## Concomitant CMV and *Clostridium difficile* colitis in an immunocompetent patient treated with Ganciclovir and fecal transplantation

**To the Editor,**

A 53-year-old patient, recently operated for duodenal ulcer, was admitted to the Clinic of Gastroenterology, Clinical Emergency and County Hospital, Constanta, presenting watery diarrhea (about 12 stools/day), abdominal pain, weight loss, nausea and altered general condition. The symptoms appeared three months ago, after prolonged treatment with ciprofloxacine for a urinary infection associated with catheter during previous surgery. The patient was diagnosed with *Clostridium difficile* colitis based on positive test for toxin A + B (immunochromatographic method) and colonoscopy, which revealed the presence of pseudomembranous colitis. During this period, he had received treatment several times with metronidazole 1500 mg/day (intravenous or orally) associated with oral vancomycin 250 mg every 6 h, and then 500 mg every 6 h and rifaximin 1200mg/day, but no significant improvements were observed.

On admission, laboratory analyses revealed anemia (Hb = 9.3 g/dl), neutrophilic leukocytosis (L = 17.6x$10^3$ µL, neutrophils = 82.7%), positive inflammatory tests (PCR = 12 mg/dl, normal value < 0.5 mg/dl) and hypoalbuminemia.

Abdominal ultrasound and CT showed normal liver, distended bowel loops with thickened wall and ascites fluid in the abdominal cavity. The tests excluded liver disease (normal aminotransferases, HBsAg-negative, anti-HCV-negative, normal AFP, normal electrophoresis), enterocolitis with other etiology (negative coprocultures for *Salmonella, Shigella, Campylobacter, Escherichia coli enterohemoragic* O157:H7), negative HIV test, positive CMV IgG ( >500 U/ml, N = < 9 U/ml) and positive CMV IgM (14.17 U/ml (N < 9 U/ml). Biopsy prelevated at colonoscopy showed endothelial and stromal cells with enlarged smudgy nuclei containing basophilic inclusion bodies characteristic for *Cytomegalovirus* colitis (Figs.1, 2). Our diagnosis was reactivation of latent CMV infection in conditions of immunosuppression caused by pseudomembranous colitis. We performed fecal transplantation and subsequent treatment with Ganciclovir for 6 weeks. After fecal transplantation, the clinical status of the patient rapidly improved, and a spectacular evolution of inflammatory tests was observed (PCR =10.8 mg/dl, 6.14 mg/dl, 3.16 mg/dl, 1 mg/dl – on the second, third, fifth and seventh day after transplantation). One week after transplantation, the stools were normal, abdominal ultrasound was normal and no ascites was present in the abdominal cavity.

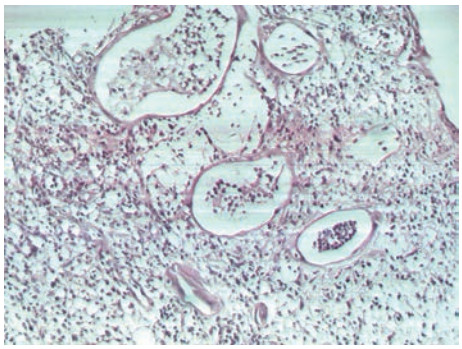

**Fig. 1**. Extensive acute inflammation with crypts abscesses and smudgy intranuclear inclusions of endothelial cells (bottom) (H&E x100)

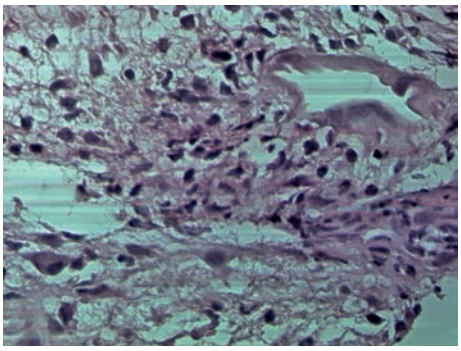

**Fig. 2.** Stromal and endothelial cells with smudgy enlarged nuclei or with basophilic intranuclear inclusions evoking a cytopathic effect of CMV (H&E x400)

