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Covering the Cover Editor of this Issue

COVERING THE COVER

Effects of preoperative endoscopic pneumatic balloon dilatation on postoperative achalasia symptoms after Heller esophageal myotomy plus Dor fundoplication

Achalasia is a motor disorder characterized by a decrease or absent esophageal body peristalsis and inability to sufficiently relax the lower esophageal sphincter (LES). Currently, laparoscopic Heller myotomy (LHM) and endoscopic pneumatic balloon dilatation (PBD) are the standard of care in the treatment of achalasia. In this retrospective study, authors tested the possible effect of having prior endoscopic balloon dilation on the effectiveness of HM (laparoscopic or open) plus Dor fundoplication (DF) procedure.

The study retrospectively enrolled 65 patients with achalasia who had undergone HM+DF between 2008 and 2016. The degree of symptoms, including weight loss, dysphagia, retrosternal pain, and regurgitation, was graded pre- and postoperatively using the Eckardt score. Patients were classified as having either classical or vigorous achalasia based on conventional manometry. Patients' demographics, laboratory values, clinical presentation, radiological imaging findings, surgical treatment, perioperative complications, pathological features, postoperative course, and long-term survival were collected and analyzed.

The distribution of patients according to sex was almost equal (49.2% male vs. 50.8% female patients). The mean age of the patients was 38.5±14.2 years. Most of the patients (93.8%) had classical achalasia. Only four patients had vigorous achalasia and did not receive preoperative endoscopic PBD because of the risk of perforation. The average duration of symptoms was 6 months. The mean preoperative LES pressure was 31.4±11.9 mm Hg. Over half of the patients (69.2%) had prior PBD, and >60% of the patients had repeated PBD before surgery. None of the patients received a botox injection during PBD. Of the patients, 50 (76.9%) underwent laparoscopic surgery, whereas 15 (23.1%) underwent open HM. Esophageal mucosal perforation occurred in 3 (4.6%) patients, which was detected during the operation and treated by primary repair.

Authors found that the mean Eckardt score was significantly lower at postoperative year 1 than at preoperative period, but having PBD showed no significant difference between the Eckardt scores.

Depending on their experience, the authors conclude that HM+DF is an effective procedure in patients with achalasia as a first-line therapy who were unresponsive to repeated endoscopic PBD treatments. See page 543.

Role of screening colonoscopy for colorectal tumors in* Helicobacter pylori*-related chronic gastritis with MDM2 SNP309 G/G homozygous: A prospective cross-sectional study in Thailand

The association of *Helicobacter pylori*-related gastritis and colorectal cancer (CRC) is inconclusive. Several studies have demonstrated that there is an association of *H. pylori* infection with CRC. Several factors may play a role in *H. pylori*-associated CRC, as being infected by cytotoxin-associated gene A-positive (CagA+) strain, or not. Screening patients with *H. pylori*-positive chronic gastritis with colonoscopy is still under debate. Mouse double minute 2 (MDM2) is an oncoprotein that acts as a negative regulator inhibiting p53 tumor suppressor activity. In previous studies, it was shown that genetic polymorphism of the *MDM2* gene (SNP309 G/G genotype) is correlated with type 4 and type 5 gastric mucosal patterns. In addition, the association of the MDM2 SNP309 polymorphism with CRC risk has been reported previously. Therefore, in the present study, authors aimed to determine the role of screening colonoscopy in patients with *H. pylori*-related chronic gastritis who carried the homozygous G/G genotype of MDM2 SNP309 and to investigate the association of MDM2 SNP309 G/G homozygosity with advanced colorectal neoplasia (CRN) susceptibility in the Thai population.

The present study included 331 patients with chronic gastritis with MDM2 SNP309 G/G genotype who had undergone esophagogastroduodenoscopy and screening colonoscopy. *H. pylori* infection was diagnosed with histopathological examination and polymerase chain reaction (PCR) on biopsy samples. Advanced CRNs were defined as adenomas with >1 cm diameter, high-

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DOI: ***10.5152/tjg.2018.270818***

grade dysplasia or invasive adenocarcinomas, villous adenomas, and >3 adenomas according to the World Health Organization classification. MDM2 SNP309 genotypes were evaluated by real-time PCR.

