Enferm Infecc Microbiol Clin. 2018;36(7):456–457

Enfermedades Infecciosas y Microbiología Clínica

www.elsevier.es/eimc

Scientific letters

Cryptococcus neoformans peritonitis in the cirrhotic patient☆

Peritonitis por Cryptococcus neoformans *en el paciente cirrótico*

Cryptococcosis primarily affects individuals with abnormal cellular immunity, especially patients with HIV in advanced stages. In recent years, its frequency has increased in immunosuppressed patients not infected with HIV, in particular in patients with cirrhosis, in whom peritonitis represents the most common clinical form.[1]

Case report

A 55-year-old male had been diagnosed 5 years earlier with chronic liver disease and was in a cirrhotic state, probably of mixed autoimmune origin as opposed to non-alcoholic steatohepatitis. In late 2016, he was given a MELD prognostic score of 19 and therefore considered for pre-transplant assessment. In recent months, he had received treatment with prednisone 30 mg/24 h, azathioprine 50 mg/24 h, furosemide, spironolactone, ursodiol, cholestyramine and omeprazole.

Two months later, he was admitted to our hospital. Complementary tests showed: haemoglobin 11 g/dl, leukocytes 9450 mm^3, platelets 163,000 mm^3, prothrombin time 44%, CRP 19 mg/l, glucose 95 mg/dl, creatinine 1.2 mg/dl, glomerular filtration rate 68 ml/min, total bilirubin 19.6 mg/dl (direct bilirubin 15.9 mg/dl), GOT 76 U/l, GPT 98 U/l, AP 105 U/l and GGT 62 U/l. Ultrasound and CT scanning of the abdomen showed chronic liver disease with signs of portal hypertension, moderate ascites and bilateral kidney stones. A study of his ascitic fluid showed: glucose 15 mg/dl, total protein 1.82 g/dl, LDH 728 U/l, leukocytes 3440 mm^3 (85% PMN) and red blood cells 2640 mm^3.

On the fourth day, he started to have signs and symptoms of fever, abdominal pain, hypotension, tachycardia, tachypnoea, oligoanuria and poor distal perfusion. We drew samples for blood culture and urine culture as well as a sample of his ascitic fluid, then started empirical treatment with meropenem and transferred him to an intensive care unit.

The patient progressed to refractory shock and multiple organ failure and died 24 h later. The microbiological results we received later showed that *Cryptococcus neoformans* (*C. neoformans*) var. *grubii* had been detected in his blood culture and ascitic fluid. Hence an ultimate diagnosis was made of septic shock secondary to spontaneous peritonitis caused by *C. neoformans* with secondary fungemia in an immunosuppressed patient with cirrhosis.

Discussion

Cryptococcosis is a systemic mycosis caused by an encapsulated yeast-like fungus belonging to the genus *Cryptococcus*. The infection is essentially acquired by inhaling yeasts present in nature. When the fungus reaches the pulmonary alveoli, an immune response occurs that under normal conditions is sufficient to control the infection; however, in immunocompromised patients, the infection may spread via the bloodstream and migrate to different tissues.[2]

In non-HIV immunosuppressed patients, infections with *C. neoformans* used to be rare; however, due to the development of organ and tissue transplants[3] and to the increase in the population receiving immunosuppressants,[4] their frequency has been seen to increase, in particular in patients with cirrhosis.[5,6]

In peritonitis due to *C. neoformans* in the patient with cirrhosis, the infection is thought to travel from silent pulmonary foci to the gastrointestinal tract via the bloodstream and lymphatic system. The fungus infects the host through fungal overgrowth due to antibiotic pressure or translocation to the ascitic fluid due to gastrointestinal bleeding.[7]

In up to 40% of patients with chronic liver disease, the diagnosis is made after death. These patients are characterised by having a higher MELD prognostic score, a higher rate of cryptococcaemia, mechanical ventilation, septic shock and a higher likelihood of positive antigen tests.[8] This profile strongly resembles that of our patient.

Diagnosis is primarily microbiological. Staining with India ink stains the entire preparation except the capsule and thus enables a presumptive diagnosis. Culture requires at least 3–4 days of incubation and establishes the definitive diagnosis; however, techniques such as MALDI-TOF may shorten this period.[9] Capsular antigen detection is a technique with high sensitivity and specificity. Even so, false positives due to the presence of rheumatoid factor or in the serum of patients with bacteraemia or neoplasms have been reported. Molecular techniques represent valid alternatives when conventional techniques are not effective.

