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REVIEW

De novo autoimmune hepatitis in liver transplant: State-of-the-art review

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Abstract

In the two past decades, a number of communications, case-control studies, and retrospective reports have appeared in the literature with concerns about the development of a complex set of clinical, laboratory and histological characteristics of a liver graft dysfunction that is compatible with autoimmune hepatitis. The *de novo* prefix was added to distinguish this entity from a pre-transplant primary autoimmune hepatitis, but the globally accepted criteria for the diagnosis of autoimmune hepatitis have been adopted in the diagnostic algorithm. Indeed, *de novo* autoimmune hepatitis is characterized by the typical liver necro-inflammation that is rich in plasma cells, the presence of interface hepatitis and the consequent laboratory findings of elevations in liver enzymes, increases in serum gamma globulin and the appearance of non-organ specific auto-antibodies. Still, the overall features of *de novo* autoimmune hepatitis appear not to be attributable to a univocal patho-physiological pathway because they can develop in the patients who have undergone liver transplantation due to different etiologies. Specifically, in subjects with hepatitis C virus recurrence, an interferon-containing antiviral treatment has been indicated as a potential inception of immune system derangement. Herein, we attempt to review the currently available knowledge about *de novo* liver autoimmunity and its clinical management.

Key words: *De novo* autoimmune hepatitis; Plasma-cell hepatitis; Liver transplant; Hepatitis C virus recurrence; Antiviral therapy; Autoimmunity; Differential diagnosis

Core tip: A post-transplant pathological entity that is characterized by liver enzyme peaks, circulating auto- and alloantibodies and histological findings of interface hepatitis and plasma-cell infiltrates has been described and is considered to be a diagnostic challenge. Although the optimization of the immunosuppressive regimen should be an efficacious tool for both its prevention and treatment, rescue onsets can occur with scenarios that threaten the graft and the patient's life. Hepatitis C recurrence is not the only pathogenic context of its occurrence in liver transplants, thus the clinical interest in this condition remains high.

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INTRODUCTION

Liver transplantation (LT) represents the rescue therapy for end-stage liver disease (ESLD). The management of LT recipients is a complex issue because the natural history of the long-term survivors has been observed to depend on the possible development of unpredictable clinical complications such as acute and chronic rejection, *de novo* autoimmunity, and fibrosing cholestatic hepatitis[1-3]. For nearly two decades, the literature has provided information about series of LT patients, including children and adults, who develop transaminases increases, histological features of plasma-cell infiltrate and typical autoimmune liver serology. This phenomenon has been observed to be particularly challenging when it occurs during treatment with interferon for hepatitis C virus (HCV) recurrence[4]. While the recurrence of genuine autoimmune hepatitis (AIH) after LT should be dreaded in the mid-long-term[5-8], true *de novo* AIH can develop unpredictably in any period following LT, particularly in the setting of HCV recurrence. The hypotheses regarding the pathogenic pathways are not conclusive, and the examined risk factors have primarily focused on immunosuppression reductions or withdrawals, predisposing graft and/or host haplotypes and the use of immunomodulating agents. A prompt diagnosis and appropriate treatment of *de novo* AIH can prevent disease progression and graft loss.

COMMON DEFINITIONS AND CURRENT KNOWLEDGE

Autoimmune-based liver graft injury typically characterized by features of AIH, but occurring in transplant recipients for ESLD not caused by a previous autoimmune liver disease, has been described over the years in pediatric and adult LT. Likely because of its incomplete understanding, this disease has not yet been given a universally accepted denomination. The most common name of this condition, *i.e.*, *de novo* autoimmune hepatitis, was first used in 1998[9] (herein, "*de novo*" followed by the acronym AIH will be used), but has also been called post-LT AIH-like hepatitis[10], graft dysfunction mimicking AIH[11], posttransplant immune hepatitis[12], plasma-cell hepatitis[4,13], and *de novo* immune hepatitis[14]. The earliest descriptions of *de novo* AIH were reported in 1998 in pediatric patients and in 1999 in adult LT recipients who presented laboratory, autoimmune and histological features consistent with classic AIH[9,15]. A series of subsequent reports and studies increased the awareness of this disease in both children[12,16-30] and adults[4,11,13,14,31-53]. The experiences published thus far appear to be very heterogeneous in terms of methodology, patient identification and population size.

