Rapidly progressive dementia by cryptococcal meningitis: A case report

Annelise Velasco de Azevedo-Pereira1,2,*, Juan-Diego Martínez-Lemus1,3, Delia Giraldo-Peñuela1,4, Fabian Cervantes-de la Hoz1, Neiry Zapa-Perez1,6, Hellen Kreinter-Rosenbaum1,7, Claudio Alejandro Jimenez-Monsalve1,8


Abstract

Dementias constitute a group of degenerative diseases that affect different domains within human cognition. While the usual course is chronically progressive, a small group of patients develops a subacute deterioration in months, an entity that is called rapidly progressive dementia. For these patients, an approach based on considering reversible etiologies is mandatory, and its diagnosis must be taken into consideration not only in immunocompromised patients by the human immunodeficiency virus (HIV) but also in patients with other causes of immunosuppression. We report the case of a patient with chronic use of steroids that developed rapidly progressive dementia as the sole manifestation of cryptococcal meningoencephalitis.

Keywords: Dementia, cryptococcal meningitis, immunological deficiency syndromes, glucocorticoids

Demencia rápidamente progresiva por meningitis criptocócica: Reporte de caso

Resumen

Las demencias constituyen un grupo de enfermedades degenerativas que afectan diversos dominios dentro de la cognición humana. Si bien el curso habitual es crónico y progresivo, una proporción de pacientes desarrollan un deterioro subagudo en meses, formando una entidad denominada demencia rápidamente progresiva. Es necesario realizar un abordaje basado en la búsqueda activa de etiologías reversible, y su diagnóstico debe tenerse en cuenta no solo en pacientes inmunocomprometidos por el virus de la inmunodeficiencia humana, sino también en pacientes con otra causa de inmunosupresión. En el presente artículo reportamos el caso de un paciente inmunocomprometido por uso de corticoides que desarrolló una demencia rápidamente progresiva como la manifestación de una meningoencefalitis criptocócica.

Palabras clave: Demencia, meningitis criptocócica, síndromes de deficiencia inmunológica, glucocorticoides

Introduction

Dementia is a clinical syndrome characterized by a progressive deterioration of two or more cognitive domains (i.e., orientation, memory, language, praxias, sense-perception and/or social cognition) with a functional impairment that affects daily life activities. The most common screening tools used for cognitive assessment when dementia is suspected are the Mini-Mental State Exam (MMSE) and the Montreal Cognitive Assessment (MoCA)1,2,3. Both range from 0 to 30 points, and a score of <24 points suggest dementia. Rapidly progressive dementia (RPD) refers to a quick but progressive establishment of symptoms of dementia (weeks to months) in less than a 2-year period4. It is important to distinguish this definition from delirium, which is an acute fluctuating confusional state that develops over days to weeks5.

Multiple causes of RPD have been described. A 3-year cohort study showed that approximately 29.5% were caused by immune-mediated encephalopathies, 19.7% by infectious diseases, 18.4% by other immune-mediated diseases (Behcet’s disease, sarcoidosis, central nervous system (CNS) vasculitis, Hashimoto encephalopathy), 11.5% by prion diseases, and 8.2% by non-prion neurodegenerative diseases6. There have been several infectious diseases related to RPD, such as herpes simplex virus encephalitis, tubercular meningitis, cryptococcal meningitis, neurocysticercosis, subacute sclerosing panencephalitis, human immunodeficiency virus (HIV) infection, progressive multifocal leukoencephalopathy, and neurosyphilis7.

Cryptococcal meningitis (CM) is an uncommon cause of RPD. An 8-year retrospective study found that from 187 patients with RPD, 39 (20.8%) were caused by an infection, and only...
one was caused by Cryptococcus sp. This fungal infection, particularly the one caused by Cryptococcus neoformans, is more common in immunocompromised patients. Approximately 7-8% of HIV-positive patients will have CM. Here we present a case of a patient with a history of chronic use of steroids who presented RPD due to CM.

**Case report**

A 64-year-old male, previously independent for his activities of daily living (ADL) (Barthel Index for ADL of 100/100), with a history of systemic hypertension, chronic obstructive pulmonary disease, psoriasis, and long-term use of steroids (prednisolone 60 mg daily), presented to the emergency room with the chief complaint of cognitive impairment and altered consciousness. He used to work as a carpenter and his family reported that he started to have discrete memory disturbances (how to design furniture) two months before the current admission. One month later, he presented a moderate cranial trauma that led to a faster deterioration, with progressive and severe memory loss, visual and auditory hallucinations, social isolation, fluctuating consciousness, and complete dependence on his ADL. He had been on a recent trip to a rural area with high levels of humidity to work in soil removal.

