

## LETTERS TO THE EDITOR

## Ribavirin for Chronic Hepatitis E in Liver-Transplant Setting: A Safe and Highly Effective Therapy

### To the Editor:

Hepatitis E virus (HEV) chronic infection has been increasingly recognized among immunocompromised patients. HEV infection is a cause of graft hepatitis in liver-transplant (LT) recipients and may result in chronic infection, progressive fibrosis, and end-stage liver disease in this population, which seems to have a higher risk when compared with non-LT patients.<sup>1</sup>

The authors report 5 cases of HEV chronically infected LT recipients, successfully treated with ribavirin. These represent 3.5% of the 141 LT recipients with persistent unexplained elevated liver enzymes, tested by HEV-RNA PCR after other possible causes were excluded. Prevalence of HEV infection, in the setting of transplantation, is not well known. However, it seems low in western transplant cohorts. Behrendt et al<sup>2</sup> recently suggested that testing only patients with elevated liver enzymes is a reasonable approach, as we do in our center.

In 4 patients, familial amyloidotic polyneuropathy was the initial liver disease, and the fifth patient had Wilson's disease. As expected, considering these diagnoses, our patients were younger than in other series, with a mean age of 32 years at the time of transplant (range, 27 to 35 y). The time between the transplant and the evidence of HEV infection had a wide range (4 mo to 11 y). No patients had an acute rejection episode after undergoing transplantation. Only 1 patient had an acute self-limited symptomatic episode of hepatitis, followed by persistent raised transaminases levels. In the remaining 4 patients, acute hepatitis was asymptomatic, no abnormalities were detected during physical examination and HEV infection was diagnosed after the detection of persistent abnormal

liver enzymes levels. All patients had persistently normal platelet count and hemoglobin level, and only 1 had mild impaired renal function. Two patients were infected by genotype 3 and in the other 3 cases, HEV was not genotyped. At the time of the infection diagnosis, 4 patients were medicated with tacrolimus. The use of tacrolimus (rather than cyclosporine A) and a low platelet count are the main independent predictive factors for chronic infection.<sup>1</sup> Reductions in immunosuppressive therapy seem to result in viral clearance in only one third of these patients. Recent data suggests that various immunosuppressive regimens can differentially affect HEV replication: in vitro steroids have no significant effect on HEV replication, calcineurin inhibitors promoted replication of HEV and mycophenolic acid inhibits HEV replication.<sup>3</sup> Application of this knowledge into clinical practice needs confirmation by large comparative trials, before these data can influence the choice of immunosuppressive regimens. In our patients we reduced the overall level of immunosuppression. All of our patients were also treated with ribavirin at a dose of 800 to 1200 mg daily during 6 months. After 3 months of therapy, all patients had undetectable viremia. All of them completed the treatment, and no adverse effects were reported. At the end of therapy, all patients had undetectable HEV-RNA. Six months after finishing antiviral therapy, all achieved sustained virological response (SVR) and had normal levels of liver enzymes. In our case series, ribavirin monotherapy showed to be safe and highly effective. We had no adverse effects, namely anemia. Therefore, we maintained the same dose of ribavirin, which may justify our excellent results. Thus, some studies reported the appearance of clinical resistance with lower doses. With 6 months of therapy, SVR was achieved in all of our patients. Shorter courses can be related with recurrence cases. In the recent series by Kamar et al,<sup>4</sup> all patients who failed to clear HEV during the initial course of ribavirin therapy showed a SVR when retreated for a longer period. All of our patients have > 18 months of follow-up, with no signs of recurrence. In a real world setting, ribavirin for 6 months in weight-based dose showed excellent results, however this needs to be confirmed in large, randomized, controlled trials.

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## Portal Hypertension Related to Schistosomiasis Treated With a Transjugular Intrahepatic Portosystemic Shunt

### To the Editor:

Hepatosplenic schistosomiasis represents the most common form of chronic intestinal schistosomiasis. Liver

The authors declare that they have nothing to disclose.

DOI: 10.1097/MCG.0000000000000545

The authors declare that they have nothing to disclose.