It is known that CMV colitis is usually caused by the reactivation of a latent CMV infection in patients with immunosuppression. Cases have been reported in HIV and ulcerative colitis (UC) patients [1-3]. Numerous studies and case reports have described an association between the presence of CMV infection and increased colectomy and

mortality rates in UC patients [2, 3], but only a few cases of co-infection with CMV and *Clostridium difficile* colitis have been published [4, 5].

We emphasize the importance of recognition and treatment of CMV reactivation in refractory cases of *Clostridium difficile* colitis. Fecal transplantation is a highly effective therapeutic method in patients with refractory *Clostridium difficile* colitis or in multiple relapses.

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**Conflicts of interest:** none to declare.

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## The first report of oxcarbazepine-induced vanishing bile duct syndrome

**To the Editor,**

A 55-year-old female was admitted to our hospital because of jaundice and pruritus. She had a diagnosis of Sjögren Syndrome for 6 years and was using no drugs except artificial tears for xerophthalmia. She had no history of alcohol abuse. Four weeks previously she was diagnosed with epilepsy, and oxcarbazepine was started with a dose of 300 mg twice daily. Physical examination was normal except the presence of marked yellow discoloration of the eyes and skin. Liver function tests were found to be elevated with a total bilirubin level of 22.7 mg/dL (Normal range: 0.1-1), and a conjugated bilirubin level of 19.1 mg/dL (Normal < 0.25). Other laboratory investigations were as follows; aspartate aminotransferase: 77 IU/L (Normal range: 5-35), alanine aminotransferase: 110 IU/L (Normal range: 5-40), alkaline phosphatase: 480 IU/L (Normal range: 90-260), gamma-glutamyl transferase: 1255 IU/L (Normal range: 7-32). Abdominal ultrasonography and magnetic resonance cholangiopancreatography showed no pathological changes of liver, gallbladder and bile ducts. Investigations for hepatitis A, B, C, Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus were negative. Wilson disease and primary biliary cirrhosis were excluded, as well as autoimmune hepatitis (negative anti-nuclear, anti-smooth muscle and anti-liver kidney microsomal type 1 antibodies). Toxic hepatitis due to oxcarbazepine was suspected, and the drug was changed to levetiracetam by the neurologist. On the same day, a liver biopsy was performed. Histopathological examination of the liver biopsy specimen was consistent with vanishing bile duct syndrome (VBDS) (Figs. 1,2).

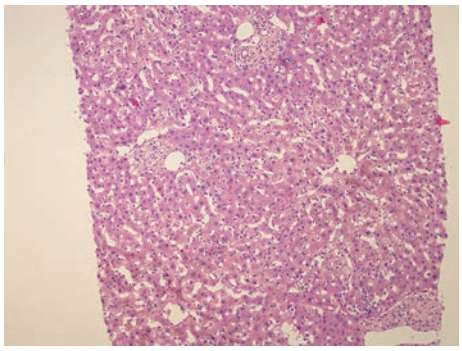

**Fig. 1.** Portal tracts with minimal inflammation containing eosinophils. Hepatic arterioles and a venule can be distinguished, but no bile duct nor ductular reaction . Canalicular cholestasis around the central vein (H&E x100).

