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Histopathological study comparing native and post-transplant recurrent chronic hepatitis C with emphasis on confounders with acute cellular rejection

Estudo histopatológico comparativo da hepatite crônica C nativa e recorrente pós-transplante com ênfase em achados semelhantes à rejeição celular aguda

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ABSTRACT

Introduction: Histological analyses of post-transplant liver biopsies may be difficult in distinguishing recurrent chronic hepatitis C (CHC) from other causes of graft dysfunction, especially acute cellular rejection (ACR). **Objective:** The aim of this study was to compare the histological characteristics of liver biopsies with CHC in transplant and non-transplant patients with hepatitis C virus (HCV) infection and assess the occurrence of findings common to ACR. **Methods:** We studied 40 biopsies from non-transplant and 30 biopsies from post-transplant patients, according to the Ishak score for necroinflammatory activity grade and stage of fibrosis. We also assessed the inflammatory infiltrate, steatosis, ductal changes, portal endotheliitis and central perivenulitis. **Results:** We found predominance of mild grade and stage in both groups. The portal inflammatory infiltrate was also mild and mainly lymphocytic in the two groups. Ductal changes were more frequent in the non-transplant patients. Steatosis was also mild in both groups, but predominated in non-transplant CHC patients. Portal endotheliitis occurred in 42.5% and 40% in non-transplant and post-transplant CHC, respectively. The frequency of centrilobular endotheliitis was similar in both groups. **Conclusion:** Histological findings in chronic hepatitis C are similar in non-transplant and post-transplant patients. In addition, morphological features characteristic of ACR are also observed in HCV infection of native livers as well as in the graft of patients with recurrent infection after transplantation.

Key words: chronic hepatitis C; liver transplantation; graft rejection; pathology.

INTRODUCTION

Cirrhosis secondary to hepatitis C virus (HCV) infection is currently the main indication for liver transplantation in several countries[1]. However, virtually all patients with chronic hepatitis C (CHC) who undergo transplantation develop recurrent infection during graft reperfusion in which viral titers reach pre-transplant levels a few hours after the procedure[2-4]. Infection recurrence is the leading cause of graft dysfunction and loss and is often associated with a faster progression to cirrhosis in comparison with non-transplant patients[2, 5]. Therefore, post-transplant monitoring is crucial for early diagnosis of disease recurrence and progression, since it allows timely initiation of antiviral treatment[6].

One of the differential diagnoses of recurrent HCV infection after liver transplantation is acute cellular rejection (ACR), which is also a frequent cause of early graft dysfunction[2]. In patients with graft dysfunction, histological analysis of liver biopsy is used to identify the undergoing process. However, distinguishing between infection recurrence and immunological rejection is challenging since some histological findings are common to both conditions[3, 7]. Nevertheless, timely identification of ACR is essential: it leads to important therapeutic decisions, such as change in the immunosuppressive regimen, which can itself exacerbate the recurrent HCV infection or promote opportunistic infections.

The histological diagnosis of HCV infection is based on the grade of necroinflammatory activity and fibrosis stage[8, 9]. One of

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the main systems currently used for this evaluation is the Ishak score[9]. Other often analyzed histological parameters include steatosis, portal lymphoid follicles or aggregates, bile ducts injury and endotheliitis[10]. The diagnosis of ACR is based on the presence of mixed portal inflammatory infiltrate composed of activated lymphocytes, neutrophils and eosinophils, endotheliitis and ductal injury. HCV infection can also present with endotheliitis and biliary ductal injury[11]. In this case, the presence of lobular necroinflammatory activity, interface hepatitis and steatosis help establish the diagnosis of HCV infection, since they are absent in cases of ACR[12].

Several studies have been conducted to determine factors that increase sensitivity of histological analysis of liver graft biopsy in identifying viral relapse[2]. Anyway, we deemed it important that others be developed to compare simultaneously the histological characteristics of the liver in HCV infection in transplant and non-transplant patients, in addition to analyzing the frequency with which histological changes common to ACR occur.

