HISTOPLASMOSIS IN RIO GRANDE DO SUL, BRAZIL: A 21-YEAR EXPERIENCE

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SUMMARY

Of 156 cases of histoplasmosis observed in the State of Rio Grande do Sul (Brazil), during a 21-year period (1978-1999) 137 were included in this study. Sixty-seven per cent of the patients had hematogeneous disseminated histoplasmosis, 24% had a self-limited syndrome (acute pulmonary histoplasmosis, histoplasmoma or primary pulmonary lymph node complex), and 9 per cent had chronic pulmonary histoplasmosis. Clinical, mycological, and epidemiological data were reviewed and commented.

KEYWORDS: Histoplasmosis; Histoplasma capsulatum; HIV infection; Brazil.

INTRODUCTION

Before 1980 only three small surveys of histoplasmmin skin test were performed6,10,11 and four cases of histoplasmosis were reported1,5 or quoted1 in natives of the State of Rio Grande do Sul. However, since 1981 thirty nine cases of the mycosis have been published3,7-9,12,14-16,18-24. In addition, in 1996 a histoplasmmin skin test survey revealed 89 per cent of reactors amongst young men aged between 17 to 19 years of age, living in the Jacuí River valley26.

The increase in the number of recognized cases of histoplasmosis and the existence of an high endemic area in the state led us to review the clinical protocols of 137 native patients diagnosed in Porto Alegre, in the period between 1978 and 1999. A comment on our findings is presented.

PATIENTS AND METHODS

The clinical and microbiological protocols of 156 patients with histoplasmosis, diagnosed in a 21-year period (1978-1999), in Porto Alegre, were reviewed. Criteria for diagnosis included: detection of the microorganism resembling H. capsulatum var. capsulatum in tissue cut sections stained by Gomori’s methenamine silver (GMS) or by isolation in culture or both. Less frequently by serology (complement fixation test or immunodiffusion test) associated with the existence of compatible symptoms.

RESULTS

One hundred and thirty seven of the 156 patients were native of Rio Grande do Sul. One hundred and one were males and 36 were females; with age ranging from 19 months to 77 years (average 37 years); 129 were Caucasian and 8 were black.

The distribution of these patients by the clinical forms they presented was as follow: primary pulmonary lymph node complex (4 cases); acute pulmonary histoplasmosis (19 cases); residual lesions (10 cases); chronic pulmonary histoplasmosis (12 cases); and, disseminated histoplasmosis (92 patients).

Primary pulmonary lymph node complex: Primary pulmonary lymph node complex was recognized by chance in four patients (aged between 21-42 years), one man and three females. All patients had been submitted to surgery due to a carcinoid tumor, an adenocarcinoma, a hydatid cyst and an Aspergillus fumigatus fungus ball, respectively. Calcified lung node lesions were detected and histologically examined. Yeast forms of H. capsulatum var. capsulatum were disclosed in GMS stained cut of the lung and of the lymphnodes.

Acute pulmonary histoplasmosis: Nineteen patients presented this form of the disease. Eighteen of them fulfilled the diagnostic criteria of a primary type of acute pulmonary histoplasmosis: an acute onset of symptoms (cough, weight loss, fever, and night sweats) associated with a radiologic picture of diffuse micronodular lesions in both lung fields. In three of the patients bilateral lymph node enlargement was also observed. Twelve of these patients were males and 6 females, with ages ranging from 8 to 59 years. With the exception of seven cases diagnosed as a group (3 patients of a same family, two brothers and a couple), the remaining infections occurred in an isolated fashion. Six of these cases were previously published18-20,22.

One of the remaining patients presented the reinfection type of acute...
pulmonary histoplasmosis. She was a 39 year-old woman who became ill following a heavy exposure while cleaning the same chicken house where she was primarily infected one year before. Another patient presented with a mild disease with flu-like symptoms and non calcified lung lesions (Fig. 1).

Diagnosis was based on histologic examination of biopsied lung tissue in 12 patients; on immunodiffusion test in five patients; and on the similarity of the disease that appeared concomitantly in the 3 members of a family, one of which was biopsied.

