

# Uncommon case of *Mycobacterium bovis* brain abscess complicated by suppurative fistula, and review of the literature

Irene Panero, Rafael San-Juan, Carla Eiriz, Daniel García-Pérez, Igor Paredes, Carlos González, Raúl Recio, Octavio Carretero, Alfonso Lagares, Pedro A. Gómez

**Introduction.** *Mycobacterium bovis* is an infrequent cause of central nervous system tuberculosis in Spain, with few cases described in the literature. Since compulsory pasteurization of milk and implementation of eradication programs on infected cattle, human sporadic illness with this organism has dramatically declined in developed countries.

**Case report.** A 71-year-old immunocompromised male, who presented a calvarial lytic lesion. A craniotomy for the total resection of the lesion was performed and the microbiology results were positive for *M. bovis*, therefore antituberculous therapy was initiated. Despite of the correct treatment, the patient developed a tuberculous abscess that required an aggressive surgical management followed by a suppurative fistula. Based on the treatment of tuberculous lymphadenitis, we decided to perform a conservative management with antituberculous therapy (isoniazid + rifampicin + ethambutol + moxifloxacin + steroids during 12 months) and avoided new surgical cleanings of the surgical bed obtaining a good response and a good clinical evolution.

**Conclusions.** As far as we know, this is the first case reported of a suppurative fistula after the resection of a cerebral abscess caused by *M. bovis*, therefore, there is no report in the literature about the treatment of this complication.

**Key words.** Antituberculous therapy. Calvarial lytic bone lesion. *Mycobacterium bovis*. Suppurative fistula. Tuberculoma. Tuberculous abscess.

## Introduction

Central nervous system (CNS) infections caused by *Mycobacterium bovis* are rare, with few cases described in the literature. Most of the reported cases have been related to the bacillus Calmette-Guérin (BCG), a live attenuated strain of wild type *M. bovis*, that is used in the treatment of superficial bladder carcinoma and widely used for vaccination against tuberculosis [1]. Report of cases of CNS infection due to *M. bovis* wild type is exceptional.

*M. bovis* is one of the seven species included in the named *M. tuberculosis* complex [2]. Since compulsory pasteurization of milk and implementation of eradication programs on infected cattle, human sporadic illness with this organism has dramatically declined in developed countries. However, in other nations with less rigorous eradication programs or consumption of unpasteurized milk, morbidity and mortality due to *M. bovis* is still a significant problem [3].

We report an uncommon case in an immunocompromised patient, who presented sporadic cal-

varial lesion, followed by brain abscess and suppurative fistula caused by *M. bovis*.

## Case report

A 71-year-old male was attended at the emergency room due to a traumatic brain injury (TBI) after an accidental fall. A liver transplant had been performed one year before due to intrahepatic portal hypertension related to nodular regenerative hyperplasia. The immunosuppressive treatment included prednisone, tacrolimus, and mycophenolate mofetil. He also received trimethoprim-sulfamethoxazole prophylaxis.

Cranial axial computerized tomography (CT) was performed, which revealed a calvarial lytic bone lesion, with no other relevant findings (Fig. 1).

Physical and neurological examination was unremarkable, but given the medical history and the radiological findings, the study was completed with a cranial magnetic resonance image (MRI). MRI showed a lytic lesion in the right frontal bone with

Department of Neurosurgery (I. Panero, C. Eiriz, D. García-Pérez, I. Paredes, A. Lagares, P.A. Gómez); Unit of Infectious Diseases (R. San-Juan); Department of Internal Medicine (C. González); Microbiology Department (R. Recio, O. Carretero). University Hospital 12th October. Madrid, Spain.

### Corresponding author:

Irene Panero Pérez MD. Department of Neurosurgery. University Hospital 12th October. Avda. Córdoba, s/n. E-28041 Madrid (Spain).

### E-mail:

ipanero903@hotmail.com

### Accepted:

09.09.19.

