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Cerebral tuberculosis - a diagnostic challenge

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Abstract

English:

Background: *Central nervous system (CNS) tuberculosis (TB) accounts for 1% of all cases of TB and is a major cause of mortality and morbidity. Cerebral tuberculomas represent 30% of CNS TB and is a diagnostic challenge.*
Case presentation: *A 42-year-old male patient, known with alcoholic cirrhosis, performs a cerebral computer tomography (CT) after a lipothymic episode accompanied by right hemiparesis, which showed multiple parenchymal ring-lesions (inflammatory-infectious substrate/secondary tumours). Subsequently, the thoracic-abdominal-pelvic-CT-scan reveals micronodular diffuse pulmonary infiltrate and right pleural effusion. Cerebral Magnetic resonance imaging (MRI) describes bilateral infra/supratentorial lesions, raising the suspicion of tuberculomas. HIV serology was negative, cerebrospinal fluid showed no pleocytosis, but high protein level, pleural lymphocytosis in the pleural effusion and positive GeneXpert test in bronchial aspirate. The diagnosis of military TB with cerebral tuberculomas was established. The outcome was favourable under antituberculous treatment initially associated with corticosteroids. At two months the patient had a significant improvement in pulmonary lesions, but while some cerebral lesions decreased in size other lesions increased (paradoxical reaction). At the 14-month end-of-treatment re-evaluation there was an important regression in number and size of the brain lesions.*
Conclusions: *The diagnosis of cerebral tuberculoma remains a challenge for the clinician due to non-specific clinical and radiological findings. The survival rate is over 80% with early diagnosis and correct treatment.*

Keywords

cerebral tuberculoma • miliary tuberculosis • cerebral lesions • paradoxical reaction

Tuberculoza cerebrală – o provocare diagnostică

Rezumat

Romanian:

Context*: Tuberculoza (TB) sistemului nervos central (SNC) reprezintă 1% din totalul cazurilor de TB și este o cauză majoră de mortalitate și morbiditate. Tuberculoamele cerebrale constituie 30% din TB-SNC și reprezintă o provocare diagnostică.*
Prezentarea cazului*: Pacient de sex masculin în vârstă de 42 ani, cunoscut cu ciroză hepatică toxic-nutrițională, efectuează un examen Computer Tomograf (CT) cerebral în urma unui episod lipotimic însoțit de hemipareză dreaptă, ce evidențiază multiple leziuni inelare parenchimatoase (substrat inflamator-infecțios/tumoral secundar). Ulterior, CT-ul toraco-abdomino-pelvin descrie infiltrat pulmonar micronodular difuz și revărsat pleural drept. Imagistica prin Rezonanță Magnetică (IRM) cerebrală descrie leziuni inelare bilaterale infra/supratentoriale, ridicând suspiciunea de tuberculoame. Serologia HIV a fost negativă, lichidul cefalorahidian fără pleiocitoză dar cu nivel crescut de proteine, lichidul pleural evidențiază limfocitoză iar testul GeneXpert este pozitiv în aspiratul bronșic. Se stabilește diagnosticul de TB miliară cu tuberculoame cerebrale. Sub tratament antituberculos asociat cu corticoterapie sistemică, rezultatul final a fost favorabil. La două luni se observă o ameliorare semnificativă a leziunilor pulmonare, dar cu toate că unele leziuni cerebrale au scazut în dimensiuni, altele s-au mărit (reacție paradoxală). La reevaluarea de la 14 luni, finalul tratamentului, se observă netă regresie numerică și dimensională a leziunilor cerebrale.*
Concluzii*: Diagnosticul de tuberculom cerebral rămâne o provocare pentru clinician din cauza nespecificității clinice și imagistice. Rata de supraviețuire este de peste 80% dacă diagnosticul este stabilit precoce și tratamentul instituit rapid.*

Cuvinte-cheie

tuberculom cerebral • tuberculoză miliară • leziuni cerebrale • reacție paradoxală

