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## Editorial

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**E-mail:** [Haluk\\_Yuzugullu@dfci.harvard.edu](mailto:Haluk_Yuzugullu@dfci.harvard.edu)**Volume 1 : Issue 1****Article Ref. #: 1000LROJ1e001****Article History:****Received:** April 17<sup>th</sup>, 2015**Accepted:** April 20<sup>th</sup>, 2015**Published:** April 20<sup>th</sup>, 2015**Citation:**

Yuzugullu H, Gursoy-Yuzugullu O. Targeted therapy for hepatocellular carcinoma: what's new? *Liver Res Open J.* 2015; 1(1): e1-e3.

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# Targeted Therapy for Hepatocellular Carcinoma: What's New?

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Hepatocellular carcinoma (HCC), one of the most frequent neoplasms worldwide, causes more than 700,000 deaths per year, and is the third cause of cancer-related mortality.<sup>1-3</sup> HCC occurs after years of damage to hepatocytes with inflammatory conditions due to Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infection resulting in chronic hepatitis and/or cirrhosis. The disease incidence is decreasing due to Hepatitis B Virus (HBV) vaccination, whereas rates are steadily increasing in Europe and United States possibly due to increased obesity and Hepatitis C Virus (HCV) infection.<sup>3</sup> The latest antiviral drug, Sofosbuvir (Sovaldi, Gilead), has achieved notable success in clinical trials and approved against HCV and gives great hopes for treatment and hopefully preventing HCV induced liver cancer. Unfortunately, other risk factors like alcohol abuse, fungal toxins, obesity, and poor diet are also associated with HCC and will not be easily wiped out anytime soon.

If diagnosed early, HCC can be cured with surgery or liver transplant. However, most HCC cases can only be diagnosed at advanced stages, and are accompanied with chronic liver disease such as hepatitis and fatty liver disease. Sorafenib, the only approved multi-kinase inhibitor, is the current first line therapy for the advanced HCC and can only lead to survival benefit of 2-3 months. Sorafenib inhibits the growth of blood vessel formation and the cancer cells by targeting key kinases like RAF-1, B-RAF, VEGFR and PDGFR.<sup>4</sup> Since the approval of Sorafenib, drug companies have spent tremendous effort for testing variety of molecular therapies targeting angiogenesis to oncogenic signaling pathways many of which still under clinical evaluation. Unfortunately, none of these drugs could exhibit superior efficacy to Sorafenib. The failure of these inhibitors can be explained by their lack of efficacy, toxicity and coexisting genetic and epigenetic alterations.<sup>2</sup> Thus, more radical approaches are required to treat HCC. Several clinical trials are currently testing the safety and efficacy of multi-tyrosine kinase inhibitors and other targeted therapy agents alone or in combination with Sorafenib in advanced HCC. Here, we summarize the current state and emerging novel targeted therapies as well as ongoing clinical trials for the treatment of HCC.

Unlike many solid tumors showing strong "oncogene addiction", in which the proliferation and survival of cancer cells depends on a single oncogene and usually responsive to its inhibitor or antibodies (such as Gefitinib targeting EGFR in lung cancer, Vemurafenib targeting BRAF in melanoma and Crizotinib targeting ALK in Non Small Cell Lung Cancer (NSCLC)), no such oncogene dependency has been shown in HCC yet. Genome sequencing of HCC patients have identified several driver genes.<sup>5-7</sup> Notably, these studies confirmed that mutations in driver genes such as EGFR, BRAF, PIK3CA or KRAS, are rarely mutated in HCC. Instead, recurrent mutations of TP53 and CTNNB1 (*beta-catenin*) are highly frequent in more than half of HCC cases.<sup>6</sup> Recent studies also identified novel mutations in the promoter of Telomerase reverse-transcriptase (TERT) gene in great percentage of HCC patients.<sup>8,9</sup> TERT promoter mutations are one of the most frequent events in liver cancer causing an increase the

expression of telomerase transcript. The increased expression of telomerase gene helps hepatocytes to bypass the senescence barrier. Nevertheless, these mutations are in general hard to target for HCC therapies.

Deep-sequencing effort also identified novel activating mutations in JAK1 gene implicated in JAK-signal transducer and activator of transcription (JAK-STAT) signaling pathway; and RPS6KA3 gene in Ras/Mitogen-activated protein kinase (MAPK) pathways.<sup>6,7</sup> Given the role of JAK/STAT signaling pathway in the tumor growth and survival, preclinical studies have shown that JAK1 inhibition represents an attractive new therapeutic target for HCC. An antisense oligonucleotide inhibitor of STAT3 has just completed phase I/II clinical trial for advanced HCC with encouraging results. Moreover, focal amplifications of cell cycle gene CCND1 and deletions of CDKN2A were observed in HCC suggesting that HCC tumors are good candidates of CDK inhibitor trials. Furthermore, focal gene amplification of the genes encoding the receptor tyrosine MET, and FGF-receptor ligand (FGF19) and downstream signaling genes MYC has been observed in HCC. A phase III trial of tivantinib, a small molecule inhibitor against c-MET showed an overall survival advantage of 7.2 months in MET-high patients.<sup>10</sup> These observations suggested that a patient stratification strategy based on activated signaling pathways or mutation signatures should become a norm for HCC clinical trials, like in other cancer types. A recent preclinical study showed that activation of MAPK signaling pathway leads to Sorafenib resistance and combined inhibition of MAPK and Sorafenib significantly prolonged the survival of mice.<sup>11</sup> Combinations of MEK inhibitors and Sorafenib are being evaluated in clinical trials for advanced HCC.

Several epigenetic targets, many of which are chromatin-remodelling enzymes like ARID1A, ARID2, KMT2A and MLL3 are also found to be frequently mutated in HCC and the role of these mutations in HCC and how to target these mutant genes are yet to be discovered. Other targeted agents undergoing clinical evaluation can be summarized as follows: VEGFR inhibitors (Tivozanib, Axitinib, Lenvatinib and Regorafenib), anti-endoglin antibody targeting angiogenesis (TRC105), anti-IGF-1R monoclonal antibody (cixutumumab), Hedgehog (Hh) pathway targeting inhibitor (LDE225), small molecule inhibitor targeting NF- $\kappa$ B and the Wnt signal transduction pathways (CF102), inhibitor of Transforming Growth Factor- $\beta$  (TGF- $\beta$ ) (LY2157299), proteasome inhibitor (Oprozomib), lipid nanoparticle formulation of a small interfering RNA (siRNA) directed against PLK1 (TKM-080301) and hypoxia activated pro-drug (TH302). These agents are now being tested in the clinic either as mono-therapy or in combination with Sorafenib or other chemotherapy agents.

Recently, advances in immunotherapy has shown notable success for advanced melanoma, renal cell carcinoma and lung cancer treatment. Companies also have shown great interest

to target immune checkpoints for advanced hepatocellular carcinoma. Current immunotherapy options available against HCC can be summarized as: checkpoint inhibitors activated T-cell therapy, vaccines and oncolytic virus therapy. Of these, checkpoint inhibitors have recently shown dramatic clinical success. Cancer cells escape being attacked by the immune cells via expressing cell surface agents such as Programmed cell death protein ligand (PD-L1). The goal of immunotherapy is to block such immune-suppression mechanisms to turn on the patient's own immune system to destroy cancer cells. Different checkpoint inhibitors in trials against HCC are: an antibody targeting anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) (Tremelimumab), an antibody targeting anti-programmed cell death protein 1 (PD-1) (Pembrolizumab) and an anti-PD-L1 antibody (MPDL3280A) and multiple others. Other immunotherapy trials include activated T-cell therapy (Immucell-LC activated T-lymphocyte), Dendritic Cell Vaccine (COMBIG-DC), *ex vivo* Expanded Allogeneic NK Cell (MG4101) and Oncolytic Adenovirus injection (Telomelysin). However, these agents may not be available for patients with hepatitis due to viral infection since activation of the immune system in the presence of viral hepatitis can cause hepatocyte damage.

To sum up, although substantial effort has been spent to cure this dismal disease, further efforts are needed to understand HCC pathogenesis and revolutionize the current therapy. Continued work is required for better rational design of combination therapies, possibly including immunotherapy and promising targeted therapy agents.

#### CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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## Review

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E-mail: [david.sass@jefferson.edu](mailto:david.sass@jefferson.edu)**Volume 1 : Issue 1****Article Ref. #: 1000LROJ1101****Article History:****Received:** February 18<sup>th</sup>, 2015**Accepted:** March 23<sup>rd</sup>, 2015**Published:** March 24<sup>th</sup>, 2015**Citation:**Shah SC, Sass DA. "Cardiac Hepatopathy": A review of liver dysfunction in heart failure. *Liver Res Open J.* 2015; 1(1): 1-10.**Copyright:**

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# "Cardiac Hepatopathy": A Review of Liver Dysfunction in Heart Failure

**Shailja C. Shah<sup>1</sup> and David A. Sass<sup>2\*</sup>**<sup>1</sup>Fellow, Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, 1468 Madison Ave, New York, NY 10029, USA<sup>2</sup>Associate Professor of Medicine, Division of Gastroenterology and Hepatology, Sidney Kimmel Medical College, Jefferson University, 132 S. 10th Street, Main Building, Suite 480, Philadelphia, PA 19107, USA**ABSTRACT**

The unique dual circulation of the liver confers relative protection against ischemic injury; however, low oxygen tension in the microcirculation (sinusoidal blood of the hepatic acinus) may render hepatocytes in zone 3 relatively vulnerable to ischemic injury and necrosis. Severe congestive heart failure is associated with two distinct forms of liver dysfunction under the umbrella term "cardiac hepatopathy". The two entities include: jaundice related to passive congestion (congestive hepatopathy from backward cardiac failure) and acute hepatocellular necrosis caused by impaired hepatic perfusion (hypoxic hepatitis from forward cardiac failure). This article provides a comprehensive, up-to-date review on the topic and focuses on the epidemiology, pathology, pathogenesis, clinical manifestations, diagnostic testing and treatment strategies pertaining to liver disease in circulatory failure.

