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Research review

Pathologic sequelae of allosensitization in liver transplantation

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ABSTRACT

The long-term impact of allosensitization between ABO compatible donor/recipient pairs in liver transplantation is unclear. Accumulating clinical evidence suggests that donor-specific antibody formation may lead to antibody-mediated rejection and is causally linked to pathologic injury, graft loss, and death. Although this immune-mediated graft dysfunction is increasingly being associated with poor outcomes, the specific pathologic sequelae are not defined. Herein, we examine the relationship between allosensitization, antibody-mediated rejection, and subsequent graft pathology.

Immune-mediated tissue injury in the setting of ABO incompatibility is well described after orthotopic liver transplantation (OLT) [1,2]. However, the impact of preformed alloantibodies, or posttransplant *de novo* antibody formation, in ABO compatible pairs remains controversial in liver transplantation. Early observations suggest that a positive crossmatch at the time of transplant may be associated with a higher incidence of graft loss [3–5]. More recent studies note the association of preformed class I and II donor-specific antibodies (DSAs) with severe graft injury [6], graft loss [7], and an increased risk of death [8]. Although preformed DSAs disappear in approximately 85% of patients post-OLT, persistent DSAs with a high mean MFI are thought to be responsible for antibody-mediated rejection (AMR) [5]. With an estimated prevalence of approximately 10% post-OLT, immune-mediated graft dysfunction is increasingly becoming a clinical reality. However, the long-term pathologic sequelae in the transplanted allograft are unknown.

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1. Antibody-mediated rejection

Since the early 1970s, the transplanted liver allograft is thought to be relatively resistant to AMR from preformed DSAs in the absence of the ABO barrier between a donor and a recipient [9]. This resistance may be due to the large size of the liver with dual circulation, dramatic regenerative capacity, low distribution of human leukocyte antigen (HLA) class II in the microvasculature, and Kupffer cell phagocytosis of immune complexes [10]. However, by the mid-1980s, HLA antibody formation was beginning to correlate with post-transplant liver pathology [4,11]. For example, the presence of a positive crossmatch, as well as class I and class II DSAs, is associated with vanishing bile duct syndrome [12,13] (Table). Vanishing bile duct syndrome is a well-known variant of chronic rejection. Preformed antibodies are also loosely linked to refractory thrombocytopenia and allograft failure [11]. At present, the risk factors for developing DSAs, in addition to known sensitizing events (i.e. blood transfusion, prior transplant, and so forth), continue to be defined. There is some reasonable evidence that a cyclosporine-based immunosuppression regimen, high model for end-stage liver disease score, and lower quality organs (donor risk index >1.5) significantly contribute to *de novo* DSA formation with a negative effect on outcomes [20]. Identification of the IgG3 subclass of preformed or *de novo* DSAs may be associated with the highest risk of allograft damage [21].

1.1. *Presensitization*

Preliminary experimental and clinical data from the 1980s suggested that post-OLT outcomes were comparable regardless of the crossmatch result [22,23]. However, evidence from several large centers began to identify inferior 1-mo outcomes by the presence of a positive crossmatch before transplant in the early 1990s [4,5]. In 1992, Demetris *et al.* at the University of Pittsburgh reported some very important observations. Twenty-six patients transplanted between November 31, 1989 and September 9, 1990 were crossmatch positive before transplant, compared with 52 recipients that were crossmatch negative [24]. In this cohort, presensitized recipients had a significant prolongation of early graft dysfunction and had a higher incidence of acute cellular rejection, both overall and within the first 10 d of transplant. Histologic findings associated with preformed antibodies included platelet margination in the central veins and sinusoids within 90 min of revascularization. Later biopsy specimens revealed neutrophilic portal venulitis followed by cholangiolar proliferation and hepatocellular swelling mimicking preservation injury, endothelial activation, and relapsing episodes of acute cellular rejection. The authors' suggest that presensitization may have a direct deleterious effect on allograft function and survival. A recent study by O'Leary *et al.* [8] analyzed pretransplant samples from 1270 liver recipients. In this cohort, patients with preformed DSAs were more likely to be female with autoimmune liver disease with a higher model for end-stage liver disease score. Preformed class I DSAs were found in 84 patients (6.6%) *versus* preformed class II DSAs found in 50 patients (3.9%). Both class I and II were found in an additional 50 patients (3.9%). The authors' make an interesting observation that class I DSAs persisted in only 5% of recipients *versus* 23% for class II. Importantly, class II was associated with an increased risk of early rejection and independently correlated with the risk of death.

1.2. De novo *DSA post-OLT*

Several studies have reported that *de novo* DSA after transplantation of the kidney, pancreas, bowel, and heart is associated with higher rejection rates and reduced survival [25,26]. With early reports illustrating that approximately 65% of liver recipients had measurable DSA post-OLT, Kasahara *et al.* found that if patients had DSA within the first month after living donor liver transplant, 100% experience rejection compared with only 17% with no DSA [27]. However, despite the association between DSA posttransplant and rejection, the actual incidence of *de novo* DSA formation remains uncertain. Recently, Kaneku *et al.* [28] reported a single-center experience including 749 liver transplant recipients with pretransplant and posttransplant serum samples available for evaluation in retrospective fashion. The overall prevalence of *de novo* DSA formation at 1-y post-OLT was 8.1% (61 recipients). Importantly, 58 of 61 recipients developed DSA against HLA class II antigens exclusively, the majority of which were directed at the DQ locus. The use of cyclosporine and low calcineurin inhibitor levels were associated with increased DSA formation. The authors' concluded that patients with *de novo* DSA at 1 y have a higher risk of death and graft loss. Unfortunately, given the retrospective nature of several large studies to date, it is difficult to define the temporal relationship between *de novo* DSA formation post-OLT and subsequent graft loss and/or death.

1.3. *The role of component 4d staining*

Although AMR continues to be difficult to identify clinically, specific findings in OLT recipients with unexplained graft dysfunction may include cholestasis without a cause, refractory thrombocytopenia, decreased complement levels, and circulating immune complexes [29]. To date, complement component 4d (C4d) staining has been of some assistance in diagnosing AMR. Although C4d may be visualized using immunofluorescence as a sign of AMR [30–32], there are several confusing inconsistencies surrounding the anatomic location, signal intensity, and inter-laboratory variation in liver transplant samples.

Kozlowski *et al.* [33] reported the natural history of 19 patients with a positive crossmatch before transplant. Interestingly, 15 of these 19 recipients converted to negative crossmatches post-OLT. Three of the remaining four patients developed AMR with graft dysfunction and measurable DSA. They note that linear C4d staining in the liver sinusoids, graft dysfunction, tissue injury, and demonstration of DSAs may be pathognomonic for liver AMR. A follow-up study by this group adds further support to the sinusoidal nature of C4d deposition [34]. The authors speculate that the liver sinusoids contain low-pressure nonpulsatile blood flow, which may promote antibody–endothelial antigen interaction leading to complement deposits.