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ARAŞTIRMA / RESEARCH

Prognostic value of the morphological features of postperfusion liver biopsies in liver transplantation

Karaciğer naklinde postperfüzyon karaciğer biyopsilerindeki morfolojik bulguların prognostik değeri

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Abstract

Purpose: The aim of this study was to show the potential prognostic effects of morphological findings for the graft function, rejection and survival by evaluating the postperfusion liver biopsies.

Materials and Methods: Sixty six cases who underwent cadaveric liver transplantation between 2006-2010 were included. The representative slides of postperfusion subcapsular wedge biopsies were evaluated for intrasinusoidal neutrophilic infiltration, microvesicular steatosis, hepatocyte swelling, hepatocellular necrosis, endothelial swelling, bile duct epithelial changes, cholangiolar proliferation and sinusoidal congestion/hemorrhage. The associations between the histopathological features and early allograft dysfunction, mortality rate and rejection status were statistically analysed.

Results: Intrasinusoidal neutrophilic infiltration was grade 1 in 40 (60%), grade 2 in 24 (36%), and grade 3 in 2 cases (4%). The presence of grade 2-3 intrasinusoidal neutrophils was found to be significantly associated with mortality rate. The presence of sinusiodal congestion/hemorrhage was statistically related to the rejection. The presence of sinusiodal congestion/hemorrhage was significantly associated with shorter overall survival.

Conclusion: Intrasinusoidal neutrophilic infiltration is promising to be a possible histopathological predictor for mortality. In addition, the presence of sinusoidal congestion can be a candidate as a prognostic factor both for rejection and overall survival based on our study.

Keywords:. Liver transplantation, postperfusion biopsy, graft dysfunction, prognosis

Öz

Amaç: Bu çalışmada, perfüzyon sonrası karaciğer biyopsileri değerlendirilerek morfolojik bulguların greft fonksiyonu, rejeksiyon durumu ve sağkalım üzerindeki potansiyel prognostik etkilerinin gösterilmesi amaçlanmıştır.

Gereç ve Yöntem: 2006-2010 yılları arasında kadavradan karaciğer nakli yapılan 66 olgu çalışmaya dahil edildi. Postperfüzyon kama biyopsilerine ait kesitler, intrasinüzoidal nötrofilik infiltrasyon, mikroveziküler steatoz, hepatosit şişmesi, hepatoselüler nekroz, endotelyal şişme, safra kanalı epitel değişiklikleri, kolanjiyolar proliferasyon ve sinüzoidal konjesyon/hemoraji açısından değerlendirildi. Histopatolojik özellikler ile erken allogreft disfonksiyonu, mortalite oranı ve rejeksiyon durumu arasındaki ilişkiler istatistiksel olarak analiz edildi.

Bulgular: İntrasinüzoidal nötrofilik infiltrasyon 40 olguda (%60) derece 1, 24 olguda (%36) derece 2 ve 2 olguda (%4) derece 3 idi. Derece 2-3 intrasinüzoidal nötrofil varlığının mortalite oranı ile, sinüzoidal konjesyon/kanama varlığının rejeksiyon ile istatistiksel olarak anlamlı şekilde ilişkili olduğu saptandı. Ayrıca sinüzoidal konjesyon/hemoraji varlığının, daha kısa sağkalım süresi ile istatistiksel olarak anlamlı şekilde ilişkili olduğu bulundu.

Sonuç: İntrasinüzoidal nötrofilik infiltrasyon, mortaliteyi öngörmek için olası bir histopatolojik belirleyici olma umudu taşımaktadır. Ayrıca çalışmamıza göre sinüzoidal konjesyon varlığı hem rejeksiyon hem de sağkalım için prognostik faktör olarak aday olabilir.

