Pulmonary *Aspergillus niger* intracavitary colonization. Report of 23 cases and a review of the literature

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Summary

In this study we have compared clinical data obtained from 40 reported cases of pulmonary *Aspergillus niger* intracavitary colonization in the literature and those of our series 23 cases. Additionaly six of our cases have been summarized. Our findings revealed a similar occurrence of male sex, active tuberculosis, diabetes mellitus, systemic oxalosis, and lethal outcome in both groups. In conclusion, *A. niger* is not the most frequent causative agent of saprophytic aspergillosis neither is the most pathogenic species of *Aspergillus.* Despite that, when pulmonary *A. niger* intracavitary colonization is associated with diabetes the prognosis is generaly poor, probably due to acute oxalosis.

Key words

Aspergillus niger, Oxalosis, Diabetes mellitus, Aspergillosis, Intracavitary colonization, Lung.

Colonización intracavitaria pulmonar por *Aspergillus niger*. Relato de 23 casos y revisión de la literatura

Resumen

En este estudio comparamos los datos clínicos obtenidos de 40 casos clínicos de colonización intracavitaria pulmonar por *Aspergillus niger* presentados en la literatura con nuestra serie de 23 casos. Además seis de nuestros casos clínicos son presentados de forma resumida. Los resultados indicaron una ocurrencia similar de sexo masculino, tuberculosis activa, diabetes mellitus y oxalosis sistemica y curso fatal en los dos grupos. Aunque *A. niger* no es el agente más frecuente de colonización intracavitaria pulmonar, ni el más patógeno del género *Aspergillus,* cuando está asociado a diabetes tiene un pronóstico grave, probablemente por una severa oxalosis aguda.

Palabras clave

Aspergillus niger, Oxalosis, Diabetes mellitus, Aspergilosis, Colonización intracavitaria, Pulmón

Despite being an ubiquitous fungus living indoors and outdoors, *Aspergillus niger* is not the most frequent agent of aspergillosis [1,2]. Compared with *Aspergillus fumigatus*, *A. niger* has larger conidia [3], which remain attached to each other and also to the substract [4]; therefore, their dispersion by air and arrival to the alveoli are more difficult than those of *A. fumigatus*. In addition, *A. niger* is less virulent to mice than *A. fumigatus* and *A. flavus* [5], probably because it is less termotolerant [3] and its conidia are readily ingested by the alveolar macrophages [6].

A. niger may cause allergic bronchopulmonary disease, invasive aspergillosis or may be a colonizer of natural or preformed cavities of the human body [7,8].

As an allergen, *A. niger* causes extrinsic alveolitis [9,10] and allergic bronchopulmonary aspergillosis [11-14]. Occasionally or exceptionally *A. niger* has been implicated as an agent of invasive disease: keratitis [15], endophthalmitis [16], primary cutaneous aspergillosis [17,18], necrotizing otitis [19], necrotizing tracheobronchitis [20], was isolated from blood culture [21,22], in several occasions was involved in chronic [23-31] or acute necrotizing pulmonary aspergillosis [32-46]. Sometimes associated with hospital construction [47] *A. niger* has also been recovered from cutaneos lesions of burned patients [48], diabetics [49], bone marrow recipients [50,51], postoperative wounds [52], and, in an unusual case, *A. niger* infected a silicone mammary implant [53]. However, *A. niger* is more frequently a colonizer of natural [54-60] or preformed cavities [61] of the human body.

This paper will tabulate the clinical and laboratory variables seen in our series of 23 patients with pulmonary *A. niger* intracavitary colonization and compare them with 40 other cases gathered from the literature. Additionally it will repot in some detail six ot the most characteristic cases in our series.

MATERIAL AND METHODS

In the last eighteen years (1977-1995) a series of 23 cases of *Aspergillus niger* intracavitary colonization were diagnosed in our service. The diagnoses were all ascertained by a combination the following criteria: 1) radiological features of fungus ball; 2) detection of antibo-

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dies to *A. niger* by immunodiffusion test; 3) presence of characteristic conidial head in the direct examination of specimen obtained from the intracavitary mass and/or in sections of the ball; and, 4) isolation of *A. niger* from specimens obtained by transthoracic needle aspiration, surgery or necropsy.

