

Chronic meningitis by *Cryptococcus gattii* in an immunocompetent patient: a case report

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Abstract: This paper aims to present an unusual case of neurocryptococcosis in an immunocompetent patient. As the previous literature proposes, the diagnosis is usually not evident and there is a delay in the cases resolution due to the symptoms being nonspecific, the tests being very sensitive, as well as the unusual neurological condition of fungal origin in a patient with no evidence of immunodeficiency. The history of alcoholism and the diagnosis of long-term type 2 diabetes raises the hypothesis that the patient had immunosuppression events. The diagnosis was made through hospital support in conjunction with a multidisciplinary team. Discussing the present case helps to elucidate the possible diagnoses involved in chronic meningitis, especially in fungal meningitis.

Keywords: Chronic Meningitis; Fungal Meningitis; *Cryptococcus gattii*.

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1. Introduction

Chronic meningitis involves inflammation of any of the three layers of the meninges and is defined according to the time of onset. To have chronic meningitis, in addition to the clinical symptoms, there must be evidence of increased cellularity in the cerebrospinal fluid (CSF) and an involvement time of more than four weeks without spontaneous resolution [1]. The most common CSF laboratory findings in chronic meningitis are leukocyte pleocytosis and elevated protein [2].

The list of possible diagnoses, particularly in high-risk patients, including those who are immunocompromised, is extensive, with the three most common etiologies of chronic meningitis being fungal infections, tuberculosis, and neoplasia [2]. A retrospective review of previously healthy patients who were diagnosed with chronic meningitis found that the most common cause was an infectious disease, followed by malignancy, with over a third of cases remaining idiopathic. Patients with chronic meningitis usually have a subacute onset of symptoms, including fever, headache, and vomiting. Symptoms may remain static, fluctuate and/or slowly worsen [3].

Among the infectious causes of chronic meningitis, the current article will deal with the encapsulated fungus *Cryptococcus gattii*. Neurocryptococcosis is a common clinical entity in patients with Acquired Human Immunodeficiency Syndrome (AIDS) or patients with some degree of immunosuppression. In immunocompetent patients, it is considered rare and may lead to a mistake in the etiology of meningoencephalitis affections [4].

Meningoencephalitic cryptococcosis have an annual incidence of 223,000 cases and 180,000 deaths in patients with advanced HIV infection, most of whom live in sub-Saharan Africa. Worldwide, it is estimated that *C. neoformans* causes 95% of cases of cryptococcosis and *C. gattii* the remaining 5% [5]. In published studies from Australia; Papua New

Guinea; British Columbia, Canada; and the U.S. Pacific Northwest, the mortality rate among patients who have *C. gattii* infections ranges from 13% to 33% [6]. In Brazil, according to [7], there are no epidemiological data on the occurrence, magnitude, and significance of cryptococcosis at the national level.

Common symptoms of cryptococcosis include fever, cough, dyspnea, night sweats, malaise, and chest pain. Pulmonary infection caused by *C. gattii* can be more severe than that caused by *C. neoformans*. Nodules, mass-like lesions, cavitory lesions, inflammatory infiltrates, and pleural effusions can be observed on radiographs, but the severity of the lesions depends on the patient's immune status [8]. Magnetic resonance imaging (NMR) is restricted to neuroimaging in which heterogeneous cysts with surrounding vasogenic edema are present, leading to the differential diagnosis of a fungal infection [9].

This paper aims to present an unusual case of neurocryptococcosis in an apparently immunocompetent patient. The diagnosis was made through the bronchoalveolar lavage and biopsy, with hospital support in conjunction with a multidisciplinary team. The patient underwent treatment with intravenous antifungals during hospitalization, continuing treatment with oral antifungals at home. Discussing the present case helps to elucidate the possible diagnoses involved in chronic meningitis, especially in fungal meningitis.

2. Case Report

Male patient, 56 years old, industrial painter retired for two years, diabetes mellitus (DM) type two for about fifteen years, hypertensive, immunocompetent (there was no history of prolonged use of corticosteroids or immunobiologicals, no diagnosis or recent treatment for neoplasia, and he was not reactive to HIV, tuberculosis, hepatitis, and syphilis), is referred to a reference hospital due to persistent and daily headache, associated with dizziness and imbalance when walking for about six months.

About a year, the patient started having headaches in the frontotemporal region, that evolves with severe occipital headache, pulsating in nature, radiating to the frontal region, as well as speech disorders (stuttering, "slurred" speech), ataxia, and loss of strength in the lower limbs associated with paresthesia, weakness, and difficulty walking.

