Disseminated cryptococcal infection in a patient with a remote renal transplant

Kelli Li MD, Abid Khan MD, Sharmistha Mishra MD PhD MSc, Alice Zhabokritsky MD MSc

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A 55-year-old woman was admitted to hospital with pneumonia; she had received a renal transplant for polycystic kidney disease 14 years prior. Her post-transplant history included chronic allograft nephropathy, with a baseline creatinine of 250 (normal 42–102) µmol/L. The patient had no other comorbidities. Her medications included prednisone 5 mg/d, cyclosporine A 50 mg twice daily (average 2-hour postdose cyclosporine level of 500–700 ng/L) and mycophenolate mofetil (MMF) 500 mg twice daily.

Three weeks before her admission, the patient had travelled to a cottage in Prince Edward Island, but reported no contact with farms, animals or bird droppings. The following week, she developed nonbloody diarrhea, and her outpatient transplant team suggested stopping MMF because of its known association with diarrhea. Ten days before admission, the patient developed a mild headache and lethargy, accompanied by dry cough and nausea. The day before admission to hospital, she developed a fever. In the emergency department, the patient was febrile (38.2°C), hypertensive (blood pressure 186/99 mm Hg) and tachycardiac (104 beats/min). The patient's peripheral oxygen saturation was 97% on room air. Initial bloodwork showed the following: leukocyte count 8.4 (normal 4–11) × 10^9/L, creatinine 358 (normal 42–102) µmol/L, potassium 4.6 (normal 3.5–5) mmol/L and urea 32.5 (normal 3–7) mmol/L. Chest radiographs and computed tomography scans showed bibasilar areas of consolidation with superimposed pulmonary edema (Figure 1). Blood samples were collected for cultures and the patient was started on piperacillin-tazobactam with renal dose adjustments for a presumed diagnosis of pneumonia. Dialysis was initiated for volume overload and cyclosporine A was stopped, in addition to MMF.

Over the next 48 hours, the patient remained febrile and hypertensive, with deterioration in her level of consciousness. On the third day after admission, she developed subtle meningismus, intermittent myoclonic jerks of her lower extremities and symmetric weakness in a pyramidal pattern, affecting her arms and legs. The proximal muscle groups in her arms and legs were slightly weaker (4− out of 5 on the Medical Research Council scale) than the distal muscle groups (4 out of 5), but muscle tone and bulk were grossly normal. Bilaterally, her deep tendon reflexes were brisk and plantar responses were upgoing. Testing for coordination and sensory deficits did not show any substantial abnormalities.

KEY POINTS

- Patients with solid organ transplants are at risk of invasive cryptococcal infection because of long-term immunosuppressive therapy.
- There has been a shift in the epidemiology of invasive cryptococcal infections over the last 10 years, with an increased incidence among patients without HIV.
- Cryptococcal meningoencephalitis should be considered in immunocompromised patients with nonspecific neurologic symptoms and fever.
- Concurrent cytomegalovirus viremia with invasive cryptococcosis may be associated with increased morbidity and death.

An urgent, magnetic resonance imaging (MRI) scan of the brain showed abnormal, bubble-like, T_2-hyperintense signal foci without diffusion restriction involving the bilateral basal ganglia, with mild vasogenic edema (Figure 2). A lumbar puncture showed a protein count of 0.9 (normal 0.15–0.45) g/L, a cerebrospinal fluid (CSF)-to-serum glucose ratio of 48% (normal > 60%), and a leukocyte count of 6 (normal 0–5) × 10^6/L (39% neutrophils, 25% lymphocytes and 34% monocytes) in the CSF. The patient's opening pressure was 38 (normal < 20) cm H_2O.

Given the presence of fever, altered level of consciousness, MRI findings of basal ganglia lesions and an elevated opening pressure in this immunocompromised patient, we made a presumptive diagnosis of cryptococcal meningitis. We started empirical treatment with intravenous liposomal amphotericin B at 4 mg/kg/d with oral flucytosine 1500 mg postdialysis. Shortly after we began treatment, the cryptococcal antigen serology came back positive both in the serum and CSF, with a titre of > 1:1024 (Meridian Bioscience Cryptococcal Antigen Latex Agglutination System). On the fourth day after admission, the patient had progressive respiratory decompensation, requiring intubation. On the fifth day, her blood cultures were positive and *Cryptococcus neoformans* was identified by matrix-assisted laser desorption/ionization. Subsequently, CSF and respiratory cultures also showed heavy growth of *C. neoformans*. Cerebrospinal fluid bacterial cultures, an acid-fast bacilli smear, viral polymerase chain reaction for herpes viruses and West Nile virus and testing for syphilis were negative. Quantitative blood cytomegalovirus (CMV) polymerase chain reaction was positive at 3.6 × 10^4 copies/mL and her HIV test was negative.

