Original Article
Re-examination of sinusoidal deposition of complement 4d in liver allografts: experience from a single institution

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Abstract: Complement 4d (C4d) is a marker of complement activation that has been used to evaluate humoral rejection in renal and heart allografts. Studies suggested a role for C4d detection in liver allografts in diagnosing acute cellular and humoral rejection but none correlated this with the pre-transplant liver disease. Our study analyzed the association of C4d deposition in liver allografts with the pre-transplant liver disease. C4d deposition was evaluated by indirect immunofluorescence and correlated with lymphocytotoxic crossmatch results, post-transplant clinicopathological diagnosis and type of pre-transplant liver disease. Allograft biopsies were classified by the native liver disease. After excluding 20 patients with rare liver diseases; C4d deposition was evaluated in 506 biopsies from 310 patients including 25 with PSC, 198 with viral hepatitis and 87 with other diseases. C4d immunoreactivity distribution was not different among biopsies from patients with different lymphocytotoxic crossmatch results. Sinusoidal C4d deposition was noted in 11.9% of biopsies and 15.2% of patients (in one or more biopsies). 26% (9/35) of biopsies from patients with PSC had sinusoidal C4d deposition; more frequently than from patients with viral hepatitis 12% (43/348) (p=0.04) and other liver diseases 7% (8/123) (p=0.005). In conclusion, C4d deposition in liver allografts is independent of the crossmatch results. It occurs with a variety of pathologic abnormalities and underlying liver diseases; but is more frequent in patients with PSC. This suggests that mechanisms other than allo-immunity activate complement. The mechanisms and clinical significance of C4d deposition in liver allografts in patients with PSC remain to be determined.

Keywords: Liver allograft, complement, rejection, primary sclerosing cholangitis, lymphocytotoxic antibody

Introduction

Complement system, an innate immune system, plays a significant role in the defense against infectious agents, neoplastic transformation as well as in the development of autoimmune diseases. It consists of multiple activation pathways responding to different inciting signals. The classic pathway of complement activation involves the binding of an antigen to an antibody followed by a tightly controlled sequential activation of several components with eventual formation of a terminal membrane attacking complex. Along this activation pathway, complement 4 is activated, further processed and then a stable product called complement 4d (C4d) is formed and this can be detected by immunoassay. C4d as a marker of complement activation has been widely accepted and used to evaluate acute antibody-mediated and cellular rejection in kidney, heart and pancreas allografts in recent years [1, 2]. Few studies also suggested that vascular deposition of C4d in liver allografts may contribute to the development of chronic rejection [3, 4].

Liver transplantation is currently the main modality to treat end-stage liver disease. Rejection of the transplanted liver allograft remains a major complication leading to signifi-
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cant allograft dysfunction and loss. Several small retrospective studies revealed inconclusive data on the role of C4d deposition in liver allografts as a marker to diagnose humoral and/or acute cellular rejection [5, 6]. One of the largest studies in a cohort of ABO compatible liver allografts suggested that C4d deposition occurs with acute cellular rejection, centrilobular necroinflammation, biliary obstruction, chronic rejection and primary non-functional allografts [7]. These findings suggest that various mechanisms may contribute to C4d deposition in the liver allografts. These mechanisms may include the underlying pre-transplant liver disease especially when the systemic pathology persists as in autoimmune diseases. However, the association of C4d deposition in the liver allograft with the pre-transplant liver disease is not clear.

Our study aimed to determine the overall C4d immunoreactivity in a large series of consecutive liver allograft biopsies and the association of C4d deposition in the liver allograft with the type of underlying pre-transplant liver disease.

Methods and material

Patients and methods

After appropriate institutional review board approval, our database was accessed and a total of 674 consecutively performed liver allograft biopsies from 350 patients from January 2009 to July 2010 were retrieved. The type of the underlying pre-transplant liver disease was determined by clinical history and histologic diagnosis in the explanted native liver. 569 allograft biopsies from 330 patients had immunofluorescent study for C4d (testing rate 84%). 20 patients had rare liver diseases and were excluded from further analysis. 506 biopsies from the remaining 310 patients were included in the final analysis. C4d deposition was analyzed by indirect immunofluorescence on frozen liver allograft biopsy material. Due to the short follow-up period of this study no attempt was made to correlate the presence of C4d deposition in the allograft with the allograft’s and patient’s long term outcomes.

