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Limbic encephalitis associated with tuberculous mediastinal lymphadenitis

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ABSTRACT

Introduction: Limbic encephalitis represents an autoimmune disorder that is commonly associated with malignancies. It is also seen in association with infectious or systemic autoimmune diseases. The literature reports two case reports of limbic encephalitis associated with tuberculosis.

Case Report: We report the case of a 42 year-old male referred to our clinic for a non-resolving pneumonia. He was found to have a limbic encephalitis associated with mediastinal tuberculous lymphadenitis. The diagnosis was made on a needle aspirate from a mediastinal lymph node obtained through endobronchial ultrasound. A paradoxical radiological progression was noted during therapy. He was successfully treated by anti-tuberculous drugs with clinical and radiological improvement.

Conclusion: Limbic encephalitis is associated with tuberculosis and should be included as part of the central nervous system involvement with tuberculosis. Endobronchial ultrasound has been shown to be useful in the diagnosis of mediastinal tuberculous lymphadenitis.

1. Introduction

Limbic encephalitis represents an autoimmune disorder that can occur in association with cancers, infections or systemic autoimmune diseases. Confusion, irritability, depression, psychosis, sleep disorders and hallucinations can be seen in patients with limbic encephalitis. Also noted is short-term memory loss, epileptic seizures and behavioral changes. In this paper we report a case of limbic encephalitis associated with mediastinal tuberculous lymphadenitis diagnosed with the use of endobronchial ultrasound-guided transbronchial aspiration and successfully treated with anti-tuberculous regimen.

2. Case report

A 42 year-old male patient with no prior medical history was referred to our clinic following multiple courses of antibiotics for a non-resolving right upper lobe (RUL) pneumonia. He was complaining of excessive sweating, chills, and cough. The patient reported unintentional weight loss of 14 Kg over the last 4 months. A previous CT scan of the chest showed RUL cavitary infiltrates with large mediastinal adenopathies. PCR-TB on the bronchoalveolar washing (BAW) was negative. His serology for connective tissue disease and HIV infection were also negative.

Upon presentation to our institution he was complaining of abdominal pain, headache, fever, and chills. On physical examination he was conscious, not very cooperative, and disoriented to place, time and persons. He had no focal neurological deficit with normal reflexes and cranial nerves exam. His preliminary labs showed a mild leukopenia (WBC = 3700) with thrombocytopenia (platelets count = 80,000), a slightly elevated ESR (35 mm/h) with normal chemistries and liver function tests. A chest X-Ray showed mediastinal widening and increased lung markings in the RUL (Fig. 1). An enhanced CT scan of the brain showed no abnormalities. A CT scan of the abdomen and pelvis with IV contrast showed splenomegaly with few enlarged peri-portal lymph nodes and a large mediastinal multiloculated cystic necrotic adenopathy mainly in the right para-tracheal area along with multiple subcarinal and right hilar adenopathies (Fig. 1). He was admitted to the regular ward and started on Ceftazidime and Clindamycin for a suspected necrotizing pneumonia. Bronchoscopy showed whitish secretions draining from the apical segment of the RUL. Endobronchial Ultrasound (EBUS) showed multiple enlarge lymph nodes at the 4R station with the largest one measuring 2.9 cm. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) from the adenopathy revealed numerous acid-fast bacilli consistent with mycobacterial infection. On the 6th day of his stay, and after being started on five anti-tuberculous drugs (Isoniazid, Rifampin, Ethambutol,