**KEYWORDS:** Congestive hepatopathy; Hypoxic hepatitis; Ischemic hepatitis; High-gradient ascites; Nutmeg liver; Heart failure.**ABBREVIATIONS:** LVAD: Left-ventricular assist device; SAAG: Serum ascites-albumin gradient; IVC: Inferior Vena Cava; LFTs: Liver Function Tests; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; TIPS: Transjugular Intrahepatic Portosystemic Shunt; GGT: Gamma Glutamyl Transpeptidase; LDH: Lactate dehydrogenase; PT: Prothrombin Time; INR: International Normalized Ratio; ICU: Intensive Care Unit; RAAS: Renin-angiotensin-aldosterone system; MARS: Molecular Adsorbent Recirculating System.**INTRODUCTION**

The relationship between cardiac and hepatic dysfunction has been a well-recognized entity for over two centuries.<sup>1</sup> Yet, the complexity and nuances of the association still remain a topic of intense interest and research. Studies dealing with this topic are relatively few, not rarely with contradictory results. There are several reasons for the variant results: heart failure etiology has changed over the years, being mainly related to rheumatic valvular disease in the earliest studies and to ischemic cardiomyopathy more recently.<sup>2</sup> Also, the outcome of heart failure has dramatically improved due to superior medical therapies, not to mention widespread use of heart transplantation. Thus, cardiac cirrhosis, once the paradigm of liver involvement in heart failure, is now rare.

Concomitant hepatic and cardiac disorders may be categorized according to etiology. That is: (i) cardiac disease affecting the liver, (ii) hepatic disease affecting the heart, or (iii) cardiac and hepatic disease secondary to a shared etiology.<sup>3,4</sup> In this review, we chose to focus on "cardiac hepatopathy", or hepatic pathology secondary to cardiac dysfunction.<sup>2</sup> As will

be described herein, “cardiac hepatopathy” includes a spectrum of altered clinical, biochemical, histological, and hemodynamic disturbances. It is classically described in the setting of either acute or chronic heart failure. However, clinical and pathogenetic factors related to both conditions often co-exist.

## MACRO- AND MICROCIRCULATION OF THE LIVER

In order to understand the range of hepatic abnormalities that characterize cardiac hepatopathy, it is important to first appreciate the unique anatomy and physiology of the liver.

### Macrocirculation

The liver has a rich dual blood supply derived from both the portal and systemic vascular compartments: the portal vein supplies two thirds of hepatic blood flow and the hepatic artery is responsible for the remaining third.<sup>5</sup> Although the blood supply from the portal vein is less oxygenated compared to the hepatic artery, the portal vein supply is full of nutrients as it drains the vascular beds of the stomach, intestine, and spleen. An understanding of how the liver regulates its dual blood supply is also critical, especially with respect to compensatory mechanisms in the face of hemodynamic compromise. In order to maintain constant sinusoidal pressure to the hepatic beds, the liver employs an autoregulatory mechanism whereby a decrease in blood flow *via* the portal vein is matched by a compensatory dilation of the hepatic artery and thus increased flow and maintenance of perfusion.<sup>5</sup> However, the opposite does not hold in that a decrease in hepatic arterial blood flow that occurs secondary to a reduced cardiac output in left heart failure is not matched by a compensatory increase in portal venous inflow.<sup>1,6,7</sup>

### Microcirculation

Liver architecture has been traditionally described in terms of the *histological* unit and the *functional* unit. The histological (or “classical”) unit of the liver is the **lobule**, while the functional unit of the liver is the **acinus**.<sup>8</sup> The classical lobule is hexagonal in shape, bounded by the portal triads with the central vein at the center, and can be divided into concentric, centrilobular, midzonal, and periportal parts. The acinus is diamond-shaped and has at its center a line connecting two portal triads. The acinus is divided into zone 1 (periportal), zone 2 (transition), and zone 3 (centrilobular) according to the direction of flow of oxygen- and nutrient-rich blood from zone 1 closest to the portal triad to zone 3 surrounding the terminal hepatic vein.<sup>9</sup>

## CONGESTIVE HEPATOPATHY

Congestive hepatopathy refers to the spectrum of chronic liver injury attributed to passive hepatic congestion arising in the setting of right-sided heart failure or any cause of increased central venous pressure,<sup>10</sup> including biventricular failure from cardiomyopathy,<sup>11</sup> severe pulmonary hypertension or cor

pulmonale,<sup>12</sup> constrictive pericarditis<sup>13</sup> as well as valvulopathies such as mitral stenosis<sup>14</sup> and tricuspid regurgitation. This condition was first described by Dame Sheila Sherlock in her seminal work on the topic in 1951.<sup>1</sup>

### Histopathology and Pathogenesis

On gross examination, the congested liver is an enlarged, purple-hued organ with prominent hepatic veins. The cut surface conforms to the classic “nutmeg” appearance, reflecting the alternating pattern of hemorrhage and necrosis of zone 3 (red) with normal or slightly steatotic areas in zones 1 and 2 (yellow) (Figure 1).

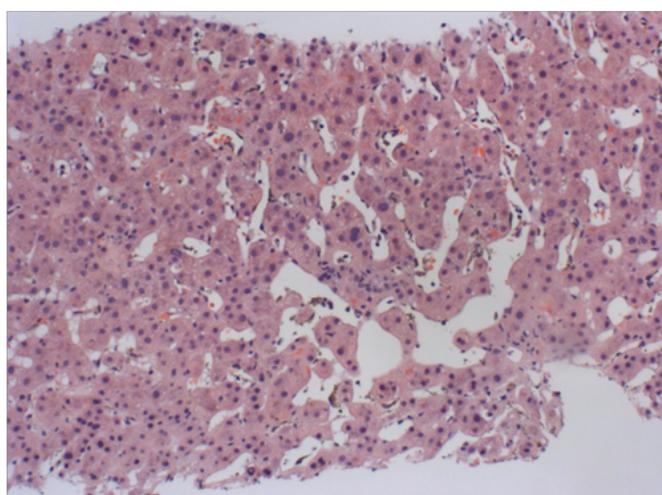


**Figure 1:** Cut surface of the congested liver reminiscent of the classic “nutmeg appearance” which is caused by chronic passive congestion of the central veins with hemorrhage and necrosis in zone 3. Red cells pool and distend the sinusoids around the central vein. These regions develop a darker red-violet color, in contrast to the surrounding tan liver parenchyma.

In the face of decreased perfusion, zone 1 hepatocytes are the least susceptible to necrosis, while zone 3 hepatocytes are the most susceptible. Furthermore, zone 3 hepatocytes are the most susceptible to damage induced by passive congestion secondary to right heart failure (Figure 2). Hepatic sinusoids lack a basement membrane and have a characteristic fenestrated, discontinuous endothelial lining that also contains macrophages specific to the liver (Kupffer cells). The hepatocytes themselves are separated from the sinusoids by an interstitial space, the Space of Disse. Under normal physiologic conditions, free flow through the sinusoidal fenestrations ensures a low hydrostatic pressure.<sup>15</sup> With passive congestion of the liver in right heart failure, the increased hydrostatic pressure produces sinusoidal edema and hemorrhage, which eventually compromises oxygenation.

Although the pathogenesis of fibrosis in cardiac hepatopathy is relatively well-characterized, it still remains unclear as to why some cardiac patients develop hepatic pathology and others do not, as the stage of congestive heart failure does not

seem to correlate well with hepatic fibrosis and cirrhosis.<sup>1,2,15-17</sup> Prolonged or repeated episodes of hepatic congestion with fibrosis may very rarely lead to so-called “cardiac cirrhosis”. It must be noted, however, that the entity of cardiac cirrhosis, also referred to as congestive cirrhosis, is somewhat elusive, with some authors not considering it true cirrhosis.<sup>18</sup> Uniquely, the fibrosis of cardiac hepatopathy is predominantly around the central hepatic veins with relative sparing of the portal tracts (“reverse lobulation”), although extension is possible with repeated attacks.<sup>1,18,19</sup> This is distinct from other etiologies of cirrhosis, in which fibrosis generally occurs first in the area around the portal tract.



**Figure 2:** H/E section of liver (10x magnification) with sinusoidal dilation in zone 3. As the severity of the lesion increases, the sinusoids around the central vein become distended with extravasated red cells and there is adjacent hepatocyte plate atrophy.

### Incidence

The incidence of congestive hepatopathy, significant fibrosis or cardiac cirrhosis ranges between 15% to 65% of patients with significant heart failure.<sup>2,20,21</sup> By today's accounts cardiac cirrhosis is rare. In a study by Myers et al.<sup>2</sup> of 83 subjects with heart failure, significant fibrosis with architectural distortion was found in only 19% of cases with only one individual having an established diagnosis of cirrhosis. In a smaller series of 59 patients awaiting cardiac transplant or Left-ventricular assist device (LVAD) placement, congestive changes were seen universally with 19% having histologic changes consistent with cirrhosis.<sup>22</sup>

### Clinical Features

In the majority of patients, the clinical picture is dominated by signs and symptoms of right-sided heart failure rather than those of liver disease (Table 1). Hepatomegaly is the most common manifestation with reports as high as 95% to 99% in acute or chronic heart failure. A mild, dull, right upper quadrant pain is often present and is likely secondary to hepatomegaly and stretching of Glisson's capsule. An additional physical find-

ing includes a *pulsatile* liver, which essentially results from volume overload of the right atrium.<sup>23</sup> Importantly, loss of the pulsatile liver in chronic cardiac disease is more concerning than its positive presence,<sup>23,24</sup> as loss of pulsatility implies progression to cardiac fibrosis or cirrhosis and warrants attention.

Symptom/Sign	Patients with acute or chronic heart failure showing sign/symptom (% range)
Hepatomegaly	95-99%
Marked hepatomegaly (> 5cm below right costal margin)	49-57%
Peripheral edema	71-77%
Pleural effusion	17-25%
Ascites	7-20%
Splenomegaly	20-22%
Jaundice	10-20%

Data extracted from Richman, SM et.al. a study of 175 patients with right-sided heart failure.<sup>25</sup>

**Table 1:** Congestive Hepatopathy: Signs and symptoms.

Other common, yet nonspecific, findings include peripheral edema, pleural effusion, splenomegaly, and jaundice (Table 1). Ascites is also clinically present in up to 20% of patients with congestive hepatopathy (although 41% at autopsy have ascites).<sup>25</sup> However, it must be noted that the ascites is a result of right-sided heart failure and not intrinsic liver dysfunction, as is the case in other causes of cirrhosis. Although the Serum ascites-albumin gradient (SAAG) is greater than 1.1 g/dL, consistent with portal hypertension, the ascitic fluid protein level is characteristically high, oftentimes >2.5 g/dL. This high protein content is an indication of the preserved synthetic function of the liver,<sup>26</sup> a finding unique to cardiac cirrhosis and critical in differentiating it from other causes of cirrhosis. The underlying pathophysiology of cardiac ascites remains uncertain, but some have proposed that sinusoidal hypertension with disruption of fenestrae ultimately allows for exudation of a protein rich fluid.<sup>6,26</sup> Other useful ascitic fluid parameters are the Lactate dehydrogenase (LDH), and red cell counts, as these generally tend to be higher in cardiac cirrhosis.<sup>26</sup>

Congestive changes can readily be seen on abdominal imaging. Liver ultrasonography typically shows hepatomegaly with a homogeneous increase in echogenicity throughout the liver and dilation of the suprahepatic veins and Inferior Vena Cava (IVC). Computed tomography and magnetic resonance imaging will similarly demonstrate hepatomegaly, distension of the hepatic veins and IVC, early reflux of contrast material from the right atrium to the IVC, and a heterogeneous, mottled-appearing liver parenchyma, often referred to as a mosaic pattern, which corresponds to the nutmeg liver seen on gross inspection.<sup>27</sup> Ascites, pleural and pericardial effusions are also frequently reported.