The earliest description of autoimmunity-related graft dysfunction in children[9] concerned 7/180 children who were observed for at least 5 years after LT. All seven of the patients presented histological features that were suggestive of *de novo* AIH: hypergammaglobulinemia, high titers of antinuclear antibodies (ANA), and/or smooth muscle antibodies (SMA) and/or liver kidney microsomal (LKM) or even "atypical" LKM (only kidney stained) autoantibodies, and 6/7 exhibited satisfactory responses to steroids and azathioprine[9]. In this cohort, 5/7 patients had donor-HLA-DRB1*03:01 and/or HLA-DRB1*04:01 allele for human leukocyte antigen (HLA)[9], but the frequency was similar to the control group. Shortly after this description, a particularly severe course of *de novo* AIH in a pediatric population was described by Gupta *et al*[18] in 2001. These authors reported on 6/115 LT recipients with at least 5 years of post-LT observation who developed *de novo* AIH. The diagnosis was definitively confirmed by International Autoimmune Hepatitis Group (IAHG)[54,55] score in only one child, and the results from the other children indicated probable *de novo* AIH[18]. Regardless, severe progression to bridging fibrosis occurred in 80% of the patients, and graft loss occurred in 33% despite steroid and azathioprine treatment[18]. In the past decades, the monitoring of graft dysfunction with possible autoimmune etiology was globally sensitized for adult LT recipients. Particular focus was put on patients with HCV recurrence who developed *de novo* AIH features during or following an interferon-based antiviral treatment course. At our hospital, 9/44 LT patients who were treated from 2001 to 2004 with pegylated interferon (Peg-IFN) and ribarivin (RBV) for HCV recurrence experienced graft dysfunction compatible with *de novo* AIH[32]. Despite prompt treatment, 2/9 of these patients died, one had graft failure, and one required re-LT. Among the 5 patients

for whom remission was obtained, 3 experienced HCV-RNA relapse. In this series, no association was observed between the HLA type and the development of *de novo* AIH. In contrast, the administration of granulocyte colony-stimulating factor (GCSF) for the treatment of neutropenia appeared to be a protective factor while the use of anti-lymphocyte antibodies was significantly correlated with the development of *de novo* AIH in this cohort[32]. Fiel *et al*[4] reported series of 214 biopsies from 38 LT recipients between 1994 and 2006 that met the criteria for plasma-cell hepatitis. A high rate (55%) of acute graft rejection was reported in this population. The patients received one of the following treatments either alone or in combination: azathioprine, 6-mercaptopurine, prednisone, methyl-prednisolone, mycophenolate mofetil (MMF), and increased doses of a calcineurin inhibitor. Satisfactory outcomes were observed in 40% of the patients, and among the remaining patients, 10 died, 3 underwent re-LT, and 10 developed disease progression to cirrhosis[4]. More recently, cases of plasma-cell hepatitis during or after triple antiviral therapy with Peg-IFN, RBV and telaprevir have been described. Ikegami *et al*[38] reported 3 cases of plasma-cell hepatitis development during Peg-IFN and RBV treatment, shortly after the completion of triple regimen with telaprevir. Because significant drug-drug interactions are known to occur between calcineurin inhibitors and telaprevir, the patients received reduced doses of cyclosporine during telaprevir co-administration and were closely monitored for cyclosporine levels[38]. Following the onset of plasma-cell hepatitis, all cases were rescued with immunosuppressive regimen optimization *via* steroid pulses, increased cyclosporine doses, and/or the addition of MMF. In one case, the antiviral treatment was stopped for safety issues[38].

