CASE REPORT

Pulmonary Zygomycosis caused by Cunninghamella bertholletiae in a child with acute lymphoblastic leukemia*

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Abstract

Zygomycosis is an invasive mycotic disease caused by fungi of the class Zygomycetes. Infections caused by zygomycetes, are known for their difficulty of diagnosis and treatment. *Cunninghamella bertholletiae (Cb)*, is a saprobic fungus commonly found in the soil of temperate climates. Pulmonary infections caused by *Cb* are being identified with increasing frequency among patients on immunosuppressive therapy, and these infections usually have a fatal outcome. We present a rare case of pulmonary zygomycosis caused by *Cb* in a 10 year – old male child with acute lymphoblastic leukemia. In spite of intensive antifungal chemotherapy (iv liposomal amphotericin B 7 mg/Kg once daily) following clinical diagnosis, he died of pulmonary failure. Hippokratia 2008; 12 (1): 43-45

Key words: cunninghamella bertholletiae, acute lymphoblastic leukemia; pulmonary zygomycoses;

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Invasive fungal infections are serious and often fatal complications in immunocompromised patients. *Candida* species, *Aspergillus* species, and *Cryptococcus neoformans* are the most common pathogens of these infections[1,2]. *Cb* (class Zygomycetes, order Mucorales) is a saprobic fungus in the soil of temperate climates. Pulmonary infections caused by this fungus are being identified with increasing frequency among patients on immunosuppressive therapy, and these infections usually have a fatal outcome. Including the present case only six children with *C. b* have been described thus far[3].

Case report

A 10 year-old, previously healthy, boy was admitted to our department, on 25th November 2001 with a suspicion of acute leukemia. He has a two weeks history of fatique and fever (38.5° C) and he was pale and tired. The laboratory findings on admission are presented on Table 1. More than 80% of peripheral blood leucocytes (WBC of 118x103/μl) were lymphoblasts.The patient's bone marrow aspirate on 26th November 2001 showed 86% lymphoblasts of FAB-L3 morphology and mature-B-cell acute lymphoblastic leukemia (ALL) immunophenotype (CD19+ and CD20+). The treatment was started on 28th November accorting to 903 –MRC chemotherapy protocol whith is one of the main protocol of the UKCCSG NHL trial and is used for the patients with B- cell leukemia. He received 2 courses of this protokol: a) CHOP on 28th November (Cyclophosphamide, Vincristine, Doxorubicin iv, day 1, prednisolone per os, days 1-7 and intrathecal Methotrexate and Hydrocortisone, day 1, b) COPADM 1 on 13th December 2001 (Cyclophosphamide IV, days 2-4, Vincristine iv, day 1, Doxorubicin iv, day 2, prednisolone per os, days 1-5 and intrathecal Methotrexate and Ara – C, day 1).

Table 1. Labotatory findings on admission

WBC (x 10^3/μl)		118	Creatinin	mg/dl	0.9
GR	%	13	Uric acid	mg/dl	8.9
Blasts	%	86	Ca	mg/dl	8.22
HCT	%	21	P	mg/dl	41
Hb	g/dl	6.8	K	mmol/L	4.5
PLT	x 10^3/μl	15	Na	mmol/L	142
SGOT	IU/L	91	LDH	IU/L	493
SGPT	IU/L	51			
Urea	mg/dl	34	Albumin	g/dl	4.8

He was supported by GCSF, packed red cells and platelets but nonetheless presented with severe anaemia (Hb: 5 g/dl), thrombocytopenia (Platelets < 10.000) and prolonged neutropenia (granulocytes < 200/μl) as well as fever (38.5° C).

The patient who had already been immunosuppressed for a considerable period of time due to polychemotherapy, was treated with a combination of a beta lactam antibiotic (ceftriaxone 100 mg/kg once daily) and an aminoglycoside (netilmicin: 7.5 mg/kg once daily). The patient had negative blood cultures for bacterial pathogens but 3 days later from the starting of the empirical antibacterial treatment, he presented with cough, chest pain, dyspnoea, crepitations on auscultation, and hypoxia. The laboratory

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Table 2 . *Laboratory findings during the supportive care period*

WBC	400	200	600	1,500	70
Hb	5	4.3	3.7	3.8	2.6
PLT	6,000	13,000	6,000	32,000	18,000
Urea	93	130	148	150	199
Creatinine	1,4	1,7	1,9	2,3	2,7

findings during the period of supportive care because of myelosuppresion are listed on table 2. Chest X-ray revealed findings compatible with possible aspergillosis (Figure 1). He received additional liposomal amphoteri-

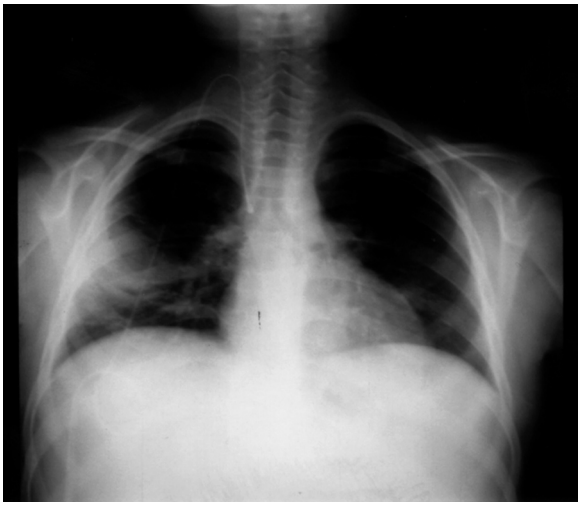

Figure 1. Chest X-ray findings

cin B (7 mg/kg once daily). Twenty four hours later the patient presented serious dyspnoea and hypoxia (PO_2 75%) and was transferred to the intensive care Unit of our Hospital, where he was incubated. Cultures of two bronchial protected specimens revealed a fast growing mold which was identified as *Cb*. The patient deteriorated with diffuse hemorrhage and heart failure, and he finally died.

