REVIEW ARTICLE

# *Cunninghamella bertholletiae* Infection

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**ABSTRACT**

*Cunninghamella* is a member of the Family Cunninghamellaceae and of the Order Mucorales. *Cunninghamella* is an opportunistic fungi that rarely causes invasive mucormycosis, however, it can lead to a fatal infection in immunocompromised patients. *C. bertholletiae* is the only species that has been established to be a human pathogen. Clinical presentations vary from localized infection to multifocal infection, and most of the patients have poor outcome due to delayed diagnosis and treatment. Therefore, empirical treatment with broad spectrum antifungal agents including surgical debridement is mandatory once there is clinical suspicion. (*J Infect Dis Antimicrob Agents 2014;31:37-49.*)

**Note:** This case had been presented and discussed in the Interhospital Case Conference on Infectious Disease (ICCID) on 16 May 2013, Bangkok, Thailand.

**Mycologic aspects**

In Mucormycosis, *Rhizopus* spp. is the most common cause of human invasive fungal diseases while *Mucor* spp., *Rhizomucor* spp., *Absidia* spp., *Apophysomyces* spp., *Saksenaea* spp., *Cunninghamella* spp., *Cokeromyces* spp., and *Syncephalastrum* spp. are less frequently accounted for Genus *Cunninghamella* comprises of approximately sixteen species that are important in medical mycology and biotechnological process. *C. bertholletiae* is the only species that usually leads to fatal invasive disease in humans. However, other species have rarely been reported to be human pathogens, for example *C. echinulata* was linked to human infections in studies using molecular identification. It is a saprophytic, ubiquitous fungus that is found in soil, sewage, air, water and vegetation, especially in the Mediterranean and subtropical zones. It was first isolated from soil in Brazil by Stadel in 1911.[2] *Cunninghamella* colonies can grow rapidly and turn mature within 4 days in Sabouraud dextrose agar. The colonies appear cottony white to tannish-grey in color (Figure 1). The mycelium is 0.5-2 cm tall. Schell WA et al. demonstrated the species identification of *Cunninghamella* spp. by evaluation of temperature tolerance. *C. bertholletiae* is able to grow at a temperature as high as 45°C whereas *C. elegans* fails to thrive in temperatures over 40°C.[1] Microscopically, hyphae appear to be non-septate or sparsely septate with broad, branching, and erect

**Keywords:** *Cunninghamella bertholletiae,* zygomycosis

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sporangiophores. The hyphae may become more septate with age. The sporangiophores end in globose or pyriform-shaped vesicles which are covered by several one-celled sporangioles (Figure 2). Furthermore, chlamydoconidia and zygospores may also present.[1-3]

