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CASE REPORT

# Cryptococcal Meningitis in an HCV-Positive and IVDU- and HIV-Negative Patient: A Case Report and Literature Review

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**Background:** Cryptococcal meningitis (CM) is a central nervous system (CNS) infection that occurs mainly in immunocompromised individuals such as those with human immunodeficiency virus (HIV) infection. However, the prevalence of CM in immunocompetent patients has increased. Although CM has been reported in patients with hepatitis C virus (HCV) infection, it has not yet been fully established whether there is an association between both conditions. CM has also been reported in patients with intravenous drug use (IVDU), which is related to the immunosuppression caused by these drugs.

**Case Presentation:** We report the case of a 24-year-old man who presented with meningitis secondary to *Cryptococcus gattii* infection. He had a history of IVDU and HCV infection, was HIV-negative and without antiviral treatment. The patient received adequate antifungal treatment during induction, consolidation, and maintenance phases. His condition relapsed, requiring dose adjustment, with an excellent response during clinical follow-up for both meningitis and HCV infection. A brain biopsy was requested during relapse to rule out other co-infection.

**Conclusion:** The case of an individual diagnosed with cryptococcal meningitis, who had a history of IVDU and HCV infection, is presented. The coexistence of such events could shadow the prognosis of this group of subjects, related to immunosuppression that can be caused through different pathways. Having HCV and being a IVDU simultaneously could increase the risk of *Cryptococcus* infection.

**Keywords:** hepatitis C, cryptococcal meningitis, HIV infection, cryptococcosis, intravenous drug use

## Introduction

Cryptococcosis is a systemic fungal infection caused by encapsulated yeasts of the genus *Cryptococcus* and should be considered a global public health concern. This genus comprises two pathogenic species: *C. neoformans* and *C. gattii*. *C. neoformans* has two varieties: var. *grubii* (serotype A) and var. *neoformans* (serotype D), and there is also an AD hybrid. *C. gattii* consists of serotypes B and C.[1] *C. neoformans* has a wide geographic distribution and behaves as an opportunistic infection, whereas *C. gattii* is more frequently reported in tropical and subtropical areas, causing severe infections in non-immunosuppressed patients.[2] Cryptococcal meningitis (CM) has been associated with cases of host defense mechanism involvement, with human immunodeficiency virus (HIV) infection being the most frequent cause;[3] however, the prevalence of CM in non-HIV patients has increased over the last decades due to the increased use of immunosuppressive therapies and the increased number of transplanted individuals,[4] and non-HIV patients already outnumber HIV patients in some reports, including more than a thousand individuals with CM. Likewise, the clinical symptoms of CM subjects with or without immunosuppression may vary, which could lead to delayed diagnosis.[5,6]

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Hepatitis C virus (HCV) co-infection and systemic cryptococcosis has been reported,[7,8] in both cases. These organisms have long incubation periods and negative regulation of specific immunity, which help them to persist in human tissues for years.[9] However, whether HCV can promote *Cryptococcus* persistence and dissemination in humans is still unclear.[9]

In this paper, we report the case of a non-HIV individual with co-infection with HCV and *C. gattii* meningitis, and a history of intravenous drug use (IVDU).

## Case Report

A 24-year-old man with a history of intravenous drug use (IVDU), low educational level and socioeconomic status, who reported severe headache and paresthesia in the right side of the head. Upon admission to the hospital, the patient had normal vital signs, and no jaundice. Neurological examination did not show any evidence of impaired consciousness or strength, nor any signs of meningeal disease. Paraclinical tests showed the following results: aspartate aminotransferase (AST) 136 U/L, alanine aminotransferase (ALT) 68 U/L, positive IgG antibodies for HCV, 109,910 IU/mL viral load (amount of viral genetic material in a person's blood) for HCV, normal CD3 count, and normal flow cytometry results. HIV infection was ruled out, and abdominal ultrasound and computed tomography (CT) scan showed no abnormalities.

One week later, he presented with generalized tonic-clonic seizures and somnolence. Lumbar puncture (LP) revealed high opening pressure (OP), and cerebrospinal fluid (CSF) revealed lymphocytic pleocytosis and high proteinorrachia (≥ 45 mg/dL). China ink test in the CSF showed encapsulated blastoconidia suggesting *Cryptococcus*, with positive *Cryptococcal latex* in 1/512 dilutions, so induction phase was initiated with amphotericin B and fluconazole. *Cryptococcus gattii* was observed in the last CSF culture report. Magnetic resonance imaging (MRI) of the brain revealed altered signal intensity in the head of the caudate nucleus and contrast-enhanced lesions in the splenium of the corpus callosum, lenticular nucleus, and anterior limb of the left internal capsule, consistent with CM (Figure 1).

