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Review Article

The Diagnosis of Acute Antibody-Mediated Rejection in ABO-Incompatible Liver Transplants

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Liver transplantation (LT) across the ABO-blood type barrier is prone to antibody-mediated rejection (AMR), which often leads to a deleterious clinical outcome. While it is of paramount importance to make an early diagnosis of AMR, the morphologic features of AMR in the liver are not specific, and the differential diagnosis is often difficult or even impossible on a morphologic basis alone. The clinical utility of C4d immunostaining is limited in the liver, unlike other organs, further complicating the situation. Therefore, the diagnosis of AMR in the liver requires integration of clinical, morphologic, immunopathologic, and serological evidence.

Key Words: ABO-incompatible transplantation, Liver, Acute antibody-mediated rejection, C4d
중심 단어: ABO 부적합, 이식, 간, 급성 항체매개형 이식거부반응, C4d

Introduction

Liver transplantation (LT) across the ABO-blood type barrier (ABO-incompatible; ABOi) poses a significant risk of graft failure due to antibody-mediated rejection (AMR) caused by anti-donor blood group A/B antibodies(1). Therefore, it is important to make a correct and timely diagnosis followed by prompt initiation of the appropriate management. However, the diagnosis of AMR in liver is not straightforward and too often difficult. In this review, the pathologic features and the diagnosis of AMR in ABOi LT are briefly discussed.

General Considerations in Liver Transplantation

Liver is considered a relatively tolerogenic organ less susceptible to AMR and the resistance is attributed to a variety of characteristic features of liver which contribute to the clearing and dilution of antibodies or antigen-antibody complexes, such as Kupffer cell phagocytosis, large sinusoidal surface area, dual afferent hepatic blood supply, and secretion of soluble MHC class I antigens(2). Therefore, it was expected that liver would be a more plausible target for ABOi transplantation but it turned out that the hurdle for ABOi transplantation is higher in liver and kidney was the first organ to be successfully transplanted across ABO blood group barrier(3).

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General Pathologic Features of Acute Allograft Rejection

Allograft rejection is a form of immunologic reaction initiated by a host (i.e. recipient) after exposure to a foreign (i.e. donor) antigens. In common with other forms of immune reactions, allograft rejection is generally classified according to a major immunopathogenic mechanism. Thus, cellular rejection is mediated by immune cells infiltrating into grafted organs, a majority of which are T lymphocytes and anti-donor antibodies play an axial role in AMR.

In morphological aspects, cellular rejection is easier to demonstrate because the offender cells are readily recognized under light microscope as small dark round cells infiltrating into interstitium and tubules (as

in renal allograft) or portal tract and bile ducts often involving venules (as in hepatic allograft)(4). In contrast, the instigating antibodies of AMR are not visible under light microscope and the intragraft plasma cells are not indicators of AMR since the antibodies are produced in other organs and the roles of intragraft plasma cells are mainly in maintaining cytokine milieu. Thus, reliable histologic diagnosis of AMR had to wait for the advent of C4d immunostaining(5).

The Role of C4d in the Diagnosis of AMR

C4d is a degradation product of C4 produced in the process of complement cascade after antigen antibody interaction. It is covalently bound to the vascular surface and thus can be detected by immunostaining while other components of complement system are washed away into the blood stream(5). Positive reaction to C4d on immunostaining is a diagnostic indicator of acute AMR after renal(6,7) or cardiac(8) allograft strongly decorating interstitial capillary structures. However, the significance of C4d staining is not the same in different organs and in liver it is not clearly established(9,10).

Morphology of Hyperacute Rejection in Liver

Hyperacute rejection is caused by preformed anti-donor antibodies in the recipient and is the prototype of AMR. In liver, it presents in slightly different temporal context and the manifestation is not as "hyperacute" as in kidney, in which the characterstic findings are already encountered in the operation room. Therefore, some authors prefer the term, "primary AMR" but the basic morphologic features are equivalent to those of hyperacute rejection in other organs(11).

Pathologic features of "hyperacute rejection" can be found in failed ABOi LT and grossly, the liver is enlarged and hemorrhagic with random areas of necrosis and thrombosis in large vessels. Microscopically, inflammatory vasculitis can be found and blood vessels show reactive endothelial cells with aggregate/sludge of platelets/neutrophils(11).