Due to the acute worsening of the condition, he was referred to a referral hospital. A lumbar puncture was requested, which showed clear and colorless cerebrospinal fluid, with hyperproteinorrachia (301.86mg/dL), hyperglycorrachia (137mg/dL), and increased cellularity (405 cells) with a predominance of lymphocytes (83%). Laboratory tests and tumor markers were requested, which did not show any noteworthy changes. The medical team then decided to start empiric treatment for *Listeria Monocytogenes* rhomboencephalitis with Ampicillin of twelve grams daily for six weeks. After antibiotic therapy, the patient was discharged with significant symptomatic improvement.

Six months passed, he began to notice a pulsatile headache, of moderate intensity in the parietal region, bilateral, without irradiation, worsening with head movement and tilting, and partial improvement with the use of over-the-counter analgesics. Associated and concomitant, he had dizziness that eventually made walking impossible, referring to episodes of nausea and vomiting. He had associated photophobia and phonophobia.

Two months ago, he noticed unintentional weight loss that amounted to ten kilos at the time. During the same period, he started having episodes of night sweats, with the occasional need to change his bed linen, about twice a week.

The patient reported that about a month ago he noticed an episode of neck pain and stiffness, which resolved spontaneously. He also had an episode of loss of consciousness and recovery in about a minute, with vertigo and falling from his height.

So, he was transferred to the tertiary care service due to the progressive worsening of the condition. He denied fever, mental confusion, loss of strength, and respiratory symptoms. On physical examination, he had a blood pressure of 124/72 mmHg, heart rate of 103bpm, respiratory rate of 16 mpm, and axillary temperature of 36.6°C, saturating 96%

in room air. He had left apex inspiratory snoring. The remainder of the physical examination was within normal limits.

He performed laboratory tests that had slight alterations that are not worthy of note. Tumor markers were negative. Antinuclear factor and inflammatory tests were requested, which were negative. He had IgG reactive to cytomegalovirus and toxoplasmosis, IgM negative for both. HIV, tuberculosis, hepatitis and syphilis tests were again performed and had non-reagent results. CSF had normal opening pressure (21.5cmH₂O), mild pleocytosis (75% lymphocytes), and hyperproteinorrachia (503mg/dL). The history of CSF values is shown in Table 1. Cultures and AFB were negative.

Table 1. Biochemical values of the cerebrospinal fluid.

| LCR | OP | Protein | Glucose | Celularity | Cultures |
|---------------|------|---------|-----------|------------|----------|
| 1 year | - | 301 | 137 (182) | 405 (L83%) | Negative |
| D1 | 21,5 | 503 | - | 310 (L75%) | Negative |
| D7 | 6,6 | 392 | 99 (226) | 268 (L76%) | Negative |
| D21 | 6,7 | 287 | 102 (219) | 88 (L65%) | Negative |

Notes: D1 = first day of hospitalization; Pa = opening pressure in cm; Glucose () serum value; cellularity () lymphocytes, percentage; values in mg/dL Cultures: direct mycological, bacterioscopic and AFB.

Imaging tests were requested to exclude neoplastic processes. CT and MRI of the skull, as well as MRI of the neuraxis, showed slight unremarkable alterations. Chest CT showed clusters of hilar lymph nodes on the left with a necrotic aspect, as well as subsegmental atelectasis of the left upper lobe with associated traction bronchiectasis and micronodular opacities with bronchial endoluminal filling (shown in Figure 1). Total abdomen CT, upper digestive endoscopy, and colonoscopy showed no noteworthy alterations.

Bronchoalveolar lavage and biopsy of the endobronchial lesion were performed, as well as mediastinoscopy for excision and biopsy of the mediastinal lymph node. The findings had a positive culture for *Cryptococcus gattii* sensitive to amphotericin B, and with that, the diagnosis of chronic meningitis of fungal etiology was defined. On the seventh day of hospitalization, treatment with liposomal amphotericin B at a dose of 4mg/kg/day for 14 days was started and CSF collection was scheduled at the beginning and end of treatment. The patient evolved well and was discharged with a prescription of fluconazole 750mg twice a day for 18 months and with no symptoms. In two subsequent consultations, the patient did not mention complaints and maintains treatment with fluconazole, currently remaining 10 months for the end of treatment.