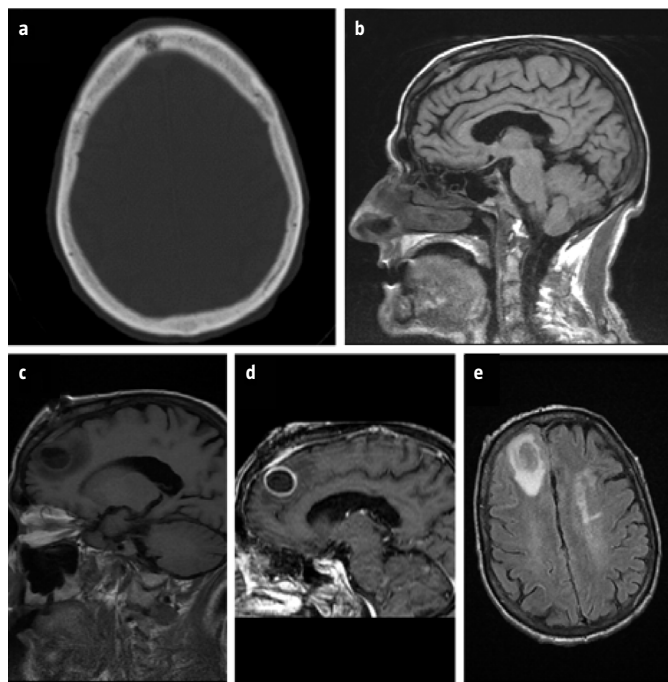
### How to cite this paper:

Panero I, San-Juan R, Eiriz C, García-Pérez D, Paredes I, González C, et al. Uncommon case of *Mycobacterium bovis* brain abscess complicated by suppurative fistula supurativa, and review of the literature. Rev Neurol 2019; 69: 417-22. doi: 10.33588/rn.6910.2019194.

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**Figure 1.** a) Axial computerized tomography of the head: bone window reveals a small focal lytic area; b) Cranial MR: sagittal T<sub>1</sub>-weighted images showed epidural collection that infiltrates and encroach the sagittal superior sinus; c) Postsurgical cranial MR: sagittal T<sub>1</sub>-weighted images showed an hypointense lesion, exist a hydroaerial level inside the formation and presents perilesional edema; d) Axial T<sub>2</sub>-weighted images showed an isointense lesion with a hyperintense contour; e) Sagittal T<sub>1</sub>-weighted images showed a ring enhancement lesion.



a small epidural collection (Fig. 1). A biopsy of the cranial vault was programmed. The patient presented again to the emergency room with fever and seizures, and, finally, a craniotomy was performed. The lesion was more yellowish and softer than the remaining bone tissue, and a minimal epidural collection of seropurulent appearance was found below the bone, which was removed without injuring the duramatter.

An urgent PCR (Xpert MTB/RIF assay) for *M. bovis* was positive in surgical samples and therefore antituberculous therapy was initiated composed by four antibiotics: pyranzinamide + isoniazid + rifampicin and ethambutol. The biopsy of the bone tissue revealed chronic granulomatous lesion. TC-body was performed without findings and blood cultures were sterile. The patient's purified protein derivative test was negative. Finally, two weeks later, cultures yielded growth of *M. bovis*, susceptible to all first-line tuberculostatics, with the exception of pyranzinamide.

Ten days after surgery, the patient presented fever, drowsiness, disorientation and headache. A new MRI showed a right frontal lobe intra-axial lesion, with thick wall, and ring-enhancing mass with perilesional edema. These findings were compatible with a tuberculoma or tuberculous abscess or a post-surgical pyogenic abscess (Fig. 1). Initially, conservative management was decided. Ethambutol was removed from the treatment and moxifloxacin was added, due to its greater sensitivity to *M. bovis*. After twenty days of admission the patient was asymptomatic with a control MRI showing no significant changes. Few days later, he was discharged under treatment.

