Contents

Images of the issue

Massive bleeding from a gastric varix coil migration in a liver transplant patient

A rare case of intestinal obstruction
L. Iliescu, L. Toma, M. Grasu, V. Herlea ......................................................................................................................... 250

Editorials

Challenges in organizing a transplantation system
G. Tsoulfas, C. Svoronos ......................................................................................................................................................... 251

Red pepper: from the kitchen to the pharmacy
M. Bortolotti........................................................................................................................................................................ 253

Capsule endoscopy for colorectal cancer and polyp screening
O. Pascu, L. Ciobanu ............................................................................................................................................................. 257

Role of Helicobacter pylori infection in the thyroid diseases
G. Fiorini, A. Zullo, V. Castelli, G. Lo Re, J. Holton, D. Vaira .......................................................................................... 261

Original Papers

Risk of colorectal cancer in Crohn’s disease patients with colonic involvement and stenosing disease in a population-based cohort from Hungary

Infectious complications of TNF-α inhibitor monotherapy versus combination therapy with immunomodulators in inflammatory bowel disease: analysis of the Food and Drug Administration Adverse Event Reporting System
P. Deepak, D.J. Stobaugh, E.D. Ehrenpreis ..................................................................................................................... 269

Oral glutamine challenge improves the performance of psychometric tests for the diagnosis of minimal hepatic encephalopathy in patients with liver cirrhosis
R. Irimia, C. Stanciu, C. Cojocariu, C. Sfarti, A. Trifan ................................................................................................. 277

Transient elastography for the detection of hepatocellular carcinoma in viral C liver cirrhosis. Is there something else than increased liver stiffness?
D. Feier, M. Lupsor Platon, H. Stefanescu, R. Badea .................................................................................................... 283
Contents

(continued)

Treatment of hepatocellular carcinoma in a tertiary Romanian center. Deviations from BCLC recommendations and influence on survival rate


Dynamics of the Romanian waiting list for liver transplantation after changing organ allocation policy

L. Gheorghe, S. Iacob, R. Iacob, G. Smira, C. Pietrareanu, D. Hrehoret, V. Brasoveanu, C. Gheorghe, I. Popescu ................................................................. 299

Reviews

Aflatoxins as a cause of hepatocellular carcinoma

M.C. Kew .................................................................................................................................................................. 305

MicroRNA in colorectal cancer: new perspectives for diagnosis, prognosis and treatment


Sentinel node mapping in anal canal cancer: systematic review and meta-analysis


Case reports

An invasive extragastrointestinal stromal tumor curably resected following imatinib treatment

M. Muto, M. Fujiya, T. Okada, M. Inoue, H. Yabuki, Y. Kohgo .............................................................................. 329

Effect of infliximab induction therapy on secondary systemic amyloidosis associated with Crohn’s disease: case report and review of the literature

A. Pukitis, T. Zake, V. Groma, E. Ostrovskis, S. Skuja, J. Pokrotnieks .................................................................... 333

Premalignant lesion of heterotopic pancreas combined with gastritis cystica profunda in gastric fundus

M. S. Lee, B. S. Cho, J. S. Park, H. C. Koo, H. Y. Han, D. W. Kang ........................................................................... 337

Combined hepatocellular carcinoma - cholangiocarcinoma harboring a metastasis of colon adenocarcinoma

B. Pintea, L. Di Tommaso, A. Destro, M. Roncalli .................................................................................................. 341
Contents
(continued)

Technique / Case report

Gastric heterotopic pancreas can be identified by endoscopic direct imaging with submucosal endoscopy

H. Kobara, H. Mori, S. Fujihara, N. Nishiyama, K. Tsutsui, T. Masaki ................................................................. 345

Clinical imaging

Intracavitary applications of ultrasound contrast agents in hepatogastroenterology


Book review

WHO Classification of Tumours of the Digestive System .................................................................................................. 354

Calendar of Events .......................................................................................................................................................... 355

Letters

Non-invasive alternative methods to hepatic venous pressure gradient measurement

T. Kawada ........................................................................................................................................................................... 357

Reply

B. Procopeț, M. Tanțău, C. Bureau .................................................................................................................................... 357

