RSVM

Revista de la Sociedad Venezolana de Microbiología 2009; 29:62-65

Caso clínico

Severe brain co-infection by *Cryptococcus neoformans* and *Mycobacterium tuberculosis* in a patient with non-bacillary lung tuberculosis

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Recibido 06 de marzo de 2009; aceptado 16 de junio de 2009

***Abstract*:** An exceptionally rare case of concurrent central nervous system infection by *Cryptococcus neoformans* and *Mycobacterium tuberculosis* in a 25-year-old otherwise healthy Chinese student who very recently joined Italian post-doctoral courses is described, together with diagnostic and therapeutic difficulties encountered in a six-month-long hospitalization period, when only transient and/or negligible immune system impairments were detected. A non-bacillary pulmonary tuberculosis probably preceded both brain complications. This episode of very infrequent concurrent infections, should enforce the need of maintaining an elevated clinical suspicion for opportunistic infections and tuberculosis, even in absence of an obvious immunodeficiency, and related epidemiological clues.

***Key words*:** Brain co-infection, cryptococcosis, tuberculosis, opportunistic infections

Co-infección cerebral grave por *Cryptococcus neoformans* y *Mycobacterium tuberculosis* en un paciente con tuberculosis pulmonar no bacilífera

***Resumen*:** Se describe un caso excepcionalmente raro de una co-infección del sistema nervioso central por *Cryptococcus neoformans* y *Mycobacterium tuberculosis* en una estudiante china de 25 años de edad, sin ningún otro tipo de enfermedad, que recientemente participó en un curso post-doctoral en Italia, junto con las dificultades diagnósticas y terapéuticas encontradas durante un período de seis meses de hospitalización, durante el cual se detectaron alteraciones transitorias y/o insignificantes del sistema inmune. Probablemente, ambas complicaciones cerebrales fueron precedidas por una tuberculosis pulmonar no bacilífera. Este episodio de infecciones simultáneas muy poco frecuentes debe reforzar la necesidad de mantener una elevada sospecha clínica de tuberculosis e infecciones oportunistas, aún en ausencia de una evidente inmunodeficiencia e indicios epidemiológicos relacionados.

***Palabras clave*:** co-infección cerebral, criptococosis, tuberculosis, infecciones oportunistas

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Introduction

While the incidence of pulmonary and extrapulmonary tuberculosis is growing in patients with advanced age, immunocompromised subjects, and immigrants coming from developing countries [4,10], (where also brain complications are seen with a frequency greater than that of the general population), the concomitant occurrence of cerebral cryptococcosis plus brain and respiratory tuberculosis in a young and otherwise healthy patient without an evident cause of immunodeficiency and without an obvious exposure, is exceedingly rare (unique, according to all the available literature resources) [12]. In fact, associated central nervous system (CNS) cryptoccosis and tuberculosis had not been ever reported to the best of our knowledge, in absence of a full-blown immunodeficiency (like that descending from an uncontrolled HIV disease).

Case report

A 25-year post-doctoral female student coming from Popular China, with a mute anamnesis, no significant epidemiological clues, and continued, prior wellness, a few days after her arrival in Bologna (Italy) to follow a Master Course at the local University, was hospitalized due to the sudden appearance and rapid worsening of hyperpyrexia, cough, headache, vomiting, and neck and lumbar stiffness. After obtaining a lumbar puncture, the cerebrospinal fluid