Searching the literature we have assembled another series of 40 cases *A. niger* intracavitary colonization which were compared to ours regarding clinical and laboratory findings. The diagnosed of these 40 cases were based on specific criteria described in the reviewed papers. Diagnoses were confirmed by mycological examination of sputum in 26 cases, bronchial secretion in 9, lung resection in 6, lung biopsy in 3, and in 9 cases by necropsy. Immunodiffusion to *A. niger* was referred positive in 7 patients. Skin test reactivity to *A. niger* antigenic extracts was documented in two patients [62,63].

RESULTS

From the 23 pulmonary *Aspergillus niger* intracavitary colonizations included in our series two cases have been published elsewhere [27,64]. Twenty one patients (91.3%) were males and the mean age was 45.7 years, ranging from 23-66 years (Table 1). Nineteen patients (82.6%; 95% Confidence Interval: 53.5-90.3) had tuberculosis, which in four was active at the moment of the fungal colonization diagnosis. Seven patients (30.4%) were diabetics. Cough, expectoration, and hemoptysis were the most frequent complaints (Table 2). The chest roentgenographic findings were typical of fungus ball in seventeen patients (73.9%). Associated conditions and laboratory variables can be seen in tables 3 and 4. Serum precipitins (immunodiffusion) against *A. niger* antigens were positive in 18 patients (78%). Among the 8 patients with positive fungal identification 6 (75%) presented an *A. niger* conidial head in tissue sections.

Table 1. Clinical features of 23 patients with pulmonary *Aspergillus niger* intracavitary colonization.

Nº	Age-Sex	Underlying condition	Symptoms, course prior to diagnose	Therapy	Outcome
1	26 M	Cured TB	C, S, WL,6m	Cavernostomy	Cured
2	60 M	Cured TB	Hf, D, 2m	None	Died
3	49 M	Active TB, DM	HM, C, S, WL, 3m	None	Died
4	56 M	Cured TB, COPD	Hs, C, S, D, 4y	None	Died
5	49 M	Active TB, COPD	Hs, C, S, D, 1y	None	Died
6	47 M	Cured TB	HM,C, S, D,WL, 5m	Radiotherapy	Improve
7	38 M	Active TB, COPD	Hf, C, S, D, 1y	Radiotherapy	Died
8	46 M	Cured TB, DM	HM, C, S, 1m	Lobectomy	Cured
9	59 M	COPD, lung cancer	C, S, WL, 5m	None	Unknow
10	56 M	Cured TB	Hs, C, S, 4y	None	Died
11	34 M	Active TB	HM, C, S, F, 1m	None	Unknown
12	66 M	Cured TB, DM	H s, C, S, WL,1m	None	Died
13	43 M	Cured TB	H s, C, S,F, WL, 1y	None	Cured
14	36 M	Cured TB, renal failure	C, S, WL, 10m	None	Unknown
15	53 M	Cured TB	HM, C, S, D, 2m	None	Improved
16	23 M	Cured TB	Hs, C, S, D, 6m	None	Unknow
17	55 M	Cured TB	C, S, WL, 2w	None	Died
18	38 M	Cured TB	Hs, C, S, WL, 3m	Segmentectomy	Cured
19	51 F	Bronchiectasis, DM	HM, C, S,D, 1m	Lobectomy	Cured
20	34 M	Cured TB, DM	HM, C, S,WL, 2m	Segmentectomy	Cured
21	37 F	Lung abscess	HM, C, S,WL, 1m	None	Unknown
22	30 M	Cured TB, DM	Hs, C, S, F, 5y	Lobectomy	Cured
23	66 M	DM	Hs, C, S, 1m	Segmentectomy	Cured

TB, tuberculosis; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; C, cough; S, sputum; F, fever; WL, weight loss; D, dyspnea; H, hemoptysis: s - slight, M - masive, f - fatal.

Table 2: Comparison of signs and symptoms observed in patients reported in the literature with our patients affected by *Aspergillus niger* intracavitary colonization.