Porcelain gallbladder and cancer - an association to be revised

Puia, A. Puia ....................................................................................................................................................................... 358

Celiac disease in older adults

Singh, S. Shergill, G.K. Makharia .................................................................................................................................. 359

„Standard of care” treatment for chronic viral C hepatitis in 2013 in Romania

Sporea, M. Curescu, R. Sirli ................................................................................................................................................ 360

Abdominal pain after minor trauma in a patient with Crohn’s disease

G. Maconi, M. Monteleone, F. Furfaro, C. Bezzio, M. Tonolini, G. Sampietro ............................................................. 361

Cardiac arrest after transjugular intrahepatic porto-systemic shunt creation in a 28 year-old patient with end stage liver disease secondary to cystic fibrosis

R. Miraglia, M. Piazza, K. Cortis, A. Arcadipane, A. Luca ................................................................................................. 362

Guidance for Authors ......................................................................................................................................................... 363
Risk of Colorectal Cancer in Crohn’s Disease Patients with Colonic Involvement and Stenosing Disease in a Population-based Cohort from Hungary

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ABSTRACT

Background & Aims: Since data is limited regarding the risk of colorectal cancer (CRC) in Crohn’s disease (CD) patients who present with stenosing disease in the colon, this study was undertaken to assess CRC risk in such patients, using a population-based, Veszprem province database, which includes incidental patients diagnosed between January 1, 1977 and December 31, 2011.

Methods: Data from 640 incidental CD patients were analyzed (M/F ratio: 321/319, age-at-diagnosis: 28 years (IQR: 22-38)). Both hospital and outpatient records were collected and comprehensively reviewed.

Results: CRC was diagnosed in six CD patients during a follow-up of 7759 person-years. Sixty-two patients presented with colonic/ileocolonic disease and a stenotic lesion in the colon with a follow-up of 702 person-years (median:10.5, IQR:5-16years). Colorectal cancer developed in 6.5% (equaling 0.57/100person-years), the SIR (6.53, 95%CI:2.45-17.4) was increased with four patients observed versus 0.61 expected. In a Kaplan-Meier analysis, the probability of developing CRC was 5.5% and 7.5% after 5- and 10 years, respectively, versus 0.4% in patients with other phenotypes (HR:18.8, p<0.001). A sensitivity analysis included patients with stenosing colonic lesion at diagnosis or during follow-up (n=91, follow-up:1180 person-years,median:12, IQR: 6-17years). The probability of developing CRC was 3.6% and 4.9% after 5- and 10 years, respectively.

Conclusions: The risk of CRC in CD patients presenting with or developing a stenotic lesion in the colon is high even after a short disease duration, suggesting the need for careful surveillance.

Key words: Crohn’s disease – colorectal cancer – behavior – stenosing – location.
Infectious Complications of TNF-α Inhibitor Monotherapy versus Combination Therapy with Immunomodulators in Inflammatory Bowel Disease: Analysis of the Food and Drug Administration Adverse Event Reporting System*

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ABSTRACT

Background & Aim: Incremental increase in the risk of serious infections with combinations of tumor necrosis factor-alpha (TNF-α) inhibitors and immunomodulators compared to monotherapy with these agents in inflammatory bowel disease (IBD) is unclear. Our aim was to analyze whether there is such an incremental increase in the odds of serious infections.

Methods: The FDA Adverse Event Reporting System (2003 - June 2011) was queried for ‘Primary Suspect’ reports of various infections with TNF-α inhibitors, systemic corticosteroids and immunomodulators with usage indication of IBD. Odds ratios (ORs) were calculated for baseline odds of infections as well as serious infections (requiring hospitalization and/or death) with monotherapy and combination therapy (compared to 5-Aminosalicylates) as well as incremental increase in odds for dual or triple combination therapy (compared to monotherapy or dual combination therapy respectively) using Fisher’s exact test with SPSS 20 (IBM Co. Armonk, NY, USA).