The *H. pylori*-positive group comprised 180 (54.36%) patients. There were no significant differences in the mean age between patients with *H. pylori* (-) and (+), but there were significantly more male patients in the *H. pylori* (-) group. Patients with chronic gastritis who had *H. pylori* infection and who had MDM2 SNP309 G/G homozygosity had a higher prevalence of overall CRN (OR: 1.98, 95% CI: 1.24-2.16; p=0.01) and advanced CRN (OR: 2.09, 95% CI: 1.56-2.80; p=0.01). In multivariate analyses, *H. pylori* infection demonstrated an increased risk of overall and advanced CRN (OR: 4.24, 95% CI: 1.76-5.21; p=0.01).

Authors concluded that patients with chronic gastritis who show MDM2 SNP309 G/G homozygosity with *H. pylori* infection may have an increased risk of advanced CRN. Therefore, screening colonoscopy in these patients may aid the early diagnosis and treatment of CRC. See page 555.

Reactivation rates in patients using biological agents, with resolved HBV infection or isolated anti-HBc IgG positivity

Hepatitis B virus (HBV) infection is a global public health problem. It is estimated that there are 300 million HBV carriers in the world, of whom approximately 600,000 die annually from liver disease caused by HBV. An efficient control of HBV infections requires a concerted action of both innate and adaptive immune responses. However, the use of tumor necrosis factor (TNF)-α inhibitors is gaining popularity in many autoimmune diseases, which may cause reactivation of HBV infection in susceptible individuals.

Authors conducted a retrospective review of patients who had a serologically proven past HBV infection (anti-hepatitis B core (HBc) immunoglobulin G (IgG) positive, hepatitis B surface antigen (HBsAg) negative, and HBs antibody (anti-HBs) positive or negative), were treated with a TNF-α inhibitor or ustekinumab, and whose HBV DNA levels were measured at the beginning of the treatment and during follow-up.

Among 278 patients who received biologic treatment for various reasons, 60 patients had evidence of past HBV infection. After exclusion of patients who may cause possible errors, 29 patients remained for analysis. Three patients were given prophylaxis, and no reactivation was observed during follow-up. HBV reactivation was seen in 5 (17.2%) patients (1 had resolved HBV and 4 had isolated Hbc IgG positivity). The reactivation rate increased to 19.2% when only patients who did not receive prophylaxis were evaluated. Of these patients, 3 were using adalimumab, 1 infliximab, and 1 ustekinumab. It was controlled by antiviral therapy that was started in the early period.

Authors conclude that drugs that block TNF-α and ustekinumab cause an increase in viral replication. In the literature, the HBV reactivation rate was approximately 1% in HBsAg-negative and anti-HBC IgG-positive cases, whereas it was found to be as high as 17.2% in our study. Patients receiving the biologic agents should be evaluated for HBV serology before treatment and carefully monitored for HBV reactivation during and after treatment. See page 561.

Do bad habits bring a double constipation risk?

Constipation is a global health problem, which may be a sign of chronic diseases or cancer. Although the importance of good dietary habits, fluid intake, and regular exercise is known to avoid constipation, the association of bad habits regarding defecation, such as postponing, reluctance, or avoiding defecation anywhere but at home, with chronic constipation has not been well assessed in the literature.

In the present study, authors conducted a cross-sectional observational study in a tertiary hospital setting. A questionnaire was divided into three parts: collecting demographic data, determining the Rome III criteria for functional constipation whether it was met or not, and questioning hygiene-dietary habits that might influence the onset or persistence of constipation. Sample size analyses were conducted previously, and a minimum sample size of 378 subjects was estimated for the study.

A total of 426 subjects completed the questionnaire, and 415 were eligible for analyses. There were 119 (28.7%)

male and 296 (71.3%) female patients included in the study. The mean age of the subjects was 43.8±11.9 years. There was no difference between the sexes in terms of age frequencies. Thyroid disease was the most common comorbidity (8.7%) in the study cohort.

Overall, 100 (24.1%) subjects reported feeling constipated, and 26.5% fulfilled the Rome III criteria. The mean duration of constipation was 113±66 months. The Rome III criteria was met more often by female than by male patients (32.1% vs. 12.6%; p<0.001). The hygiene-dietary habits questionnaire revealed that females showed a significantly more irregular defecation timetable, more likely postpone defecation, less comfortable while defecating outside the home, and suffered more stress. Among independent risk factors, being female, persistently postponing defecation (OR 1.94; 95% CI 1.13-3.34), having a regular schedule (OR 0.39; 95% CI 0.23-0.67), and avoiding defecation anywhere but at home (OR 2.38; 95% CI 1.4-4.1) were estimated to be related with constipation, with binary logistic regression method. Fiber-rich diet, fluid intake, and exercise habits were not related to constipation.

