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An Unusual Case of a Dematiaceous Fungus with an Exclusive Cerebral Involvement After ABO-Incompatible Renal Transplantation

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 46-year-old
Final Diagnosis: Dermatological fungus involving brain in an ABO-incompatible renal transplantation
Symptoms: Seizures
Medication: —
Clinical Procedure: —
Specialty: Nephrology

Objective: Rare disease

Background: *Cladophialophora carrionii* was detected postoperatively in a cerebral space-occupying lesion of a patient who had undergone ABO-incompatible renal transplantation. The infection was successfully treated with oral terbinafine and itraconazole.

Case Report: An otherwise healthy 46-year-old man underwent ABO-incompatible renal transplantation. Postoperatively, he was hemodynamically stable and the graft was functioning well. Within 2 weeks, the patient developed clinical depression, followed by seizures and left-side hemiparesis. There were no skin findings. Radiological investigation showed 2 space-occupying lesions in the brain parenchyma. The patient's condition improved after partial frontal lobectomy and microsurgical abscess evacuation, with a short course of liposomal amphotericin B and a combination of oral terbinafine and itraconazole. Microbiological examination of the pus showed growth of *C. carrionii*, which predominantly causes subcutaneous mycoses.

Conclusions: It is very rare for melanized fungal infections to cause an exclusively cerebral disease without any skin involvement. Furthermore, among established cases, *C. carrionii* is a very rarely detected pathogen.

MeSH Keywords: ABO Blood-Group System • Kidney Transplantation • Organ Transplantation

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Background

ABO-incompatible renal transplantation is a well-established method that allows organ transplant across ABO-incompatible blood groups with the use of B-cell-depleting therapies. Dematiaceous fungi cause various fungal infections of skin and soft tissue, including phaeohyphomycosis, chromoblastomycosis, and mycetoma. Phaeohyphomycosis is seen in immunocompromised patients, especially allograft recipients. *Cladophialophora carrionii* (previously *Cladosporium carrionii*) is one of the fungal pathogens that can cause subcutaneous phaeohyphomycosis. It is introduced via minor skin trauma, and it appears as cauliflower-like lesions, usually over the lower limbs. The lesions show characteristic sclerotic bodies on histopathology. It is extremely uncommon for the fungal pathogen to cause phaeohyphomycosis without any skin lesions [1].

This report presents an unusual case of ABO-incompatible renal transplantation, in which the patient developed left-sided hemiparesis during the postoperative period. Cerebral phaeohyphomycosis was detected, without any dermatological manifestations.

Case Report

A 46-year-old man with end-stage renal disease of unknown etiology, on maintenance hemodialysis, was admitted to the hospital for renal transplantation. He did not have a related donor of a compatible blood group. The organ donor was his wife, who had type B blood; the recipient had type O blood. ABO-incompatible renal transplantation was planned. Between the donor and recipient, HLA mismatch was 5/6 and anti-HLA antibody was within acceptable limits. Clinical examination, detailed history taking, and pre-transplant evaluation of the donor did not reveal any ailments.

In his preoperative assessment, the patient was 64 kg, nondiabetic, and nonhypertensive, and his baseline anti-B antibody titer was 1: 512. He had a history of pulmonary tuberculosis for which he had completed the requisite course of antitubercular treatment. According to the institutional protocol for ABO-incompatible transplantation, 14 days prior to expected date of transplantation, the patient received single dose of intravenous rituximab (200 mg) followed by oral tacrolimus (1.5 mg, twice daily), oral mycophenolic acid (360 mg, 3 times daily), and oral prednisolone (20 mg, once daily).

The patient was then admitted and started on ABO-antibody desensitization with plasma exchange, using fresh frozen plasma of donor blood group (blood type B) as replacement fluid for all sessions of plasma exchange, and intravenous immunoglobulin (5 g) after each plasma exchange. Meanwhile, he continued to be on maintenance hemodialysis 3 times per week.

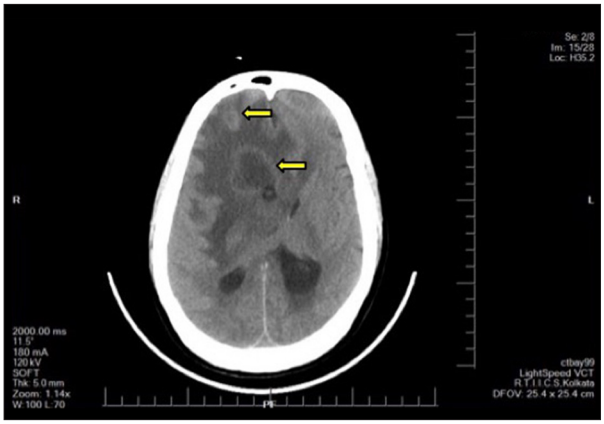

Figure 1. Plain, noncontrast computed tomography scan showing 2 lesions (yellow arrow) in the right frontal lobe, exerting a mass effect. These lesions were suspected to be the abscess.