PATHOGENESIS INSIGHTS

Although the pathogenesis of *de novo* AIH in LT has not yet been fully clarified, it is generally accepted that this entity shares similar *movens* mechanisms with classical AIH. The susceptible genetic milieu given by HLA DRB1*0301 and/or DRB1*0401 alleles has been implicated in AIH pathogensis while its role in *de novo* AIH is inconclusive. It is thought that the presentation of antigens, either by the recipient or donor-presenting cells, triggers the memory T cells of the host's immune system, which results in consequent self-directed immune reactions[8,56-58]. The auto-reactivity of the T cells is stimulated by a cause that is independent of chronic inflammatory *noxa* and possibly leads to the endogenous presentation of self-epitopes[59]. This phenomenon is known as "epitope spreading"[59-61]. The mechanisms that are thought to contribute to the genesis of liver graft autoimmunity are at least in part induced by immunosuppressive agents[8]. Calcineurin inhibitors may cause the impairment of T-reg cells function[8] *via* the recognition of self-antigens of the type Ⅱ major histocompatibility complex (MHC) by the T cells in a manner similar to that observed in graft-*vs*-host disease, by inducing a reduction in the production of interleukin-2 which is normally required for the survival and the proliferation of T-reg cells[62]. Notably, interactions between immunosuppressors and the maturation of the T cells have been hypothesized to exert even greater influence on immature immunity *e.g.*, in child LT recipients[63].

Moreover, viral molecular mimicry is believed to be among the potential causes of *de novo* autoimmunity[59], particularly the one exhibited by ubiquitous viruses, such as cytomegalovirus, Epstein-Barr virus and parvovirus, which are often found to infect immunosuppressed subjects and have been confirmed to be involved in a series of LT developing autoimmune features[49,64].

With special regard to the recurrence of HCV, the possible mechanisms that characterize *de novo* AIH in this setting have recently been delineated[2]. Specifically, it is hypothesized that interferon-alpha (acting on specific interferon-stimulated genes and in the context of the up-regulation of class I MHC) stimulates the activation of T-cells which, through the intensification of pro-inflammatory activity, enhance the presentation and release of antigens[2]. Apart from the virtuous effect on viral clearance, the recognition of viral antigens at the same time may lead to the expression of self-antigens, which can result in an alloimmune reaction sustained by memory T-cells[2,42,65].

HISTOLOGICAL FEATURES

In complex clinical settings in which different parameters (*e.g.*, the presence of autoantibodies without signs of effective liver injury) can mislead diagnosis, if a reasonable clinical suspicion emerges the liver biopsy should be performed. Thus far, the commonly observed histological characteristics of *de novo* AIH have been assimilated with those already described for classic AIH. Interface hepatitis and portal tract mononuclear infiltrate rich in plasma-cells are typical findings (Figure 1) along with accentuated lobular inflammation and necrosis, hepatocellular rosette (Figure 2) and features of centrolobular perive-nulitis[1,66]. The interpretation of the liver histology is more complex for *de novo* AIH than for primary AIH because the former may be affected by conditions that resemble autoimmune liver injury and that by definition do not affect native livers, such as acute and chronic rejection[1]. A particularly abundant presence of plasma cells in the portal tract and an intense interface inflammation generally address the diagnosis but do not exempt from a careful differential appraisal[67,68]. Moreover, some intrinsic variables may influence the reading of liver allograft biopsy, such as the primary diagnosis that led to LT, the time from LT,

