Ranitidine induced hepatitis

To the Editor,

Ranitidine and other H₂-receptor antagonists (H₂RA) are considered extremely safe, resulting in utilization without requiring a prescription [1]. Despite this, ranitidine rarely can be associated with severe hepatotoxicity [2]. We describe a case of ranitidine induced hepatitis with a clinical evaluation eliminating alcohol, viral, biliary tract, primary liver disease and other medications as potential confounders.

A 27 year old male, without significant past medical history, presented to our emergency room with jaundice and mild right upper quadrant discomfort of three days duration. No active alcohol or illicit drug use was reported. Medication history at presentation revealed only over-the-counter ranitidine for intermittent epigastric pain and heartburn. Physical examination was significant for jaundice and mild right upper quadrant tenderness without hepatosplenomegaly. Laboratory data revealed a WBC count of 4,300/mm³, AST 1385 U/L, ALT 2544 U/L, total bilirubin of 10.7 mg/dl, direct bilirubin of 7.5 mg/dL, alkaline phosphatase 199 U/L, ferritin >1650 ng/ml, iron saturation of 62.1%, PT 14.5 seconds, and INR 1.47. Acute viral hepatitis panel on admission was negative for hepatitis A, B and C. Abdominal CT revealed a 6 mm stone in the gallbladder.

Further serologic evaluation during admission revealed negative CMV and EBV serologies along with the absence of anti-mitochondrial, anti-nuclear and anti-smooth muscle antibodies. Alpha-1-antitrypsin and ceruloplasmin serum levels were normal. Hemochromatosis genetic testing was negative. Endoscopic retrograde cholangiopancreatography (ERCP) showed a normal cholangiogram without ductal dilatation, cholelithiasis or sludge. Percutaneous liver biopsy revealed mild portal inflammation of predominantly small lymphocytes, a few eosinophils with mild lobular inflammation and steatosis (Figs. 1, 2). Intra-hepatic cholestasis was present, but no viral cytopathic effect or evidence of iron overload was noted. Trichrome stain demonstrated minimal portal fibrosis. These findings were histologically consistent with drug-induced hepatitis.

Ranitidine was discontinued at admission and the patient slowly improved, resulting in discharge on day 7. All laboratory abnormalities returned to normal spontaneously over the following 7 weeks. Sequential liver function testing was performed for 12 months after resolution, with all values remaining in the normal range.

The mechanism of hepatotoxicity due to ranitidine remains unclear. Based on the clinical characteristics of hepatitis and its rarity, these episodes were presumed to be idiosyncratic in origin [1]. Recently, investigations have
been performed to determine the molecular mechanism underlying ranitidine hepatotoxicity, suggesting a role for lipopolysaccharides [3].

Many reports available in the literature did not contain sufficient detail to confirm ranitidine as the cause. Hepatotoxic medication use, recent blood transfusion and/or alcohol use appeared as confounders in multiple situations [4-6]. Others did not perform a complete evaluation, including autoimmune hepatitis serology [4, 7], hepatobiliary imaging (ERCP, ultrasound) [7] and/or liver biopsy [7, 8]. Hepatitis onset after introduction of ranitidine can vary from days to months [2, 4].

In contrast, our patient was not found to have any other plausible cause for acute hepatitis. Endoscopic, histologic and radiologic evaluation only revealed changes consistent with drug-induced hepatitis. Therefore, a thorough history should be obtained, including over-the-counter medications, to determine if ranitidine is a potential cause for an episode of acute hepatitis.

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References

More on serum markers of liver fibrosis: are they still clinically limited?

To the Editor,

We read with much interest the article by Parsian et al. on serum hyaluronic acid (HA) and laminin (LN) as biomarkers in liver fibrosis appearing in the June issue of the Journal [1]. They suggest that measurement of HA and LN concentrations in patients with chronic viral or autoimmune hepatitis can discriminate between individuals with and without liver fibrosis, and those with small and large fibrotic lesions assessed by using the modified Knodell scoring system [2]. Unfortunately, patients with higher serum HA and LN concentrations had also greater inflammation grades, so there may be a hesitation regarding whether one is measuring the former or the latter. Moreover, because the Knodell scoring system [2, 3] measures fibrosis extent semi-quantitatively, an overlap between these different degrees of fibrotic changes is possible and may be responsible for the still limited sensitivity and specificity of serum HA and LN observed in the Dr Parsian article.