Two months after a cranial MRI was performed showing a similar size and the patient remained asymptomatic. The patient was readmitted to the emergency department two months later because of headache, mild drowsiness and gait imbalance. A new MRI was performed that revealed an increase of the size of the lesion and more edema with mass effect (Fig. 2). Since the clinical and radiological findings worsened, a new craniotomy with resection of the lesion was performed. The tumor outcropped in the cortex and infiltrated the superior sagittal sinus, the appearance was violaceous and had a hard-gummy consistency. An en bloc-resection was performed. The biopsy showed a lesion composed of fibrous tissue with activated fibroblasts and inflammatory infiltrate with lymphoplasmacytic predominance. A new Xpert MTB/RIF assay was positive in surgical samples although the mycobacterial culture was sterile. The patient was discharged without complications and continued with isoniazid and rifampicin.

One month later he was reassessed in the emergency department because of dehiscence of the craniotomy wound with output of seropurulent material. So, an urgent surgical repair was performed. So, moxifloxacin was newly added to the tuberculostatic treatment. Nevertheless, in the postoperative course, the wound presented a new dehiscence due to the reappearance of a suppurative fistula. A control MRI showed good radiological evolution, with no abscess and less edema (Fig. 3). A new intervention was carried out to place a drainage in the porocephaly cavity and was kept for three weeks. Even so, the wound presented a new dehiscence requiring another surgery with a rotational flap of the dermis in order to repair the skin defect of the wound. Finally, 3 months later the patient could be discharged with isoniazid and rifampicin, being moxifloxacin discontinued.

The subsequent clinical and radiological evolution was favorable (Fig. 3). There were no further

complications in the wound and the tuberculostatic treatment was kept for 12 months.

## Discussion

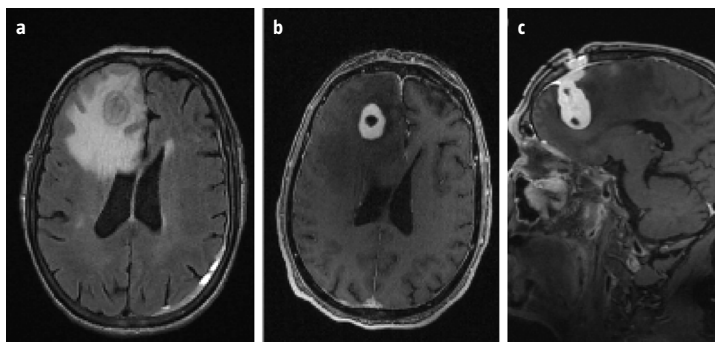
We presented an unusual case of *M. bovis* CNS infection with an unfavorable outcome despite adequate treatment. Complications following BCG vaccination or carcinoma bladder treatment have been infrequently described; and only a few cases of CNS infection have been reported [4]. This situation is favored in patients with immunodeficiency. In our case, the patient was a solid-organ transplant recipient. Our patient had never lived with animals and even less with cows; he had always taken pasteurized milk, had not received treatment with attenuated BCG for bladder cancer; but was vaccinated for tuberculosis with attenuated BCG in childhood.

Initially, the patient presented a lytic lesion in the frontal calvarian bone. Calvarial tuberculosis (CTB) is a rare entity. It happens in only 0.01% of all patients with mycobacterial infections. The incidence of CTB, however, seems to be on the rise, especially in developing countries due to immunodeficiency, malnutrition or poor socio-economic conditions. In 1842 Ried et al reported the first case in the literature [5]. Since then, a few cases-series have been reported. Among all active tuberculosis cases, approximately 1-2% have involvement of the skeletal system of which only 0,2-1,3% constitute CTB [6]. Raut et al reported 42 cases of CTB over a 10-year period and concluded that it was an entity more frequent in young people [7]. The frontal and the parietal bones are more commonly involved [5,8]. It is believed that skull affectation occurs as a consequence of the haematogenous seeding of bacilli to the diploe from a primary tuberculous infection elsewhere in the body.