Results: TNF-α inhibitor (OR 1.95; CI, 1.06-3.59) and immunomodulator (OR 9.99; CI, 1.28-78.16) monotherapy as well as in combination augmented baseline odds of serious infection for IBD patients. No incremental increase in the odds with combination therapy was seen when an immunomodulator was added to a TNF-α inhibitor (OR 0.37; CI, 0.05-2.80) and when both were used with a systemic corticosteroid (OR 0.91; CI, 0.50-1.66). Variations in these were seen for the individual infection subtypes.

Conclusions: TNF-α inhibitor and immunomodulator monotherapy increase the baseline odds of acquiring a serious infection. Combination therapy with these drugs does not further increase the odds of serious infections compared to monotherapy.

Key words: Immunosuppressive agents / adverse effects – inflammatory bowel diseases / complications – opportunistic infections / epidemiology – antibodies, monoclonal / adverse effects – Tumor Necrosis Factoralpha / antagonists & inhibitors.
Oral Glutamine Challenge Improves the Performance of Psychometric Tests for the Diagnosis of Minimal Hepatic Encephalopathy in Patients with Liver Cirrhosis

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ABSTRACT

Background & Aims. Minimal hepatic encephalopathy is difficult to diagnose due to the lack of a gold standard test. Oral glutamine challenge has been found to increase blood ammonia in cirrhosis leading to secondary cognitive impairment. The aim of this study was to evaluate the value of oral glutamine challenge in improving the psychometric performance for the diagnosis of minimal hepatic encephalopathy, and the risk of this condition for overt hepatic encephalopathy in cirrhotic patients.

Methods. Fifty-four cirrhotics (34 males; mean age 55.2 years) and 16 healthy controls were included. Minimal hepatic encephalopathy was assessed by the psychometric hepatic encephalopathy score. Arterial ammonia concentrations and psychometric tests were evaluated 60 minutes before and after a 20 g oral glutamine load. Follow-up lasted 12 months.

Results. At baseline, 29 (53.7%) of 54 patients had minimal hepatic encephalopathy and significantly more (79.63%) post-glutamine (p<0.0001). Baseline arterial ammonia levels significantly raised post-glutamine in cirrhotics (85.2±20.8µg/dL versus 159.8±66.0µg/dL, p<0.0001), while in controls they remained unchanged (p=0.064). For the diagnosis of minimal hepatic encephalopathy, baseline arterial blood ammonia showed an area under the ROC curve of 0.54 (CI95%: 0.402-0.680, p=0.58), with no significant post-glutamine changes (0.53, CI95%: 0.389-0.667, p=0.77). Ten patients (18.51%) developed overt hepatic encephalopathy, among which 9 had minimal hepatic encephalopathy (4 at baseline, 5 post-glutamine). At multivariate analysis, MELD score (1.5187, CI95%: 1.0690-2.1574, p=0.0197) was an independent predictor of the overt hepatic encephalopathy.

Conclusions. In cirrhotic patients, an oral glutamine load improves the psychometric diagnostic performance for minimal hepatic encephalopathy. MELD score has been independently related to overt hepatic encephalopathy.

Key words: minimal hepatic encephalopathy – oral glutamine challenge – psychometric test – ammonia.
Transient Elastography for the Detection of Hepatocellular Carcinoma in Viral C Liver Cirrhosis. Is there something else than Increased Liver Stiffness?

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ABSTRACT

Background & Aims: Liver stiffness (LS) is increased in liver cirrhosis, higher values being associated with complications, among them the development of hepatocellular carcinoma (HCC). However, LS values alone cannot accurately differentiate patients with HCC. Therefore, our aim was to study the performance of LS measurement data and common biomarkers for the detection of HCC in HCV related liver cirrhosis.

Methods: We performed a case matching study comparing HCV cirrhotic patients with and without HCC (72 in each group) that were identical in terms of sex, age, BMI and duration of HCV infection. All patients underwent LS measurement, endoscopy, liver imaging and liver function tests. A multiple regression analysis was performed and a HCC detection model was calculated, which was further validated in another group of 40 HCV infected cirrhotics, of whom 52% had HCC.

