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Cryptococcal Meningitis in Patient with Chronic Myeloid Leukemia

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Abstract

Objective: This study aimed to report the case of a female patient with chronic myeloid leukemia affected by cryptococcal meningitis. **Case report:** ML, white, 48 years old, female sex, previously diagnosed with chronic myeloid leukemia that has been refractive to the use of imatinib and who has recently begun using nilotinib, was admitted complaining of sudden and disabling migraine in the last 1 month associated with asthenia, adinamia, anorexia, disinterest for daily activities, dizziness, nausea, and vomiting. She evolved with ataxia, and started to stroll with help and showed decrease of muscular strength in her upper limbs. She also presented episodes of decrease of consciousness, with look fixation, no respond to sound stimulation, and short-term hearing loss. The cerebrospinal fluid showed presence of *Cryptococcus* sp. and, therefore, we began treatment with intravenous liposomal amphotericin B in the dose of 3 mg/kg/day, for 6 weeks. A new cerebrospinal fluid analysis, at the end of treatment, also showed rare structures that are compatible with *Cryptococcus* sp. As sequelae, she continued with hearing loss in her right ear and enhancement in her right auditory canal, seen in the magnetic resonance imaging. After stabilization and clinical improvement, she was discharged. After 3 weeks, she was hospitalized again with degeneration of the condition, and died due to intracranial hypertension secondary to cryptococcal infection. **Final Considerations:** This report reinforces the need of reflecting on fungi pathologies, especially in immunosuppressant patients, as well as the importance of early diagnosing and making a fast intervention, with the aims of providing quality of life and comfort to the patient and of minimizing neurological sequelae to the patient.

Keywords

Meningitis, Cryptococcal, Leukemia, Myelogenous, Chronic, Case Reports

1. Introduction

Recently, cryptococcosis is one of the systemic infections with higher worldwide prevalence [1]. The risk factors related to cryptococcosis development are associated with low cellular immunity and are common in immunosuppressed individuals, such as patients with systemic erythematosus lupus, diabetes, kidney failure, transplanted and neoplasm bearers [2].

In Europe and in North America, the central nervous system infection through *Cryptococcus neoformans* affects up to 10% of the HIV seropositive population. Mortality in developed countries may even reach until 20% [3]. In developing countries, infections in this site remain one of the main opportunistic infections and may reach 65% mortality rates, which correspond to 600 thousand deaths per year in immunosuppressed people [4].

Leukemias affect individuals in all ages. Until 2016, estimates showed 60,140 people diagnosed with the disease, which corresponds to 3.4% of all cancers [5]. In Brazil, estimates from the Department of Health show 5540 new cases of leukemia in men and 4530 in women. These values correspond to an estimated risk of 5.63 new cases for every 100 thousand men and 4.38 for every 100 thousand women [6].

Epidemiological data for chronic myeloid leukemia (CML) indicate that in every 100 thousand inhabitants, one or two will have the disease [7]. According to the National Cancer Institute, estimates showed that 8220 people were diagnosed with the disease and 1070 people died due to it in 2016 [8].

Therefore, it is not unusual that opportunistic diseases, such as central nervous system infections, are found in patients with leukemias. However, as far as we know, there is not a case report of cryptococcal meningitis in patients with CML.

We aimed to report the case of a patient with CML affected by cryptococcal meningitis.

2. Case Report

ML, white, 48 years old, female sex, previously diagnosed with CML that has been refractive to the use of imatinib and who has recently begun nilotinib, was admitted complaining of sudden and disabling migraine in the last one month that spread to the neck region and lasted for some minutes, which was relieved with dipyrone and tramadol, without ceasing. Her condition was associated with asthenia, anorexia, disinterest for daily activities, dizziness, nausea, and vomiting.

CML diagnosis was performed one year ago, when the patient came to her physician with complaints of weakness and diziness. At that moment, the physical exam demonstrated massive splenomegaly and paleness. Anemia, thrombocytosis and leucocytosis with shift to promyelocytes were present at the blood examination.

The patient evolved with ataxia, and started to stroll with help and with de-

crease of muscular strength in the upper limbs. She also evolved with episodes of decrease of consciousness, with look fixation, no response to sound stimulation, and short-term hearing loss.

On the physical examination, she was pale, apathetic, disoriented with axial ataxia, generalized areflexia and hearing loss. Hospitalization was requested after laboratorial and imaging exams were performed. The cerebrospinal fluid analysis (**Table 1** and **Figure 1**) showed the presence of *Cryptococcus* sp. and then treatment began with intravenous liposomal amphotericin B in the dose of 3 mg/kg/day, for 6 weeks. The manometry was normal. In the end of treatment, a new cerebrospinal fluid analysis also showed rare structures that are compatible with *Cryptococcus* sp.