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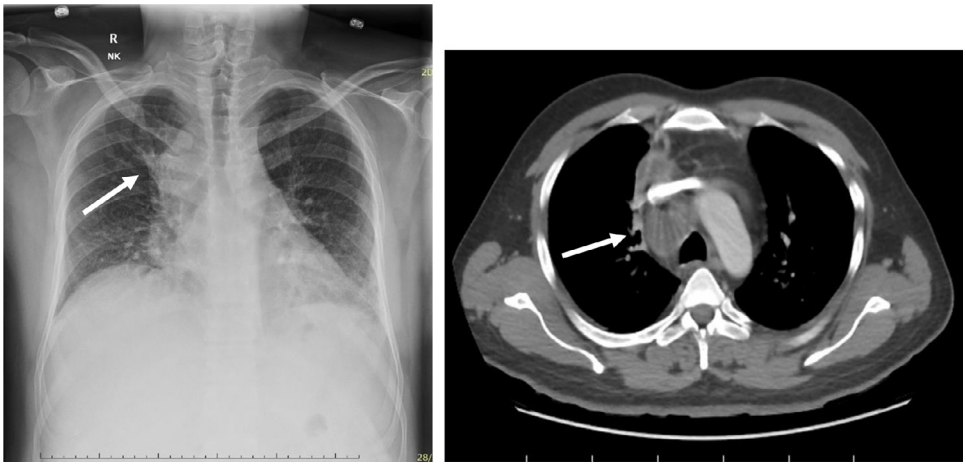

Fig. 1. Chest X-ray upon presentation (a) revealed mediastinal widening and increased lung markings in the right upper lobe; CT scan of the chest upon presentation (b) a large right para-tracheal lymph node is noted (arrow).

