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Cryptococcosis in Patients Living with Hepatitis C and B Viruses

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Abstract Cryptococcosis, a systemic fungal infection, has become a significant, global public health problem. Patients with liver disease have an increased predisposition to infections, such as Cryptococcosis. To report the underlying disease, the variety of etiologic agents involved and the outcomes of the Cryptococcosis in patients living with HBV and/or HCV, we reviewed 34 medical records of patients who were diagnosed with Cryptococcosis by the Mycology Laboratory of Santa Casa Hospital, Porto Alegre, Brazil. Males corresponded to 79 % of the patients, and the average patient age was 46.9 years. The cultures of 26/34 patients were positive: 25 patients were infected with *Cryptococcus neoformans* and one with *C. gattii*. A total of 14 deaths (41 %) occurred. As a criterion of our study, all patients had viral hepatitis infection: 27 (80 %) were infected with HCV, five (15 %) were infected with HBV, and two patients were infected with both viruses. Because HBV and/or HCV are transmitted among drug users through infected blood, and the end-stage cirrhotic liver must be transplanted, these two population types were well represented in this study and were analyzed in detail. Cryptococcosis patients living with HCV and/or HBV appear to have the same symptoms, mean age and gender distribution as the general Cryptococcosis population. Once Cryptococcosis affects the brain, a high mortality rate ensues; therefore, physicians must be aware of the possible occurrence of this disease in patients living with HCV and HBV.

Keywords Cryptococcosis · Viral hepatitis · HBV · HCV

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Introduction

Cryptococcosis, a systemic fungal infection disease, is caused by one of two encapsulated yeast species: *Cryptococcus neoformans* or *C. gattii*. *C. neoformans* has a wider geographic distribution and behaves as an opportunistic infection. *C. gattii* is more frequently found in tropical and subtropical areas and produces severe infections in patients who are not immunosuppressed [1, 2]. However, sporadic cases of

Cryptococcosis caused by *C. gattii* have been reported in other temperate regions [3, 4].

Cryptococcus usually enters the host by inhalation of the infectious propagule. Transplacental spread to a fetus has been described, but it is rare [5], and infection through organ transplantation from a donor with active Cryptococcal infection can occur [6]. Cryptococcosis may be related to conditions that modify host-defense mechanisms. It has been reported that up to 90 % of diagnosed cases of this mycosis have been associated with AIDS [2]. Patients with liver disease have an increased predisposition to infections that are often secondary to impaired phagocytic function; reduced complement levels, the use of corticosteroids and the antibacterial agents, and invasive procedures may increase the risk of Cryptococcosis [7, 8]. A case–control study reported that several infectious diseases, including Cryptococcosis, were found to be more common among patients infected with hepatitis C virus (HCV) [9].

Hepatitis B (HBV) and HCV lead to chronic liver inflammation and are the most common causes of liver cirrhosis and cancer [10]. Approximately 600,000 people die every year due to the acute or chronic consequences of HBV, which is transmitted between individuals, including from mother to infant; the transmission often occurs through unsafe injection practices, sexual contact and blood transfusions [11]. HCV infection also results from exposure to infected blood and can cause liver disease ranging in severity from a mild illness lasting a few weeks to a serious, lifelong illness. More than 350,000 people die every year from HCV-related liver diseases [12].

When studying the epidemiology of Cryptococcosis, some authors have described cases of patients infected with hepatitis virus [13, 14] or have described cases of coinfection [7, 8, 15–18]. However, detailed epidemiologic data regarding the clinical significance of coinfection between hepatitis virus and Cryptococcosis are scarce. The purpose of this study was to report the underlying diseases in patients living with HBV/HCV, as well as the variety of etiologic agents involved and the outcomes of Cryptococcosis disease.

Materials and Methods

In this study, we retrospectively included those patients who had, according to their medical records, received medical and laboratorial diagnoses of Cryptococcosis and HBV/HCV at the Mycology Laboratory of Santa Casa Hospital, Porto Alegre, RS, Brazil from January 1, 1993, to December 31, 2011. A Cryptococcosis case was confirmed by one of the following methods: India ink preparations, culture in Sabouraud Dextrose Agar and latex agglutination test. All tests were performed using cerebral spinal fluid (CSF), blood, urine or lung biopsies. When a culture was positive, an agar medium containing canavanine–glycine–bromothymol blue was used to differentiate between *C. neoformans* and *C. gattii* [19].

From patient medical records, the following data were selected for analysis: gender, age, infected sites/organs, underlying diseases, HIV, HBV and HCV status, titers of Cryptococcal antigens, antifungal treatments, time elapsed between the culture and outcomes, and the species identified in the culture. The clinical outcome was based on the report of hospital discharge or patient death while hospitalized.