In terms of hemodynamic parameters, heart failure patients exhibit an increased right atrial pressure and the free and

wedged hepatic venous pressures are also commonly elevated, with a normal hepatic venous pressure gradient.<sup>28,29</sup> This finding of normal intrahepatic portal pressures is clinically relevant and likely underlies, at least in part, the minimal hepatic symptomatology associated with the majority of cases of cardiac hepatopathy.

Histologically, relative sparing of the portal tracts from fibrosis – a distinguishing factor of cardiac cirrhosis compared to other etiologies of cirrhosis as previously noted – also likely contributes to the lack of stigmata classically associated with portal hypertension. Spider angiomas and portosystemic shunts like hemorrhoidal plexus varices, caput medusae, and esophageal varices are very rarely, if at all, present in cases of cardiac hepatopathy.<sup>6,15,30</sup> Even with progression to cirrhosis, hepatic symptoms and manifestations of portal hypertension do not predominate, which is again in contrast to cirrhosis of other etiologies.

Congestive heart failure results in a broad range of liver biochemical abnormalities. Generally, a hepatocellular pattern with predominantly elevated transaminases is seen in hypoxic hepatitis, which is a rare occurrence given that the liver is relatively protected from hypoperfusion and hypoxia. More contemporary research describes the biochemical profile in congestive heart failure as mostly cholestatic. In their study in the 1960s, Richman et al. correlated alterations in Liver Function Tests (LFTs) with either acute or chronic decompensated right-sided heart failure regardless of etiology or severity of heart disease.<sup>25</sup> In acute dysfunction, both excretory function and parenchymal destruction were most pronounced, while a cholestatic pattern was most pronounced in chronic decompensation, findings that have been corroborated in a more recent study by Myers et al.<sup>2</sup>

Elevated serum bilirubin is also a common finding in cardiac hepatopathy, except perhaps in constrictive pericarditis,<sup>31,32</sup> with reports of mild elevation (usually <3 mg/dL and mostly unconjugated) in up to 70% of patients.<sup>6,15,25</sup> The hyperbilirubinemia in congestive heart failure is multifactorial and likely results from a combination of hepatocellular dysfunction, obstruction secondary to passive congestion and pressure atrophy of the canaliculi, pulmonary infarction, bile thrombi, hemolysis, and medications.<sup>1,31</sup> Increases in the serum bilirubin have been shown to correlate with the severity of right atrial pressure and passive congestion.<sup>1,33</sup> Bilirubin is significantly more elevated in patients with physical exam findings of volume overload, such as S3 gallop or pulmonary crackles, thus implicating its value as a prognostic factor and indicator of more severe hemodynamic dysfunction.<sup>4</sup> Despite the common finding of hyperbilirubinemia, the presence of clinical jaundice is not common.

Decreased albumin (seen in about 30-50% of cases) is a very nonspecific finding, as it is overwhelmingly common in hospitalized patients and those with chronic diseases. With respect to synthetic function, Prothrombin Time (PT) may be more

useful than albumin level at tracking progression of cardiac hepatopathy based on the observation that PT fails to correct with Vitamin K<sup>34</sup> but does usually correct with compensation of heart failure, suggesting a direct effect on hepatic synthesis. The PT is mildly abnormal in 80% of cases. Although serum ammonia level is occasionally increased, hepatic encephalopathy is not a salient feature of congestive heart failure.<sup>35</sup>

### Treatment

The cornerstone of management of all forms of congestive hepatopathy, from asymptomatic, mild elevations in hepatic indices to cardiac cirrhosis is targeted toward treating the underlying cardiac dysfunction and any triggers accounting for acute decompensation. Reversibility of biochemical aberrations in cardiac hepatopathy was described as early as 1930 when Jolliffe et al. reported normalization of liver biochemistries with restoration of appropriate cardiac function.<sup>24</sup>

Jaundice, hepatic congestion and ascites may respond dramatically to therapy with diuretics; however these drugs should be used with caution to avoid dehydration, hypotension and hepatic ischemia by precipitating zone 3 necrosis.<sup>36</sup> It is of vital importance to maintain an adequate cardiac output. Serial large-volume paracenteses can relieve symptoms in those with diuretic-refractory tense cardiac ascites<sup>6,37,38</sup> but over time can lead to protein loss and exacerbate the protein malnutrition commonly seen in those with advanced heart failure. Transjugular Intrahepatic Portosystemic Shunts (TIPS) or peritoneal-venous shunts are contra-indicated in this population as they can lead to exacerbation of the underlying heart failure. Cautious use of anticoagulants is advised because patients have a baseline mild increase in PT/INR and are especially sensitive to warfarin and other related compounds.<sup>39</sup> In patients refractory to medical therapy who are suitable operative candidates, both LVAD implantation<sup>40,41</sup> and cardiac transplantation<sup>42</sup> have been shown to improve and reverse the congestive liver injury associated with the failing heart. In select patients with established cirrhosis, combined heart and liver transplant is a feasible option.<sup>43</sup> Recently, there has been a report of possible reversal of cardiac cirrhosis with heart transplantation alone, effectively removing the source of the insult.<sup>44</sup> However, such cases are the exception.

### Prognosis

Over time, hepatic function typically remains stable and even when cardiac cirrhosis and ascites ensue, patients with congestive hepatopathy rarely develop other features of hepatic insufficiency.<sup>1</sup> Fulminant liver failure, although documented, seems to be restricted to those with superimposed ischemic liver injury rather than passive congestion alone.<sup>45,46</sup>

Several studies have addressed the prognostic importance of liver function abnormalities in predicting short and

long-term outcomes. According to the CHARM investigators, abnormal levels of total bilirubin, direct bilirubin, alkaline phosphatase, and albumin are statistically significant prognosticators of outcome. Total bilirubin was reportedly more predictive of adverse prognosis than even the New York Heart Association functional class, left ventricular ejection fraction, diabetes mellitus, and serum creatinine.<sup>20,47</sup> Batin et al demonstrated that the greatest prognosticators in chronic heart failure were AST and total bilirubin,<sup>48</sup> while in a Japanese chronic heart failure study, total bilirubin, alkaline phosphatase and GGT levels were all associated with worsened outcomes.<sup>49</sup>

### HYPOXIC HEPATITIS

Hypoxic hepatitis is defined as an acute and reversible significant elevation of serum AST and ALT levels to more than 20 times the upper limit of normal in the absence of known acute hepatitis or hepatocellular injury and with an appropriate clinical picture specifically involving acute circulatory, cardiac, or respiratory failure.<sup>50</sup>

More recent literature has proposed *hypoxic hepatitis* as a more appropriate name than “shock liver”<sup>51</sup> and/or “ischemic hepatitis”<sup>52</sup> given that, regardless of etiology (cardiogenic or otherwise), the underlying mechanism appears to be hypoxia even in the absence of ischemia.<sup>34</sup> Classically, “ischemic hepatitis” was used because of the histological appearance of centrilobular necrosis, loss of hepatocytes, and sinusoidal congestion with erythrocyte extravasation, but a characteristically unremarkable inflammatory infiltrate.<sup>34,53</sup> Although centrilobular necrosis is a critical part of the disease, histologic confirmation is seldom obtained.<sup>50,53</sup>

### Incidence

Because of increased awareness and recognition of the possibility of hypoxic hepatitis accounting for elevated aminotransferases, it is now identified as the most common cause of acute liver injury, even exceeding drug-induced liver injury and acute viral hepatitis.<sup>53,54</sup> It is well-reported that the incidence is highest in cardiac care and surgical intensive care units, with some reports identifying up to 22% of patients<sup>55</sup> compared to a recently reported 11% in medical intensive care units<sup>50</sup> and less than 1% incidence in the non-critical care units.<sup>56</sup>

### Histopathology and Etiopathogenesis

Cardiovascular disease is recognized as the most common cause of hypoxic hepatitis, underlying over 70% of cases, while the remaining 30% of cases are split equally between respiratory failure and sepsis.<sup>57,34</sup> The association of heart disease with increased proclivity toward developing hypoxic hepatitis might stem from passive congestion of the liver compromising its relative resistance to ischemia and hypoxia. The liver is normally well-equipped to compensate for and withstand hemody-

namic derangements as evidenced by the low incidence of hepatic damage in the face of shock and circulatory collapse. However, the compensatory mechanisms are notably overwhelmed in the face of persistent hypotension or severe hypoxemia and underlying cardiac dysfunction. Virtually any cause of shock or hemodynamic instability can result in ischemic injury to the liver (see table 2 for a complete list of causes).

<p><b>Heart Failure with or without cardiogenic shock</b></p> <ul style="list-style-type: none"> <li>- Right ventricular failure               <ul style="list-style-type: none"> <li>- Right ventricular myocardial infarction</li> <li>- Pulmonary embolism</li> <li>- Cor pulmonale</li> <li>- Primary pulmonary hypertension</li> </ul> </li> <li>- Left ventricular failure               <ul style="list-style-type: none"> <li>- Ischemic cardiomyopathy</li> <li>- Non-ischemic dilated cardiomyopathy</li> <li>- Valvular dysfunction</li> </ul> </li> </ul>
<p><b>Hypovolemic shock</b></p> <ul style="list-style-type: none"> <li>- Hemorrhage</li> <li>- Dehydration</li> <li>- Major burns</li> </ul>
<p><b>Other systemic disorders</b></p> <ul style="list-style-type: none"> <li>- Major trauma (crush injury)</li> <li>- Sepsis</li> <li>- Heat stroke</li> <li>- Vasculitis</li> </ul>
<p><b>Rare causes</b></p> <ul style="list-style-type: none"> <li>- Sickle cell crisis</li> <li>- Carbon monoxide poisoning</li> <li>- Dissecting aortic aneurysm</li> <li>- Hepatic artery occlusion in the setting of a liver transplantation or with pre-existing portal vein thrombosis</li> </ul>

Table 2: Causes of Hypoxic Hepatitis.

