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Review

Early post-operative acute phase response in patients with early graft dysfunction is predictive of 6-month and 12-month mortality in liver transplant recipients

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ABSTRACT

Early allograft dysfunction (EAD) after liver transplantation is mostly a reversible event caused by factors related to ischemia/reperfusion (I/R) injury. EAD represents a hepatic injury associated with pre- and early post-transplant inflammatory cytokine responses. Aim of the present study was to evaluate the prognostic and diagnostic value of CRP in liver transplant recipients with EAD.

Materials and methods: Forty-seven patients with EAD were compared with 115 non-EAD patients. Pre- and post-transplant parameters were analyzed. EAD was defined based on postoperative liver function tests such as INR, bilirubin and liver enzymes. Statistical analysis was performed using SPSS version 18.0.

Results: Pre-transplant liver enzyme were not significantly different in the two groups. At day 3, 5 and 10 post-transplant CRP was significantly higher in patients with EAD than in non-EAD patients ($p \leqslant 0.001$ for all investigations) and remained consistently high in patients with EAD and low in non-EAD patients. EAD patients with high CRP at post-transplant days 3 and 5 showed lower survival at 6-month and 12-month post-transplant than patients with low CRP.

Conclusion: Our results indicate a prognostic and diagnostic value of CRP in patients with early graft dysfunction and predict 6-month and 12-month mortality in liver transplant recipients.

Contents

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; AUC, area under curve; CI, confidence interval; Cr, creatinine; CRP, C-reactive protein; CMV, cytomegalovirus; EAD, early allograft dysfunction; ELISA, enzyme linked immunosorbent assay; ESLD, end stage liver diseases; GGT, gamma-glutamyl transpeptidase; HBV, hepatitis B virus; HCs, healthy controls; HCV, hepatitis C virus; ICAM-1, intercellular adhesion molecule; ICU, intensive care unit; IL, interleukin; INR, international normalized ratio; IP-10, interferon gamma-induced protein 10 (CXCL10); IU, international unit; LTx, liver transplant; MCP-1, monocyte chemoattractant protein; MELD, model for end-stage liver disease; MIG, monokine induced by gamma interferon(CXCL9); NK, natural killer; NO, nitric oxide; NPV, negative predictive value; OLT, orthotopic liver transplantation; OR, odds ratios; PAI-1, plasminogen activator inhibitor; PPV, positive predictive value; ROC, receiver operating characteristic; TACE, trans catheter arterial chemoembolization; VCAM-1, vascular cell adhesion molecule.

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1. Introduction

Orthotopic liver transplantation (OLT) has become the most effective treatment strategy for acute liver failure and end stage liver diseases (ESLD) [1]. EAD is mostly a reversible graft dysfunction after the OLT procedure and presents in many transplant patients [1].

EAD was defined as the presence of one or more of the following postoperative laboratory analyses reflective to liver function: bilirubin $\geqslant$10 mg/dL on day 7, international normalized ratio $\geqslant$1.6 on day 7, and alanine or aspartate aminotransferases >2000 IU/l within the first seven days [2]. EAD is a poorly defined clinical entity that represents a condition in which the liver graft shows some degree of hepatic injury but functions sufficiently to support life. Although most authors agree that the graft function finally recovers, EAD is associated, in turn, with increased recipient susceptibility to sepsis, longer intensive care unit and hospital stay, graft loss, and greater morbidity and mortality [1]. Although inflammatory responses increased after liver transplantation the role of these parameters in EAD remains a controversial issue. Expression of inflammatory genes such as CRP and high serum or plasma levels of pro-inflammatory responses were reported previously in liver transplant recipients with EAD but they did not study association of these proinflammatory response and mortality in patients with EAD [3–6]. Early intragraft inflammatory response in liver transplant recipients is associated with chronic rejection [7]. In an experimental liver transplant study, Lautenschlager et al. showed that the early inflammatory infiltrate consisted of all major types of inflammatory leukocytes, including T lymphoblasts, B plasmablasts, and plasma cells, lymphocytes and monocytes [8]. Although some inflammatory cytokines are increased in liver donors at the time of organ procurement, there are no apparent adverse effects arising from these inflammatory responses on the function and quality of the donor liver after transplantation [9]. Aim of the present study was the evaluation of the prognostic and diagnostic value of systemic inflammatory responses in patients with EAD.

CRP is a classical acute phase reactant protein from the pentraxin family [10]. It is synthesized by hepatocytes in response to inflammation, trauma, and tissue damage, has a plasma half-life of 19 h and is catabolized by hepatocytes [10]. Even though CRP has been known for >80 years, its exact physiological role remains largely unknown [11]. Activation of complement, pro- and anti-inflammatory effects, contribution to coagulation and fibrinolysis and modulation of NO bioavailability are known physiological roles of CRP [11]. Although CRP is synthesized by hepatocytes, its serum level increased significantly in cirrhotic patients with bacterial infection [12]. Correlation of high CRP gene expression with a need for therapeutic interventions due to graft-related complications was reported by Berberat et al. [3].

Monocytes/macrophages produce neopterin in response to activated T cells [13]. Neopterin is produced from guanosine triphosphate by activated human monocytes, monocyte-derived dendritic cells and macrophages [13]. Release and production of neopterin is stimulated mainly by IFN-γ released by activated Th1-lymphocytes during a cellular immune response [13]. The association of neopterin with mortality in renal transplant recipients, patients with cardiovascular disease, malignancies and patients admitted to the ICU because of sepsis and multiorgan dysfunction have been studied previously [13].

The CD30 molecule, a member of the tumor necrosis factor/nerve growth factor receptor superfamily, is a relatively large 120-kd glycoprotein that is preferentially expressed on T cells that secrete Th2-type cytokines [14]. A soluble form of CD30 (sCD30) is released into the bloodstream after activation of CD30 T cells [14]. Interaction of CD30L with cells expressing CD30 induces signals that initiate cell proliferation or cell death [15]. Serum levels of sCD30 are increased in patients with inflammatory responses [16–19].

2. Materials and methods

2.1. Patients

The following parameters were measured in available sera of 162 cirrhotic patients (aged 51.4 ± 11.2 years, 46 female, 5 living donors) who consecutively underwent LTx. Original liver diseases were chronic viral hepatitis C and/or B in 49 patients, alcohol abuse in 52, congenital or autoimmune disease, including cryptogenic cirrhosis, biliary disease, metabolic liver disease, autoimmune hepatitis and amyloidosis in 61 patients. Preoperative and demographic parameters were analyzed including age, gender, severity of liver disease (determined by MELD score), bilirubin, INR, and albumin, viral infection status of CMV, HBV and HCV, re-transplantation, intra-operative parameters including infusions of