Transplant surgery was done when the patient's anti-B antibody titer was 32 on 3 consecutive occasions. He received 6 sessions of plasma exchange, and 6 doses (total of 30 g) of intravenous immunoglobulin before the operation. He also received induction therapy with thymoglobulins (3 mg/kg body weight) in 2 divided doses on day 0 and day 1 of surgery and intravenous methylprednisolone (500 mg) on day -1 and day 0 of surgery. Meanwhile, the other immunosuppressive medications were continued. There were no complications following the transplantation surgery during the postoperative period up to discharge.

Postoperatively, the patient's graft functioned well, with steady and rapid normalization of renal and other metabolic parameters. Although the patient was recovering well and there was no detectable neurological deficit, he was found to be depressed. A psychiatry consultation was done, and patient was started on antidepressants. He showed some improvement in his mood. He was discharged on the 11th postoperative day, with a good urine output and normal serum creatinine of 0.9 mg/dL. Along with his other medications, prophylaxis for *Pneumocystis jiroveci* and cytomegalovirus infections was started.

The day after discharge, the patient was brought to the emergency department with complaints of vomiting and altered sensorium following a probable seizure episode. He was hemodynamically stable and was maintaining adequate oxygenation in the room air. On neurological examination, he was found to have extensor plantar reflex on the left side. A noncontrast computed tomography (CT) scan (Figure 1) of the brain revealed 2 space-occupying lesions in the right frontal lobe with extensive surrounding edema and gross midline shift to the left. The lesions showed a hypodense center with a hyperdense wall. Magnetic resonance imaging (Figure 2) was done next, and the results confirmed the CT findings, with further delineation of the brain parenchyma.

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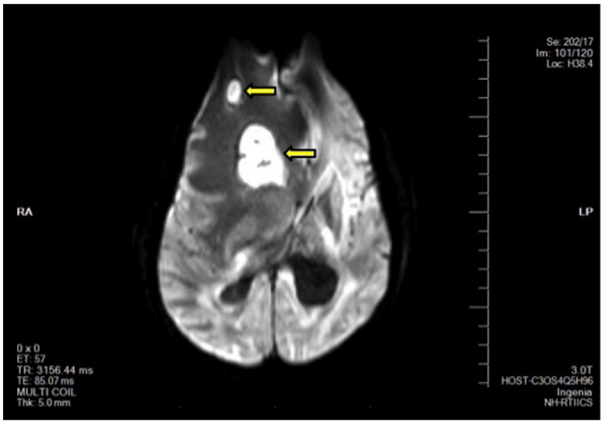

Figure 2. Magnetic resonance imaging of right frontal lobe showing intraparenchymal lesions (yellow arrow) with perilesional edema and mass effect. This image shows the suspected fungal abscess.

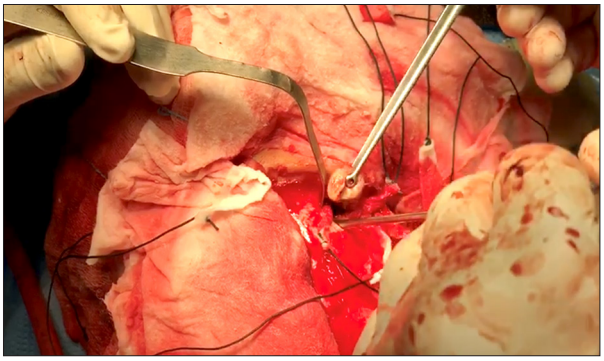

Figure 3. Microsurgical abscess evacuation during partial frontal lobectomy.

The patient was started on empirical broad-spectrum antibiotics, intravenous piperacillin and tazobactam, after samples were sent for culture. He was given other supportive care with anticonvulsants. As infection was suspected, mycophenolic acid was withdrawn and other immunosuppressants were continued. The tacrolimus level was 4.9 ng/mL. The patient was on oral prednisolone, which was stopped, and he was then started on intravenous dexamethasone. To protect his airways, he was prophylactically intubated and put on mechanical ventilation. With the clinical suspicion of a possible invasive fungal infection, he was started on liposomal amphotericin B. The liposomal amphotericin B was given in full therapeutic dose (5 mg/kg every 24 hours) because the renal function was stable with a good urine output. Further investigation for a fungal infection showed serum galactomannan for aspergillosis to be negative, and the toxoplasma antibody panel was negative. Additionally, the patient was given other therapeutic agents to reduce his brain edema. Liver enzymes were raised and a possibility of disseminated fungal infection was considered. He was therefore started on ursodeoxycholic acid.