### Clinical features

Patients with hypoxic hepatitis tend to be older, predominantly male and acutely ill in the intensive care unit.<sup>55</sup> Signs and symptoms of acute liver injury are usually absent, in contrast to other causes of acute liver injury. The clinical presentation is usually consistent with cardiac compromise<sup>53,57</sup> although some individual studies have reported a variety of other symptoms, ranging from predominantly gastrointestinal with nausea, vomiting and diarrhea<sup>58</sup> to an encephalopathic picture with altered mental status or even coma.<sup>34,59</sup> The latter picture of acute fulminant hepatic failure, although rare, is more likely to occur in the presence of underlying congestive heart failure or cirrhosis.<sup>34</sup> There are no unique physical examination findings although some patients exhibit right upper quadrant tenderness to palpation.

Despite the potential nonspecific and variable symptomatology, hypoxic hepatitis is more commonly diagnosed incidentally with routine liver function tests anywhere from 2-24 hours after an episode of systemic hypotension. Laboratory abnormalities in hypoxic hepatitis are consistent with a hepatocellular pattern. First, there is a marked increase in aminotransferases and Lactate dehydrogenase (LDH), with AST and LDH rising most sharply and peaking in the first 12-48 hrs, while the rise and peak ALT is not as dramatic.<sup>50,59</sup> Moreover, maximal elevation of ALT is less than AST and given the longer half-life of

ALT, it reaches normal levels later than AST. Even so, the aminotransferase levels characteristically fall by greater than 50% within 72 hours of resolution of the underlying insult and return to normal within 7-10 days.<sup>34,50,60</sup> Increases in LDH level tend to be massive and ALT/LDH ratio of less than 1.5 often distinguishes ischemic injury from other forms of acute hepatitis.<sup>61</sup> It is of interest to note that the liver may not retain its normal architecture after regeneration if the reticular framework is damaged. The most common compensatory responses seem to be either thickening of hepatocellular plates with preservation of trabecular and cord-like pattern or nodular masses of hepatocytes.<sup>19,62</sup> The latter, known as nodular regenerative hyperplasia, is less common but can manifest as a grossly granular or nodular liver.<sup>18</sup>

The integrity of hepatic synthetic function is also compromised in hypoxic hepatitis, as determined by PT/INR. If the INR remains above 1.5 despite adequate stores of Vitamin K, the diagnosis of acute liver failure is appropriate.<sup>63</sup> Synthetic function is also of prognostic importance, with INR above 2.0 associated with an independent increase in mortality.<sup>50</sup>

Elevated lactate is also a common biochemical abnormality in hypoxic hepatitis although Fuhrmann et al. noted its lack of independent predictive value in mortality.<sup>50</sup> Rarely, laboratory abnormalities can even include consumptive coagulopathy, which can be asymptomatic or symptomatic and most often related to the underlying etiology. Bilirubin may be mildly elevated and tends to peak after the transaminases and LDH levels begin to decline. The effects of systemic hypotension are not isolated to the liver, and increases in creatinine level from acute tubular necrosis are nearly universal early in the clinical course.

The differential diagnosis for hypoxic hepatitis includes acute viral hepatitis, autoimmune hepatitis, drug-induced liver injury (e.g. acetaminophen), acute Wilson's disease and acute vascular thrombosis e.g. hepatic artery and portal vein thrombosis. While viral hepatitis and alcoholic hepatitis can usually be differentiated from hypoxic hepatitis based on the ALT:AST and AST:ALT ratios, respectively, it may be difficult to differentiate drug-induced hepatitis from hypoxic hepatitis.

### Treatment

Early recognition and management is critical and is the primary prognostic factor. The importance of recognizing hypoxic hepatitis is underscored by reports of associated mortality in Intensive Care Unit (ICU) patients of over 50%.<sup>50,53</sup> However, its role as an independent risk factor in ICU patients is still uncertain, as one report found that hypoxic hepatitis was only an independent risk factor in those requiring vasopressor therapy.<sup>50</sup> Importantly, the cause of death is usually not due to hepatic failure but related to the underlying precipitating factor itself, such as sepsis or cardiac decompensation.<sup>50,53</sup> Moreover, although encephalopathy is frequently noted in hypoxic hepatitis, it most of-

ten is not a true hepatic encephalopathy and is actually a consequence of the inciting factor leading to hypoxic brain damage.

Because this entity is essentially an observed laboratory abnormality, albeit an alarming one, treatment is targeted at identifying and addressing the inciting event. Awareness of potential exacerbating factors, such as mechanical ventilation or vasoconstrictors that may compromise hepatic blood flow, as well as metabolic monitoring to prevent derangements like hypoglycemia and lactic acidosis<sup>50</sup> are essential. Also important is recognizing that other organs may be implicated, including initiation of systemic inflammatory response syndrome with possible disseminated intravascular coagulation,<sup>64</sup> new or worsened respiratory compromise with hepatopulmonary syndrome,<sup>65</sup> cardiac compromise with myocardial infarction, or renal compromise with acute kidney injury.

Several experimental therapies have been described. To improve hepatosplanchnic blood flow, infusion of renal-dose dopamine<sup>66</sup> has been suggested, but to date no proven clinical benefit has been shown. Adenosine infusion has been used in animal models but there are no human data to support its use in this setting. Other investigators have suggested a role of antioxidants<sup>6</sup> or N-acetylcysteine,<sup>67</sup> however these findings are only limited to case reports and thus need to be corroborated in randomized controlled trials. Nitric oxide has shown some promise, given its role as an endothelin antagonist and consequent ability to counter vasoconstriction of hepatic vascular beds in ischemia.<sup>68</sup> Similarly, research has been focused on angiotensin receptor II blockers and ACE inhibitors as possible antagonists of Renin-angiotensin-aldosterone system (RAAS) activation, a pathway very much implicated in hypoxic hepatitis.<sup>69</sup> Molecular Adsorbent Recirculating System (MARS) and single-pass albumin dialysis, both of which have shown benefit in acute and acute-on-chronic liver failure, have also been researched as potential therapeutic modalities in hypoxic hepatitis but with uncertain benefit.<sup>70-72</sup> To date, no liver-specific treatments have been proven to improve outcome. Furthermore, hypoxic hepatitis is not an indication for liver transplantation as the hepatic derangements are reversible with correction of the underlying disorder.

### Prognosis

The majority of patients with hypoxic hepatitis follow a benign self-limited course with complete resolution of transaminases to normal values within 3 to 7 days of the inciting event.<sup>57</sup> However, because this hepatic ailment occurs in the critically ill patients, survival in most series is rather poor. In the largest published series to date (142 episodes in 10 years of surveillance): the 1-month and 1-year survivals were 53% and 28% respectively.<sup>53</sup> Fulminant hepatic failure rarely occurs and seems to be restricted to patients with longstanding congestive heart failure, cardiac cirrhosis<sup>45</sup> or other forms of chronic liver disease.

**CONCLUSION**

Hepatic injury as a consequence of cardiac disease is a relatively common, but often poorly recognized, syndrome. An understanding of the hepatic circulation and normal liver architecture is important to appreciate how the hemodynamic changes of heart failure affects the liver, leading to the associated clinical, biochemical and histologic features. The hepatic manifestations of “congestive hepatopathy” and “hypoxic hepatitis” may range from mild liver enzyme abnormalities to progressive liver injury and, rarely, liver failure. A team approach characterized by collaboration amongst both cardiologists and hepatologists is critical for optimizing patient care and maximizing positive outcomes.

**CONFLICTS OF INTEREST**

The authors have no conflicts of interest to disclose.

**PERSONAL ACKNOWLEDGEMENTS**

The authors wish to thank Suganthi Soundararajan, MD, Department of Pathology, Drexel University College of Medicine, Philadelphia, PA for kindly providing the pictures.

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## Case Report

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**Volume 1 : Issue 1**

**Article Ref. #: 1000LROJ1102**

### Article History:

**Received:** April 10<sup>th</sup>, 2015

**Accepted:** April 22<sup>nd</sup>, 2015

**Published:** April 22<sup>nd</sup>, 2015

### Citation:

Goodwin JD, Schmidt J, Mantry P. Metastatic liver disease - presenting as multiple hepatic cysts. *Liver Res Open J.* 2015; 1(1): 11-13.

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# Metastatic Liver Disease - Presenting as Multiple Hepatic Cysts

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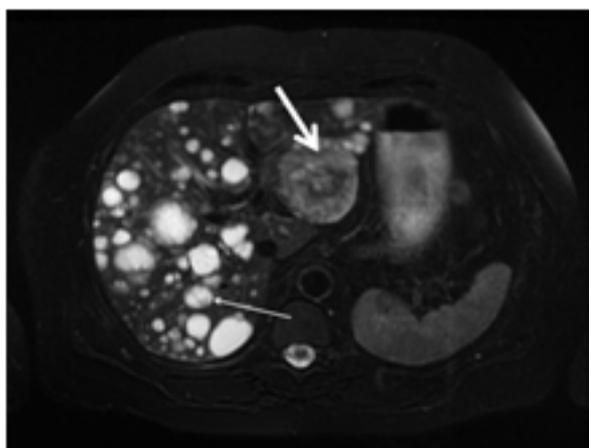
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**ABBREVIATIONS:** CT: Computed Tomography, MRI: Magnetic Resonance Imaging, FNA: Fine Needle Aspiration, H&E: Hematoxylin and Eosin, HMB-45: Human Melanoma Black-45, BRAF: B-RAF gene, IHC: Immunohistochemical, CTL: Cytotoxic T Lymphocyte, MEK: Mitogen activated protein kinase.

A 59 year-old woman with a history of successfully treated Hepatitis-C, Systemic Lupus Erythematosus, and a remote history of melanoma of the scalp presented to our center for evaluation of abdominal pain, nausea, vomiting, and malaise. An outpatient CT scan revealed numerous cystic liver lesions. A liver ultrasound from one year prior to admission showed a mildly heterogeneous and echogenic liver texture with no observed masses or dilated ducts. Her genotype 1b Hepatitis-C virus had been successfully treated with Pegylated interferon, Ribavirin, and Telaprevir 9 months prior to presentation. A liver biopsy revealed stage I fibrosis 6 months prior to presentation.