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Introduction

Central nervous system (CNS) tuberculosis (TB) accounts for 1% of all cases of active TB and it is often caused by the haematogenous dissemination of *Mycobacterium tuberculosis* from primary pulmonary infection [1]. Cerebral TB can manifest as cerebritis, meningitis, tuberculomas, or tuberculous abscesses, mostly being severe and with a high rate of mortality and morbidity [2]. Risk factors for CNS TB include chronic alcoholism, malignancies, malnutrition, and immunosuppression [3]. Approximatively 30% of the parenchymal lesions of CNS TB are represented by cerebral tuberculoma, found as either solitary or multiple lesions in any site of the intracranial space and it may or may not associate meningitis [4]. CNS TB diagnosis is difficult when an extra-neural TB involvement is not found.

We report the case of a patient with multiple cerebral tuberculomas in which the diagnosis was confirmed due to concomitant extra-neural foci of TB, which offered safer and more accessible sites for diagnostic samplings.

Case presentation

A 42 years old white male, non-smoker was brought to the Emergency Room with a sudden loss of consciousness accompanied by right hemiparesis. He was complaining of fever and mild headache for the past 2 weeks. His medical history included alcoholic hepatic cirrhosis. The clinical examination revealed fever (38.2˚C), abolished vesicular murmur on the right basal side, abdominal collateral circulation with moderate quantity of ascitic fluid, and right hemiparesis. Blood pressure was 110/60 mmHg, heart rate of 63 bpm and oxygen saturation of 93%. The rest of the physical examination was within normal limits. The blood tests showed inflammation with erythrocyte sedimentation rate (ESR) >46 mm, C-Reactive Protein (CRP) of 19 mg/dL), white blood cells (WBC) of 13.800/mmc, haemoglobin of 10.2 g/dl, alkaline phosphatase (ALP) of 128 U/L, total bilirubin of 1.9 mg/dL, a spontaneous international normalized ratio (INR) of 1.8 and HIV test was negative. The other results were within normal limits.

Cerebral computerized tomography (CT) was performed and revealed multiple parenchymal brain lesions with contrast enhancement and peri-lesional oedema (Figure 1). The thoracic-abdominal-pelvic CT scan found micronodular diffuse lung-milled infiltrate and right pleural effusion with hepato-splenomegaly and ascites (Figure 2).

A cerebral magnetic resonance imaging (MRI) scan was performed that described multiple supra- and infratentorial nodular lesions (approximately 30 in number), with sizes up to 15 mm, with iso- to hypointense center on T1 and T2-weighted images, that associate ring enhancement and peri-lesional oedema (Figure 3).

Cerebrospinal fluid (CSF) analysis showed normal cell count, protein level of 121 mg/dl, lactic acid level of 20.2 mg/dL, and glucose level of 70 mg/dL. Acid fast stains were negative, as well as India ink and Gram stains. Polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* and adenosine deaminase (ADA) measurements were not performed. The analysis of the pleural fluid revealed a transudate, with 275 cell/mm^3, 88% lymphocytes and ADA within normal limits. PCR for *M. tuberculosis* was negative. Sputum examination did not identify any common pathogen and acid-fast bacilli (AFB) smear was also negative.

A bronchoscopy examination was carried out, and the smear from the bronchial aspirate was negative for AFB but the GeneXpert MTB/RIF test was positive and showed no resistance for RMP.

Antituberculous treatment with isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA), and ethambutol (EMB) (HRZE) in doses

