CASE REPORT

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Cryptococcal meningitis in a patient with chronic hepatitis C treated with pegylated-interferon and ribavirin

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Various adverse events have been reported during combination therapy with pegylated (PEG)-interferon-α and ribavirin, although opportunistic infections, especially cryptococcal meningitis, are very rare. A 61-year-old woman complained of headaches and a fever during treatment of a chronic hepatitis C virus (HCV) infection. She had been treated for 7 months. Her headaches were refractory to analgesics, and she developed subtle nuchal rigidity. The cerebral spinal fluid (CSF) revealed a white blood cell count of 205/mm^3, 51 mg/dL protein, 35 mg/dL glucose, and negative *Cryptococcus* antigen. The CSF culture resulted in no growth. Five days later, the CSF was positive for *Cryptococcus* antigen. We administered amphotericin B and flucytosine, followed by fluconazole. Approximately 2 months later, she was discharged. For the first time, we report a case of cryptococcal meningitis during the treatment of chronic HCV with PEG-interferon-α and ribavirin.

Keywords: *Cryptococcus*; Meningitis; PEG-interferon-α; Ribavirin; Hepatitis C

INTRODUCTION

Cryptococcus neoformans is a ubiquitous fungal pathogen that causes human diseases ranging from asymptomatic colonization of the lungs to severe meningitis and generalized infections [1].

Subtle defects in the cellular immune response are thought to explain the occurrence of infectious diseases in immunocompromised patients, including defective lymphocyte proliferation, leukocyte migration disorders, interleukin-2 deficiency, and defects in humoral immunity. Cryptococcal infections have also been reported consistently in patients with idiopathic CD4 lymphopenia [2].

There are reports of *Listeria monocytogenes* [3] and pneumococcal [4] meningitis after therapy with interferon and ribavirin for hepatitis C virus (HCV) infection. We present the first reported case of cryptococcal meningitis in a noncirrhotic patient with chronic HCV infection who was undergoing treatment with pegylated (PEG)-interferon-α and ribavirin.

CASE REPORT

A 61-year-old woman began treatment with PEG-interferon-α2b (80 μg subcutaneous [1.5 μg/kg/wk]) and ribavirin (1,000 mg daily per os) for chronic HCV infection in February 2008. Her HCV was genotype 1b, and the viral load was 5.08 × 10^5 IU/mL according to serology (AMPLICOR, Roche Molecular Systems, Pleasanton, CA, USA). She was negative for antihuman immunode-

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ficiency virus (HIV). Prior to beginning combination treatment with PEG-interferon and ribavirin, the laboratory assessment showed a white blood cell (WBC) count of 7,400/mm^3 (polymorphonuclear leukocytes [PMNLs] 59.1%, lymphocytes 0.2%, and monocytes 9.4%), hemoglobin level of 11.8 g/dL, platelet count of 227,000/mm^3, blood urea nitrogen/creatinine level of 18.2/0.89 mg/dL, and glucose level of 103 mg/dL. The prothrombin time was 12.7 seconds (international normalized ratio, 0.99). The primary care physician reported an unremarkable abdominal ultrasound. The treatment was continued for 28 weeks; she had headaches without fever for 4 to 5 days after each PEG-interferon injection, which resolved spontaneously or with analgesics. She had a rapid virologic response after 4 weeks and an early virologic response after 12 weeks of treatment. She had been given low-dose ribavirin (400 mg daily for 3 months) before admission because of low hemoglobin (7.1 g/dL). She received the last shot of PEG-interferon (80 μg) 4 days before admission.

She was admitted with a 5-day history of headaches and fever on 1 September 2008. On examination, she appeared ill, was febrile, and complained of headaches and nausea. Her blood pressure was 125/85 mmHg, pulse was 90 beats per minute and regular, and temperature was 39.1°C. Examinations of the heart, lungs, and abdomen were normal, as was the neurological examination. We prescribed acetaminophen.

On admission, her WBC count was 2,700/mm^3 (PMNLs 72.0%, lymphocytes 19.0%, and eosinophils 1.3%), the hemoglobin level was 8.4 g/dL, and the platelet count was 74,000/mm^3. The electrolytes and liver function tests were within normal limits. A chest X-ray was unremarkable. Precontrast and postcontrast brain computed tomography (CT) were normal. Abdominal CT revealed no evidence of cirrhosis but a fatty liver with borderline hepatomegaly.