At our center, an abdominal MRI revealed greater than 50 hepatic cysts and cystic masses. A dominant 6 cm cystic mass in segment 2 was notable for peripheral enhancement and evidence of intralesional hemorrhage. A 2 cm complex appearing cystic mass was also noted at the junction of segments 6 and 7. No ascites or splenomegaly was observed (Figure 1). Further work-up with an EGD and liver FNA were performed. The EGD revealed an 8 mm ulcer in the gastric fundus (Figure 2) as well as multiple small nodules in the gastric body. Biopsies of the gastric ulcer and nodules were consistent with malignant melanoma.



**Figure 1:** Abdominal MRI showing numerous hepatic cysts and cystic masses. A 6 cm mass in segment 2 (thick white arrow) is remarkable for mild peripheral enhancement and intralesional hemorrhage. A 2 cm complex appearing cystic mass is noted at the junction of segments 6 and 7 (thin white arrow).



Figure 2: Endoscopic image of ulcer in the gastric fundus.

FNA of the 6 cm cystic hepatic mass showed small to intermediate sized epithelioid cells infiltrating and replacing the hepatic parenchyma on H&E stain (Figure 3A). HMB-45 (Figure 3B) and Melan A (Figure 3C) immunohistochemical staining highlight melanocyte differentiation. Staining for S-100 was also positive. Analysis for BRAF mutation was negative.

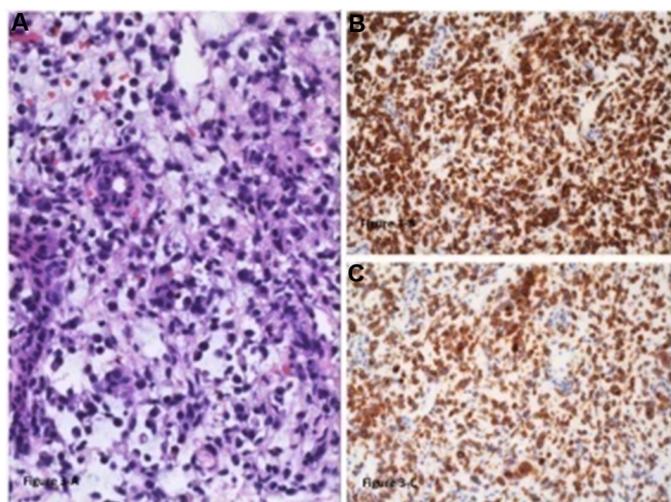


Figure 3: Liver with metastatic melanoma. (A) Hepatic parenchyma replaced by melanoma - small, non pigmented, epithelioid cells with scant cytoplasm and hyperchromatic nuclei. (Hematoxylin-eosin, original magnification x200) (B) HMB45 immunohistochemical stain shows diffuse cytoplasmic staining in the tumor cells. (Original magnification x200) (C) Melan A/MART-1 immunohistochemical stain shows diffuse cytoplasmic staining in the tumor cells. (Original magnification x200).

Cystic hepatic metastases commonly occur due to necrosis and cystic degeneration of rapidly growing hypervascular tumors such as melanoma, sarcoma, carcinoid, neuroendocrine tumors, as well as some lung and breast tumors.<sup>1</sup> Alternatively, some cystic metastases occur due to the cystic nature of the primary tumor (pancreatic or ovarian cystadenocarcinomas).<sup>2</sup> Melanoma accounts for nearly 5% of new cancer diagnoses yearly; 4% of which are metastatic at the time of diagnosis.<sup>3</sup> Liver involvement is seen in as many as 50% of metastatic cases. The 10-year survival rate for patients with metastatic melanoma is

less than 10%.<sup>4</sup>

Radiologic characterization of liver metastases is often performed with magnetic resonance imaging. Non-contrast imaging typically reveal lesions with a cystic appearance due to liquefactive necrosis. Hyper-intense appearance on T1 images is often noted due to paramagnetic substances such as melanin and extracellular haemoglobin. Contrast enhanced imaging is notable for the presence of hyper-vascular lesions.<sup>5</sup> Diagnosis of liver metastases is made by pathology on liver biopsy. Positive IHC staining for Melan A, HMB-45 and S-100 constitute the classic immuno-profile for melanoma.

Some patients with limited disease burden may be candidates for surgical metastasectomy. Medical therapy in advanced melanoma is focused on the use of immunotherapy such as interleukin-2 or the anti-CTL antigen-4 monoclonal antibody, Ipilimumab. Patients with BRAF mutations may be candidates for additional targeted therapies such as BRAF inhibitors (eg, Vemurafenib or Dabrafenib) and/or MEK inhibitors (eg, Trametinib).<sup>6</sup>

Our patient was started on Ipilimumab as palliative therapy. This case highlights a difficult diagnosis in the setting of complex liver cystic masses – an assessment of previous history and repeated biopsies are often needed to clinch the diagnosis.

#### CONFLICTS OF INTEREST

The authors declare no conflicts of interest to report with respect to the content of this article.

#### ACKNOWLEDGEMENTS

**Speaker's Bureau/Advisor/Consultant:** Gilead Sciences, BMS, Janssen, Abbvie, Salix, Onyx, Genentech.

**Research Grants:** Gilead, BMS, Abbvie, Salix, Vertex, Santaris, Bioalliance, Vital Therapies, ISIS, Merc.

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## Research

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Khafaga S, Khalil K, Abdou M, Miada M, Shedid M, Mosaad M. Acute variceal bleeding in patients with liver cirrhosis with and without diabetes. *Liver Res Open J.* 2015; 1(1): 14-20.

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# Acute Variceal Bleeding in Patients with Liver Cirrhosis with and without Diabetes

**Khafaga S<sup>1</sup>, Khalil K<sup>1</sup>, Mohamed Abdou<sup>1</sup>, Miada M<sup>1</sup>, Mahmoud Shedid<sup>2</sup> and Mohammad Mosaad<sup>2,3\*</sup>**<sup>1</sup>Department of Internal Medicine, Faculty of Medicine, Suez Canal University, Ismailia, Egypt<sup>2</sup>Department of Endemic and Infectious diseases, Faculty of Medicine, Suez Canal University, Ismailia, Egypt<sup>3</sup>Department of Internal Medicine, Taibah University, Prince Naif Ibn Abdulaziz, Tayba, Medina Saudi Arabia**ABSTRACT**

**Objectives:** To study the effect of diabetes mellitus on presentations, course, and outcome of acute variceal bleeding in cirrhotic patients.

**Methods:** We compared 2 matched groups of patients, a diabetic group and non-diabetic group, where all of the patients presented with acute esophageal varices due to liver cirrhosis. All patients underwent history taking, clinical examination, emergency treatment, upper endoscopy, laboratory investigations and abdominal ultrasound; they followed up until hospital discharge.

**Results:** The diabetic group showed statistically significant unstable course in 73.3% of them compared to 36.6% in the control; more attacks of melena ( $2.2 \pm 1.03$ ) compared to control ( $1.7 \pm 0.88$ ), and also had significantly disturbed level of consciousness compared to control (36.7% versus 10% respectively); moreover they have significantly more right and left lobe enlargement than control (70% versus 26.7%, and 66.7 versus 40% respectively), significantly more echogenic liver (70% versus 33.3), highly significant more portal vein dilatations (73.3% versus 16.7%) and highly significant more collaterals (50% versus 23.3%); the splenic size was also significantly more enlarged in diabetics (60%) than control (40%), and the splenic vein diameter was significantly more dilated in diabetics (33.3%) versus control group (6.7%); finally the mortality was more in the diabetic group.

**Conclusions:** Diabetic patients with acute variceal bleeding may show more morbidity and mortality rates.

**KEYWORDS:** Diabetes; Esophageal varices; Liver cirrhosis.

**INTRODUCTION**

Variceal bleeding is one of the major complications of portal hypertension; Gastro-esophageal varices are present in 40-60% of patients with cirrhosis and their rupture constitutes the most common lethal cause of mortality in those patients. It is associated with a mortality of at least 20% at 6 weeks despite improvements in therapy,<sup>1-3</sup> and the 1-year recurrence rate of variceal bleeding is 60% if no preventive treatment is given.<sup>4</sup> However, it has decreased from 47% to 13% with the use of pharmacological, endoscopic, and radiological intervention.<sup>5,6</sup> The presence of esophageal varices correlates with the severity of liver disease as it is found in about 40% of Child A, and 85% of Child C patients.<sup>7</sup> Various factors have been proposed as predictors of outcome of variceal bleed such as age of the patient, gender, stage of cirrhosis, etiology of the disease, associated conditions like renal failure, Hepatocellular carcinoma (HCC), and Diabetes Mellitus (DM) which is frequently associated with cirrhosis.<sup>8</sup> Regardless the cause for diabetes, hyperglycemia induces splanchnic hyperemia, increases portal pressure and may increase the risk of variceal bleeding.<sup>9</sup> Moreover, the higher mortality rate in patients

with diabetes is not only due to the complications of DM but also due to increased risk of hepatocellular failure in long-term follow up.<sup>10</sup> In our country, both variceal bleeding due to cirrhosis and diabetes mellitus are common causes of morbidity and mortality which warrants an in-depth study of such relationship.

## OBJECTIVES

To study the effects of diabetes mellitus on presentation, course, and mortality of acute variceal bleeding in cirrhotic patients.

## METHODS

### Study Type

This is a prospective case-control study which was carried out at the Internal Medicine Department and Gastroenterology Endoscopic Unit of Suez Canal University Hospital, Egypt. The study conformed to the Declaration of Helsinki for Human Rights and was approved by the University's Research Ethics Committee.

### Patients

Sixty cirrhotic patients (who met the inclusion criteria) with acute variceal bleeding with or without DM were included in the study. The patients were divided into two groups which were matched for age and gender: Group 1 (diabetic group, who were labelled as diabetics based on their history regardless of the cause of diabetes), included 30 consecutive cirrhotic patients with variceal bleeding and had a history of DM, and Group 2 (control group) which included 30 cirrhotic patients with variceal bleeding and had no history of DM. All patients were recruited prospectively at the time of admission during the period from October 2013- June 2014 after screening of 287 patients.

### Inclusion Criteria

Adult patients aged  $\geq 18$  years, both sexes, with liver cirrhosis and variceal bleeding with or without DM, patient's gave written informed consent and including the adherence.

### Exclusion Criteria

Severely decompensated patients as those with HCC with bleeding, patients in hepatic encephalopathy, non variceal bleeding, and patients' refusal to participate in the study.