3. Discussion

Chronic meningitis can be a diagnostic dilemma, and delays in correct diagnosis and treatment can lead to worse neurological outcomes [10]. The present case had a delay in diagnosis of about one year. The proposed initial diagnosis was rhomboencephalitis of bacterial etiology. Patients with neurological affection by *L. monocytogenes* present signs and symptoms like those reported in the general population with community-acquired bacterial meningitis but may present a longer prodromal phase, generating diagnostic confusion and possibly passing on a case of chronic meningitis [11].

Chronic meningitis courses with inflammation in the CSF and usually affects several regions of the nervous system simultaneously, including the brain, cranial nerves, nerve roots, and spinal cord. The most common presenting symptoms include headache, nausea, vomiting, cranial neuropathies, and polyradiculopathy. Occasionally, the inflammation is not limited to the CSF and can cause cortical dysfunction or myelopathy [12,13].

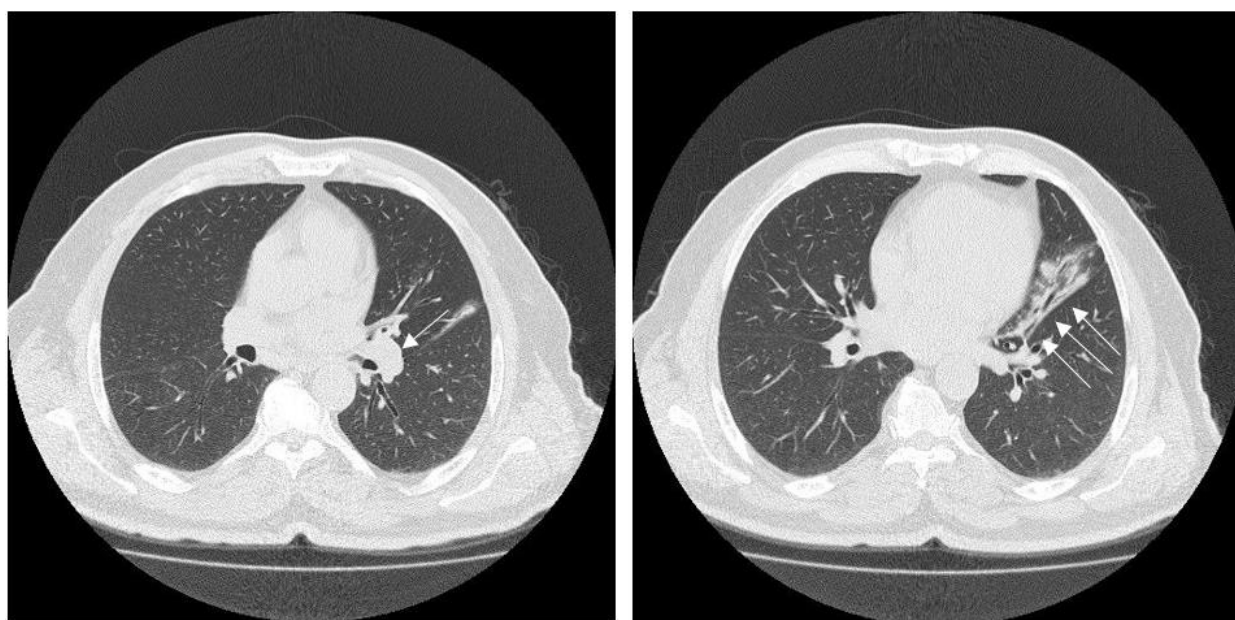


Figure 1: Chest CT, arrow pointing hilar lymph nodes with a necrotic aspect at left. And three arrows pointing micronodular opacities with bronchial endoluminal filling at right.

The main diagnostic considerations when evaluating a patient who has chronic inflammation of the central nervous system (CNS) is to define the possible etiology and duration of the disease, and several of them, being neoplastic, autoimmune, and infectious, cause acute meningitis and rarely persist for more than a few weeks [2].

Neoplastic involvement of the central nervous system should be considered a differential diagnosis in patients with signs and symptoms of chronic meningitis. Patients are classically present with signs and symptoms of multifocal neuraxial involvement due to involvement of the cerebral hemispheres, brainstem, cranial nerves, spinal cord, or nerve roots. The most common presenting symptoms include headache, encephalopathy, nuchal rigidity, diplopia, weakness, and radicular pain. Cranial neuropathies can include trigeminal neuropathy, facial weakness, and hearing loss. A high index of suspicion should be considered for the diagnosis of neoplasia when the multifocal neuraxial disease is found in a patient with known malignancy, but it is also common for patients with neoplasia to present isolated syndromes, such as symptoms of increased intracranial pressure, cauda equina syndrome, or cranial neuropathy [14].