Patient evolved with improvement of her consciousness level, but with permanence of the condition of disorientation, anterograde amnesia, ataxia, migraine, continuous bilateral hearing loss that is more prominent to the right, and dizziness. The magnetic resonance showed periventricular enhancement that is compatible with a meningeal inflammatory process. After stabilization and clinical improvement, the patient was discharged using fluconazole, but she returned after 3 weeks with degeneration of her condition. She was hospitalized and deceased due to intracranial hypertension secondary to cryptococcal infection. Cranial CT scan was performed and intracranial hypertension was present. Neurosurgery evaluation revealed the need for external ventricular derivation. The surgery was performed but inspite that, in the next hours the conscience level decreased and orotraqueal intubation was needed. 24 hours after, the patient deceased because of refractory hypotension.

3. Discussion

Cryptococcosis is a mycosis caused by an encapsulated yeast, the *Cryptococcussp*, which currently presents two species: *Cryptococcus neoformans* (serotypes A and D) and *Cryptococcus gattii* (serotypes B and C) [9] [10]. The cryptococcal meningoencephalitis is diagnosed in around 1 million patients per year, causing more than 600 thousand deaths per year [11]. The most common age is between 30 and 50 years old [12]. However, it is an uncommon condition in immunocompetent patients [13]. Regarding sex, men present around 70% of the cases, whereas women, 30%. This rate may be related to the influence of estrogens or to work exposures [14].

The scope of cryptococcosis by *C. neoformans* predominates when it is associated with conditions of low cellular imunity [15]. In our case, the CML must have been the primordial risk factor that lead to immunosuppression.

Cryptococcosis is a rare condition at childhood. Imunnocompettent individuals disease is mainly restricted to respiratory system while imunnocompromised patients commonly experiment hematogenical dissemination of the disease [12].

The initial clinical presentation of cryptococcosis with neurological symptoms, like in the present case, is not uncommon, because the fungus survives in

Table 1. Laboratorial examinations requested during patient's admission.

Blood count	
Red blood cells	2.63 million/mm^3
Hemoglobin	8.8 g/dL
Hematocrit	24.10%
Mean corpuscular volume	91.63
Mean corpuscular hemoglobin	33.46
Mean corpuscular hemoglobin concentration	36.51
RDW	19.00%
Leukocytes	7500 (segmented: 33%; eosinophils: 18%; T lymphocytes: 15%; monocytes 2%. 32% are large-sized cells, moderate nucleus/cytoplasm ratio, irregular nucleus, heterogeneous condensate chromatin)
Platelets	19,2000
Clotting tests	
Prothrombin time, seconds	11.5; activity: 88.70%
INR	1.03
Time of partial thromboplastin, seconds	25.30 seconds; ratio: 1.02
Electrolytes	
Magnesium	2.3 mg/L
Serum calcium	7.30 mg/L
Sodium	142 mg/L
Potassium	2.0 mg/L
Kidney and liver function and hepatic necrosis enzymes	
Urea	8.1 mg/dL
Creatinine	0.4 mg/dL
Total bilirubin (direct bilirubin; indirect bilirubin)	0.39 (0.19; 0.20)
TGO	10.0 U/L
TGP	33.0 U/L
Alkaline phosphatase	84.0 U/L
Gama GT	133.0 U/L
Others	
VHS	90 mm
Lactate dehydrogenase	1108.0
Folic acid	7.62 ng/mL
Glucose	85.0 g/dL
Serologies	
HIV1 and 2 antibodies	Non-reagent
Anti-HbCIgM	Non-reagent
Anti-HbS	Non-reagent
HbsAg	Non-reagent
Anti-VHC	Non-reagent
VDRL	Non-reagent

RDW: red cell distribution width; INR: International Normalized Ratio; TGO: serum glutamic oxaloacetic transaminase; TGP: serum glutamic-pyruvic transaminase; VHS: erythrocyte sedimentation rate; VHC: hepatitis C virus.