(CSF) examination showed an opalescent fluid, with mild pleocytosis (125 leukocytes/µL, with large predominance of mononuclear cells), increased albumin levels (1.72 g/L), and very low glucose levels (0.17 g/L); both microscopy and culture examination, plus the search of the yeast-specific polysaccharide antigen by a commercial agglutination assay, tested positive for *Cryptococcus neoformans* only. On the other hand, when looking for an expected, concurrent immunodeficiency, HIV and HTLV serologies tested negative, and an enlarged immunological-autoimmune-rheumatological workup failed in retrieving an evident underlying immunodeficiency or immune-related disorders: only a proportional reduction of CD4+ T-lymphocyte count was disclosed (29%, leading to an absolute value of 299 cells/µL), together with a slight alteration in selected chemotactic, phagocytic, and killing assays of polymorphonuclear leukocytes, in absence of other recognizable causes of immune system impairment or disorder. Every exposure to pigeon droppings or other respiratory infectious diseases (including tuberculosis) was carefully ruled out. Our patient immediately underwent treatment with high-dose i.v. fluconazole (800 mg/day), followed after two weeks by i.v. liposomal amphotericin B (at 3 mg/Kg/day), since the attained negativization of all mycological assays (achieved after three weeks), did not significantly stop the clinical and especially the neurological deterioration (including weight loss, persistent-irregular fever, asthenia, moderate headache, dizziness, and appearance of focal deficits of oculomotor nerves, leading to diplopia and strabismus). After five comprehensive weeks of systemic antifungal treatment, CSF pleocytosis, increased albumin content and decreased glucose levels were still present, together with the demonstration of intrathecal immunoglobulin synthesis, and persistently negative cryptococcal searches. Only at this time we had the first notice of the slow growth of *Mycobacterium tuberculosis* from the first obtained and cultured CSF, in absence of other positive microscopical and culture searchs on repeated sputum, bronchoalveolar lavage fluid, and urine searches, and in absence of a positive Mantoux intradermal reaction. Already upon admission, the CT scan of the thorax pointed out some small nodular lesions (1-12 mm diameter) at right basal segments, but five weeks thereafter (just when a diagnosis of tubercular meningitis was finally achieved, and an isolate antifungal therapy delivered with mycological success), an increased number of infiltrates with greater size were demonstrated, with tendency to initial cavitation of the largest ones (Figure 1). At this time, a post-hoc diagnosis of a possible non-bacillary pulmonary tuberculosis preceding CNS localization and the overwhelming cryptococcosis, was strongly hypothesized. A series of contrast-enhanced CT examinations of the brain, initially negative for lesions, during the subsequent weeks showed numerous leptomeningeal lesions involving temporal, frontal, ponto-cerebellar, and hypothalamic sites, interpreted as infectious-inflammatory localizations, and better evident with the aid of the magnetic resonance imaging (MRI), when the involvement of base and fourth ventricle cisterns, and associated cranial nerves, became also apparent (Figures 2 and 3). Repeated CSF examinations pointed out a persistently increased leukocyte count (represented by 80-90% by mononuclear cells), increased albumin content, and low glucose levels, with microscopic, culture, and PCR search remaining positive for *M. tuberculosis* for the first two months. After the first notice of a positive *M. tuberculosis* CSF culture, an antitubercular treatment including five drugs (isoniazid, rifampin, etambuthol, pirazinamide and streptomycin) was immediately started and continued for five overall months at our Department. In detail, after the first two months, due to a persistently positive CSF examination and deteriorating clinical-neurological conditions, the anti-tubercular regimen was further potentiated based on the addition of fluoroquinolones (three months), and linezolid too (two months). Neither resistance to antitubercular drugs, nor genetic determinants of resistance to all anti-tubercular drugs, have been found throughout the entire study period.

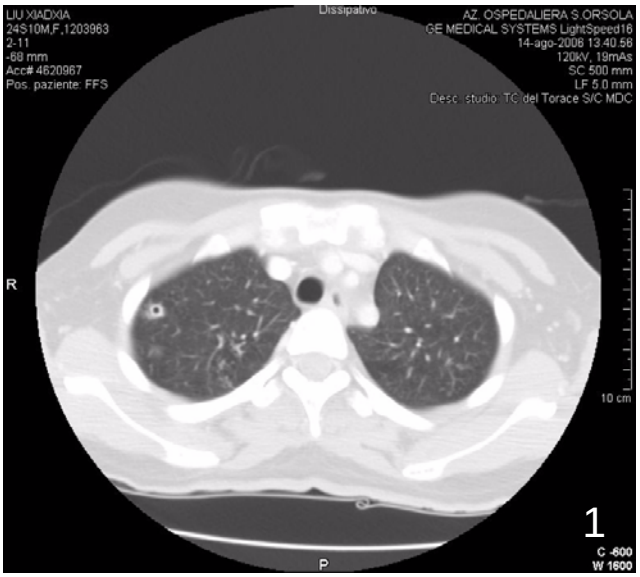

Figure 1. High-resolution thorax computerized tomography (CT) scan, showing multiple, nodular parenchimal lesions, with evident cavitation of one of them.