Symptoms and signs	Literature (n=40)		Our series (n=23)	
	n	% (95% CI)*	n	% (95% CI)
Cough and expectoration	26	65.0 (48.3-78.9)	21	91.3 (70.5-98,5)
Hemoptysis	22	55.0 (38.7-70.4)	19	82.6 (60.5-94.3)
Fever	13	32.5 (19.1-49.2)	5	21.7 (8.3-44.2)
Weight loss	6	15.0 (6.2-30.5)	10	43.5 (24.0-65.1)
Weakness	3	7.5 (2.0-21.5)	6	26.1 (11.1-48.7)
Cachexia	2	5.0 (0.9-18.2)	2	8.7 (1.5-29.5)
Breathlessness	4	10.0 (3.3-24.6)	7	30.4 (14.1-53.0)
Cyanosis	1	2.5 (0.1-14.7)	1	4.3 (0.2-24.0)
Chest pain	1	2.5 (0.1-14.7)	4	17.4 (5.7-39.6)
Anorexia	4	10.0 (3.3-24.6)	0	0.0 (0.0-17.8)

* 95% Confidence interval

Table 3. Associated conditions with *Aspergillus niger* intracavitary colonization.

Condition	Literature (n=40)		Our series (n=23)	
	n	% (95% CI)*	n	% (95% CI)
Pulmonary oxalosis	10	25.0 (13.2- 41.5)	6	26.1 (11.1- 48.7)
Systemic oxalosis	1	2.5 (0.1-14.7)	1	4.3 (0.2-24.0)
Acute invasive aspergillosis	2	5.0 (0.9-18.2)	0	0.0 (0.0-17.8)
Chronic necrotizing pulmonary aspergillosis	4	10.0 (3.3-24.6)	2	8.7 (1.5-29.5)
Uremia	1	2.5 (0.1-14.7)	1	4.3 (0.2-24.0)
Allergic bronchopulmonary aspergillosis	1	2.5 (0.1-14.7)	0	0.0 (0.0-17.8)

* 95% confidence interval

Treatment and outcome variables (Table 5). Fourteen patients did not receive any treatment; 7 patients underwent surgical resection; the remaining two patients (Cases 6 and 7) with massive hemoptysis, had no conditions for surgery and were submitted to radiotherapy.

Ten patients survived: 7 cured by surgery, one by spontaneous lysis of the ball (Case 13) and the remaining two patients improved slightly their clinical codition. Eight patients died: two as a result of hemoptysis (Cases 2 and 7), one of systemic oxalosis (Case 17), and the remaining five patients of unknown cause. Five patients were lost to follow-up.

REPRESENTATIVE CASES

Case 1. A 26 year-old, white, male patient (LAS) with a past history of treated tuberculosis, began to present cough with purulent expectoration, adynamia, anore-

Table 4. Laboratory variables of *Aspergillus niger* intracavitary colonization.

Diagnostic finding	Literature (n=40) n	% (95% CI)*	Our series (n=23) n	% (95% CI)
A. niger immunodiffusion	7	17.5 (7.9-33.4)	18	78.3 (55.8-91.7)
Sputum				
Fragments of fungus ball	-		1	4.3 (0.2-24.0)
A. niger isolation	26	65.0 (48.3-78.9)	(**)	
Bronchial secretion				
A. niger isolation	9	22.5 (11.4-38.9)		-
Transthoracic biopsy				
A. niger conidial head	-		1	4.3 (0.2-24.0)
A. niger isolation	2	5.0 (0.9-18.2)	2	8.7 (1.5-29.5)
Tissue section				
Collection procedure				
Biopsy	1	2.5 (0.1-4.7)	2	8.7 (1.5-29.5)
Surgery	6	15.0 (6.2-30.5)	6	26.1 (11.1-48.7)
Necropsy	9	22.5 (11.4-38.9)	1	4.3 (0.2-24.0)
Fungal identification				
A. niger conidial head	8	20.0 (9.6-36.1)	5	21.7 (8.3-44.2)
A. niger isolation	15	37.5 (23.2-54.2)	4	17.4 (5.7-39.5)

(*) 95% Confidence interval
(**) Isolation of *A. niger* from sputum was not utilized as a diagnostic criteria in our serie.

Table 5. Treatment and outcome in *Aspergillus niger* intracavitary colonization.