Results: In the HCC group, LS was significantly higher (42 vs 27 kPa, p<0.0001). In the multivariate analysis higher values of LS, alanine-aminotransferase (ALAT), alpha-fetoprotein (AFP) and interquartile range (IQR) of LS measurements were independently associated with the presence of HCC (p<0.0001 for all parameters; Odds Ratios of 8.27, 1.01, 1.04 and 1.16, respectively). The detection model combining the four variables showed a good diagnostic performance in both training and validation groups, with AUROCs of 0.86 and 0.8, respectively. All variables were also positively correlated with tumor size.

Conclusion: In HCV related cirrhosis, HCC is associated with increased LS and IQR values and high ALAT and AFP levels. By combining these four parameters into a regression model, liver cancer may be noninvasively predicted with good accuracy.

Key words: liver cirrhosis – hepatocellular carcinoma – liver stiffness – interquartile range – detection model.
Treatemnt of Hepatocellular Carcinoma in a Tertiary Romanian Center. Deviations from BCLC Recommendations and Influence on Survival Rate

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ABSTRACT

Background & Aim. The Barcelona-Clinic Liver Cancer (BCLC) staging system is based on the results obtained in the setting of several cohort studies and randomized clinical trials. We have evaluated the applicability of the BCLC staging system and the effect of treatment allocation according to BCLC on the survival rate and prognosis in patients with hepatocellular carcinoma (HCC) in a tertiary center.

Methods. Treatment indications for 473 patients referred to our center with the diagnosis of HCC were retrospectively analyzed. Patients were split in three groups: a group treated according to BCLC recommendation, an overtreated group and an undertreated group. The survival rate was calculated using the Kaplan Meier method and compared using the log-rank test.

Results. Patients distribution according to BCLC staging system was: 17 patients (3.6%) in very early stage (O), 161 (34.0%) in early (A), 140 (29.6%) in intermediate (B), 82 (17.3%) in advanced (C) and 73 patients (15.4%) in terminal stage (D). Only 275 patients (58.1%) from stage 0, A-D were treated according to BCLC. The mean survival rate in stage 0 and A was higher for patients receiving curative treatment in comparison with undertreated patients (41 vs 28 months, p< 0.05). Overtreated patients in stage B or C had a better survival than patients treated according to BCLC (25 months vs 21 months, p=0.973, and 28 months vs 4 months, p=0.308, respectively), without statistical significance. Patients in stage B and C treated according to BCLC recommendations had a better survival than those undertreated (21 months vs 13 months, p=0.002, and 4 vs 3 months, p=0.036, respectively).

Conclusions. Deviations from BCLC recommendations occur in 40% of patients with HCC. Undertreatment results in a decreased survival of patients diagnosed with HCC. Overtreated BCLC-B and C patients have an increased survival in comparison with those treated with standard therapy.

Key words: hepatocellular carcinoma (HCC) - Barcelona Clinic Liver Cancer (BCLC) - HCC treatment - survival rate - prognosis.
Dynamics of the Romanian Waiting List for Liver Transplantation after Changing Organ Allocation Policy

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ABSTRACT

Aim: The aim of the present study was to characterize the dynamics of the Romanian waiting list (WL) for liver transplantation (LT) over two periods: 2004-2007 vs. 2008-2011.

Methods: 1,085 patients listed for LT during the time period 2004-2011 were included in our analysis.

Results: Death on the WL was significantly higher before 2008 (37% vs. 26.4%, p=0.0001) and risk of dying while on WL was 60% higher. Waiting time on the WL was 75% longer and time until LT was 102% longer before 2008 compared to the second time period (p=0.0001). After 2008, 62.3% of patients were listed for LT with Child Pugh class C compared to 22.1% before 2008 (p<0.0001).

Conclusion: A significant reduction of mortality has been registered on the Romanian WL for LT after 2008, despite the increased severity of liver disease in patients listed for LT.