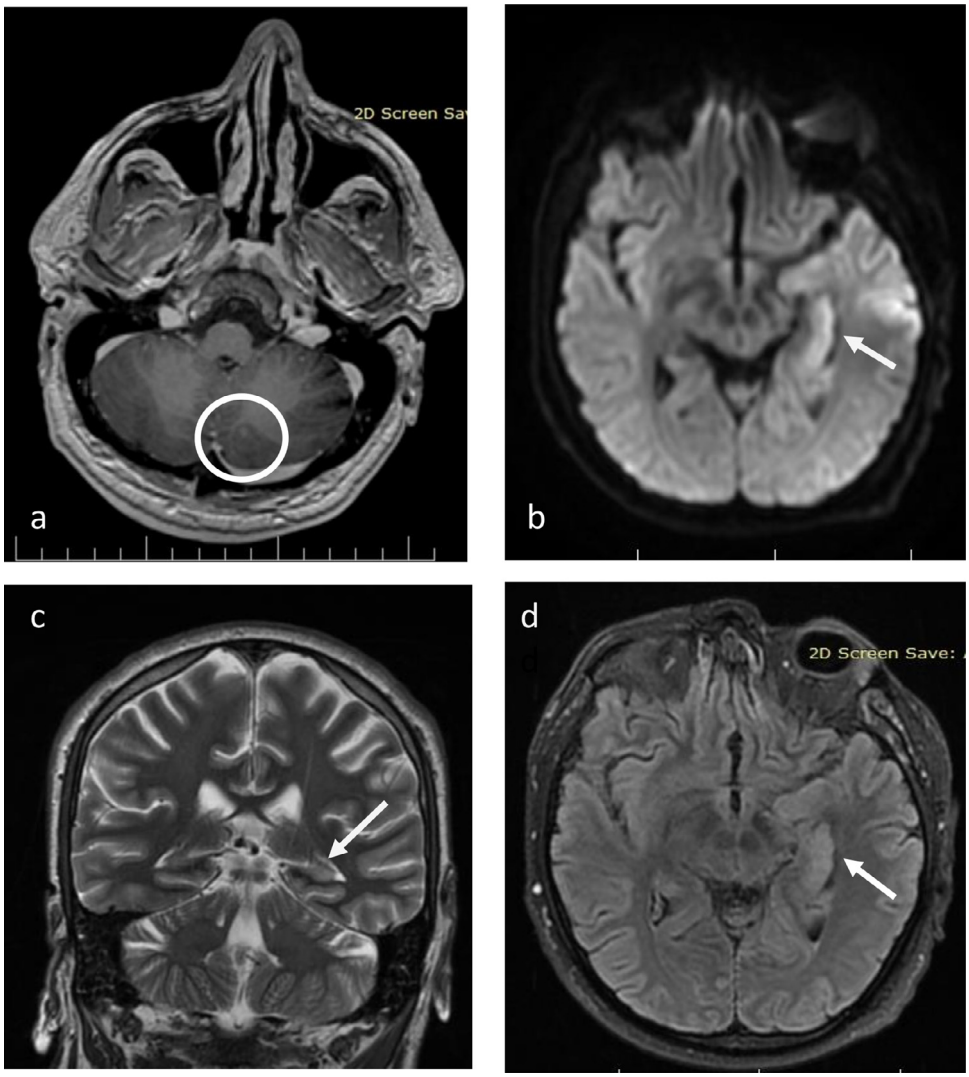

Fig. 2. Post-contrast T1 sequence (a) showing a tiny enhancing lesion in the cerebellum suggestive of granuloma (encircled).
Axial Diffusion (b), coronal T2SE (c) and axial FLAIR (d) show signal increase and mild diffusion restriction in the left limbic system ((hippocampal area and amygdala) compatible with limbic encephalitis (arrows).

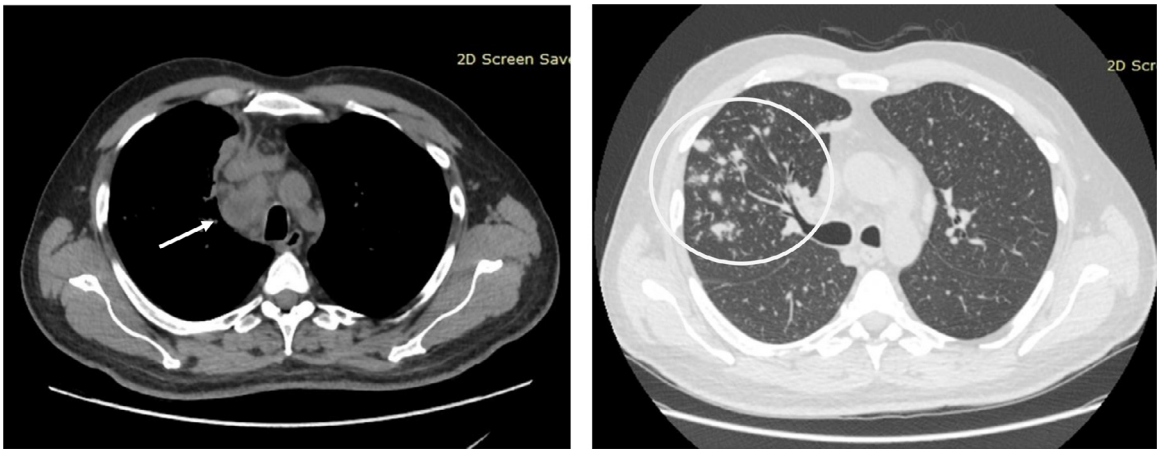

Fig. 3. Follow-up chest CT after 8 weeks of anti-TB drugs shows a decrease in the size of the mediastinal lymphadenopathies (arrow in mediastinal window) with development of new peri-bronchial nodularities in tree-in-bud distribution affecting mostly the right upper lobe (encircled in lung window).

Pyrazinamide, Moxifloxacin), the patient became more confused with impaired short-term memory and visual hallucinations. An MRI of the brain demonstrated an increased signal intensity on T2/FLAIR in the left hippocampal gyrus and ipsilateral amygdala with faint diffusion restriction, beside multiple tiny enhancing cortical and/or leptomeningeal foci at the supra and infratentorial levels (Fig. 2). Those findings were suggestive of granulomas with limbic encephalitis. An EEG showed no evidence for epileptic activity. Over the next few days, his clinical status improved with periods of defervescence, and improved level of consciousness. He was discharged home on hospital day twelve. Culture of the BAW taken from the RUL grew a multisensitive strain of Mycobacterium tuberculosis.