METHODS

In this retrospective study, we conducted a search at the computerized database of the University Hospital Clementino Fraga Filho (Universidade Federal do Rio de Janeiro [UFRJ]) using the key words "chronic hepatitis C", "liver transplant" and "hepatitis C virus" to identify patients with HCV infection who underwent liver biopsy between 2002 and 2012. Liver biopsy was performed in patients with elevated aminotransferase levels.

We excluded from the analysis the biopsies of patients who had undergone transplantation less than six months before the study, and those with histological sections with less than six completely represented portal tracts, clinical and/or histological evidence of ACR, fibrosing cholestatic hepatitis, biliary and/or vascular diseases secondary or not to the transplant, and coinfected with the hepatitis B virus and/or human immunodeficiency virus.

After this exclusion, we selected for analysis 40 liver biopsies from patients with native livers with HCV infection (non-transplant) and 30 with recurrent HCV infection at least six months after liver transplantation (post-transplant CHC). The diagnosis of infection was confirmed in all patients by polymerase chain reaction. Information about patients' gender, age and viral genotype were obtained when available.

For each biopsy we analyzed five histological sections using a Nikon E200 microscope. Each of the sections was stained with hematoxylin and eosin (HE), Masson's trichrome and Gomori's reticulin.

The study was conducted after approval by the Medical Ethics Committee of the University Hospital Clementino Fraga Filho-UFRJ, under registry number 064/11.

Histological analysis

For histological analysis, we considered the following parameters: grade of necroinflammatory activity and stage of fibrosis according to the Ishak score[9], portal and periportal changes, and ductal epithelium and parenchymal abnormalities.

Grade and stage

Based on the Ishak score[9], we classified the grade of necroinflammatory activity as G1-G6 = mild, G7-G12 = moderate, and G13-G18 = marked. We considered the stage of fibrosis in those cases classified with E1 and E2 as minimum/mild, in those with E3 and E4 as moderate, and in the ones with E5 and E6 as marked.

Portal and periportal findings

Based on the Ishak score[9], we classified interface hepatitis as absent (A0), minimum (A1), mild (A2), moderate (A3) and marked (A4), and the intensity of the inflammatory portal infiltrate as mild (D1 and D2), moderate (D3) or marked (D4). As for the cell types present in the inflammatory infiltrate, we analyzed the presence of lymphocytes, eosinophils and neutrophils, which were classified as present or absent. The presence of at least three eosinophils in at least one portal tract by analyzed biopsy was determined as the cut-off point in the analysis of portal eosinophils. Portal endotheliitis was considered mild when presenting only a small focus of inflammatory infiltrate permeating the venular endothelium, moderate when affecting up to 50% of the venular circumference, and severe when more than 50% of the circumference of the portal vein was involved.

Ductal epithelium findings

In evaluating the epithelium of the interlobular bile ducts, we analyzed the frequency of degeneration, atrophy, ductopenia, ductal exocytosis and ductular proliferation. In evaluating ductal exocytosis, we also considered the ratio between the number of portal tracts with bile ducts presenting exocytosis over the total number of portal tracts present at the analyzed biopsy and we presented the average, minimum and maximum values we found. We characterized ductopenia as the absence of bile ducts in more than 50% of the represented portal tracts.

Parenchymal findings

We analyzed the frequency of steatosis, central perivenulitis (with or without centrilobular vein endotheliitis) and apoptosis. Steatosis was considered mild when lipid vacuoles were present in 5%-30% of the hepatocytes, moderate when 31%-60%, and marked when occurring in more than 60%. Central perivenulitis and apoptosis were classified as present or absent.

Additional analyses

We applied the Banff criteria (portal inflammation, bile duct damage and venous endothelial inflammation – endotheliitis) to evaluate the occurrence of ACR-like findings in both groups[13]. In order to assess the rapidity with which fibrosis develops in transplanted patients, we analyzed the stage of fibrosis in relation to the moment in which the biopsy was obtained.