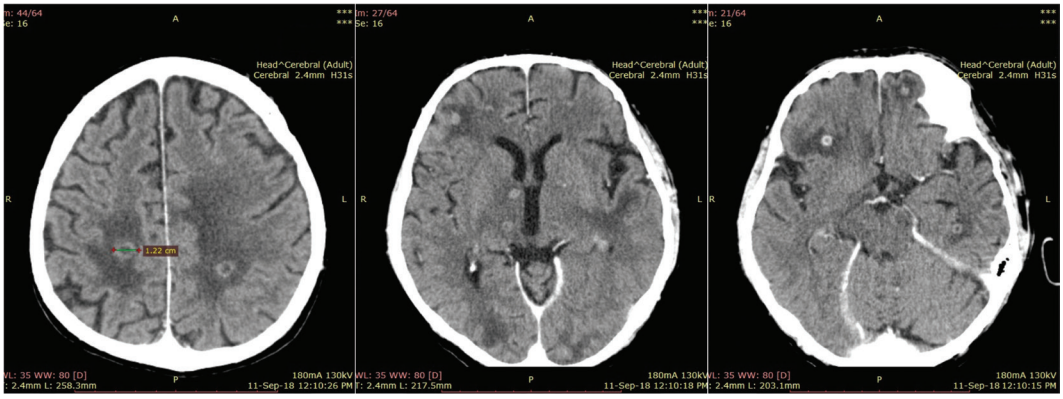


Figure 1. Initial Cerebral CT scan: multiple space-occupying lesions, diffusely distributed throughout the cerebral parenchyma, hyperdense with contrast enhancement that associates significant peri-lesional oedema.

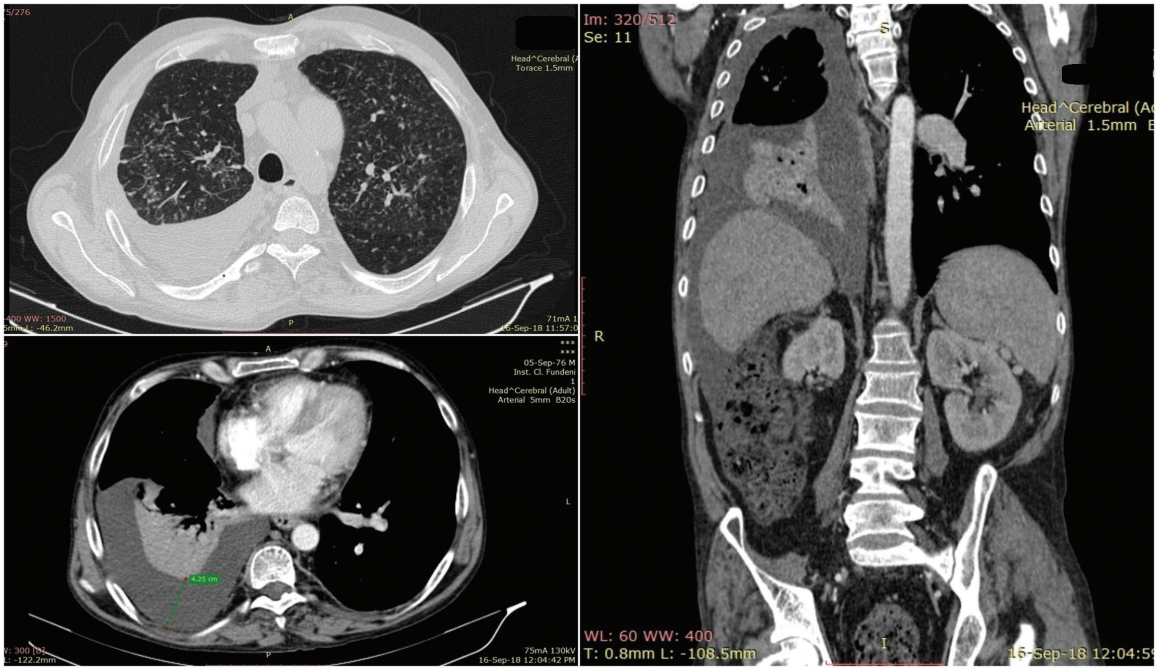


Figure 2. Initial thoracic-abdominal-pelvic CT scan: At the pulmonary level, it describes diffuse pulmonary micronodular infiltrate, with a miliary appearance that associates right pleural effusion and underlying lung collapse. At the abdominal level, hepato-splenomegaly and interhepato-diaphragmatic ascites fluid are described.

