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CASE REPORT

Severe brain co-infection with *Cryptococcus neoformans* and *Mycobacterium tuberculosis* in a young, otherwise healthy student recently immigrated from China

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Summary
Introduction: While the incidence of pulmonary and extrapulmonary tuberculosis is growing in patients of advanced age, immunocompromised subjects, and immigrants coming in from developing countries [Keller A, Delavelle J, Howarth N, Bianchi S, Garcia J. Spinal and neuro-tuberculosis in an Asian immigrant. *JBR-BTR* 2002;**85**:136—7; 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], 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 [Silber E, Sonnenberg P, Koornhof HJ, Morris L, Saffer D. Dual infective pathology in patients with cryptococcal meningitis. *Neurology* 1998;**51**:1213—5.].
Case report: An exceptionally rare case of concurrent central nervous system infection with *Cryptococcus neoformans* and *Mycobacterium tuberculosis* in a 25-year-old otherwise healthy Chinese student, who had very recently joined an Italian post-doctoral course, is described. Also described are the diagnostic and therapeutic difficulties encountered in a five-month hospitalization period, when only transient and/or negligible immune system impairments were detected.
Conclusions: This episode of very infrequent concurrent infections should emphasize the need to maintain an elevated clinical suspicion for opportunistic infections and tuberculosis, even in the absence of an obvious immunodeficiency and related epidemiological clues.

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Introduction

While the incidence of pulmonary and extrapulmonary tuberculosis is growing in patients of advanced age, immunocompromised subjects, and immigrants coming in from developing countries (in whom brain complications are also seen with a frequency greater than that of the general population),[1,2] 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.[3] In fact, to the best of our knowledge, associated central nervous system (CNS) cryptococcosis and tuberculosis has not ever been reported in the absence of a full-blown immunodeficiency (such as that arising from an uncontrolled HIV disease).

Case report

A 25-year-old post-doctoral female student from China, with an unremarkable medical history and with no significant epidemiological clues, who had been well up until a few days after her arrival in Bologna to follow a Masters 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.

A lumbar puncture was performed, and examination of the cerebrospinal fluid (CSF) showed an opalescent fluid, with mild pleocytosis (leukocytes 125×10^6/l, large predominance of mononuclear cells), an increased albumin level (1.72 g/l), and a very low glucose level (0.17 g/l). Both microscopy and culture examination, plus a search for the yeast-specific polysaccharide antigen, tested positive for *Cryptococcus neoformans* only. However, when looking for an expected, concurrent immunodeficiency, serology for HIV and human T-lymphotropic virus (HTLV) were found to be negative, and an expanded immunological—autoimmune—rheumatological workup failed to reveal an evident underlying immunodeficiency or immune-related disorder. Only a proportional reduction of CD4+ T-lymphocyte count was found (29%, leading to an absolute value of 299×10^6 cells/l), together with a slight alteration in selected chemotactic, phagocytic, and killing assays of polymorphonuclear leukocytes, in the absence of other recognizable causes of immune system impairment or disorder.

Exposure to pigeon droppings or other respiratory infectious diseases (including tuberculosis) were ruled out. Our patient immediately underwent treatment with high-dose IV fluconazole (800 mg/day), followed after two weeks with IV liposomal amphotericin B (at 3 mg/kg/day), since the negative results attained for all mycological assays (achieved after three weeks) did not result in any significant arrest in the clinical and especially the neurological deterioration (including weight loss, persistent-irregular fever, asthenia, moderate headache, dizziness, and the appearance of focal deficits of oculomotor nerves, leading to diplopia and strabismus).

After five completed weeks of systemic antifungal treatment, CSF pleocytosis and increased albumin and decreased glucose levels were still present, together with the findings of intrathecal immunoglobulin synthesis and persistently negative cryptococcal searches. It was only at this time that we were able to observe the first slow growth of *Mycobacterium tuberculosis* from the original cultured CSF, in the absence of other positive microscopic and culture searches on repeated sputum, bronchoalveolar lavage fluid, and urine searches, and in the absence of a positive Mantoux intradermal reaction.

In a computed tomography (CT) scan of the thorax on admission, some small nodular lesions (1—12 mm diameter) were in evidence in the right basal segments, but five weeks later (at the point when a diagnosis of tubercular meningitis was finally achieved and an isolate antifungal therapy delivered), an increased number of infiltrates with greater size was demonstrated, with a tendency to initial cavitation of the largest ones. A series of contrast-enhanced CT examinations of the brain, initially negative for lesions, showed numerous leptomeningeal lesions during the subsequent weeks involving temporal, frontal, pontocerebellar, and hypothalamic sites, interpreted as infectious-inflammatory localizations; these were better evident with the aid of magnetic resonance imaging (MRI), when the involvement of base and fourth ventricle cisterns and associated cranial nerves also became apparent (Figure 1).

Repeated CSF examinations pointed to a persistently increased leukocyte count (represented by 80—90% mononuclear cells), increased albumin content, and low glucose levels, with microscopic, culture, and PCR investigations remaining positive for *M. tuberculosis* for the first two months. At the first signs of a positive *M. tuberculosis* CSF culture, anti-tubercular treatment including five drugs (isoniazid, rifampin, ethambutol, pyrazinamide, and streptomycin) was immediately started and continued for months. After the first two months, due to a persistently positive CSF examination and deteriorating clinical—neurological conditions, the anti-tubercular regimen was further potentiated with the addition of fluoroquinolones (for three months) and linezolid (for two months).