Retrospective or concurrent T and B lymphocyte flow cytometric crossmatch was performed in 321 cases (out of 350, testing rate of 91.7%). Briefly, recipient serum was incubated with donor lymphocytes then a fluorescent labeled antihuman globulin was added and analyzed by a flow cytometer for the presence of bound IgG antibodies. An increase in the level of IgG binding compared to a negative control indicated a positive crossmatch result.

Histological examination

18-gauge liver core tissue biopsies were placed in 10% buffered formalin, processed routinely, cut into 4 um sections, stained with hematoxylin and eosin and Masson’s trichrome stain, and used for histological diagnosis by light microscopy. An additional liver allograft biopsy was also collected and submitted fresh for C4d indirect immunofluorescent staining. Specifically, the additional slide was fixed in acetone for 10 minutes, air dried for 5 minutes and rehydrated in phosphate buffered saline (PBS, pH 7.2) for 5 minutes. The indirect immunofluorescent staining included an incubation with a primary mouse anti-C4d antibody (ABD Serotec, 2222-8004; at 1:50) for 30 minutes at room temperature, rinsing in PBS (twice, for a total of 5 minutes), incubation with an FITC anti-mouse IgG antibody for 30 minutes at room temperature and then rinsing in PBS (twice, for a total of 5 minutes). The slide was immediately examined by fluorescent microscopy after cover glass mounting using Aqua Mount. Positive and negative controls were included with every batch of staining. Renal biopsy with known C4d immunoreactivity was included as a positive control and replacement of primary antibody by an isotype matching antisera in the solution as a negative control. 10% sinusoidal staining was the cutoff for positive C4d deposition and areas with necrosis were excluded.

Histologic diagnosis was performed by experienced pathologists in routine clinical practice (RP, LY, AB and XL). The diagnosis of acute cellular rejection and chronic rejection was made according to Banff criteria [8, 9] and retrospectively confirmed by good response to increased immunosuppressant treatment for acute cellular rejection. Diagnosis of HCV hepatitis was made based on the presence of classic histologic findings including lobular and/or portal hepatitis in the context of serum levels of HCV RNA. Biliary flow impairment was diagnosed by the standard criteria of surgical pathology and confirmed by the presence of biliary leak, stricture or infection. The diagnosis of vascular inju-
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Descriptive statistics were computed for all variables. These included means, standard deviations and percentiles for continuous variables, and frequencies and percentages for categorical variables. Differences between the study groups were assessed using fisher’s exact test for categorical variables and welch modified two-sample t-test for continuous variables. All P-values were two-sided and statistical significance was set at P<0.05. All statistical analyses were performed using R software package 3.01 (R Development Core Team, 2013; R Foundation for Statistical Computing, Vienna, Austria).

Results

C4d immunoreactivity was not dependent upon flow cytometric lymphocytotoxic crossmatch results or ABO incompatibility

In our study, we correlated the C4d immunoreactivity with the flow cytometric lymphocytotoxic crossmatch results status. Among 350 patients in this cohort, 321 patients (91.7%) had crossmatch results: 94 had negative T and B cell crossmatch, 180 had positive B cell crossmatch only and 47 had positive T and B cell lymphocytotoxic crossmatch results. A total of 609 biopsies were obtained from these 321 patients. The C4d testing rates did not differ among biopsies from patients with different lymphocytotoxic crossmatch results. In addition, the distribution of C4d immunoreactivity was not significantly different among biopsies from these groups (Table 1).