This study was approved by the Ethics Committee at the Santa Casa Hospital (number 363/11), which waived the informed consent requirement.

The statistical analysis was performed using the PASW program, version 18 (formerly SPSS statistics). Fisher's exact test was used to examine the differences in categorical data, and the nonparametric Kruskal–Wallis test was used to analyze the differences between the median ages; $p < 0.05$ was considered to be significant.

Results

Thirty-four patients were enrolled in the study (Table 1). The majority of the Cryptococcal cases were diagnosed with CSF ($n = 20$, 59 %) followed by blood ($n = 7$, 20 %), lung biopsy ($n = 4$, 12 %) and urine ($n = 3$, 9 %) (Table 1). Nearly three-quarters of the patients were male ($n = 27$, 79 %), and the average age was 46.9 years old. One patient was asymptomatic. The patients who reported symptoms frequently experienced headache (56 %) and fever (53 %) (Table 1).

Cryptococcal antigen was positive in 30/34 patients, and the titers ranged from 1:4 to 1:131,072. Cultures were positive in 26/34 patients: 25 patients were infected with *C. neoformans,* and only one patient was infected with *C. gattii*.

Table 1 Cryptococcus cases coinfected with viral hepatitis diagnosed in the Mycology Laboratory of Santa Casa Hospital, Porto Alegre, RS, Brazil

no.	Gender/Age (years)	Clinical features	Underlying diseases	HIV/ hepatitis	Diagnostic	Treatment	Outcome (days)
1	F/32	fever, headache, cough	kidney transplantation	neg/C	CNS/*C. neoformans*	Flu	improved (32)
2	F/38	fever, confusion, nausea, shortness of breath	systemic lupus erythematosus	NA/B	CNS/*C. neoformans*	AmB+Flu+5fc	improved (34)
3	F/68	cough, shortness of breath	diabetes, CKD	NA/B	Lungs/*C. gattii*	Itra	improved
4	M/27	vomit, diarrhea, nausea	tuberculosis, toxoplasmosis, herpes	pos/C	CNS/*C. neoformans*	AmB+Flu	death (15)
5	M/30	vomit, headache, weight loss	diabetes	neg/C	CNS/*C. neoformans*	AmB+Flu	improved (50)
6	M/32	fever, weight loss, cough	histoplasmosis	pos/B	Blood/*Cryptococcus* sp.	none	death (8)
7	M/53	fever, weight loss, nausea, shortness of breath	diabetes, liver cirrhosis	NA/C	Blood/*C. neoformans*	Flu	improved
8	M/46	jaundice, sleepy	none	neg/B C	Kidney/*C. neoformans*	AmB+Flu	death (22)
9	M/70	fever, jaundice, shortness of breath	CKD, liver cirrhosis	NA/C	Kidney/*C. neoformans*	none	death (3)
10	M/37	fever, headache, weight loss, seizures	histoplasmosis, tuberculosis	pos/B	CNS/*C. neoformans*	AmB+Flu	improved (65)
11	M/50	-	tuberculosis	pos/C	Lungs/*C. neoformans*	AmB	death (9)
12	M/50	fever, cough, dizziness, weight loss	tuberculosis	pos/C	Blood/*Cryptococcus* sp.	Flu	death (40)
13	M/45	confusion, sleepy	liver cirrhosis	neg/C	CNS/*C. neoformans*	AmB	death (5)
14	M/50	headache, fever, night sweats	liver transplantation	neg/C	CNS/*C. neoformans*	AmB+Flu	improved (28)
15	F/67	sleepy	liver transplantation, arterial hypertension	neg/C	CNS/*C. neoformans*	AmB+Flu	improved (90)
16	M/67	fever, diarrhea	Liver transplantation, Kaposi's sarcoma, diabetes, CKD	neg/C	Kidney/*C. neoformans*	AmB+Flu	death (58)
17	M/56	headache, vomit, diarrhea	liver transplantation, CKD	neg/C	CNS/*Cryptococcus* sp.	AmB	death (6)
18	F/66	headache, vomit, nausea	liver transplantation	NA/C	CNS/*C. neoformans*	AmB+Flu	improved (32)
19	M/58	headache, confusion	liver transplantation, arterial hypertension, diabetes	neg/C	Blood/*C. neoformans*	AmB+Flu	death (12)
20	M/57	headache, confusion	liver transplantation, arterial hypertension, diabetes	NA/C	Blood/*Cryptococcus* sp.	Flu	improved
21	F/61	headache, shortness of breath	liver transplantation, diabetes	neg/C	Lungs/*Cryptococcus* sp.	AmB+Flu	improved (24)
22	M/44	fever, headache, seizures, dizziness	liver transplantation	neg/C	Blood/*Cryptococcus* sp.	Flu	improved (9)
23	F/52	headache, vomit	liver transplantation	NA/C	CNS/*C. neoformans*	AmB+Flu	improved (24)
24	M/56	fever, seizures	liver transplantation, cytomegalovirus	NA/C	Blood/*C. neoformans*	AmB +Flu+ 5fc	death (20)
25	M/51	fever, headache	liver transplantation, arterial hypertension	NA/C	CNS/*Cryptococcus* sp.	AmB+Flu	improved (20)
26	M/50	fever, headache, vomit	liver transplantation, herpes	NA/C	CNS/*C. neoformans*	AmB+Flu	improved (37)
27	M/40	headache, seizures	liver transplantation, diabetes	NA/C	CNS/*C. neoformans*	AmB+Flu	improved
28	M/31	headache, fever, seizures	drug user, tuberculosis, cytomegalovirus	pos/C	CNS/*C. neoformans*	AmB	death (45)
29	M/36	headache, vomit	drug user, histoplasmosis, candidiasis	pos/B	CNS/*Cryptococcus* sp.	AmB	improved (29)
30	M/35	fever, diarrhea, headache	drug user, tuberculosis	pos/C	CNS/*C. neoformans*	AmB+Flu+Itra	death (88)
31	M/42	fever, seizures, weight loss	drug user, tuberculosis, histoplasmosis	pos/C	CNS/*C. neoformans*	AmB	death (18)
32	M/34	headache, seizures	drug user, toxoplasmosis	pos/C B	Lungs/*C. neoformans*	Flu+ Ketoconazole	improved (22)
33	M/28	fever, headache, cough	drug user, toxoplasmosis, candidiasis	pos/C	CNS/*C. neoformans*	AmB	improved (1)
34	M/36	fever, weight loss, confusion	drug user, tuberculosis, CKD	pos/C	CNS/*C. neoformans*	AmB	improved (51)