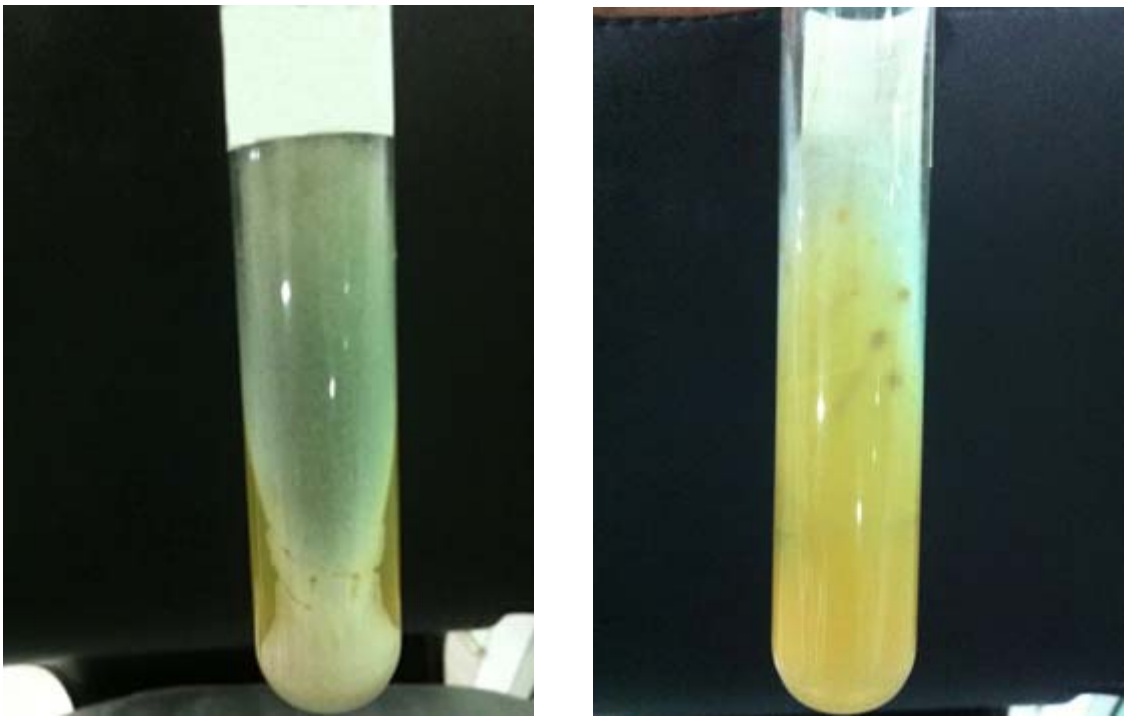

**Figure 1. White, cottony colonies of *C. bertholletiae* grow on Sabouraud dextrose agar.**

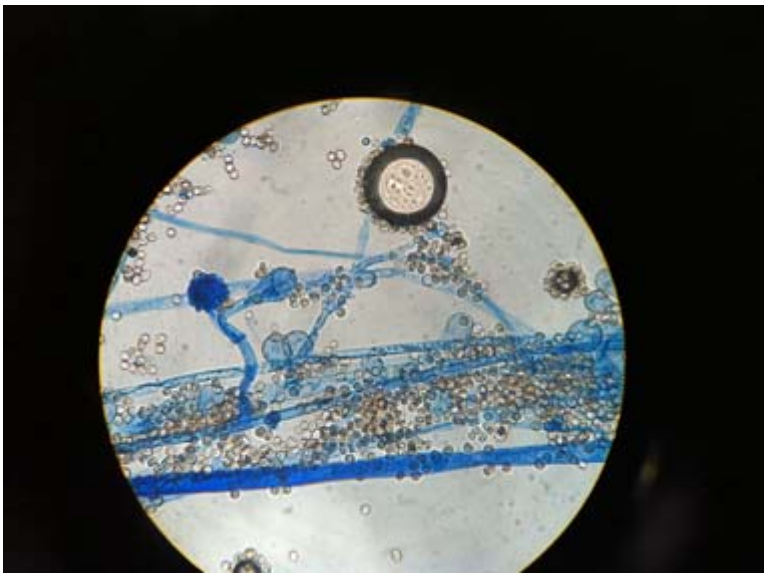

**Figure 2. Non-septate hyphae with broad, branching sporangiophores which end in globose and are covered by several one-celled sporangioles.**

**Diagnosis**

*Cunninghamella* spp. can be found as environmental contaminations. Interpretation of the culture result should be dependent upon the patient's clinical condition. Blood culture has rarely yielded this organism.[4] Conventional carbohydrate utilization is a very intricate and time consuming technique for species identification. From the previously reported cases, diagnosis was almost obtained from tissue cultures and histopathology. With state-of-the-art molecular technologies, identification of this organism by using amplification of internal transcribed spacer 1 (ITS1) and ribosomal RNA gene has been developing. The base pairs of ITS1 region was analyzed and compared with the reference strain in GenBank database.[5]

**Pathogenesis and risk factors**

*C. bertholletiae* is a rare cause of human mucormycosis, and particularly a more invasive disease in immunocompromised patients. It was first reported as human infection in 1958.[2] Inhalation of contaminated fungal spores from the environment has been speculated as a major source of transmission. Hence, the vast majority of this infection manifests in pulmonary disease, disseminated infection secondary to pulmonary disease, and rhino-orbito-cerebral infection. Another route of infection that has been proposed is direct inoculation from trauma. Additionally, probable nosocomial origin was reported in a patient who developed a gangrenous ulcer after undergoing closed reduction and cast for tibia fracture.[6] Skin and osteoarticular infection following direct inoculation and peritonitis after continuous ambulatory peritoneal dialysis have also been reported.[7-8]