A follow up 4 weeks later revealed a slow clinical improvement. The patient was kept on 4 anti-tuberculous drugs: Isoniazid, Rifampin, Ethambutol, and Pyrazinamide. The patient was seen again 6 weeks later with further improvement of his symptoms and reported weight gain. The follow up CT scan chest showed an interval decrease in the size of the mediastinal necrotic adenopathies with development of peribronchial nodules in tree-in bud distribution affecting mostly the RUL but also the RLL, which could be due to endobronchial tuberculosis (Fig. 3). An MRI of the brain at the same time showed a resolution of the findings suggestive of limbic encephalitis but with significant interval increase in the number of the lesions involving the brain at the supra and infra-tentorial levels (Fig. 4). We counted more than 50 lesions. In the context of the clinical and radiological discrepancy, the patient was kept on quadruple anti-tuberculous regimen for a total of 4 months then switched to bitherapy (Isoniazid, Rifampin). Nine weeks later a follow up CT scan chest showed significant disease response evidenced by a significant decrease in the size and extent of the peribronchial nodules and a decrease in size of the mediastinal adenopathies (Fig. 5). The follow up brain MRI showed also a significant decrease in size and number of the intracranial lesions (Fig. 6). He will continue a total of 9 months of bitherapy.

3. Discussion

Limbic encephalitis (LE) corresponds to a group of autoimmune conditions characterized by inflammation of the limbic system [1]. LE is caused by a reaction of the immune system against several different neuronal antigens, as a response to various stimuli such as tumors, cancers, infections and generalized autoimmune disorders [2]. There are two forms of autoimmune LE: paraneoplastic LE (PLE) which is associated with a tumor or cancer, most commonly small cell cancer, breast cancer, testicular tumors, teratomas, Hodgkin's lymphoma and thymomas [3]; and non-paraneoplastic LE (NPLE) when LE occurs in the absence of cancer, such as in the case of infection (herpes simplex virus or syphilis) or systemic autoimmune disorders [2]. There are only 2 cases in the literature that report an association between LE and tuberculosis [4,5].

LE is clinically characterized by an acute or subacute onset of short-term memory disorders, psychiatric disorders, confusion and temporal lobe epilepsy [6]. The brain MRI shows on T2 and FLAIR sequences hyperintensities in the limbic regions such as the internal part of the temporal lobe, hippocampus and amygdala, cingulate gyrus, fornix and hypothalamus, which could be helpful in the diagnosis of LE [7]. Autoimmune LE can be categorized as either group I or group II according to the location of their neuronal antigens, with group I antibodies targeting intracellular antigens and group II antibodies targeting antigens on the cell surface. Although searching for the antibodies is not mandatory for the diagnosis, it might have implications for treatment response, association with an underlying malignancy, and overall long-term prognosis [8]. Our patient was diagnosed with LE based on typical clinical and radiological findings in a patient with positive AFB aspirate from his mediastinal adenopathies., therefore a search for specific antibodies nor a CSF examination were not performed. As the radiologic findings resolved well on anti-tuberculous drugs; we speculate that the LE was related to tuberculosis. As the patient improved nicely on anti-tuberculous drugs immunotherapy was no longer considered.

Central nervous system (CNS) involvement with *Mycobacterium tuberculosis* accounts for approximately 1% of all cases of tuberculosis [9]. CNS tuberculosis can be classified into two categories: intracranial (tuberculous meningitis, tuberculous encephalopathy, tuberculous vasculopathy, CNS tuberculoma (single or multiple) and tuberculous brain abscess); or spinal (Pott's spine and Pott's paraplegia, non-osseous spinal tuberculoma and spinal meningitis) [10]. CNS tuberculomas produce variable symptoms depending on their location. Low-grade fever, headache vomiting, seizures, focal neurological deficit, and papilledema are characteristic clinical features of supratentorial tuberculomas. Infratentorial tuberculomas are more common in children and may present with brainstem syndromes, cerebellar manifestations, and multiple cranial nerve palsies [11–13]. Treatment of a tuberculoma is based on anti-TB treatment regimens. A paradoxical response or paradoxical progression of the intracranial tuberculoma is reported when expansion of an intracerebral tuberculoma or newly detected lesions are seen on follow up images after initiation of the anti-TB medications [14,15]. This phenomenon is regarded as highly suggestive of CNS tuberculosis [16]. The tuberculomas typically increases in size or number 1–7 months after initiating the anti-tuberculous therapy. These aggravated lesions can be misdiagnosed as treatment failure or other tumorous pathology. In our case, the patient received a 5 drugs regimen for his severe tuberculosis as we were concerned about a potentially resistant strain in a critically ill patient with disseminated

