

Zygomycosis: A report of eleven cases and a review of the Brazilian literature

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Summary

Eleven cases of zygomycosis (mucormycosis) observed throughout an eighteen year period (1982–2000) have been reviewed. The most important demographic and clinical data of seven patients were tabulated. The remaining four are related as illustrative cases. Seven patients presented with the pulmonary form of the disease; two patients presented with pulmonary manifestations associated with sinusitis; and two patients presented with the rhinocerebral form. Predisposing conditions, in decreasing order of frequency, were diabetes mellitus (6), renal transplantation (2), associated with pancreas-kidney transplantation and diabetes (1), bone marrow aplasia (1), and chronic obstructive lung disease treated with corticosteroids (1). The diagnoses were based on the detection of characteristic zygomycetous hyphae in tissue. The causative organism was isolated and identified in only four cases; three were due to *Rhizopus arrhizus*, and one to *Absidia corymbifera*. In addition the Brazilian literature on zygomycosis is reviewed.

Key words

Zygomycosis, Mucormycosis, Zygomycetes, *Rhizopus arrhizus*, *Absidia corymbifera*

Zigomicosis: informe de once casos y revisión de la literatura brasileña

Resumen

Se revisaron once casos de zigomicosis (mucormicosis) observados durante un periodo de dieciocho años (1982-2000). Los datos demográficos y clínicos más importantes de siete pacientes fueron tabulados. Los cuatro restantes fueron reportados como casos ilustrativos. Siete pacientes presentaron la forma pulmonar de la enfermedad, dos pacientes presentaron manifestaciones pulmonares asociadas con sinusitis; y dos pacientes presentaron la forma rinocerebral. Fueron condiciones predisponentes, en este orden de frecuencia: diabetes mellitus (6), trasplante renal (2), trasplante pancreas-riñón en paciente con diabetes (1), aplasia de médula ósea (1) y enfermedad pulmonar obstructiva crónica tratada con corticosteroides (1). El diagnóstico fue hecho por la detección de las hifas características en el tejido; sin embargo, el aislamiento y la identificación del organismo causal fue hecha solamente en cuatro casos: *Rhizopus arrhizus* (3) y *Absidia corymbifera* (1). Se comenta la revisión de la literatura brasileña sobre zigomicosis.

Palabras clave

Zigomicosis, Mucormicosis, Zigomicetes, *Rhizopus arrhizus*, *Absidia corymbifera*

Zygomycosis is a group of opportunistic infections caused by species of zygomycetes in the order Mucorales. The agents of zygomycosis (or mucormycosis) normally reside in the environment. The abundant airborne sporangiospores may be inhaled or contaminate wounds or burns of patients with predisposing conditions, such as diabetes or immunosuppression, or trauma, and cause a spectrum of diseases. Zygomycosis results from the invasion of the major blood vessels by the fungus, which grows in their walls and lumen causing thromboembolism, ischemia, and necrosis of the tissues. The infection is usually acute and rapidly progressive; however, chronic forms and colonization of some the sinuses and other anatomic sites have been reported [1,2].

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Aceptado para publicación el 4 de Febrero de 2002

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Apdo. 699, E-48080 Bilbao (Spain)
1130-1406/01/10.00 Euros

Table 1. Clinical data on seven cases with zygomycosis.

Case No.	Patient Age, Sex	Clinical form/Lesions	Predisposing conditions	Agent	Therapy /Outcome
1	44, M	Pulmonary/Lobar consolidation	Lung transplantation	Zygomycetes	None/Died
2	69, M	Pulmonary/ Lobar consolidation and pleural effusion	Chronic obstructive pulmonary disease and corticoids	<i>Rhizopus arrhizus</i>	Amphotericin B /Died
3	41, F	Pulmonary/Lobar consolidation and pleural effusion	Diabetes mellitus	<i>Rhizopus arrhizus</i>	Amphotericin B /Died
4	55, F	Pulmonary/Multiple masses	Diabetes mellitus	Zygomycetes	Amphotericin B /Alive
5	25, M	Rhinocerebral/Cephalic structures	Diabetes mellitus	Zygomycetes	Amphotericin B and surgery/Alive
6	62, F	Rhinocerebral/Cephalic structures	Diabetes mellitus	Zygomycetes	Amphotericin B /Alive
7	48, M	Pulmonary/Lobar consolidation and paranasal sinus	Politraumatism	Zygomycetes	Amphotericin B /Died

In the paper we present the data of 11 cases of zygomycosis collected throughout an eighteen year period in Porto Alegre, RS (Brazil). We also review the Brazilian literature on the mycosis.