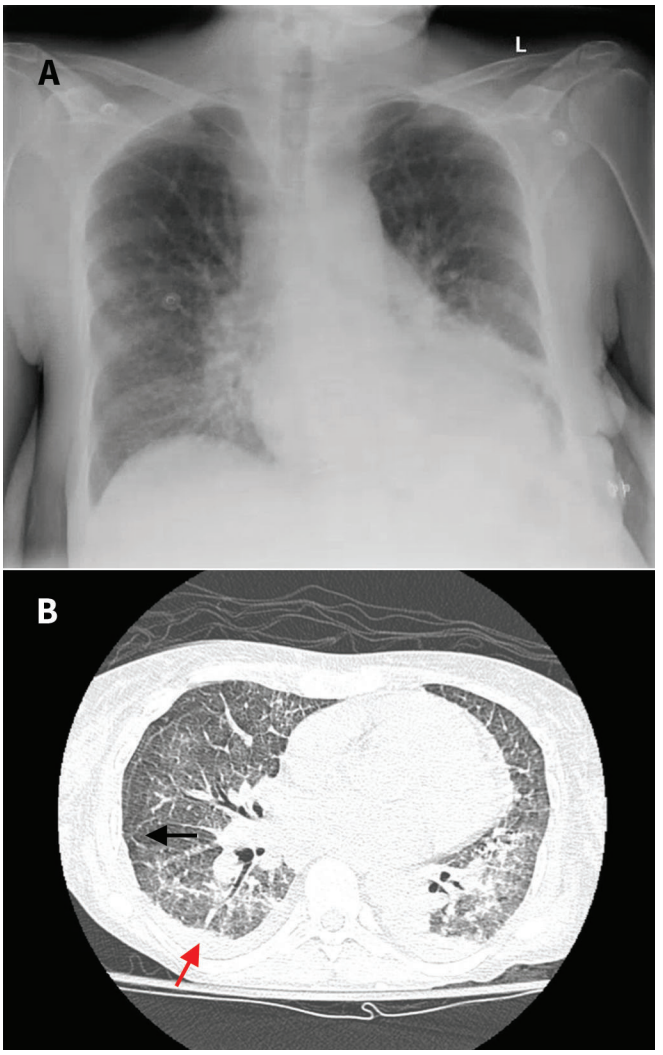

Figure 1: (A) Chest radiograph of a 55-year-old woman showing small, bilateral areas of consolidation in the lower lungs, with prominent diffuse interstitial markings. (B) A noncontrast-enhanced computed tomography scan of the chest showing consolidative densities, predominantly in the lower lobes, with interlobular septal thickening (black arrow) and small bilateral pleural effusions (red arrow). The images suggested an infectious or inflammatory process with superimposed pulmonary edema.

Our patient had persistently elevated opening pressures requiring daily therapeutic lumbar punctures, targeting a > 50% reduction to an opening pressure of < 15 cm H_2O. A lumbar drain was placed on day 6, and the following day, prednisone was replaced with a dexamethasone taper to treat the patient's vasogenic edema. Her CSF culture remained positive until day 9 postadmission, and on day 13, the lumbar drain was removed because the opening pressures had normalized. By week 9, the patient transitioned to consolidation therapy with oral fluconazole 800 mg postdialysis, but there was minimal neurologic recovery. She remained dependent on dialysis throughout her hospital stay. After she experienced recurrent episodes of line-associated and nosocomial sepsis, the patient was transitioned to comfort-focused care after nearly 6 months of being in hospital.