The natural source of the infection was established by the isolation of \textit{H. capsulatum} var. \textit{capsulatum} from chicken manure (6 cases); it was presumed to be from chicken manure (6 cases) or from bat guano (5 cases); and, in two cases the source of the infection remained unknown.

Ten patients improved spontaneously, 9 were treated with ketoconazole or itraconazole. Five of the 19 patients had been treated for tuberculosis prior to the diagnosis.

\textbf{Histoplasmoma}: Ten asymptomatic patients presented well circumscribed, non calcified pulmonary nodule, ranged from 9 mm to 2 cm in diameter (Fig. 2). Eight patients had a solitary nodule; one patient 2 nodules; and, the remaining 3 nodules. Eight cases were detected by chance on screening chest X-ray; 2 cases were detected in resected lung for carcinoma. The ten patients ranged from 10 to 67 years of age; five were males and 5 females.

\textbf{Chronic pulmonary histoplasmosis}: Chronic pulmonary histoplasmosis was diagnosed in 12 patients with ages between 14 to 64 years. All presented symptoms either of a chronic pulmonary infection or of a chronic obstructive disease. Radiologically, non-cavitate pulmonary infiltrates were observed in 8 patients; and, large cavities in both upper lobes in 4 patients. Diagnosis was obtained by histologic examination of biopsied lung tissue in 10 patients and isolation of the fungus from bronchoalveolar lavage specimen in 2 patients.

In 3 of the 4 patients with cavitary disease an \textit{A. fumigatus} fungus ball developed after they were clinically cured of the histoplasma infection (Figs. 3 and 4). One of these patients was a subject of report prior to being colonized\textsuperscript{21}. 

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{Primary pulmonary histoplasmosis, diagnosed by transthoracic fine needle aspiration: CT scan shows in the right lung a focus of consolidated parenchyma, hilar lymph node enlarged, and a linear opacity between them.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig2.png}
\caption{Histoplasmoma: CT scan shows well-circumscribed subpleural nodule.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig3.png}
\caption{Treated chronic pulmonary histoplasmosis: CT scan shows empty cavities in both upper lobes.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig4.png}
\caption{The same patient from figure 3: developed bilateral \textit{A. fumigatus} fungus ball.}
\end{figure}
Disseminated histoplasmosis: Ninety-two (67%) of the 137 patients presented the disseminated form of the mycosis. With the exception of one child, case previously reported, with the acute form, the remaining patients in which ages varied between 22 to 77 years had the chronic disseminated type. Seventeen of these patients had no evidence of any associated condition, 65 had HIV infection, 4 had diabetes mellitus, 3 had lymphoma, one was under therapy with cytotoxic agents, and one was a kidney allograft recipient.

The diagnosis was established by disclosing the fungus in GMS stained cut sections of biopsied tissue (75 of 81 patients), or by isolation of the fungus in culture (42 of 56 patients), or by both techniques. Blood culture (Isolator) and culture of broncoalveolar lavage specimen were more helpful for the diagnosis in HIV infected patients. The immunodiffusion test was performed in 53 patients with positive results in 62% of them.

Multiple organs, as usual, were involved, but their number and frequency varied according the predisposing conditions (Table 1). The lung was the most frequently affected organ in both groups: AIDS (Fig. 5) and non-AIDS patients (Figs. 6 and 7). Curiously the involvement of the CNS and of the adrenal glands was observed more frequently in patients in which no predisposing conditions were detected. Involvement of the CNS was documented in 4 AIDS patients and in 9 patients presenting no evidence of associated conditions. In 5 of these 9 patients, all of them presenting signs of chronic meningitis and hydrocephalus (Fig. 8), the fungus was detected at the time of the ventricular-peritoneal shunt replacement due to an unexplained and repeated occlusion (3 to 5 times) of the prosthetic device. In one of the AIDS patients tuberculosis and cryptococcosis were associated. Involvement of the adrenal was only observed in non-AIDS patients: in one of them calcified areas were observed in both glands (Figs. 9 and 10).