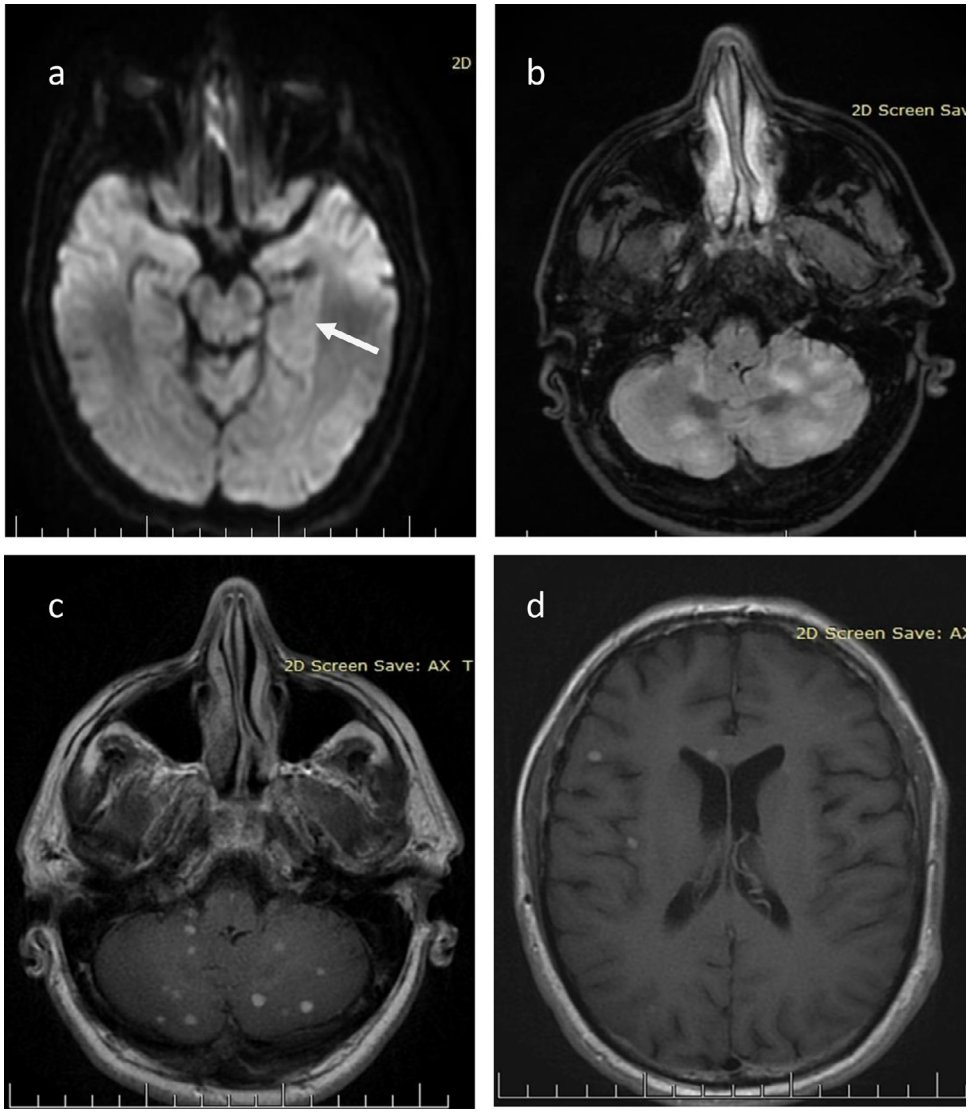

Fig. 4. MRI exam 8 weeks after therapy showed resolution of the limbic encephalitis (arrow a) with normal appearance of the limbic system on the Diffusion sequence but with significant interval increase in the number of the enhancing nodular lesions (granulomas) in both cerebellar and cerebral hemispheres (FLAIR sequence b, T1 SE post-contrast sequence c and d).

