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MYCOBACTERIUM AVIUM COMPLEX (MAC): AN UNUSUAL POTENTIAL PATHOGEN IN CEREBROSPINAL FLUID OF AIDS PATIENTS

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SUMMARY

Mycobacterium avium complex (MAC) is frequently isolated from patients with late complications of Acquired Immunodeficiency Syndrome (AIDS), especially in North America and Europe. However, its isolation from the central nervous system (CNS) has been seldom reported in these countries. MAC infections in AIDS patients in African and Latin American countries are believed to be uncommon. We report the isolation of MAC from cerebrospinal fluid (CSF) of 11 AIDS patients out of 1723 (0.63%) seen at "Centro de Referência e Treinamento - AIDS", São Paulo and discuss the significance of its isolation.

KEYWORDS: *Mycobacterium avium* complex (MAC); Cerebrospinal fluid (CSF); Acquired immunodeficiency syndrome (AIDS).

INTRODUCTION

Since the initial description of Acquired Immunodeficiency Syndrome (AIDS) in 1981, mycobacterial disease have represented an important group of opportunistic infections [13, 15, 23].

These mycobacterial diseases are usually caused by *Mycobacterium tuberculosis (M. tuberculosis)* or *Mycobacterium avium* complex (MAC) [1]. MAC is composed of two species called *M. avium* and *M. intracellulare* [16], indistinguishable by routine identification tests employed in clinical laboratories [29, 30].

In Brazil tuberculosis has been the most common infection reported in AIDS patients after oral candidiasis and *Pneumocystis carinii* pneumonia [26]. In contrast little is known about the frequency of MAC infections [1, 4]. BARRETO et al. [2], at Instituto de Infectologia Emilio Ribas (São Paulo, Brazil), isolated MAC from 23 (18.4%) out of 125 patients with persistent fever, anemia and leucopenia among 2628 admitted to the hospital between May 1990 and April 1992.

Since the description of the first AIDS cases [24],

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disseminated disease has become the most frequent clinical form of MAC infection. The impact of opportunistic infections due to MAC in AIDS varies from region to region. In North America and Europe, MAC has been described as the most frequent systemic bacterial infection in this group of patients [15, 31]. In the United States, the prevalence of disseminated MAC disease ranges between 17 to 24% [17] and about 50% at autopsy [9]. However, it is extremely rare in Africa, South America and Asia [18].

While the incidence of tuberculous meningoencephalitis is higher in HIV positive than HIV negative patients [3], there is little information regarding MAC isolation from CSF and its pathogenicity in relation to the CNS [20, 22, 30].

OBJECTIVES

In this report we describe uncommon findings of MAC in CSF of 11 patients with AIDS in São Paulo (Brazil) and discuss its probable clinical significance.

MATERIALS AND METHODS

The records of the Bacteriology Department, Instituto Adolfo Lutz, for the period from January 1989 to August 1990 were reviewed and the charts of patients from whom MAC was isolated from CSF were analyzed in detail at "Centro de Referência e Treinamento AIDS".

The diagnosis of AIDS was confirmed according

Table 1

Clinical description of 11 AIDS patients, with MAC isolated from cerebrospinal fluid.