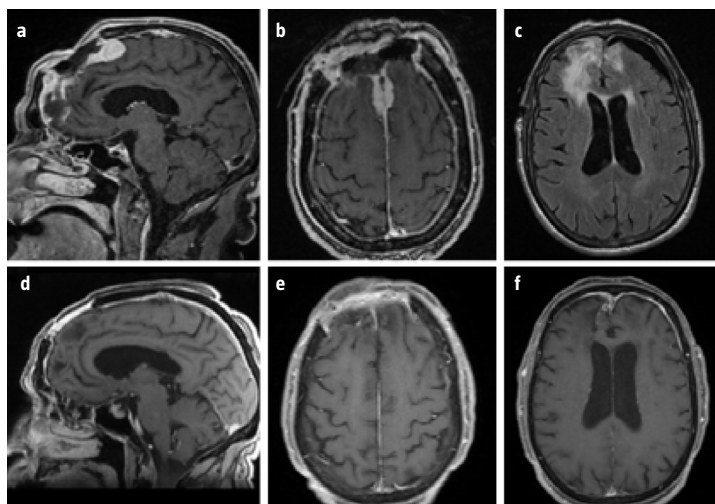
Surgical intervention may be required, especially in cases with large extradural collections causing neurodeficits or large scalps swellings, but is not indicated for small lesions [6,9,10]. It is usually not possible to reach a conclusive diagnosis on the basis of imaging or symptomatology alone; being therefore the surgery necessary for a microbiological or histological confirmation [5]. Other authors propose a radical debridement and subsequent medical therapy, obtaining in their series better rates of response and healing [10,11].

The post-surgical development of a frontal abscess was unexpected in our patient. Lymphatic and/or venous dissemination after the prior calvarian surgery is a possible explanation. Tuberculomas are

**Figure 2.** Typical MR appearances of a tuberculous abscess: a) Axial T<sub>1</sub>-weighted image showed a hypo-intense mass (37 × 24 mm) occupying the right frontal lobe with isointense periphery with perilesional edema; b). Gadolinium-enhanced axial T<sub>1</sub>-weighted image showed a lesion with a thick capsule with an intense peripheral enhancement and central non-enhancing caseus core; c) Gadolinium-enhanced sagittal T<sub>1</sub>-weighted showed that the lesion reaches the previous lytic lesion of the calvarian.



**Figure 3.** Upper images showed a cranial RM performed 1 month after the last surgery T<sub>1</sub>-gadolinium-enhanced sagittal (a) and axial (b, c) images showed a poroencephaly cavity with anfractuosa edges that enhance contrast, disappearance of the abscess, but it continues presenting hyperintensity of signal that has expanded to the left hemisphere. Lower images showed a cranial performed after one year with antituberculous therapy. T<sub>1</sub>-gadolinium-enhanced axial (d) and sagittal (e, f) images showed a decrease of the poroencephaly cavity with small subdural collections with peripheral contrast enhancement and minimal remains of edema.



relatively rare in the CNS, they account for 10% to 30% of intracranial masses in tuberculous-endemic areas. The most common manifestation of tuberculosis in the CNS is tuberculous meningitis, followed by tuberculomas and less frequent by a tuberculous abscess [12,13]. It is necessary to make the differen-