The acetaminophen successfully eliminated her headaches, until she complained of severe headaches refractory to analgesics on the sixth hospital day. The neurological examination disclosed subtle nuchal rigidity without other abnormalities. We examined the cerebrospinal fluid (CSF) and began administration of empiric acyclovir, ceftriaxone, and vancomycin for suspected meningitis. CSF analysis revealed a 205/mm^3 WBC count (PMNLs 45%, monocytes 36%, and lymphocytes 19%), 51 mg/dL protein level, 35 mg/dL glucose level, and negative polymerase chain reaction (PCR) results for tuberculosis, enterovirus, herpes simplex virus, and cryptococcal antigen (RapidID Yeast Plus test, Remel, Santa Fe, NM, USA). The CSF culture resulted in no growth. Five days later, the CSF showed a 60/mm^3 WBC count (PMNLs 18%, monocytes 16%, and lymphocytes 66%), 137 mg/dL protein level, 34 mg/dL glucose level, and positive *Cryptococcus* antigen. The patient was administered amphotericin B (33 mg daily for 30 days) and flucytosine (1 g four times a day per os for 2 weeks), followed by fluconazole (400 mg daily for 5 weeks). On the 41st hospital day, the CSF was negative for cryptococcal antigen. On the 66th hospital day, the CSF was within normal limits (Table 1). On the 69th hospital day, she was discharged with no symptoms and a negative HCV RNA reverse transcription (RT)-PCR result (Fig. 1). In February 2009, she had a negative HCV RNA RT-PCR result 6 and 12 months after discontinuing the PEG-interferon and ribavirin therapy (i.e., a sustained virologic response).

DISCUSSION

The current standard therapy for patients with chronic HCV infection is PEG-interferon-α plus ribavirin [5]. Both drugs have antiviral and immunomodulatory activities [6,7]. Interferon-α is a cytokine with an important function in innate immunity against viruses. Interferon-α attaches to cell surface receptors that signal via Janus-activated kinase and signal transducers and activators of transcription, resulting in the induction of multiple interferon-stimulated genes. These genes encode double-stranded RNases, inhibitors of viral protein translation, and proteins that destabilize viral messenger RNA. Interferon-α also causes the overexpression of genes involved in the immune response, resulting in the activation of natural killer cells, maturation of dendritic cells, proliferation of memory T cells, and prevention of T cell apoptosis [5]. Interferon-α inhibits T cell immunity in several ways. It inhibits the interleukin 2-induced proliferation of peripheral T lymphocytes [8], inhibits the production of interleukin 12, the central immunoregulatory cytokine of CD4 T cells [9], and maintains the survival of anergic CD4 T

Table 1. The results of the cerebral spinal fluid analyses

Variable	Hospital day				
	6	11	41	51	66
RBC, /mm^3	-	1	1	3	1
WBC, /mm^3	205	60	108	42	18
PMNLs	45	18	1	1	-
Monocytes	36	16	4	20	22
Lymphocytes	19	66	96	78	77
Eosinophils	-	-	-	1	1
Protein, mg/dL	51	137	116	104	60
Glucose, mg/dL	35	34	30	30	46
Culture	Neg	Neg	Neg	Neg	Neg
Cryptococcus Ag	Neg	Pos	Pos	Neg	Neg
Haemophilus Ag	Neg	Neg	Neg	Neg	Neg
Pneumococcus Ag	Neg	Neg	Neg	Neg	Neg
Meningococcus Ag	Neg	Neg	Neg	Neg	Neg
Group B *Streptococcus* Ag	Neg	Neg	Neg	Neg	Neg
Neisseria meningitides/Escherichia coli	Neg	Neg	Neg	Neg	Neg
HSV IgG/M	-	Neg/Neg	Neg/Neg	Pos/Neg	Neg/Neg
HSV type I PCR/type II PCR	Neg/Neg	Neg/Neg	Neg/Neg	Neg/Neg	Neg/Neg
VZV IgG/M	-	Pos/Neg	Neg/Neg	Pos/Neg	Neg/Neg
Mycobacterium tuberculosis PCR and hybridization	Neg	Neg	Neg	Neg	Neg
India ink	Neg	Neg	Neg	Neg	Neg

RBC, red blood cells; WBC, white blood cells; PMNLs, polymorphonuclear leukocytes; Neg, negative; Pos, positive; Ag, antigen; HSV, herpes simplex virus; PCR, polymerase chain reaction; VZV, varicella zoster virus.

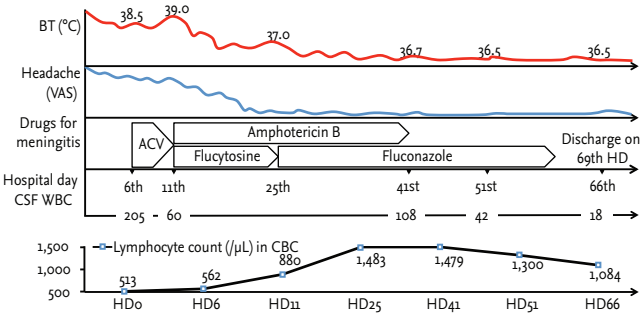

Figure 1. Overall clinical course. BT, body temperature; VAS, visual analogue scale; ACV, Acyclovir + Ceftriaxone + Vancomycin; HD, hospital day; CSF, cerebrospinal fluid; WBC, white blood cell; CBC, complete blood count.

cells [10].

