

CHRONIC *Aspergillus sp.* MENINGITIS SUCCESSFULLY TREATED WITH FLUCONAZOLE

CASE REPORT

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ABSTRACT - We a case of chronic *Aspergillus sp.* meningitis in a healthy 43-year-old woman successfully treated with fluconazole given orally (300 ms/day). The diagnosis was made by detection of anti-aspergillus antibodies and positive culture to *Aspergillus sp.* in the cerebrospinal fluid.

KEY WORDS: *Aspergillus sp.*, meningitis, fluconazole.

Meningite crônica por *Aspergillus sp.* tratada com sucesso com fluconazol: relato de caso

RESUMO - Uma mulher hígida de 43 anos apresentou quadro de meningite causada por *Aspergillus sp.* O diagnóstico foi firmado pela detecção de anticorpos anti-aspergillus e por culturas positivas para *Aspergillus sp.* no líquido. Pelo seu bom estado geral e recusa em receber tratamento hospitalar com anfotericina, a paciente foi tratada com fluconazol (300 mg por dia, via oral), por 4 meses. Houve resolução completa do quadro meningítico.

PALAVRAS-CHAVE: *Aspergillus sp.*, meningite, fluconazol.

Central nervous system (CNS) aspergillosis has become more frequent in recent years because the increasing number of immunocompromised patients¹⁻⁶. The pathological findings include cerebral infarcts, hemorrhage, abscesses, granulomas, vascular invasion and rarely isolated meningitis. The diagnosis is difficult and usually made at autopsy^{5,7,8}.

We report a case of *Aspergillus* meningitis in an immunocompetent patient successfully treated with fluconazole.

CASE REPORT

A 43-year-old single woman, teacher, resident in Curitiba was admitted to Hospital das Nações, due to a headache more intense in nuchal region associated with stiff neck. The symptoms had begun for 11 days and did not improve with use of common analgesics. The patient also complained of asthenia, chills and nausea. The patient's past medical history was unremarkable. She denied any drug addiction, diabetes, cancer, weight loss, infectious diseases or use of corticosteroids. At the time of admission, her blood pressure was 140/80 mm Hg, pulse rate 86 bpm, temperature 37.6°C. General physical examination was normal. Eye, nose and paranasal sinuses showed no abnormalities. The neurologic examination was normal, except for a slight neck rigidity.

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Table 1. CSF examination.

Date m/d	Cells /mm ³	Differential cell/count (monocytes)	Red cells/ mm ³	Glucose (mg/dL)	Protein (mg/dL)	<i>Aspergillus</i> sp.	<i>Cryptococcus</i> Culture and latex	Comments
02/25	21	100%	336	34	94	-	negative	
02/29	1029	64%	10	53	84	-	negative	
03/08	522	100%	32	39	110	-	negative	
03/12	713	100%	-	36	174	-	negative	<i>Mycobacterium tuberculosis</i> PCR negative
03/23	329	100%	7	46	50	Positive*	negative	Fluconazole started
04/12	68	82%	5	47	36	Positive**	-	
05/28	21	100%	3	60	35	Positive**	-	
07/12	6	100%	2	64	34	Positive**	-	

-, not done; * culture and immunodiffusion test for antibodies; ** only immunodiffusion test for antibodies; m, month; d, day.

The laboratory data showed a hematocrit value of 41% and a white blood cell (WBC) count of 8,300/mm³, with normal differential count. The chest X-ray was normal. A spinal tap showed normal opening pressure. The cerebrospinal fluid (CSF) was clear; with 21 cells/mm³ (100% lymphocytes) protein 91 mg/dL; glucose 34 mg/dL. VDRL was not reactive and cultures were negative for common fungi or bacteria. In the following CSF samples, leukocytes and protein increased, as shown in Table 1.

The patient stayed 12 days at the hospital, and was submitted to several radiological and laboratory tests. Computerized axial tomography and resonance magnetic imaging were normal. The enzyme-linked immunosorbent assay (ELISA) for HIV 1 and 2 was repeatedly negative. Other two samples of CSF were collected and cultures to bacteria and fungi were negative, slide latex agglutination (SLA) tests to cryptococcal antigen, *Haemophilus influenzae*, *Neisseria meningitidis*, *Streptococcus pneumoniae* were negative.

The patient was followed on consultations and five CSF examinations were done during a follow up period of a month, when the diagnosis was finally established. In the first CSF sample, a polymerase chain reaction (PCR) to *Mycobacterium tuberculosis* was negative. In the next CSF sample, culture to fungi was positive to *Aspergillus* sp and the immunodiffusion test showed presence of antibodies against *Aspergillus* sp. Other immunological tests to *Histoplasma*, *Cysticercus* and *Sporothrix* were negative.

At the time of diagnosis of *Aspergillus* meningitis, treatment with amphotericin was indicated, but the patient refused to be readmitted. As a therapeutic alternative, fluconazole (300mg/day) PO was started and kept for 4 months. The medication was well tolerated, without side-effects. During treatment, headache subsided and the CSF abnormalities improved, the culture to fungi was negative and immunodiffusion test was negative.

After two years of treatment, the patient is asymptomatic, without any sign/symptom of systemic disease or recurrence of meningitis.

