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Cerebral Tuberculoma in a Lung Transplant Patient

Banderas Montalvo E[1], Pérez González V[1], Alonso Moralejo R[1], Ruiz Morales J[2] and De Pablo Gafas A[1]

[1]*Pulmonology Department, Hospital 12 de Octubre, Madrid-Spain*
[2]*Neurology Department, Hospital 12 de Octubre, Madrid-Spain*

Abstract

The risk of infection caused by *Mycobacterium tuberculosis* in transplanted patients increases 20-74 times compared to general population, with an incidence in Spain from 0, 4-0, 8%, and is higher in lung transplant patients. Almost 50% of the tuberculosis cases might be disseminated. The infection of central nervous system (CNS) is not common, less than 1%, presenting as meningitis, tuberculomas or cerebral abscess. We present a 55 years old patient with a diagnosis of lung tuberculosis 40 months after lung transplantation. One month later, he started with neurologic symptoms and persistent fever, with radiologic findings compatible with cerebral tuberculomas. Corticoid therapy was added to tuberculostatic treatment. One month later, he presented seizures that were controlled with anticonvulsant treatment. In every transplanted patient with space occupying lesions in central nervous system and infectious symptoms cerebral tuberculosis must be suspected like one possible diagnosis.

Keywords: Tuberculosis; Tuberculomas; Transplantation; Lung

Introduction

Tuberculosis remains as one of the most severe and prevalent infections worldwide. In transplanted patients tuberculosis is quite important, mainly because of the delay in treatment related with difficulties in the diagnosis and toxicity of tuberculostatic treatment [1]. The risk of acquiring tuberculosis in transplanted patients increases between 20 to 74 times in comparison with the rest of the population [2]. The prevalence of tuberculosis in transplant patients varies from 2 to 6.5%. The risk factors for developing the infection are being a lung transplant patient [3-5], immunosuppressive therapy, exposition to *Mycobacterium tuberculosis* and previous comorbidities. The involvement of the CNS in this infection is approximately 1%, nevertheless is one of the most severe manifestations, tuberculomas are rare and a challenge for their diagnosis. The risk of infection of the CNS increases in young and immunosuppressed patients as the lung transplant patients [6-8].

Case Report

A 55 year old man, born in Spain, diagnosed of usual interstitial pneumonia by videothoracoscopy in 2008. He underwent a right single lung transplant in May 2010, having a negative pre-transplant tuberculin skin test with a negative booster test. During the post transplantation period, he developed moderate renal failure, hypercholesterolemia, cytomegalovirus (CMV) syndrome in January 2011 with CMV infection in April 2013, and an atherotrombotic ictus in the right medial cerebral artery.

In September 2013, he presented a functional decrease with unspecific radiology (Figure 1), a bronchoscopy with bronchoalveolar lavage was done, and in which *Mycobacterium Tuberculosis* complex was isolated. Tuberculostatic treatment was started with isoniazid 300 milligrams (mg) per day, ethambutol 1200 mg per day, pyrazinamide 1750 mg per day, rifabutin 300 mg per day and pyridoxine. Immunosuppression was maintained with tacrolimus, everolimus and prednisone 7.5 mg per day. Prophylaxis was made with cotrimoxazole and inhaled amphotericin B.

Fifteen days later, he started with loss of fine movements of the left hand and fine tremor that increased during the next week without neurological focality. He maintained daily fever. In the physical examination claudication of the left superior limb and weakness of distal and extensor muscles were found. A magnetic resonance imaging (MRI) was made (Figure 2) in which 8 supratentorial uptake lesions were found, some cortical, in both hemispheres with vasogenic oedema and peripheral ring form uptake, that suggested multiple tuberculomas as first possible diagnosis, at this time anticonvulsant treatment with levetiracetam was started with 1000 mg every 12 hours. At this moment the patient had two negative BAAR in sputum and maintains the tuberculostatic treatment. A lumbar puncture was