	Literature (n=40) n	% (95% CI)*	Our series (n=23) n	% (95% CI)
Treatment (**)				
Surgery				
Monaldi drainage	1	2.5 (0.1-14.7)	-	
Cavernostomy	-		1	4.3 (0.2-24.0)
Lobectomy	6	15.0 (6.2-30.5)	6	26.1 (11.1-48.7)
Pneumonectomy	2	5.0 (0.9-18.2)	-	
Antifungal therapy				
Topical treatment	3	7.5 (2.0 -21.5)	1	4.3 (0.2-24.0)
Systemic administration				
Amphotericin B	2	5.0 (0.9-18.2)	1	4.3 (0.2-24.0)
Fluconazole	1		-	
Radiotherapy	-		2	8.7 (1.5-29.5)
None	6	15.0 (6.2-30.5)	14	60.9 (38.8-79.5)
Not record	15	37.5 (23.2-54.2)	-	
Outcome				
Survived	14	35.0 (21.1-51.7)	10	43.5 (23.9-65.2)
Died	11	27.5 (15.1-44.1)	8	34.8 (17.2-57.2)
Unknown	12	30.0 (17.1-46.7)	5	21.7 (8.3-44.2)

(*) 95% Confidence interval
(**) Possible more than one

xia and weight loss. A chest roentgenogram (April/76) revealed fibroatelectatic retraction and necrotic cavities in both upper lobes of the lung. In spite of the absence of acid-fast bacilli in his sputum, he received tuberculostatics and corticosteroids. Then, dark fragments (2-4mm) began to be expectorated; a network of hyaline, septate, dichotomously branched hyphae were disclosed on microscopic examination of these fragments; no fungal growth was obtained by inoculation of these fragments onto Sabouraud dextrose agar (SAB).

Another radiogram (June/76) revealed an homogeneous mass (5 cm in diameter) within the lung cavity. In January 1977, he was submitted to a cavernostomy and a fungus ball was removed. Histologic sections of the ball revealed similar aspects as those of the expectorated fragments; sections of the resected tissue shown hyaline septated, branched hyphae invading the lung parenchyma; isolates from the culture of the ball and also from pulmonary tissue inoculated onto SAB were identified as *A. niger*. The patient received amphotericin B intravenously during one month; after discharge he remained well for nine years.

Comment: Occasionally, chronic necrotizing pulmonary aspergillosis may result from the invasion of the lung parenchyma by an *A. niger* colonizing a lung cavity. In this patient perhaps it was a consequence of corticosteroids therapy.

Case previously reported [27].

Case 3. This patient (TKF) was a 49 year-old, white, alcoholic man, who had a history of chronic pancreatitis and diabetes. He complained of cough with purulent expectoration, asthenia and weight loss for three months. The patient was undernourished; laboratory examination revealed blood glucose 242 mg/dl; blood urea 29 mg/dl; and creatinine 0,85 mg/dl; a chest X-ray showed, among other abnormalities, a thick walled cavitary lesion with a mass inside it in the upper segment of the right lower lobe (Figure 1). The patient presented a voluminous hemoptysis. Microscopic examination of the specimen obtained by an aspirative transthoracic needle biopsy revealed hyaline, septate hyphae, yeast-like cells and calcium oxalate crystals; *A. niger* and *Candida albicans* grew up in culture. Calcium oxalate crystals were also found in sputum examination.

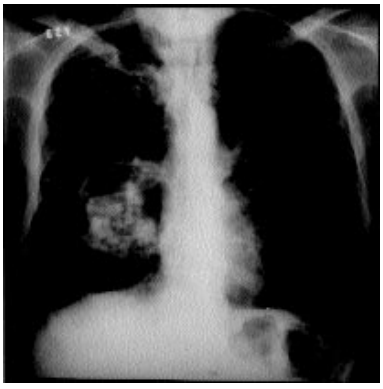

Figure 1. Case 3 - Chest roentgenogram of a patient in which coexist active tuberculous lesions with a fungus ball.

A bronchoscopy was done. A chronic suppurative inflammatory reaction was seen in histologic sections of the biopsied bronchial mucosa; calcium oxalate crystals were also seen. Smears of the aspirated material from the cavity revealed acid fast bacilli that later on grew in culture and were identified as *Mycobacterium tuberculosis*. In spite of treatment the patient died. No necropsy was performed.

Comment: Viable elements of *M. tuberculosis* and *A. niger* were present inside the same cavitary lesion, a very unusual finding. However, the association of *A. niger* and *C. albicans* in a cavity, although uncommon, has already been reported [29].

Case 8. In April 1980 MAM, a 46 year-old, white, diabetic man left the hospital cured from his tuberculosis. Then he began to present cough, purulent expectoration, and voluminous hemoptysis, in spite of the general good

state of the patient. A chest roentgenogram shown a cavitary lesion in the right upper lobe surrounded by an apparently healthy area of the pulmonary parenchyma. The thick-walled cavity was partially filled with an irregular mass; there was also thickening of the adjacent pleura (Figure 2). Five sputum samples did not reveal acid-fast bacilli, however, calcium oxalate crystals were seen.

