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ORIGINAL PAPER

A Single Biopsy is Valid for Genetic Diagnosis of Eosinophilic Esophagitis Regardless of Tissue Preservation or Location in the Esophagus

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ABSTRACT

Background & Aims: A new gene expression profile test may distinguish eosinophilic esophagitis (EoE) and gastroesophageal reflux disease (GERD), but the optimal tissue preparation and biopsy location are unknown. We aimed to determine if formalin-fixed paraffin-embedded (FFPE) and RNA-later (RNAL) preserved specimens from newly diagnosed EoE patients have equivalent gene expression scores and whether scores vary by esophageal biopsy location.

Methods: We analyzed prospectively collected and banked esophageal biopsies from EoE patients and GERD controls. Paired FFPE and RNAL samples from the distal, mid, and proximal esophagus were used. RNA was extracted, and gene expression for a previously constructed 96 gene panel was quantified with a summary expression score. Scores were compared between EoE and GERD patients, between FFPE and RNAL samples, and between the different esophageal locations.

Results: A total of 72 samples, representing paired FFPE and RNAL specimens from 9 EoE cases and 3 GERD controls, were analyzed. Overall median gene expression scores were similar between FFPE and RNAL (238 vs 227; $p=0.64$), correlation was excellent between FFPE and RNAL (Spearman's rho=0.90; $p<0.001$), and there were no differences by biopsy level. Median gene scores distinguished EoE from controls (134 vs 402; $p=0.02$), and overall agreement between preservation methods and EoE case status was perfect (kappa=1.0; $p<0.001$).

Conclusions: Gene expression scores were equivalent in FFPE and RNAL, and were also similar across three esophageal locations. This implies that a single biopsy in either FFPE or RNAL from anywhere in the esophagus may have the potential for genetic diagnosis of EoE.

Coping Strategies and Irrational Beliefs as Mediators of the Health-Related Quality of Life Impairments in Irritable Bowel Syndrome

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ABSTRACT

Background & Aims: Irritable bowel syndrome (IBS) is a chronic and disabling gastrointestinal disorder. Although considerable research has underlined the influence of coping mechanisms as the determinants of the quality of life (QOL), only limited data are available regarding the specific coping mechanisms used by IBS patients to manage illness in daily life. Irrational cognitions are known to emerge in stressful situations such as chronic diseases, and it has been proposed to have implications in the QOL. The aim of this study was to explore the relationship between coping styles and irrational beliefs in predicting the effects of IBS symptoms on the health-related QOL (HRQOL).

Methods: A cross-sectional study was performed at two tertiary gastroenterology centers. A sample of 70 consecutive IBS patients and 55 healthy controls was studied. All participants completed the Brief Cope Inventory, the Dysfunctional Attitudes Scale, the Short-Form Health Survey and a demographic questionnaire.

Results: All the HRQOL scores of the group with IBS were significantly lower than the HRQOL scores of the healthy group [Pillai's trace $V = 0.404$, $F(8, 116) = 9.833$, $p < 0.001$]. Irritable bowel syndrome patients used more problem-focused coping and avoidant-oriented coping than healthy subjects. The impact of IBS symptoms on HRQOL distress is mediated by irrational beliefs and avoidant oriented coping.

Conclusions: Our findings highlight the role of irrational cognition and coping mechanisms in patients with IBS. The results underline the importance of the evaluation of psychological aspects of IBS with the possibility of having more tailored treatments for these patients.

Does Infliximab Short Infusion have a Beneficial Impact on the Quality of Life in Patients with Inflammatory Bowel Diseases? A Single Centre Prospective Evaluation

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ABSTRACT

Background & Aims: Infliximab (IFX) is an anti-tumor necrosis factor alpha agent used in inflammatory bowel diseases (IBD) therapy. Usually, it is administered over a 2-hour intravenous infusion. However, shortening the infusion duration to 1 hour has proved to be feasible and safe. In the present study we evaluated whether shortening the IFX infusion could affect the patients quality of life (QoL) compared to the standard protocol.

Methods: Subjects affected by IBD receiving IFX were prospectively recruited. The main criterion to shorten the infusion was the absence of IFX-related adverse reactions during the previous three 2-h infusions. For each patient, demographic, clinical and anthropometric data were collected. A questionnaire investigating their overall/job/social/sexual QoL was administered. Ordinal regression was performed with odds ratios (OR) for significant independent variables.