At admission, vital signs were unremarkable. Neither fever nor skin lesions were documented. On neurological examination, he had fluctuating consciousness that varied from mutism to psychomotor agitation with episodes of hallucinatory behavior. The rest of the examination was normal.

He had normal initial laboratory analysis including complete blood count, renal and hepatic function tests, serum electrolytes, vitamin B12, folic acid, glycemia, lipidic profile, non-treponemal test, and HIV 1 and 2 antibodies. Brain computerized tomography (CT) scan did not reveal any occupant lesion. Cerebrospinal fluid (CSF) analysis showed high opening pressure in 65 cm H2O, lymphocytic pleocytosis (20 leukocytes/mL) with high protein levels (256 mg/dL) and low glucose concentration (0 mg/dL). India ink stain test showed encapsulated yeast and cryptococcus antigen resulted positive. Multisensitive Crypto- coccus neoformans was isolated using BD Phoenix™ automated identification and susceptibility testing system (Becton, Dickenson and Company, Franklin Lakes, New Jersey, United States), and the resistance pattern was identified employing Sensititre™ YeastOne™ YO9 AST plates (Thermo Fisher Scientific, Waltham, Massachusetts, United States). A chest CT scan with contrast showed a single nodule located in the left inferior pulmonary lobe, indicating pulmonary cryptococcosis.

With these findings, a diagnosis of RPD overlapped with multifactorial delirium and intracranial hypertension syndrome due to cryptococcal meningitis was made. After the therapeutic evacuation of approximately 20 mL of CSF, the patient became more collaborative without fluctuation in the level of consciousness. Treatment with 800 mg of oral fluconazole and 0.7 mg/Kg daily of intravenous amphotericin deoxycholate was initiated. Periodic therapeutic lumbar puncture every 24 hours on two occasions were necessary due to persistent consciousness fluctuation and high opening pressure (50 and 47 cm H2O respectively). Topiramate 50 mg daily was initiated due to refractory intracranial hypertension. Although his vital signs were stable and no early brain herniation signs were reported, five days after admission the patient presented a cardiac arrest with sudden asystole rhythm that required 20 minutes of advanced cardiopulmonary reanimation without response.

**Discussion**

We reported a case of a patient with a history of steroid-related immunosuppression that presented as an RPD with mnestic and behavioral symptoms, overlapped with delirium, and intracranial hypertension syndrome caused by cryptococcal meningitis. The expositonal background of a recent trip to a rural area where the patient worked with soil led to the initial clinical suspicion and further analysis, revealing an infectious etiology of dementia.

Cryptococcosis is a common opportunistic systemic mycosis caused by members of the encapsulated yeast genus Cryptococcus. The etiological agents of the disease are classified into two species, i.e., Cryptococcus neoformans (serotypes A, D, and AD) affecting both immunocompetent and immunocompromised hosts, and Cryptococcus gattii (serotypes B and C) usually found in immunocompetent individuals. Cryptococcus neoformans has been isolated most frequently from debris around pigeon roosts and soil contaminated with decaying pigeon or chicken droppings. Also, this infection has been strongly correlated with older age, poor quality of the skin, and use of steroids.

We conducted a comprehensive literature review of all the original studies reporting RPD as the main manifestation of CM. We reviewed the PubMed, Scopus, LILACS, and SciELO databases between October 2021 and December 2021, without language restriction, using the MeSH terms (“cryptococcal meningitis”) AND (“cognitive symptom” OR “dementia”). We included all original studies, including cohort, case-control, cross-sectional studies, case series, and case reports, that reported a complete description of human subjects with CM who developed RPD, defined as the progressive appearance of non-fluctuating cognitive signs or symptoms in less than 2 years with consequent dependence in ADL. Patients with acute and fluctuating cognitive symptoms indicative of delirium, or unknown time of onset of symptoms, were excluded from this review. From the resulting studies, we determined baseline immunosuppression status, duration of symptoms, CSF findings, isolated cryptococcus species, and clinical outcome of all patients. The data extracted were processed and summarized in Table 1.