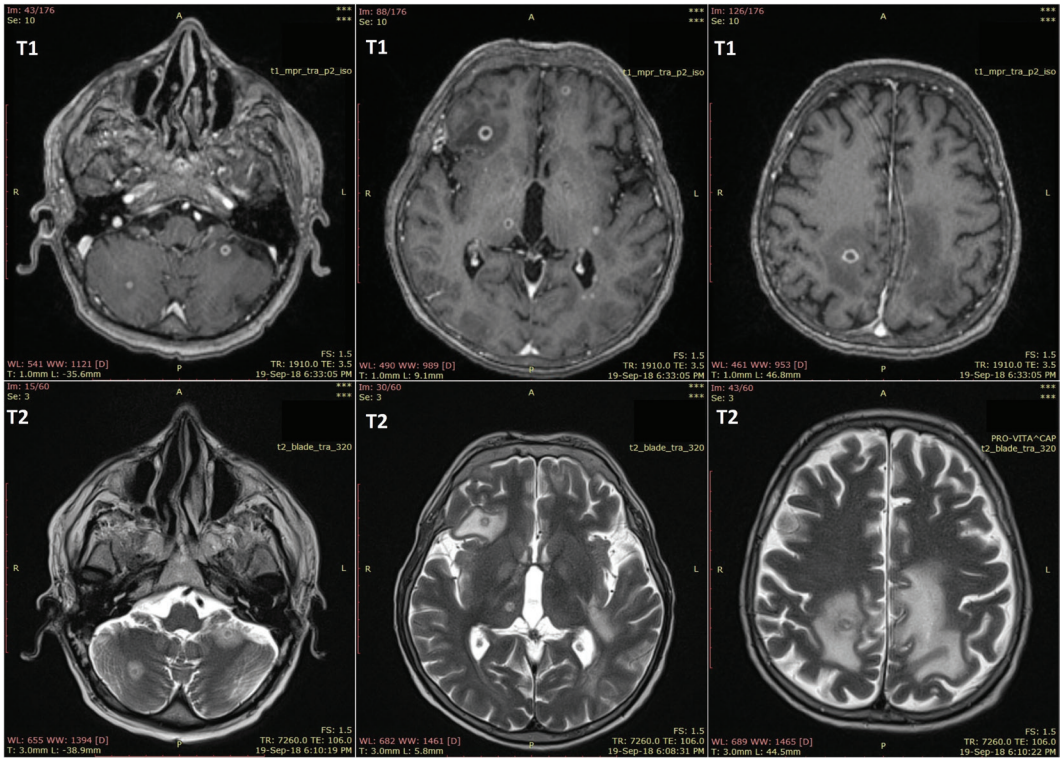


Figure 3. Initial Cerebral MRI: numerous space-occupying lesions with iso- to hypointense center on T1-weighted images, hypointense center on T2-weighted images, with peripheral contrast-enhancing and surrounding high signal intensity oedema.

calculated for the patient's weight was initiated on the day 5 from his admission, associated with corticosteroids (IV dexamethasone was given for 7 days, followed by oral prednisone 1 mg/kg body weight daily, which was tapered over eight weeks).

At the 2-month evaluation, the patient was in good general condition, with partial motor deficit. Blood tests were within normal limits. The initial cultures from the bronchial aspirate were positive for *M. tuberculosis*, and drug susceptibility testing (DST) revealed no resistance. Thoracic CT reassessment showed important regression of the interstitial micronodular infiltrates and of the right pleural effusion (Figure 4). A follow-up cerebral MRI scan showed some lesions that have decreased in size and also an increased size of lesions in the cerebellum and right frontal lobe (Figure 5, 2nd month). Anti-tuberculous treatment continued with INH and RMP maintenance therapy three times a week as directly observed therapy, until a total duration of 14 months.