Patient	Risk Group	Classification prior to mycobacteriosis diagnosis/ (Opportunistic Infections)	Clinical Picture under investigation	Indication for Lumbar Puncture (date of spinal tap)
1	Intravenous drug addict/ Bisexual	IV C1,2 (Cerebral toxoplasmosis and Oral candidiasis)	Seizures	Intracranial hypertension syndrome (12.20.89)
2	Bisexual	IV C1 (PCP and Cerebral toxoplasmosis)	Fever	Frontal headache and fever for 8 days. Neck Stiffness (04.18.90)
3	Intravenous drug addict	II (-)	Febrille pneumopathy	Sympathetic hyperactivity and loss of sphincter control (10.06.89)
4	Promiscuous heterosexual/ Intravenous drug addict	IV C1† (Cerebral toxoplasmosis)	Diarrhoea	Frontal headache and fever for 5 days (02.20.90)
5	Homosexual	IV C2 (Oral candidiasis and PCP)	Fever	Fever of unknown origin (01.24.90)
6	Bisexual	IV C1 + D‡ (Cerebral toxoplasmosis and PCP)	Fever	Drowsiness, left hemiparesis (02.23.89)
7	Bisexual	IV A1, C2 (Constitutional disease Oral candidiasis*)	None	Headache, fever for 6 days (08.11.89)
8	Bisexual	IV C1 (PCP)	None	Mental confusion, drowsiness (07.12.90)
9	Homosexual	IV C1 (PCP)	None	Headache, nausea for 2 days (06.06.90)
10	Blood Transfusion	IV A1, C1§ (Constitutional disease, Pulmonary mycobacteriosis)	None	Mental confusion (07.11.90)
11	Bisexual	IV C1,2‖ (Cerebral toxoplasmosis and cryptococcosis, oral candidiasis and PCP)	None	Spinal tap control for cerebral cryptococcosis (05.10.89)

PCP = *Pneumocystis carinii* pneumonia

§ - Patient with shigellosis
‖ - Patient with Whipple's disease

* - Patients with lymph node mycobacteriosis
† - Patient with pulmonary mycobacteriosis
‡ - Patient with Kaposi's Sarcoma

to the 1987 Centers for Disease Control (CDC) classification [5]. Spinal taps were performed if the patients had a presentation consistent with CNS involvement, except for one patient who was being investigated for a febrile syndrome.

For each chart reviewed, the following information was recorded: CSF analysis, age, sex, risk group, classification prior to mycobacteriosis diagnosis, opportunistic infections, clinical picture under investigation, indication of lumbar puncture, and time between MAC isolation from CSF and death.

A smear for acid-fast bacilli was obtained from all CSF specimens submitted to mycobacterial culture as a matter of laboratory routine. The samples were stained by the Ziehl-Neelsen and Gram methods and inoculated directly onto Lowenstein-Jensen, Sabouraud culture media and Mueller Hinton agar base containing 5% sheep blood (Difco Laboratories, Detroit, Michigan, USA). The cultures were incubated at 37°C and examined for the visible growth of bacteria and fungi according to specific standardized procedures [16, 17, 25]. When isolated, mycobacteria were identified by routine culture and biochemical test [8, 17].

In addition to spinal fluid samples, sputum, bronchial washing, bone marrow and blood samples from the same patients were cultured for mycobacteria [8, 17].

RESULTS

Of 1723 patients who underwent spinal taps, 20 (1.16%) and 11 (0.63%) had *M. tuberculosis* and MAC isolated from CSF, respectively.

(i) Table 1 shows epidemiological and clinical data for 11 HIV cases associated with recovery of MAC from CSF. Of the 11 patients, 10 were males. The patient age ranged from 24 to 57 years (average = 35.5 years old).

Cases 2, 4, 7 and 9 had headache as the neurological manifestation which lead the physician to perform the lumbar puncture; 6 and 8, drowsiness; 1, intracranial hypertension; 8 and 10, mental confusion; and 3, sympathetic hyperactivity. In case 5 a spinal tap was performed for the investigation of a febrile syndrome (no neurological manifestations were reported), and in case 11 the procedure was performed for the control of cerebral cryptococcosis.

Table 1 also list stages of HIV infection based on the CDC classification. Cases 2,4,8,9 were classified as IV C_1; 10, IVA, C_1; 1 and 11, IV $C_{1,2}$; 6, IV C_1, D; 5, IV C_2; 7, IVA, C_2; and 3, II. Among these cases, five also had cerebral toxoplasmosis (1, 2, 4, 6 and 11) and one (11) cerebral crytococcosis.