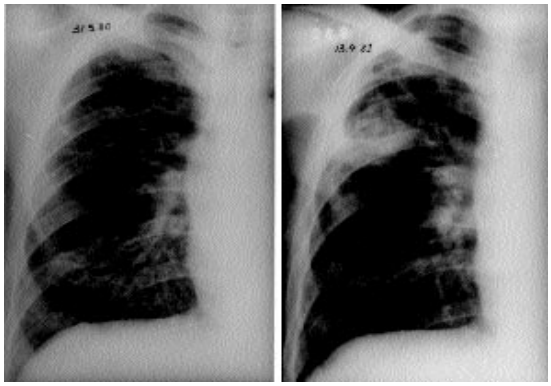

Figure 2. Case 8 - Chest x-ray showing a fungus ball within a cavitation that appear in a healthy lung parenchyma.

Fastened blood glucose was 444 mg/dl. Microscopic examination of a transcutaneous pulmonary aspirative biopsy revealed septate branched hyphae and calcium oxalate crystals (Figure 3). *A. niger* was isolated in cultures incubated at 37°C. Immunodiffusion test showed a preciptation band for *A. niger*. The patient was submitted to a right upper lobectomy. Parietal pleura was thickened and strongly attached to its dorsal surface. Segmentary and subsegmentary bronchi presented mucoid material and/or dark clamps in their lumen. At the junction of the three segments of the right upper lobe there was an irregular thick walled cavity, dark red and with granulomatous areas. Inside this cavity there was a fungus ball, which was drained by at least one anterior subsegmentary bronchus. Microscopically the intracavitary mass was composed by septate branched hyphae, some characteristic conidial heads of *A. niger* and numerous crystals of calcium oxalate. Gomori Methenamine Silver (GMS) stained sections revealed also massive fungal invasion of the cavity wall. *A niger* was isolated from intracavitary material. The patient was discharged assyntomatically but, he returned 45 days later presenting respiratory symptoms and evidence of acid-fast bacilli in sputum. He was treated with tuberculostatics at ambulatory level.

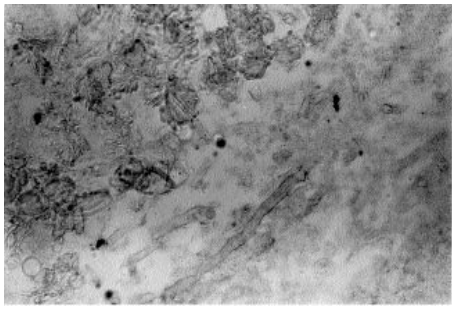

Figure 3. Case 8 - Hyaline hyphae and calcium oxalate cristals obtained by needle aspirative biopsy (Papanicolau x 100).

Comments: This patient acquired a fungus ball during hospitalization. The absence of a previous pulmonary cavity and the invasion of the parenchyma characterize chronic necrotizing aspergillosis [24]. The surgical removal of pulmonary parenchyma invaded by *A. niger* hyphae probably prevented the development of oxalosis.

Case 17. At admission, MDF, 55 year-old, black, male with a past history of cured tuberculosis complained of diarrhea, anorexia, weight loss, and adinamy. A chest radiograph (2/Feb/79) revealed multiple cavities in the right upper lobe and slight thickening of the adjacent pleura. Renal function was considered normal. The patient received symptomatic treatment. Soon he presented dispnea, intense sudoresis, cough with expectoration, abdominal pain, and cachexia. Another chest radiograph (5/Mar/79) showed a cavity with vague borders in the right upper lobe and an increase thickening of the pleura. Sputum was negative for acid-fast bacilli. Glucose was 90 mg/dl, urea was 112 mg/dl, and creatinine was 3.66 mg/dl. The patient died in the following day.