Key words: waiting list - liver transplantation - mortality.
Aflatoxins as a Cause of Hepatocellular Carcinoma

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ABSTRACT
Aflatoxins, metabolites of the fungi Aspergillus flavus and Aspergillus parasiticus, are frequent contaminants of a number of staple foods, particularly maize and ground nuts, in subsistence farming communities in tropical and sub-tropical climates in sub-Saharan Africa, Eastern Asia and parts of South America. Contamination of foods occurs during growth and as a result of storage in deficient or inappropriate facilities. These toxins pose serious public health hazards, including the causation of hepatocellular carcinoma by aflatoxin B1. Exposure begins in utero and is life-long. The innocuous parent molecule of the fungus is converted by members of the cytochrome p450 family into mutagenic and carcinogenic intermediates. Aflatoxin B1 is converted into aflatoxin B1-8,9 exo-epoxide, which is in turn converted into 8,9-dihydroxy-8-(N7) guanyl-9-hydroxy aflatoxin B1 adduct. This adduct is metabolized into aflatoxin B1 formaminopyrimidine adduct. These adducts are mutagenic and carcinogenic. In addition, an arginine to serine mutation at codon 249 of the p53 tumor suppressor gene is produced, abrogating the function of the tumor suppressor gene, and contributing to hepatocarcinogenesis. Aflatoxin B1 acts synergistically with hepatitis B virus in causing hepatocellular carcinoma. A number of interactions between the two carcinogens may be responsible for this action, including integration of hepatitis B virus x gene and its consequences, as well as interference with nucleotide excision repair, activation of p21waf1/cip1, generation of DNA mutations, and altered methylation of genes. But much remains to be learnt about the precise pathogenetic mechanisms responsible for aflatoxin B1-induced hepatocellular carcinoma as well as the interaction between the toxin and hepatitis B virus in causing the tumor.

Key words: aflatoxins - hepatocellular carcinoma - sub-Saharan Africa - Eastern Asia - South America - staple foods - contaminant.
MicroRNA in Colorectal Cancer: New Perspectives for Diagnosis, Prognosis and Treatment

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ABSTRACT
Colorectal cancer (CRC) is a common condition and represents a lethal disease, following a sequential progression from adenoma to carcinoma. Interfering with such natural history of CRC offers clues to prevention and cure, but current screening methods for CRC are still limited by unsatisfactory sensitivity and specificity. Novel diagnostic, prognostic tools are therefore being actively investigated for CRC. The discovery of microRNAs (miRNAs) has led to active research focusing on their role in cancer and several crucial pathways involving angiogenesis, cancer-stem-cell biology, epithelial–mesenchymal transition, formation of metastasis, and drug resistance. MiRNAs might soon represent novel prognostic and diagnostic tools in patients at high risk of CRC or being diagnosed with CRC. MiRNA might prove useful also as therapeutic tools, since dysregulation of miRNAs in cancer cells results in higher levels of messenger RNA (mRNA) specific to tumor promoter genes or tumor suppressor genes. Thus, novel anticancer therapies might originate from manipulation of oncogenic or tumor suppressor miRNAs in CRC. In this review, the innovative aspects of miRNA are discussed, with respect to biogenesis, their role in CRC, and their potential use as biomarkers. Before miRNAs can become available in the clinical setting, however, a number of large prospective studies are still required.

Key words: microRNA - gene - colorectal cancer.
Sentinel Node Mapping in Anal Canal Cancer: Systematic Review and Meta-Analysis

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ABSTRACT

Background & Aims: The pathological condition of inguinal lymph nodes is an independent prognostic factor in predicting tumor recurrence and overall survival in anal canal cancer. Sentinel node mapping is a non-invasive method for the detection of inguinal lymph node involvement in anal cancer. In the current study, we conducted a comprehensive search of literature in this regard and then interpreted the final results in a systematic review and meta-analysis format.

Methods: Medline, SCOPUS, and ISI Web of Knowledge were searched with the following search terms: (anal OR anus) AND sentinel. Outcomes of interest were inguinal detection rate and inguinal recurrence in patients receiving inguinal sparing radiotherapy due to pathologically negative inguinal sentinel nodes (false negative cases).

Results: Overall 16 studies (323 patients) were included in the meta-analysis. Pooled inguinal detection rate was 86.2%: 73.4-93.4%; for studies using both blue dye and radiotracer it was 90.1% [78.7-95.8] and for studies using radiotracer alone it was 72.4% [46.3-88.9]. Pooled sensitivity was 90% [79-97%].