Table 2

Biochemical and cytological findings in the cerebrospinal fluid of patients with *Mycobacterium avium* complex.

		Cerebrospinal Fuid						Mycobacteria Culture from other sites:		
Patient	Date	Protein (mg/dl)	Glucose (mg/dl) (mmol/l)	Cells (/mm3)	Limphocytes (%)	PMN (%)	MnRT (%)	Sputum	Blood	Bone marrow
1	12.20.89	14	35 1,92	378	61	36	2	NA	MAC	MAC
2	04.18.90	118	64 3,52	48	10	87	3	-	-	-
3	10.06.89	2020	12 0,66	3840	25	73	2	-	-	-
4	02.20.90	170	33 1,81	1210	2	94	4	NA	-	-
5	01.24.90	58	33 1,81	1	-	-	-	-	MAC	MAC
6	02.23.89	180	45 2,47	5	-	-	-	NA	-	-
7	08.11.89	260	38 2,09	1194	13	83	4	-	-	-
8	07.12.90	100	43 2,36	26	14	84	2	-	-	-
	08.02.90	2500	36 1,98	40	18	78	4	-	-	-
9	06.06.90	375	31 1,70	399	3	96	1	-	-	-
10	07.11.90	50	33 1,81	9		(damaged	cells)	-	-	MAC
11	03.06.89	70	27 1,48	1	-	-	-	-	-	-
	05.10.89	91	27 1,48	2	-	-	-	-	-	-
	06.19.89	96	19 1,04	4	-	-	-	-	-	-

PMN = Polymorphonuclear cells; MnRT = monoreticular cells; MAC = *M. avium* complex; NA = Not available; - = negative

Typical disseminated MAC infection was observed in cases 1, 5, and 10. These patients had MAC isolated from CSF, blood and bone marrow aspirate. In addition, MAC was isolated two and three times, respectively, from the CSF of patients 8 and 11 (Table 2).

(ii) The time between MAC isolation from CSF and death ranged from less than 10 hours to 12 months with a mean of 2.5 months.

(iii) Bacteriological analysis. All isolates were slowly growing nonphotochromogenic acid-fast bacilli, and colonies on egg-based media appeared smooth and domed. Biochemical analyses demonstrated that they do not produce niacin, nitrate reductase or urease, that they have </= 45mm of catalase activity and do not hydrolyze Tween. The organisms show resistance to most of the antimicrobial agents to which *M. tuberculosis* is usually susceptible. No aerobic bacteria or fungi were isolated from the CSF. Also, anti-toxoplasma IgG was not detected by indirect immunofluorescence in the CSF specimens from which MAC was isolated.

DISCUSSION

During the last 10 years, along with the increased incidence of AIDS, disseminated infections caused by MAC have been increasingly reported [11, 12, 15, 20]. However, there have been few reports of MAC disease from developing countries, presumably reflecting inadequate care and consequent high mortality due to infection by other more virulent organisms at earlier stages of HIV disease [6].

It is now well recognized that disseminated MAC infections develop relatively late during the course of HIV infection after the circulating CD4 + counts have fallen to less than 100 cells/mm [3 15].

When dissemination occurs, many organs may be involved with massive numbers of intracellular bacilli and little or no tissue reaction [15, 25]. The most commonly described are blood, bone marrow, liver, spleen, lymph nodes and gastrointestinal tract [15]. In contrast, CNS involvement seems to be an uncommon feature for MAC infection in AIDS patients [22].

The detection of eleven patients with MAC isolates from CSF in our series of 1723 AIDS patients is particularly striking, especially when compared to the absence of these microorganisms observed in CSF samples from non-AIDS patients detected during the preceding 10 years at our institution [27]. However, these findings cannot be used as a marker of meningoencephalitis since other disorders such as CNS infection by human immunodeficiency virus, Herpes simplex virus, *Toxoplasma gondii* and *Cryptococcus neoformans* could be present in these patients. Indeed, five of them (cases 1, 2, 4, 6 and 11) had cerebral toxoplasmosis and one (case 11) had cerebral cryptococcosis, as shown in Table 1. Furthermore, the ubiquitous nature of MAC means that caution should be taken when a diagnosis is being made on the basis of culture, which may merely signify contamination of the specimen.