Necropsy revealed the right upper lobe almost completely occupied by a large cavity. In addition, there were necrotic and hemorragic areas with retracted tissue and vessels. The cavity lumen contaminated a friable and pasty brown mass. Histologic section of the cavity wall revealed necrosis, fibrosis and granulomatosis. Granulomatous tissue was infiltrated with leukocytes. There were calcium oxalate crystals in some of these cells and also in the exsudate. Adjacent areas revealed leukocyte infiltration, thrombosis and calcium oxalate crystals. The kidneys were congested. Histopatological sections of the subcapsular cortex revealed scattered areas of tubular atrophy, glomerular sclerosis, and interstitial lymphoid infiltration. There was also fibrosis and thickening of small and median renal arteries. Calcium oxalate crystals were found in the lumen of the renal tubules.

The microscopic examination of the pulmonary cavity showed septate hyphae and a considerable number of calcium oxalate crystals. Cultures at 25 and 37°C were positive for *A. niger*.

Comments: It is surprising the development of the pulmonary intracavitary fungal mass and the patient's death in 17 days. A by-product of the fungus has impaired the renal function, leading to acute systemic oxalosis. Nime and Hutchins [57] reported a very similar case; but death occurred sooner, on the twelfth day of the patient's admission. Previously reported [64].

Case 19. A 51 year-old, Caucasian woman (LCR) was under treatment for diabetes and pneumonia. In the last two weeks she presented fever and cough with purulent expectoration. A chest X-ray revealed a cavitary lesion at the site of the consolidation. One month later, another X-ray disclosed an irregular mass within the cavitation. A fiberoptic bronchoscopy was performed because she presented hemoptysis; the bleeding site was not detected; and, microbiological examination of bronchial secretion was inconclusive, The patient was submitted to a lobectomy. A cavity containing a clotty dun-colored material was observed. In the excised lobe histological examination of this material revealed hyaline, septate, branched hyphae, many calcium oxalate crystals and characteristic conidial heads of *A. niger* (Figure 4). The patient remains well in the two years follow-up.

Comment: The association of a bacterial necrotizing pneumonia and *A. niger* fungus ball affecting a diabetic patient has already been described [65].

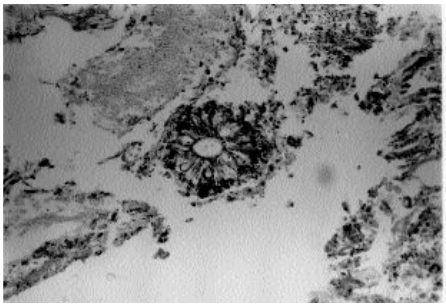

Figure 4. Case 19 - Histologic section of a fungus ball. Note typical conidial head of *A. niger* (HE x 64).

Case 20. The patient AVF, was a 34 year-old Caucasian male. He had diabetes and had had tuberculosis. In the last two months he presented hemoptysis. A chest roetgenogram revealed a cavitation in the upper segment of lower left lobe and within it a mass. Acid-fast bacilli were not disclosed in many sputum samples; however, many hyaline, septate, branched hyphae and calcium oxalate crystals were observed in 10% potassium hydroxide preparation mounting; *A. niger*. was isolated in culture; immunodiffusion for *A. niger* did not reveal any precipitin band. Blood glucose 440 mg/dl; blood urea 38 mg/dl and creatinine 1.7 mg/dl. The patient was submitted to a resection of the affected lung segment. A mass was seen within a cavitation (Figure 5). Histological sections revealed that the mass was composed of hyphae and some calcium oxalate crystals; a suppurative reaction and a palisade granulomata was observed in the wall of the cavitation; and tuberculoid granulomata with caseous necrosis was seen in the lung parenchyma. In the mycological examination of the intracavitary mass hyaline, septate, branched hyphae, characteristic conidial head of *A. niger* and calcium oxalate crystals were seen. *A. niger* was again isolated in culture. The patient recovered.

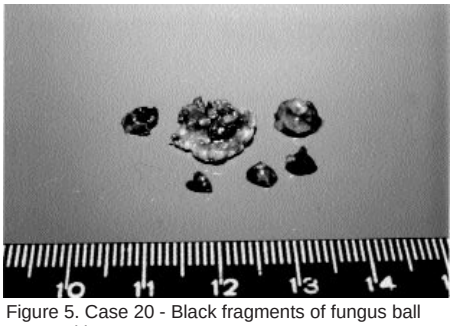

Figure 5. Case 20 - Black fragments of fungus ball removed by segmentectomy. .