DOI: 10.1097/MCG.0000000000000554

periportal fibrosis, leading to portal hypertension, is the major cause of disease morbidity and mortality, due to massive bleeding of esophageal or gastric varices.<sup>1</sup>

Hereby, we present the case of a 30-year-old Ethiopian man who was referred to our Unit for hematemesis. Emergency endoscopy showed evidence of active bleeding from varices of the lower third of the esophagus. Endoscopic rubber band ligation was performed. On physical examination, splenomegaly extending 4 cm below the costal margin and moderate ascites without neurological disorders were found. Laboratory tests showed leukopenia (white blood cells: 2410/mm<sup>3</sup>), anemia (hemoglobin: 8.3 g/dL) with a hematocrit of 25%, and thrombocytopenia (platelet: 47,000/mm<sup>3</sup>). The liver function panel revealed the following data: total bilirubin 1.7 mg/dL, alanine aminotransferase 93 U/L (upper normal limit < 41 U/L), aspartate aminotransferase 85 U/L (upper normal limit < 40 U/L), international normalized ratio 1.4, and albumin 3.4 g/dL (Child Pugh score B7). Hepatitis A, B, and C, Cytomegalovirus, Epstein-Barr virus, and human immunodeficiency virus serology tests were negative. Transferrin saturation and serum ceruloplasmin were within the normal values. Antinuclear antibody, antismooth-muscle antibody, antimitochondrial antibody, and liver/kidney microsomal antibody were also negative. Abdomen ultrasound and computed tomography revealed features of severe portal hypertension, such as splenoportal axis ectasia, splenomegaly (maximal diameter of 20 cm), splenorenal shunt, and moderate ascites. The hepatic venous pressure gradient was 24 mm Hg. Despite esophageal band ligation, a progressive anemia due to intestinal blood loss was observed and early transjugular intrahepatic portosystemic shunt (TIPS) was performed. TIPS insertion resulted in a decrease in hepatic venous pressure gradient to 9 mm Hg and a reduction of varices with a progressive increase in hemoglobin levels. After TIPS placement, no episodes of hepatic encephalopathy (HE) occurred. Repeated stool examinations demonstrated *Schistosoma mansoni* eggs; schistosoma antibodies were detected by serological test. A percutaneous ultrasound-guided liver biopsy, performed at the time of TIPS placement, did not show any sign of cirrhosis. Focal matrix degradation characterized by fragmentation and dispersion of collagen fibers, hyperplasia of elastic tissue, destruction of portal-vein radicles, sinusoidal dilatation and disarray of smooth

muscle fibers, the presence of bile pigments, and hemosiderin were observed. *S. mansoni* eggs were not detected in the liver biopsy. The patient was diagnosed with intestinal and hepatic schistosomiasis and he was treated with praziquantel 40 mg/kg. The patient's clinical conditions improved progressively and he was discharged after 10 days.

Worldwide, mansonic schistosomiasis is the second most prevalent parasitosis after malaria, with 240 million estimated infected individuals, 90% of them residing in Africa. Mortality is mainly caused by upper digestive-tract hemorrhage, resulting from portal hypertension.<sup>2</sup>

The management of acute upper gastrointestinal bleeding in schistosomiasis is similar to that of cirrhosis. Nevertheless, pharmacological treatment with  $\beta$ -blockers is controversial due to pulmonary hypertension. Although systemic vasoconstrictors can be helpful, band ligation or sclerotherapy of esophageal varices is considered as the optimal therapeutic strategy.<sup>3</sup> Although endoscopic rubber band ligation was performed promptly for our patient, the procedure was not conclusive because of rebleeding. For patients with uncontrolled bleeding after medical and/or an endoscopic approach, surgical procedures are indicated,<sup>4</sup> despite the risk of encephalopathy after surgery. HE occurs in nearly 40% of the patients undergoing proximal splenorenal shunt surgery, a percentage much greater than that of patients undergoing distal splenorenal shunt (14.8%) or splenectomy with devascularization (0%).<sup>4,5</sup> Therefore, esophagogastric devascularization with splenectomy should be considered as the most effective procedure.<sup>3,6,7</sup> Moreover, considering the fact that the hepatic function is not impaired in schistosomiasis-related disease,<sup>7</sup> the surgical treatment of portal hypertension in patients with chronic schistosomiasis has distinct features compared with cirrhotic patients. Accordingly, Ezzat et al<sup>8</sup> reported a significantly lower risk of HE after selective surgical shunt in patients with schistosomal hepatic fibrosis compared with those with cirrhosis (4.4% vs. 23.5%,  $P < 0.05$ ). In our patient, we preferred TIPS insertion, which, unlike most surgical procedures, is far less invasive and preserves the spleen and its immunological function.<sup>9</sup> Furthermore, studies reporting outcomes of surgery in schistosomiasis differ in surgical methods and they do not describe systematically indirect adverse events of splenectomy, such as infections.<sup>10,11</sup> In

our case, TIPS was a conclusive procedure, resulting in the reduction of portal pressure and the interruption of upper gastrointestinal bleeding. Recently, a paper reporting similar results has been published.<sup>10</sup>