We encountered the same problem. Hoping to overcome this potential bias, at our Institution we assessed the extent of liver fibrosis by computerized histomorphometry (Zeiss Kontron Videoplan analysis system), measuring the ratio of the mean values of the areas of portal tracts in the specimen of the entire liver biopsy in a group of 54 children with chronic hepatitis B. Although the degree of portal tract fibrosis correlated significantly with serum HA and LN (r=0.49, p < 0.0001 and r = 0.50, p < 0.0001, respectively), no cut-off value patently discriminated between patients with little or extensive lesions. Although elevated HA concentration (>100 ng/ml) identified a subgroup of patients with histology or laparoscopy-proven liver cirrhosis, several other cirrhotic children would however be missed with this cut-off because of considerable values’ overlap. Furthermore, serum concentration of LN could only differentiate patients with cirrhosis from the controls [4]. We still think this finding might depend also on poor LN degradation associated with impaired hepatic function rather than on hepatic fibrosis alone.

Pending more extensive studies, we believe that these biomarkers’ estimations, despite the statistical significance of the results, are still clinically limited and remain therefore of largely experimental interest.

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References
As demonstrated, the Knodell scoring system measures fibrosis extent semi-quantitatively and an overlap between the fibrotic stages may occur. At present the use of liver biopsy and Knodell scoring system for the assessment of the liver biopsy fragments is an important diagnostic tool in our area and our study was an attempt to clarify the relationship between the serum non-invasive tests and liver biopsies. We tried to reduce the confounding variables; for example, two independent pathologists studied the specimens blindly and the analysis of samples was also blind and the data were pooled. We categorized our patients in two groups: stage 0-2 as mild fibrosis and stage 3-6 as advanced fibrosis and we calculated the cut-off values for each group in order to decrease the data overlap. In clinical care, we wish to know whether our patients have mild or advanced liver disease, and exact staging is less important. Therefore, the determination of fibrosis stage does not need to be as exact as the pathologic scoring systems [1]: an overlap between some stages of liver fibrosis can occur, but it is not so important.

Despite the statistical significance of the results, use of these tests is clinically limited. At present this is a big problem for researchers, because LN and various ECM components such as HA are not liver specific biomarkers, since elevations occur in other diseases (lung fibrosis, rheumatoid diseases etc.). They are non-specific and when used in the diagnosis of hepatic fibrosis, other diseases should be ruled out. We concluded that serum fibrosis markers can reflect abnormal metabolism of ECM, because the ECM is an active tissue and matrix synthesis and degradation appears in it, in a dynamic process. The imbalance between synthesis and degradation of the ECN components can lead to fibrosis and progress to cirrhosis. Although we found a strong correlation between serum HA and LN concentrations with hepatic necroinflammatory lesions, we can not rely only on these two tests in clinical practice. Physicians should take into consideration all liver function tests, history and clinical manifestations (liver biopsy) in the assessment of the diagnostic value of these fibrosis tests in the staging of hepatic fibrosis. At present all research into liver disorders are dependent on liver biopsy and we also used the liver biopsy as a gold standard [2-4]. As noted, larger studies are required before the abolishing of liver biopsy in liver disease assessment. These tests are still considered to be in their infancy, but with more extensive research we are sure that these non-invasive tests will assist physicians in the precise diagnosis of liver fibrosis in the future.

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References

Is it untrue that ultrasonography guidance is superior to the blind method for liver biopsy?

To the Editor,

We read with great interest the article by Akkan Çetinkaya et al [1] published in issue 1 of J Gastrointestin Liver Dis 2010. The authors retrospectively analyzed 205 consecutive patients that had underwent liver biopsies (LB) during a 12-month period. Liver biopsy was performed via the blind method in 152 patients, and via ultrasound (US)-guidance in 53 patients. They concluded that US-guided biopsy was not superior to the blind biopsy. The authors also suggested that gastroenterologists/hepatologists should be encouraged to perform LB via the blind method. However, there are several important points that need to be addressed. We believe this paper advocates potentially unsafe messages. From our point of view, after a long experience in performing LB via ultrasound guidance, we consider that direct US control of the needle pathway during the procedure represents the guarantee that the hepatic fragment obtained by LB is adequate for histological analysis and additionally reduces the complication rates. The opinion that the blind method of LB (without visual inspection of the needle pathway) has the same chance for a successful outcome is simply not realistic (especially regarding safety of the intervention and its complication rate).

