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Case Report

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Leptomeningitis in a Person with Radiologically Isolated Syndrome and Latent Tuberculosis: A Case Report with Implications for Clinical Research

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Abstract

A 39-year-old man, followed with serial MRI of CNS for a radiologically isolate syndrome (RIS, a recently described condition considered a subclinical form of MS), was hospitalized for the occurrence of a leptomeningitis. Routine blood tests and contrast enhanced total body CT scan were unremarkable. Cerebrospinal fluid (CSF) examination showed increase of cells (22 mononuclear cells/mm3), albumin (294 mg/L), immunoglobilins G (161 mg/L) and Link Index (1.9), with 17 oligoclonal bands. Microbiological examinations of CSF (including those for Koch's Bacillus) were negative. The Mantoux reaction and the QuantiFERON test were positive, featuring a latent tuberculosis (TB). The patient started prophylaxis with rifampicin and isoniazid for four months, until a new MRI showed the disappearance of the leptomeningeal enhancement, and the stability of white matter brain and spinal cord lesions. Two other MRI scans showed a new brain Gd-enhancing lesion nine month after anti-tubercular therapy and, after additional six months, new cerebral and spinal cord areas. This case provides the following suggestions about the effects of TB infection and related therapies on the underlying autoimmune status: the infection, while actively present, did not exacerbate the RIS condition; the worsening nine months after the prophylaxis discontinuation might have been the 'natural' evolution of RIS condition. Alternative speculative hypotheses include a remote effect of the infection, of isoniazid (that was reported in some cases to trigger MS), or the result of the clearance of the infection itself. Irrespective of the existence of any interaction between RIS and TB infection, It seems important to collect cases with MS-related diseases and concomitant infections, that may provide clues about disease pathogenesis and treatment.

Keywords

Multiple sclerosis, Radiologically isolated syndrome, Tuberculous meningitis, Neuroinflammation, Mycobacterium

Introduction

Tuberculous meningitis (TBM) is a rare and severe manifestation of extra-pulmonary tuberculosis, characterized by headache, vomiting, meningeal signs, focal deficits, vision loss, cranial nerve palsies and raised intracranial pressure. The differential diagnosis of TBM includes other infectious disease, inflammatory

diseases of leptominges and meningeal carcinomatosis. Tuberculosis of the central nervous system is a still major cause of death or significant neurological disability. Consequently, prompt diagnosis and early treatment are of the utmost importance and magnetic resonance imaging (MRI) is of great help.

We describe a case of probable TBM, occurring in a person with radiologically isolated syndrome (RIS). RIS is a new entity, diagnosed when the unanticipated MRI finding of brain spatial dissemination of focal white matter (WM) lesions highly suggestive of multiple sclerosis (MS) occurs in subjects without symptoms typical of MS, and with normal neurological examinations [1]. Approximately one-third and two-thirds of individuals respectively experience clinical onset and/or radiological progression over a mean follow-up of five years [1]. However, predictors (male sex, age < 37, spinal cord involvement) of higher risk of progression have been identified and conversion to clinically isolated syndromes (CIS) was described in 84% of RIS individuals with spinal cord lesions over a median time of 1.6 years from the date of the first MRI [2]. Being RIS condition in many instances a form of subclinical MS, our case may have relevance to understand the relationship between neuroinflammation and *Mycobacterium tuberculosis*.

Case Report

A 39-year-old man, experienced transient (less than 4 hours) and migrating paresthesia (head, tongue, upper limbs). For this disturbance he performed an MRI scan of brain and spinal cord that revealed white matter lesions, compatible with inflammatory demyelinating lesions of the brain (Figure 1A-D). Not having history of previous clinical events, and the reported symptoms being nonspecific, the subject fulfilled the criteria for RIS [1].

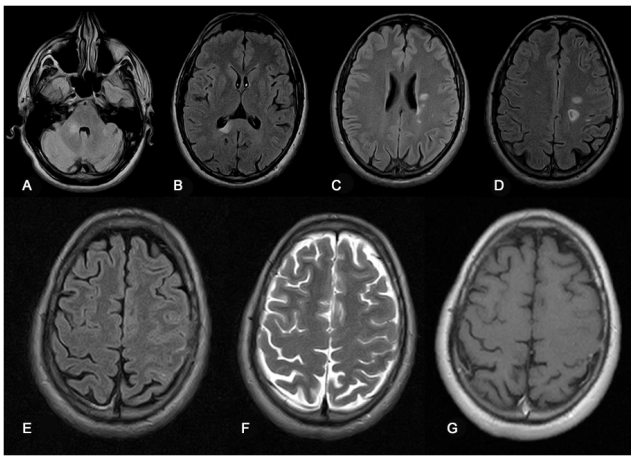

Figure 1: (A-G) First MRI examination. T2 FLAIR images showed white matter lesions compatible with inflammatory pathogenesis.