Statistical analysis

After descriptive analysis of each variable regarding frequency, we used the test of independence (Wilks' G^2) followed by the Z-test. We applied Student's *t* test to verify the occurrence of statistically significant differences between groups. We adopted a significance level of 0.05.

RESULTS

In the group of non-transplant patients, there was a predominance of the female gender (62.5%), whereas in the group with post-transplant CHC, the male gender predominated (83.4%). Average ages were 53.7 years and 55.8 years, respectively.

We were able to obtain information about the genotype in 31 non-transplant patients and in 21 patients with post-transplant CHC. Among those non-transplant, there was a predominance of genotype 1a (n = 13; 42%), followed by 1b (n = 12; 38.7%), genotype 3 (n = 4; 13%) and genotype 1 unspecified (n = 2; 6.3%). In the post-transplant group, the prevalent genotype was 1b (n = 9; 42.8%), followed by genotype 1 unspecified (n = 4; 19%), genotype 3 (n = 5; 24%) and genotype 1a (n = 3; 14.2%).

In the group of transplant patients, the time elapsed between the transplant and the biopsy that diagnosed viral recurrence ranged between 6 months and 11 years.

Histological analysis

Grade of necroinflammatory activity and stage of fibrosis

There was a predominance of mild grade and stage in both groups. A comparison between groups showed no difference between the frequencies of each of these findings (p = 0.258 and p = 0.085, respectively; **Table 1**). Cirrhosis was observed only in the group of non-transplant patients.

TABLE 1 – Comparison of grade and stage in non-transplant and transplant patients with CHC

Ishak score	Non-transplant (n = 40)	Post-transplant CHC (n = 30)	p-value (Fischer's exact test)
Grade	Mild: 32 (80%) Moderate: 8 (20%) Marked: 0	Mild: 22 (73.4%) Moderate: 8 (26.6%) Marked: 0	0.258
Stage	Minimum/mild: 26 (65%) Moderate: 12 (30%) Marked: 2 (5%)	Minimum/mild: 22 (73.4%) Moderate: 8 (26.6%) Marked: 0	0.085

CHC: chronic hepatitis C.

*Portal and periportal findings (**Table 2**)*

The frequencies of mild interface hepatitis were similar in both groups (60%; p = 0.162). Three non-transplant patients (7.5%) showed A3 interface hepatitis (moderate) that was not found in any patient in the group with post-transplant CHC.

The portal inflammatory infiltrate was predominantly lymphocytic and of mild intensity in both groups. As for the cell types in the inflammatory infiltrate, there was no significant difference between groups regarding the participation of neutrophils (p = 0.223) or eosinophils (p = 0.156). Portal endotheliitis was identified in 42.5% of the biopsies of native livers and 40% of the biopsies of transplant patients. Cases classified as mild endotheliitis prevailed in both groups, 76.5% in non-transplanted and 75% in post-transplant CHC, whereas moderate endotheliitis was present in 25% and 23.5%, respectively (p = 0.417).

Ductal epithelium findings

Both groups showed comparable frequencies of degeneration (**Figure 1**), atrophy and ductular proliferation (p = 0.202). However, the prevalence of exocytosis was higher in the non-transplant group (p = 0.049) (**Table 3** and **Figure 2**). We did not observe ductopenia in any of the histological sections.

The ratio of the number of portal spaces affected by exocytosis over the total number of portal spaces per biopsy in both groups was also comparable (**Table 4**).

TABLE 2 – Comparison of the frequency of portal and periportal findings between non-transplant and transplant patients with CHC

Portal and periportal changes	Non-transplant (n = 40)	Post-transplant CHC (n = 30)	p-value (Fischer's exact test)
Interface hepatitis (Ishak)	A0: 0 A1: 13 (32.5%) A2: 24 (60%) A3: 3 (7.5%) A4: 0	A0: 1 (3.3%) A1: 11 (36.7%) A2: 18 (60%) A3: 0 A4: 0	0.162
Presence of neutrophils	21 (52.5%)	13 (43.3%)	0.223
Presence of eosinophils	9 (22.5%)	4 (13.3%)	0.156
Portal inflammatory infiltrate	Mild: 28 (70%) Moderate: 12 (30%)	Mild: 24(80%) Moderate: 6 (20%)	0.339
Endotheliitis	Mild: 13 (76.5%) Moderate: 4 (23.5%)	Mild: 9 (75%) Moderate: 3 (25%)	0.417

CHC: chronic hepatitis C.