CLINICAL MATERIALS AND METHODS

Eleven patients in our records fulfilled the histological criteria for a diagnosis of zygomycosis: the finding of broad, nonseptate hyphae, branching at right angles in smears or in cut sections of tissues. Data on seven of these cases are presented in Table 1. The remaining four cases are related as illustrative cases.

REPRESENTATIVE CASES

Case 8. A six year-old Caucasian boy with bone marrow aplasia had been treated with prednisolone for four weeks. His blood findings showed a leukocyte count of $1000/\text{mm}^3$ and an absolute neutrophil count of 500. Complaining about fever, fatigue and epistaxis, he was hospitalized, received many blood transfusions and wide spectrum antibiotics (doxycycline and cefuroxime). After some days of improvement, he became febrile and presented nasal obstruction. An X-ray revealed opacity of the maxillary sinus and the ethmoidal cells. A punctiform skin lesion appeared near the right mammilla, which was initially erythematous but enlarged and became necrotic in three days, measuring 5 cm in diameter. A hematic bubble involved the lesion (Figure 1). A needle aspiration specimen, obtained from the lesion, microscopically revealed many wide nonseptate hyaline hyphae with right angle branching (Figure 2). *Absidia corymbifera* was identified in the isolated cultures. A Chest roentgenogram showed an extensive consolidation in the right upper lobe (Figure 3). The patient received amphotericin B (0.5 mg/kg increased to 1 mg/kg) and vancomycin. In spite of this treatment the pulmonary lesion worsened and a consolidation in the left lung appeared (Figure 4). The skin lesion increased abruptly with destruction of the pectoral muscles exposing the ribs. The patient presented then hemoptysis, necrotic sputum, signs of pulmonary insufficiency, shock, and died.

Comments: Several cases of cutaneous zygomycosis lesions have been described. The majority of which were due to local factors (traumatic implantation, especially in patients with burns). The remaining cases were associated with additional forms of zygomycosis, among which pulmonary disease was less common [3].



Figure 1. Case 8, necrotic lesion (5cm) on the thoracic wall of a patient with bone marrow aplasia.

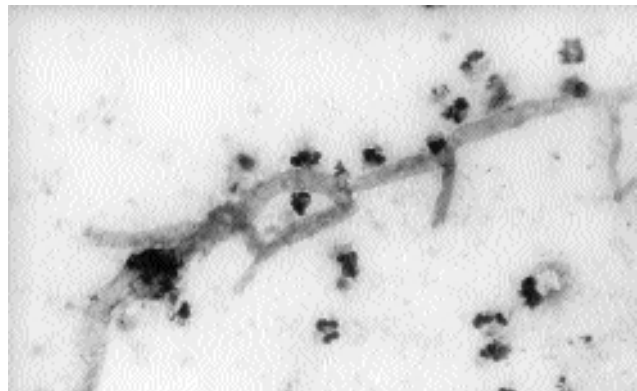


Figure 2. Case 8, showing broad, nonseptate hyphae branching at right angles from the skin lesion of the figure 1.



Figure 3. Case 8, chest X-ray showed an extensive consolidation in the right upper lobe.

Case 9. This patient, a 44 year-old man, with an acute myelogenous leukemia had been treated with daunorubicin, cytarabine, and prednisone. He sought medical attention with fever and oral candidosis. An abdominal examination disclosed enlargement of the liver and spleen. White blood cell count $2 \times 10^4/\text{mm}^3$ (90% blasts), platelets 1.5×10^3 ; bone marrow aspirate was hypercellular with 100% blast cells. A chest roentgenogram had showed consolidation with a cavitating lesion in the right lower lobe (Figure 5). A transbronchial biopsy by fiberoptic bronchoscope had been performed. Hyphae consistent with those of a zygomycete were detected in the direct examination of biopsied tissue but no growth was obtained in culture. Fluconazole, administered for candidosis, was changed to intravenous amphotericin B and antibacterial therapy (ceftriaxone, gentamicin, and oxacillin) were added.