Radiologic evaluations were made at the 2, 7 and 14 months after the treatment onset. After 14 months of treatment, the patient was in good general condition with no motor deficit and no symptoms. Cerebral MRI showed significant regression of the lesions, the one in the frontal lobe being substantially smaller and with less peri-lesional oedema (Figure 5). The comparative cerebral MRI - 3D reconstruction images at diagnosis and at the end of treatment also showed

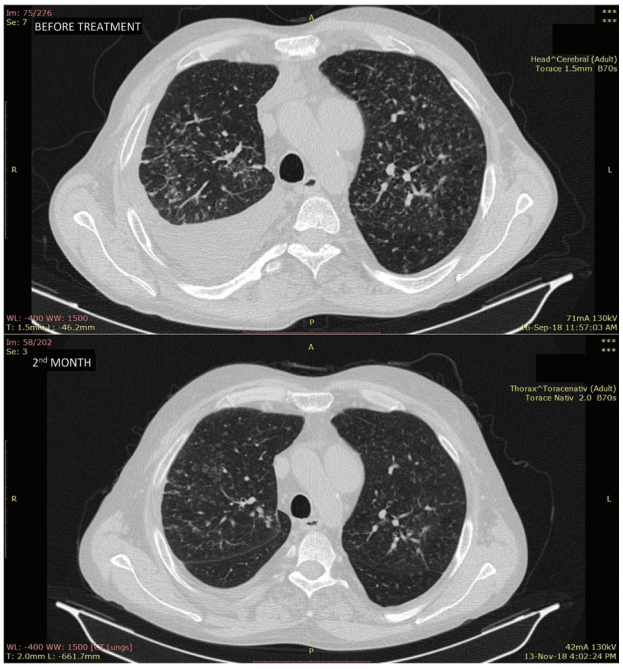


Figure 4. Comparative Thoracic CT scan: initial and after 2 months of treatment: improved radiological appearance with less interstitial micronodular infiltrates and also significant regression of right pleural effusion.

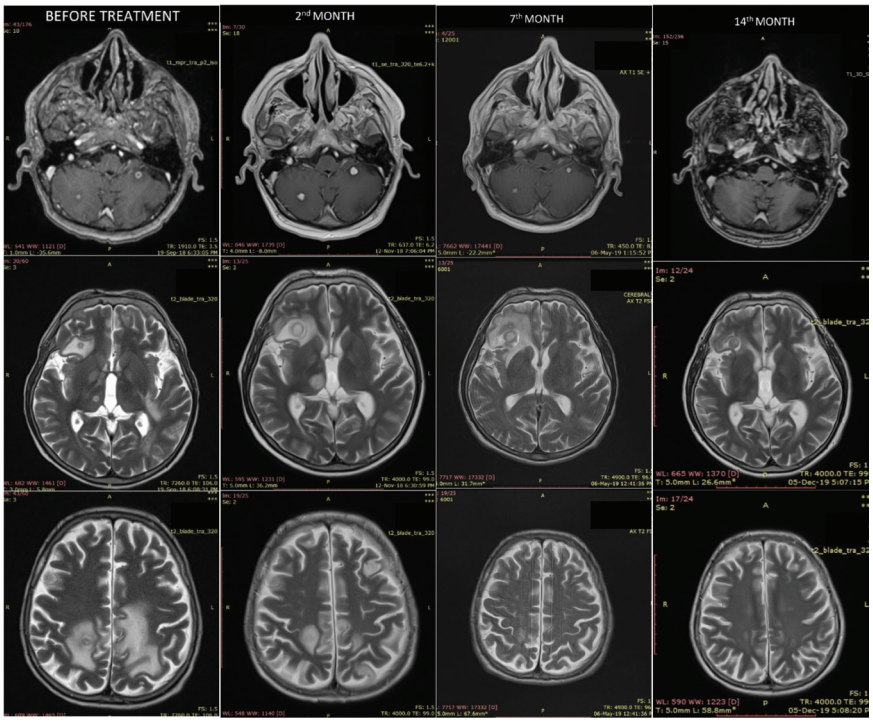


Figure 5. Comparative Cerebral MRI scan: initial and after 2, 7 and 14 months of treatment: 2nd month: paradoxical radiological reaction with an increase in the size of some lesions; 7th month: radiological improvement of all lesions; 14th month: significant numerical and dimensional regression of the lesions with small areas of cerebral oedema and the frontal lesion that remains considerably smaller.