Only 3 patients (1%) had ABO incompatibility. 7 biopsies were performed from the liver allografts in these 3 patients and 6 of the biopsies were subjected to C4d immunofluorescent study. None of the tested biopsies showed C4d immunoreactivity although all of them had histologic abnormalities including acute cellular rejection in 2 biopsies, resolving acute cellular rejection in 1 biopsy, recurrent hepatitis C in 2 biopsies and mild nonspecific inflammation in 1 biopsy.

Overall frequency of C4d deposition in liver allografts

A total of 674 liver allograft biopsies from 350 patients were retrieved for the study period and 569 cases had immunofluorescent study for C4d done (testing rate 84%). Sinusoidal C4d immunoreactivity was noted in 12% of biopsies and was more frequently observed in biopsies with significant pathologic findings including acute cellular rejection, recurrent hepatitis C, vascular abnormality and/or biliary flow impairment (15%) than biopsies with normal histology or mild nonspecific findings (3%) (p<0.001). The frequency of C4d immunoreactivity was independent of the interval of the biopsy and transplantation (10%, 14% and 12% for biopsies taken 1 week or less, between 1 week and 1 month and 1 month or more respectively, p=0.8). 5 of 39 (13%) biopsies with vascular injury and 6 of 42 (14%) biopsies with biliary flow impairment showed C4d immunoreactivity which is similar to the overall C4d positive rate in the entire cohort. Representative images of

Table 1. Frequency of C4d Immunoreactivity in Liver Allograft Biopsies in Patients with Known Lymphocytotoxic Crossmatch Results

<table>
<thead>
<tr>
<th>C4d positive, N (%)</th>
<th>C4d negative, N (%)</th>
<th>C4d not done, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsies from patients with negative T and B cell crossmatch (N=343)</td>
<td>Biopsies from patients with positive B/negative T cell crossmatch (N=185)</td>
<td>Biopsies from patients with positive T and B cell crossmatch (N=81)</td>
</tr>
<tr>
<td>31 (9%)</td>
<td>23 (12%)</td>
<td>9 (11%)</td>
</tr>
<tr>
<td>259 (76%)</td>
<td>136 (74%)</td>
<td>56 (69%)</td>
</tr>
<tr>
<td>53 (15%)</td>
<td>26 (14%)</td>
<td>16 (20%)</td>
</tr>
</tbody>
</table>

C4d: Complement 4d. *p=0.4 when the subgroup of patients with negative T and B cell crossmatch was compared to the subgroup of patients with positive B/negative T cell crossmatch. **p=0.5 when the subgroup of patients with negative T and B cell crossmatch was compared to the subgroup of patients with positive T and B cell crossmatch.
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C4d immunoreactivity and histology in a patient with recurrent hepatitis C virus infection with cirrhosis are presented in Figure 1.

Frequency of liver allograft C4d deposition in patients with common liver diseases

After excluding 63 biopsies from 20 patients with rare liver diseases, 506 biopsies from 310 patients were studied for C4d deposition by indirect immunofluorescence. Those included patients with PSC [PSC alone (n=23) and overlap syndrome of PSC and autoimmune hepatitis (n=2)], viral hepatitis [hepatitis C (n=193) and hepatitis B (n=5)] and other liver diseases [non-alcoholic steatohepatitis (NASH), alcoholic cirrhosis, cryptogenic cirrhosis, autoimmune hepatitis, acute liver failure and others (n=87)]. The classification of the underlying pre-transplant liver disease was based on the clinical history and predominant pattern of injury. PSC mainly involved the extra-hepatic and intra-hepatic bile ducts and the category of other liver diseases consisted of disease predominantly affecting the lobular hepatocytes. Sinusoidal C4d deposition was noted in 12% of biopsies and 15% of patients (in one or more biopsies). There was no gender or age difference among the mentioned three groups.