Comment: The presence of calcium oxalate crystals in sputum or bronchial specimens is an evidence of aspergillosis and, probably a fungus ball. These findings are seen even before any radiological evidence [66]. On the other hand the presence of crystals and isolation of aspergillus from sputum samples occurs in 70% of the patients [66].

REVIEW OF THE LITERATURE

A search of the literature revealed 40 cases of pulmonary *A. niger* intracavitary colonization, distributed in thirty two publications [6,23,26,28,29,39,45,57,65-87]. Nime & Hutchins [57] and Utz *et al.* [28] reported two cases each, and Farley *et al.* [66] reported five cases. In some reports the cases were not individualized: Daly *et al.* [88] one case; Varkey & Rose [89] three cases; and Tomlison & Sahn [99] six cases. In one case [79], *Aspergillus* head was confused with *Syncephalastrum* [91]. The ages of 37 patients, ranged from 15 to 78 years, with a median of 52.7 years; but it was not recorded in three cases [6,75,78]. There were 32 male patients (84,2%) and 6 female patients; sex was not recorded in two cases [75,78]. Eleven patients (27.5%; 95% CI: 15.2-43.5) had tuberculosis [6,23,45,66,77,80,81,85,86], which was active in one case [63]. Five patients (12.5%) had diabetes mellitus [26,65,66,70] and four patients (10%) underwent corticotherapy [29,73,74]. The most frequent complaints were cough, expectoration, and hemoptysis (Table 2). Dystrophic oxalosis was the main associated condition (Table 3). Laboratory findings are given in table 4.

Treatment and outcome (Table 5). Nine patients underwent surgical resection; ten other patients underwent a medical therapy, which consisted of potassium iodide [28,69,71], or antifungal instillation into the cavity [67,73,86]. Among the 25 patients followed-up, 11 died; but only one of them was submitted to surgery, pneumonectomy [45].

DISCUSSION

A case-control study of *A. niger* (Cases) and *A. fumigatus* (Controls) was carried out by Severo [61]. Association of *A. niger* infection with male patients, nosocomial infections, active tuberculosis, diabetes mellitus or a lethal outcome were statistically significant. In addition, systemic oxalosis or the presence of calcium oxalate crystals in sputum were only observed in patients with *A. niger* infections. The association of diabetes with aspergillosis and oxalosis (60%) was statistically significant ($p < 0,001$) when compared to aspergillosis and oxalosis associated with non-diabetic patients (13%). Data of this series of 23 cases and 40 cases collected from the literature are showed in tables 1 to 5. Initially there were no substantial demographic differences in the series. In table 2 it can be seen that there were no statistically significant differences regarding pulmonary symptomatology and complaints ($p>0.05$). Although reported in both groups, tuberculosis was statistically more common in our series as a predisposing factor than in the literature (82,6% and 27,5%, respectively; $p<0.05$). Regarding associated conditions there were no statistically significant differences. However, dystrophic oxalosis was by far the most common associated condition reported in both series.

Farley *et al.* [66] has suggested that diabetes contributes to the production of oxalate crystals. The acidophilic character of *A. niger* [92] and low pH necessary for oxalic acid production [93], as a by-product of an enzymatic oxalate decarboxylation [94] suggests that the association of the fungus and the disease results from the acidotic tendency of diabetes. This hypothesis is supported by some reported cases: 1) Nime & Hutchins' case [57] number one, a patient with acidosis that presented an acute fatal systemic oxalosis; 2) Metzger *et al.*'s case [65] relating the detection of oxalate crystals in the pleural fluid with pH 5,9 of a patient with *A. niger* infection; 3) Reyes & Rippon's case [49] dealing with a double fungal infection by acidophilic fungi in a diabetic patient with tissue necrosis of the foot, *A. niger* and *Mucor* spp; 4) Johnson *et al.*'s case showing a case of cutaneous infection with *Rhizopus oryzae* and *A, niger* following bone marrow transplantation [50]; and, 5) Gramacho's thesis (1995) with experimental *A. niger* infection in animals

showing that the metabolic acidosis is a risk factor to aspergillosis by *A. niger* [95].

This study tends to support the hypothesis that patients with pulmonary *A. niger* intracavitary colonization are adversely affected by diabetes mellitus, probably dependent on the tendence to acidosis of these patients. We also observed a positive association between *A. niger* and active tuberculosis and lethal outcome. Finally, we suggested that the diagnostic and therapeutic approaches must be different for each group of *Aspergillus.*

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