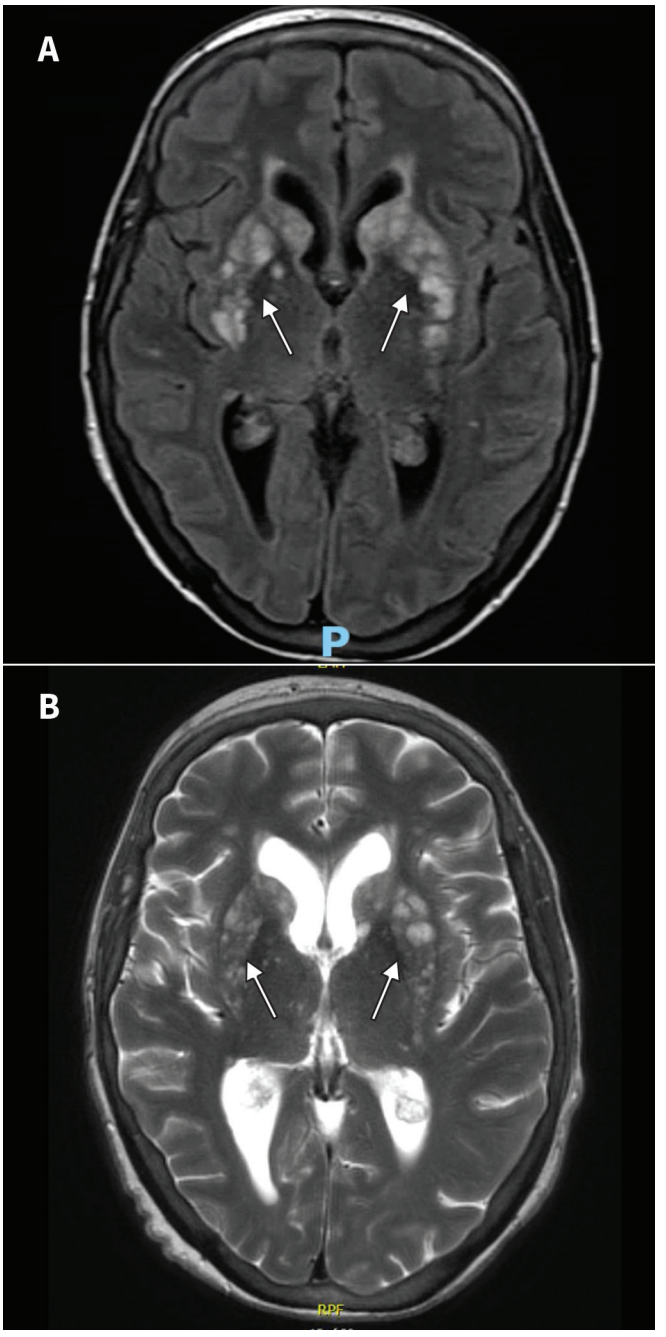

Figure 2: Axial magnetic resonance imaging of the brain without gadolinium (because of renal dysfunction), showing abnormal, bubble-like hyperintense signal foci involving the bilateral basal ganglia (arrows) on the (A) T_2-fluid-attenuated inversion recovery sequence and (B) T_2-weighted image. These images are suggestive of gelatinous pseudocyst of cryptococcal infection. There is associated mild vasogenic edema without substantial mass effect.

Discussion

Cryptococcal infections are the third most common invasive fungal infections in the post-transplant period, after candidiasis and aspergillosis, accounting for 8% of all fungal infections in this population.[1] The incidence of disseminated cryptococcosis in the post-transplant population has been reported to be between

0.3% and 5.3%, according to a review of published reports between 1998 and 2001.[2] Compared with other invasive fungal infections, cryptococcosis has a longer median time to onset from the date of transplant (575 d for cryptococcosis, 103 d for invasive candidiasis and 184 d for aspergillosis).[3]

The epidemiology of invasive cryptococcosis appears to be changing. In Canada, the estimated incidence of invasive cryptococcal infection is 63 per 100 000.[4] Before 2010, cryptococcosis occurred primarily among patients with HIV, and now more than 90% of infections occur in people negative for HIV.[5] This is partially explained by earlier initiation of effective antiretroviral therapy among people with HIV, coupled with an increase in the number of individuals undergoing transplantation and using immunosuppressive medications.