In spite of the very slow clinical—neurological response, the body weight loss, and the concurrent development of treatment adverse events (gastrointestinal disturbances, altered serum liver and pancreatic enzymes, and overwhelming sensory-motor polyneuropathies), after more than five consecutive months of hospitalization, thanks also to an extensive rehabilitation program and the undertaking of anti-tubercular chemotherapy, a very slow improvement in her clinical, neurological, and neuro-radiological picture was finally achieved, with almost complete recovery of posture, mobility, and deep tendon reflexes, which were severely compromised during the most acute phase of CNS tubercular infection.

Starting at the third month of hospitalization, all the numerous, repeated microbiological controls tested negative for both cryptococcosis and tuberculosis, when examining CSF, respiratory secretions, and urine, while the absolute CD4+ lymphocyte count rose to 399×10^6 cells/l at the last control (fifth month).

Discussion

The present case report, which describes the exceptional occurrence of two severe CNS infections — cryptococcosis and tuberculosis together with a non-bacillary pulmonary tuberculosis — in an otherwise healthy young girl who had recently come to Italy from China, with an unremarkable medical history, no evident exposure, and without obvious

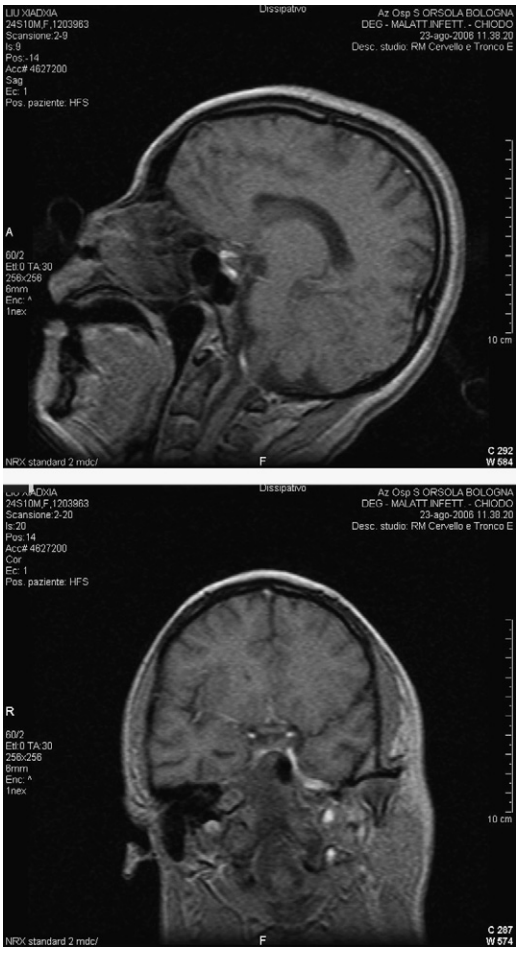

Figure 1 Magnetic resonance imaging (MRI) of the brain of our patient who developed multiple CNS localizations of a neurological and pulmonary tubercular infection, concurrent with a meningeal cryptococcosis. Numerous leptomeningeal lesions in temporal, frontal, pontocerebellar, and hypothalamic sites are interpreted as infectious-inflammatory localizations on gadolinium-enhanced MRI, which also shows the involvement of base and fourth ventricle cisterns, periventricular sites, and associated cranial nerve nuclei.

causes of immunodeficiency, is a strong invitation to take into careful consideration the most infrequent etiologies when a meningeal inflammation is detected and a first diagnosis of rare opportunism has already been made.

Episodes of CNS cryptococcosis like the one described herein, remain extremely rare events when a concurrent HIV disease is excluded;[4,5] the international literature reports only two anecdotal cases of concomitant CNS cryptococcosis and tuberculosis or tuberculoma in a South African patient with AIDS, followed in the pre-HAART era.[3] HIV infection and related diseases were repeatedly searched for 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.[6] From a pathogenetic point of view, sparse episodes of the so-called 'idiopathic CD4+ deficiency' have been anecdotally described[7,8] in patients suffering from opportunistic infections,[7] but also in asymptomatic individuals and in subjects with different, concurrent non-infectious disorders.[8]

When considering the first disease diagnosed — CNS cryptococcosis — a cryptococcal antigen test is very affordable and a highly sensitive and specific technique,[4,9] especially when microscopic and culture assays of the CSF complete the identification. On the other hand, disseminated tuberculosis, especially in CNS localizations, remains notoriously difficult to diagnose,[10] although familiarity with its clinical manifestations is reemerging following the recent, novel increase in tuberculosis incidence in the industrialized world.[1,2]

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;[4] following this, the lack of remission of the majority of the clinical—neurological signs and symptoms, and the parallel worsening of respiratory signs, are easily attributed to the concurrent tubercular infection, which was not immediately recognized by microscopic search and Mantoux intradermal reaction. This tubercular infection was only detected after the standard culture time (five weeks) and was repeatedly confirmed thereafter, while the cryptococcal disease was completely cured after three weeks of antifungal therapy.

According to recent evidence, last-generation fluoroquinolones[11] and linezolid (due to its elevated tissue penetration and its favorable in vitro activity against mycobacteria),[12] may make valuable contributions to the multi-drug treatment of CNS tuberculosis, although their extensive administration along with multiple other antitubercular drugs did not allow us to determine the specific role played by either fluoroquinolone or linezolid co-administration in our particular case report.

To conclude, in patients who develop an unexpected opportunistic infection even in the 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 undetected resulting in delayed diagnosis and treatment.

Conflict of interest: No conflict of interest to declare.

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