The patient serum contained a high titer of specific antibody to zygomycete antigens (1:800, measured by enzyme immunoassay). After clinical and radiological improvement, the patient was submitted for a lobectomy. Macroscopic examination of the excised lobe revealed parenchymal abscesses and infarctions; the subsegmental bronchus and artery were partially necrotic; subsegmental branch of the basal artery was occluded by a thrombus. Microscopic examination of cut sections stained with hematoxylin-eosin (H&E) and Gomori metenamine silver (GMS) disclosed extensive tissue invasion by wide, nonseptate hyphae, branching at right angles, especially in the wall and lumen of the thrombosed artery. Fungal culture of the surgical specimen was negative. Treatment with amphotericin B continued after the surgery (total dose 1.6 g). The patient was discharged in good conditions but died by leukemia.

Comments. This case illustrates the importance of the association of antifungal therapy with surgical procedures [4].

Case 10. Two years ago (from 1995), a 55 year-old man was submitted to a renal transplant, and he was using immunosuppressive drugs (prednisone and ciclosporine). The patient was also a diabetic and used insulin. He was admitted to a hospital complaining about cough with purulent expectoration, fever, cyanosis, nausea, and vomiting. He received amikacin and cephalexin. Six days later the patient was transferred to our hospital in diabetic ketoacidosis.

The admission laboratory findings were as follow: glycemia 474 mg/dl; uremia 77 mg/dl; qualitative ketonemia positive. The serologic test for cytomegalovirus was positive. Chest X-ray showed, in the right upper lobe, consolidation, in which CT scan revealed a central cavitation (Figure 6). A biopsy specimen from a necrotic area of the right upper lobe was obtained by fiber optic bronchoscopy. Broad non-septate hyphae invading the bronchial wall were seen. *Rhizopus arrhizus* was isolated in culture. Doses of the immunosuppressive drugs were lowered and amphotericin B administration was started. Fifteen days later, when the patient would be went to surgery, he presented a massive hemoptysis and died.

Autopsy findings included intense hemorrhagic aspect of the lung, respiratory tree fully of coagula, the posterior segmental bronchus of the upper right lobe communicated with a large cavitation (7x5 cm) with necrotic aspect and alveolar hemorrhage. Hyphae of the zygomycete were detected microscopically in the thrombosed vessels and in the wall of the cavitation.

Comments. In this renal transplanted, diabetic patient with ketoacidosis, immunosuppressive therapy,



Figure 4. Case 8, pulmonary lesion worsened, appearing consolidation in the left lung.

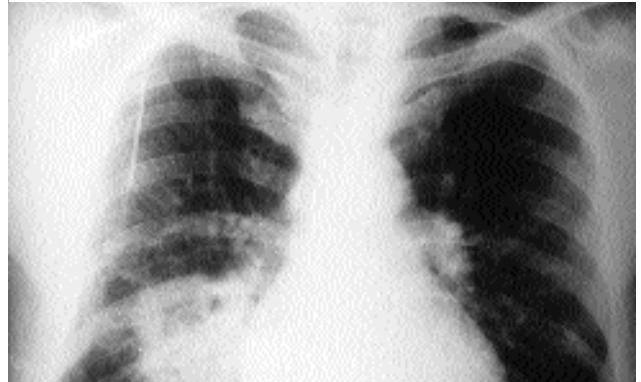


Figure 5. Case 9, chest roentgenogram showing consolidation with cavitating lesion in the right lower lobe.



Figure 6. Case 10, chest CT scan showing consolidation with central cavitation in the right upper lobe.



Figure 7. Case 11, the CT-guided fine needle transthoracic biopsy.

Table 2. Summary data of data from 27 reported cases of zygomycosis in Brazil (1959-1996).

