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Case Report

Disseminated cryptococcosis in a child with liver transplantation: a case report

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ABSTRACT

Background. *Cryptococcus neoformans* causes cryptococcosis, primarily affecting immunocompromised individuals, including solid-organ transplant recipients, and, less frequently, immunocompetent people.

Case. A 15-year-old male with congenital hepatic fibrosis, portal hypertension, and cirrhosis underwent orthotopic liver transplantation. He received perioperative antimicrobial and antifungal prophylaxis and continued immunosuppressive treatment. Thirty months post-transplant, he presented with fever, hypertension, and sacroiliac joint pain. Peripheral blood cultures showed *C. neoformans*, confirmed by pan-fungal polymerase chain reaction assay and latex agglutination tests. Despite initial treatment with intravenous (IV) fluconazole, his condition worsened, necessitating intubation for acute hypoxic respiratory failure. Magnetic resonance imaging and computed tomography scans indicated disseminated cryptococcosis with lymphadenitis, possible meningitis, and pneumonia. Treatment was escalated to IV liposomal amphotericin B and 5-flucytosine, while reducing immunosuppressive treatment. Despite negative fungal cultures on the tenth day, the patient deteriorated, developing pancreatitis, pneumonia, and massive gastrointestinal bleeding, leading to death on the 35th day of hospitalization.

Conclusion. This case shows the severity and complexity of managing disseminated cryptococcosis in pediatric liver transplant recipients. Aggressive therapy and early identification are essential for improving outcomes in these high-risk patients.

Key words: cryptococcosis, liver transplantation, immunocompromised patients.

Opportunistic fungal infections, such as cryptococcosis, primarily impact immunocompromised and rarely immunocompetent patients. *Cryptococcus neoformans* is the most common species, and inhalation is the primary route of infection.[1] The infection is typically related to immunosuppression in patients who have had solid organ transplants (SOT) and hematopoietic progenitor transplants.[2]

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Patients who are SOT recipients are at risk of cryptococcosis, with an incidence that reaches 5.3%.[3] It is usually a late-onset infection (after the first year posttransplant).[4] However, it may begin earlier, particularly in liver and lung transplant patients compared to kidney transplant patients. This may be attributed to the intensity of the immunosuppressive treatment. The lung and central nervous system (CNS) are the most commonly affected systems, but up to 61% of liver transplant patients have disseminated disease, with extrapulmonary involvement in 75% of cases. Other less frequently affected sites include the skin (nodules, papules, ulcers), soft tissue, and the osteoarticular system in 6% to 12% of patients. The liver, kidneys, and

prostate are less frequently involved. In SOT, the mortality of cryptococcosis can reach 50% with CNS involvement. Early diagnosis, timely and adequate antifungal treatment, reduction of immunosuppression, and increased intracranial pressure management are essential to improve post-transplant survival.[6]

We report a case of disseminated cryptococcosis presenting in a patient 30 months after orthotopic liver transplantation.

Family consent and permission were obtained for the case presentation.

Case presentation

A 15-year-old male patient who had been diagnosed with congenital hepatic fibrosis and developed complications of portal hypertension and cirrhosis underwent orthotopic liver transplantation 30 months ago. According to institutional protocol, he received antimicrobial and antifungal prophylaxis in the perioperative period with piperacillin-tazobactam for 48 hours, trimethoprim-sulfamethoxazole and fluconazole for 90 days, and immunosuppressive treatment (prednisolone at 20 mg/day, conventional tacrolimus at 5 mg every 12 hours). He was discharged from the hospital 18 days after his transplant. The Patient followed up regularly at Ege University Pediatric Gastroenterology, Hepatology and Nutrition Clinic, and Kent Hospital Transplant Clinic.

On admission (30 months after liver transplantation), the patient was febrile (39°C), awake, and hypertensive (145/95 mmHg). Physical examination revealed bilateral sacroiliac joint pain and motion range limitation without meningeal signs.

The hemogram disclosed a hemoglobin level of 12.8 g/dL and a leukocyte count of 17.99x10^3 µl with 82.8% segments. Laboratory data is shown in Table I. Serology for herpes simplex virus, human herpesvirus 6, Epstein-Barr virus, cytomegalovirus, and hepatotropic viruses (hepatitis A, B, C virus) were negative. In the microbiology laboratory, yeast cells more significant than normal were observed in wet preparation of the blood culture plate. Intravenous (IV) fluconazole therapy was therefore initiated empirically. The capsule was imaged using Indian ink. Color change was detected on Christensen's urea agar at the 5th hour. The brown colonies were determined

Table I. Laboratory data of the patient.