To make a diagnosis of neoplasia causing chronic meningitis, there are CSF abnormalities, with increased opening pressure (>20 cm), leukocytosis ($>4/\text{mm}^3$), hyperproteinorrachia ($>50\text{mg/dL}$) and hypoglycorrachia (<60 mg/dL). In addition, imaging studies are required. As the neoplasm involves the entire neuraxis, imaging of the entire CNS is required in patients considered for further treatment. T1-weighted sequences, with and without contrast, combined with fat suppression. T2-weighted sequences are the gold standard [15–18]. In addition to neoplasms, autoimmune diseases are possible causes of chronic meningitis. Nervous system involvement has been described in virtually all autoimmune diseases, and chronic meningitis may be coincidental in a subset of these diseases.

The most common autoimmune diseases associated with chronic meningitis include sarcoidosis, systemic lupus erythematosus (SLE), and Behçet's disease [3]. Considering the proposed case report, among the autoimmune alternatives, sarcoidosis is more closely related to the patient's history and findings: the patient had no history of oral ulcerations or skin lesions typical of Behçet; there was no complaint of weakness, listlessness, pain in the joints or spots on the skin more typical of SLE;

Sarcoidosis is an immune-mediated disease characterized by granulomatous inflammation of affected organs. The neurological involvement of sarcoidosis (neurosarcoidosis, NS) can involve the CNS or the peripheral nervous system (PNS) or both and can cause substantial morbidity. When SN affects the pachymeninges or leptomeninges, subacute meningitis syndrome can develop which can persist and become chronic meningitis [19].

There is usually evidence of co-occurring pulmonary sarcoidosis, and in that regard, one should have a tissue sample that can commonly be acquired by transbronchial biopsy guided by endobronchial ultrasound. Usually, the origin of the lymphadenopathy is mediastinal or hilar, and the biopsy generates a high diagnostic yield; mediastinoscopy may be necessary in some cases, depending on the affected anatomy [20].

For the diagnosis of SN, CSF analysis should be considered, and most affected patients have moderate pleocytosis (< 100 cells/ μL), with a predominance of lymphocytes and hyperproteinorrachia. However, this type of finding is not pathognomonic since it is not specific to the diagnostic definition of SN [21].

The diagnostic confidence of SN is greater when there is biopsy confirmation of sarcoidosis in the nervous system. However, in some cases, the neuroanatomical location may preclude biopsy due to concerns about morbidity or the opportunity to secure a diagnosis by less invasive means. In such cases, it may be preferable to establish the diagnosis of systemic sarcoidosis in the context of a neurological syndrome compatible with NS (probable neurosarcoidosis) [22].

Finally, patients with an infectious etiology of chronic meningitis may present signs and symptoms of increased intracranial pressure (ICP), however, not all infectious etiologies exhibit this behavior. First place, a possible immunocompromise of the patient must be identified, performing serology in particular. The second step includes identifying the history of possible exposure or risk behavior. Finally, CSF biochemical tests and imaging tests should be performed.

In the case of the patient in question, there was a history of treatment for a neurological condition presumably for bacteria, but with a recurrence of symptoms. CSF changes and nonspecific signs on imaging studies pointed to an infectious cause. As the patient was presumably immunocompetent, as well as not reactive to *Mycobacterium tuberculosis* and syphilis, together with his work activity, history of exposure and changes in chest CT, the hypothesis of chronic meningitis caused by fungi was assumed. Bronchial lavage and lymph node biopsy identified *C. gattii* strains and the diagnosis was made.

The infection caused by the etiological agents of cryptococcosis occurs mainly through inhalation, and the fungi affect the lungs; however, in most cases, the infection is self-limiting in immunocompetent patients. The hematogenous spread of fungi to the central nervous system has been recently documented and commonly causes meningoencephalitis [23].

C. gatti differs from *C. neoformans*, the latter being more commonly isolated in clinical aspects, ecological niche, and genetic composition. Unlike *C. neoformans*, *C. gattii* more commonly affects immunocompetent patients exposed to an environmental source that causes cryptococcomas and is known to be more resistant to antifungal agents [24]. This pathogen lives in the soil and is associated with certain trees. It was first isolated from eucalyptus but has also been isolated from other tree species in tropical and subtropical geographic distributions, especially Australia and Papua, New Guinea, and, to a lesser extent, Africa, Europe, Mexico, and South America [25].

The patient mentioned previous contact working with eucalyptus, helping in the manufacture of furniture. In addition, he lived in a wooden house for 20 years, recently moving to a brick house. His brother, also affected by cryptococcosis, lived nearby, in a house made of the same material.