### Study Procedure

During the hospital stay all patients were formally clerked with complete history taking, clinical assessment; laboratory investigations including Complete Blood Count (CBC), Liver function tests (ALT, AST, S. albumin, S. bilirubin and al-

kaline phosphates), renal function tests (S. creatinine, B. urea), fasting blood sugar, and 2 h post-prandial; also abdominal Ultrasound (US) were done for all the patients. Cirrhosis and portal hypertension were diagnosed on the basis of clinical, biochemical, virological data and imaging scanning; other data including age, gender, Child-Pugh class, site of varices and etiology of cirrhosis was recorded. Source of upper gastrointestinal bleed was confirmed by upper gastrointestinal endoscopy. Esophageal varices were graded from I-IV.<sup>11</sup> Gastric varices were classified as described by Sarin and Kumar in 1989;<sup>12</sup> the source of bleeding was identified as variceal if there was active bleeding from a varix or there were signs of recent bleeding from a varix, or there was a single varix without any other potential source of bleeding. Failure to control bleed was defined according to the Baveno III consensus report<sup>13</sup> as the occurrence of hematemesis and reduction in blood pressure of more than 20 mmHg and/or transfusion of 2 units of blood or more (over and above previous transfusions) required to keep the haemoglobin above 9 g/dL, or a drop in haemoglobin of 2 g/dL within first 24 hours of control of bleeding. The preferred therapeutic modality used was Endoscopic Variceal Ligation (EVL) with Six Shooter Saeed multi band ligation. In some patients with massive bleeding, variceal sclerotherapy with Ethanolamine Oleate was performed. Gastric varices were injected with n-butyl cyanoacrylate. No therapeutic intervention was done for patients with portal gastropathy. Somatosatin is given as 2 ampules in 500 cc glucose 5%/8 h (if the patient was not diabetic) and 2 ampules + 500 cc glucose 5% + 4 I.U regular insulin /8 h (if the patient was diabetic). Other emergency protocols in our hospital were performed until the patient became haemodynamically stable when upper endoscopy was performed; the patient was prepared by Midazolam (10 mg IV or Diazepam 5 mg IV bolus until the patient was sedated, then a mouth piece was placed and upper GI endoscopy was introduced under complete visualization, the esophagus was assessed for presence of bleeding and managed according to the guidelines by band ligation or sclerotherapy with Ethanolamine Oleate, and/or Histocryl amp (Enbucrilat 0.5 gm) in cases with fundal varices. The patient also received antibiotic, in the form of ciprofloxacin 500 mg/12 h for 5 days, PPI (Omeprazole 20 mg /12 h for 7 days), and  $\beta$ -blocker "propranolol" was given 20-240 mg/d guided by heart rate. Other causes of variceal re-bleeding as Thrombocytopenia and coagulopathy were corrected by platelet or Fresh Frozen Plasma (FFP) transfusion, if needed. Then the patient was followed up as an in-patient for at least another 2 days until melena stopped (enema was clear) and haemodynamic stable was then discharged to be followed up in out-patient sessions of upper gastrointestinal endoscopy.

### Measurement criteria for the course and outcome

As every patient had his different course pattern, we simply defined them as having stable course or unstable course. Patients were identified as having unstable course if they developed hepatic encephalopathy, spontaneous bacterial peritonitis, upper gastrointestinal re-bleeding after the initial endoscopic

treatment and/or renal impairment during the hospital stay. The death rate was also recorded in terms of mortality.

#### Data management and statistical analysis

Data collected throughout the history, basic clinical examination, laboratory investigation, and imaging results were coded, entered and analyzed using Microsoft Excel software. The data was then imported into (SPSS 13.0) software for analysis. According to the type of data the following tests were used to test differences for significance; Chi-squared and Fisher exact test, for categorical data and Student's *t*-test for continuous data. Multivariate logistic regression analysis was used to analyze the different studied variables. Continuous data were presented as the mean±SD unless otherwise specified. Categorical data were presented as numbers and percentages. P value was set at <0.05 for significant results.

#### RESULTS

There were no any statistical significant differences between the 2 groups, Table 1 shows that the mean age of the diabetic group was 53.8±10.5 compared to 52.1±11.9 in the control group; the males constitute 60% of the diabetic group, compared to 80% in the control; most of the patients live in rural areas in the diabetic and control groups (63.3%, and 76.6% respectively), and the majority of the patients were identically married (96.7%) in both groups. With regards to the status of hepatic diseases in both groups Table 2 shows that there were no significant statistical differences in both group as regard to the presence of cirrhosis, the etiology and the functional status of the liver. However, most of the diabetic group showed statistically significant unstable course in 73.3% of them compared to 36.6% in the control; moreover, the frequency of hospitals admission in the diabetics were more significant than the control (1.6 *versus* 0.7 respectively); moreover, the mortality rate was significantly higher among the diabetes. With regards the clinical manifestations, it was shown in Table 3 that diabetics have significantly more attacks of melena (2.2±1.03) compared to the control group (1.7±0.88), and also had significantly disturbed level of consciousness compared to the control group (36.7% *versus* 10% respectively). Regarding the laboratory investiga-

tions, Table 4 shows that there were no statistical significant differences for CBC, liver functions or renal functions. With regards to abdominal ultrasound evaluation in both groups Table 5 shows that diabetics had significantly more right and left lobe enlargement than control (70% *versus* 26.7%, and 66.7 *versus* 40% respectively), significantly more echogenic liver (70% *versus* 33.3), highly significant more portal vein dilatations (73.3% *versus* 16.7%) and highly significant more collaterals (50% *versus* 23.3%); the splenic size was also significantly more enlarged in diabetics (60%) than control (40%), and the splenic vein diameter was significantly more dilated in diabetics (33.3%) *versus* control group (6.7%). Finally, there was no significant difference as regard to the presence of ascites in both groups.

#### DISCUSSION

Both diabetes and liver cirrhosis are common health problems in Egypt; their presence in the same patient means a double pathological insult for the liver, which increases morbidity and mortality, regardless of the initial etiology and the cause of liver cirrhosis. This research attempted to explore how diabetic patients with acute variceal bleeding differ from those who are not diabetics. We included 2 matched groups for age and gender, a diabetic group and a control group; although we did not match for the etiology of liver cirrhosis, the majority of patients in both group have chronic HCV infection, this is mostly because HCV is the leading cause of chronic liver diseases and cirrhosis in Egypt,<sup>14</sup> and there were no differences in both group in terms of the functional status of the liver as most of them were compensated functionally. However, the diabetic group experienced significantly more unstable course for their liver diseases in their past history compared to the control, and more hospital admissions which may be attributed to their double burden. As regards the clinical manifestations at the time of admission there were no statistically significant differences, but during the hospital course the diabetic patients had significantly more attacks of upper gastrointestinal bleeding compared to control; this may be explained that they have more degree of portal hypertension as a result of the hyperglycemia and the insulin resistance,<sup>8,15</sup> or to what more recently discovered in experimental animals that Diabetes Diminishes the Portal-Systemic Collateral Vascular Response to Vasopressin *via* Vasopressin Receptor and *Gα* Pro-

Age (years)	Mean ± SD	Diabetic (n=30)		Control (n=30)		Used test	p-value
	Range	36	76	25	75		
Gender (%)	Male	18	60.0	24	80.0	$\chi^2=2.86$	0.09
	Female	12	40.0	6	20.0		
Residence (%)	Urban	11	36.7	7	23.3	$\chi^2=1.27$	0.26
	Rural	19	63.3	23	76.7		
Marital status (%)	Single	1	3.3	1	3.3	Fisher exact	1.00
	Married	29	96.7	29	96.7		

\*Significant p-value <0.05, \*\*highly significant p-value <0.01

Table 1: Demographic data of both studied groups.

		Diabetic (n=30)		Control (n=30)		Used test	p-value
Pathology (%)	Cirrhosis	29	96.7	30	100.0	Fisher exact	0.50
	Cirrhosis & HCC	1	3.3	0	0.0		
Etiology (%)	HCV	26	86.7	28	93.3	Fisher exact	0.67
	HCV & HBV	4	13.3	2	6.7		
Functional (%)	Compensated	25	83.3	24	80.0	$\chi^2=0.11$	0.74
	Decompensated	5	16.7	6	20.0		
Course (%)	Unstable	22	73.3	11	36.6	$\chi^2=8.2$	0.004**
	Stable	8	26.7	19	63.3		
Re-bleeding (%)		14	46.4	3	10	Fisher exact	0.003**
Encephalopathy (%)		11	36.6	3	10	Fisher exact	0.03*
Spontaneous Bacterial Peritonitis (%)		8	26.6	1	3.3	Fisher exact	0.0138*
Renal impairment (%)		3	10	1	3.3	Fisher exact	0.61
Duration of CLD (years)	Mean $\pm$ SD	25.5	14.4	24.5	13.7	0.28	0.78
Admission before (times)	Mean $\pm$ SD	1.60	0.4	1.3	0.7	2.2	0.046*
mortality		5	16.6	2	6.7	Fisher exact	0.26

\*Significant p-value &lt;0.05

Table 2: Mortality, hospital course and the status of hepatic disease of both studied groups.

		Diabetic (n=30)		Control (n=30)		Used test	p-value
Jaundice (%)	Yes	3	10.0	4	13.3	Fisher exact	1.00
	No	27	90.0	26	86.7		
Melena (%)	Yes	29	96.7	26	86.7	Fisher exact	0.35
	No	1	3.3	4	13.3		
No. of attacks	Mean $\pm$ SD	2.2	1.03	1.7	0.88	2.01	0.041*
Fresh bleeding per rectum (%)	Yes	1	3.3	0	0.0	Fisher exact	0.50
	No	29	96.7	30	100.0		
Spider nevi (%)	Yes	7	23.3	4	13.3	$\chi^2=1.0$	0.32
	No	23	76.7	26	86.7		
Tremors (coarse) (%)	Yes	4	13.3	1	3.3	Fisher exact	0.35
	No	26	86.7	29	96.7		
Palmer Erythema (%)	Yes	7	23.3	8	26.7	$\chi^2=0.09$	0.76
	No	23	76.7	22	73.3		
Lower limb edema (%)	Yes	1	3.3	0	0.0	Fisher exact	0.50
	No	29	96.7	30	100.0		
Consciousness level (%)	Conscious	19	63.3	27	90.0	$\chi^2=5.96$	0.015*
	Disturbed	11	36.7	3	10.0		
Suprapubic hair (%)	Normal	17	56.7	16	53.3	$\chi^2=0.07$	0.79
	Abnormal	13	43.3	14	46.7		
Gynecomastia (male n=42) (%)	Yes	14	77.8	16	66.7	$\chi^2=0.27$	0.60
	No	4	22.2	8	33.3		
Nutritional status (%)	Good	5	16.7	10	33.3	$\chi^2=2.22$	0.14
	Fair	22	73.3	18	60.0		
	Poor	3	10.0	2	6.7		

\*Significant p-value &lt;0.05, \*\*highly significant p-value &lt;0.01

Table 3: Clinical manifestations of the studied patients of both studied groups.