Since he was a non-HIV patient, treatment was started with amphotericin B deoxycholate at 1 mg/kg/day + endovenous fluconazole 800 mg/day for 4 weeks. Subsequently, consolidation therapy was initiated with oral fluconazole 800 mg/day, followed by indefinite fluconazole 200 mg/day. The patient exhibited clinical progression without neurological deficits and decreased OP (less than 20 cm $H_2O$).

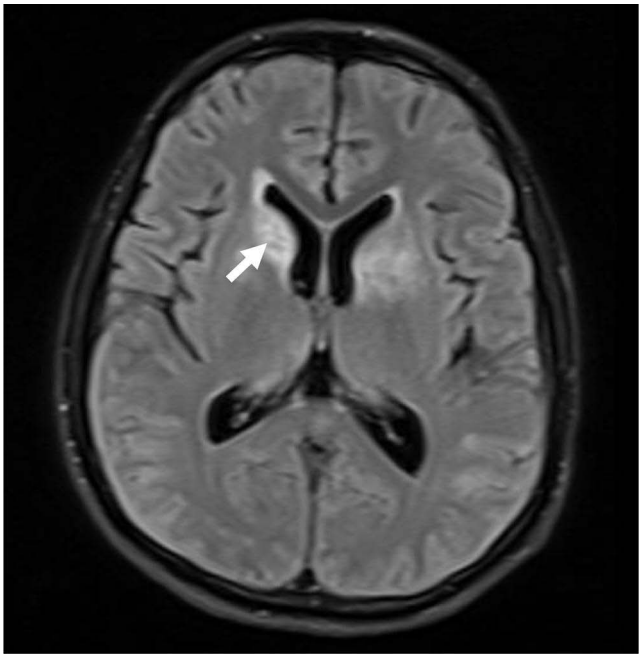

**Figure 1** Brain MRI showing altered signal intensity in the head of the caudate nucleus (arrow), lesions in the splenium of the corpus callosum, ventricular nuclei, and the anterior arm of the left internal capsule.

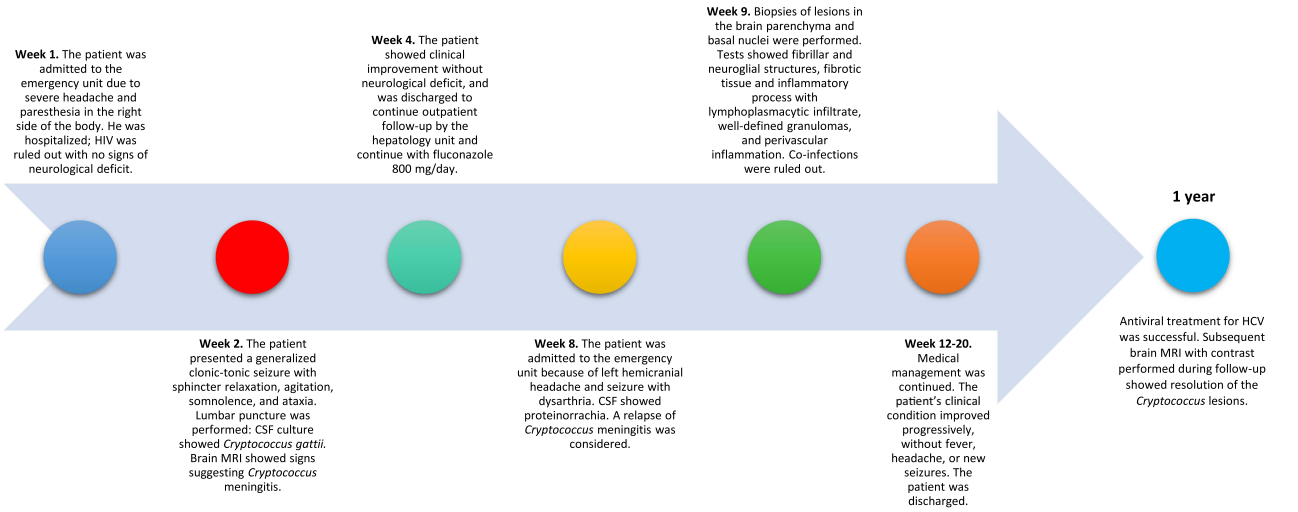


**Figure 2** Case report timeline.

One month after discharge and 10 days after changing to 200 mg/day fluconazole, the patient reported severe headache and a generalized tonic-clonic seizure with dysarthria during the postictal phase. At that time, he had not yet started antiviral treatment against HCV. During hospitalization, he was disoriented and somnolent. LP showed OP of 43 cm $H_2O$, and simple cranial CT revealed hypodensity in the left frontal cortical and subcortical areas, with CSF reporting proteinorrachy (158 mg/dL). Considering that this was a CM relapse, a combination of liposomal amphotericin B (5 mg/kg/day) and fluconazole (600 mg every 12 h) for 4 weeks was initiated, followed by consolidation and maintenance therapy with fluconazole 400 mg per day for 8 weeks (minimum) and at 200 mg per day for 6–12 months, respectively.