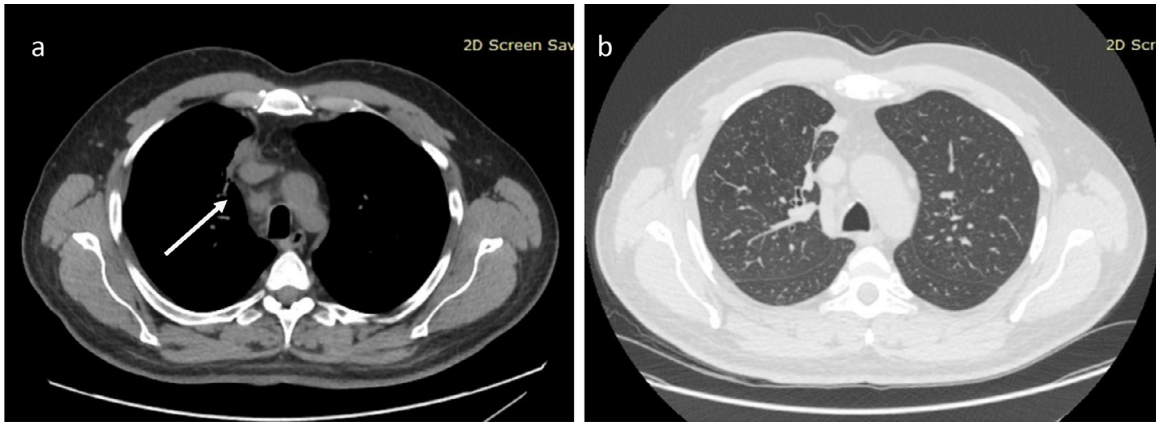

Fig. 5. Plain CT scan of the chest 6 months after initiation of anti-TB treatment showed significant decrease in the size of mediastinal adenopathies (arrow in mediastinal window a) and peribronchial nodularities (lung window b).