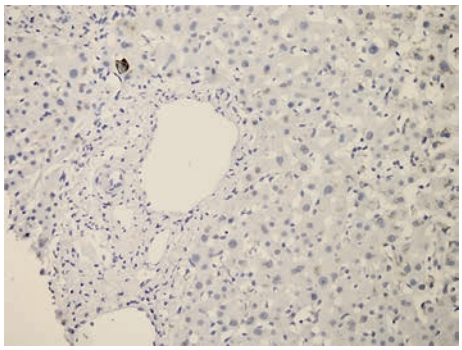

**Fig. 2.** Absence of bile ducts demonstrated by cytokeratin 7 immunohistochemical staining (cytokeratin 7 x 400).

Oral prednisolone in a dose of 60 mg/day was started. After 5 days, further immunosuppressive treatment was considered given the persistence of the elevated liver enzymes, but fever occurred. Complete blood count test revealed severe neutropenia (460/mm$^3$). Intravenous broad-spectrum antibiotics were administered and a bone marrow biopsy was performed which showed the presence of hemophagocytic syndrome. Intravenous immunoglobulin (400 mg/kg/day) was added to the therapy. However, the patient died due to septic shock on the 29th day since admittance.

Oxcarbazepine is a keto analogue of carbamazepine and is a potent anticonvulsant used in the therapy of seizures. There have been a few reports of carbamazepine-induced VBDS [1-4]. On the other hand, oxcarbazepine is known to have a lower hepatotoxic effect. A retrospective multicenter analysis

of 947 epileptic patients treated with oxcarbazepine revealed that mild elevations of alanine aminotransferase, aspartate aminotransferase and gamma-glutamyl transferase may occur during the therapy in less than 2% of the patients [5]. Only one case of severe hepatitis associated with the use of oxcarbazepine has been reported [6]. To our knowledge, this is the first report of oxcarbazepine-induced VBDS in the literature. Since the corticosteroid therapy had no effect in our patient, we suggest that further immunosuppressive therapy modalities may be required. In addition, it must be kept in mind that hemophagocytic syndrome may occur concomitantly with oxcarbazepine-induced VBDS.

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**Conflicts of interest.** None to declare.

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## Is spleen stiffness a predictor of clinical decompensation in cirrhotic patients?

**To the Editor,**

Recently, baseline spleen stiffness measurement (SSM) and MELD score have been proved to be predictors of clinical decompensation (CD) in patients with HCV related cirrhosis in a two-year follow-up scenario [1]. SSM has, however, some previously highlighted intrinsic technical drawbacks [2, 3] that may be bypassed in post-processing by modifying the calculation algorithm of each elastogram so that an increment of the scale up to 150 kPa is obtained. We present here our real life experience using SSM and modified SSM (mSSM) as long-term predictors of CD in cirrhotic patients.

Fifty-two consecutive compensated cirrhotic patients were included after signing an informed consent. All patients underwent liver and spleen stiffness measurement at baseline as previously described [4], abdominal ultrasound and liver function was assessed by usual biochemical tests. Baseline clinical, biological and elastographic data are presented in Table I. Clinical decompensation was defined as the occurrence of one of the following: variceal bleeding, development of ascites, hepatic encephalopathy (HE), jaundice (total bilirubin > 3 mg/dl), infection, spontaneous bacterial peritonitis (SBP), hepato-