To date, there have been 19 reported cases of RPD caused by CM (Table 1). Most cases were diagnosed in male patients, with a 2:1:1 ratio. The average age of onset was 54 years old, which is consistent with the usual age of onset of symptoms seen in other manifestations of CM (56,8 years old). Presenting age ranged between 22 to 81 years old, noticing that...
most of them (57.8%) were under 60 years old. The prognosis was more favorable in younger patients, who had a higher chance of complete recovery (36.3% in young vs 25% in elderly) and less deadly outcomes (9% in young vs 12.5% in elderly). This pattern was also seen in several studies that demonstrated a higher risk of death in older people.

Although this disease has been classically described in HIV-positive patients, the availability of antiretroviral treatment has made an impact in diminishing cryptococcal infection in HIV-infected patients. Consequently, more cases of CM are being diagnosed in immunosuppressed patients due to other causes, such as steroid therapy (25%), chronic liver, kidney, or lung disease (24%), malignancy (16%), and solid organ transplant (15%)12. Interestingly, in this review, of the 19 reported cases of RPD by CM, 17 patients (84.2%) did not have a known history of immunosuppression, two reported chronic usage of immunosuppressant drugs (prednisone13 and fingolimod14) and only one described a case with an immunosuppressive condition (diabetes mellitus type 2). Literature showed that chronic use of steroids represents an important risk factor for cryptococcal neuro infection (odds ratio (OR): 96.46, 95% CI: 4.82-1.932,37; p=0.003)16. Our case is the fourth reported in scientific literature of a non-HIV-positive patient with a compromised immune system.

RPD caused by CM might be a challenging diagnosis, especially in older adults and patients with cognitive baseline compromise, which could lead to underdiagnosis17. Lumbar puncture is a necessary procedure for all patients with atypical cognitive disturbance and risk factors for neuroinfection18. In cases where CM is suspected, it is mandatory to rule out delirium as the cause of cognitive impairment, especially when these disturbances have a rapid onset and fluctuate in time1,4. The literature review showed that the average duration of cognitive symptoms in cryptococcal meningitis RPD was 7.4 months. The most affected domains were memory (62%), behavior (56%), language (31%), sensory-perceptual (25%), orientation (18%), visuo-construction (12%) and abstraction (6%). Some patients were evaluated after treatment, finding improvement in MMSE that ranged from 4 to 10 points, mainly in sensory-perceptual, behavior, memory, and orientation domains12,17,19,20. Nevertheless, it has been described that cognitive deficit could persist even after complete antifungal treatment11.

There have been several variables that have shown to increase mortality rates in CM. As mentioned above, age is an important prognostic factor. Younger patients (< 60 years old) have better outcomes, in comparison to the higher risk of death in elderly10. Also, HIV seronegativity (that is, being immunocompetent, or immunosuppressed for other causes) increases mortality in CM (27% vs 19%)25, mainly due to delay in diagnosis in 65% of cases19, probably related to the low diagnostic threshold of CM in non-HIV patients. Furthermore, disseminated disease, primarily CNS compromise, has been associated with higher death rates26. Abnormal MMSE scores (<26 points) are predictive of CNS dissemination, which confers an indirect role in determining the patient’s outcome10. A retrospective case-control study showed that cognitive deficits solely represent a 33% chance of having an adverse clinical outcome16. Our case reunited all characteristics that predicted a poor clinical evolution in CM, namely: age older than 60, HIV seronegativity, a suspected disseminated disease, and cognitive impairment. All these factors combined may have led to the patient’s demise.

In conclusion, CM as a cause of RPD is uncommon. This differential diagnosis must be taken into consideration not only in HIV immunocompromised patients but also in pa-

---

Table 1. Clinical and CSF characteristics of patients with RPD by cryptococcal meningitis in current literature.