Authors conclude that modification of bad habits is more related to chronic constipation and should be the first step in the management of chronic constipation. See page 580.

Can pancreatic steatosis affect the exocrine functions of the pancreas?

Pancreatic steatosis (PS) is a term generally used to define the accumulation of fat in the pancreas. Although PS can be found to be associated with certain conditions, such as cystic fibrosis, Shwachman-Diamond syndrome, diabetes, or hemochromatosis, it may also be seen in the aging process or obesity. Steatosis may cause exocrine pancreatic insufficiency (EPI) through lipotoxicity in the acinar cells, adipocyte-mediated negative paracrine effect, or direct destruction of the acinar cells. Authors aimed to investigate the possible effect of PS on EPI by checking certain biochemical parameters and fecal elastase-1 levels in a cohort with PS detected by 3 Tesla magnetic resonance imaging (MRI).

The study group included 43 subjects with PS and 48 subjects without PS. Patients with chronic pancreatitis, chronic ethanol abuse, diabetes mellitus, gastric or pancreatic surgery or inflammatory bowel disease, celiac, and pancreatic atrophy were excluded from the study. MRI scans were reviewed by radiologists for the anatomical distribution of steatosis and localization of dominant steatosis. The severity of PS was graded into three levels: score 1: 0%-33% steatosis of the whole pancreatic tissue, score 2: 34%-66% steatosis of the whole pancreatic tissue, and score 3: 67%-100% steatosis of the whole pancreatic tissue. The incidence of non-alcoholic fatty liver disease (NAFLD) in PS was also noted. Fecal elastase-1 was assessed from stool samples, and fasting plasma glucose (FPG), triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and amylase and lipase levels were measured from serum samples. Fecal elastase-1 levels <200 μg/g were defined as EPI.

There were 31 patients in the PS group and 25 subjects in the control group after applying the exclusion criteria. There were no statistically significant differences between the groups in terms of gender and mean age (p>0.05). The mean FPG, triglyceride, HDL, LDL, total cholesterol, AST, ALT, amylase, and lipase were similar (p>0.05) in both groups. The mean fecal elastase-1 level was significantly lower in the PS group than in the control group (319.76±45.7 vs. 549.31±69.4, p=0.003). The proportion of patients with EPI was significantly higher in the PS group than in the control group (35.5% vs. 12%, p=0.042). The incidence of NAFLD was not significantly different (p=0.436) among the groups.

Authors concluded that EPI can be seen in patients with PS. The severity and anatomic distribution of steatosis (corpus-head-tail) did not differ between patients with or without EPI. See page 588.

Mesenchymal stem cells prolong the survival of orthotopic liver transplants by regulating TGF-β1 expression

Liver transplantation is a breakthrough in the treatment of liver failure and hepatocellular carcinoma. Nevertheless, graft rejection is one of the most important problems in liver transplantation. Currently, immunosuppression is the only way to avoid graft rejection, but these agents may cause significant side effects and decrease the quality of life. Many trials are conducted to prevent

rejection by immunomodulation and therefore decrease the dose of immunosuppressive agents, if needed.

In the present study, authors tried to show the possible immunomodulating effect of mesenchymal stem cells (MSCs) in a rat orthotopic liver transplantation (OLT) model. Recently, it is reported that MSCs can differentiate into organ-specific cells in vivo or may show immunomodulatory effects when they were engrafted into an acute organ injury environment, with the effect of local signals and cytokines. Therefore, MSCs may have beneficial therapeutic effects for preventing rejection in liver transplantation. Transforming growth factor (TGF)-β1 is an important cytokine in the rejection process. In this experiment, authors performed OLT from male Lewis rats (donor) to male ACI rats (recipient). Authors describe a specific way of vascular anastomosis in our experiments: superior hepatic vena cava, portal vein, and hepatic inferior vena cava were anastomosed, and they did not conduct arterial reconstruction. Recipients did not receive immunosuppression and were randomly divided into four groups of MSC application to the systemic circulation after transplantation and control. Technical details are beyond the scope of this cover paper and can be found on the original paper. The reader is encouraged to criticize the experiment setting and technical details. However, the original and important finding in this experiment is that MSC-treated rats survived over a hundred days (78-116 days, mean 98±6.6 days), whereas controls rejected allografts within 14 days, and the survival times of grafting were 6.4±0.5 days. Authors conducted a series of Western blot and histopathological examination on each group to reveal the possible effect of MSCs in the regulation of TGF-β1 expression.

In conclusion, authors report that MSCs may have a promising effect on immunomodulation after OLT. See page 601.