Histologic Features of AMR in Liver

In liver, histologic features of AMR are not specific and constellation of microscopic findings are found depending on the timing of the biopsy and the characteristics of the antibodies(11,12). Commonly present microscopic findings include clustering of neutrophils, neutrophilic portal infiltrates, red blood cell (RBC) sludging and neutrophil margination, portal edema, focal hemorrhage in space of Disse, fibrinoid degeneration of arteries, single cell or clusters of hepatocyte necrosis, patchy geographic infarction and bile ductular proliferation. Most of the above-mentioned features reflect non-specific inflammatory reaction, endothelial/vascular damage and the subsequent consequences. These findings are not specific and can be found in a variety of other conditions such as preservation injury, hypoxic injury, septic injury and biliary obstruction all of which share common pathophysiology of endothelial damage(11-13). Particularly problematic is preservation injury, which, when severe, can present in almost identical morphologic context. Helpful features in differential diagnosis are margination of neutrophils and macrophages, endothelial activation and blastic lymphocytes and eosinophils, however, it is not always possible to make a clear distinction (Fig. 1)(12). Often present late sequelae include loss of small bile ducts, obliterative arteriopathy and obstructive cholangiopathy(14,15).

The Significance of C4d Immunostaining in Liver

The clinical implication of C4d reactivity is not straightforward in liver and there are controversial reports regarding the frequency, pattern and clinical correlation(9,16). Focal deposition of C4d in liver is found in a variety of conditions and is generally regarded as of little clinical impact. There are reports that show extensive C4d deposition is associated with AMR and correlated with graft survival(10). However, C4d deposition in liver has been reported in several other conditions, such as acute cellular rejection, chronic rejection, recurrent diseases including auto-

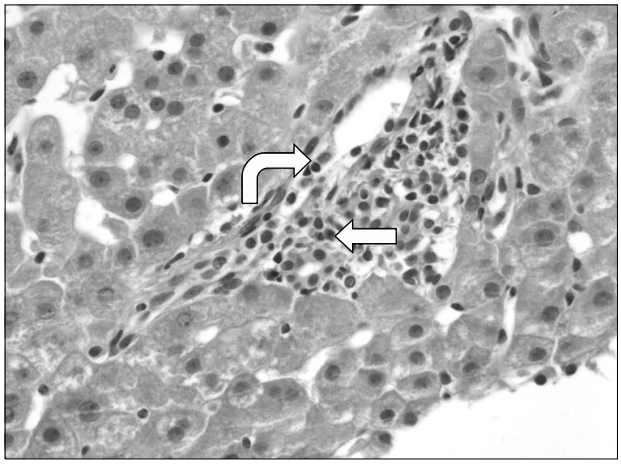

Fig. 1. Histologic features of morphologically severe preservation injury simulating AMR. Above findings are from protocol biopsy of 1 week post-transplant after ABOi LT. Portal tract shows activated endothelial cells (curved arrow) and granulocytic infiltrates (straight arrow). These findings are suggestive of AMR, however, in this patient, the level of serum transaminase was withing normal limits and C4d-immunostaining was negative. Final diagnosis of preservation injury was rendered (H&E, ×400).

immune hepatitis and even preservation injury(16-18). And it should be kept in mind that C4d is often positive in well-functioning ABOi kidney transplant(19).

Regarding the pattern of staining, it is worthwhile to cover the significance of staining in portal stroma. In view of its mechanism, it is to be expected that C4d staining is present on vascular structures and in ordinary situation of immunostaining in the practice of pathology, the decoration of stroma by markers other than mesenchymal ones, is regarded as nonspecific reaction. However, there have been reports that associate clinical outcome with C4d positivity defined as portal stromal staining(20) though the findings have not been confirmed in other studies(16). In my personal opinion, to confer significance on stromal staining is counterintuitive to most pathologists and requires thorough validation through extensive studies.

Relative consensus to date concerning C4d staining in liver can thus be summarized that the staining is sparse in native liver and that diffuse strong staining in portal microvasculature is indicative of AMR but can be found in other conditions and thus not completely specific or sensitive(16,17).

Grading of AMR

It is not surprising that there is no consensus grading system for AMR considering that the histologic diagnosi itself is not straightforward. However, it is one of second natures for pathologists to grade, and there are a few proposals for grading. One is to apply Banff rejection activity index with minor modification(20) and another is to devise a similar version(21).

Summary

AMR after ABOi LT has no highly specific histologic features and C4d immunostaining has limited utility. Therefore, the diagnosis of AMR should be defined by combined clinical, morphologic, immunopathologic and serological evidence.

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