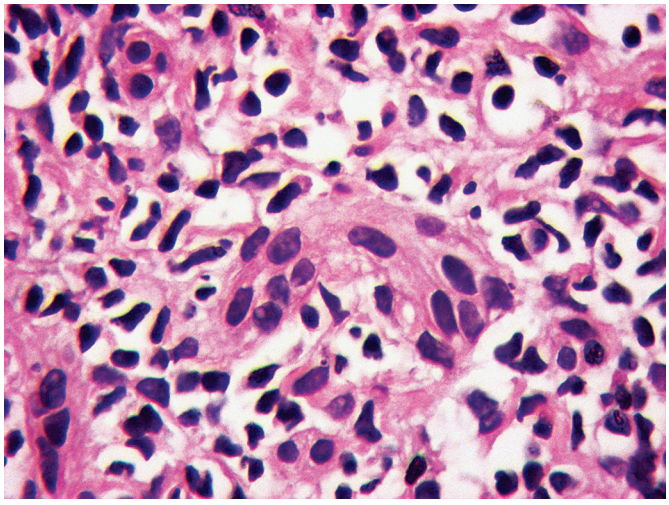

FIGURE 1 – *Native liver with chronic hepatitis C: ductal degeneration – cytoplasmic eosinophilia and loss of nuclear polarization (1,000×)*

TABLE 3 – Comparison of the frequency of ductal epithelium changes in non-transplant and transplant patients with CHC

Ductal epithelium changes	Non-transplant (n = 40)	Post-transplant CHC (n = 30)	p-value (Fischer's exact test)
Ductal degeneration	11 (27.5%)	6 (20%)	0.23
Ductal atrophy	8 (20%)	4 (13.3%)	0.226
Ductular proliferation	5 (12.5%)	6 (20%)	0.202
Ductal exocytosis	15 (37.5%)	6 (20%)	0.049

CHC: chronic hepatitis C.

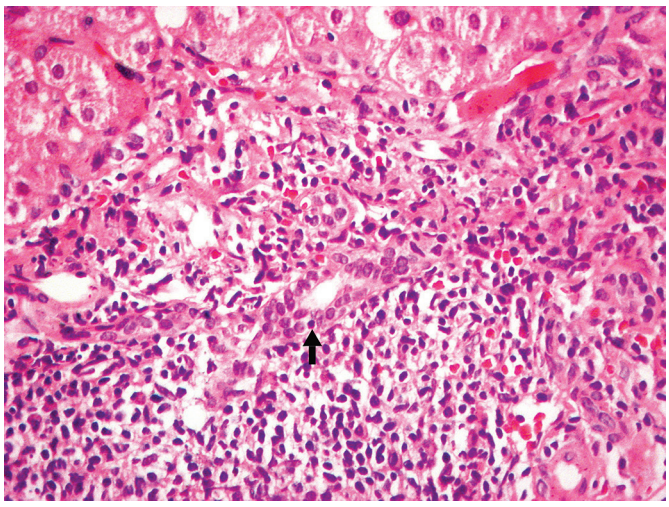

FIGURE 2 – *Native liver with chronic hepatitis C: ductal exocytosis – arrow (400×)*

TABLE 4 – Ratio of the number of portal tracts with bile ducts featuring exocytosis over the total number of portal tracts present in the analyzed biopsy in non-transplant and transplant patients with CHC

Ratio	Non-transplant (n = 40)	Post-transplant CHC (n = 30)	p-value (Fischer's exact test)
Minimum	0.05	0.05	
Maximum	0.25	0.43	
Median	0.125	0.13	0.289
Mean	0.132	0.165	
Standard deviation (n)	0.053	0.134	

CHC: chronic hepatitis C.