Results: Eighty-one patients were included (46 with ulcerative colitis - UC, 35 with Crohn's disease - CD). Sixteen received the 2-h infusion due to previous adverse reactions, and the remaining 65 underwent the 1-h schedule. Shortening the infusion to 1 hour determined a better QoL (OR=0.626). However, the QoL was negatively influenced by age (OR=1.023), female sex (OR=2.04) and severe disease activity (OR=7.242). One-hour IFX infusion induced a better outcome on work (OR=0.588) and social (OR=0.643) QoL. Long-standing disease was correlated with a slightly better sexual QoL (OR=0.93). Conversely, older age (OR=1.046), severe clinical score (OR=15.579), use of other immunomodulators (OR=3.693) and perianal CD (OR=3.265) were related to an unsatisfactory sexual life. The total number of infusions (OR=0.891), proctitis (OR=0.062) or pancolitis (OR=0.1) minimized the perception of infusion-related side effects.

Conclusion: The 1-h short infusion improves overall, social and job QoL, so that, when indicated, it should be recommended.

Opportunistic Colorectal Cancer Screening using Colonoscopy. Comparative Results between two Historical Cohorts in Bucharest, Romania

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ABSTRACT

Background & Aims: Even though Romania has one of the highest incidence and mortality in colorectal cancer (CRC) in Europe, there is currently no organized screening program. We aimed to assess the results of our opportunistic CRC screening using colonoscopy.

Methods: A single center retrospective study to include all opportunistic screening colonoscopies performed in two 18 month periods (2007-2008 and 2012-2013) was designed. All asymptomatic individuals without a personal or family history of adenoma or CRC and with complete colonoscopy performed in these two time periods were included.

Results: We included 1,807 individuals, 882 in the first period, 925 in the second period. There were 389 individuals aged below 50, 1,351 between 50 and 75 and 67 older than 75 years. There were 956 women (52.9%), with a mean age of 58.5 (median 59, range 23-97). The detection rates were 12.6% for adenomas (6.1% for advanced adenoma) and 3.4% for adenocarcinoma. Adenoma incidence (4.9% in subjects under 50, 14.7% in those aged 50 to 75, and 16.4% in those older than 75, $p<0.0001$) and size (6.3mm in subjects younger than 50, 9.2mm in those 50 to 75 and 10.8mm in those older than 75, $p=0.015$) significantly increased with age. Adenoma incidence increased in the second period (14.8% vs. 10.3%, $p=0.005$), while adenoma size decreased in the second period (8.4mm vs. 10mm, $p=0.006$). There were no procedure related complications.

Conclusions: The neoplasia detection rate was 16% (12.6% adenoma, 3.4% adenocarcinoma). Adenoma incidence and size increased with age in both cohorts. In the second screening period significantly more and smaller adenomas were detected.

Early Achievable Severity (EASY) Index for Simple and Accurate Expedite Risk Stratification in Acute Pancreatitis

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ABSTRACT

Background: Acute pancreatitis (AP) is one of the most common diseases of the gastrointestinal tract associated with significant morbidity and mortality. The assessment of severity is crucial in the management of the disease. Current methods of risk stratification in AP have a limited value, as they provide little additional information thus delaying appropriate patient care. Early recognition of severe disease may prevent serious adverse events and improve patient management as well as overall clinical outcome.

Methods/Design: The EASY trial is an observational, multicenter, prospective cohort study for establishing a simple, easy and accurate clinical scoring system for early prognostication of AP. Evaluation of simple attainable potential prognostic parameters obtained at admission (or not later than 6-12 hours afterwards) from patients diagnosed with AP will be performed to assess their potential correlation with the disease severity. The selected parameters that show the strongest correlation with severe disease course will be further utilized as potential early severity prognostic markers for prospective new patient stratification. Comparison of patients' clinical course with the obtained results of early risk stratification may validate the utilized parameters as prognostic markers. The trial has been (i) discussed and (ii) accepted in a distinguished international scientific meeting, (ii) receiving the relevant ethical approval (TÜKEB: 30595-1/2014/EKU), (ii) registered at the ISRCTN registry which is a primary clinical trial registry recognized by WHO (Trial registration number: ISRCTN10525246).

Conclusion: The EASY trial is designed to develop a simple and accurate clinical scoring system that can stratify patients with AP during the first 6-12 hours of hospitalization according to their risk for severe disease course.

Coagulation Parameters in Wilson Disease

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ABSTRACT

Background & Aims: Wilson disease (WD) is an autosomal recessive disorder of copper metabolism. Alterations of copper metabolism have been associated with changes in coagulation factors. The aim of the present study was the analysis of coagulation factors in WD patients.