White—other group; light silver—transplanted group; dark silver—drug user group

M male, *F* female, *CKD* chronic kidney disease, *neg* negative, *pos* positive, *NA* data not available, *Flu* fluconazole, *AmB* amphotericin B, *5fc* 5-fluorocytosine, *Itra* itraconazole

All patients had viral hepatitis infections: 27 (80 %) were infected with HCV, five (15 %) were infected with HBV, and two patients (5 %) were infected with HBV and HCV. Twenty-three patients were tested for HIV, and 12 were positive (Table 1). Only one patient did not have an underlying disease, seven patients were self-declared drug users, and 14 patients were submitted to liver transplantation because of the liver problems caused by HCV. One patient had systemic lupus erythematous, five had chronic kidney disease, eight had diabetes, and four had arterial hypertension. The coinfections included tuberculosis, histoplasmosis, toxoplasmosis, candidiasis, herpes simplex disease and human cytomegalovirus disease (Table 1).

Amphotericin B was administered to nine patients, five patients were administered fluconazole only, and one patient was administered itraconazole. The most often used therapy was a combination of amphotericin B and fluconazole, which was administered to 14 (41 %) patients; another two combinations of antifungal agents were used in fewer patients (Table 1). Fourteen deaths occurred (41 %).

Within-Group Observations

Because we had seven declared drug users and 14 liver transplant patients, we grouped the patients according to these characteristics; the other 13 patients were included in the "others" category.

In the three groups, the percentage of females was less than that of males ($p = 0.466$). Within the drug users group, the average age was 34.6 years (28–36 years). The liver transplant group had a higher average age (55.4 years; range 40–67 years), and the youngest liver-transplanted patient was older than the oldest patient in the drug user group ($p = 0.001$).

We also examined whether the presence of the two most-related symptoms varied among the groups; the prevalence of fever did not vary among all groups ($p = 0.501$), but headache was more common in the drug user and liver transplant groups ($p = 0.010$).

In the liver transplant group, all patients had the HCV; in the drug users group, five patients had HCV, one had HBV, and one had both viruses. In the other groups, eight patients had HCV, four had HBV, and one had both viruses ($p = 0.044$). Not all patients had an HIV diagnosis result in their paper charts; however, a characteristic of the liver transplant group seemed to be an HIV-negative result, whereas all drug users had a positive result ($p < 0.001$).