Anahtar kelimeler: Karaciğer nakli, perfüzyon sonrası biyopsi, greft disfonksiyonu, prognoz

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INTRODUCTION

The recent improvements in liver transplantation have occurred together with the progresses in surgical and preservation techniques and also in clinical treatments. One-year survival after liver transplantation reaches almost 90%[1,2]. But there are still unsolved problems such as primary nonfunction and early allograft dysfunction which cause morbidity and mortality. The definition of early allograft dysfunction is the poor function of the allograft in the first week after liver transplantation[2]. One of the most important causes of early allograft dysfunction is Harvest (preservation) injury. Ischemia and reperfusion are two major causes of harvest injury during the liver transplantation process. Ischemic injury begins with the disconnection of the liver from the donor and lasts untill the initiation of recirculation of the allograft liver. As the liver is kept cold during this time to reduce the ischemic damage, this period is called "cold ischemia time". When the reperfusion of the allograft liver begins, the warm, oxygenated blood causes another damage which is known as reperfusion injury (warm injury)[3,4,5].

The studies focusing on the relationship between the survival and primary graft dysfunction and certain morphological findings related to preservation injury in postperfusion biopsies such as intrasinusoidal neutrophilic infiltration, steatosis, hepatocyte swelling, hepatocellular necrosis, endothelial cell swelling, sinusoidal congestion/hemorrhage, epithelial changes in bile ducts and cholangiolar proliferation are limited and present controversial results[4,6-10]. In a few recent studies in which the relation between the morphological features of ischemia-reperfusion injury (IRI) in postperfusion biopsies and prognosis was evaluated, it was shown that severe ischemia-reperfusion injury had negative effect on overall survival and graft survival[11,12,13].

Based on the information in the literature, the hypothesis of our study is that the morphological findings observed in postperfusion biopsies are useful in predicting the prognosis in patients with liver transplantation. In the current study we aimed to show the potential predictive value of histomorphological findings for the graft function, rejection and survival by evaluating the postperfusion liver biopsies.

MATERIALS AND METHODS

The study protocol was approved by Dokuz Eylul University Non-invasive Research Institutional Ethics Committee (Approval date and number:2022/18-16). Sixtysix consecutive cases who underwent cadaveric liver transplantation and postperfusion biopsy in Dokuz Eylul University Hospital between 2006-2010 were included to the study. The slides of postperfusion subcapsular wedge biopsies which were fixed in 10% buffered formalin, embedded in parafin and stained with hematoxylin-eosin were evaluated by two pathologists (AA, OS).

Histopathological analysis

The histopathological features examined were intrasinusoidal neutrophilic infiltration, microvesicular steatosis, hepatocyte swelling, hepatocellular necrosis, endothelial swelling, bile duct epithelial changes, cholangiolar proliferation and sinusoidal congestion/hemorrhage. The intrasinusoidal neutrophilic infiltration was graded as 0: no intrasinusoidal neutrophilic infiltration, 1: sparse intrasinusoidal neutrophils, 2: intrasinusoidal neutrophils formed little groups/plugs, 3: severe intrasinusoidal neutrophilic infiltration. The microvesicular steatosis was grouped as mild: ≤ 30%, moderate: 31%-60% and severe: > 60%. The hepatocyte swelling was graded as 0: no hepatocyte swelling, 1: focal hepatocyte swelling and 2: diffuse hepatocyte swelling. The hepatocellular necrosis was graded as 0: no hepatocellular necrosis, 1: focal hepatocellular necrosis as single cell necrosis, 2: focal confluent necrosis and 3: confluent necrosis expanding more than 50% of the lobule. The endothelial swelling, reactive changes in bile duct epithelium, cholangiolar proliferation and sinusoidal congestion/hemorrhage were grouped as 0: present and 1: absent, semiquantitatively.

Statistical analysis

The associations between the histopathological features and each of the following: early allograft dysfunction, mortality rate and rejection status were statistically analysed by using Chi-square, Fisher exact and Mann Whitney U tests. SPSS 24.0 was used for the analysis. Overall survival rates were calculated by Kaplan – Meier (K-M) estimator, the differences between survival curves were compared by Log –

rank test. The p values less than 0.05 were accepted as significant.