Ref.	Year	Patient Age	Sex	Clinical form	Predisposing	Diagnosis	Isolated agent
[11]	59	10m	F	Gastrointestinal	Malnutrition	Necropsy	-
[11]	59	1y	F	Gastrointestinal	Malnutrition	Necropsy	-
[12]	70	23y	M	Rhinocerebral	Diabetes	Necropsy	-
[13]	73	8m	M	Meningoencephalitis	-	Necropsy	-
[14]	75	38y	F	Gastric	-	Necropsy	-
[15]	77	46y	M	Rhinocerebral	Diabetes	Surgery	-
[16]	80	15y	M	Rhinocerebral	Diabetes	Surgery	-
[17]	81	35y	F	Gastric	Corticoids	Surgery	-
[18]	82	50y	M	Gastric	Pacemaker	Necropsy	-
[19]	82	29y	F	Rhinocerebral	Diabetes	Biopsy	-
[20]	83	15y	F	Rhinocerebral	Diabetes	Biopsy	<i>Rhizopus arrhizus</i>
[21]	85	57y	F	Rhinocerebral	Diabetes	Biopsy	-
[21]	85	49y	M	Rhinocerebral	Diabetes	Biopsy	-
[22]	85	61y	M	Subcutaneous	Diabetes	Biopsy	<i>Rhizopus arrhizus</i>
[23]	86	44y	M	Disseminated	Diabetes	Surgery	<i>Rhizopus arrhizus</i>
[24]	86	38y	M	Gastric colonization	Gastric ulcer	Biopsy	<i>Rhizopus arrhizus</i>
[25]	86	20y	F	Disseminated	Acidosis	Biopsy	-
[26]	87	9y	M	Cutaneous	-	Biopsy	-
[27]	87	47y	M	Cerebral	Diabetes	Necropsy	-
[28]	87	39y	M	Rhinocerebral	Alcoholism	Surgery	-
[29]	88	23y	F	Rhinocerebral	Diabetes	Biopsy	<i>Rhizopus arrhizus</i>
[30]	89	39y	F	Chronic sinusitis	Corticoids	Surgery	-
[31]	90	34y	M	Disseminated	Leukemia	Biopsy	<i>Rhizomucor pusillus</i>
[32]	93	61y	M	Nasal septum	Diabetes	Biopsy	-
[33]	95	19y	M	Cutaneous*	Leukemia	Biopsy	<i>Absidia corymbifera</i>
[34]	96	6y	M	Rhinocerebral	-	Biopsy	-
[35]	96	62y	M	Pulmonary	Leukemia	Surgery	<i>Cunninghamella bertolletiae</i>

y = year, m = month, M = male, F = female, * 15 months previously the patient presented pulmonary zygomycosis

and concomitant cytomegalovirus infection was predisposed to bronchovascular zygomycosis. The bronchoscopic biopsy provided a prompt diagnosis. The surgery, an urgent problem [5] unfortunately was delayed.

Case 11. An associated pancreas-kidney transplantation was performed in a 33 year old woman at the end stage of a renal disease secondary to diabetic nephropathy. The post operative course was complicated by *Candida albicans* peritonitis, cytomegalovirus esophagitis and Gram negative bacilli pneumonia in the left upper lobe. After two week-treatment with fluconazole, ganciclovir and imipenem the patient had improved. Twenty days later a chest roentgenogram did not show any pulmonary lesion in the left upper lobe; however, it revealed a solitary nodule adjacent to the pleura at the right upper lobe. A CT guided fine needle transthoracic biopsy obtained (Figure 7), and from this specimen, hyphae of a zygomycete were detected. Amphotericin B was started. The patient was discharged from the hospital but continued to use amphotericin B as an out patient.

Comments. CT scans revealed significant unsuspected abnormalities in 26% of patients with zygomycosis [6]. The CT-guided fine needle transthoracic biopsy may provide additional benefit in early management of the mycosis.

This case has emphasized the importance of a surgery. As other similar cases have been healed with AMB and surgery or only with a lobectomy [7].

DISCUSSION

The main clinical forms of zygomycosis are rhinocerebral, pulmonary, cutaneous, gastrointestinal and disseminated [1,2,8-10]. However, the disease may also

manifest itself as an isolated involvement of internal organs: brain, kidney, and heart. Mucorales may also be a colonizer of anatomic sites such as stomach, vagina, external ear, sinus, or they be cause of allergic disease [1].

In the period 1959-1996, 27 cases of infection by Mucorales could be gathered in the Brazilian literature (Table 2). Eleven cases are added in the present report (Table 1 and cases 8-11). All the major clinical forms of the mycosis have been observed in Brazil. However, cases of the rhinocerebral form predominated in earlier reports, and the pulmonary form was more common in the present series. Diabetes has been the most frequent predisposing condition to the mycosis. The infection of isolated organs/sites have been reported rarely. However, two of these cases deserve to be pointed out: 1) an ulceration of the nasal septum [32]; and 2) a case of chronic sinusitis caused by an association of a Mucoraceae and an *Aspergillus* spp. [30].

The diagnosis of zygomycosis was based on histopathological examination of surgical or biopsied specimens. Isolation and identification of the agent was obtained in 12 of the 38 observed cases. As usual, the rapidly growing, thermotolerant *Rhizopus arrhizus* was most frequent. The pulmonary form of the mycosis is difficult to diagnose due to the several non-specific radiological patterns presented and the usual necessity of an invasive approach to obtain clinical material to examine [4,6,36].

We are grateful to the kindness of Dr. Leo Kaufman (CDC, Atlanta, GA, USA) for performing the serologic test in case 2.

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