Day of hospitalization	CRP (mg/L)	AST (U/L)	ALT (U/L)	Urea (mg/dL)	Creatinine (mg/dL)	WBC (10^3/µl)	Platelet count (10^3/µL)	Cryptococcus antigen	Treatment	Tac concentration (µg/L)	Culture
At admission	95	56	106	52	1.54	17.99	456			5.32	
Day 1	91	48	86	51	1.64	16.85	378			3.32	
Day 2	127	42	90	41	1.47		424			1.23	
Day 3	80	27	61	28	1.53	15.27	443			0	
Day 7	66	44	56	43	1.79	13.64	383	Positive	Fluconazole		positive
Day 14	28	24	37	21	1.71	14.5	329	Positive	L-AmB		positive
Day 21	424	15	13	29	1.49	22.1	311	Positive	L-AmB		
Day 28	124	113	35	57	1.05	33.1	98	Positive	L-AmB		
Day 35	240	1859	222	129	2	44.1	19	Positive	L-AmB		

ALT: alanine transaminase, AST: aspartate transaminase, CRP: C-reactive protein, L-AmB: liposomal amphotericin B, Tac: tacrolimus, WBC: white blood count.

on the 4th day on Staib agar. Identification of *Cryptococcus neoformans* was done by using the VITEK®MS (bioMérieux, Marcy I'Etoile, French) technique. Peripheral blood culture showed *C. neoformans* growth with susceptibility to fluconazole (minimum inhibitory concentration < 2 μg/mL) and amphotericin B (AmB) (minimum inhibitory concentration < 2 μg/mL). A pan-fungal polymerase chain reaction assay was positive for *C. neoformans.* The latex agglutination test for cryptococcal polysaccharide antigen was positive in serum. Diagnostic testing was negative for mycobacteria, and blood cultures for aerobes were also negative. A lumbar puncture could not be performed because the parents did not provide consent. The family later confirmed that they owned chickens, and his uncle had a parrot. However, the death of all the chickens ten days ago prevented the collection of their excrement. Because they thought the parrot was in excellent health, his parents did not give samples of the parrot to the laboratory. Abdominal magnetic resonance imaging (MRI) showed multiple intraperitoneal and retroperitoneal enlarged lymph nodes. Neck tomography showed multiple supraclavicular and infraclavicular lymphadenopathies. Brain MRI detected a low signal in T2 FLAIR hyperintense foci, which are evaluated primarily in favor of chronic ischemia, which was observed in the right frontal lobe deep white matter adjacent to the posterior horn of both lateral ventricles and the periventricular white matter (Fig. 1). In contrast, acute ischemia signs were not detected. Disseminated cryptococcosis with cryptococcemia was confirmed, although we could not confirm meningeal involvement. The absence of cerebrospinal fluid (CSF) findings precluded the confirmation of possible meningitis due to the headache and hypertension. Antifungal induction therapy was switched to IV liposomal AmB (5 mg/kg/day) plus 5-flucytosine (5-FC) (100 mg/kg/day) immediately. In addition, the dose of immunosuppressant therapy was reduced to 2.5 mg tacrolimus every 12 hours, 2.5 mg/day prednisolone, and 500 mg mycophenolate mofetil every 12 hours.

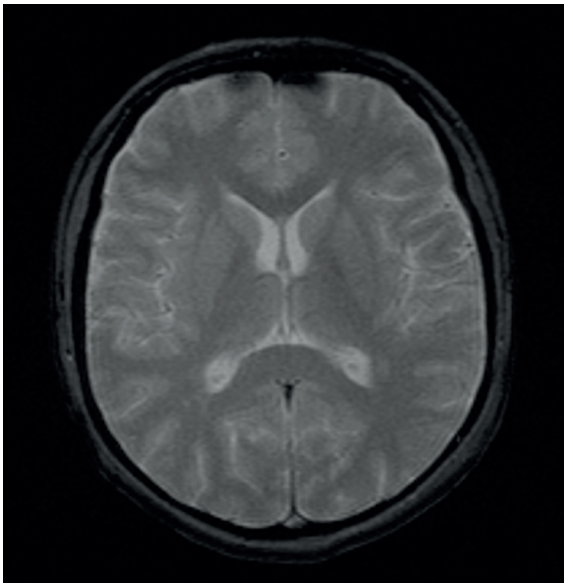

Fig. 1. Cranial MRI Spect (Day 3). Brain MRI detects the low signal in T2 FLAIR hyperintense foci in the right frontal lobe deep white matter adjacent to the posterior horn of both lateral ventricles and the periventricular white matter.