Methods: 100 patients attending a tertiary WD outpatient clinic were analyzed in a prospective cross sectional cohort study. Out of peripheral venous blood samples coagulation factors were assessed including: full blood count, INR, partial thromboplastin time (PTT), clotting factors II, V, VII, VIII, IX, X, XI, XII, XIII, von Willebrand factor/-antigen, fibrinogen, antithrombin III, protein S, protein C, activated protein C (APC) resistance. Subgroup analyses of the blood tests were performed for sex, initial clinical presentation, WD treatment and liver function.

Results: Subgroup analysis by liver function showed decreased levels of factors II, V, VII and X. Subgroup analysis by gender or clinical course of the disease did not reveal significant coagulation changes. In patients treated with trientine significantly decreased levels of factors II, VII and antithrombin III and increased von Willebrand factor/-antigen levels were detected. Factor VIII levels were significantly reduced in patients receiving zinc.

Conclusion: Although significant differences of some coagulation parameters in subgroup analysis were found, no clinically relevant alterations of the coagulation system in WD patients could be detected.

Efficacy of Interferon A-2b Monotherapy in B-Thalassemics with Chronic Hepatitis C

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ABSTRACT

Background & Aims: Monotherapy with standard or pegylated interferon (PegIFN) remains the first-line treatment for HCV infection in patients with thalassemia major (βTM), although its long-term impact is still unknown. We aimed to assess the efficacy of IFN-a2b/PegIFN-a2b (one or multiple treatment sessions) and the predictors for sustained virological response (SVR) in HCV-infected βTM patients.

Methods: Between 11/1992 and 12/2013 [median follow-up: 165.5 months (8-237)], 48 βTM HCV-infected patients [19 males, median age: 22 years (12-45)], received IFN-a2b (n=34) or PegIFN-a2b (n=14). Twenty-three patients (47.9%) had a previous splenectomy; 13/40 (32.5%) patients had Ishak stage ≥4 and 21/40 (52.5%) had siderosis grade 3-4. HCV-genotype was available in 36 patients (genotype 1: 47.2%, 2: 5.6%, 3: 25%, and 4: 22%). IL28B genotype was determined in 37 patients by means of in-house real-time PCR (CC: 27%, CT: 62.2%, TT: 10.8%).

Results: Totally, 15/48 (31.3%) achieved SVR following the first treatment and 18/48 (37.5%) after multiple courses. Splenectomy ($p=0.01$) and fibrosis grade ≥4 ($p<0.05$) were negative predictors for SVR (first course), whereas splenectomy ($p<0.05$) and age >18 ($p<0.02$) for SVR after multiple courses. In HCV-genotype 1/4 (n=25), none of the patients with CT or TT IL28B genotype achieved SVR compared to 50% of the CC patients ($p=0.004$).

Conclusions: Interferon is an effective therapeutic option in HCV-infected βTM patients. IL28B genotype was a strong predictor for SVR, together with splenectomy, age and fibrosis.

Non-Invasive Distinction of Non-Alcoholic Fatty Liver Disease using Urinary Volatile Organic Compound Analysis: Early Results

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ABSTRACT

Background & Aims: Non-Alcoholic Fatty Liver Disease (NAFLD) is the commonest cause of chronic liver disease in the western world. Current diagnostic methods including Fibroscan have limitations, thus there is a need for more robust non-invasive screening methods. The gut microbiome is altered in several gastrointestinal and hepatic disorders resulting in altered, unique gut fermentation patterns, detectable by analysis of volatile organic compounds (VOCs) in urine, breath and faeces. We performed a proof of principle pilot study to determine if progressive fatty liver disease produced an altered urinary VOC pattern; specifically NAFLD and Non-Alcoholic Steatohepatitis (NASH).

Methods: 34 patients were recruited: 8 NASH cirrhotics (NASH-C); 7 non-cirrhotic NASH; 4 NAFLD and 15 controls. Urine was collected and stored frozen. For assay, the samples were defrosted and aliquoted into vials, which were heated to 40±0.1°C and the headspace analyzed by FAIMS (Field Asymmetric Ion Mobility Spectroscopy). A previously used data processing pipeline employing a Random Forrest classification algorithm and using a 10 fold cross validation method was applied.

Results: Urinary VOC results demonstrated sensitivity of 0.58 (0.33 - 0.88), but specificity of 0.93 (0.68 – 1.00) and an Area Under Curve (AUC) 0.73 (0.55 – 0.90) to distinguish between liver disease and controls. However, NASH/NASH-C was separated from the NAFLD/controls with a sensitivity of 0.73 (0.45 - 0.92), specificity of 0.79 (0.54 - 0.94) and AUC of 0.79 (0.64 - 0.95), respectively.