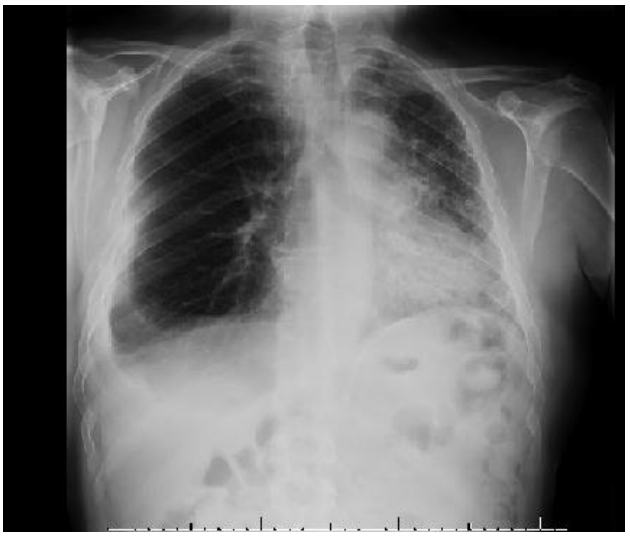

Figure 1: Thorax Rx at tuberculosis diagnosis.

***Corresponding author:** Banderas Montalvo E, Pulmonology Department, Hospital 12 de Octubre, Avenida de Córdova S/N 28041 Madrid-Spain, Tel: +34653458389; E-mail: emibanderas@hotmail.com

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made and the result showed a traumatic procedure: 13 leukocites, 54% of polymophonuclear neutrophils, 46% mononuclear cells, 11,694 hematies, glucose 56 mg/deciliter (blood sugar 92 mg/deciliter), proteins 0.59 grams/liter, allowing to exclude meningeal affection (normal macroscopic appearance, 60% of the blood glucose, normal proteins). With the diagnosis of cerebral tuberculomas the patient was discharged with tuberculostatic treatment and 60 mg of prednisone per day in a decreasing guideline until the usual dose (7.5 mg per day) was reached in order to control de perilesional oedema.

Forty days later, the patient present partial tonic-clonic seizures in the left superior limb with posterior general seizures with complete recovery and an adequate response to a single dose of intravenous diazepam and maintaining the same dose of levetirazetam. At the physical exam left superior limb weakness with tremor was observed. The MRI (Figure 3) showed a decrease in the size of the lesions (tuberculomas) and in the vasogenic oedema that surrounded them without mass effect. An electroencephalogram was realized observing some irregularities from the temporal lobe with an unspecific morphology without clear epileptic activity between crises. Tuberculostatics, corticoids and anticonvulsant treatment was maintained.

Eight months after the diagnosis, the patient keeps on with the treatment with rifabutin, isoniazid, levetirazetam and corticoids. An adequate control of the seizures was achieved with a distal slight paresia in the left hand, with an MRI (Figure 4) that shows improvement in the size of the lesions, describing a good response. A table of the progression of the case is shown in the Figure 5.

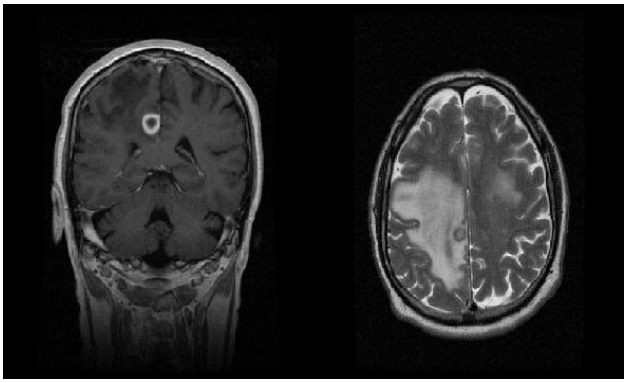

Figure 2: First MRI.