On the tenth day of treatment, fungal cultures were negative. However, the patient's general condition did not improve on the 20th day. The patient was agitated, diaphoretic, and in respiratory distress. He was intubated for acute hypoxic respiratory failure. Laboratory tests were significant for C-reactive protein 225 mg/L, procalcitonin 2.59 μg/L, urea 28 mg/dL, creatinine 1.75 mg/dL, AST 18 U/L, ALT 18 U/L, lipase 1300 U/L, amylase 890 U/L, leukocyte count 26.11x10^{3}/μl, hemoglobin 9.2 g/dL, thrombocyte 436x10^{3}/μl. Echocardiography showed no abnormality. The chest X-ray revealed multiple lung lesions, prompting the start of broad-spectrum antimicrobials and the continuation of antifungal therapy. Computed chest tomography revealed pleural effusion (3 cm), atelectasis, pneumonia with a right lobe cavitary nodule, and no mediastinal lymphadenopathy and heterogeneity of the pancreas (Fig. 2). A bronchoscopy was not performed because the parents did not provide consent. In the intensive care follow-up, respiratory distress worsened rapidly. There was no growth of other bacterial or fungal

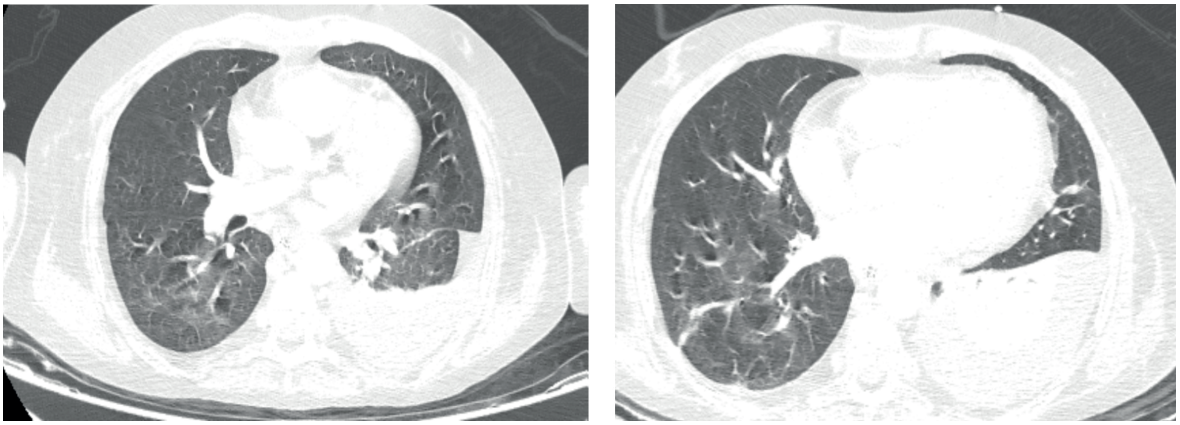

Fig. 2. Computed tomography chest. Computed tomography of the chest demonstrates a cavitary nodule, pleural effusion, and atelectasis.

microorganisms in the patient's blood culture, urine culture, or catheter culture. The patient was primarily diagnosed with pneumonia and pancreatitis, followed by massive gastrointestinal bleeding and shock, and died on the 35th day of hospitalization.

Discussion

Cryptococcosis is a widespread invasive mycosis that causes severe morbidity and mortality. *Cryptococcus neoformans* is a common environmental and human pathogen capable of causing significant illness.[7] This yeast-like encapsulated basidiomycetous fungus has been detected in various environmental sources, including bird droppings, vegetable matter, wood, soil, and dairy products.[8] The fungus typically enters the body through the respiratory system via inhalation of basidiospores or yeast cells, which can be sequestered in sanctuary locations, such as alveolar macrophages. Most immunocompetent people can independently clear the organism, but a small percentage of individuals enter a state of latent infection following inhalation that can then progress to pulmonary infection, hematogenous spread, and extrapulmonary illness.[9,10] There have been few reports of infection acquired by SOT.[11] Studies have shown that cryptococcosis in SOT recipients typically manifests as symptomatic disease and may progress much more quickly than previously.[12,13]