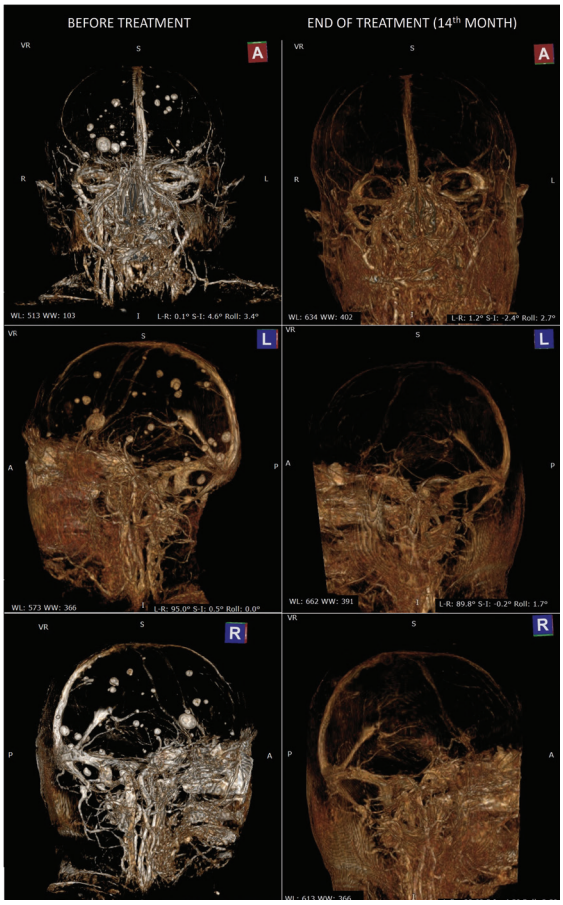


Figure 6. Comparative cerebral MRI - 3D reconstruction images: before and end-of-the treatment: complete remission of ring enhancement lesions.

the disappearance of ring enhancement lesions (Figure 6). At this moment, the treatment was considered completed, and the patient remained under periodic re-evaluation.

Discussions

CNS TB infection has one of the most severe clinical manifestations and carrying one of the highest rates of morbidity and mortality [5, 6]. Along with tuberculous meningitis, tuberculoma is the most common lesion in CNS TB and can be found in any parts of the intracranial space [7]. When tubercles in the brain parenchyma enlarge, without rupturing into the subarachnoid space, they form solitary or multiple lesions that can occur with or without meningitis [4]. Histologically, a mature tuberculoma is a granulomatous reaction consisting of a central necrotic caseous area surrounded by a capsule containing lymphocytes, epithelioid cells, fibroblasts, and giant Langhans cells [1, 3, 7].

Risk factors include young age, malnutrition, alcoholism, chronic diseases, malignancies, HIV coinfection, and the use of immunosuppressive agents [3, 5]. Our patient is a 42-year-old male without HIV infection, but with immune suppression due to malnutrition, alcoholism, and hepatic cirrhosis. The difficulty of diagnosis lies in the absence of defining clinical and paraclinical criteria for CNS TB. Clinical aspects of cerebral tuberculomas depend on their anatomical location and they are often asymptomatic [8]. The most common findings include headache, drowsiness, vomiting, fever, or weight loss. Focal or generalized seizures and hemiparesis are also frequently reported in adults, but these symptoms are regularly seen with many other space-occupying CNS lesions [1, 9]. Hemiparesis and fever were the only two symptoms of our patient. The radiological findings are non-specific and the differential diagnosis includes sarcoidosis, neurocysticercosis, metastasis, pyogenic abscesses, toxoplasmosis, multiple sclerosis, etc [7]. The features can vary based on whether the lesion is caseating with a solid center, caseating with a liquefied center, or solid, noncaseating [10]. Our patient's lesions are iso- to hypointense on T1- and T2-weighted MRI, and show ring enhancement, a specific description of caseous lesions with a solid center.