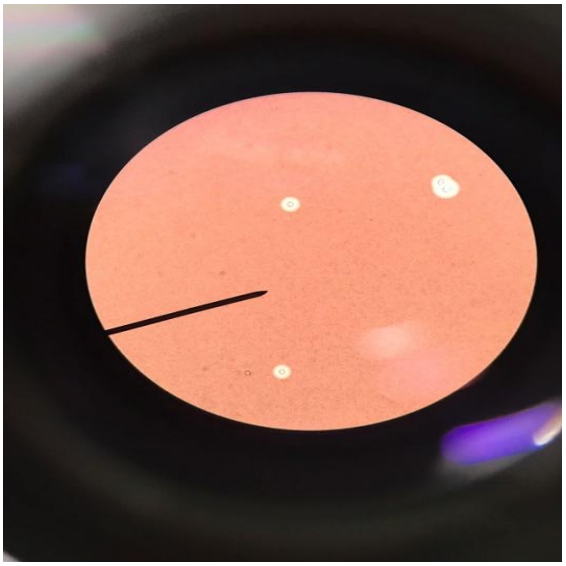

Figure 1. Microscopic analysis of the cerebrospinal fluid showing *Cryptococcos* sp.

the environment in contaminated soil with excretes of birds, and may be contracted through the inhalation of spores or dehydrated yeasts [12]. It has tropism through the central nervous system that is probably due to: high concentration of assimilable nutrients, lack of activity of the complement system, and weak or absent inflammatory response in the brain tissue. The brain is abundant in catecholamines, which the fungus may use for melanin synthesis. In addition, strains of *Cryptococcus* may survive and multiply in environments with low oxygen tension and relative high carbon dioxide tension in 37˚C temperatures, as observed in the brain tissue [16].

In the beginning of the condition, our patient had severe migraine, ataxia and generalized areflexia that suggested cerebellar involvement. Most of the cryptococcosis cases are diagnosed as meningoencephalitis of insidious character [17]. The patients were typically presenting fever and/or migraine of slow and gradual beginning, which became disabling. Thus, signs and symptoms of meningitis or acute meningoencephalitis may be absent [18].

In immunosuppressed patients, meningoencephalitis occurs acutely with predominance of the serotype A and a large variation of clinical signs, including absence of meningeal signs. The inflammation of fungi-induced meninges may interfere in the reabsorption of the cerebrospinal fluid, resulting in intracranial hypertension syndrome [9]—which also made our patient evolve to death.

Most of these data belong to patients with HIV immunosuppression, but not with CML—which until now has not been showed in literature. Subtle differences may occur due to the alteration of the baseline disease. Studies defend that unlike HIV-related cryptococcosis, whose clinical characteristics were properly described in previous papers [19] [20], the epidemiology and manifestations of cryptococcosis are not clear in noncommunicable diseases affecting the population [21].

The diagnosis of meningitis by *Cryptococcus* sp. should be confirmed through the identification of this fungus in the preparation of China's ink and/or positive culture in the analysis of the cerebrospinal fluid [22]. Virchow-Robin dilated spaces, pseudocysts (also known as "gelatinous pseudocysts" and "soap bubbles" that correspond to the spread of fungi in Virchow-Robin spaces, invading the surrounding parenchyma or in confluent Virchow-Robin spaces), intercerebral nodules in masses (also named nodular injuries, granulomas, cryptococome or fungi brain abscesses), and hydrocephaly are aspects that may be observed in brain computed tomography or encephalic magnetic resonance when the central nervous system is affected [23]. In this case diagnosis was confirmed by the presence of criptococcus on cerebrospinal fluid (picture 1).

Anti-fungi with activity against *Cryptococcus* include polyphenols (amphotericin B), flucytosine, and azoles. Echinocandins do not demonstrate in vivo activity against cryptococcus. The therapy combined with deoxycholate amphotericin B (AmB-d) and flucytosine is recommended as the first-line treatment of induction for disseminated cryptococcoses and central nervous system disease [24]. The action mechanisms of these drugs are the rupture of the fungal cell membrane and the inhibition of the DNA synthesis and fungus proteins, respectively [22] [25].

Aggressive management of intracranial hypertension is the main factor to reduce morbimortality. Other poor prognosis factors are degree of immunocompromise, prolonged corticosteroid use, HIV coinfection, mental status, delay on diagnosis, degree of leucocytosis in cerebrospinal fluid, sepsis, hi levels of criptococcal antigen titer [13]. The induction phase aims to make negative or effectively reduce the fungal burden and the minimal period of treatment is 2 weeks. The consolidation phase comprises maintenance of the mycologic negativity and normalization of clinical and laboratorial parameters for at least 8 weeks [24] [26].

4. Final Considerations

The case provides an association that has not been mentioned in the specialized literature: CML and cryptococcal meningitis. It reinforces the need of reflecting on fungi pathologies, especially in immunosuppressant patients, as well as on the importance of early diagnosis and fast intervention, with the aim of providing the patient a quality of life and comfort and of minimizing neurological sequelae.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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