Notwithstanding a very slow clinical-neurological response, the body weight loss, and the concurrent development of treatment adverse events (like gastrointestinal disturbances, altered serum liver and pancreatic enzymes, and overwhelming sensitive-motor polyneuropathies). After more than six consecutive months of hospitalization, thanks also to an extensive rehabilitation program and the prosecution of anti-tubercular chemotherapy, a very slow ameliorement of clinical, neurological, and neuroradiological features was finally achieved, with almost complete recovery of station, march, and deep tendon reflexes, which were severely compromised during the most acute phase of CNS tubercular infection. Starting with the third month of hospitalization, all the numerous, repeated microbiological controls tested negative for both crypto coccosis and tuberculosis, when examining CSF, respiratory secretions, and urine, while the absolute CD4+ lym-

phocyte count rose up to 399 cells/µL, at the last available control (sixth month).

Figure 2 and Figure 3. A magnetic resonance imaging (MRI) of the brain, in our patient who developed multiple CNS localizations of a neurological and pulmonary tubercular infection, concurrent with a prior, meningeal cryptococcosis. Numerous leptomeningeal lesions in temporal, frontal, ponto-cerebellar, and hypothalamic sites are interpreted as infectious-inflammatory localizations at a gadolinium-enhanced MRI, which also shows the involvement of base and fourth ventricle cisterns, periventricular sites, and associated cranial nerves nuclei.

Later, our patient was followed by another Hospital in her native country (China), where the last available notices referred us a continuation of anti-tubercular therapy for two more months, and further ameliorement of clinical, neurological, and radiological conditions.

Discussion

The present case report, which describes an exceptional concurrence of two severe CNS infections like cryptococcosis and tuberculosis, together with a non-bacillary pulmonary tuberculosis in an otherwise healthy young girl who recently come from China with a mute medical history, no evident exposure, and without obvious causes of immunodeficiency, is a strong invitation to take into careful consideration also the most infrequent ethiologies, when a meningeal inflammation is detected, and a first diagnosis of rare opportunism is already made. The described episodes of CNS cryptococcosis remain extremely rare events when a concurrent HIV disease is excluded [9,11], so that the international literature reports one single, anecdotal case of concomitant CNS cryptococcosis and tuberculosis in a Sudafrican patient with AIDS, followed in the pre-HAART era [12], but HIV infection and related diseases were repeatedly searched and excluded in our patient, whose proportionally reduced absolute CD4+ lymphocyte count and a slight impairment of some leukocyte functions could be attributed to the underlying, invasive CNS and pulmonary tuberculosis, as repeatedly observed [1]. From a pathogenetic point of view, sparse episodes of the so-called "idiopathic CD4+ deficiency" have been anecdotally described [2,6], in patients suffering from opportunistic infections [2], but also in asymptomatic individuals, or in subjects with different, concurrent non-infectious disorders [6]. When considering the first diagnosed opportunism (CNS cryptococcosis), cryptococcal antigen search is a very affordable, highly sensitive and specific technique [5,9], especially when microscopic and culture assays of the CSF complete the recognition. On the other hand, disseminated tuberculosis (and especially CNS localizations) remain notoriously difficult to be diagnosed [8], although familiarity with its clinical manifestations is coming back, after the recent, novel increase of incidence of tuberculosis in the industrialized world, too [4,10]. In our case, the significance of clinical and radiological signs at chest examinations made shortly after admission, increased only after culture isolation of *Mycobacterium tuberculosis* from the CSF, while our patient could possibly suffer from a slowly progressive non-bacillary lung tuberculosis since several weeks. From a therapeutic point of view, the apparently limited clinical (but not microbiological) response to the first high-dose fluconazole cycle prompted an early shift to liposomal amphotericin B [9], but in our particular case the lack of remission of the majority of clinical-neurological signs and symptoms, and the parallel worsening of respiratory signs may be easily attributable to the concurrent tubercular infection, which was not immediately recognized at microscopic search and Mantoux intradermal reaction, but was detected only after the standard culture time (five weeks), and repeatedly confirmed thereafter, while cryptococcal disease was completely cured after three weeks of antifungal therapy. According to recent evidences, also last-generation fluoroquinolones [7], and linezolid too (due to its elevated tissue penetration and its favorable *in vitro* activity against Mycobacteria) [3], may contribute to the multi-drug associated treatment of CNS tuberculosis, although their administration in an extensive association including multiple anti-tubercular drugs did not allow us to extrapolate the specific role played by either fluoroqui-