RESULTS

Of the 66 cases, 19 (29%) were female and 47 (71%) were male, with a mean age 39.12±17.56 (range 7-77) years. Chronic hepatitis B was the most common etiological factor with 20 cases (30%), and chronic hepatitis D was also accompanying in 10 of these cases. The other ethiologic factors were ethanol abuse in 7 patients, chronic hepatitis C in 6 patients, chronic hepatitis B and hepatocellular carcinoma in 5 patients, both chronic hepatitis B and C in 2 patients, chronic hepatitis C and hepatocellular carcinoma in 2 patients, autoimmune hepatitis in 2 patients, chronic hepatitis B and D and hepatocellular carcinoma in 2 patients, hemochromatosis in 2 patients, Wilson's disease in 2 patients, chronic hepatitis B and ethanol abuse, primary sclerosing cholangitis, primary biliary cirrhosis, toxic hepatitis, alveolary hydatid cyst, chronic hepatitis B and C and hepatocellular carcinoma, neuroendocrine tumor in 1 patient each. Nine patients were regarded as cryptogenic liver cirrhosis since no primary cause could be detected. .

Table 1. Histopathological features and the results of the statistical analysis with early dysfunction, mortality rate and rejection status.

Histopathological feature	Case number (n= 66)	*p value* (early dysfunction)*	*p value* (mortality rate)**	*p value* (rejection)***
Intrasinusoidal neutrophils • Grade 0 • Grade 1 • Grade 2 • Grade 3	 0 40 (60%) 24 (36%) 2 (4%)	0.069	0.04	0.356
Hepatocyte swelling • Grade 0 • Grade 1 • Grade 2	 37 (56%) 20 (20%) 9 (14%)	0.327	0.81	0.519
Hepatocellular necrosis • Grade 0 • Grade 1 • Grade 2 • Grade3	 0 33 (50%) 31 (47%) 2 (3%)	0.276	0.23	0.08
Microvesicular steatosis • Absent • Mild • Moderate • Severe	 57 (86%) 6 (9%) 3 (5%) 0	0.450	0.616	0.331
Endothelial swelling • Present • Absent	 5 (8%) 61 (92%)	1.0	1.0	0.263
Reactive changes in bile duct epithelium • Present • Absent	 19 (29%) 47 (71%)	0.771	0.259	0.117
Cholangiolar proliferation • Present • Absent	 23 (35%) 43 (65%)	1.0	0.474	0.333
Sinusoidal congestion / hemorrhage • Present • Absent	 25 (38%) 41 (62%)	0.596	0.161	0.045

:** The associations between the histopathological features and early allograft dysfunction, which were statistically analysed by using Chi-square test. *:** The associations between the histopathological features and mortality rate, which were statistically analysed by using Chi-square test. *****:** The associations between the histopathological features and rejection status, which were analysed by Chi-square test.