**Table I**. Baseline clinical, biological and elastographic data in our patients.

| Variable | Not decompensated | Decompensated | p |
|---|---|---|---|
| N | 29 | 23 | |
| Etiology (VHC/VHB/-OH/mixt) | 18/4/6/1 | 10/6/6/1 | |
| Gender (M/F) | 14/15 | 13/10 | |
| Age (years) | 57.34; 57 (±8.67; 37-74) | 54.13; 53 (±9.21; 33-70) | NS |
| Body Mass Index (kg/m$^2$) | 27.16; 27 (±4.15; 18.40-35.10) | 26.06; 25.4 (±4.02; 18.70-32.50) | NS |
| AST (IU/L) | 84.55; 71 (±68.38; 23-349) | 74.52; 73 (±55.85; 12-278) | NS |
| ALT (IU/L) | 71.31; 51 (±67.83; 5-337) | 53.43; 52 (±34.54; 8-140) | NS |
| AP (IU/L) | 238.21; 227 (±102.32; 88-675) | 275.96; 263 (±126.15; 99-742) | NS |
| Gamma-GT (IU/L) | 140.48; 75 (±151.34; 16-563) | 75.87; 53 (±52.63; 16-184) | NS |
| Albumin (g/l) | 3.73; 3.8 (±0.90; 2.60-5.50) | 3.29; 3.2 (±0.54; 2.40-4.40) | 0.05 |
| Total bilirubin (mg/dl) | 1.60; 1.28 (±0.97; 0.58-4.60) | 2.93; 1.3 (±3.39; 0.36-11.9) | 0.04 |
| Creatinin (mg/dl) | 0.74; 0.67 (±0.26; 0.27-1.64) | 0.75; 0.7 (±0.31; 0.25-1.63) | NS |
| Platelets | 121.36; 120 (±62.24; 14-276) | 100.61; 84 (±43.46; 53-227) | NS |
| INR | 1.35; 1.25 (±0.26; 0.99-2.05) | 1.48; 1.47 (±0.31; 1.10-2.27) | NS |
| Child Pugh class (A/B/C) | 16/11/2 | 6/13/4 | |
| Child Pugh score* | 6.52; 6 (±1.35; 5-10) | 7.74; 8 (±1.66; 5-11) | 0.005 |
| MELD score | 7.48; 7.35 (±4.53; -0.87-22.7) | 9.47; 8.73 (±5.95; 0.64-25.7) | NS |
| EV grade (0/1/2/3) | 8/11/9/1 | 4/7/9/3 | |
| Portal vein diameter (mm) | 12.8; 13 (±1.44; 10-17) | 13.85 (±1.97; 10-18) | 0.05 |
| Spleen L diameter (mm) | 148.51; 150 (±24.53; 107-200) | 160.73; 160 (±24.16; 116-214) | 0.05 |
| LSM (kPa) | 33.92; 22.8 (±22.43; 4-75) | 34.4; 34.3 (±12.04; 9-75) | NS |
| SSM (kPa) | 56.59; 57 (±14.27; 29.8-75) | 62.12; 75 (±19.15; 14.6-75) | NS |
| mSSM (kPa) | 60.33; 57 (±22.99; 30-143) | 83.79 (±40.37; 15-143) | 0.01 |

* Not included in the multivariate analysis, because it includes Albumin and Total Bilirubin. LSM: liver stiffness measurement; SSM: spleen stiffness measurement; mSSM: modified spleen stiffness measurement; EV: esophageal varices.

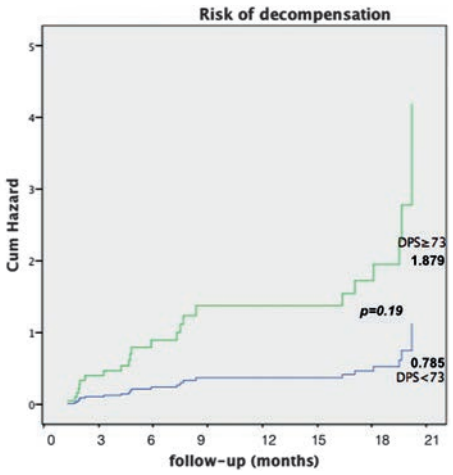


**Fig. 1**. Cumulative Risk of decompensation according to the baseline value of Decompensation Prediction Score (DPS).

renal syndrome (HRS), hepatocellular carcinoma (HCC) and death or liver transplantation.

During the median follow-up period of 13 months (range 1-28), 23(44%) patients became decompensated: ascites 7 patients, infection/SBP 6 patients, variceal bleeding 4 patients, HE and HCC 3 patients. Three (5.6%) patients died and 14(26.4%) had more than one episode of CD.

In multivariate analysis baseline mSSM [OR: 1.085 (95%CI: 1.02-1.15); p=0.01], albumin [OR: 0.17 (95%CI: 0.03-0.76); p=0.02] and bilirubin [OR: 1.64 (95%CI: 0.99-2.71); p=0.05] were found to be independent predictors of CD.