The predisposition for central nervous system (CNS) infection was observed in all three groups ($p = 0.652$). In the liver transplant group, death occurred in fewer patients (28 %) than in the drug users group (43 %) and in the others group (54 %), but these differences were not statistically significant ($p = 0.440$).

All drug users had concomitant infections ($p < 0.001$), and in all groups, at least one patient had one underlying disease (Table 1). Because a patient can have more than one concurrent disease, the statistical analysis could not be performed. The treatments differed significantly between the groups ($p = 0.002$, Table 1).

Discussion

This study described patients affected by *Cryptococcus* who were living with viral hepatitis. The patients described do not represent the absolute occurrence of *Cryptococcus* spp. in viral hepatitis patients in the studied hospital because the patients were included based on the medical information on their paper charts.

The male predominance in this study was in accordance with Brazilian studies [13, 20], and studies performed in other countries, such as the USA, Australia, New Zealand, France and Malaysia [14, 21–23]. The reason for this predominance is not known; however, increased environmental exposure, hormonal influences and/or genetic predisposition could be contributing factors [21].

The most frequent clinical manifestations among patients who were coinfected with cryptococcus and HCV/HBV were the same main symptoms for Cryptococcosis patients [13, 24].*Cryptococcus* spp. have a tendency to attack the CNS [2], as observed in most of the patients.

The age range found in this study aligned with those in other studies on *Cryptococcus*; in a study in Malaysia, the patient ages ranged from 9 months to 66 years [23]; in Brazil, the patient ages ranged from 19 to 69 years [20]; and in HCV studies in the USA, the mean patient age was 48.4 years [9]. In reports of this coinfection, the patient ages ranged from 39 to 59 years [7, 8, 15–18]. Although Cryptococcosis can occur

during childhood [25], in this study, this disease was not observed in children. When grouped, the average age of the transplant patients was higher than that of the other studied groups. Because of its slow and silent onset, hepatitis C is often first diagnosed in a late stage, when therapeutic options are already limited [26]. For patients with end-stage liver disease, liver transplantation is the only therapeutic option [27], which could explain the declining age in this group.

We identified only one patient who was infected with *C. gattii*—a 68-year-old woman who had the following underlying diseases: HBV, diabetes and renal insufficiency. The patients infected with *C. neoformans* had the following underlying diseases: drug addiction, liver transplantation, systemic lupus erythematosus, chronic kidney disease, diabetes and arterial hypertension. The widespread use of immunosuppressant therapy for transplant conditioning and cancer chemotherapy and steroid use for systemic lupus erythematosus and other diseases has increased the number of patients who are susceptible to opportunistic infections, such as Cryptococcosis [14]. While many of these comorbidities may predispose patients to Cryptococcosis, other diseases, such as renal failure, could be a consequence of treatment with antifungal drugs that are usually nephrotoxic [14].

In a case–control study of HCV patients and non-HCV patients, the authors concluded that several infectious diseases were more common among HCV-infected patients, including Cryptococcosis [9]. Because most patients who were analyzed in the current study had HCV, it is expected that many patients were coinfected with other diseases. The coinfections occurred more frequently in the drug user patient group. It is known that cocaine can modulate the immune system by depressing it, which can result in the progression of HIV to AIDS and increases the risk of developing secondary, opportunistic infections [28].

In many countries, HCV transmission rates decreased substantially with the introduction of routine blood screening [26]. Today, after the eradication of transfusion-related infections, intravenous drug use is considered to be the main cause of HCV transmission in some countries [26].

The drug users were infected with all viruses included in this study. This fact is in accordance with studies in Vietnam [29], and in a review study that included 77 countries, the prevalence of HCV among drug-injected users was 60–80 % in 26 countries and >80 % in 12 countries. For HBV, reports are available for 59 countries, and the incidence among hepatitis patients ranged from 5 to 10 % in 21 countries and was >10 % in ten countries [30]. HBV, HCV and HIV are known to share similar routes of transmission; thus, coinfection is commonly encountered [28].

In a Brazilian study, the general mortality of Cryptococcosis patients was 45–65 % [31]. The present study reports that 41 % of all patients died during hospitalization for Cryptococcosis treatment.

Cryptococcosis in patients living with HCV/HBV seems to have the same symptoms, mean age and gender distribution as the general population with Cryptococcosis. In summary, our data show that Cryptococcosis remains a significant complication in immunosuppressed patients, such as organ transplant recipients, drug users and patients with HBV/HCV liver disease. It is important to highlight that once Cryptococcosis affects the brain, patients have a high mortality rate. Therefore, physicians must be aware of the possible occurrence of Cryptococcosis in patients living with HCV/HBV.

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Conflict of interest The authors declare that they have no conflict of interest.

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