As demonstrated in Table 2, sinusoidal C4d deposition was noted in 26% (9/35) of biopsies obtained from patients with PSC, 12% (43/348) of biopsies from patients with viral hepatitis and 7% (8/123) of biopsies from patients with other liver diseases (p=0.008). Approximately 28%, 16% and 9% of patients with PSC, viral hepatitis and other liver diseases respectively.
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Table 2. Frequency of Sinusoidal Deposition of C4d in Liver Allografts in Patients with Various Pre-transplant Liver Diseases

<table>
<thead>
<tr>
<th></th>
<th>Total patients (M/F)</th>
<th>Mean age (SD)</th>
<th>C4d positive patients (%)</th>
<th>Total biopsies</th>
<th>C4d positive biopsies (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(PSC) + (PSC+AIH)</td>
<td>25 (14/11)</td>
<td>46.2 (14.7)**</td>
<td>7 (28%)***</td>
<td>35</td>
<td>9 (26%)****</td>
</tr>
<tr>
<td>HCV + HBV</td>
<td>198 (155/43)</td>
<td>56.2 (6.8)</td>
<td>32 (16%)</td>
<td>348</td>
<td>43 (12%)</td>
</tr>
<tr>
<td>Other liver diseases*</td>
<td>87 (44/43)</td>
<td>51.0 (13.9)</td>
<td>8 (9%)</td>
<td>123</td>
<td>8 (7%)</td>
</tr>
</tbody>
</table>

PSC: Primary Sclerosing Cholangitis, AIH: Autoimmune Hepatitis, HCV: Hepatitis C Virus, HBV: Hepatitis B Virus, SD: Standard Deviation, C4d: Complement 4d. *Other liver diseases: include nonalcoholic steatohepatitis, crypogenic cirrhosis, alcoholic cirrhosis, autoimmune hepatitis alone, acute liver failure and others. **p=0.002 and 0.1 compared to chronic viral hepatitis (HCV + HBV) group and other liver diseases group respectively. ***p=0.2 and p=0.04, compared to chronic viral hepatitis (HCV + HBV) group and other liver diseases group respectively. ****p=0.04 and 0.005, compared to chronic viral hepatitis (HCV + HBV) group and other liver diseases group respectively.

Table 3. Common Pathologic Findings in Liver Allografts with Sinusoidal C4d Deposition in Patients with Various Pre-transplant Liver Diseases

<table>
<thead>
<tr>
<th></th>
<th>C4d positive biopsies</th>
<th>Acute Cellular Rejection</th>
<th>Vascular abnormality</th>
<th>Biliary impairment</th>
<th>Chronic Hepatitis</th>
<th>Steatosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSC + (PSC+AIH)</td>
<td>9</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>HCV + HBV</td>
<td>43</td>
<td>3*</td>
<td>1</td>
<td>3</td>
<td>34*</td>
<td>3</td>
</tr>
<tr>
<td>Other liver diseases**</td>
<td>8</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

PSC: Primary Sclerosing Cholangitis, AIH: Autoimmune Hepatitis, HCV: Hepatitis C Virus, HBV: Hepatitis B Virus, C4d: Complement 4d. *One case had concurrent acute cellular rejection and recurrent hepatitis C. **Other liver diseases: include nonalcoholic steatohepatitis, crypogenic cirrhosis, alcoholic cirrhosis, autoimmune hepatitis alone, acute liver failure and others.

had at least one biopsy with C4d deposition (p=0.06).

The association between C4d deposition in the post-transplant liver allograft and different pathologic abnormalities

As demonstrated in Table 3, common pathological findings in 9 liver allografts with sinusoidal C4d deposition in patients with PSC included biliary impairment (4/9; 44%), acute cellular rejection (2/9; 22%), vascular abnormality (1/9; 11%), non-specific chronic hepatitis (1/9; 11%) and steatosis (1/9; 11%). In 43 liver allografts from patients transplanted for chronic viral hepatitis, common pathological findings in liver allografts with sinusoidal C4d deposition included chronic hepatitis (34/43; 79%), acute cellular rejection alone (2/43; 5%), concurrent chronic hepatitis and acute cellular rejection (1/43; 2%), biliary impairment (2/43; 7%), steatosis (3/43; 7%) and vascular abnormality (1/43; 2%). In 8 patients with other various liver diseases including nonalcoholic steatohepatitis, cryptogenic cirrhosis, alcoholic cirrhosis, autoimmune hepatitis and acute liver failure; common pathological findings in liver allografts with sinusoidal C4d deposition included acute cellular rejection (2/8; 25%), vascular abnormality (3/8; 38%), chronic hepatitis (2/8; 25%) and biliary impairment (1/8; 13%).