The cultures from the two bronchial protected specimens on Sabouraud dextrose agar incubated at 30°C, on Blood agar incubated at 37°C and on Chocolate agar incubated at 37°C, yielded the mold *Cb*. The colony of the mold had very rapid growth, cottony texture, white to gray color on the surface (Figure 2); reverse pale, and good growth at 45°C. The microscopic appearance of the colony revealed hyphae hyaline, broad, aseptate or with very infrequent septa, sporangiophores branched, terminating in a swollen vesicle with 1 – spored sporangiolia (each becoming a sporangiospore) covering the entire surface, sporangiospores spherical to ovoidal (Figure 3).

Discussion

Cb is a rare cause of zygomycosis in humans often associated with trauma and immunosuppression. *Cb* is the only species of the genus known to cause disease both in humans and animals[4,5]. Only six children including the

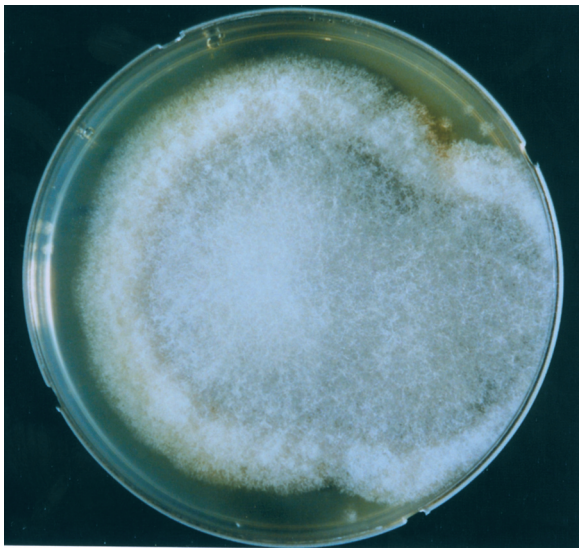

Figure 2. Macroscopic appearance of C. bertholletiae

present case have been described with *Cb* infection (Table 3). Leukemia is the most common underlying illness. With one exception all children reported to date have had a pulmonary focus of disease[3,7]. Only two children out of six survived. The patients who survived pulmonary infection underwent lobectomy and received therapy with amphotericin B.

The disease caused by *Cb* tends to follow a malignant course ending in death. Pulmonary mucormycosis is lethal, especially in patients with hematologic conditions; The mortality rate approaches 75%[9]. Antifungal treatment alone is known to be inferior to combined medical and surgical therapy for patients with pulmonary zygomycoses[10]. However, surgical intervetion might not be possible in patients with hematologic malignacies because of bone marrow depression or multilobular lung involvement. On the other hand the diagnosis of a fungal infection can be initially missed in quite a few cases and where positive

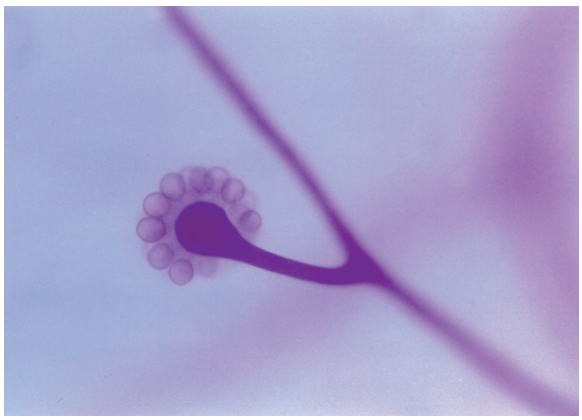

Figure 3. Microscopic morphology of *Cunninghamella bertholletiae* showing simple sporangiophore forming a swollen, terminal vesicle around which single-celled, globose to ovoid, sporangiola develop on swollen denticles (Lactofuchsin staining, X400)

Table 3. Cases of Cunninghamella infections in pediatric patients

Year/Ref	Age (Yr)	Sex	Undelying Disease	Involved organs	Amphotericin B	Outcome
/[6]	8	Male	Acute leukemia	lungs, spleen, gastrointestinal track, brain, kidneys	No	Died
/[7]	13	Male	Hepatitis, nephritis, anemia, congestive heart failure	heart, spleen, kidney	No	Died
/[8]	3	Male	Acute megakaryoblastic leukemia	Lungs	Yes	Survived
/[8]	7	Male	Acute lymphocytic leukemia	Lungs	Yes	Died
/[3]	16	Female	Acute lymphocytic leukemia	Lungs	Yes	Survived
Present case	10	Male	Acute lymphoblastic leukemia	Lungs	Yes	Died

cultures of clinical specimens confirm the cause of infection after death.

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