A second MRI scan, performed after two months to check possible evolution (in the absence of symptoms or signs), showed cerebral edema with leptomeningeal enhancement in the left frontal cortex (Figure 2A-C, arrows). Because of this MRI picture the subject was hospitalized and a diagnostic process was implemented. The following exams were normal: routine blood tests and protein electrophoresis, serology for herpes viruses (cytomegalovirus, Epstein-Barr virus, *Varicella zoster*, Herpes simplex 1/2) hepatitis viruses (B and C) HIV, *Treponema pallidum*, *Borrelia burgdoferi*, Mycoplasma, Chlamydia, Toxoplasma, Brucella, Aspergillus and Candida, oncomarkers, autoantibodies, C3, C4, folate and vitamin B12. Typing for HLA-B*08, HLA-B*27 was negative. The radiological picture remained substantially unchanged at a third MRI exam (twenty days after hospitalization).

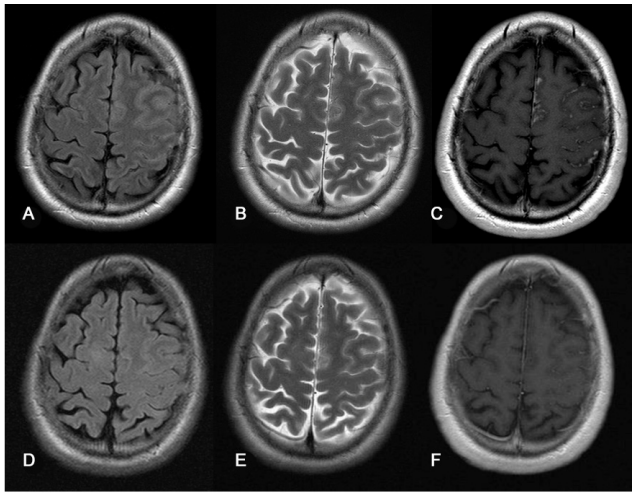

Figure 2: (A-F) Second MRI examination after two months. **(A)** In the rolandic subarachnoid spaces and in the inter-emispheric region is evident a reduced visualization of subarachnoid spaces in T2 FLAIR. **(C)** Mild enhancement after gadolinium injection. **(F)** After 5 months this enhancement decreased, **(D)** a reduced visualization of subarachnoid spaces remained.

Cerebrospinal fluid (CSF) was clear and showed the following data: 22 mononuclear cells/mm^3, glucose 64 mg/dl, protein 54.1 mg/dl, increased albumin (294 mg/L), IgG (161 mg/L) and Link Index (1.9), with presence of 17 oligoclonal bands (type two pattern). Microbiological examination of CSF (microscopy for common germs and Koch's Bacillus (BK), bacterial culture for common germs and BK, PCR for neurotropic viruses and BK, direct search for cryptococcus antigen and cryptococcus culture) was negative. CSF cytology showed marked lymphocytosis without patterns of lymphoproliferative diseases. A total body computerized tomography was normal. Standard and sleep deprivation electroencephalogram showed very modest electrical alterations in frontal lobes with left prevalence. The Monteux Intradermal reaction resulted positive (an infiltrate diameter > 5 mm). Accordingly, QuantiFERON test was positive (> 4; normal range 0.00-0.35). A diagnosis of probable TBM was done, even though we were not able to shed light on further etiologic cues: the patient is a white man, with a negative history for past contact with TB cases, as well as for relevant past medical conditions.

During hospitalization, the patient underwent a cycle of 21 days of therapy with acyclovir, and then started Rifampicin 600 mg and Isoniazid 300 mg daily, with B6

vitamin 300 mg daily, which continued for four months, until a new MRI showed the disappearance of the leptomeningeal enhancement, and the stability of white matter brain and spinal cord demyelinating lesions (Figure 2D-F, arrows). He has been followed with serial MRIs: nine months after anti-tubercular therapy discontinuation a new MRI showed a new brain Gd-enhancing lesion and after additional six months (last MRI scan) new cerebral and spinal cord areas appeared, at level of C2-C3 and C5-C6, without gadolinium enhancement (Figure 3A-C). Currently the patient remains asymptomatic.