Discussion

C4d as a marker of complement activation has been increasingly used clinically to aid in the diagnosis of humoral rejection in kidney, heart and pancreatic transplants. However, a recent study on immunohistochemistry staining for C3d and C4d in lung allografts showed no correlation with each other, histopathology or donor specific HLA antibodies [10]. These findings challenge the universal utility of C4d as a marker of antibody-mediated allograft rejection across different types of organ allografts. Its value in diagnosing liver rejection (either humoral and/or acute cellular rejection) is also less clear and remains controversial at the most. The conflicting nature of the current literature may be due to the heterogeneity of the studies, the different detection methods for C4d immunoreactivity and the various definitions of C4d immunoreactivity. For example, some of the studies were performed on ABO-incompatible or ABO-compatible but positive lymphocytotoxic crossmatch liver [3, 7, 11]. While immunofluorescent staining for C4d is considered the gold standard, more C4d stud-
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ies in liver allografts used immunohistochemistry [3, 7, 11]. In the current study, we used immunofluorescent staining to investigate the C4d immunoreactivity in a large series of consecutively performed liver allograft biopsies.

In our cohort, the rate of C4d deposition in liver allografts was only 12.4% at biopsy level. Our current C4d immunoreactivity rate is consistent with the reported rate of 8.9% by Bellamy COC et al [7] in a cohort of ABO-compatible liver allografts but lower than the 33-34% reported by Sakashita H et al [12]. The C4d immunoreactivity in our study was mainly at the lobular sinusoid in line with a previous report by Bellamy COC et al [7]. Only rare cases had immunofluorescence in hepatic arteries and they always involved less than 3 portal tracts in our study; consistent with a previous report that C4d deposition in portal vessels and central vein endothelia was only rarely observed with the immunofluorescence method [11]. Therefore only cases which had immunofluorescence in at least 10% lobular sinusoids were reported and considered positive for C4d deposition in this study. Also, in line with other reports (Sakashita H et al [12] and Bellamy COC et al [7]) we observed C4d immunoreactivity in liver allografts demonstrating a variety of histologic findings. However, no association between liver allograft C4d deposition and the post-transplant pathologic diagnosis was identified in our study.

Our current findings are consistent with several previous studies. Intrahepatic complement activation correlated with initial poor function and was associated with intrahepatic lactic acidosis in the donor during cold storage and after reperfusion [13]. Also, C4d immunoreactivity was reported in liver allografts with acute cellular rejection, chronic rejection, centrilobular necroinflammation, biliary impairment, primary non-functioning and in liver allografts from patients with lymphocytotoxic crossmatch [7, 12] and there was no clear correlation between C4d immunoreactivity with the histological diagnosis in ABO compatible liver allografts [12]. Collectively, these results suggest that C4d immunoreactivity in liver allografts may not necessarily be a clinically relevant marker for humoral and/or acute cellular rejection. Universal testing for C4d immunoreactivity in all liver allograft biopsies may not be necessary. Our results also suggest that C4d immunoassay may not be useful in diagnosing humoral and/or acute cellular rejection in liver allografts in patients with ABO-compatible but positive lymphocytotoxic crossmatch status. Whether immunoassay for C4d deposition in liver allograft biopsies should be performed in selected clinical settings such as ABO-incompatibility or positive lymphocytotoxic crossmatch status with detectable donor-specific antibody after transplantation to help diagnose humoral and/or acute cellular rejection remains to be determined as suggested by Kozlowski T et al [11].