In the following days, new seizure episodes with disorientation, somnolence, fever, and emesis occurred. A new cranial CT scan showed ventriculomegaly, and MRI showed multiple nodular lesions in the brain parenchyma and near the basal nuclei. A biopsy was performed for these lesions, which showed negative PAS, Gomori, and Ziehl-Neelsen staining. However, fibrillar and neuroglial structures, fibrotic tissue and inflammation with lymphoplasmacytic infiltrate, well-defined granulomas, and perivascular inflammation were identified. Negative results were obtained in smears and cultures for *Mycobacterium tuberculosis*, cultures for bacteria and fungi, PCR for *M. tuberculosis*, and KOH. The patient continued treatment without neurological involvement, fever, headache, or seizures. LP showed an OP of 5 cm $H_2O$ and cranial CT scan during follow-up did not show ventriculomegaly, so the patient was discharged 3 months after readmission. Upon discharge, the patient was prescribed fluconazole 800 mg per day, and was followed by the infectious disease unit, and was prescribed with sofosbuvir/velpatasvir 400/100 mg per day for 12 weeks, as well as antiseizure management with levetiracetam. HCV load remained under 12 U/mL at one month of treatment, at the end of treatment, and 3 months after termination, so the antiviral treatment was considered successful. Brain MRI with contrast was performed during follow-up, which showed resolution of the *Cryptococcal* lesions. The case timeline is shown in Figure 2.

In this case report, all procedures were performed in accordance with the ethical and bioethical standards of the Scientific Committee of the medical institution, Hospital Universitario del Valle, and the 1964 Declaration of Helsinki and its subsequent versions. The patient's informed consent was obtained before his participation and the publication of the study and its images. Ethical approval is not required to publish the case details in accordance with local or national guidelines.

## Discussion

Clinical manifestations of CM differ in some aspects between patients with and without HIV infection. When comparing CM individuals with and without HIV infection, factors associated with HIV infection such as being <45 years, <5000 leukocytes/$mm^3$, and fungemia have been reported, with a mortality of 18% and 37% in non-HIV and HIV patients, respectively. Risk factors associated with mortality included concurrent *Pneumocystis* pneumonia, altered consciousness, infection caused by members of the *C. gattii* species complex, and anemia.[3]

This case report is about a young patient with a diagnosis of CM, with a history of HCV infection, IVDU, and no HIV. Cases of cryptococcosis associated with HCV have been reported; however, most of the individuals had additional conditions favoring immunosuppression such as cirrhosis, mixed cryoglobulinemia, and chronic therapies with interferon and ribavirin, which may lead to immunosuppression.[1,9–11] Our patient had not received HCV antivirals at the time of CM presentation.

When comparing individuals with and without HCV, it was found that other infections transmitted through the blood, such as HIV and hepatitis B, were more frequent in patients with HCV as were other infections associated with immunosuppression, those who are such as cytomegalovirus (CMV), toxoplasmosis, cryptococcosis, tuberculosis (TB), sexually transmitted diseases (STDs) (gonococcus, chlamydia, syphilis, and genital herpes), and bacterial infections (peritonitis, sepsis, endocarditis, cellulitis, and anthrax). After excluding potentially immunosuppressed patients, such as HIV-positive patients and patients with organ transplantation and cirrhosis, HCV infection remained significantly associated with CMV, Cryptococcus, TB, and STDs,[7] El-Serag et al concluded that patients with HCV infection had a significantly high prevalence of *cryptococcal* infection compared to controls (0.4% vs 0.1%).

Comparative models with healthy volunteers, serum from patients with chronic HCV infection showed a lower level of C5b-9 and a reduced antimicrobial effect. Similarly, liver biopsies from infected subjects showed reduced mRNA expression of C9.[12] HCV has two proteins: 3/4A (NS3/A4) protein and 5A (NS5A) protein, which contribute to immune dysregulation and reduced host response by cleaving Toll-like receptors (TLRs) and altering cytokine signaling. Together, these proteins provide a hypothetical mechanism supporting opportunistic infection by HCV.[13] Apparently, some immune markers, such as NKp30 and IGF-R1, are positively regulated in HCV patients with or without HIV co-infection, while others appear to be selectively regulated in subjects monoinfected with HCV (CD10, CD80, CCL-7 CCL20, and CX3CL1).[14]