| Case number | Age (years) | Sex | Immunosuppression | Symptoms duration (months) | WBC (cell/mL) | PMN (%) | Lymphocytes (%) | Proteins (mg/dL) | Glucose (mg/dL) | India ink negative | Cryptococcal antigen (%) | Culture | Cryptococcus species | Outcome | Year  | Reference |
|-------------|-------------|-----|-------------------|--------------------------|--------------|---------|----------------|----------------|----------------|----------------|----------------|----------------|---------|------------------|---------|-------|------------|
| 1           | 67          | F   | No                | 2                        | 12           | 3       | 12             | 23             | 10             | Positive        | Positive         | C. neoformans    | Death   | 1984             | 16      | 18    |            |
| 2           | 22          | M   | No                | 1                        | 100          | 0       | 0              | 0              | 0              | Positive        | Negative         | C. neoformans    | CR      | 1995             | 23      | 22    |            |
| 3           | 56          | M   | No                | 15                       | 25           | NR      | NR             | 337            | 15             | Positive        | Negative         | NR                 | PR      | 1999             | 25      | 25    |            |
| 4           | 44          | M   | No                | 2                        | 15           | NR      | NR             | 1,470          | 35             | Positive        | Negative         | C. neoformans    | Death   | 2002             | 26      | 26    |            |
| 5           | 70          | M   | No                | 36,1                      | 15           | 85      | 209            | 30             | Negative        | 1,4             | Positive         | C. neoformans    | MMSE 26 | 2004             | 17      | 17    |            |
| 6           | 57          | M   | No                | 12                       | 222          | 63      | 331            | 15             | Positive        | 1,4             | Positive         | C. neoformans    | MMSE 24 | 2004             | 19      | 19    |            |
| 7           | 25          | M   | No                | 7                        | NR           | 105     | 32,43          | Negative        | 1,4             | Positive         | C. neoformans    | CR      | 2006             | 13      | 13    |            |
| 8           | 63          | M   | Prednisone        | 24                       | NR           | 302     | NR             | Negative        | 1,4             | Positive         | C. neoformans    | CR      | 2006             | 13      | 13    |            |
| 9           | 28          | F   | No                | 3                        | 5            | NR      | NR             | 125            | 15             | Negative         | Negative         | C. neoformans    | CR      | 2009             | 28      | 28    |            |
| 10          | 62          | M   | No                | 12                       | 103          | 5       | 95             | 137            | 15             | Negative         | Positive         | NR                 | MMSE 30 | 2009             | 20      | 20    |            |
| 11          | 49          | M   | No                | 2                        | 40           | NR      | NR             | 337            | 13             | Negative         | Positive         | C. neoformans    | CR      | 2010             | 29      | 29    |            |
| 12          | 35          | F   | No                | 3                        | 35           | 0       | 100            | 96             | 70             | Positive        | 1/100            | Positive         | C. neoformans    | CR      | 2013             | 30      | 30    |            |
| 13          | 61          | F   | No                | 2                        | 52           | NR      | NR             | 547            | 37             | Negative        | 1/128            | Positive         | C. neoformans    | CR      | 2014             | 31      | 31    |            |
| 14          | 54          | M   | DM II             | 3                        | 360          | 17      | 83             | 1,416          | 12             | Positive        | Positive         | C. neoformans    | PR      | 2015             | 15      | 15    |            |
| 15          | 72          | F   | No                | 5                        | 51           | NR      | NR             | 197            | 82             | Negative        | Negative         | C. neoformans    | PR      | 2016             | 0       | 0     |            |
| 16          | 63          | M   | Fingolimod        | 1                        | 74           | 10      | 90             | 323            | NR             | Negative        | 1/024            | Negative         | C. neoformans    | PR      | 2016             | 14      | 14    |            |
| 17          | 81          | F   | No                | 4                        | 24           | NR      | 98             | 336,5          | 18             | Positive        | Negative        | NR                 | CR      | 2016             | 33      | 33    |            |
| 18          | 58          | M   | No                | 6                        | 262          | NR      | 70             | 1,955          | 20             | Negative        | Negative        | C. neoformans    | PR      | 2020             | 54      | 54    |            |
| 19          | 48          | M   | No                | 12                       | 35           | 3       | 97             | 788            | 5              | Negative        | 1/64             | Positive         | C. gottii  | PR      | 2021             | 35      | 35    |            |
| 20          | 64          | M   | Prednisone        | 2                        | 20           | 60      | 40             | 256            | 0              | Positive        | Negative         | C. neoformans    | Death   | 2021             | This case | 21   |            |

CR: Complete recovery; CSF: cerebrospinal fluid; DM II: Diabetes mellitus type II; F: Female; M: Male; MMSE: Mini-mental State Examination; NR: Not reported; PMN: Polymorphonuclear cells; PR: Partial recovery; WBC: White blood cells.
tients with other causes of immunosuppression; nevertheless, most reported cases are in immunocompetent hosts. In patients with CM, having any cognitive impairment resulted in statistically significant adverse clinical outcomes. The main cognitive domains affected are behavior, memory, and language. Independent variables that increased the mortality rate were age older than 60, non-HIV status, and disseminated disease. A delayed treatment represents a worse prognosis; therefore, early diagnosis plays an important role in their clinical evolution.

Ethical disclosure

Conflict of interest. None

Sources of funding for our research. Authors

Protection of human and animal subjects. Consent Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Confidentiality of data. No data that identifies patient are revealed

References