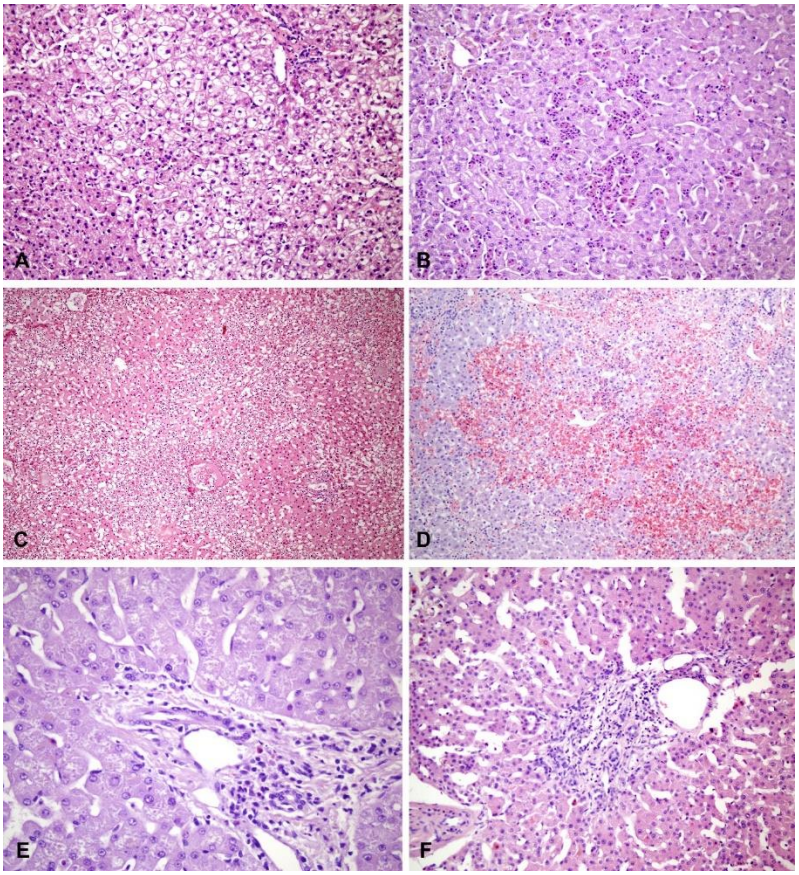

Figure 1. Histopathological features. A: Hepatocyte swelling, H&E, x20. B: Intrasinusoidal neutrophilic infiltration, H&E, x20. C: Confluent necrosis, H&E, x20. D: Sinusoidal congestion/hemorrhage, H&E, x10. E: Endothelial swelling, H&E, x40. F: Cholangiolar proliferation, H&E, x20.

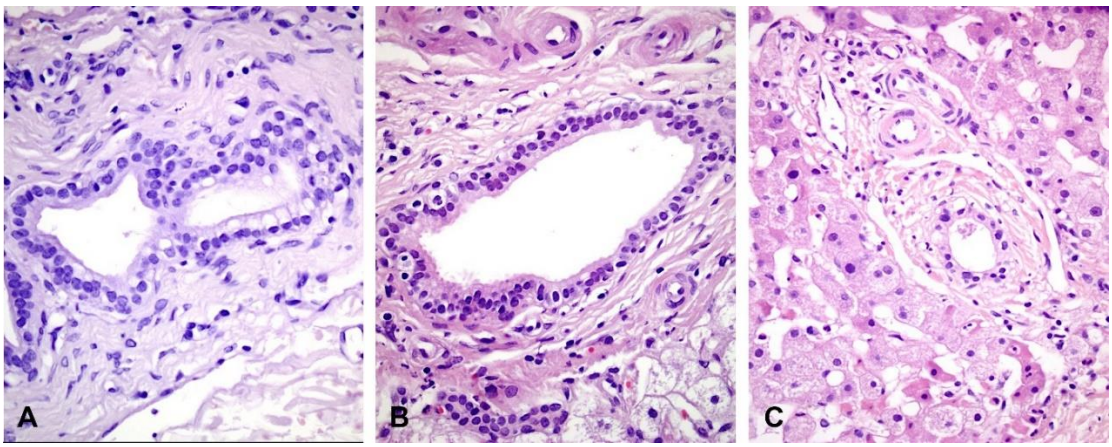

Figure 2: Epithelial changes in bile ducts. A: vacuolization, B: apoptosis, C: nuclear pleomorphism in epithelial cells, H&E, x40.

The mean cold ischemia time was 401.2±157 minutes (range 35-755). The mean follow-up time was 39.9±19.3 months. Ten patients (15%) were dead and 56 (85%) were alive in follow-up. Twentyone patients (31.8%) had early hepatic dysfunction. Acute rejection was seen in 11 patients (16.6%) and chronic rejection was seen in 4 patients (6%). The mean survival time was 54.2 months. Five-year survival rate was 86.7%.

Intrasinusoidal neutrophilic infiltration was grade 1 in 40 (60%), grade 2 in 24 (36%), and grade 3 in 2 cases (4%). Hepatocyte swelling was absent in 37 cases (56%), while 20 cases (30%) were grade 1 and 9 cases (14%) were grade 2. Hepatocellular necrosis was determined as grade 1 in 33 (50%), grade 2 in 31 (47%), and grade 3 in 2 (3%) cases. Fiftyseven cases (86%) showed no microvesicular steatosis, whereas mild microvesicular steatosis was detected in 6 (9%) cases, moderate in 3 (5%) cases. No cases had severe microvesicular steatosis. In addition, endothelial cell swelling in 5 cases (8%), biliary tract epithelial changes in 19 cases (29%), cholangiolar proliferation in 23 cases (35%) and sinusoidal congestion/hemorrhage in 25 cases (38%) were detected (Figure 1 and 2). The histopathological features of the cases are shown in Table 1.