	Diabetic (n=30)		Control (n=30)		t-test	p-value
	Mean (SD)		Mean (SD)			
Hb	9.02	2.2	8.7	2.5	0.417	0.680
Platelet count	144.8	89.7	133.3	56.8	0.540	0.593
Total serum bilirubin	1.47	0.96	1.6	0.9	0.337	0.738
ALT	52.5	37.8	55.9	65.02	0.233	0.817
AST	71.3	85.2	69.8	101.2	0.058	0.954
Albumin	3.057	0.43	2.96	0.57	0.767	0.449
Alkaline Phosphatase	33.7	9.59	31.1	7.9	1.445	0.159
S. creatinine	1.18	0.59	0.9	0.25	1.057	0.299
B. urea	63.5	45.6	51.8	26.9	1.130	0.268
PT	16.34	3.42	16.3	3.01	0.004	0.997
INR	1.399	0.48	1.3	0.43	1.064	0.296
FBS	150.9	66.7	80.9	13.7	5.350	<0.0001**
PPS	238.4	108.6	115.8	9.01	6.078	<0.0001**

\*Significant p-value <0.05, \*\*highly significant p-value <0.01

Table 4: Laboratory investigations of both studied groups.

		Diabetic (n=30)		Control (n=30)		$\chi^2$ test	p-value
		No.	%	No.	%		
Right lobe	Normal	8	26.7	18	60.0	$\chi^2=9.5$	0.002**
	Enlarged	21	70.0	8	26.7		
	Shrunken	1	3.3	4	13.3		
Left lobe	Normal	10	33.3	18	60.0	$\chi^2=4.3$	0.038*
	Enlarged	20	66.7	12	40.0		
Echogenicity	Echogenic	9	30.0	20	66.7	$\chi^2=8.1$	0.004**
	Bright (fatty) liver	21	70.0	10	33.3		
Portal vein	Normal	8	26.7	25	83.3	$\chi^2=19.5$	<0.0001**
	Dilated	22	73.3	5	16.7		
Collaterals	Yes	15	50.0	7	23.3	$\chi^2=15.6$	<0.0001*
	No	15	50.0	23	76.7		
Spleen size	Normal	12	40.0	18	60.0	$\chi^2=4.6$	0.032*
	Enlarged	18	60.0	12	40.0		
Splenic vein diameter	Normal	20	66.7	28	93.3	$\chi^2=6.7$	0.0098**
	Dilated	10	33.3	2	6.7		
Ascites	Absent	27	90.0	26	86.7	Fisher exact	0.99
	Mild /moderate	3	10.0	4	13.3		

\*Significant p-value <0.05, \*\*highly significant p-value <0.01

Table 5: Abdominal ultrasound evaluation of the studied patients.

teins Regulations;<sup>16</sup> the presence of diabetes itself, is a risk factor to control variceal bleeding.<sup>17</sup> However, the hypothesis that the veins themselves may be directly affected by the diabetes as a part of the vasculopathy<sup>18</sup> need to be tested. In our study, diabetics also showed more significantly impaired consciousness level compared to control which may be attributed to the more attacks and more blood loss which may increase the degree of their encephalopathy.<sup>19</sup> As regards the laboratory investigations at the time of admission, there were no significant differences, apart from the blood sugar; even the liver enzymes in both groups were nearly identical, although a recently published mega trial

concluded that serum ALT concentrations were independently associated with type 2 diabetes in both sexes.<sup>20</sup> Contrary of the clinical presentation and laboratory investigations in our study, the ultrasound showed that the diabetics are significantly morphologically different from the control group; they have more hepatomegaly and splenomegaly, increased portal pressures with more dilated portal veins and more collaterals. In addition, their livers appeared more fatty and bright; this raised the hypothesis that these morphological differences may be attributed to diabetes alone as it is the only variable between the 2 groups. Based on our knowledge and previous studies we can

understand the presence of bright fatty liver and hepatomegaly in the diabetics;<sup>21,22</sup> we can also partially explain the presence of collaterals and portal veins dilatation;<sup>23,24</sup> but all of these were not reflected on the laboratory investigations or the clinical presentations except the increased frequency of bleeding; even the presence of ascites were comparable in both groups which may be due to the comparable levels of serum albumin that could not be overcome by the degree of portal hypertension in diabetics. However, the limitation of this study is relatively small sample size, and the results of the study should be addressed and re-evaluated on larger groups.

## CONCLUSION

Patients with acute variceal bleeding due to liver cirrhosis and diabetes are mostly presenting with more evidence of portal hypertension, more attacks of bleeding and less responsiveness to pharmacological treatments.

## ETHICAL CONSIDERATIONS

This study was approved by the University's Research Ethical Committee and an informed consent was taken from all the participants prior to recruitment into the study.

## CONFLICTS OF INTEREST

We have not any conflict of interest to declare.

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## Case Report

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Volume 1 : Issue 1

Article Ref. #: 1000LROJ1104

**Article History:**

Received: April 15<sup>th</sup>, 2015

Accepted: May 4<sup>th</sup>, 2015

Published: May 5<sup>th</sup>, 2015

**Citation:**

Chen S, Mizrahi M, Nubani A, et al. Acute liver injury during co-treatment with levetiracetam and temozolomide. *Liver Res Open J.* 2015; 1(1): 21-25.

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# Acute Liver Injury during Co-treatment with Levetiracetam and Temozolomide

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**ABSTRACT**

Drug-induced liver injury (DILI) accounts for approximately 10 percent of all cases of acute hepatitis. The patterns of acute injury include any form of hepatic injury, but the most common problems are cholestasis, hepatocellular damage, or a mixed type. DILI is often reversible, and discontinuation of the offending agent usually results in a complete recovery; however, some cases may lead to chronic liver injury, cirrhosis, and even death. Temozolomide (TMZ) is an alkylating, anti-neoplastic agent used for the treatment of refractory anaplastic astrocytoma, newly-diagnosed Glioblastoma multiforme (GBM) and metastatic melanoma. Levetiracetam (LEV) is an established second-generation antiepileptic drug and is most commonly approved as adjunctive treatment of partial-onset seizures with or without secondary generalization. When administered separately each of these drugs is considered to be relatively safe and only few cases of severe liver injury can be found throughout the literature; however, LEV and TMZ are commonly used together in the treatment of brain malignancies. We report three patients who presented with jaundice during treatment with TMZ and LEV, and propose a mechanism for liver sensitization by LEV for TMZ-induced injury.

**KEYWORDS:** Levetiracetam; Temozolomide; Liver injury; MGMT; Glioblastoma multiform.

**ABBREVIATIONS:** LEV: Levetiracetam; TMZ: Temozolomide; MGMT: O-6-methylguanine-DNA methyltransferase; DILI: Drug-induced liver injury; MRI: Magnetic Resonance Imaging; INR: International Normalized Ratio; TB: Total Bilirubin; LFTs: Liver function tests; ALL: Acute Lymphocytic Leukemia.

**INTRODUCTION**

Drug-induced liver injury (DILI) accounts for 2-5% hospitalizations due to jaundice, and 10% of all cases of hepatitis in adults. However, the last can reach even more than 40% in elderly patients. The overall incidence of drug hepatotoxicity ranges between 1/10,000 to 1/100,000<sup>1-3</sup> and it is the most common cause of acute liver failure in developed countries.<sup>4,5</sup>

Antiepileptic drugs are frequently used for secondary prevention of seizures in patients with brain malignancy. LEV has a novel structure and unique mechanisms of action. Unlike other anti-epileptic drugs, it inhibits calcium release from intra-neuronal stores.<sup>6</sup> It is commonly used due to its low incidence of adverse events<sup>7</sup> and low risk of drug interactions, which attributed to its limited hepatic metabolism and minimal effect on protein binding of other drugs.<sup>8</sup> Moreover, it lacks cytochrome P450 isoenzyme-inducing potential and is not associated with clinically significant pharmacokinetic interactions with other drugs.<sup>6</sup> Therefore,

it is not surprising that only few case-reports depict significant hepatotoxicity as a result of treatment with LEV.<sup>9</sup>

TMZ is an orally administered alkylating agent which used for the treatment of GBM and was demonstrated to prolong overall survival when added to radiotherapy.<sup>10</sup> The anti-neoplastic effect of TMZ is attributed to the methylation of a guanine group in DNA. The resulting O6-methylguanine mispairs with thymine upon DNA replication, and therefore arrests the cell cycle.<sup>11</sup> There are a few cases reported in the literature describing TMZ induced liver injury.<sup>12</sup> The fact that TMZ metabolizes mainly by spontaneous hydrolysis in the plasma to active metabolites and non-significantly by the liver<sup>13</sup> implies that the chances for pharmacokinetic interaction are low. Yet, a pharmacodynamic interaction cannot be excluded. Nonetheless, hepatic toxicity of this commonly used drug combination has not been previously reported. Here we present three patients with brain malignancy that were treated with TMZ and LEV and developed severe liver injury and suggest a potential mechanism responsible for this toxicity.

## CASE REPORTS

### Case 1

A 60-year-old man was admitted to our hospital because of jaundice, weakness, pale stools, and dark urine. His past medical history included GBM diagnosed 6 months previously, which presented with seizures. He underwent brain biopsy and was treated with a short course of TMZ (150 mg of TMZ per day, calculated based on body surface area of 2.2 m<sup>2</sup>). After 42 days of treatment, he developed a tonic-clonic seizure, for which he was treated with LEV. His Liver function tests (LFTs) were normal.

Initial assessment revealed a marked jaundice without confusion or somnolence. Laboratory tests revealed total bilirubin (TB) 322 mol/L, alanine aminotransferase (ALT) 375 U/L (normal range NR 0-40 U/L), aspartate aminotransferase (AST) 222 U/L (NR 0-35 U/L), alkaline phosphatase (ALP) 411 U/L (NR 40-130 U/L), gamma-glutamyl transpeptidase (GGT) 709 U/L (NR 8-61 U/L), and prothrombin time 36.6 sec (NR 25-40 seconds), INR 1.0 (NR 1-1.4 ratio). Antinuclear antibodies (ANA), antimitochondrial antibodies (AMA) and serum complement (C3, C4) were all negative or normal. Viral serology for hepatitis A, B, and C, EBV, and CMV were negative as well. Serum level of ceruloplasmin was normal. An abdominal ultrasound revealed normal liver size with no evidence of focal lesion, no evidence of gallbladder or bile duct stones, and no evidence of ascites. Duplex examination revealed normal flow in the hepatic and portal veins. A cerebral CT scan demonstrated multiple ring enhancing lesions with no change from previous test.