The recommended treatment for disseminated cryptococcosis in a non-HIV patient consists of amphotericin B combined with flucytosine (at least 2 weeks), followed by fluconazole, until the lapse of 10 weeks. In patients with kidney dysfunction such as our patient, amphotericin B deoxycholate may trigger nephrotoxicity; thus it is safer to use lipid formulas.[10]

This case leads us to believe that in a patient with cirrhosis who has spontaneous peritonitis refractory to empirical antibiotic treatment, a negative bacterial culture and a high red blood cell count in his or her ascitic fluid, the possibility of *Cryptococcus* infection should be considered.

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DOI of original article: https://doi.org/10.1016/j.eimc.2017.10.011

☆ Please cite this article as: Sena Corrales G, Perez Medina MI, Costo Muriel C, Reguera Iglesias JM. Peritonitis por *Cryptococcus neoformans* en el paciente cirrótico. Enferm Infecc Microbiol Clin. 2018;36:456–457.

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2529-993X/

Sofosbuvir plus daclatasvir as an alternative for patients on haemodialysis with genotype 2 hepatitis C virus infection

Sofosbuvir más daclatasvir como alternativa en pacientes con infección por el virus de la hepatitis C genotipo 2 en hemodiálisis

Dear Editor,

Treatment of hemodialyzed patients with HCV infection is challenging and data on safety and effectiveness of the new direct-acting antivirals (DAAs) are scarce and concentrated in genotypes 1 and 4.[1,2] For patients with genotype-2-HCV (gen2-HCV) infection and estimated glomerular filtration rate (eGFR) < 30 mL/min, current guidelines recommend pegylated interferon-α (PEG-IFN) and dose-adjusted ribavirin when treatment has been elected before kidney transplantation.[2] Preferred regimens for gen2-HCV-infection without renal impairment are sofosbuvir/velpatasvir (SOF/VEL), daclatasvir (DCV) + sofosbuvir (SOF) and SOF + ribavirin.[3,4] Although SOF is restricted to patients with eGFR ≥ 30 mL/min, real world data in patients with lower eGFR show a good effectiveness rate with increased side effects.[5] SOF toxicity may be driven by accumulation of GS-331007, a metabolite eliminated renally and partially extracted by hemodialysis. Recently, growing evidence of the safety and effectiveness of SOF in hemodialyzed patients has arisen[1,6] with 100% sustained viral response at 12 weeks (SVR12).

We hereby describe the case of a 50-year-old Moroccan immigrant with chronic kidney disease stage 5 on hemodialysis. On September 2015, he had an acute gen2-HCV-infection. Twelve months later, his HCV viral load was 2,708,805 IU/mL and elastography was 9.1 kPa. IL28B genotype was CT. A 12-weeks course of daily SOF400 mg plus DCV60 mg was started. On hemodialysis days, patient was instructed to take SOF and DCV after the hemodialysis session. SOF/VEL was not available at that time. During HCV treatment he continued taking his chronic medications that included gemfibrozil, omeprazole, nifedipine, calcifediol, sevelamer, cinacalcet, folic acid, calcium acetate/magnesium carbonate and sodium bicarbonate; carvedilol was replaced by doxazosin to avoid bradycardia. The patient was closely monitored with weekly clinical visits, weekly blood cell count, biochemistry (including liver function tests) and electrocardiogram. Therapeutic drug monitoring was not available. He had no side effects besides a grade 2 self-limited episode of vomits 3 days after starting medication. He successfully achieved SVR12.

Best option for gen2-HCV patients in hemodialysis is unknown and DAAs' data come from case reports or small case series. Desnoyer et al. included only one gen2-HCV patient successfully treated with SOF + ribavirin[6]; other studies report no gen2-HCV cases or no extractable data.[5] In our opinion, until more treatment options become available, SOF + DCV could be a good option if treatment is elected before kidney transplantation. This combination may be better tolerated and more effective than PEG-IFN + ribavirin. It is mandatory to monitor them very closely for hepatobiliary and cardiovascular side effects.

Financial support

None.

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2529-993X/