The septins, proteins that are broadly conserved across species and are involved in a multitude of processes, including regulation of cytokinesis, exocytosis, control of cell cycle, diffusion barrier for proteins, vesicle trafficking, and maintenance of cell polarity; are a subfamily of GTP-binding proteins closely related and preserved in all species except higher plants, which form filament or ring-like structures by end-to-end binding. These proteins regulate critical processes as they are bound to cell membrane components and can participate in transport and exocytosis mechanisms across the plasma membrane. Interaction with bacterial but also with viral hosts has been reported; SEPT6 interacts with HCV NS5b viral proteins, non-structural protein 5b is an essential component of HCV for viral transcription and genome [forming a complex with host A1hnRNP proteins and promoting HCV replication]. During infection, increased co-immunoprecipitation of SEPT2 with SEPT6 has been evidenced, possibly due to an increase in the polymerization of septins and interaction with viral NS5b in HCV-infected cells, favoring their replication.[15,16]

IVDU has been considered a new risk factor for CM given its associations with cases of apparently immunocompetent individuals with IVDU and *cryptococcal* infection,[17–21] although cases of IVDU with central nervous system (CNS) cryptococcosis and HCV have also been reported.[19,22] Several mechanisms that may alter immunity in IVDU cases have been proposed, which include alterations of the hypothalamic-pituitary-adrenal axis and the autonomic nervous system after prolonged exposure to opioids, and suppression of the suppressor T-cells response, an important mechanism in *cryptococcal* disease. In IVDU individuals possible mechanisms of immunosuppressive compromise include altered function of natural killer cells, T cells, B cells, neutrophils, dendritic cells and/or macrophages, altered expression of cytokines and chemokines, and weakened integrity of the intestinal barrier, all of which contribute to decreased capacity to control pathogens and limit their further elimination.[23] In vitro studies have shown that morphine, heroin, and methamphetamine enhance HCV replication: Just as fentanyl increased HCV and HBV replication in hepatocytes.[24]

These results are related to the direct effects of heroin on opioid receptors located in immune cells, which may decrease antibody production, phagocytosis, and cytokine production. Similarly, in animal models, methamphetamine use alters antigen processing and facilitates *Cryptococcal* dissemination from the lung to the brain.[18,25–28] In our study patient, the main risk factor for CM development was his immunocompromised state.

Cocaine may affect macrophage and CD4 lymphocyte function and may also activate HIV expression in these cells. Chemokine analyses of cocaine-treated macrophages by real-time reverse transcription-polymerase chain reaction (RT-PCR) and Luminex assays evidenced increased expression of interleukin-10, a cytokine known to promote HIV replication.[29,30] Considering that HCV replication is 10–100 times higher than HIV replication, cocaine abuse could be a catalyst for the presence of these infections.[31]

The challenge of associating IVDU and HCV infection is enhanced by the revelation that the estimated number of people with IVDU worldwide was 14.8 million in 2021, 38.8% of which had HCV infection.[32]

CM treatment includes antifungal therapy and intracranial pressure control, with prolonged antifungal therapy during the induction, consolidation, and maintenance phases. In non-HIV individuals with neurological complications, such as our patient, the induction phase should continue for 6 weeks.[33] For individuals with poor initial response, the induction phase may be longer.[34,35]

IVDU are considered to have worse general health conditions when compared to the general population due to barriers resulting from socioeconomic issues such as discrimination, criminalization and unstable housing. Therefore, it is crucial to approach HCV infection as an important public health problem that requires several strategies for its control, including early and universal detection, with widespread screening of all people over 18 years of age and high risk groups, which would facilitate early diagnosis and access to treatment; harm reduction, through needle exchange programs, opioid substitution therapy, and education to reduce transmission among IVDU users; and finally, prevention is required in healthcare settings, implementing strict infection control practices to prevent transmission in medical settings.[36]

## Conclusion

Although *Cryptococcus* primarily affects immunocompromised individuals, the number of cases in immunocompetent patients has increased in recent years. Among the individuals at risk for Cryptococcal infections are those using intravenous drugs and those infected with HCV, as happened in this case report. Consequently, CM should be considered a differential diagnosis in patients with a history of HCV and IVDU presenting with CNS involvement.

Similarly, some infectious diseases are more common in patients with HCV; therefore, HCV should be identified selectively in individuals with these conditions. Immunosuppression may occur in patients with HCV due to T-cell dysfunction, dysregulation of innate immunity, and exhaustion of adaptive immunity, allowing an immunocompetent patient to present with disseminated cryptococcosis or CM. Other risk factors, such as HCV infection and IVDU, could predispose patients to cryptococcal infection. However, due to the progressive increase of CM in young and healthy individuals or individuals with few comorbidities, further research is required to determine the most appropriate treatment and identify risk factors that have not yet been established for this population.

Integrating HCV and IVDU treatment has important implications for practice, research, and policy. Effective integration involves combining HCV treatment with harm reduction and substance use disorder services, including testing, education, and counseling within these programs. Collaboration among healthcare providers, addiction specialists, and mental health workers is crucial.

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## Disclosure

The authors report no conflicts of interest.

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