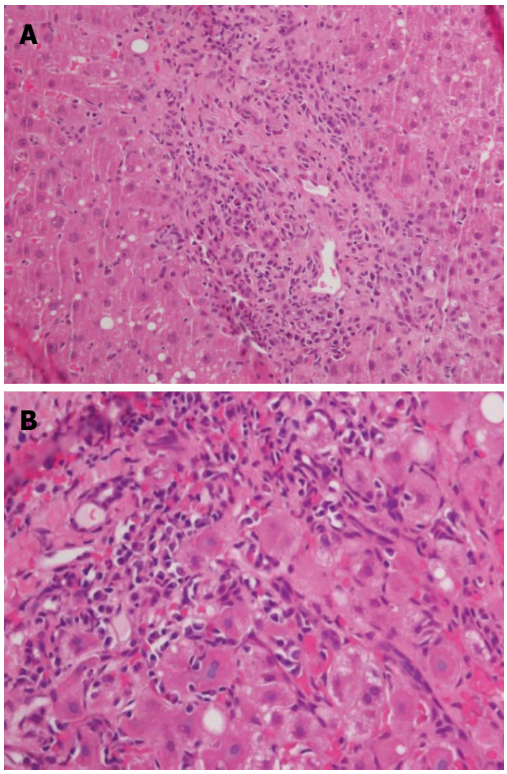

Figure 1 The portal tract. A: A moderate plasmacellular infiltrate. There is moderate interface hepatitis. The bile duct is regular. HE staining, 10 ×; B: A moderate chronic inflammatory infiltrate with plasma-cells. There is moderate interface hepatitis. The bile duct is regular. HE staining, 20 ×.

the immunosuppressive regimen, the center's previous experience in and awareness of the field, and the quality of information exchange between the clinician and pathologist[1,69].

CLINICAL ONSET AND DIFFERENTIAL DIAGNOSIS

The currently available data regarding the incidence of *de novo* AIH indicate rates of 5%-10% in pediatric LT recipients and 1%-2% in adult LT recipients, suggesting an infrequent post-LT complication in adults. Nonetheless, this disease should be considered when liver necrosis enzymes increase occurs in LT recipient, regardless of the post-LT epoch of development. Beginning with this laboratory finding, a differential algorithm is crucial for a correct diagnostic conclusion. Contextually, the elevation of gamma-globulin levels should be observed and graded, and the non-organ specific autoantibodies should be characterized[7,8] by an expert laboratory. In this sense, smooth-muscle antibodies positivity appears to be the most pathognomonic finding. With these concerns, the liver biopsy is performed and the histological features of *de novo* AIH should be observed to predominate over other etiologies of liver damage[66]. It is of note that in some cases, the diagnosis of *de novo* AIH arises from a standard one-year post-LT biopsy in the absence of prior major clinical or laboratory findings. Recently, an evaluation of the significance of non-organ specific autoantibodies was performed in a large transplanted population and revealed that the presence of serological autoimmunity seldom occurs in parallel with concrete clinical manifestations of autoimmune hepatitis[36]. This finding suggests, and it is indeed also our real-life experience, that liver biopsy is the most reliable diagnostic tool. The exclusion of possible distinct causes of graft dysfunction should comprise acute and chronic rejection, HCV recurrence focusing on its autoimmune-like presentation, biliary obstruction/stenosis, vascular complications, recurrent disease in recipients who received LT for primary biliary cirrhosis or primary sclerosing cholangitis and *ex novo* viral infections. Alternative biliary complications should be carefully excluded, particularly in patients who present with rapid laboratory deterioration including hyperbilirubinemia, which could reflect either a mechanical obstruction or the progression of underlying misrecognized *de novo* AIH to the deterioration of liver functionality. The application of the internationally agreed scoring systems for the diagnosis of AIH[54,70] to clinical, laboratory and histological parameters should definitely (or with high likelihood) confirm a suspected diagnosis of *de novo* AIH in subjects with consistent scores for whom the abovementioned alternative diseases can be excluded. However, in LT setting the immunosuppressive therapy could interfere with some of the parameters of the diagnostic criteria for the genuine AIH (*e.g.,* autoantibody profile). A complete response to the standard immunosuppressive regimen for AIH (*i.e.*, generous steroids doses in association with azathioprine) further supports the diagnosis. Notably, the steroids introduction for *de novo* AIH should be based on a meticulous diagnostic evaluation, particularly in patients with HCV recurrence, to prevent the exacerbation of viral replication[4].