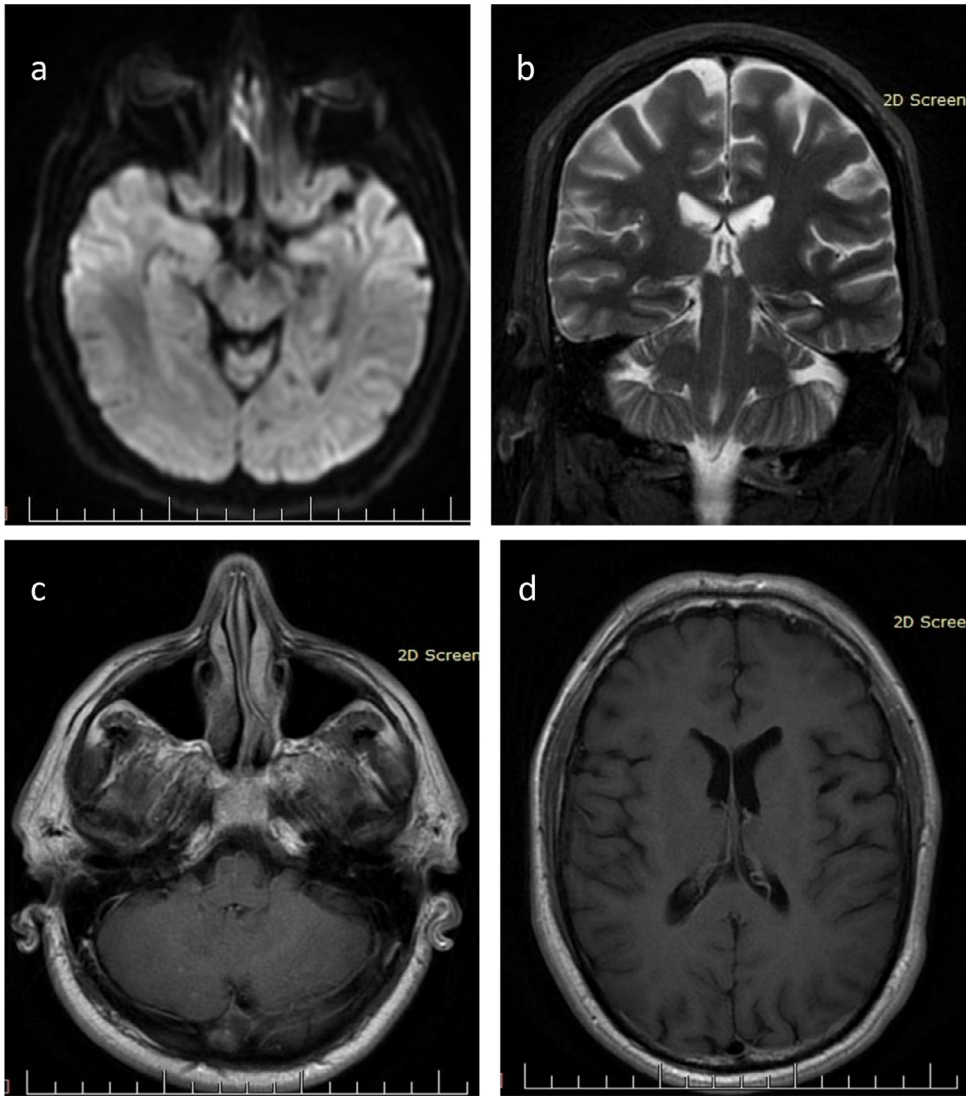

Fig. 6. Follow-up MRI (6 months after initiation of therapy) shows significant decrease in size and number of the intracranial lesions and normal appearance of the limbic system (axial Diffusion a, coronal T2SE b, axial post-contrast T1SE c and d).

tuberculosis. As the culture showed a multisensitive strain the anti-tuberculous regimen was de-escalated to a 4 drugs regimen (Isoniazid, Rifampin, Ethambutol, and Pyrazinamide). After 10 weeks of therapy, the patient had a significant clinical improvement with worsened radiological findings, that was explained by the "paradoxical progression" and therefore we expanded the duration of therapy.

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive technique allowing sampling of mediastinal lymph nodes via fine needle aspiration under direct sonographic visualization. It has a low rate of morbidity, and has demonstrated utility in the diagnosis of mediastinal lymphadenopathy secondary to malignancy, lymphoma and sarcoidosis [17–21]. Diagnosis of mycobacterial lymph node infection by EBUS-TBNA was first reported in 2009 [22]. Recently several studies have shown that EBUS-TBNA is a safe and well tolerated procedure in the assessment of patients with mediastinal tuberculous lymphadenitis and demonstrates good sensitivity for a microbiologic diagnosis of isolated mediastinal lymphadenitis. When culture and histological results are combined with high clinical suspicion, EBUS-TBNA demonstrates excellent diagnostic accuracy (78%–91% (95% confidence intervals, 84–94%)) and negative predictive value (56%–89% (95% confidence intervals, 82–93%)) for the diagnosis of mediastinal tuberculous lymphadenitis [23–25]. Our patient had negative AFB and PCR-TB on the regular BAW and was diagnosed with tuberculous lymphadenitis based on numerous AFB on the EBUS-TBNA tissue therefore he was started earlier on anti-TB treatment and a mediastinoscopy was avoided.

4. Conclusion

EBUS has been shown to be useful in the diagnosis of mediastinal tuberculous lymphadenitis. LE should be included as a part of the spectrum of CNS involvement with tuberculosis. A paradoxical progression evidenced by radiological worsening of tuberculomas during the therapy course should be suspected and should not prevent the continuation of the treatment.

Declaration of Competing Interest

There is no financial interest or any conflict of interest to declare.

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None.

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