Parenchymal findings

Steatosis was predominantly mild in both groups (**Table 5**). Moderate steatosis was not observed in any non-transplant patient, but occurred in four patients with post-transplant CHC ($p = 0.033$). In contrast, central perivenulitis was more frequent in transplant patients (40%) compared with non-transplant patients (20%; $p = 0.034$) (**Figure 3**). There was no difference between groups in the frequencies of centrilobular vein endotheliitis or apoptosis ($p = 0.276$ and $p = 0.388$, respectively).

ACR-like findings

In the non-transplant group we observed the presence of all Banff criteria[13] for ACR. Excluding the portal inflammatory infiltrate, which was present in all cases, we observed that 13 cases (32.5%) had only one ACR-like finding, whereas 12 cases (30%) had two findings, totaling 25 biopsies (62.5%) of non-transplant patients in whom we observed at least one of the diagnostic criteria for ACR. Applying the same criteria for the transplant group, we observed that 14 cases

(46.6%) presented only one finding, and three cases (10%) showed two findings (**Figure 4**), totaling 17 (56.6%) transplant patients in whom we observed at least one of the ACR diagnostic criteria.

TABLE 5 – Comparison of the frequency of parenchymal findings in non-transplant and transplant patients with CHC

Parenchymal findings	Non-transplant (n = 40)	Post-transplant CHC (n = 30)	p-value (Fischer's exact test)
Apoptosis	16 (40%)	11 (36.6%)	0.388
Steatosis	Mild: 22 (55%) Moderate: 0	Mild: 14 (46.6%) Moderate: 4 (13.4%)	0.033
Central perivenulitis	8 (20%)	12 (40%)	0.034
Endotheliitis of centrilobular vein	7 (17.5%)	7 (23.3%)	0.276

CHC: chronic hepatitis C.

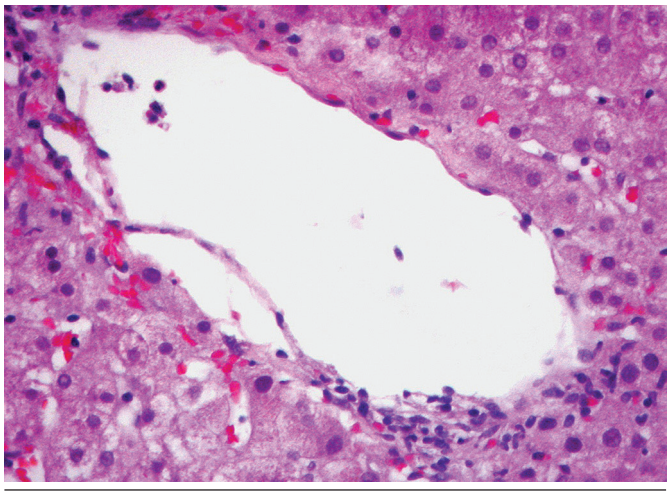

FIGURE 3 – *Native liver with chronic hepatitis C: perivenulitis with centrilobular vein endotheliitis (400×)*

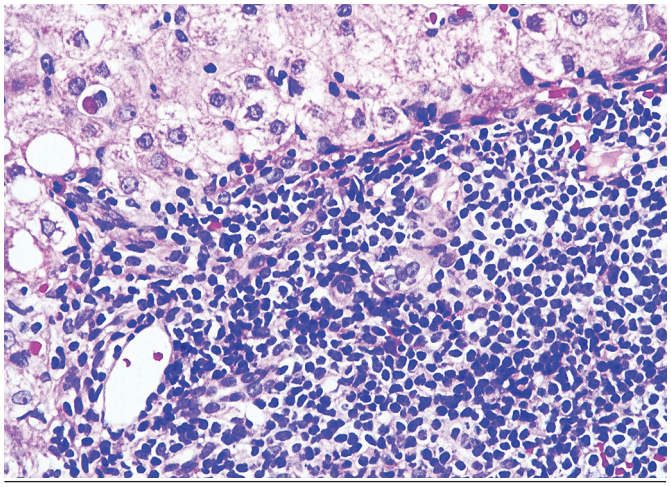

FIGURE 4 – *Recurrent post-transplant chronic hepatitis C: ductal lesion and endotheliitis (400×)*

Analysis of the stage of fibrosis with respect to time to obtain the biopsy after transplantation

Fibrosis was present in 12 of 13 patients biopsied within the first two years after transplantation. Among these patients, nine were genotype 1. Information about the donors' age was available in only six cases; in these, the average age was 49.2 years (range: 24-68 years).