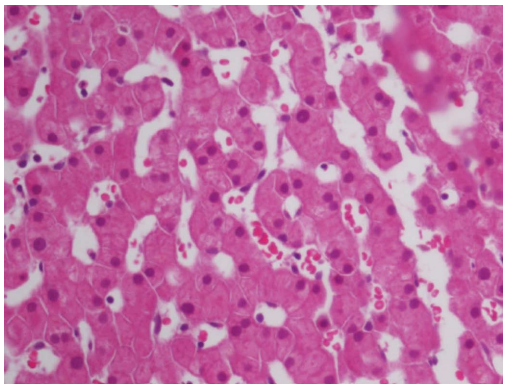

Figure 2 The lobule shows hepatocellular rosettas. HE staining, 20 ×.

The typical features that are common to each potential etiology of late graft dysfunction may be purposely reassumed to aid the differential diagnosis (Table 1). Nevertheless, despite apparently well-delineated diagnostic proceedings, a sharp distinction

Table 1 Differential features of *de novo* autoimmune hepatitis from other resembling etiologies of late graft dysfunction[1,2,7,8,58]

	de novo AIH	HCV recurrence	Acute rejection	Chronic rejection
Laboratory onset	HBV/HCV/HIV/CMV/EBV negative Moderate liver enzymes increase High IgG concentrations Positivity for ANA, SMA, LKM, atypical LKM (anti-GSTT1), and/or AMA	HCV-RNA positive Low-moderate liver enzymes increase ANA frequently positive SMA, AMA, LKM rarely positive	Transaminases elevation Immunosuppressants levels under protective limits Autoantibodies negative or mild positive	Transaminases normal/slightly increased Immunosuppressants levels under protective limits Autoantibodies negative/mild positive
Clinical presentation	Onset variable from indolent to overt, may follow an antiviral treatment for HCV recurrence, especially when viral clearance is obtained IAHG probable/definite diagnosis	Gradual progression to cirrhosis except severe forms	Rapidly progressive deterioration of liver function scores	Silent onset Slow progression to deterioration of liver function scores
Histology	Portal tract infiltrate rich in plasma-cells Interface hepatitis Rosette Lobular inflammation ± bridging/confluent necrotic foci	Chronic logistic infiltrate Possible interface hepatitis Confluent/bridging necrosis Progression to cirrhosis Possible fibrosing cholestatic hepatitis	Central perivenulitis Hepatic venous endothelitis Mononuclear/mixed portal infiltrate Bile ducts inflammation	Biliary inflammatory and ischemic pattern: bile ductopenia and inflammation, artheriolar/capillary obliterative features or loss
Treatment	Prednis(ol)one ± MMF/azathioprine	Antiviral treatment Immunosuppression levels monitoring	Steroids bolus Adjustment of immunosuppressive regimen	Steroids bolus Switch to/addition of a new immunosuppressant and/or optimization of current regimen)

AIH: Autoimmune hepatitis; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; CMV: Cytomegalovirus; EBV: Epstein-Barr virus; ANA: Antinuclear antibody; SMA: Smooth muscle antibody; LKM: Liver kidney-microsomal antibody; GSTT1: Glutathione S-transferase T1; AMA: Anti-mitochondrial antibody; IAHG: International autoimmune hepatitis group; MMF: Mycophenolate mofetil.

of *de novo* autoimmunity, particularly from forms of graft rejection, continues to be frequently question of nuance[4,34,65,66,71].

RISK FACTORS, PREVENTION AND TREATMENT

The current knowledge of *de novo* AIH suggests that whether and when a patient who has undergone LT for autoimmunity-unrelated liver disease will develop *de novo* AIH are not predictable. The relatively recent increase in the awareness of this clinical entity has effectively resulted in numerous reports in literature, but their heterogeneity continues to preclude the identification of clear predictive and risk factors of *de novo* AIH. Nevertheless, some studies have been conducted with this purpose. A large case-control study was conducted in the United States by Venick *et al*[17] with data from 788 grafts received by 619 children in a single center during an approximately twenty-year period. Among patients, 41 children who developed a *de novo* AIH (6.6%) were successively compared with control subjects who were matched in terms of the year of LT, age at LT and initial diagnosis[17]. None among the variables that were compared (age, gender, race, initial diagnosis, ischemia time, graft type, Epstein-Barr virus and cytomegalovirus infections, HLA haplotype and immunosuppressive regimen) was found to be different between the two groups[17]. In contrast, the authors found that the number of patients in mono-immunosuppression, the number of patients to whom steroids were discontinued and the number of those who presented an allograft rejection were all higher in the group of *de novo* AIH[17]. Notably, in nearly all of the patients, prednisone with or without MMF was found to be a successful treatment choice[17].