Conclusions: Sentinel node biopsy is a promising method for inguinal lymph node staging in anal cancer. Combined blue dye and radiotracer technique can maximize the inguinal detection rate. Location of the tumor is highly associated with the detection of inguinal sentinel nodes. Despite fairly high pooled sensitivity, no definite conclusion can be made regarding false negative rate of this technique due to low sample size and sub-optimal quality of the included studies. Large multicenter studies with long and consistent follow up are needed to definitely validate this technique in the future.

Key words: anal cancer – sentinel node – inguinal – systematic review – meta-analysis.
An Invasive Extragastrintestinal Stromal Tumor Curably Resected Following Imatinib Treatment

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ABSTRACT
Extragastrointestinal stromal tumors (EGISTs) are rare tumors located outside the gastrointestinal tract. While curable resection is accepted as a noninvasive EGIST treatment, the therapeutic strategy for invasive EGISTs has not yet been established. The present report is the first to show a case of invasive EGIST completely resected after downsizing the tumor with imatinib treatment. A 69-year-old female had multiple masses adjacent to the stomach and ileocecum. The primary lesion measured 18 cm in size and had invaded the stomach, pancreas and liver. The histological findings of fine-needle aspiration samples revealed a proliferation of dysplastic spindle cells that exhibited immunoreactivity for anti-c-kit antibodies. The masses were therefore diagnosed as multiple GISTs with invasion to other organs, with origin difficult to determine at the time. Nineteen months after the imatinib treatment, the tumors were downsized and distinct from the stomach, pancreas and liver. Accordingly, the tumors were regarded to be EGISTs derived from the mesentery. Because they slightly regressed 26 months after treatment, surgery was applied to remove the EGISTs. The intraoperative findings showed no invasive signs, and the tumors were completely removed. The histological findings revealed the presence of dysplastic and c-kit-positive spindle cells in the tumor with an MIB-1 index of more than 5%, resulting in a final diagnosis of high-risk EGIST derived from the mesentery. No recurrence was detected for 16 months after resection.

In conclusion, preoperative treatment with imatinib followed by curable resection is a feasible option to cure invasive EGISTs. Key words: extragastrointestinal stromal tumor – imatinib – surgery – pre-operative chemotherapy – conversion chemotherapy.
Effect of Infliximab Induction Therapy on Secondary Systemic Amyloidosis Associated with Crohn’s Disease: Case Report and Review of the Literature

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ABSTRACT
Secondary systemic (AA) amyloidosis is reported as a serious complication that occurs in long-standing Crohn’s disease (CD), with an incidence of 0.3–10.9%. Various therapeutic approaches using medicines and elemental diet have been recommended, but still there are no established standards of treatment for secondary systemic amyloidosis in CD. Only a few studies have shown the role of TNFα inhibitors in the treatment of AA amyloidosis over a long term period. We report the case of a 24-year-old male with CD complicated by AA amyloidosis with renal and gastrointestinal tract involvement treated with infliximab as induction therapy. Intestinal AA amyloidosis progression occurred at the same time with the development of CD as an early complication, whereas duration of CD prior to the diagnosis of renal AA amyloidosis was 6 years. Infliximab therapy (3 infusions) caused a significant decrease of serum amyloid A protein (by 97.9%), C-reactive protein (by 70%), improvement of disease activity index, and CD caused clinical symptoms. At the same time gradual progression of the renal damage (reduction of renal function) was not affected by the treatment. Direct efficacy of infliximab infusions on serum amyloid protein level may support the hypothesis of TNFα induced reduction on the progression of AA amyloidosis described in previous study reports. Targeted histological analysis of tissue biopsy is crucial to clarify the presence of AA amyloidosis in CD induced multiorgan damage cases. Key words: Crohn’s disease - secondary systemic amyloidosis - infliximab.
Premalignant Lesion of Heterotopic Pancreas Combined with Gastritis Cystica Profunda in Gastric Fundus