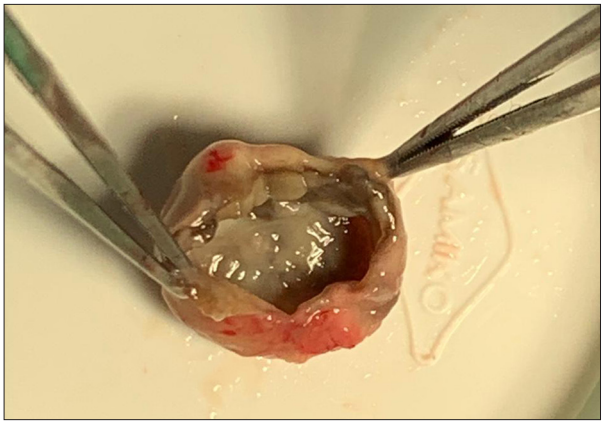

Figure 4. Encapsulated fungal abscess after evacuation.

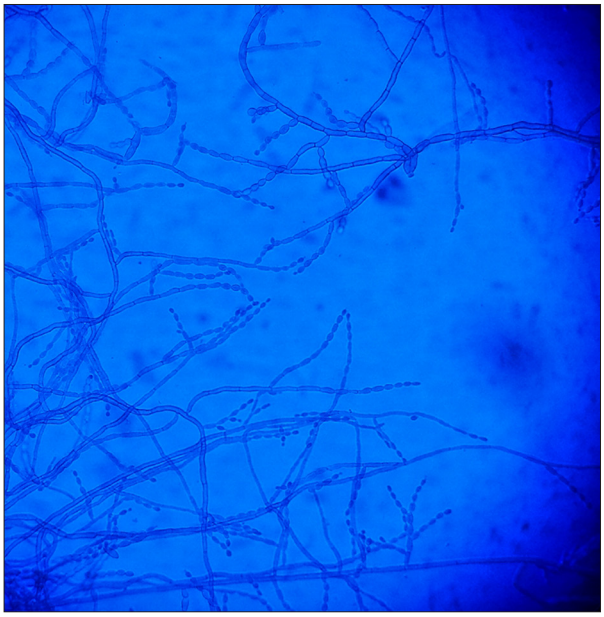

Figure 5. Lactophenol cotton blue mount (at ×48): Septate hyphae with conidiophores bearing long chains of spindle-shaped conidia suggestive of *Cladophialophora* genus.

A follow-up CT scan done 2 days later did not show any improvement in the brain lesions. The patient had progressive left-sided hemiparesis, and 4 days after admission, he was taken up for a decompression craniotomy. Partial frontal lobectomy was done with microsurgical evacuation of the abscesses (Figures 3, 4), and the brain lesion was sent for biopsy. Postoperatively, the patient was stable and continued to recover with an adequate urinary output; however, the renal function decreased with an increase in serum creatinine to 2 mg/dL. The rise in serum creatinine later normalized, and the patient was thereafter extubated on the second postoperative day.

On microbiological examination, the staining of the pus from the cranial space-occupying lesions showed fungal elements (Figure 5), and histopathology showed phaeohyphomycosis (Figure 6).

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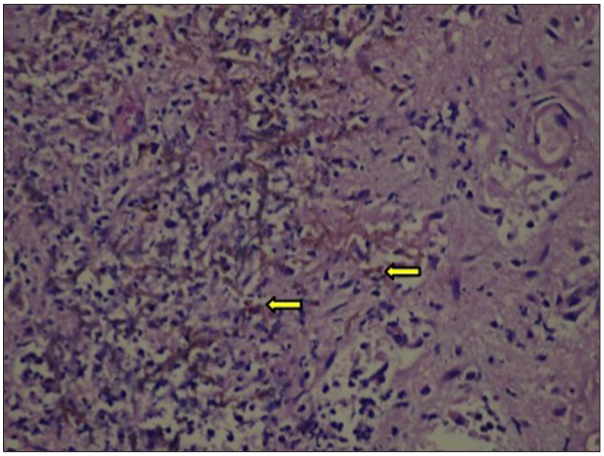

Figure 6. On histopathology, pigmented septate fungal hyphae are visible. Yellow arrows indicate the pigmented fungal bodies (hematoxylin and eosin stain, ×200).

