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ABSTRACT N. CO02

TEV E PATOLOGIE CARDIOVASCOLARI

HEPATIC FIBROSIS AS PREDICTOR OF CANCER-ASSOCIATED THROMBOSIS IN PATIENTS WITH INTRAHEPATIC CHOLANGIOCARCINOMA.

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Background and aims: Cholangiocarcinoma (CCA) is an aggressive malignancy with a steadily increasing incidence worldwide, particularly of the intrahepatic variant (iCCA). Consequently, identifying factors that may modify the natural history of this disease has become the focus of interest in multiple studies. While the relationship between hepatic fibrosis and the development of CCA has been previously explored, the contribution of fibrosis-induced coagulation imbalance to disease progression remains unclear. This study aimed at investigating the relationship between advanced liver fibrosis, hemostasis activation, and occurrence of cancer-associated thrombosis (CAT) in patients with iCCA.

Methods: Fifty iCCA patients who underwent curative liver surgery were studied. Graft wedge biopsies served as controls (n=10). Histological evaluation was performed on archival formalin-fixed, paraffin-embedded samples using the Ishak Fibrosis Score (IFS, 0-6). Immunohistochemical staining was performed to assess tissue factor (TF), FX, fibrinogen and von Willebrand factor (vWF). Portal vein microthrombosis highlighted by fibrin deposition within the vessel lumen was quantified using Martius Scarlet Blue (MSB) staining. Immunofluorescence (IF) analysis for TF and FX was performed on patient-derived organoids (PDOs, n = 10). Extracellular vesicles (EVs) isolated from iCCA-PDO media were analyzed by flow cytometry (FACS) using Calcein-AM, EpCAM-PE, and Annexin V markers. EV-induced platelet activation was evaluated by FACS using CD41, CD62P, and Annexin V markers.

Results: iCCA patients showed a procoagulant profile with increased coagulation activation and impaired fibrinolysis compared to controls. In iCCA, patients with advanced fibrosis (IFS 4–5, n= 16) showed a more prominent expression of TF, FX, vWF, and fibrinogen than patients with fibrosis stages ≤3 (n=34). Furthermore, the degree of fibrosis correlated with either TF expression by malignant bile ducts or the number of portal vein microthrombosis ($p<0.05$). IF analysis in iCCA-PDOs confirmed a marked TF and FX upregulation, whereas EVs from iCCA-PDO media promoted platelet activation.

Conclusion: Hepatic fibrosis is closely linked to CAT occurrence in iCCA patients, and associated with increased expression of TF and platelet activation by malignant cholangiocytes. This fibrosis-coagulation interplay underscores the need to unravel the mechanisms promoting CAT development in CCA progression.

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