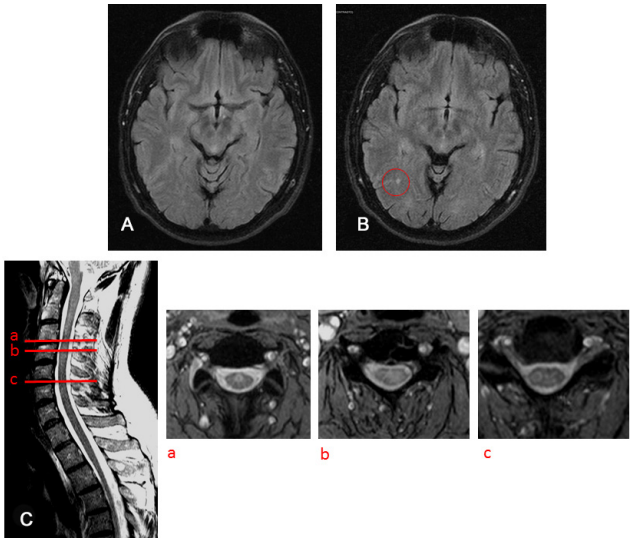

Figure 3: (A-C) MRI follow-up. New lesions in cervical spinal cord were evident.

Discussion

This case raises two points: one is more pragmatic and concerns the clinical management of patients with apparent CNS complication of *Mycobacterium tuberculosis*, in the absence of a direct demonstration of the microbe; the other one is more complex and deals with the relationship between mycobacteria and neuroinflammation. Concerning the first point, the lack of microscopic, cultural or PCR evidence of mycobacterium is not a rare event. Nonetheless, with positive Mantoux test and QuantiFeron, the preventive therapy for latent TB is indicated for 3 months. The disappearance of leptomeningeal involvement after anti-TB treatment indirectly supports the mycobacterial etiology.

The relationship between mycobacteria and neuroinflammation is multifaceted. It is known that mycobacteria, as components of complete Freund adjuvant, are needed together with myelin auto-antigens to induce the animal model of MS experimental autoimmune encephalomyelitis (EAE). However, the so-called "adjuvant approach" has long been known to be protective for EAE: the observation is that the exposure to mycobacterium or Freund adjuvant before immunization with myelin autoantigens prevents the development of EAE. Along this line, vaccination with Bacillus Calmette-Guerin (BCG) seems to be beneficial in neuroinflammation, reducing MRI disease activity in patients with early MS and in people with CIS, where a preventive effect on conversion to definite MS was also observed [3, 4]. In the context of the relationship between mycobacteria and neuroinflammation there are recent investigations on the association between *Mycobacterium avium* subspecies *paratubercolosis* (MAP) and MS in Sardinia: significant differences between patients and controls in MAP DNA and humoral response against MAP proteins were reported, along with the presence of antibodies cross-recognizing MAP epitopes and myelin epitopes in sera and cerebrospinal fluid of MS patients [5]. Lastly, the possible effects of anti-tubercular treatments on neuroinflammation should be taken into account. The case of a patient with diagnosis of primary progressive MS and concomitant isoniazid (INH) therapy, started after positivity of tuberculin skin test, was recently described. The authors hypothesized that INH, in a genetically susceptible individual, may activate CNS auto-reactive T cells and ultimately initiate a demyelinating disease [6].

Conclusion

A single case report, also with some uncertainties about the diagnosis of tuberculosis, does not allow to draw firm conclusions about the effects of the infection and related therapies on the underlying autoimmune status. The infection, while actively present, did not exacerbate the RIS condition. The lack of any interaction between these concomitant events is plausible: the MRI progression may represent a 'natural' evolution of the RIS condition. Alternative, speculative hypotheses to explain the worsening after nine months from anti-tubercular therapy discontinuation might be a remote effect of the infection, or of isoniazid [6], or the result of the clearance of the infection itself. Irrespective of the existence of any interplay between RIS and TBM, it is important to collect experience on cases of neuroinflammatory diseases and concomitant infectious conditions since this effort may provide answers to important questions about disease pathogenesis and treatment.

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