In conclusion, we believe that schistosomiasis has to be included in the differential diagnosis of portal hypertension, as its prevalence in Europe might increase due to migration from endemic regions. Although existing guidelines on TIPS indication do not consider this procedure as a therapeutic option for schistosomiasis-related portal hypertension,<sup>12</sup> in our opinion, TIPS should be taken into account as it represents an effective and less invasive approach compared with surgery. Therefore, for the better management of schistosomiasis portal hypertension, prospective studies are needed.

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## Ocular Toxoplasmosis Reactivation in a Patient With Inflammatory Bowel Disease Under Treatment With Azathioprine

### To the Editor:

Thiopurines are used widely in the treatment of inflammatory bowel disease (IBD); however, they are associated with opportunistic infections.<sup>1</sup> It is important to maintain a surveillance of symptoms suggestive of infections in these patients.

We expose the case of a 33-year-old woman originally from Nigeria who presented with a 24-hour history of visual loss in the left eye and periorbital pain. She was diagnosed of ulcerative colitis, and treated with mesalazine and azathioprine 100 mg/24 hours for 12 months because of corticoid dependency.

All authors contributed equally to this work. The authors declare that they have nothing to disclose.  
DOI: 10.1097/MCG.0000000000000521

Her visual acuity was reduced to counting fingers in the left eye. Ophthalmoscopy examination showed a focus of chorioretinitis on the edge of an old chorioretinal scar with retinal detachment and the presence of retinal vasculitis with venous and arterial involvement. Blood test and cranial computed tomography were normal. Serological tests for HIV, *Treponema pallidum*, Epstein-Barr, and cytomegalovirus were negative and the toxoplasma serology showed negative IgM and positive IgG antibodies. Clinical and ophthalmoscopic findings were highly suggestive of ocular toxoplasmosis reactivation in an immunocompromised patient, and she was treated with sulfadiazine, pyrimethamin, folic acid, and prednisone for 2 months. The response was satisfactory with retinal reapplication over 2 weeks and complete recovery of visual acuity after 3 months.

Ocular toxoplasmosis is the most common cause of retinochoroiditis worldwide, usually presenting as photophobia, blurred vision, and even blindness. In immunosuppressed patients, greater extension and severity have been described, even with mortality due to intracranial lesions. It is caused by the protozoal parasite *Toxoplasma gondii*, and in the United States, 22.5% of the population 12 years or older has been estimated to be infected. Cats are the principal hosts and humans and other vertebrate animals are the intermediate hosts. It is fundamentally transmitted through the oral and the transplacental routes.

The diagnosis is based on clinical and ophthalmoscopic findings. Serology can support it, confirming exposure to the parasite, but the diagnosis of ocular toxoplasmosis cannot be made on the basis of serological tests because IgG titers are usually low, and IgM can be negative because isolated ocular reactivation is usually insufficient to produce a systemic immune response,<sup>2</sup> as shown in our case.

The treatment of toxoplasma chorioretinitis in immunocompetent patients is controversial because the lesions usually resolve spontaneously. Treatment is indicated in immunosuppressed patients and in the presence of severe vitritis or lesions localized in the macula or the optic nerve in immunocompetent patients. Sulfadiazine-pyrimethamine, prednisone, and folic acid (for the prevention of leukopenia and thrombocytopenia due to pyrimethamine) is the standard treatment.<sup>1</sup>

Ocular toxoplasmosis reactivation has been reported in immunocompromised patients with ankylosing spondylitis<sup>3</sup> or after cardiac transplant,<sup>4</sup> but no cases have been reported in IBD patients or relating to the use of thiopurines. In our opinion, ocular toxoplasmosis should be considered in the differential diagnosis of IBD patients treated with thiopurines presenting with ocular symptoms, especially if they come from countries with high endemicity. The diagnosis should be established as early as possible to avoid fatal complications or severe sequelae.

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## Mycosis Fungoides–like Eruption and Infliximab

### To the Editor:

The increased use of TNF- $\alpha$  inhibitors has led to focus on their

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The authors declare that they have nothing to disclose.

DOI: 10.1097/MCG.0000000000000517