After entering the host, macrophages attack fungal spores by means of phagocytosis and oxidative killing. Neutrophil plays an important role by using oxidative cytotoxic system to enhance fungal killing.[9] From previous *in vivo* and *in vitro* studies, the host defense mechanism against *Cunninghamella* spp. was different from *Aspergillus* spp. and other Mucorales. *C. bertholletiae* exhibited the greater resistance to human polymorphonuclear (PMN)-induced damage than *Rhizopus* spp. The larger spores of *Cunninghamella* spp. are the significant virulence factor that impedes the phagocytosis. These fungi could suppress interleukin-8 release and increase tumor necrosis factor alpha from neutrophils more than that of *Rhizopus* spp. These mechanisms diminished chemotactic signals and reduced recruitment of neutrophils.[10] Additionally, *C. bertholletiae* displayed a greater resistance to deferasirox than *Rhizopus* spp. that resulted in enhanced capacity for iron extraction from the host. This contributed to promotion of fungal growth and supported its pathogenesis *in vivo*.[2]

*C. bertholletiae* infection more commonly affects immunocompromised patients. More than 98% of patients coexisted with immunodeficiency states in order of frequency i.e. leukemia[11-14], bone marrow transplantation[15-17], solid organ transplantation[18-20], diabetes mellitus, nonmalignant hematologic disease[21], deferoxamine-based therapy[22], AIDS[8] and cirrhosis.[23] Only two cases were reported in immunocompetent patients.[24-25]

**Clinical presentation**

*C. bertholletiae* infection has a variety of clinical presentation like other Mucorales. Pulmonary infection is the most common site of infection because it is a primary portal of infection.

Disseminated infection occurs commonly in immunocompromised patients, particularly in patients with hematologic diseases, especially hematologic malignancy or organ transplantation, and has been the most common manifestation. A majority of disseminated cases were diagnosed postmortem. Clinical features are diverse and dependent on organ involvement. The affected organs that have been previously reported were lungs, heart, spleen, brain, kidneys, liver, thyroid gland, skin and soft tissue, and vertebra. Systemic symptoms such as fever, fatigue, and myalgia were frequently reported. Moreover, some cases developed sepsis and multi-organ failure.

In pulmonary infection, one-third of patients developed hemoptysis even though hyphal angioinvasion was identified from pathological findings. The heart was the second most commonly infected organ secondary to hematogenous or contiguous spreading such as involvement of coronary artery, endocardium, myocardium and pericardium. Rhino-orbito-cerebral infection was also found in a few cases. Central nervous system infection commonly presented with brain abscesses from dissemination, concurrent with endocarditis, or spreading from adjacent fungal rhino-sinusitis. Cutaneous and osteoarticular infection occurred following direct inoculation or disseminated infection. Typical cutaneous findings are necrotic lesions with creamy white exudates and granules or skin nodules.[2] A summary of previously reported *C. bertholletiae* infection was shown in Table 1.

**Treatment**

Invasive fungal infection usually has a fatal outcome and high mortality especially among immunocompromised patients. Upon clinical suspicion, empirical treatment with broad spectrum antifungal agents is recommended while waiting for definite diagnosis. In *vitro* studies showed terbinafine and posaconazole had lower MIC against *C. bertholletiae* 0.03-0.25 µg/mL and 0.06-1 µg/mL, respectively. The MIC of amphotericin B ranged from 0.25 to 4 µg/mL. Voriconazole, itraconazole, caspofungin and 5-flucytosine showed higher MIC levels i.e. 0.5->16 µg/mL, 0.125->64 µg/mL, 4->16 µg/mL and 32->64 µg/mL, respectively.[26-28] Amphotericin B deoxycholate(ABD) has been recommended as a standard antifungal agent for mucormycosis, but the efficacy is limited by its nephrotoxicity. Lipid formulations of amphotericin can be used in case of nephrotoxicity. However, the optimal dose and duration of these agents have still been unknown. Although terbinafine showed good *in vitro* efficacy, its pharmacokinetics has limited the clinical use. From two clinical studies, posaconazole 800 mg per day was used as salvage therapy in patients who were intolerant or refractory to standard antifungal treatment. The average duration of posaconazole ranged between 30 to 292 days, and the overall response rate ranged from 60 to 79%.[29-30] However, clinical studies of antifungal treatment for *C. bertholletiae* are limited, and only 33% of patients who received antifungal drugs survived.

In addition to antifungal treatment, surgical debridement of infected tissue could improve outcome. Fifty-seven percent of patients who suffered from *C. bertholletiae* infection recovered after undergoing surgical debridement, while solely 11% of the patients recovered by receiving antifungal therapy alone. Nevertheless, surgical intervention was limited in patients with some underlying conditions, multifocal infection, delayed diagnosis, and unstable condition.