In our study, there was no evidence of an association between C4d immunoreactivity and crossmatch results. This result was different from the findings reported by Bellamy et al [7]. The difference may be at least in part due to the different methods used for crossmatch testing results. Bellamy and his colleagues used the standard National Institutes of Health complement-dependent cytotoxic method that detects only complement fixing antibodies whereas we used flow cytometry that is significantly more sensitive and detects lower level of antibodies regardless of their complement fixing capability. In addition, they used immunohistochemistry performed on formalin-fixed, paraffin-embedded liver biopsies and we used immunofluorescence on frozen liver biopsies, the gold standard of C4d detection.

Interestingly, we observed an association of C4d deposition in the post-transplant liver allografts with the underlying pre-transplant liver diseases. More specifically, approximately 26% of liver allograft biopsies from patients with PSC prior to liver transplantation showed C4d deposition in the post-transplant liver allograft although C4d deposition occurred in liver allografts in patients with various underlying liver diseases. The staining pattern was sinusoidal. Further analysis showed the sinusoidal C4d deposition in liver allografts in patients with pre-transplant PSC was not associated with a particular pathologic diagnosis in the liver allografts or clinical evidence of vascular abnormality or biliary impairment. These findings suggest that mechanisms in addition to allo-immunity may activate complement. While in native liver, C4d deposition is noted in 83% of autoimmune hepatitis biopsies, 40% of hepatitis C biopsies, 89% of hepatitis B biopsies in a cohort of pediatric inflammatory liver
diseases by immunohistochemistry [14]; the frequency of C4d immunoreactivity in liver allografts in patients with autoimmune hepatitis, hepatitis C and hepatitis B is low in our series which may reflect the immunosuppressed status of these patients after liver transplantation.

While the mechanism and clinical significance of C4d deposition in liver allografts in patients with PSC remains undetermined; one possible explanation is the high incidence of complications after liver transplantation in these patients including hepatic artery thrombosis, biliary anastomotic complications including stricture and bacterial cholangitis and/or recurrent PSC [15]. Alternatively, it may be due to the underlying autoimmune abnormalities and activation of complement system in patients with PSC. One study clearly showed elevated C3d and C4d serum levels in patients with PSC when compared to patients with extrahepatic obstructive cholestasis and normal controls [16]. In addition, a case was reported of low levels of C3, C4 and CH50 in one patient with PSC and the return of these markers to normal levels after successful surgical treatment [17]. Further, elevated levels of circulating immune complexes were identified in 21 of 24 (88%) patients with PSC. These findings support the hypothesis that circulating immune complexes in patients with PSC are associated with activation of complement via the classical pathway. These findings are also in line with previous studies showing the presence of many autoantibodies in patients with PSC [18, 19]. These autoimmune abnormalities may not abate even after liver transplantation as many patients also have concurrent idiopathic inflammatory bowel disease. In addition, C4d immunoreactivity in the liver allografts in patients with pre-transplant PSC may be due to the common use of Roux-en-Y choledochojejunostomy rather than the ordinary end-to-end anastomosis and the concurrent idiopathic inflammatory bowel disease [15, 20] which allow bacterial toxins to enter the portal circulation from the intestine and subsequently activate the complement system in the liver allografts. Indeed, in one study, blood C4 level was significantly decreased in the active ulcerative colitis and a trend to increase the complement hemolytic activity in severe colitis was noted indicating complement activation in ulcerative colitis [21]. Alternatively, C4d in liver allografts may be a bystander subsequent to any significant liver injury either due to biliary impairment, vascular abnormality, chronic hepatitis, abnormal autoimmunity or alloimmunity.

In summary, C4d deposition in liver allografts is a low frequency event and with no evidence of association with lymphocytotoxic crossmatch results. The current data suggest that, while complement activation occurs in liver allografts with a variety of pathologic abnormalities and in patients with various underlying liver diseases, it occurs with greater frequency in patients with PSC compared to other common liver diseases. These findings suggest that mechanisms other than alloimmunity may activate complement. The mechanism and clinical significance of C4d deposition in liver allografts in patients with PSC remain undetermined and further studies are needed to explore this. Prospective large studies are needed to determine the clinical significance of C4d deposition in liver allografts in patients with PSC.

Disclosure of conflict of interest

None.

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