The proposed diagnosis was drug induced liver injury (DILI). TMZ and LEV were discontinued and treatment with

hydrocortisone (100 mg tid) was started. The patient's state of liver failure continued to deteriorate for the next few days (total bilirubin 321 mol/L). However, 4 days after discontinuation of TMZ and LEV, LFTs began to improve and 6 weeks later, they returned to the normal range.

It should be noted that the patient was also treated with herbal remedies (*Lineum usitatissimum*, *Fumariaceae*, *Curcuma longa*, and *Silybum marianum*), of which none were found to cause a liver injury in literature review.

### Case 2

A 63-year-old woman presented with jaundice of 3 days duration. She did not have any additional complaints. Three months previously she had been diagnosed by brain biopsy with an astrocytoma, which had presented with speech disturbances and right hand weakness in addition to sight disorder in the right temporal visual field. She had been treated with TMZ (135 mg per day calculated based on body surface area of 1.82 m<sup>2</sup>) and LEV for the last 5 weeks. A week before admission, a treatment with fluconazole was initiated due to oral thrush. Blood tests taken one month before admission revealed normal LFTs.

On admission physical examination revealed a markedly icteric woman without confusion or somnolence. Laboratory blood tests disclosed the following results: TB 486 mol/L, ALT 2,682 U/L (NR 0-40 U/L), AST 1,162 U/L (NR 0-35 U/L), ALP 1,159 U/L (NR 40-130 U/L), GGT 1,191 U/L (NR 8-61 U/L), PTT 25.1 sec (NR 25-40 seconds) and INR was 1.03 (NR 1-1.4 ratio). A triphasic CT scan of the liver was normal. ANA, AMA and C3 C4 were all negative. Viral serology for hepatitis A, B, and C, EBV, and CMV were negative for acute infection. Serum ceruloplasmin was normal.

The proposed diagnosis was DILI, and TMZ and LEV were stopped, and 5 days after discontinuation of TMZ and LEV, LFTs improved though they did not return to the normal range (TB 577 mol/L three weeks later), the patient underwent liver biopsy with the evidence of cholestatic injury and bile duct damage due to the used drugs, after few days her conditions were deteriorated and the patient succumbed.

### Case 3

A 32-year-old man was hospitalized due to jaundice and weakness. Four months previously a diagnosis of GBM was made at brain biopsy, which had presented expressed in speech disorder and sense disturbances in his left hand that lasted several minutes. Past medical history was positive for Acute Lymphocytic Leukemia (ALL) from which he recovered following chemotherapy and radiation. During the first 14 days of treatment with TMZ (130 mg per day calculated based on body surface area of 1.76) he developed a tonic-clonic seizure. LEV was then given in combination with TMZ. His Liver function tests (LFTs) at the initiation of treatment were normal.

Initial assessment revealed a markedly icteric man without confusion or somnolence. Results on admission were TB 252 mol/L, ALT 425 U/L (NR 0-40 U/L), AST 125 U/L (NR 0-35 U/L), ALP 89 U/L (NR 40-130 U/L), GGT 134 U/L (NR 8-61 U/L), PTT 13.1 sec (NR 25-40 seconds), and INR 1.23 (NR 1-1.4 ratio).

An abdominal ultrasound revealed normal liver size with no evidence of focal lesion, no evidence of gallbladder or bile duct stones, and no evidence of ascites. Further investigation included abdominal CT supported these findings. ANA, AMA and C3 C4 were all negative or normal respectively. Viral serology for hepatitis A, B and C, EBV, and CMV were negative for acute infection. Serum ceruloplasmin was normal.

A Magnetic Resonance Imaging (MRI) revealed post surgical changes involving the right hemicalvarium. An enhanced mass posterior to the surgical bed and in continuity with the posterior horn of the right lateral ventricle was noted with no difference from previous examination.

The proposed diagnosis was DILI. Treatment with LEV was halted, the patient continued to receive TMZ, and the dose of dexamethazone was elevated from 4 mg to 10 mg a day. On follow-up examination 4 months later, no recurrent liver injury was noted.

## DISCUSSION

LEV is an antiepileptic drug that is often used to prevent seizures in patients with brain malignancy due to its low incidence of drug-drug interactions and hepatotoxicity. Moreover, since LEV is excreted by the kidney, no adjustment is required in patients with hepatic impairment. A literature search for TMZ hepatotoxicity revealed only three case reports of sustained cholestasis. An additional 16 cases of cholestatic hepatitis or cholestasis associated with TMZ were identified in the FDA spontaneous reporting system between 2007 and 2010.<sup>14</sup> In addition, reactivation of hepatitis B in a silent carrier can occur under TMZ treatment.<sup>15</sup> Tests for antigens to hepatitis B were negative in our three patients, as mentioned above.

The diagnosis of DILI in our three patients was based on the temporal relationship between TMZ and LEV administration. Hepatic injury was observed in 5-12 weeks following the

initiation of the combination treatment in our patients. Furthermore, recovery from hepatic injury was also related temporally to discontinuation of the drugs, with improvement in all three cases 4-5 days after discontinuation of these medications. Thus, despite the low frequency of liver injury with each drug given alone, the occurrence of liver injury in these three patients raised the possibility of synergism between these two drugs in inducing the liver damage and led us to look for possible explanation for such toxic synergism for the liver. Nevertheless, a casual relationship cannot be inferred from this association. It should be noted that liver biopsies were not taken from these three patients due to the clear impression of DILI, as mentioned above. Biopsy would have amounted to an invasive procedure that was not expected to change patient management, particularly in the light of their significant CNS malignancies.

In order to quantitatively assess the potential for drug interaction between LEV and TMZ in each case, we calculated the drug interaction probability score (DIPS, Table 1).<sup>16</sup> Scores range from -9 to 11, where values below 2 correlate with doubtful interaction. The scores calculated for the cases depicted here range between 2 and 3, which correlate with a possible interaction.

The mechanism of interaction between LEV and TMZ is not clear. As mentioned above, the anti-neoplastic effect of TMZ is attributed to the methylation of a guanine group in DNA which results in O6-methylguanine mispairs with thymine, and therefore arrests the cell cycle. However, this effect of TMZ depends on the inhibition of the O-6-methylguanine-DNA methyltransferase (MGMT) gene, a DNA-repair protein that removes alkyl groups from the O6 position of guanine, the important site of DNA alkylation.<sup>17</sup> Moreover, it was shown that a key mechanism for resistance to TMZ is MGMT over expression.<sup>18</sup> On the other hand, it has been hypothesized that LEV is the most potent MGMT inhibitor among several antiepileptic drugs.<sup>19</sup> In fact, LEV was shown to cause a p53-mediated inhibition of MGMT, thereby sensitizing GBM cells to TMZ.<sup>19</sup> Hence, it is not surprising that the combination of LEV and TMZ has been suggested to contribute to the effect of TMZ on GBM cells *in vitro*.

However, this effect of LEV can serve as two-edged sword, given the fact that low MGMT levels may expose hepatocytes to potential damage by TMZ, since MGMT plays a crucial role in the defence against the alkylating agent cytotoxicity. In

Case	Age	Gender	Disease	Duration of treatment* (months) LEV / TMZ / both	Maximal INR	Maximal TB	DIPS score**
1	60	Male	GBM	3 / 2 / 2	1.00	322	2
2	63	Female	Astrocytoma	2 / 1 / 1	1.03	486	2
3	32	Male	GBM	3 / 3 / 3	1.23	252	3

\*The duration of treatment (months) before the appearance of liver injury.

\*\*DIPS score evaluate the potential for drug interaction (between LEV and TMZ), values between 2-4 represent possible interaction.

INR: International Normalized Ratio; TB: Total Bilirubin.

Table 1: Summarizes data from the three patients presented above.

fact, it was shown in mice that diurnal variation of glucocorticoid levels modulates expression of the MGMT gene, which correlates with the risk of dacarbazine-induced hepatotoxicity.<sup>20</sup> Specifically, glucocorticoids upregulate MGMT gene expression in hepatic cells. Upregulated MGMT gene expression removes the mutagenic DNA adduct O6-alkylguanine that is produced by exposure to alkylating agents, preventing hepatic cell death by promoting recombination and repair of double-strand breaks. LEV is a potent MGMT inhibitor, acting in opposition to the effects of glucocorticosteroids. When administered in combination with TMZ, LEV may therefore enhance the risk of liver injury.

In the current cases one may raise a question as to the real cause for the liver injury, since two patients were treated with concomitant agents (herbal medications or fluconazole) that may cause such complication by themselves. However, a review of literature revealed that none of the herbal medications that patient 1 had taken (*Lineum usitatissimum*, *Fumariaceae*, *Curcumin*, and *Silybum marianum*) are known to cause a liver damage; in fact, several recent studies have shown a protective effect of these medications in states of liver injury.<sup>21-24</sup> Nevertheless, no study examined the combination of these herbal medications, thus, potential liver toxicity cannot be excluded. As to the second patient who was treated with fluconazole, although LFT abnormalities are associated with all of the azoles, these abnormalities are more likely with itraconazole and ketoconazole than with fluconazole<sup>25,26</sup> and the later seems to have a lower risk of treatment discontinuation because of adverse events.<sup>27</sup> Moreover, toxicity is dosage-related, and is detected during weeks 2-6 after initiation of therapy.<sup>1</sup> Furthermore, most of these patients have asymptomatic elevation of serum transaminase levels, and reported cases of symptomatic hepatic injury are rare.

An additional question that should be mentioned is the rarity of liver injury with LEV and TMZ. Although we describe three patients who developed liver complication following concomitant administration of LEV and TMZ, thousands of patients taking the same treatment do not develop liver injury, suggesting additional genetic or environmental susceptibility factors. Therefore, until more validated data are available, caution should be exercised when using both medications concomitantly.

## CONCLUSION

In conclusion, it appears that LEV and TMZ may have drug-to-drug interaction. Combined treatment with LEV and TMZ may enhance the risk for development DILI, in comparison to treatment with either of these drugs alone. Therefore, liver enzymes follow-up should be considered when giving LEV and TMZ concurrently until more reliable prospective data becomes available.

## CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

## ACKNOWLEDGMENTS

We acknowledge Miss. Roemi Lilach for editing this paper. There was no outside funding in support of this research.

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