Other modalities have been studied as adjunctive

**Table 1. Summary of reported cases of *Cunninghamella bertholletiae* infection.**

| Patient No. | Year report | Age, sex | Underlying condition | Immune status | Clinical presentation | Organ involvement | Treatment | Outcome | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1959 | 8,M | Lymphosarcoma | CMT, PRED | N/A | Vocal cord, lung, heart, GI tract | N/A | Dead | (21) |
| 2 | 1979 | 53,M | CLL | CMT | Fever | Lung | N/A | Dead | (32) |
| 3 | 1981 | 69,M | DM | IVMP | Gangrene right leg | Leg | ABD, Surgery | N/A | (21) |
| 4 | 1982 | 59,M | Hematopoietic dysplasia | N/A | N/A | Lung, liver | None | Dead | (21) |
| 5 | 1982 | 13,M | Hepatitis, aspergillosis | IVMP | N/A | Heart, kidney, spleen | None | Dead | (21) |
| 6 | 1983 | 70,M | Thalassemia, DM, hemochromatosis | Deferoxamine | N/A | Sinus, ears, orbit, brain | ABD 3 days | Dead | (21) |
| 7 | 1983 | 40,M | HT, ESRD, post KT | IVMP, AZA, PRED | Chest pain, dyspnea at 4 weeks after KT | Heart, lung, liver, spleen, GI tract | None | Dead | (33) |
| 8 | 1985 | 42,M | Thalassemia, splenectomy | azacytidine, neutropenia | Right pleurisy, skin lesion, arthralgia, lymphadenitis | Skin, pleura, lymph node | ABD | Survive | (21) |
| 9 | 1988 | 48,F | Myelodysplasia, splenectomy | Deferoxamine | Fever, cough, headache | Lung | ABD, surgery | Dead | (22) |
| 10 | 1988 | 19,F | Wilson's disease, livertransplant | IVMP, CSA | Fever, pneumonia | Lung, heart, thyroid, brain, mediastinum, thymus | ABD | Dead | (34) |
| 11 | 1988 | N/A | CLL | N/A | Pneumonia with PCP | Lung | N/A | Dead | (35) |
| 12 | 1989 | N/A | AIDS | N/A | N/A | Skin, joint | N/A | N/A | (8) |

NOTE: ABD, amphotericin B deoxycholate; ABLC, amphotericin B lipid complex; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; AZA, azathioprine; BMT, bone marrow transplantation; CAPD, continuous ambulatory peritoneal dialysis; CHF, congestive heart failure; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CMT, chemotherapy; CSA, cyclosporine A; solumedrol, methylprednisolone; ESRD, end stage renal disease; F, female; FCZ, fluconazole; FSGS, focal segmental glomerulosclerosis; GI tract, gastrointestinal tract; GVHD, Graft-versus-host disease; IP, intraperitoneum; ITZ, itraconazole; IVMP, intravenous methylprednisolone; KT, kidney transplantation; LAMB, liposomal amphotericin B; M, male; MMF, mycophenolate; NB, nebulized; NHL, non-Hodgkin's lymphoma; N/A, data not available; PCP, *Pneumocystis jerovecii* pneumonia; PCZ, posaconazole; PRED, prednisolone; Ref., Reference; TBF, terbinafine; VCZ, voriconazole; 5-FC, flucytosine

**Table 1. Summary of reported cases of *Cunninghamella bertholletiae* infection (continued).**

| Patient No. | Year report | Age, sex | Underlying condition | Immune status | Clinical presentation | Organ involvement | Treatment | Outcome | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| 13 | 1990 | 61,M | Alcoholism | N/A | Pneumonia | Lung | ABD | Dead | (25) |
| 14 | 1990 | N/A | AML | N/A | N/A | Dissemination included thyroid gland | N/A | Dead | (36) |
| 15 | 1993 | 3,M | AML | CMT, neutropenia | N/A | Lung | ABD | Survive | (11) |
| 16 | 1993 | 7,M | Relapsed AML | CMT, neutropenia | N/A | Lung | ABD | Dead | (11) |
| 17 | 1994 | N/A | Leukemia | CMT, neutropenia | Pneumonia | Lung | N/A | Dead | (37) |
| 18 | 1994 | N/A | Leukemia | CMT, neutropenia | Pneumonia | Lung | N/A | Dead | (37) |
| 19 | 1994 | N/A | Leukemia | CMT, neutropenia | Pneumonia | Lung | N/A | Dead | (37) |
| 20 | 1997 | 63,M | DM, pulmonary fibrosis | N/A | N/A | Lung | N/A | Dead | (38) |
| 21 | 1998 | 16,F | ALL | Neutropenia | Fever, pleurisy, hemoptysis | Lung | ABD then ABLC, surgery | Survive | (39) |
| 22 | 1999 | 35,M | AML | Neutropenia | Pericarditis, cardiac failure | Pericardium, heart, lung, kidney, spleen | ABD then VCZ | Dead | (40) |
| 23 | 2000 | 60,F | ALL | Neutropenia | Massive hemoptysis | Lung | ABD then LAMB | Dead | (20) |
| 24 | 2000 | 51,M | ALL | Neutropenia | Fever, hemoptysis | Lung | LaMB | Dead | (20) |

