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A CASE REPORT OF INTRASPINAL PARACOCCIDIOIDOMYCOSIS

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SUMMARY

The authors report a case of paraplegia caused by a lumbar intraspinal paracoccidioidomycosis (PCM) granuloma. Clinical neurological diagnosis of a compressive spinal cord lesion was confirmed by spinal magnetic resonance imaging (MRI). Patient was submitted to surgery with total excision of the lesion. Histopathological analysis confirmed the diagnosis of PCM. Patient is on sulfamethoxazole/trimethoprim combined with fluconazole and is experiencing positive neurological recovery.

KEYWORDS: Paracoccidioidomycosis; Spinal cord; Treatment.

INTRODUCTION

Paracoccidioidomycosis (PCM) is the most important systemic mycosis of the tropical Americas and can affect any organ, causing symptomatic or asymptomatic lesions. PCM can mimic other diseases, which must be considered in making the differential diagnosis[34].

PCM was first described in 1908 by a Brazilian physician, Adolpho LUTZ[18]. The first reference to the possibility that PCM could affect the central nervous system (CNS) was by PEREIRA and JACOBS in 1919[30], but it was not until 1943 that MAFFEI et al. published the first histopathologically proven case[20].

In a literature review of neuroparacoccidioidomycosis (NPCM), DEL NEGRO et al. 1954[10] identified 17 cases. CORREA reviewed the literature up until 1992[5] and found 175 cases, of which 145 were in Brazil. PLÁ et al. in 1994[32] reviewed cases from the last 10 years, published up until 1994, and found 22 cases.

Involvement of the SNC and the meninges by the *Paracoccidioides brasiliensis* (*Pb*) usually occurs associated with a wider spread of the infection. It is very uncommon for the SNC to be the only organ system involved [26, 27]. The incidence of SNC involvement varies according to the different studies. MACHADO FILHO & MIRANDA[19] found 2 cases of probable NPCM in a series of 386 PCM patients. PEREIRA[31] found 9.65 % from 145 PCM autopsied cases studied. RAPHAEL[33], in a prospective study of 55 PCM cases, found 14 patients with symptoms suggestive of CNS involvement. NPCM cases may not be recorded because of lack of neurological examination and incomplete autopsy (particularly of the spinal cord and meninges in asymptomatic cases).

On the other hand, the growing number of NPCM cases reported could be due to a better diagnostic work-up of these patients, especially since computerized tomography (CT) and MRI became available.

NPCM has different clinical presentations: meningeal, meningoencephalic, tumoral, or a combination of the above. The tumoral lesions (nodules, cysts, granulomas, and abscesses) are the most frequently observed. The cerebral hemispheres are the most frequently affected site, and the spinal cord the least[26, 27]. The location, number, and extent of lesions are responsible for the different signs and symptoms that may occur, such as intracranial hypertension, focal symptoms, meningitis, myelitis, or ataxia.

We report a case of a patient that became paraplegic as a consequence of a spinal cord infection by *Pb*.

CASE REPORT

The patient is a 37-year-old male born and currently residing in the city of Resende, Rio de Janeiro State, Brazil. He was referred to the Hospital Evandro Chagas on April 1, 1993, complaining of weight loss and a cough with dark-colored sputum. The chest x-ray showed a diffuse pulmonary infiltrate. Diagnosis of pulmonary PCM was confirmed based on a positive *Pb* sputum test. The method used for the detection of anti-*Pb* antibodies was

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the double immunodiffusion (IDD) test, which was positive at a titer of 1:8. The patient was placed on sulfamethoxazole and trimethoprim (SMZ/TMP) and took the medication irregularly. In May 1994 the pulmonary lesions resolved and he abandoned treatment.

On February 7, 1996 he returned to the hospital because of anemia, weight loss of 16 kg, and cough with dark-colored sputum. He complained of paresthesia in the left thigh beginning 5 months previously. The chest x-ray showed a diffuse bilateral reticulomicronodular pattern. PCM reactivation was confirmed by a *Pb*-positive sputum test and an IDD titer of 1:16, and SMZ/TMP was prescribed. In October 1996 the pulmonary lesion had cleared completely and the patient abandoned treatment again.

On January 23, 1997, he was admitted to the hospital, complaining of weakness in the lower limbs and numbness in his right leg. Symptoms had started in the right leg and resolved spontaneously. He went on to develop a drooping right foot.

A spinal CT scan was scheduled, but the patient refused to submit to it at the time.

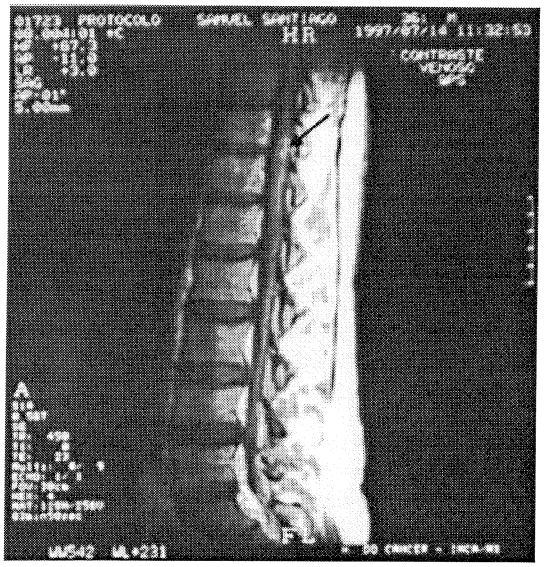

Fig. 1 - MRI showing a T_{12} spinal cord oval lesion.