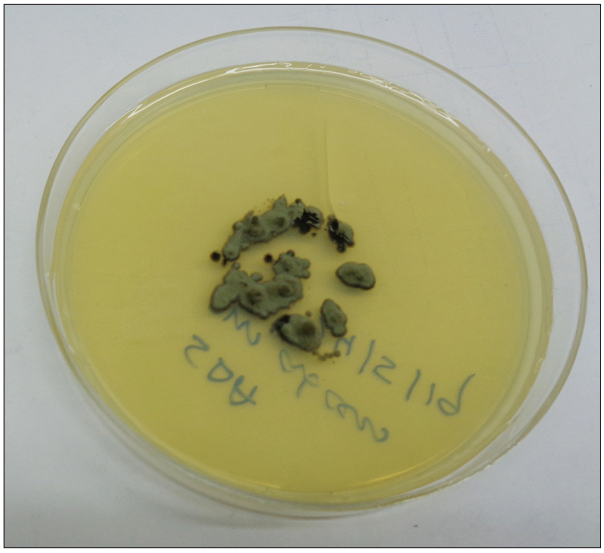

Figure 7. Colony morphology showed a slow-growing mold, initially gray-brown and turning olive-black with jet black reverse at the end of 2 weeks of incubation, characteristic of dematiaceous fungi.

The patient was completely undressed and examined under appropriate lighting, and no skin lesions were detected. Liposomal amphotericin B was discontinued.

The patient was started on oral terbinafine dose (500 mg once daily). Considering his deranged hepatic parameters, azoles were avoided. Further investigations with fungal culture of the organism revealed the species. The tests showed growth at 25°C and 37°C, but not at 42°C, and the urease test was negative. Based on these phenotypic characters, the fungus was identified as *Cladophialophora carrionii* (Figures 7).

The patient showed gradual clinical improvement, started taking food orally, regained hemodynamic stability without any inotropes, maintained adequate oxygenation in room air, was euvolemic, passed a good amount of urine, and had normal metabolic parameters. A follow-up on postoperative day 7 showed substantial improvement in brain imaging. Additionally, hepatic parameters had improved, so oral itraconazole (200 mg once daily) was added. A follow-up CT scan was done a week later and showed reduction in the size of the lesion. The patient continued to show improvement with a combination of oral terbinafine and itraconazole.

Discussion

Invasive fungal infections are a significant complication in solid organ transplant cases and a major cause of mortality in organ recipients. The most common fungal infection is candidiasis, followed by aspergillosis and cryptococcosis [2]. According to Shoham and Mars [2], the risk of posttransplant invasive fungal infection is highest in small bowel transplant. The risk is about 1.3% in renal transplant cases. Factors that influence the risk of these infections developing include the patient's environmental exposure, the immunosuppressive therapies, any breach in mucocutaneous barrier, and other comorbid conditions. Donor grafts are also an increasingly identified mode of transmission of fungal infection [3]. Most infections start in the respiratory tract or skin and may then disseminate to multiple organs including the central nervous system.

Cladophialophora is a dematiaceous fungus. Dematiaceous fungi are characterized by the presence of melanin or melanin-like pigments within the cell walls. These are extensively present in the environment, and they can cause infections including mycetoma, chromoblastomycosis, and phaeohyphomycosis [4].

Chromoblastomycosis and phaeohyphomycosis are superficial or subcutaneous skin infections with pathognomic thick-walled muriform cells showing the presence of sclerotic bodies. The infections are diagnosed by visualization of these sclerotic bodies or medlar bodies, which look like copper pennies, in clinical specimens. Dematiaceous fungi are more common in tropical and subtropical regions such as India, China, South America, and Africa, where melanized fungal infections are endemic [5].

Clinical manifestations of phaeohyphomycosis and chromoblastomycosis typically involve the skin and can be divided into nodular, verrucous, plaque, and cicatricial types. The likelihood of dissemination is very low, and cases of bone, lung, or brain infection are rare. Phaeohyphomycosis has superficial, cutaneous, and subcutaneous forms, and systemic disease with lung, brain, or paranasal sinus involvement is extremely uncommon [3]. Infections are characterized by impaired clearance of the fungi by the human host due to a multitude of

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fungal virulence factors. Such virulence factors include thermotolerance; the presence of melanin in the cell wall, which interferes with proteolytic enzyme breakdown and protects the organism against nitric oxide defenses and phagocytosis; and fungal adherence factors. Dematiaceous fungi are increasingly acquiring prominence for pathogenesis in immunocompromised patients including transplant recipients.

