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Covering the Cover Editor of this Issue

COVERING THE COVER

Investigation of the JAM-A (rs790056) and LFA-1 (rs8058823) gene variants in Turkish patients with colorectal cancer

Colorectal cancer (CRC) is mainly caused by sporadic somatic mutations, while underlying germline alterations are also components of CRC pathogenesis. Although numerous hereditary conditions predisposing to CRC have been identified along with the progress in genomic medicine, there still remain great opportunities for further identification of inherited CRC susceptibilities that will allow targeted screening and treatment.

This study investigates whether polymorphisms in the lymphocyte function-associated antigen-1 (LFA-1) and junctional adhesion molecule-A (JAM-A) genes predispose individuals to CRC or promote its metastasis. LFA-1 is an integrin molecule on leukocytes, and JAM-A is its corresponding receptor harboring a binding domain. The LFA-1–JAM-A interaction has potential implications for anti-tumor immune response and progression to metastatic phase. In the study, blood samples from 82 CRC patients and 67 healthy controls were studied for polymorphisms in restrictions segments in the LFA-1 (rs8058823) and JAM-A (rs790056) genes. The JAM-A rs790056 genotype CC was found to increase the risk of CRC by three times. The GC haplotype, LFA-1 rs8058823 G with JAM-A rs790056 C, was more frequent in patients with CRC. Inversely, the AT haplotype, LFA-1 rs8058823 A with JAM-A rs790056 T, was frequent in the control group.

The study casts a new light on the potential involvement of LFA-1 and JAM-A proteins in CRC pathogenesis as well as CRC susceptibility caused by their genetic variations. Genetic variants in defined tumorigenic pathways are well known. Nevertheless, we need to look for novel pathways and genes to fill-in our knowledge gaps with regards to CRC genetic architecture. See page 872.

Metabolic acidosis in critically ill patients with cirrhosis: Epidemiology and short-term mortality risk factors

Critically ill patients with cirrhosis have markedly high mortality rates reaching approximately 50% despite the considerable advances in intensive care. Complex acid-base disturbances and primarily metabolic acidosis are frequent and crucial in these patients. Regardless of the predisposing factors, clinical and prognostic implications of metabolic acidosis on critically ill patients with cirrhosis have not been well-defined.

This study aims to explore the epidemiology of critically ill patients with cirrhosis patients with metabolic acidosis and delineate the factors affecting their short-term mortality. The study population consisted of 975 patients with cirrhosis admitted to the intensive care unit (ICU) in a single institution. Their demographic, clinical, laboratory, and follow-up data were collected from a public database. Totally, 52% of patients with cirrhosis had metabolic acidosis when admitted to the ICU. Demographic characteristics were similar between the acidotic and non-acidotic groups. The etiology of cirrhosis was also similar except the alcoholic liver disease being more common in acidotic patients. The clinical courses of acidotic patients were more aggressive with more frequent infections, hepatorenal syndrome, hepatic encephalopathy, circulatory dysfunction, and acute/chronic liver failure. Acidotic patients were also found to have an approximately two-fold mortality rate during the first 7, 14, and 28 days when compared to the non-acidotic counterparts ($p<0.001$ for each). The risk factors for the mortality of acidotic patients were found to be hyperbilirubinemia, hyponatremia, a higher international normalized ratio, lower pH, and hyperlactatemia. The authors evaluated the feasibility of substituting serum creatinine in the model for end-stage liver disease (MELD) score with serum lactate to create an alternative model for the prediction of short-term mortality. Derived MELD-MA score was found to better predict the 7-day, 28-day, and in-hospital mortality rates for acidotic and non-acidotic patients with cirrhosis (AUC MELD-MA: 0.79 vs MELD: 0.70 for the 28-day mortality).

This is a study that specifically addresses the characteristics of metabolic acidosis in critically ill patients with cirrhosis. The results underscore that acidosis is a crucial metabolic derangement that deserves the utmost attention and care. Furthermore, metabolic acidosis is a red flag for short-term mortality of critically ill patients with cirrhosis, and it is of paramount importance to guide the medical treatment and consideration of liver transplantation. See page 883.

Growing burden of non-alcoholic fatty liver disease in Turkey: A single-center experience

Non-alcoholic fatty liver disease (NAFLD) affects one-fourth of the world's population and is yet to be the leading cause of liver diseases. Epidemiologic and clinical studies demonstrated that the attributes of NAFLD show a marked variation across different populations.

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The characteristics of NAFLD need to be better understood to improve screening, diagnosis, and management strategies.

Published in this issue is the characterization of an established NAFLD cohort in Turkey that stands-out as a high-risk population with prevalent metabolic syndrome. The study retrospectively reported patients with biopsy-proven NAFLD and nonalcoholic steatohepatitis (NASH) over 4 years in a tertiary referral center. The center performed liver biopsies in cases of unexplained hepatosteatosis along with biochemical or imaging abnormalities and high liver stiffness measurements in some cases, but only patients with NAFL or NASH were included in the cohort. The cohort included 468 adult, middle-aged, patients (median age, 47; range, 18–71) with near-equal gender distribution. Patients were mostly overweight or obese, i.e., 61.0% and 32.8% of them, respectively, and 63% met the metabolic syndrome criteria. There was a high comorbidity prevalence with more than one-third having hypertension and type 2 diabetes mellitus. Histology was interpreted using the NAFLD Activity Score (NAS) and the Steatosis, Activity, Fibrosis (SAF) algorithms, yielding a high prevalence (90%) of NASH in the cohort. The patients with NASH were found to have an aggressive course with 95.9% of them having severe diseases and 34.9% with significant fibrosis (≥F2).

The study uncovers the attributes of NAFLD in Turkish population revealing an aggressive clinical course and unfavorable histology. Future studies with concomitant elastography and biopsy results may provide a further insight in the non-invasive prognostic assessment of NAFLD. See page 892.

Palliative resection of the primary site in advanced gastroenteropancreatic-neuroendocrine tumors improves survival

Gastroenteropancreatic neuroendocrine tumors (GEP-NET) encompass a heterogeneous group, including cancer of the gastrointestinal tract and pancreas. Surgery is the mainstay treatment for localized diseases and curable metastases. However, surgery for incurable diseases is controversial. It can prevent complications from tumors' local invasion and endocrine functioning but with possibly increased morbidity and mortality.

This study investigates whether the palliative resection of primary tumors in patients with metastatic GEP-NET will provide a survival advantage over medical therapy alone. The study includes retrospective comparisons and multivariate analyses of 53 metastatic GEP-NET patients in a single institution over 11 years. All 53 patients were administered with long-acting somatostatin analogues, and 23 patients had also undergone palliative resection of primary tumor, while others were followed up with medical therapy only. The demographic characteristics of the two groups were similar; the resected group had a higher rate of foregut and midgut tumors. The occurrence of tumor necrosis, lymphovascular invasion, perineural invasion, chromogranin A levels, and primary tumor sizes were also similar between the groups, whereas the Ki67 index was higher in the unresected cases. The resected group experienced a dramatic overall survival benefit with a 5-year rate of 90.5% versus 45.9% in the unresected group, and a progression-free survival benefit of 60 months versus 14 months in the unresected group. The survival advantage was confirmed with the Cox regression analyses.

The treatment for GEP-NETs has witnessed a substantial progress during the last decades with biological and targeted therapies and immunotherapies emerging along with well-established surgical methods. Nevertheless, cases with advanced incurable metastatic diseases still lack a consensus regarding the choice or sequence of therapeutic options. This study demonstrates that surgery may still play a role, although randomized controlled studies are required to establish a definite role. See page 910.