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 of 23 cases. Additionally 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 generally 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

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 sistémica 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 substrate [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 cutaneous 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 report in some detail six of 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-
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 diagnosis of these 40 cases was 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 nine 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.

**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 condition. 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, anorexia, fever, and weight loss. Mycological examination of sputum was positive for *A. niger*. Bronchial secretion and bronchial biopsy were positive for *A. niger* with conidial head in the direct examination. Hemoptysis occurred on the fifth day of hospitalization, and radiological examination of the chest showed a lesion with characteristics of fungus ball. A diagnosis of acute invasive pulmonary aspergillosis was made. Surgical resection was performed, and the patient died on the fifth post-operative day. Autopsy showed *A. niger* conidial head in the direct examination, as well as necrotizing pneumonia and spontaneous lysis of the fungus ball.

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

<table>
<thead>
<tr>
<th>No</th>
<th>Age-Sex</th>
<th>Underlying condition</th>
<th>Symptoms, course prior to diagnosis</th>
<th>Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26 M</td>
<td>Cured TB</td>
<td>C, S, WL, 6m</td>
<td>Cavernostomy</td>
<td>Cured</td>
</tr>
<tr>
<td>2</td>
<td>60 M</td>
<td>Cured TB</td>
<td>Hf, D, 2m</td>
<td>None</td>
<td>Died</td>
</tr>
<tr>
<td>3</td>
<td>49 M</td>
<td>Active TB, DM</td>
<td>HM, C, S, WL, 3m</td>
<td>None</td>
<td>Died</td>
</tr>
<tr>
<td>4</td>
<td>56 M</td>
<td>Cured TB, COPD</td>
<td>Hs, C, S, D, 4y</td>
<td>None</td>
<td>Died</td>
</tr>
<tr>
<td>5</td>
<td>49 M</td>
<td>Active TB, COPD</td>
<td>Hs, C, S, D, 1y</td>
<td>None</td>
<td>Died</td>
</tr>
<tr>
<td>6</td>
<td>47 M</td>
<td>Cured TB</td>
<td>HM,C, S, D, WL, 5m</td>
<td>Radiotherapy</td>
<td>Improve</td>
</tr>
<tr>
<td>7</td>
<td>38 M</td>
<td>Active TB, COPD</td>
<td>Hf, C, S, D, 1y</td>
<td>Radiotherapy</td>
<td>Died</td>
</tr>
<tr>
<td>8</td>
<td>46 M</td>
<td>Cured TB, DM</td>
<td>HM, C, S, 1m</td>
<td>Lobectomy</td>
<td>Cured</td>
</tr>
<tr>
<td>9</td>
<td>59 M</td>
<td>COPD, lung cancer</td>
<td>C, S, WL, 5m</td>
<td>None</td>
<td>Unknown</td>
</tr>
<tr>
<td>10</td>
<td>56 M</td>
<td>Cured TB</td>
<td>Hs, C, 4y</td>
<td>None</td>
<td>Died</td>
</tr>
<tr>
<td>11</td>
<td>34 M</td>
<td>Active TB</td>
<td>HM, C, S, F, 1m</td>
<td>None</td>
<td>Improved</td>
</tr>
<tr>
<td>12</td>
<td>66 M</td>
<td>Cured TB, DM</td>
<td>Hs, C, S, WL, 1m</td>
<td>None</td>
<td>Died</td>
</tr>
<tr>
<td>13</td>
<td>43 M</td>
<td>Cured TB</td>
<td>Hs, C, S, F, WL, 1y</td>
<td>None</td>
<td>Died</td>
</tr>
<tr>
<td>14</td>
<td>36 M</td>
<td>Cured TB, renal failure</td>
<td>C, S, WL, 10m</td>
<td>None</td>
<td>Unknown</td>
</tr>
<tr>
<td>15</td>
<td>53 M</td>
<td>Cured TB</td>
<td>HM, C, S, D, 2m</td>
<td>None</td>
<td>Unknown</td>
</tr>
<tr>
<td>16</td>
<td>23 M</td>
<td>Cured TB</td>
<td>Hs, C, S, D, 6m</td>
<td>None</td>
<td>Unknown</td>
</tr>
<tr>
<td>17</td>
<td>55 M</td>
<td>Cured TB</td>
<td>C, S, WL, 2w</td>
<td>None</td>
<td>Died</td>
</tr>
<tr>
<td>18</td>
<td>38 M</td>
<td>Cured TB</td>
<td>Hs, C, S, WL, 3m</td>
<td>Segmentectomy</td>
<td>Cured</td>
</tr>
<tr>
<td>19</td>
<td>41 M</td>
<td>Bronchiectasis, DM</td>
<td>HM, C, S, D, 1m</td>
<td>Lobectomy</td>
<td>Cured</td>
</tr>
<tr>
<td>20</td>
<td>34 M</td>
<td>Cured TB, DM</td>
<td>HM, C, S, WL, 2m</td>
<td>Segmentectomy</td>
<td>Cured</td>
</tr>
<tr>
<td>21</td>
<td>37 F</td>
<td>Lung abscess</td>
<td>HM, C, S, WL, 1m</td>
<td>None</td>
<td>Unknown</td>
</tr>
<tr>
<td>22</td>
<td>30 M</td>
<td>Cured TB, DM</td>
<td>Hs, C, S, F, 5y</td>
<td>Lobectomy</td>
<td>Cured</td>
</tr>
<tr>
<td>23</td>
<td>66 M</td>
<td>DM</td>
<td>HM, C, S, 1m</td>
<td>Segmentectomy</td>
<td>Cured</td>
</tr>
</tbody>
</table>

| 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: massive; I: fatal.