Based on the regression equation, we calculated a decompensation prediction score (DPS): 4.56 + (0.82*mSSM) + (0.496*Bilirubin) - (1.77*Albumin). For a cut-off value of 73, DPS had an AUROC to predict CD of 0.7 (95%CI: 0.53-0.85) and correctly classified 38 (73%) patients (McNemar p=0.013). Patients with DPS≥73 at baseline had a two-fold higher cumulative risk of decompensation, without reaching a level of significance (Fig. 1).

In this small heterogeneous population of cirrhotics followed for a limited period of time we found that mSSM is an independent predictor of CD. Association with markers of liver function (such as Albumin and Bilirubin) may have additional benefits. Although not completely confirmed, our data support the conclusion of Collechia et al [1], that SSM may have an even more important clinical relevance, besides its previously demonstrated roles: non-invasive prediction of large esophageal varices [4] and clinically significant portal hypertension [5].

Further larger studies are required to address this issue, in parallel with efforts to develop a modified probe and software (with frequency correction and depth optimization), since mSSM is not the real spleen stiffness value, but only an estimation of the actual one.

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## Autologous fascia lata repair of hiatal hernia

**To the Editor,**

Failures after antireflux surgery usually occur within the first 2 years after the initial operation. Herniation of the fundoplication into the chest and paraesophageal hernia are linked to an enlarged hiatus. Mesh reinforcement decreases the rate of slippage in the thorax but is associated with specific complications. Several randomized controlled trials (RCTs) report no such complications, but mesh erosion and esophageal stenosis are presented in case reports using synthetic or biologic reinforcement [1]. A higher postoperative dysphagia rate seems to be a reasonable price to pay for avoiding an intrathoracic wrap migration.

In the search for a better tissue tolerated patch, the tendency evolved from polypropylene and PTFE to porcine small intestinal submucosa. Expectations linked to allografts consisting of sterilized human dermal collagen seem to be fulfilled as no erosions, strictures, or persisting dysphagia were encountered even in patients with perigastric infections [2]. Regarding the choice between glue, tacks or sutures for affixing

the reinforcement patch, the consensus recommends care in the use of tacks which can penetrate phrenic vessels or cause pericardial tamponade.

The use of fascia lata for the repair of diaphragmatic hernias was first recommended by Janes [3] in 1931, but the only published series is that of Brain and Maynard [4] in 1963. The approach was by thoracotomy and led to a low recurrence rate (5%) and a few cases of mild disfagia. Bjelovic [5] was the first to use the abdominal approach. Recent experimental studies demonstrated a moderate shrinkage but no macroscopic signs of inflammation, abcedation, or significant adhesion formation around the grafts. At microscopy the organization process consisted of fibrosis, neovascularization and peritoneal integration [6].

We performed, to the best of our knowledge, the first intervention of autologous fascia lata repair in our country. The patient, a 62 year old male, had a long history of heartburn, dysphagia and regurgitation. Upper digestive endoscopy and CT described a paraesophageal hernia of considerable size with an enlarged hiatus. In order to prevent a slippage of the plication, a hiatoplasty with autologous fascia lata was selected. The 8 by 5 cm strip was harvested from the right thigh. The gap was sutured by approximating the epimysium to the edge of the remaining fascia lata in order to avoid the typical muscle herniation. After the enlarged hiatus (6/6 cm) was sutured both in a posterior as well as in a left lateral direction, the graft was placed with the deep surface towards the diaphragm and fixed with superficial sutures. The Nissen fundoplication was performed using the standard technique. The immediate and short-term outcomes were uneventful. No dysphagia, nausea or any other specific complaints were recorded during the first three months.

Reinforcement of a hiatoplasty with autologous fascia lata transfer seems to be a good option as a resistant and easy to tolerate tissue is being dealt with. Considering that very few similar data are available, RCTs and at least two years of follow-up are mandatory for confirming the advocated advantages.

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**Conflict of interest.** None to declare.

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