Cryptococcus neoformas and *Cryptococcus gattii* are the 2 cryptococcal species most commonly associated with infection in humans. *C. neoformans* has a ubiquitous environmental distribution and can be found in soil, decaying wood and bird droppings.[1] The most common mode of transmission is through inhalation of fungal spores in the environment, which we suspect was the case for our patient. *C. neoformans* infection is most often reported in immunocompromised patients and is the most common cause of meningitis among patients in the advanced stages of HIV infection.[1] In contrast, *C. gattii* usually affects immunocompetent hosts,[1] and is typically found in tropical and subtropical regions, although outbreaks have been reported in British Columbia.[1,4]

Cryptococcal meningoencephalitis should be considered in immunocompromised patients with nonspecific neurologic symptoms and fever, as was the case in our patient. More than 75% of patients report an insidious headache, whereas signs of meningismus occur in fewer than 25% of patients.[6] Other common symptoms include altered level of consciousness (about 50%), visual disturbances (about 20%) and seizures or neurologic deficits (< 10%), which may signify a space-occupying lesion such as a cryptococcoma.[6] Radiographic manifestations include meningoencephalitis, granulomas (cryprococcomas) and gelatinous pseudocysts, typically seen in the basal ganglia.[7] Differential diagnosis for basal ganglia lesions in immunocompromised patients includes cryptococcosis, as well as cerebral toxoplasmosis, viral encephalitis and malignant disease.[7]

Immunosuppressive therapy, particularly therapy that affects cell-mediated immunity, influences the risks and outcomes of systemic cryptococcal infections. In general, T-cell–depleting antibodies are associated with the greatest increased risk of cryptococcosis in the post-transplant period.[8] Calcineurin inhibitors, such as cyclosporine A and tacrolimus, are associated with lower 90-day mortality rates and increased long-term survival compared with azathioprine or MMF.[7] Calcineurin inhibitor–based immunosuppressive regimens are also associated with fewer central nervous infections than azathioprine or MMF-based regimens.[9] An increased risk of *C. neoformans* infection has been reported among patients receiving long-term steroids for autoimmune conditions; however, there is limited evidence linking the dose and duration of steroids and risk of cryptococcal infection among transplant recipients.[10]

Our patient presented with severe disseminated *C. neoformans* infection 14 years after her renal transplant. We identified another case report describing a patient who presented 13 years after renal transplantation with recurrent urinary tract infections that were eventually linked to a cryptococcoma in the transplanted kidney.[11] The patient in this report had received pulse steroids and changes in her immunosuppressive regimen 3 years before presentation because of rapidly declining renal function. In contrast, our patient was clinically stable on an immunosuppressive regimen of prednisone 5 mg/d for more than 10 years, in combination with cyclosporine A and MMF. In the immediate post-transplant period, her transplant was complicated by acute rejection that was treated with antithymocyte globulin, with no subsequent complications requiring T-cell depletion therapy or pulse steroids.

Our patient had several risk factors for a poor outcome, including a high CSF cryptococcal antigen titre, a decreased CSF-to-serum glucose ratio, an elevated intracranial pressure and an altered level of consciousness.[6] Furthermore, she had concurrent CMV viremia, which has been associated with increased death among patients with AIDS.[12] The impact on morbidity and death from concurrent CMV and opportunistic fungal infections is not well understood in the post-transplant setting. Recent ex vivo data from transplant recipients showed that CMV infection results in blunted cytokine responses to comorbid infections, potentially explaining the immunomodulatory effects of CMV in this population.[13]

Conclusion

We report a case of disseminated cryptococcosis with meningoencephalitis, pneumonia and concurrent CMV viremia in a patient who had undergone renal transplantation many years prior and who was on stable immunosuppressive therapy, including low-dose daily prednisone. Invasive fungal infections, such as cryptococcosis, should be considered in patients who present with fever and nonspecific neurologic symptoms, to support early recognition and management.

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The section Cases presents brief case reports that convey clear, practical lessons. Preference is given to common presentations of important rare conditions, and important unusual presentations of common problems. Articles start with a case presentation (500 words maximum), and a discussion of the underlying condition follows (1000 words maximum). Visual elements (e.g., tables of the differential diagnosis, clinical features or diagnostic approach) are encouraged. Consent from patients for publication of their story is a necessity. See information for authors at www.cmaj.ca.

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Affiliations: Divisions of General Internal Medicine (Li), Nephrology (Khan) and Infectious Diseases (Mishra, Zhabokritsky), Department of Medicine, Faculty of Medicine, University of Toronto; Division of Infectious Diseases (Mishra), Department of Medicine, St. Michael's Hospital, Unity Health Toronto, Toronto, Ont.

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Correspondence to: Alice Zhabokritsky, Alice.Zhabokritsky@one-mail.on.ca