The typical analysis of CSF from patients with tuberculous meningitis shows lymphocytic pleocytosis, hypoglycorrhachia, and elevated protein levels, the latter being the only modification in the patient's chart [1, 3, 11].

Early diagnosis is extremely important because clinical outcomes and survival rates mostly depend on prompt treatment [9]. It should be emphasized the importance of extensive screening for tuberculosis (full-body CT, Thoracic X-ray, abdominal ultrasound, AFB smear sputum), knowing that CNS TB associates miliary tuberculosis in 30-50% of cases [3]. The fact that the lung lesions were bacteriologically confirmed, allowed us to consider that the cerebral lesions are also tuberculous, and initiate specific treatment. Anti-tuberculosis chemotherapy (ATT) is the standard treatment for intracranial tuberculomas and includes RMP, INH, PZA, and EMB. Additionally, corticosteroids in the early stages may improve outcomes by reducing local inflammation and intracranial pressure [5].

Up to a quarter of properly treated TB patients may experience a paradoxical increase in tuberculomas size and number. This uncommon reaction is due to an Immune Reconstitution Inflammatory Syndrome (IRIS) and has an onset median time of three months after starting ATT [5]. This reaction represents an excessive immune response against *M. tuberculosis* (alive or dead) that may occur in either HIV-infected or, more rarely, uninfected patients [12]. Some studies have estimated the frequency of TB-IRIS between 2% and 23% in HIV uninfected patients with a higher percentage in those with disseminated TB or undiagnosed RMP resistance [5, 13, 14]. The most

frequent manifestations of paradoxical TB-IRIS include recurrent fever, worsening dyspnoea, and new or enlarging tuberculomas. Although there is no standard treatment for TB-IRIS, depending on the location and severity of the lesions, systemic corticosteroid therapy for four to six weeks improves the outcome of certain forms such as symptomatically enlarged cerebral tuberculoma [12].

In our case, after two months of specific treatment, TB-IRIS occurred. Systemic corticosteroids were administrated for eight weeks and anti-tuberculous therapy was continued until 14 months.

When the *M. tuberculosis* strain is sensitive to all drugs the guidelines recommend two months of HRZE attack therapy that continues with HR for up to 12-18 months with imaging reassessment [8, 15]. Corticosteroids are associated in the first two months with the role of reducing local inflammation and peri-lesional oedema. Acknowledging the fact that many variables can affect the response of the disease to therapy, some studies suggest that treatment duration should be adapted to the radiological response [16, 17]. After 12 months of treatment over two-thirds of the patients still have contrast-enhancing lesions [16]. Continuation of ATT beyond 18 months provides no additional benefit [18].

Considering the good general condition of the patient, the complete remission of the symptoms and the significant reduction of the cerebral lesions, we concluded that it is convenient to end the ATT after 14 months of administration. The patient remained under medical observation for periodic evaluations.

Conclusion

Being a rare condition with various clinical and imaging manifestations, CNS TB remains a challenge for any clinician. Extensive screening for tuberculosis is extremely important in these cases. Our patient had multiple cerebral tumours that were reinforced as tuberculous only after lung lesions were bacteriologically confirmed. It is necessary to consider that cerebral tuberculomas may be complicated by a paradoxical increase in size, despite proper medication. After attack therapy was started, TB-IRIS occurred, but only with lesions enlargement and no new clinical manifestations. ATT and corticotherapy were continued with a favourable outcome. We, therefore, emphasize the importance of regular clinical and radiological follow-up. Taking into consideration the CNS TB high mortality and morbidity associated rate, early diagnosis and prompt treatment are essential for a better survival rate.

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