Cryptococcus spp. cause up to 8% of fungal illnesses after SOT and are the third most common cause of fungal infection after *Candida* and *Aspergillus spp.*[14] *Cryptococcus spp.* are observed in up to 5.3% of liver transplants and more commonly appear in kidney transplant recipients than in other patients.[3,5]

Most cases of cryptococcal infection in SOT recipients occur after the first year following transplantation.[4] In a large surveillance study, the median time to onset cryptococcosis following transplantation was 575 days.[14] The possibility of an unexplained pretransplant infection and graft transmission should be explored in early-onset infection, especially if it develops within the first 30 days following transplantation.[15,16] In our patient, the disease was late-onset, occurring after 30 months. Late-onset infections most likely result from primary infection rather than from reactivation.[13] In our case, the point source was possibly a chicken or parrot. However, no samples were taken from the chickens or parrot; thus, we cannot confirm transmission from bird to human. However, the findings strongly support zoonotic transmission.

The CNS is the most common site of symptomatic cryptococcosis, affecting approximately 80% of patients with the disease and typically presenting as subacute or chronic

meningitis.[15,16] Headache, fever, and confusion are the most common symptoms, and ataxia, amaurosis, and cranial nerve palsies can also occur.[11] The second most common manifestation of cryptococcosis is respiratory disease, which can appear in the form of respiratory consolidations, nodular or cavitary infiltrates, miliary patterns, or pleural effusion. In the case presented, disseminated involvement (meningeal, pulmonary, and lymphatic) by *Cryptococcus neoformans* was documented.

Direct microscopy of sputum, bronchoalveolar lavage, CSF, blood, urine, peritoneal lavage, or organ biopsy can aid in cryptococcosis diagnosis. Fungal cultures can be collected from these types of samples. *Cryptococcus* antigens in serum and CSF can be detected using a latex agglutination test. In patients with cryptococcosis affecting the CNS, cranial imaging may reveal leptomeningeal enhancement, encephalomalacia, infarcts, cerebellitis, hydrocephalus, and transverse myelitis.[7,17,18] In our case, the CSF sample could not be obtained because a lumbar puncture and bronchoalveolar lavage could not be performed; however, *Cryptococcus neoformans* was detected in the peripheral blood culture, and the antigen test was positive. There was no growth of other bacterial or fungal microorganisms in the patient's blood, urine, or catheter cultures, so an additional nosocomial infection was not considered. Therefore, the patient's death was thought to be most likely due to cryptococcal infection.

Treatment recommendations for cryptococcosis vary depending on the site of infection and the host's immunological status. According to the Infectious Diseases Society of America (IDSA), the recommended induction and consolidation therapy for CNS and disseminated disease is AmB deoxycholate (1 mg/kg per day IV) plus flucytosine (100 mg/kg per day orally in 4 divided doses) for two weeks (for the non–human immunodeficiency virus-infected, non-transplant population, follow the treatment length schedule for adults), followed by fluconazole (10–12 mg/kg per day orally) for eight weeks; for AmB-intolerant patients, either liposomal AmB (5 mg/kg per day) or AmB lipid complex (5 mg/kg per day).[15] For solid transplant recipients with cryptococcosis, reducing the immunosuppressive drug regimen to the lowest possible level is an essential step in antifungal therapy. Following the detection of cryptococcus in our patient, we arranged his treatment according to the literature and reduced immunosuppressive agents.

The mortality rate in disseminated cryptococcosis is around 17% and increases to almost 50% when the CNS is involved, particularly in the presence of factors predictive of 90-day mortality, such as cryptococcosis, compromise in the state of consciousness, and intracranial hypertension.[1,19] Our patient's response to treatment was unfavorable and he experienced complications, leading to death.

Cryptococcosis is a rare infection among SOT children. We recommend that immunocompromised patients avoid owning birds and regions contaminated with bird droppings due to the risk of cryptococcosis transmission from pets to humans.

Ethical approval

Family consent and permission were obtained for the case presentation.

Author contribution

Study conception and design: DB, PY, MK; data collection: BK, SYA, SA; analysis and interpretation of results: GKA,PY, ZŞB; draft manuscript preparation: PY, DB, SA. All authors revised the manuscript and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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