nolones or linezolid co-administration, in our particular case report.

To conclude, in patients who developed an unexpected opportunistic infection even in absence of evident causes of immunodeficiency, underlying disorders and obvious risk factors, the clinical suspicion for further, underlying disorders should not be disregarded, since additional, unsuspected disorders could remain missed or delayed in their diagnosis and treatment (like a possible non-bacillary pulmonary tuberculosis, in our case).

References

1. Antas PR, Ding L, Hackman J, Reeves-Hammock L, Shintani AK, Schiffer J, et al. Decreased CD4+ lymphocytes and innate immune responses in adults with previous extrapulmonary tuberculosis. J Allergy Clin Immunol. 2006; 117:916-23.
2. Duncan RA, Von Reyn CF, Allegro GM, Toossi Z, Sugar AM, Levitz SM. Idiopathic CD4+ T-lymphocytopenia – four patients with opportunistic infections and no evidence of HIV infection. N Engl J Med. 1993; 328:393-8
3. 3. Johnson JL, Hadad JD, Boom WH, Daley CL, Peloquin CA, Eisenach KD, et al. Early and extended early bactericidal activity of levofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. Int J Tuberc Lung Dis. 2006; 10:605-612
4. 4. Keller A, Delavelle J, Howarth N, Bianchi S, Garcia J. Spinal and neurotuberculosis in an Asian immigrant. JBR-BTR. 2002; 85:136-7.
5. Manfredi R, Moroni A, Mazzoni A, Nanetti A, Donati M, Mastroianni A, Coronado OV, Chiodo F. Isolated detection of cryptococcal polysaccharide antigen in cerebrospinal fluid samples from patients with AIDS. Clin Infect Dis. 1996; 23:849-50.
6. Manfredi R, Calza L, Chiodo F. A new syndrome of long-term idiopathic, severe CD4+ lymphocytopenia, isolated pararesis and conjunctival ischemic microangiopathy. J Biol Regul Homeost Agents. 2004; 18:33-7.
7. Park IN, Hong SB, Oh YM, Kim MN, Lim CM, Lee SD, et al. Efficacy and tolerability of daily-half dose linezolid in patients with intractable multidrug-resistant tuberculosis. J Antimicrob Chemother. 2006; 58:701-4.
8. Paull AE, O'Reilly MA, Stanley PA. Disseminated tuberculosis: still a diagnostic challenge. Med J Austr. 1999; 170:482-5.
9. Saag MS, Graybill RJ, Larsen RA, Pappas PG, Perfect JR, Powderly WG, et al. Practice guidelines for the management of cryptococcal disease. Infectious Diseases Society of America. Clin Infect Dis. 2000; 30:710-8.
10. Sabbatani S, Manfredi R, Legnani G. Chiodo F. Tuberculosis in a metropolitan area of northern Italy: epidemiological trends and public health concerns. Eur J Epidemiol. 2004; 19:501-3.
11. Sabbatani S, Manfredi R, Pavoni M, Consales A, Chiodo F. Voriconazole proves effective in long-term treatment of a cerebral cryptococcoma in a chronic nephropathic HIV-negative patient, after fluconazole failure. Mycopathologia. 2004; 158:165-71.
12. Silber E, Sonnenberg P, Koornhof HJ, Morris L, Saffer D. Dual infective pathology in patients with cryptococcal meningitis. Neurology. 1998; 51:1213-5.