Ribavirin is an oral nucleoside analogue with broad virustatic activity against viral pathogens. The mechanism of action of ribavirin against HCV is not understood completely. Ribavirin appears to have minimal direct activity against HCV replication, but it may lead to the rapid, lethal mutation of virions or depletion of intracellular guanosine triphosphate, which is necessary for viral RNA synthesis [5]. Ribavirin also possesses immunomodulatory activity [7] and inhibits T cell proliferation [11]. The immunosuppressive effect of both drugs is synergistic [12].

Common side effects of PEG-interferon-α and ribavirin combination therapy include fatigue, flu-like symptoms, hematological abnormalities, and neuropsychiatric symptoms. Neutropenia occurs at a rate of 18% to 20% during PEG-interferon-α and ribavirin therapy and is the most common indication for reducing the dose of PEG-interferon. A rapid decrease in the neutrophil count may occur within the first 2 weeks of therapy and usually stabilizes over the next 4 weeks as steady-state concentrations of PEG-interferon are achieved. The neutrophil count rapidly returns to

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baseline after therapy is discontinued [13].

One study found that only African-Americans had baseline neutropenia, and bacterial infections developed in approximately 18% of the HCV patients receiving interferon-α and ribavirin therapy; however, no patients with neutropenia developed bacterial infections [14]. Other studies support the notion that the rate of infectious complications during interferon-based therapy for HCV is not related to neutropenia [15,16]. Puoti et al. [17] reported an independent association between neutropenia and acute respiratory infections in HCV patients treated with PEG-interferon and ribavirin. Antonini et al. [18] reported that 23% of the patients receiving PEG-interferon (α-2a or α-2b) and ribavirin developed various infections, including respiratory infections, cellulitis, dental abscesses, and gastroenteric infections, that were significantly ($p < 0.01$) associated with age, especially age > 60 years. They also demonstrated the lack of an association between infections and the occurrence or duration of neutropenia during PEG-interferon-based anti-HCV treatment [18].

Bani-Sadr et al. [19] observed 18 bacterial infections in 17 of 383 patients with HIV/HCV coinfections who received at least one dose of interferon plus ribavirin. According to univariate analysis, the risk factors for these infections included a longer history of HCV infection and low hemoglobin concentrations, prothrombin levels, and leukocyte, neutrophil, and platelet counts. The HCV infection duration and the prothrombin level remained significantly associated with the risk of bacterial infection according to multivariate analysis [19].

Treatment-induced neutropenia is not uncommon, but opportunistic infections are rare in patients with chronic HCV treated with interferon and ribavirin. Approximately one-half of the non-HIV-infected patients with cryptococcal meningitis had underlying diseases (malignancies, diabetes mellitus, corticosteroid treatment, rheumatologic diseases, liver cirrhosis, or chronic kidney disease) and lymphoma, and high initial cryptococcal antigen titers are independent risk factors of mortality [20].

Cryptococcal meningitis can be confirmed by CSF culture or a latex agglutination assay for cryptococcal polysaccharide antigen. The antigen test is very sensitive and specific, and it shows positive results in the CSF and serum in nearly 100%, and approximately 75% of patients who have meningitis, respectively [21]. False-positive results are uncommon, generally low in titer, more likely in serum than in CSF, and can be due to assay interference by rheumatoid factor. The rare patient with *Trichosporon asahii* infection can have a positive antigen test, because both fungi share cross-reacting antigens [21]. While our patient did not have a positive CSF culture, the positive antigen tests were sufficient to diagnose cryptococcal meningitis. The initial negative result for cryptococcal antigen could have occurred if the titer was lower than the level of detection or if it was a false negative. The second CSF study was done because the patient's symptoms did not improve, and a positive cryptococcal antigen test and elevated CSF protein level were detected.

In our patient, diminished chemotactic and phagocytic macrophage functions and a depressed inflammatory response associated with older age [18] and altered T-cell function caused by PEG-interferon-α and ribavirin, along with inherent T-cell dysfunction induced by HCV infection, might have increased her susceptibility to cryptococcal infection. We were misled initially by the flu-like symptoms, which occurred after each PEG-interferon injection. However, we considered the causes of on-going fevers and headaches, especially in the mid- and late-phases of the scheduled treatment. Fortunately, the patient had an undetectable HCV RNA level at the end of treatment and 6 months and 1 year after discontinuing therapy, to which the disturbed immune system and good patient compliance might have contributed. For the first time, we report a case of cryptococcal meningitis during the treatment of chronic HCV with PEG-interferon-α-2b and ribavirin.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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