DISCUSSION

In this comparison of histological sections of liver biopsies of non-transplant CHC patients and post-transplant CHC patients we observed that cirrhosis was present only in non-transplant patients, while moderate steatosis occurred only in transplant patients. Despite the presence of central perivenulitis in both groups, this finding was significantly more frequent in the post-transplant group. Regarding the other analyzed parameters, we found no significant differences between groups.

The absence of cirrhosis in transplant patients was probably due to the relatively short follow-up time after transplantation (up to four years in most patients). In studies evaluating the occurrence of cirrhosis in transplant patients, the average interval between transplantation and identification of cirrhosis was 9.5 years[4].

In HCV infection, steatosis is associated with the same mechanisms of insulin resistance, except for patients infected with genotype 3, in whom the accumulation of fat is usually more prominent and a result of direct interference of the viral infection on lipid metabolism within the hepatocyte[7]. Therefore, steatosis is a frequent finding both in native and in grafted livers. Steatosis in HCV infection is characterized mainly by macrovesicles, mostly of mild to moderate intensity, without the characteristic centrilobular distribution of steatosis associated with non-alcoholic fatty liver disease[7]. In our study, there was a predominance of mild steatosis in both groups, whereas moderate steatosis was present only in transplant patients. We believe that genotype did not influence this result, since among the five patients with genotype 3 included in the study, only one of the transplant patients had moderate steatosis.

The expression "central perivenulitis" has been suggested to describe inflammatory changes and injuries affecting the centrilobular region[7]. It is mainly found in ACR, but is also present in other liver diseases[14]. In fact, we found central perivenulitis also in non-transplant patients and in a frequency greater than that observed by other authors[3, 15]. Although we have included

patients with only CHC and excluded other liver diseases in which central perivenulitis can be present, we speculate that immunological phenomena occurring in this group could account for this finding. Another finding inconsistent with other studies was the presence of centrilobular vein endotheliitis, observed in 17.5% of the non-transplant patients, in contrast with the absence of identification of this parameter by other authors[3, 15].

In both groups, interface hepatitis was predominantly mild, unlike what was reported by some authors on recurrence of HCV infection[16]. However, the time elapsed after transplantation in most biopsies included in other studies was shorter than in ours[16]. It is possible that interface activity may increase as the recurrence of viral infection progresses. In other studies, portal inflammation was absent or was classified as minimal in half of the cases[16], in contrast to our findings of predominantly mild portal inflammation in all patients after the transplant.

The lobular findings in recurrent CHC are generally similar to those found in biopsies of native livers. However some authors report more marked lobular inflammation in the first[17, 18]. Saxena *et al.* (2002)[19] described a significant increase in the amount of apoptotic bodies in biopsies from transplant patients with recurrent hepatitis C when compared with biopsies from native livers. This was not observed in our study, since apoptosis was present in 40% of the biopsies of non-transplant patients and 36% of the transplant patients. The different methodologies of the two studies, both in the quantification of apoptotic bodies, and in the time elapsed between transplantation and biopsy, prevent a comparative analysis of the results.