DISCUSSION

Aspergillus is second only to *Candida* in the frequency of opportunistic mycosis among immunocompromised hosts. This condition is more frequent in patients with leukemia, lymphoreticular neoplasms, those on long-term use of steroid, large spectrum-antibiotics, cancer chemotherapy, those on immunosuppressant drugs following renal or cardiac transplantation. More recently CNS *Aspergillus* infection is a well recognized complication in patients with acquired immunodeficiency syndrome. In all these patients, cellular immunity is greatly impaired⁹⁻¹³.

The infections can be divided in two types: localized or disseminated. The latter usually occurs in compromised host, and CNS involvement is present in 40-60% of cases. Invasion of the CNS occurs either by direct extension from an area adjacent to the brain, or by hematogenous route. In some patients, the mechanism of CNS penetration is unclear. The direct extension to the brain may occur from adjacent structure, i.e., ear, nose, paranasal sinuses; orbit; and sphenoid sinus or following head trauma. Iatrogenic introduction of *Aspergillus* into the CNS has been described following spinal tap, craniotomies, and after implantation of radioactive yttrium for pituitary ablation^{4,14}.

The hematogenous route is usually associated with lung and gastrointestinal infections in immunosuppressed host, but it can also result from direct blood-stream inoculation of fungus during illicit drug use or following open heart surgery¹⁵.

CNS aspergillosis can present as subcortical hemorrhagic infarcts in cerebral hemispheres; abscesses; granulomas; mycotic aneurysms; and meningitis. The subcortical infarctions, hemorrhage and mycotic aneurysms reflect the vascular invasion of small and large cerebral vessels, leading to thrombosis or destruction of the internal elastic lamina of cerebral arteries^{4,16}. Brain abscesses present as multiple lesions with hyphae, a focal mixed polymorphonuclear and mononuclear reaction, and usually occurs in the frontal and temporal lobes. Granuloma formation is seen in those patients who have had aspergillosis for a prolonged period of time, particularly if the lesions are limited to the CNS and/or adjacent paranasal sinuses or orbit^{17,18}. Spinal cord compression has also been recorded. Meningitis as the predominant clinicopathological process has been reported in only a few cases^{9,12,15,17}. In autopsy series the meninges were focally involved in areas adjacent to local infection in cerebral hemispheres¹⁹.

There are not pathognomonic features in CSF examination in patients with CNS aspergillosis. CSF is usually clear; with normal or increased opening pressure; the glucose level may be normal or depressed; the protein is elevated (above 100mg/dL); pleocytosis is usually less than 600 cells/mm³ with a variable distribution of polymorphonuclear and mononuclear cells. Positive CSF cultures to *Aspergillus* are rare^{5,7,20}. *Aspergillus* rarely invades the meninges, and the lack of diffuse meningeal involvement might be the reason of relative paucity of CSF findings¹⁹.

Diagnosis of CNS aspergillosis is difficult. Positive CSF culture gives a straight diagnosis, however they are usually negative. Therefore, other tests may be helpful in the diagnosis of this life-threatening pathology. Morrow et al.¹⁵ described the presence of antibodies by double immunodiffusion in 2 out of 3 patients, who had negative cultures but antibodies were shown by double immunodiffusion. These patients were cured after treatment with antifungal drugs. Western blot analysis can be used for detection of *Aspergillus* antigen in CSF. The presence of prominent 110KD band can be a prognostic marker in fatal aspergillosis²¹. Our case showed both positive cultures and immunodiffusion test, but only after many CSF samplings.

The treatment of choice for CNS meningitis is amphotericin B, or amphotericin plus flucytosine^{1,9,22}. However, successful treatment is not the rule, perhaps reflecting a late diagnosis or may be related to poor response to antifungal drug^{1,9,22,23}. Other therapeutic alternatives include the use of parenteral or oral imidazole compounds, e.g. fluconazole and itraconazole^{1,9,23,24}. Mikolich et al.²⁵ reported the use of itraconazole with success in an immunocompetent patient with *Aspergillus* meningitis. More recently, Renard et al.³ reported another case of neuroaspergillosis associated with neurotuberculosis in an immunocompetent woman treated with antituberculous agents and itraconazole with good outcome. In a minority of patients with clinical tuberculosis a risk factor can be identified. However, most patients develop tuberculosis, and possibly some fungal infections, e.g. aspergillosis, as a result of complex interaction of environmental and genetic factors, like NRAMP 1 (natural-resistance-associated macrophage protein 1) polymorphism in tuberculosis²⁷.

Fluconazole is a synthetic broad-spectrum triazole compound with good properties for treatment of CNS infections. It is more water-soluble than itraconazole or ketoconazole, and unlike these drugs, fluconazole is only approximately 11% protein-bound, what results a good penetration

into CSF, with levels reaching 70-80% of simultaneous serum levels. Fluconazole is well absorbed after oral administration, has a long half-life in the CNS compartment, and the side effects are minimal comparing with amphotericin B^{3,28}. The treatment must be continued for at least 6 weeks or until evidence of active CNS infection has disappeared. This includes a normal CSF formula, negative CSF culture or antigen titers.

The findings in this case emphasize the importance in establishing an etiologic diagnosis in chronic meningitis, in order to choose the most appropriate therapy. This is the first report of neuroaspergillosis successfully treated with fluconazole. Fluconazole might be considered an alternative therapy to *Aspergillus* meningitis in selected patients.

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