Human infection with cryptococcosis begins after inhalation of environmental basidiospores or desiccated yeast cells. These forms of fungi reach the lung alveoli and in immunocompetent hosts; then, antigen-presenting cells such as macrophages become active and elicit cell-mediated immunity [26].

Cryptococcal meningoencephalitis is an extremely rare cause of central nervous system disease in immunocompetent patients. It is believed that the mechanism is due to high exposure to a highly pathogenic cryptococcal strain or to some immunological deficit that the patient has that was not detected. In this sense, alcohol, DM, cirrhosis, and autoimmune diseases can cause this state of undetected immunosuppression, causing the host to become temporarily immunosuppressed [27]. The patient in question had been using alcohol abusively for ten years, as well as having been diagnosed with type 2 DM for about fifteen years.

DM is a known risk factor for certain infectious diseases, as diabetic individuals are immunocompromised due to uncontrolled diabetes mellitus, notably hyperglycemia. The immunocompromised state is invariable in all uncontrolled diabetic patients, due to the negative effects of the hyperglycemic environment, which favors immune dysfunction with damage to neutrophil function, impairment of the antioxidant system, and humoral immunity [28].

The clinical presentation of cryptococcal meningoencephalitis in individuals without immune compromise included headache (73%), constitutional symptoms (fever, weight loss, and night sweats; 68%), and altered mental status (42%). Despite being closely related to predisposing factors such as solid organ transplants or malignancies, no significant predisposing factor was reported in 30% of patients with CNS involvement [29]. Two of the most dangerous complications of cryptococcal meningitis are elevated intracranial pressure and hydrocephalus, and more than half of immunocompromised patients will develop intracranial hypertension, more common than in immunocompromised patients [3].

The diagnosis of cryptococcal meningitis should be considered in patients with a subacute presentation of headache and fever and with a history of exposure if they are not immunocompromised. CT and MRI are nonspecific for the diagnosis of cryptococcal meningitis, but they can reveal hydrocephalus, cerebral edema, leptomeningeal enhancement, or cryptococomas, in addition to being able to show no alterations [29,30].

Lumbar puncture is the diagnostic procedure of choice [30]. CSF in cryptococcal meningitis is characterized by lymphocytic pleocytosis, elevated fluid protein, and low glucose concentration. In patients with cryptococcal meningitis who are immunocompromised, the CSF profile may be bland with an almost normal white blood cell and protein count. CSF culture is considered the gold standard and will be positive in over 90% of cases. Cryptococcal antigen testing is important in the early detection of cryptococcal CNS disease.

Antigen testing yields rapid results compared to culture, and both the latex agglutination test and enzyme-linked immunosorbent assay (ELISA) test have sensitivity and specificity greater than 90%, although sensitivity is lower for uninfected individuals by HIV and should not be used to rule out disease [31].

Amphotericin B plus flucytosine as well as maintenance of possible neurological disorders is the treatment of choice. It should be associated with flucytosine since compared to Amphotericin B alone it is associated with better survival of patients with cryptococcal meningitis [29]. As flucytosine is not available in Brazil, we chose to associate treatment with fluconazole for 18 months, with this longer treatment being used to prevent the disease from reappearing.

4. Conclusion

The purpose of the present study was to report a case of chronic meningitis in an immunocompetent patient, so, it was carried out a discussion of possible differential diagnoses that could explain the etiology of this condition.

As the previous literature proposes, the diagnosis is usually not evident and there is a delay in the cases resolution due to the symptoms being nonspecific, the tests being very sensitive, as well as the unusual neurological condition of fungal origin in a patient with no evidence of immunodeficiency. The history of alcoholism and the diagnosis of long-term type 2 DM raises the hypothesis that the patient had immunosuppression events.

The diagnosis was possible due to the patient's clinical condition, his occupational and exposure history, changes in chest CT, CSF biochemical changes, and positive culture for *C.gatti* in bronchial washings and mediastinal lymph node, thus being the cause of meningitis presumably fungal patient's chronicle.

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Research Ethics Committee Approval: The Free and Informed Consent Form (FICF) was presented to the patient, as well as the same Confidentiality Term for carrying out the present case. The project was submitted to the Teaching and Research Council (CEP) of the hospital responsible for the hospitalization of the patient in question and subsequently submitted to the Ethics and Research Committee of the same institution. The study was approved by the Brazil platform, via consubstantiated opinion (CAAE) number 68479923.7.0000.5346, opinion number 5.989.123.

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Conflicts of Interest: None.

Supplementary Materials: None.

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