In statistical analysis, there was no significant relation between the histopathological features and early hepatic dysfunction. The relation between the presence of intrasinusoidal neutrophils (the grade 2-3) and mortality rate was statistically significant (p=0.04). Also the presence of sinusoidal congestion/hemorrhage showed statistically significance with the rejection (p=0.045). The other histopathological features did not show significant relation with rejection and mortality. The histopathological features and the results of the statistical analysis with early dysfunction, mortality rate and rejection status are summarized in Table 1.

In survival analysis, the only parameter related to estimated overall survival was sinusoidal congestion/hemorrhage. The presence of sinusoidal congestion/hemorrhage was associated with significantly shorter survival (109.65 vs 75.62 months) (log rank; p=0.031). Other parameters did not show significant relation to overall survival

DISCUSSION

In the current study, we found significant relationship between the presence of grade 2 or 3 intrasinusoidal neutrophils and mortality rate and between the presence of sinusiodal congestion/hemorrhage and the rejection. Furthermore the presence of sinusiodal congestion/hemorrhage was significantly associated with shorter overall survival in survival analysis.

There are several clinical factors known to be related to graft failure in orthotopic liver transplantation such as ABO blood group incompatibility, elevated donor transaminase levels, prolonged cold and warm ischemia time, the use of reduced-size liver grafts and retransplantation[4]. However little is known about the possible histopathological findings which can predict the graft failure or poor prognosis in liver transplantation. Several studies focusing on the relation between various histopathological features in postperfusion liver biopsies and outcome are present in the literature[4,6-10].

In 1990, Kakizoe et al. found that various histopathological features in postperfusion liver biopsies such as hepatocellular necrosis, inflammation, steatosis, hepatocyte swelling showed no relation with graft failure and mortality in 87 cases[8]. In contrast, Abraham et al. evaluated 38 "time zero" liver biopsies for the neutrophilic infiltration, hepatocyte swelling, zone 3 hemorrhage, zone 3 necrosis, cholestasis, apoptotic cells and showed that apoptosis, hepatocellular swelling, centrilobular necrosis and hemorrhage were related to graft failure and also hepatocellular swelling was related to rejection significantly[9]. In another study where hepatocellular necrosis, ballooning, inflammation, cholestasis, cholangiolar proliferation, micro/macrovesicular steatosis, lipopeliosis, kupffer cell hyperplasia, portal tract fibrosis and acute cellular rejection were evaluated in 80 postperfusion liver biopsies, a strong relation was found between the presence of intrasinusoidal neutrophils and hepatocellular necrosis and the preservation injury in early period after transplantation[4]. Similarly, Angelescu et al. interpreted hepatocellular necrosis, intrasinusoidal granulocytes and steatosis in 47 intraoperative allograft biopsies and determined that severe hepatocellular necrosis showed strong association with elevated levels of transamines, high incidence of primary graft failure and decreased synthetic function of the liver[6]. Also, in another study including 88 cases, Kocbiyik et al. examined the postperfusion liver biopsies for lobular neutrophilic infiltration, hepatocellular necrosis, hepatocellular

ballooning, micro/macrovesicular steatosis and cholestasis[7]. They concluded that intrasinusoidal neutrophilic infiltration and hepatocellular necrosis were significantly associated with early hepatic poor function.

On the other hand, in a study of 162 cases, lobular neutrophilic infiltration, hepatocellular necrosis, macro/microsteatosis, fibrotic bridges, cholestatic changes, sinusoidal dilatation and glucogenized nuclei were evaluated in postperfusion liver biopsies by Busquets et al. and no statistical association was detected between morphological features and graft failure, except moderate macrovesicular steatosis[10].

In a recent study with 408 cases, hepatocellular necrosis, apoptosis, balloon degeneration, steatosis, cholestasis and neutrophilic infiltration were evaluated and it was reported that the presence of intrasinusoidal neutrophils had a negative prognostic effect[14].