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

<table>
<thead>
<tr>
<th>Symptoms and signs</th>
<th>Literature (n=40)</th>
<th>% (95% CI)*</th>
<th>Our series (n=23)</th>
<th>% (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough and expectoration</td>
<td>26</td>
<td>65.0 (48.3-78.9)</td>
<td>21</td>
<td>91.3 (70.5-98.5)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>22</td>
<td>55.0 (38.7-70.4)</td>
<td>19</td>
<td>82.6 (60.9-94.3)</td>
</tr>
<tr>
<td>Fever</td>
<td>13</td>
<td>32.5 (19.1-49.2)</td>
<td>5</td>
<td>21.7 (8.3-44.2)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>6</td>
<td>15.0 (6.2-30.5)</td>
<td>10</td>
<td>43.5 (24.0-65.1)</td>
</tr>
<tr>
<td>Weakness</td>
<td>3</td>
<td>7.5 (2.0-21.5)</td>
<td>6</td>
<td>26.1 (11.4-48.7)</td>
</tr>
<tr>
<td>Cachexia</td>
<td>2</td>
<td>5.0 (0.9-18.2)</td>
<td>2</td>
<td>8.7 (1.5-29.5)</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>4</td>
<td>10.0 (3.3-24.6)</td>
<td>7</td>
<td>30.4 (14.1-53.0)</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>1</td>
<td>2.5 (0.1-14.7)</td>
<td>1</td>
<td>4.3 (0.2-24.0)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1</td>
<td>2.5 (0.1-14.7)</td>
<td>4</td>
<td>17.4 (5.7-39.6)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1</td>
<td>10.0 (3.3-24.6)</td>
<td>0</td>
<td>0.0 (0.0-17.8)</td>
</tr>
</tbody>
</table>

* 95% Confidence interval

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

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

* 95% confidence interval

[105]
A. niger immunodiffusion & n % (95% CI) & A. niger immunodiffusion & n % (95% CI) \\
A. niger conidial head & n % (95% CI) & A. niger conidial head & n % (95% CI) \\
A. niger isolation & n % (95% CI) & A. niger isolation & n % (95% CI) \\
A. niger conidial head & n % (95% CI) & A. niger conidial head & n % (95% CI) \\
A. niger isolation & n % (95% CI) & A. niger isolation & n % (95% CI) \\

(*) 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.

<table>
<thead>
<tr>
<th>Treatment (**)</th>
<th>Literature (n=40)</th>
<th>Our series (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>n % (95% CI)</td>
<td>n % (95% CI)</td>
</tr>
<tr>
<td>Monaldi drainage 1</td>
<td>2.5 (0.1-14.7)</td>
<td>-</td>
</tr>
<tr>
<td>Cavernostomy    -</td>
<td>1.0 (0.0-14.7)</td>
<td>-</td>
</tr>
<tr>
<td>Lobectomy       6</td>
<td>15.0 (6.2-30.5)</td>
<td>6</td>
</tr>
<tr>
<td>Pneumonecomy     2</td>
<td>5.0 (0.9-18.2)</td>
<td>-</td>
</tr>
<tr>
<td>Antifungal therapy</td>
<td>n % (95% CI)</td>
<td>n % (95% CI)</td>
</tr>
<tr>
<td>Topical treatment 3</td>
<td>7.5 (2.0-21.5)</td>
<td>1</td>
</tr>
<tr>
<td>Systemic administration</td>
<td>5.0 (0.9-18.2)</td>
<td>1</td>
</tr>
<tr>
<td>Amphotericin B 2</td>
<td>5.0 (0.9-18.2)</td>
<td>1</td>
</tr>
<tr>
<td>Fluconazole 1</td>
<td>8.7 (1.5-29.5)</td>
<td>-</td>
</tr>
<tr>
<td>Radiotherapy    -</td>
<td>60.9 (38.8-79.5)</td>
<td>14</td>
</tr>
<tr>
<td>None            6</td>
<td>15.0 (6.2-30.5)</td>
<td>1</td>
</tr>
<tr>
<td>Not record      15</td>
<td>37.5 (23.2-54.2)</td>
<td>-</td>
</tr>
<tr>
<td>Outcome</td>
<td>n % (95% CI)</td>
<td>n % (95% CI)</td>
</tr>
<tr>
<td>Survived        14</td>
<td>35.0 (21.1-51.7)</td>
<td>10</td>
</tr>
<tr>
<td>Died            11</td>
<td>27.5 (15.1-44.1)</td>
<td>8</td>
</tr>
<tr>
<td>Unknown         12</td>
<td>30.0 (17.1-46.7)</td>
<td>5</td>
</tr>
</tbody>
</table>

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

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. 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 tuberculostatic and corticosteroids. Then, dark fragments (2-4 mm) began to be expectorated; a network of hyaline, septate, dichotomously branched hyphae were disclosed on microscopic examination of these fragments; no fungal identification 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 showed 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.

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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. 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 tuberculostatic and corticosteroids. Then, dark fragments (2-4 mm) began to be expectorated; a network of hyaline, septate, dichotomously branched hyphae were disclosed on microscopic examination of these fragments; no fungal identification 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 showed 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 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. 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 precipitation 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 assymptomatically 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.

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 adenome. 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 hemorrhagic 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].
**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 roentgenogram 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 4. Case 19 - Histologic section of a fungus ball. Note typical conidial head of A. niger (HE x 64).](image)

**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 [26,63,66,70] 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 acidic 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 coloniza-

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