Fig. 2 - Detail of lesion showed on Figure 1.

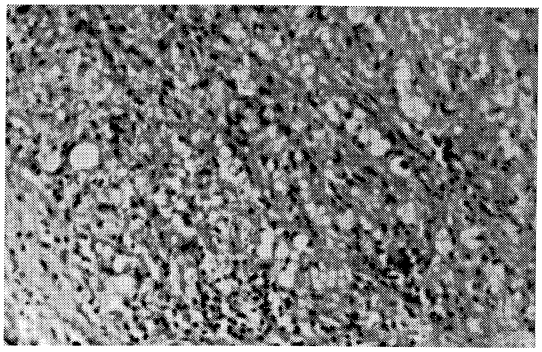

Fig. 3 - Histopathological examination showing mononuclear cell infiltrate mainly composed by histiocytes (HE, x 20).

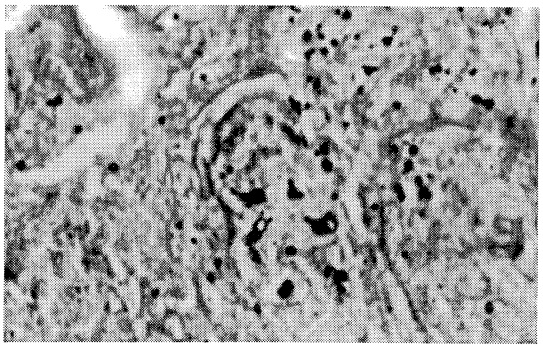

Fig. 4 - Round yeast forms with variable size and gemulation images (silver stain, x 40).

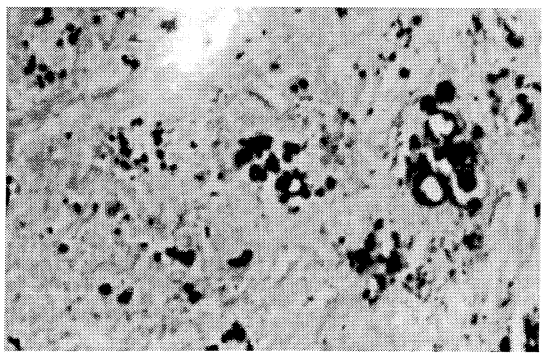

Fig. 5 - Round yeast forms with variable size and gemulation images (silver stain, x 40).

On July 1, 1997, he returned to the hospital with a 7-day history of paraplegia. The neurological examination revealed a T12 tactile, thermal, and algesic anesthesia. Deep reflexes were symmetrical, patellar 1, and ankle 0. A bilateral Babinski sign was elicited. He complained of urinary retention and sexual impotence. Diagnosis was made of a spinal cord lesion.

The chest x-ray showed an almost complete regression of the interstitial infiltrate and fibrosis in the upper third lung. Cardiac area was normal. He was admitted to the hospital and began receiving I.V. dexametazone 40mg on the first day, followed by a gradual reduction. His strength improved in a matter of days.

Plasma cortisol measured after administration of ACTH was 22.48 µg/dl (time zero); 24.48 µg/dl (30 min); and 28.36 µg/dl (60 min).

IDD anti-*Pb* was positive at 1:2 and negative for histoplasmosis. HIV, HTLV-I/II, syphilis, mycological and BAAR sputum tests were negative. The other biochemical blood, urine, and feces tests, abdominal ultrasound and spinal column x-ray were also normal.

Cerebrospinal fluid (CSF) was clear with 1 mononuclear cell and 10 red cells with protein assay of 57 mg%, Cl 112 mEq/L, and glucose 75mg%. The syphilis, tuberculosis, fungus (PCM, histoplasmosis, and cryptococcosis), toxoplasmosis, herpes, cytomegalovirus, HIV, HTLV I/II tests were all negative.

The spinal MRI showed an oval T12 spinal lesion of about 1 cm in diameter that enhanced with gadolinium (Fig.1, 2). Patient was submitted to surgery in August 1997. Diagnosis of PCM was confirmed by histopathological examination (Fig.3, 4 & 5) with mucicarmin stain being negative. He is currently on SMZ/TMP 800/160mg PO TID and fluconazole 200mg/day, prednisone 7.5mg and physical therapy.

Follow-up: After three months taking SMZ/TMP plus fluconazole, patient has gradually improved his motor, sensory, bladder, and sexual functions. He is now able to walk by himself using a cane.

DISCUSSION

There are very few PCM cases with spinal cord involvement reported in the medical literature, four of which with histopathological analysis confirmed[2,4,21,24,28,29,35]. FARAGE FILHO et al.[11] report a case of spinal meningeal PCM granuloma (i.e., located inside the spinal canal, but external to the medulla), confirmed at surgery. There are reports of other 10 cases of probable spinal cord involvement without etiologic confirmation[3,6,10,16,25,33,38]. Motor, sensory, and autonomic signs and symptoms vary depending on the level and location of the spinal cord lesion[3,29].