The prognostic importance of severe IRI in postperfusion liver biopsies comes to the fore in the few recent publications with a high number of cases, focusing on the relationship between IRI and prognosis. In these studies, IRI was grouped as absent, minimal, mild, moderate and severe, mainly according to hepatocyte necrosis and neutrophilic infiltrate[11-13]. Takahiro et al., in their study with the highest number of cases on this subject with 506 cases, showed that the findings of moderate-to-severe IRI were an independent predictor of early graft dysfunction[13]. They also found that the severity of IRI was associated with shorter patient and graft survival[13]. In parallel, another large series showed that 1-year graft and patient survival rates were significantly lower in the severe IRI group, and the presence of severe IRI was an independent predictor of 1-year graft survival[12]. In the other study, in which the presence of neutrophilic infiltrate was evaluated seperately in addition to IRI evaluation and the congestion was also examined, neutrophilic infiltrate was not associated with early graft dysfunction, while the presence of congestion was detected to be significantly related to early graft dysfunction. Besides, severe IRI was also shown to be significantly associated with shorter graft and patient survival[11]. In our study, unlike these studies, the possible prognostic effect of all morphological parameters that can be observed in postperfusion biopsies and that may be associated with IRI were evaluated separately.

Interestingly, a study in which gene expression analysis was performed, showed that even liver tissues obtained by postperfusion biopsies exhibited specific gene expression patterns that may predict early graft dysfunction and may be used to determine the risk for patients[15]. The results of the molecular analysis revealed by this study are also important in terms of providing evidence that postperfusion liver biopsies are of prognostic importance.

Although there are inconsistent results in these studies, hepatocellular necrosis and intrasinusoidal neutrophilic infiltration are the most common histopathological features seem to be related to poor clinical outcome in liver transplantation. Hepatocyte swelling, centrilobular hemorrhage, apoptosis, cholestasis and macrovesicular steatosis are the other morphological findings which were found as associated to graft failure, early dysfunction or rejection. Our findings, especially the ones related to the prognostic effects of intrasinusoidal neutrophilic infiltration, are consistent with the literature, although hepatocellular necrosis which is one of the most common morphologic parameters shown to be associated with prognosis, was not found to be related to early hepatic dysfunction, mortality rate or rejection in our study. On the other hand, sinusoidal congestion, which is a finding that does not stand out in terms of prognostic value in studies in the literature except one study [11], was found to be a more promising finding in the prediction of prognosis in our study. Another point to be noted is sinusoidal congestion is counted as one of the findings of hyperacute antibody mediated rejection (AMR)[16], however none of our cases had the clinical findings of hyperacute AMR and showed very early graft loss.

The limitations of our study are the retrospective design, heterogeneous case population including patients with variable etiologies and the lack of molecular analysis. In our case series consisting of cases up to 2010, since AMR was not yet defined at that time and we did not have the necessary data for accurate evaluation of AMR, such as serum donor-specific antigen levels and C4d immunohistochemical staining, the fact that the presence of rejection in our cases could only be evaluated as acute cellular rejection (T cell-mediated) and chronic rejection, is another limitation of our study. Despite all this, we think that we have obtained valuable data to predict the prognosis of liver transplantation with our study in which all morphological parameters seen in postperfusion biopsies are evaluated separately, on

this subject which has limited and contradictory information in the literature, and we believe that our study will contribute to the literature.

In conclusion, intrasinusoidal neutrophilic infiltration is promising to be a possible histopathological predictor for mortality. In addition, the presence of sinusoidal congestion can be a candidate as a prognostic factor both for rejection and overall survival based on our study. Postperfusion biopsies may play a key role in rapid identification of the risk of graft dysfunction, as they are early biopsies taken at the time of liver transplantation. The earlier the risk is identified, the more effective clinical intervention is possible and the prognosis of patients can be improved. It is obvious that the morphologic findings seen in these biopsies carry potential to have predictive value for clinical outcome. Further studies with larger case numbers are needed to designate the certain histopathological predictors.

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