NOTE: ABD, amphotericin B deoxycholate; ABLC, amphotericin B lipid complex; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; AZA, azathioprine; BMT, bone marrow transplantation; CAPD, continuous ambulatory peritoneal dialysis; CHF, congestive heart failure; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CMT, chemotherapy; CSA, cyclosporine A; solumedrol, methylprednisolone; ESRD, end stage renal disease; F, female; FCZ, fluconazole; FSGS, focal segmental glomerulosclerosis; GI tract, gastrointestinal tract; GVHD, Graft-versus-host disease; IP, intraperitoneum; ITZ, itraconazole; IVMP, intravenous methylprednisolone; KT, kidney transplantation; LAMB, liposomal amphotericin B; M, male; MMF, mycophenolate; NB, nebulized; NHL, non-Hodgkin's lymphoma; N/A, data not available; PCP, *Pneumocystis jerovecii* pneumonia; PCZ, posaconazole; PRED, prednisolone; Ref., Reference; TBF, terbinafine; VCZ, voriconazole; 5-FC, flucytosine

**Table 1. Summary of reported cases of *Cunninghamella bertholletiae* infection (continued).**

| Patient No. | Year report | Age, sex | Underlying condition | Immune status | Clinical presentation | Organ involvement | Treatment | Outcome | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| 25 | 2000 | 61,F | ADPKD S/P KT | IVMP, MMF, tacrolimus, basiliximab | Pneumonia | Lung | ABD, 5-FC then LAMB, NB ABD | Dead | (20) |
| 26 | 2000 | 55,M | NHL | CMT, PRED | Fever, pleurisy, hemoptysis | Lung | ABD then LAMB, ITZ | Survive | (20) |
| 27 | 2000 | 46,F | CML S/P BMT, splenectomy, GVHD | PRED, CSA, solumedrol | Severe pneumonia at 7 months after BMT | Lung, skin | LAMB | Dead | (17) |
| 28 | 2001 | N/A,M | S/P allogeneic BMT | N/A | N/A | Lung | ABD, surgery | Dead | (16) |
| 29 | 2002 | 48,F | FSGS S/P KT | Tacrolimus, MMF, PRED, OKT3 | CHF, lung cavity, leg cellulitis at 15 weeks after KT | Lung, heart, skin, brain, liver, spleen | None | Dead | (19) |
| 30 | 2004 | 54,M | DM S/P KT | Tacrolimus, PRED | Ulcerated skin nodule at 5 months post KT | Skin | Surgery, ITZ | Survive | (18) |
| 31 | 2004 | 54,F | ALL | Neutropenia | Severe pneumonia | Lung | ABD | Dead | (41) |
| 32 | 2004 | 44,M | ALL | N/A | Chest pain, dyspnea, right hemiparesis | Heart, lung, liver, brain, GI tract, spleen, kidney | ABD | Dead | (14) |
| 33 | 2004 | 32,M | Pure red cell aplasia | Steroid | Chest pain, right foot drop, Homer's syndrome | Heart | ABD, PCZ | Dead | (42) |
| 34 | 2005 | 68,M | DM, myelodysplasia | Desferrioxamine | Fever, pleurisy, left hemiparesis, skin infection | Skin, brain, heart, kidney, spleen | None | Dead | (43) |

NOTE: ABD, amphotericin B deoxycholate; ABLC, amphotericin B lipid complex; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; AZA, azathioprine; BMT, bone marrow transplantation; CAPD, continuous ambulatory peritoneal dialysis; CHF, congestive heart failure; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CMT, chemotherapy; CSA, cyclosporine A; solumedrol, methylprednisolone; ESRD, end stage renal disease; F, female; FCZ, fluconazole; FSGS, focal segmental glomerulosclerosis; GI tract, gastrointestinal tract; GVHD, Graft-versus-host disease; IP, intraperitoneum; ITZ, itraconazole; IVMP, intravenous methylprednisolone; KT, kidney transplantation; LAMB, liposomal amphotericin B; M, male; MMF, mycophenolate; NB, nebulized; NHL, non-Hodgkin's lymphoma; N/A, data not available; PCP, *Pneumocystis jerovecii* pneumonia; PCZ, posaconazole; PRED, prednisolone; Ref., Reference; TBF, terbinafine; VCZ, voriconazole; 5-FC, flucytosine