**Table.** Literature review.

	Age (years) /Sex	Clinical presentation	Risk factor	History of tuberculosis/ Vaccination	Brain CT/MRI	Treatment	Outcome/ Follow-up
Pedersen et al [30]	6/Female	Symptoms of increased intracranial pressure	Lymphoblastic leukemia	No/Vaccination five months before	Enhancing mass (left temporal lobe) + ring enhancing	Craniotomy + isoniazid + rifampicin + ethambutol	Death, 10 weeks later
Heath et al [31]	29/Female	Fever, euphoric papilloedema, disartria, mild left hemiparesis	Hodgkin's disease	Raw milk with calcified abdominal lymphnodes	Multiple small enhancing brain lesions	Biopsy, quadruple antituberculous therapy <sup>a</sup>	Death, 6 weeks later
Guest et al [3]	31/Female	Headache, neck pain, lethargy	No	No	Multiple enhancing lesions	Biopsy, isoniazid + rifampicin + ethambutol	Death, 5 weeks later
Tardieu et al [32]	5/Male	Fever, meningeal sings	No	Vaccination at age 8 days	Hydrocephalus, enhancing mass (left temporal lobe)	CSF samples/ isoniazid + rifampicin + ethambutol, 18 months	Recovery/ 4 years
	4/Female	Fever, meningeal sings	No	Vaccination at age 3 years	Normal CT	CSF samples/ isoniazid + rifampicin + ethambutol, 18 months	Recovery/ 3 years
Coppes et al [21]	6/Female	Headache, fever, nuchal rigidity	Lymphoblastic leukemia	No	Enhancing left temporal lobe mass + ring enhancing	Craniotomy + isoniazid + rifampicin + pyranzinamide, 12 months	Recovery/–
Stone et al [33]	3/Female	Headache, fever	Lymphoblastic leukemia	No	Hydrocephalus	CSF samples/ isoniazid + rifampicin + pyranzinamide + streptomycin, 12 months	Recovery/–
	5/Male	Headaches, rhinorrhea, weight loss	Lymphoblastic leukemia	No	Normal CT	CSF samples/ isoniazid + rifampicin + pyranzinamide + streptomycin, 12 months	Recovery/–
Golub et al [1]	73/Male	Headache, dizziness, tremor	Transitional bladder carcinoma	No/Intravesical treatment with BCG three years before	Three enhancing mass (left frontal, temporal and basal ganglia)	Biopsy + isoniazid + rifampicin + ethambutol + moxifloxacin	Recovery/–
Sheron et al [34]	74/Male	Dizziness, vertigo, gait ataxia, vomiting	Transitional bladder carcinoma	No/Intravesical treatment with BCG one year before	Enhancing mass (cerebellum)	Biopsy + isoniazid + rifampicin + ethambutol + moxifloxacin	Recovery/–

BCG: bacillus Calmette-Guérin; CSF: cerebrospinal fluid; CT: computerized tomography. <sup>a</sup> Treatment not specified in the report.

tial diagnosis of these last two entities. Normally, the clinical course of the tuberculoma is subacute, and presents headache, intracranial hypertension, seizures, and papilledema. The MRI showed an iso-intense to gray matter lesion on T<sub>1</sub>-weighted images and may have a slightly hyperintense rim. Tuberculous abscess presents with fever, headache and neurologic focal signs and the MRI showed a central area of hyperintensity on T<sub>2</sub>-weighted images and greater mass effect and edema [13].

The appearance of tuberculomas as a consequence of the start of tuberculosis treatment has been re-

ported; this worsening course is known as 'paradoxical response' [2,12,14-19].

Nonetheless, the clinical-radiological evolution after four months of antituberculous therapy in our patient was not as expected, presenting clinical and radiological worsening. So, finally a surgery was performed. In the literature it is reported that initially a conservative management must be carried out and that surgery should be reserved for certain cases: when the diagnosis is in doubt, atypical imaging features, typical suspected tuberculoma that does not respond to empiric therapy or increase in

size. Surgical treatment is also proposed in cases in which the patient presents clinical data of intracranial hypertension, focal neurological deficit or consciousness alterations [12]. In our case, we performed a microsurgical radical excision. After surgery the histopathological examination a lesion composed of fibrous tissue with activated fibroblasts and inflammatory infiltrate with lymphoplasmacytic predominance was observed; it must to be note that these characteristics are most typical in the tuberculoma than in the tuberculous abscess [12,13,20,21]. The staining was negative and nor growth was obtained in LJ cultures; however the Xpert MTB/RIF assay still showed positivity to *M. bovis*. It is reported in the literature that Xpert MTB/RIF presents a sensitivity of 50-55% and specificity of 95-100% in diagnosing tuberculosis [13,22].

