearm lesion after 11 weeks.

We believe that this patient's FSGS resulted from his cryptococcal skin infection, for several reasons. First, for many years FSGS was suspected to be caused by a T cell-related humoral substance that affects the podocytes [2–4]. This theory is supported by basic science studies [5]; the reappearance of FSGS after transplantation [6]; the ability to abrogate the disease using pre-transplant plasmapheresis [7], and the resolution of nephrosis when a kidney from a patient with FSGS is transplanted into a patient without FSGS [8]. The glomerular permeability factor is yet to be identified, but it may be released by T-cells in response to microorganisms, drugs or neoplasms. Second, we gathered several cryptococcal cases related to NS [9–18], in some of them the proteinuria actually responded to anti-fungal treatment (Table 1)

[11–13,16]. There is growing information regarding the association between cryptococcal infection and idiopathic NS [19]. In half of cases, cryptococcal infection was diagnosed within a year from NS diagnosis, and in some, almost concurrently. The close temporal association between NS diagnosis and cryptococcal infection, both rare occurrences by themselves, argue for the causality between infection and nephrosis, since in some cases there was not even enough time of immunosuppression (if administered) to predispose the patient for invasive fungal disease. This, along with NS resolution when withholding or tapering immunosuppression, is another causality supportive evidence.

Third, patients with NS who are infected with cryptococcosis have



Fig. 9. Left forearm lesion after 25 weeks.

an unusually increased probability (35%) of cutaneous cryptococcosis [19], which is in contrast to the supposedly rarity of PCC. This again raises the possible causality of subclinical cutaneous cryptococcosis as a cryptic cause of immune imbalance resulting in NS. Even pulmonary cryptococcosis and other deep-seated infections may be subclinical, and cryptococcosis may be accidentally found when evaluating newly diagnosed NS [11,12,16].

Lastly, the association between immune complex glomerulonephritis and other fungal infections: *Aspergillus fumigatus* [20], *Candida albicans* [21] and onychomycosis of unidentified organism [22] was also reported. In the latter, a 28 year-old healthy female with onychomycosis developed collapsing FSGS when she was treated with griseofulvin, which was blamed for the renal function deterioration. Unexpectedly, her FSGS was rapidly resolved, and we propose that onychomycosis caused FSGS and griseofulvin was beneficial.

Physicians prescribing azoles must be vigilant of drug-drug interactions. Our patient was discharged with CSA and statins, both interact with fluconazole which may increase CSA levels and results in toxicity, as occurred in our case. CSA and statins should also not be administered concomitantly because of the risks for both CSA hepatic toxicity and statin myotoxicity.

To conclude, we report a case of PCC suspected to be the cause of FSGS. Although most opportunistic infections develop among patients with iatrogenic immunosuppression, it may be that in rare occasions, autoimmune idiopathic diseases may result from an immune imbalance caused by an undiagnosed infection or malignancy. If diagnosed early and correctly, antimicrobial chemotherapy rather than immunomodulation may save patients from grave outcomes. Further basic-science and epidemiology studies are required in order to shed more light on this subject.

Table 1
Case reports of cryptococcal infection suspected to be the cause of nephrotic syndrome.

| Reference | Age/Sex | Fungus type | Immuno-suppression | Nephrotic syndrome | Renal pathology | Duration of NS until Cryptococcus diagnosis | Antifungal Tx/Response of NS | Invasive fungal infection |
|---------------------------|---------|--|--|--------------------|--|---|------------------------------|---------------------------|
| Current case | 74/M | <i>C. neoformans</i> var. <i>neoformans</i> (genotype D) | High dose prednisone (21 months) & CSA (1 month) | + | FSGS | 21 months | LAMB&FLC/+ | PCC, BSI, LN |
| Kubo et al. [11] | 80/F | <i>C. neoformans</i> | None | + | Immune-complex GN (+ subepithelial humps) | 3 weeks | FLC/+ | Pulmonary infiltrate |
| Nakayama et al. [12] | 68/M | <i>C. neoformans</i> | Low dose prednisone (for RA) | + | Necrotizing GN, crescents & mesangial proliferation, pauciimmune podocyte effacement | 2 months | FLC/+ | Pulmonary nodule |
| Ogami et al. [13] | 26/M | <i>Cryptococcus</i> spp (not cultivated) | High dose prednisone (8 months) & azathioprine (2 weeks) | + | MCD | 8 months | FLC/+ | PCC |
| Suarez-Rivera et al. [16] | 11/F | <i>Cryptococcus</i> spp (not cultivated) | None | + | Crescentic GN, focal segmental fibrinoid necrosis, subepithelial deposits (IgG, C3, kappa, Lambda) | 3 months | LAMB&FLC/- (ESRD) | Mediastinal mass |

M- male, F- female, NS- nephrotic syndrome, Tx – treatment, CSA – cyclosporine A, FSGS – focal segmental glomerulosclerosis, LAMB- liposomal amphotericin B, FLC – fluconazole, PCC – primary cutaneous cryptococcosis, BSI – blood stream infection, LN – lymphnodes, GN – glomerulonephritis, ESRD- end stage renal disease, MCD – minimal change disease, AMB – amphotericin B, CNS – central nervous system.

Author's contributions

R.C treated the patient, contemplated the concept of the relation between the fungal infection and the nephrotic syndrome, conducted the literature search and wrote the manuscript. T.F and F.B treated the patient and together with R.BA critically reviewed the manuscript.

Declaration of interests

All authors declare they have no conflict of interests

Funding

This work was not funded by any source.

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