Conclusions: This pilot study suggests that urinary VOCs detection may offer the potential for early non-invasive characterisation of liver disease using 'smell prints' to distinguish between NASH and NAFLD.

REVIEW

Overview of Biological Therapy in Ulcerative Colitis: Current and Future Directions

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ABSTRACT

The treatment of ulcerative colitis (UC) has changed over the last decade. It is extremely important to optimize the therapies which are available nowadays and commonly used in daily clinical practice, as well as to stimulate the search for more powerful drugs for the induction and maintenance of sustained and durable remission, thus preventing further complications. Therefore, it is mandatory to identify the patients' prognostic variables associated with an aggressive clinical course and to test the most potent therapies accordingly.

To date, the conventional therapeutic approach based on corticosteroids, salicylates (sulfasalazine, 5-aminosalicylic acid) or immunosuppressive agents is commonly used as a first step to induce and to maintain remission. However, in recent years, knowledge of new pathogenetic mechanisms of ulcerative colitis have allowed us to find new therapeutic targets leading to the development of new treatments that directly target proinflammatory mediators, such as TNF-alpha, cytokines, membrane migration agents, cellular therapies.

The aim of this review is to provide the most significant data regarding the therapeutic role of drugs in UC and to give an overview of biological and experimental drugs that will become available in the near future. In particular, we will analyse the role of these drugs in the treatment of acute flare and maintenance of UC, as well as its importance in mucosal healing and in treating patients at a high risk of relapse.

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Review of Computed Tomographic Colonography from a Surgeon's Perspective

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ABSTRACT

New research has addressed many of the early concerns of Computed Tomographic colonography (CTC) and these studies are now beginning to shape clinical practices. A review of the literature demonstrates that the sensitivity of CTC in screening for large polyps (≥ 1cm) or cancers in the large intestine is as high as that of conventional optical colonoscopy, however, the sensitivity decreases with the diameter of the polyp. Despite this, CTC is well tolerated, more acceptable to patients than optical colonoscopy and therefore may improve colorectal cancer screening compliance. This review not only describes the diagnostic accuracy and sensitivity of CTC, and the evolving role of CTC as a primary colon cancer screening option, but also the recent studies that have demonstrated the additional value of CTC utilization for practicing clinicians.

The Role of Skp2 and its Substrate CDKN1B (p27) in Colorectal Cancer

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ABSTRACT

Colorectal cancer is one of the most frequent cancers worldwide, having the fourth mortality rate among cancers in both sexes. Numerous studies are investigating the signaling pathways and different factors involved in the development and progression of colorectal cancer. It has recently been shown that the S-phase kinase-associated protein 2 (Skp2) overexpression plays an important role in the pathogenesis of colorectal cancer. We review the role of Skp2 and its ubiquitin-proteasome pathway in colorectal cancer. The F-box protein Skp2, a component of the SCF (Skp1-Cullin 1-F-box) E3 ubiquitin-ligase complex, has been shown to regulate cellular proliferation, cancer progression and metastasis by targeting several cell cycle regulators for ubiquitination and subsequent 26S proteasome degradation. The best known protein substrate of the Skp2 is the cyclin-dependent kinase inhibitor 1B (CDKN1B), also known as $p27^{Kip1}$. Overexpression of Skp2 and loss of CDKN1B (p27) was strongly associated with aggressive tumor behavior and poor clinical outcome in a variety of cancers, including colorectal cancer. An efficient interaction between Skp2 and CDKN1B (p27) requires the presence of an essential activator of the SCF-Skp2 complex, the cyclin-dependent kinase subunit 1 (Cks1) cofactor. Alterations in the Skp2, Cks1 and CDKN1B (p27) expression have major effects on colorectal carcinogenesis and may serve as an important and independent prognostic marker. Furthermore, we highlight that Skp2 may be a promising therapeutic target for colorectal cancer, and development of Skp2 inhibitors would have a great impact on colorectal cancer therapy.