In the current study, there were no statistically significant differences between the two groups in terms of the number of biopsy specimens, specimen fragmentation or the number of portal tracts and central veins in each specimen. There was no mortality or major complications in their study.

Yet, these results should be cautiously interpreted. Our main concern is the sample size, although authors did mention this issue. It is widely reported that LB is an invasive procedure associated with mild complications in 30% of cases and responsible for serious complications, including severe bleeding and death in 0.5% of cases [2].
Bearing in mind these numbers, the minimum sample for adequate comparison between two groups in terms of serious complications rates should be much higher (several thousands). Also it is surprising that the rates of minor complications are not recorded. Indisputably, sampling in both types of procedure is widely confirmed to be adequate – safety is the main concern behind utilization of US and therefore all complications should be monitored and reported.

Several studies showed that complications have appeared more often in “blind” than in “US-guided” biopsies [3–6]. In a prospective study, Riley et al [7] reported that US examination before the LB forced a change of the site of biopsy in 15.1% of the cases due to interposition of lung, gallbladder, large central vessel, ascites, colonic loop, and slim liver edge.

In many countries ultrasound examination is performed both by radiologists and by clinicians. In other countries, the US examination is performed only by radiologists. Therefore, we think that blind biopsy is acceptable for clinicians (gastroenterologists/hepatologists) in the countries where only radiologists perform ultrasound examination. In the countries where clinicians perform US examination, we cannot recommend blind biopsies because the US guided method is likely to reduce the risk of complications and could improve the quality of specimens obtained, as recommended by the AASLD guidelines [8].

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References

Reply,

We read the letter by Zerem et al and first of all we thank them for their interest. As we stated in the title, ultrasound (US)-guided biopsy was not superior to the blind method in our study. In the text, we also stated that complication rates and adequacy of specimens had been more acceptable with US-guided method and we supported these findings with literature [1-4]. However, we can conclude that the blind method may yield satisfactory results in terms of complication rates and adequacy of specimens with prior exclusion of contraindications such as congenital anomalies and mass lesions by US examination.

There might be some reasons for this unexpected result. Firstly, all the patients in our study had compensated liver disease. Secondly, all patients underwent US prior to the blind biopsy procedure to exclude contraindications. Coagulation tests were performed on all patients. Thirdly, the number of patients was low in our study.

It is not logical to advocate the blind method for every patient without prior examination. However, the complication rate was low and specimens were adequate for the histologic examination when conditions were as in our study. As stated by Zerem et al, US-guided biopsy is more suitable [5]. However, the blind method is another option following examination via US and hematologic parameters especially when US-guided biopsy is not available. There is a need for more extensive studies to verify these results.

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References
Primary neuroendocrine tumor of the extrahepatic biliary tree mimicking Klatskin tumor

To the Editor,

A 77-year-old man during his scheduled follow up for colon cancer underwent blood tests and radiological imaging. The patient had been subjected to a sigmoidectomy 12 years before for colon cancer and had remained asymptomatic. The blood tests showed elevated liver enzymes and conjugated bilirubin. Tumor markers (CEA, CA19.9, AFP) were negative. The abdominal CT revealed a circumscribed mass in the porta hepatis, dilated intrahepatic bile ducts and atrophy of the left liver lobe. Due to the doubtful interpretations of the radiological findings, magnetic resonance imaging (MRI and MRCP) was carried out (Fig. 1). In addition, an intrahepatic bile duct dilation was described at the source of the lesion, which led to the suspicion of a Klatskin tumor. This could not be confirmed by Fine Needle Aspiration due to its position.

Neuroendocrine tumors are slow-growing neoplasms derived from the neuroendocrine system. About 54.5% of neuroendocrine tumors arise within the gastrointestinal system [1]. Neuroendocrine tumors of the bile duct are rare and account for 0.2–2% of all gastrointestinal neuroendocrine tumors [2]. The most common presenting symptom is jaundice and the most common anatomic sites where they occur are the common bile duct (58%), perihilar region (28%), cystic duct (11%), and common hepatic duct (3%) [3]. Similar to other tumors of the biliary tree, these lesions are difficult to diagnose and almost impossible to distinguish from cholangiocarcinoma.