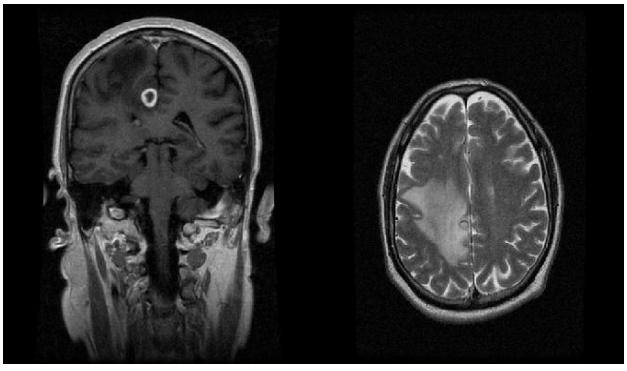

Figure 3: Second MRI.

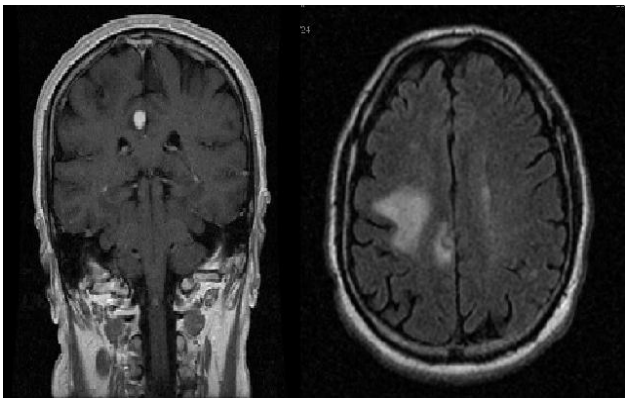

Figure 4: Third MRI.

Discussion

Spain is one of the countries with the higher number of solid organ transplantation, this is why the rate of infections related with transplants is higher, including tuberculosis. The prevalence of tuberculosis in transplanted patients in Spain varies from 0.4 to 0.8% with an incidence of 2072 cases per 10^5 inhabitants per year [2,9]. There are few reviews about these types of infections in lung transplantation; nevertheless some series describe an incidence between 2.5 and 6.5% [10]. Only one third of the cases have previous exposition, the rest of infections are acquired in the post-transplant or transmitted by de donor. According to the series that describe tuberculosis in transplanted patients, it develops between the sixth month and the first year after transplantation.

The patients with positive tuberculin skin test (induration higher than 5 millimeters) who are being evaluated for a possible transplantation must be interrogated about previous prophylaxis or treatment, if they do not have it, and after verifying that there is no active tuberculosis, isoniazid should be started and maintained for 9 to 12 months. These patients must be regularly monitored with sputum microscopy and sputum cultures during the first year after the beginning of isoniazid [11,12]. In our case report the tuberculin skin test and the booster test were negative before the transplantation.

Tuberculosis risk is increased in these patients because of the impairment of the cellular immunity. The majority of the cases present as lung tuberculosis, even though there are certain series that describe almost 39% of disseminated tuberculosis, nevertheless the CNS involvement remains quite rare. In the review made by the Spanish Network of Infection in Transplantation, 14.3% presented disseminated tuberculosis, only one case had meningitis and it was not a lung recipient. There are few cases of tuberculomas in solid organ recipients, but it might appear even after 11 years post transplantation. Our case report is one of the first that describe cerebral tuberculomas in a lung transplanted patient.

Tuberculomas are a rare form of presentation of tuberculosis. The diagnosis is quite difficult because of their unspecific insidious nature that may simulate certain aggressive neoplasms, or even other space occupant lesions like pyogenic abscesses, other granulomatose infection like cysticercus. The risk of development increases in young immunosuppressed patients, like solid organ transplanted patients. The symptoms are headache, vomit, dizziness and in some cases hemiparesis, seizures and papilledema (space occupying lesions); sometimes fever may appear. The diagnosis is made with the clinic, a