CSF examination did not provide any diagnostic help, as is consistent with the literature[33]. Attempts to isolate *Pb* in the CSF were negative. One of the rare reports of a positive identification of *Pb* in the CSF was made by LEVY et al.[17] in a case of PCM meningitis. Immunoenzymatic reactions are more sensitive, but there is the possibility of cross-reaction with *Histoplasma capsulatum* and *Cryptococcus neoformans*. On the other hand, a CSF positive *Pb* serology without CNS involvement can occur, if the blood-brain barrier is affected in any way[16].

In the neuroimaging differential diagnosis of intraspinal NPCM, other infections, tumors, cysts, and granulomatous diseases must be considered[36]. The space- occupying lesion that is revealed might be produced by another fungus[37], tuberculosis, schistosomiasis[12], cysticercosis[14], other parasites[7], or tumors. MOURA et al.[25] reported a case in which a patient with a spinal lesion was treated with fluconazole based solely on clinical evidence and had an excellent outcome. These authors believe that clinical treatment should be introduced as soon as the PCM diagnosis is made. There are cases, however, in which total regression is not achieved. PACHECO et al.[28] believe that in cases of intraspinal growing lesions surgery is the most efficient diagnostic method since it is as the same time, therapeutic. COLLI et al.[4] also suggest surgery for those patients, since regression with conventional treatment is slow and the reversibility of neurological deficits depends on promptness of spinal cord decompression.

Presence of a single lesion with no other evidence of PCM activity gave us no laboratory indication that the spinal cord lesion was caused by *Pb*, even though our patient had a previous history of PCM and his IDD titer was 1:2, which can occur in cured patients[13]. We thought it desirable to have the etiologic agent identified. A needle biopsy was ruled out because of the risk of meningeal dissemination. Because of the signs and symptoms of spinal cord compression the patient received dexametazone and experienced a fair motor and sensory improvement, but was still unable to stand or walk unassisted. The positive response to dexametasone treatment indicates that inflammation and thus edema are an important mechanism in the pathogenesis of neurological symptoms in NPCM. However prolonged use of corticosteroids in infectious diseases without specific therapy can result on important worsens of lesions, as described by ROCHA et al.[35]. The decision to operate the patient was also based on the risk that the lesion could deteriorate and the patient develop transverse myelitis with an irreversible deficit. In the medical literature, surgery is considered when there is a single lesion that is surgically accessible with signs of spinal cord compression[26, 27].

Patient was placed on fluconazole, since this drug is effective in PCM and reaches a good CNS concentration[23, 27]. He also received SMZ/TMP. This drug is a good alternative as monotherapy[26, 27], but the patient had been taking it irregularly since 1993, which could have produced drug resistance, so a combination therapy was chosen. The association of SMZ/TMP to fluconazol was previously used with success in two of our patients with neuroparacoccidioidomycosis, which had also took sulfonamides irregularly. We didn't find, on literature, references to antagonism between these drugs.

Amphotericin B was ruled out, since it has to be administered intrathecally. Other imidazolic drugs like ketoconazole and itraconazole attain a poor SNC concentration. There are reports of good results with ketoconazole at doses of 800 to 1200 mg in SNC fungus infections[8]. There are reports of adrenal insufficiency with low doses of ketoconazole, although this occurs more frequently at high doses[1]. The patient already had evidence of a low adrenal reserve, so that option was ruled out. Because of this functional alteration, he received 7.5mg of prednisone. Functional adrenal involvement in PCM depends on the extent of glandular destruction, resulting in subclinical to overt Addison's disease[39].

Non-compliance with PCM treatment is a difficult issue, ranging up to 30% in different reports. Efficacy of sulfanolamic treatment in PCM when the patient takes the drug regularly is as high as 90%, according to a 10-year follow-up, but when taken irregularly the efficacy drops to 20%[41].

There are different causes for non-adherence: social, cultural, economic, and geographic (patients generally live in rural areas, far from hospitals). The extended duration of therapy (24 months) is also an important factor for treatment drop out[40,41].

In this particular patient, irregular use of medication was probably the cause of recurrence and thus the spinal lesion.

Although there are already reports of NPCM in HIV patients[15], HIV/PCM is an infrequent association[22]. However, this could be an emerging problem, since immune deficiency facilitates fungus dissemination.

RESUMO

Registro de um caso de paracoccidioidomicose intra-medular.

Os autores registram um caso de paraplegia causada por uma lesão granulomatosa de PCM intramedular. O diagnóstico clínico neurológico de uma lesão compressiva intramedular foi confirmado pelo exame de ressonância nuclear magnética da coluna, que mostrou lesão captante de contraste a nível de T12. O paciente foi operado e a lesão totalmente retirada. O exame histopatológico da peça operatória confirmou o diagnóstico de PCM. O doente está em uso de SMZ/TMP e fluconazol com boa recuperação neurológica.

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