In addition to the parameters related to the grade of necroinflammatory activity, other portal changes have been evaluated in the comparison between CHC in native livers and CHC recurrence in transplanted livers, among them, bile duct lesions. Similarly to Poulsen and Christoffersen (1969)[20], we morphologically classified the injury to the bile duct epithelium as degeneration, proliferation, atrophy and exocytosis. All these findings were more frequent in the non-transplant group, with the exception of ductular proliferation, which showed no significant difference between the groups. Other authors also highlighted the presence of changes in bile ducts in 30% of non-transplant patients[3]. This frequency was lower than the one found in our study, in which ductal exocytosis was observed in 37.5% of the native livers. Considering that those authors studied ductal exocytosis along with other unspecified biliary duct findings[3], we suggest that our results are superior to theirs in relation to ductal exocytosis. Since there is evidence that the damage to the epithelium of bile ducts is associated with a higher degree of portal inflammatory activity[7], we also correlated the intensity of portal inflammatory infiltrate with the several presentations of ductal injury. We did not observe correlation between these findings in any of the groups, even for exocytosis, which had a statistically significant difference between groups. Also regarding ductal exocytosis, we did not find a significant difference in the ratio between the number of portal spaces with affected bile ducts and the total number of portal tracts present in the analyzed biopsy. There is no uniformity in the literature on morphological characterization of ductal injury in CHC[3, 7], which complicates the comparison of the results. In addition to the challenges of morphological characterization, the pathogenesis of the ductal injury on the HCV infection is not established, and the possibilities of direct injury by the virus and/or immunological mechanisms should be considered[21], which increases the number of variables that can determine ductal injury. These evidences point to a need for further studies to better clarify the interaction between HCV and the epithelium of the bile ducts, and consequently the ductal lesions observed in CHC.

The time of fibrosis development in transplant and non-transplant patients infected by HCV is variable[11]. Even though the stage of fibrosis was mild in both groups, it is important to highlight that already in the first two years after transplant, fibrosis was present in almost all samples. Considering that the time course of HCV infection is lower in this group, this result points to a greater progression of fibrosis in the post-transplantation period when compared with infection in native livers, as previously reported by other authors[4, 7].

In summary, our findings show that the histological findings in the liver of patients with post-transplant CHC resemble those of non-transplant patients. In addition, morphological findings characteristic of ACR are also observed in HCV infection of native livers as well as in the graft of patients with recurrent infection after transplantation. We conclude, based on these findings, that liver biopsy as an isolated diagnostic method in patients with recurrent CHC after liver transplant may be insufficient to accurately establish the differential diagnosis with ACR.

CONFLICT OF INTEREST

The authors report no conflict of interest.

RESUMO

Introdução: *A análise histológica de biópsias hepáticas pós-transplante pode trazer dificuldades na distinção entre hepatite crônica C (HCC) recorrente e outras causas de disfunção do enxerto, sobretudo rejeição celular aguda (RCA).* ***Objetivo:*** *Comparar as características histológicas de biópsias hepáticas de pacientes transplantados e não transplantados portadores de HCC, além de avaliar a presença de achados comuns à RCA.* ***Métodos:*** *Foram estudadas 40 biópsias de pacientes não transplantados e 30 de transplantados, de acordo com o escore de Ishak para grau de atividade necroinflamatória e estágio de fibrose. Foram ainda avaliadas as características do infiltrado inflamatório, da esteatose, das alterações ductais e da endotelite portal e da perivenulite central.* ***Resultados:*** *Em ambos os grupos, houve predomínio de leve grau de atividade necroinflamatória e leve fibrose. O infiltrado inflamatório portal também foi leve e predominantemente linfocítico em ambos os grupos. Alterações ductais foram mais frequentes em pacientes não transplantados. Esteatose também foi leve em ambos os grupos, mas predominou nos pacientes não transplantados. Endotelite portal ocorreu em 42,5% e 40% em HCC não transplantada e HCC pós-transplante, respectivamente. A frequência de endotelite centrolobular foi semelhante nos dois grupos.* ***Conclusão:*** *Os achados histológicos na HCC são semelhantes em pacientes transplantados e não transplantados. Além disso, características morfológicas da RCA estão presentes na HCC, tanto em fígados nativos como em enxertos de pacientes com infecção recorrente após transplante.*

Unitermos: *hepatite C crônica; transplante de fígado; rejeição de enxerto; patologia.*

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