Table 1
Organ involvement in 91 patients presenting with chronic disseminated form of histoplasmosis

<table>
<thead>
<tr>
<th>Involved organ</th>
<th>Predisposing conditions</th>
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<tr>
<td></td>
<td>AIDS (65 %)</td>
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<tr>
<td>Lungs</td>
<td>37 (56.9)</td>
</tr>
<tr>
<td>Skin</td>
<td>31 (47.6)</td>
</tr>
<tr>
<td>Lymphnodes</td>
<td>15 (23.0)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>13 (20.0)</td>
</tr>
<tr>
<td>Liver</td>
<td>12 (18.4)</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>09 (13.8)</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>04 (06.1)</td>
</tr>
<tr>
<td>Spleen</td>
<td>04 (06.1)</td>
</tr>
<tr>
<td>Genito urinary tract</td>
<td>03 (04.6)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>01 (01.5)</td>
</tr>
<tr>
<td>Heart and joints</td>
<td>01 (01.5)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>01 (01.5)</td>
</tr>
<tr>
<td>Adrenal</td>
<td>0</td>
</tr>
<tr>
<td>Larynx</td>
<td>0</td>
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* Diabetes mellitus (4 patients); lymphoma (3 patients); and therapy with cytotoxic agents for multiple mieloma and renal allograft recipient (one patient each)

Fig. 5 - Disseminated histoplasmosis in AIDS patient, diagnosed by transbronchial biopsy.

Fig. 6 - Disseminated histoplasmosis in a diabetic patient: CT scan shows a consolidation and cavity with air-fluid interface in the left upper lobe.

DISCUSSION

Histoplasmosis is endemic in the State of Rio Grande do Sul particularly in the Jacuí river valley, where \textit{H. capsulatum var. capsulatum} was isolated from soil and 89 per cent of the young men were reactors to histoplasmin skin test.

Almost all the clinical forms of the disease have been recognized to occur in natives of the State.

Three findings are interesting to note. The first one: delays in diagnosis of disseminated histoplasmosis complicating AIDS are most frequently a result of not performing a biopsy in a mucocutaneous lesion. The second one: in three of the four patients with cavitate chronic
pulmonary form, the cavity was colonized by *A. fumigatus* after they were clinically cured. The third one: five patients with chronic meningitis and hydrocephalus needed a shunt replacement due to the obstruction of the prosthetic device by *H. capsulatum* var. *capsulatum*. Aspergillus fungus ball developed in a cavitation of chronic pulmonary histoplasmosis was reported as early as 1960[^1]. Malfunction ventricular shunt caused by *H. capsulatum* var. *capsulatum* has been documented only rarely[^1][^4][^17][^25], in one of the patients the mycosis was only recognized after the isolation of the fungus in culture of the ventricular fluid. Immunologic testing of cerebrospinal fluid should be considered in this kind of patients[^1].

**RESUMO**

Histoplasmose no Rio Grande do Sul, Brasil: uma experiência de 21 anos

De 156 casos de histoplasmose observados no Estado do Rio Grande do Sul (Brasil), durante um período de 21 anos (1978-1999), 137 foram incluídos neste estudo.

Sessenta e seis porcento dos pacientes tinham histoplasmose de disseminação hemática, 24% tinham uma síndrome autolimitada.
(histoplasmosis pulmonar aguda, histoplasmona ou complexo primário linfonodo-pulmonar) e 9% tinham histoplasmosis pulmonar crônica. Os dados clínicos, micológicos e epidemiológicos foram revisados e comentados.

ACKNOWLEDGEMENTS

We are gratefully acknowledged to Dr Leo Kaufman (CDC, Atlanta, GA, USA) for performing serologic assays in the beginning of this study, afterwards providing antigens for immunodiffusion tests and identification of one strain of H. capsulatum var. capsulatum by exoantigen (in isolate without macroconidia, CDC 92-033214).

REFERENCES