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ABSTRACT

Heterotopic pancreas, also known as ectopic pancreas, is found mainly in the stomach, duodenum, or jejunum. Pancreatic intraepithelial neoplasia (PanIN) is the non-invasive precursor of pancreatic cancer and gastritis cystica profunda (GCP) is considered a precursor of gastric cancer. As with most putative cancer precursor lesions, the diagnosis and treatment of these lesions has been controversial. A patient with no history of gastric surgery visited our institution for a regular evaluation. Endoscopy showed a 2 x 2 cm sized, protruding mass lesion with overlying normal mucosa on the fundus of stomach. Endoscopic ultrasound (EUS) and computed tomography (CT) led to the possible diagnosis of a gastrointestinal stromal tumor with cystic change. Laparoscopic gastric wedge resection was performed with intra-operative endoscopic guidance. Microscopic examination identified the mass as pancreatic tissue. Furthermore, it demonstrated PanIN, grade 3 (PanIN-3) mixed pancreatobiliary and intestinal type, arising in the heterotopic pancreas and associated with GCP. This report describes a rare case of a PanIN lesion combined with GCP as precursors of precancerous lesions in heterotopic pancreas and stomach.

Key words: heterotopic pancreas - gastritis cystica profunda - PanIN - stomach.
COMBINED HEPATOCELLULAR CARCINOMA - CHOLANGIOCARCINOMA

HARBORING A METASTASIS OF COLON ADENOCARCINOMA

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ABSTRACT

Combined hepatocellular carcinoma-cholangiocarcinoma (cHCC-CC) represents a rare form of primary hepatic neoplasia. We report an unusual case of tumor-to-tumor metastasis: a cHCC-CC harboring a metastasis of colon adenocarcinoma developed in a 59 year old patient with alcohol-related liver cirrhosis. To the best of our knowledge, this is the first case of such a simultaneous occurrence.

Key words: hepatocellular carcinoma - cholangiocarcinoma - combined hepatocellular carcinomacholangiocarcinoma - liver metastasis
TECHNIQUE / CASE REPORT

Gastric Heterotopic Pancreas Can Be Identified by Endoscopic Direct Imaging with Submucosal Endoscopy

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ABSTRACT

Heterotopic pancreas (HP) is pancreatic tissue found outside the usual anatomical location of the pancreas, typically in the upper gastrointestinal tract. Asymptomatic HP is considered a benign submucosal tumor (SMT) that can be followed without intervention. However, invasive surgery or endoscopic resection is often inappropriately applied in cases of HP due to the difficulty of preoperative diagnosis by endoscopic ultrasonography (EUS) and tissue sampling error. Therefore, it is very important to distinguish HP from neoplastic SMTs, such as gastrointestinal stromal tumor (GIST), preoperatively. Herein, we describe two asymptomatic gastric HP cases that were distinguished by endoscopic direct imaging (EDI) on submucosal endoscopy with a mucosal flap method (SEMF). In the two patients, EUS-guided fine needle aspiration (FNA) biopsy failed to accurately diagnose two SMTs, consistent with the suspicion of a GIST on EUS. Accordingly, we attempted to perform bloc biopsy using SEMF as a novel method for obtaining tissue samples for two indefinite SMTs. Direct endoscopic imaging via a dissected submucosal tunnel revealed a yellowish, multi-nodular mass identified as pancreatic tissue. Histopathology of the bloc biopsy confirmed the diagnosis of HP. Our findings indicate that the characteristic EDI findings of gastric HP may distinguish these lesions from neoplastic SMTs. Additional evaluations of this approach are warranted.

Key words: heterotopic pancreas – submucosal tumor – diagnostic techniques – endoscopic imaging – submucosal endoscopy.
Intracavitary Applications of Ultrasound Contrast Agents in Hepatogastroenterology

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ABSTRACT
The era of the real time low mechanical index (MI) contrast enhanced ultrasound (CEUS) began in 2004. Since then, CEUS with second generation contrast agents like SonoVue has been able to offer a new clinical utility both in diagnosis and in interventional therapies. Intracavitary administration of SonoVue is an off-label, extravascular application of CEUS. There are two distinct applications in gastroenterology that are currently emerging: contrast agent injection into physiological cavities and injection into non-physiological cavities and fistulas. Numerous reports on the extravascular or intracavitary administration of SonoVue have been published and the results are positive, even though larger prospective studies are still lacking.

Key words: ultrasound contrast agents - intracavitary applications - low mechanical index (MI) - SonoVue.