Thus the isolation of MAC from autopsy material with histologic changes compatible with a specific inflammatory reaction was of help in establishing a definitive diagnosis of CNS disease in these eleven patients. CHAPMAN[7] reported a case of MAC CNS infection whose autopsy showed granulomatous meningitis. JACOB et al. [19], in New York (USA), reported 16 cases of MOTT CNS infection (15 MAC and 1 *M. fortuitum*) in AIDS patients. The autopsy performed on three of these cases showed extensive involvement of liver, gastrointestinal tract, bone marrow, lymph nodes and CNS with light inflammatory activity, loose granulomas without Langhans's giant cells and alcohol-acid fast bacilli observed at most sites. This is the first substantial evidence that MAC may play a pathogenic role in the CNS. However, unfortunately, autopsy could not be performed in our cases. On the other hand, if performed, it could not have provided any additional information to clarify MAC pathogenicity in relation to the CNS. A poor or no tissue response is frequently observed in AIDS patients, which probably reflects their inablility to mount an effective immune response [15, 25, 28].

In contrast to the above data, the presence of MAC in five patients provided strong evidence in favour of its pathogenic role. Patient 1, 5 and 10 had typical disseminated infection, whereas cases 8 and 11 had repeated isolation of multiple colonies of MAC from CSF. This latter implication is well reported by KLEIN et al. [22].

In our series all patients had moderate to marked protein elevation, ranging from 50 to 2020 mg/dl, which is a common finding in AIDS patients with neurological disease [14]. However, several CNS diseases such as HIV encephalitis, toxoplasmosis, cryptococcosis and brain

primary lymphoma, which usually attack AIDS patients, make the interpretation of CSF findings quite treacherous. Therefore, it is impossible to confirm a diagnostic hypothesis of CNS mycobacterial infection based only on chemocytological findings.

HOLLANDER [15] suggested that patients with marked pleocytosis should raise the suspicion of infection caused by pathogens other than HIV. In our series, pleocytosis was documented in eight patients studied at the time of MAC isolation. In none of them did we diagnose CNS infections caused by other bacteria or fungi. It should be pointed out that patients with pleocytosis above 1000 and neutrophilic pleocytosis lead the physician to treat them for undetermined bacterial meningitis (data not shown).

Taking into account either Davidson's criteria [10] for a definitive diagnosis of non-M. tuberculosis complex disease, or a case of meningeal lesion described by KLATT et al. [21] at autopsy in 12 AIDS patients, it seems reasonable to admit the possibility that these organisms played an opportunistic role in cases 1, 5, 8, 10 and 11. Therefore, we may conclude that further and more extensive investigations should be performed in order to determine MAC pathogenicity for the CNS in AIDS patients.

RESUMO

Complexo *Mycobacterium avium*: um patógeno potencial pouco comum no líquido céfalo – raquidiano de pacientes com AIDS

O complexo *Mycobacterium avium* (CMA) é frequentemente isolado de pacientes com complicações tardias de Síndrome de Imunodeficiência Adquirida (AIDS), especialmente na América do Norte e Europa. Entretanto, existem poucos relatos do isolamento deste complexo a partir do sistema nervoso central (SNC) nestes países. Acredita-se que infecções pelo CMA sejam raras entre pacientes portadores de AIDS em países da África e América Latina. Neste trabalho relatamos o isolamento do CMA do líquor de 11 pacientes portadores de AIDS dentre 1723 (0.63%) atendidos no Centro de Referência e Treinamento - AIDS, de São Paulo, e discutimos a significância deste achado.

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