Despite the correct antituberculous therapy the patient developed a suppurating fistula in the wound, which required multiple surgical repairs. It should be noted that in none of the surgical repairs the abscess cavity was cleaned, only the repair of the skin was performed, requiring in the third and he last surgery a cutaneous rotational flap. As far as we know, this is the first study describing a *M. bovis* brain suppurating fistula; and its management. It is known that *M. bovis* was historically a common cause of tuberculous lymphadenitis. Infectious Disease Society of America recommends surgical excision for cervical lymphadenitis only in unusual circumstances, and these circumstances are not explicitly defined [23-25]. Surgical excision should also be considered as an adjunct to antibiotic therapy for disease caused by drug-resistant organism or in those cases involving uncontrolled paradoxical upgrading reactions or fluctuant lymph nodes [23-29]. Management of this patient was partially decided based on the experience of the treatment of cervical lymphadenitis.

To our knowledge, only 10 patients with CNS infections due to *M. bovis* have been reported to date, most of them were *M. bovis* meningitis. Only seven patients developed a tuberculoma, as in our case; but in none of them they developed a suppurating fistula (Table) [1,3,21,30-34].

In conclusion, *M. bovis* is an infrequent cause of CNS tuberculosis in our country. Brain biopsy or surgical excision are reserved in case of doubt in the diagnoses or worsening evolution with antituberculous therapy. As far as we know, this is the first case reported of a suppurative fistula after the resection of a cerebral abscess caused by *M. bovis*, therefore, there is no report in the literature about the treatment of this complication. Based on the

treatment of tuberculous lymphadenitis, we decided to perform a conservative management with anti-tuberculous therapy (isoniazid + rifampicin + ethambutol + moxifloxacin) and avoided new surgical cleanings of the surgical bed, obtaining a good response and a good clinical evolution.

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### Caso insólito de absceso cerebral por *Mycobacterium bovis* complicado con fístula supurativa y revisión de la bibliografía

**Introducción.** *Mycobacterium bovis* es una causa infrecuente de tuberculosis del sistema nervioso central en España, del cual existen pocos casos descritos en la bibliografía. Desde la pasteurización obligatoria de la leche y la implementación de programas de erradicación del ganado infectado, la enfermedad esporádica humana con este organismo ha disminuido drásticamente en los países desarrollados.

**Caso clínico.** Varón inmunoafectado de 71 años, que presentaba una lesión lítica esporádica en la calota. Se realizó una craneotomía de la lesión y los resultados de microbiología fueron positivos para *M. bovis*, por lo que se inició tratamiento con terapia antituberculosa. A pesar del tratamiento correcto, el paciente desarrolló un absceso tuberculoso, que requirió un tratamiento quirúrgico agresivo, seguido de una complicación con una fístula supurativa. Sobre la base del tratamiento descrito para la linfadenitis tuberculosa, se decidió realizar un tratamiento conservador de la fístula supurativa, sin realizar nuevas limpiezas del lecho quirúrgico, y mantener de manera prolongada la terapia antituberculosa (isoniacida + rifampicina + etambutol + moxifloxacino + esteroides durante 12 meses), con lo que presentó una buena evolución clínica.

**Conclusiones.** Hasta la fecha, éste es el primer caso descrito de una fístula supurativa después de la resección de un absceso cerebral causado por *M. bovis*, por lo que no existe en la bibliografía artículo alguno que describa el tratamiento adecuado de esta complicación.

**Palabras clave.** Absceso tuberculoso. Fístula supurativa. Lesión ósea lítica en calota. *Mycobacterium bovis*. Terapia antituberculosa. Tuberculoma.