CASE REPORTS

Premalignant and Malignant Lesions of the Heterotopic Pancreas in the Esophagus: a Case Report and Review of the Literature

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ABSTRACT

Heterotopic pancreas is a congenital pathology of the gastrointestinal tract, particularly rare in the esophagus. Both symptomatology and findings during preoperative examinations are non-specific and therefore do not often lead to an accurate diagnosis, which is usually revealed only by histopathological assessment of a resected specimen. We report an unusual case of a patient suffering from severe dysphagia caused by heterotopic pancreas in the distal esophagus with chronic inflammation and foci of premalignant changes. This article also reviews 14 adult cases of heterotopic pancreas in the esophagus previously reported in the literature, with the aim of determining the clinical features of this disease and possible complications including rare premalignant lesions and malignant transformation. Especially with regard to those complications, we suggest that both symptomatic and incidentally found asymptomatic lesions should be resected.

Primary Hepatic Neuroendocrine Tumor after 4 years Tumor-free Follow-up

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ABSTRACT

Background: A primary hepatic neuroendocrine tumour (PHNET) is a very rare disease. The liver represents the preferential site for neuroendocrine tumors' metastases.

Case presentation: A 45-year old Caucasian female who presented with nausea, vomiting, diarrhea, accompanied by diffuse abdominal pain was found to have on contrast-enhanced computer tomography an encapsulated, partially cystic liver mass. The patient underwent an uneventful left atypical hepatic resection. Histopatological and immunohistochemical examination revealed a slowly growing (G1) hepatic neuroendocrine tumour. Post surgery, the specific neuroendocrine markers (serum Chromogranin A and 24h urinary 5 hydroxy-indolacetic acid) were within normal range. Further functional imaging investigations were performed. No other lesions were found making probable the diagnosis of PHNET. The patient is presently after 4 years of follow-up with no local recurrence or distant metastases.

Conclusions: The diagnosis of PHNET is a medical challenge that requires a thorough longterm follow-up in order to exclude an occult primary neuroendocrine tumour.

A Case of Primary Pancreatic non-Hodgkin B-cell Lymphoma Mimicking Autoimmune Pancreatitis

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ABSTRACT

Non Hodgkin lymphoma frequently involves the gastrointestinal tract, in particular the stomach and the small bowel. Rarely, it can also be a cause of pancreatic masses. Clinical presentation is often non-specific and may overlap with other pancreatic conditions such as carcinoma, neuroendocrine tumours and autoimmune pancreatitis. We report a case of primary pancreatic lymphoma in a young woman with jaundice, fever and abdominal pain mimicking autoimmune pancreatitis. Clinical evaluation included the abdominal Computed Tomography scan, Magnetic Resonance Imaging and an upper gastrointestinal endoscopy that revealed a large duodenal mass. Endoscopic biopsies were performed and eventually histological examination was coherent with a diagnosis of primary pancreatic lymphoma.

Nephrotic Syndrome after Infliximab Treatment in a Patient with Ulcerative Colitis

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ABSTRACT

Tumor necrosis factor (TNF)-targeted therapies are increasingly used to treat a variety of inflammatory and autoimmune diseases. They are now used worldwide, and this class of medication has revolutionized the treatment of these diseases and the quality of life for patients but it also poses risk of developing various side effects including infections, exacerbation of some neurological manifestations, cutaneous lesions or induces antibody production. Renal complications are uncommon and poorly recognized. This report describes a probable case of infliximab-induced focal segmental glomerulosclerosis clinically presented as a severe nephrotic syndrome in a patient with ulcerative colitis.

Primary Peritoneal Serous Psammocarcinoma: a Case Report

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ABSTRACT

Background: Psammocarcinomas (PCas) are rare epithelial tumors, usually originating in the ovaries or the peritoneum. These tumors are morphologically characterized by extensive psammomatous calcifications, invasiveness and low-grade cytological features.

Case report: We present the case of a 54-year-old woman who was referred to our department with an umbilical tumor and increasing abdominal girth. The patient had had an umbilical hernia for more than 20 years. The CA 125 level was normal. The CT scan showed small peritoneal nodules at the level of the Douglas pouch, including the posterior wall of the uterus, and the entire colon, as well as large nodules located on the caecum and the sigmoid colon. We performed partial enterectomy, total colectomy with ileo-rectal anastomosis, omentectomy, total histerectomy and bilateral adnexectomy, pelvic peritonectomy of the Douglas pouch. Pathology findings were consistent with F.I.G.O. stage IIIC peritoneal PCa. The patient received adjuvant chemotherapy with Taxol and Carboplatin. To date, twelve months after surgery, the follow-up shows no evidence of disease.

Conclusion: Standardized treatment protocols are hindered by the rarity of the PCas. However, literature concludes that optimal debulking is mandatory, whereas the efficacy of adjuvant chemotherapy remains to be elucidated.