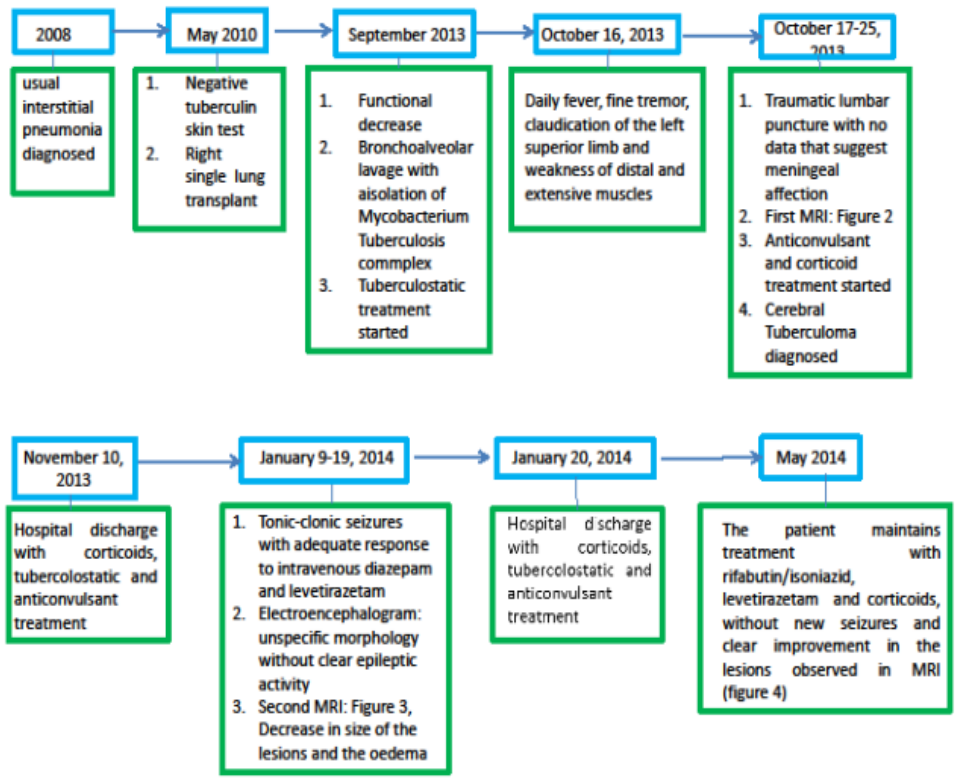

Figure 5: Evolution chart.

normal cerebrospinal liquid except if there is concurrent meningitis, and by radiology. The cranial scanner might show hypo dense lesions surrounded by an uptake ring. The MRI is quite useful; it allows locating the lesion and if there is associated oedema. It distinguish the lesion state with T1 and T2 based in its nature, if it is caseating or non-caseating. Cerebral tuberculomas may be distinguished from the entities mention before (neoplasms, abscesses, cysticercus) by their lower T2 weighted [6] because of its lipid content. Diagnosis should be tried with noninvasive tests but if it is not possible, neurosurgical biopsy must be the next step.

The treatment is medical, with four tuberculostatic at the beginning and continues with two drugs for a minimum of 12 to 24 months according to the patient's evolution and tolerance. This represents a problem for solid organ transplanted patient because of the interactions between immunosuppressive drugs and tuberculostatics [1,2]. Rifampicin represents the biggest problem because it accelerates the metabolism of tacrolimus, cyclosporine and corticoids, allowing allograft rejection and increasing mortality. As an alternative, rifabutin might be used; it has less effect on the immunosuppressive drugs levels. If there is perilesional oedema corticoids must be added, or the dose increased with a slow posterior decrease. The neurosurgical indications in these patients are limited to those in which intracranial pressure increases even with medical treatment, seizures that do not respond to the anticonvulsant medical therapy or compression symptoms. Follow-up must be made one month, 3 months and 6 months after the diagnosis with radiology imaging (preferable MRI) in order to control the lesion and its progress. There is few literature of CNS tuberculosis in lung transplant recipients, so there is a lack of information about the outcome of this entity, in the general population the prognosis has improved, with an 80% of survival with appropriate medical treatment [6], but as said before there is few information of this disease in lung transplant recipients.

Conclusion

Mortality of tuberculosis in transplanted patients is high, varying from 13 to 40%, and even though there are few cases reported of CNS tuberculosis this is the most dangerous form of presentation. This is why in every transplanted patient that presents neurological symptoms CNS tuberculosis must be considered and rule out in any of its forms of presentation.

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