Singh et al. [4] reported a case of *Cladophialophora bantiana* in a patient who had undergone small bowel and right hemicolon allograft transplantation. According to their review of the literature, 50% of patients who developed such infections were renal transplant patients. None of the renal transplant patients reported in the review developed any systemic infections. The transplant recipients had a median age of 44 years, and among the infected patients, a stark majority (74%) showed skin and soft tissue infections. These infections occur at a median period of 2 years after transplantation. Systemic infections (phaeohyphomycosis) causing brain abscess were seen in the liver transplant patients, with the earliest occurring at 44 days after transplantation. All the brain abscess cases in the review manifested with the presence of ring-enhancing lesions on CT scan. Most of the patients (42%) were on immunosuppressive therapy with cyclosporine, azathioprine, tacrolimus, and cyclophosphamide. Additionally, 48% of the patients showed a record of environmental exposure to possibly contaminated material. Our patient was exceptional as he presented with exclusive cerebral involvement, within 2 weeks of the renal transplant procedure. Thorough preoperative evaluation had not showed the presence of any pre-existing infections.

In an extensive review of chromoblastomycosis in the context of solid organ transplantation, Kumbhakar and Miko [5] found only 19 cases reported from 1985 to 2018. Of those patients, 84% were kidney transplant recipients and 68% resided in tropical or subtropical zones. *Cladophialophora carrionii*, the same organism detected in our patient, was found in only 1 patient, a 58-year-old man from Tunisia. Similar to reviews by other authors [3], the review by Kumbhakar and Miko [5] showed a median time to chromoblastomycosis occurrence of 29 months after transplantation. Only 2 patients in the review had disseminated disease, and the review did not show a single case in 33 years in which organ involvement occurred without any dermatological manifestation. This finding emphasizes the uniqueness of our case in which the patient presented with only cerebral fungal abscess without any skin lesions.

Although a study by Santos et al. [6] in 2017 failed to show an increase in the incidence of melanized fungal infections, it revealed a generalized increase in the incidence of transplant-associated chromoblastomycosis due to an increasing number of solid organ transplantations and improved diagnostic techniques. Their search of the literature showed that almost all cases of chromoblastomycosis had extensive cutaneous involvement. In contrast, our patient atypically had a distinct absence of any dermatological manifestations, presenting with only cerebral phaeohyphomycosis. Visceral involvement was infrequent in the Santos et al. [6] study, with only 3 out of 56 patients showing organ involvement.

Men are at greater risk of disease caused by dematiaceous fungi, primarily due to occupational exposures associated with agricultural labor, gardening, farming, and forestry, which involve regular contact with contaminated soil and vegetative material. However, our patient was a shopkeeper by occupation, and he did not have a history of such habitual exposures. Detailed history taking and complete skin examination did not show any cutaneous trauma.

Most authors have shown itraconazole and terbinafine to be effective antifungal treatment, both as monotherapy and in combination. Itraconazole is a low-cost drug that is effective against a large variety of melanized fungal infections. Most authors have not considered suspension of immunosuppressants necessary for treatment of these infections. Treatment of chromoblastomycosis is with procedures such as surgery, cryosurgery with liquid nitrogen, or carbon dioxide laser; drugs such as posaconazole, imiquimod, flucytosine, terbinafine, or supersaturated potassium iodide; and methods such as local heat application. The most commonly used drugs are itraconazole and terbinafine, which are used at high doses for prolonged periods. Cure rates of 100% have been seen with terbinafine monotherapy in some studies [7].

Our patient showed improvement within a week of starting oral terbinafine 500 mg once daily, and clinical improvement was sustained with the addition of oral itraconazole 200 mg once daily. On subsequent follow-up visits, the patient's metabolic parameters were stable and his neurological condition was good.

Conclusions

While melanized fungal infections are seen in cases of solid organ transplantation, they commonly present with skin lesions and rarely have an exclusive visceral involvement. Among cases of deep mycoses, melanized fungal infections with *Cladophialophora* as the causative organism are seen very rarely. The rarity of our case is more extreme because the patient had phaeohyphomycosis in the brain without any cutaneous manifestations. While the median time in most cases is 20–30 months post transplantation, our patient presented with focal neurological defect within 2 weeks of transplant surgery. A combination of oral terbinafine and itraconazole was effectively used to treat the patient, and he recovered well.

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The clinical significance of the case is that the patient presented soon after transplantation with only systemic symptoms. Melanized fungal infections must be kept in mind with a rise in their incidence, particularly in tropical and subtropical countries such as India. Even among established cases, *C. carrionii* is a very rarely detected pathogen.

Acknowledgement

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Conflict of interest

None.

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