**Table 1. Summary of reported cases of *Cunninghamella bertholletiae* infection (continued).**

| Patient No. | Year report | Age, sex | Underlying condition | Immune status | Clinical presentation | Organ involvement | Treatment | Outcome | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| 35 | 2005 | 42,M | AML S/P BMT, GVHD | Steroid MMF, sirolimus | Pneumonia at 26 days after BMT | Lung | ABD | Dead | (15) |
| 36 | 2006 | 57,F | ALL | N/A | Fever | Lung | LAMB, PCZ, surgery | Survive | (44) |
| 37 | 2007 | 17,F | Relapsed ALL | CMT, neutropenia | N/A | Lung | ABD, surgery | Survive | (13) |
| 38 | 2008 | 10,M | Mature B-ALL | CMT, neutropenia | N/A | Lung | ABD | Dead | (45) |
| 39 | 2008 | 15,F | AML S/P BMT, GVHD | PRED | Pneumonia at 6 months after BMT | Lung | ABD | Dead | (46) |
| 40 | 2008 | 60,F | Scleroderma | N/A | Hemoptysis, dyspnea | Lung | ABD, ITZ | Survive | (47) |
| 41 | 2010 | 16,F | Multi-visceral transplant, short bowel syndrome, ganglioneuroma | Immunosuppressive drug, neutropenia | N/A | Skin | ABD, surgery | Survive | (48) |
| 42 | 2010 | 10,F | Relapsed AML post BMT, GVHD | Immunosuppressive drug | N/A | Lung | ABD | Dead | (49) |

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**Table 1. Summary of reported cases of *Cunninghamella bertholletiae* infection (continued).**

| Patient No. | Year report | Age, sex | Underlying condition | Immune status | Clinical presentation | Organ involvement | Treatment | Outcome | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| 43 | 2010 | 50,F | T cell ALL | CMT | Discomfort in chest and upper extremities, right hemiparesis | Lung, brain, skin, heart, liver, GI tract, spleen | ABD | Dead | (50) |
| 44 | 2011 | 42,M | AML S/P BMT | Neutropenia | Fever, pleurisy at 10 days after BMT | Lung, heart, brain, kidney, liver, spleen, thyroid | LAMB | Dead | (50) |
| 45 | 2012 | 53,F | AML S/P cord blood transplant, GVHD | Neutropenia, PRED | Fever, hemoptysis at 13 days after transplant | Lung | LAMB | Dead | (51) |
| 46 | 2012 | 68, N/A | B cell lymphoma | CMT, PRED | Necrotic skin lesions at leg | Skin | VCZ | Survive | (52) |
| 47 | 2012 | 52,M | ESRD S/P KT, graft rejection, on CARD | | Fever, vomit, abdominal pain | Peritoneum | Remove catheter, FCZ and ITZ via IP | Survive | (53) |
| 48 | 2013 | 22,F | Hemophagocytic lymphohistiocytosis | CMT, PRED | Fever and lung nodule at 22 days after CMT | Lung, intestine | FCZ | Dead | (54) |
| 49 | 2013 | 17,N/A | ALL post BMT, BVHD | Neutropenia | Septic emboli | Lung, skin, bone marrow | LAMB, PCZ, TBF | Dead | (55) |

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therapies, for example Segal et al conducted a study of hyperbaric oxygen therapy (HBO) in addition to surgical resection and effective antifungal agents in 14 patients. Unfortunately, it was difficult to conclude the exact benefit of HBO therapy.[31] Treatment of coexisting conditions such as hyperglycemia, ketoacidosis, neutropenia, or discontinuation of iron chelating agents or immunosuppressive drugs are also necessary to combat infection.

## CONCLUSION

*C. bertholletiae* is a fatal opportunistic fungal infection in immunocompromised patients. Clinical manifestations vary from localized infection to disseminated disease, and are indistinguishable from other invasive fungal infections. Successful treatment requires high clinical suspicion, microbiologic diagnosis from clinical specimen, and prompt effective antifungal treatment including adequate surgical treatment.

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