In our case, the solitary lesion of the confluence and left hepatic duct was an incidental finding. The patient did not have any symptoms, in contrast to all the previously 15 reported cases of hilar neuroendocrine tumors [3, 4], where jaundice is the most common, and perhaps the only presenting symptom in 93% of cases. The circumscribed mass in the porta hepatis was diagnosed as a Klatskin tumor and this diagnosis was suggested by the intrahepatic biliary dilatation of the left liver lobe. Therefore the patient was subjected to a left hepatectomy (segments II, III and IV), excision of the extrahepatic biliary tree and right hepaticojejunal anastomosis.

In conclusion, biliary neuroendocrine tumors can be very difficult to diagnose preoperatively. However, since aggressive surgical resection is the primary treatment for biliary neuroendocrine tumors and the only therapy that offers a chance of cure, they should be differentiated from non-neuroendocrine tumors for therapeutic strategy.

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References
3. Chamberlain RS, Blumgart LH. Carcinoid tumors of the extrahepatic...
Emergence of Crohn’s disease in Juvenile Idiopathic Arthritis during treatment with etanercept: a causal link or a mere coincidence?

To the Editor,

Anti-tumor necrosis factor-α (anti-TNF-α) biological agents (etanercept, infliximab and adalimumab) are widely used for the treatment of several autoimmune diseases, showing varying efficacy [1]. We present a case report of Crohn’s disease (CD) onset in a patient with Juvenile Idiopathic Arthritis (JIA) during treatment with etanercept, suggesting a possible causative role of this anti-TNF-α agent in CD occurrence.

A 17-year-old female was admitted to our department and diagnosed with CD, based on standard criteria. She had had a history of oligoarticular JIA from the age of 2 and had been previously treated with NSAIDs, methotrexate and cyclosporine. At the age of 13, treatment with etanercept and leflunomide was initiated, limiting the relapses during the last 4 years. In order to succeed efficacy for both JIA and CD, therapy with infliximab was introduced. An allergic reaction appeared and infliximab was discontinued. Treatment with adalimumab, at conventional doses, was started, with an excellent response. During a 12-month follow-up, the patient remained on adalimumab therapy, steroid-free, with clinical remission of both CD and JIA.

Etanercept is a recombinant dimer of human tumor necrosis factor (TNF) receptor proteins fused and bound to human IgG1 that acts competitively to inhibit the binding of TNF to its cell surface receptor. Numerous studies confirm the efficacy of etanercept in spondyloarthropathies and JIA [1,2], while others indicate low efficacy of etanercept in CD [3]. However, the new onsets as well as flares of inflammatory bowel disease (IBD) reported during treatment with etanercept have raised a number of questions regarding the triggering role of etanercept in gut inflammation [1-5]. Braun et al reported that patients with ankylosing spondylitis treated with etanercept had more flares and even some new onsets of IBD, as compared with those treated with infliximab and adalimumab [4]. Although there is a well-known genetic linkage between spondyloarthropathies and IBD [6], it is difficult to establish whether etanercept had an unambiguous causative role. Juvenile idiopathic arthritis, on the other hand, has no clear genetic linkage with IBD; recent reports, though, have identified the occurrence of IBD in at least 15 patients with JIA during treatment with etanercept [2,5].

A different TNF-binding pattern seems to be responsible for the low efficacy of etanercept in CD, compared to other anti-TNF agents [3]. Haraoui et al demonstrated possible pathways responsible for both its low efficacy in CD and its triggering role in new onsets of CD: etanercept dimer binds to 2 of the 3 binding sites of the TNF molecule, while infliximab fills all 3 binding sites. At the same time, etanercept soluble TNF complexes are less stable relatively to infliximab. Furthermore, infliximab binds specifically to TNF-α, whereas etanercept binds and neutralizes both TNF-α and lymphotoxin-α [1]. Etanercept, in addition, cannot bind to peripheral blood cells and lamina propria mononuclear cells derived from CD patients and cannot induce caspace-3 activation and apoptosis of inflammatory cells via direct binding to the tmTNF (membrane bound TNF), whereas infliximab and adalimumab can [1]. Infliximab and etanercept also have different effects on the cytokine production of T lymphocytes upon nonspecific stimulation [7,8], possibly inducing CD in genetically predisposed patients [1]. The binding patterns outlined above, may be responsible for the low efficacy of etanercept in IBD and the increased probability of IBD development in patients with JIA during treatment with etanercept. However, the exact IBD-triggering pathways warrant further research.

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References