In 2008[33], a study examined the potential role in the pathogenesis of *de novo* AIH of immunoglobulin subtype 4 (IgG4), which has been implicated in different autoimmune diseases[72]. Four of 72 (5.6%) adult living donor LT recipients who underwent transplantation within a 10-year period at a single center were diagnosed with *de novo* AIH[33]. The serum and liver tissue levels of IgG4 of these patients were adequately measured and found to be normal with the exception of one patient who exhibited only a mild positivity and thus suggesting that IgG4 is not a plausible co-factor in the development of *de novo* AIH[33].

Lodato *et al*[73] compared LT recipients treated with GCSF to those who did not receive GCSF in terms of the incidence of *de novo* AIH. A significantly lower incidence was observed in the GCSF group, which supports the protective immunomodulatory effect of GCSF against liver autoimmunity in the post-LT setting[73].

Several studies[14,74-76] were conducted that focused on the role of the glutathione S-transferase T1 (GSTT1) gene as a risk factor for *de novo* AIH development. Aguilera *et al*[77] identified in patients who present with *de novo* AIH, specific antibodies produced against donor GSTT1 gene due to a mismatch between the wild-type carried by the donor and recipient's null genotype. Moreover, a retrospective analysis of liver biopsies from patients with *de novo* AIH who expressed GSTT1-Ab was conducted by the same authors to explore the presence of complement component 4d (C4d)[77]. C4d-positivity was observed to localize in the portal tracts of nearly all of the *de novo* AIH specimens, while in two control groups, sinusoidal C4d-positive pattern was present in 4/7 biopsies from patients who experienced rejection[77]. Finally, this question was further explored in successive studies that identified the influence of the type of immunosuppression on the definite clinical manifestations of GSTT1 genetic mismatch[78]. In the latter data, among 35 LT recipients a significantly greater proportion of those who did not produce anti-GSTT1 antibodies and did not manifest *de novo* AIH was observed among the patients who received tacrolimus (± MMF) than among those who received cyclosporine[78]. In a study of a GSTT1-mismatch positive LT population, the male gender of the donor and non-alcohol related pre-LT disease were found to be predictive of *de novo* AIH[79].

In another study[80] an enhanced immunosuppressive regimen that included steroids in addition to tacrolimus and MMF, has been shown to be protective against late graft rejection. In turn, as reported in the above-mentioned studies, the occurrence of rejection was implied to be a predisposing factor for the appearance of *de novo* AIH[17]. Indeed, a study of a large series of adult LT recipients with features compatible with acute rejection observed that more than half of the patients were effectively diagnosed with *de novo* AIH[4].

Finally, it is worth noting that in LT recipients for HCV-related end-stage liver disease, HCV *per se* can be associated with serum autoimmunity profile positivity and the systemic manifestations of this condition[81,82]. Indeed, HCV infection is thought to incite autoimmune injury in genetically predisposed subjects[83].

Corticosteroids remain the milestone of the treatment of *de novo* AIH but should be accompanied by the optimization of calcineurin inhibitors posology[84]. Azathioprine or MMF should be added, whereas calcineurin inhibitors and steroids do not provide prompt benefit[84].

CONCLUSION

De novo autoimmunity in LT is a complex clinico-pathological issue due to both the incomplete understanding of its pathogenesis and its challenging diagnostic interpretation. Fortunately, growing experience and sensitivity to this post-LT complication have been elicited by numerous reports in the literature, in-depth pathophysiological studies and the sharing of real-life experiences of therapeutic approaches. Steroids seem to be successful in most cases, but there is no universally accepted therapeutic scheme, and the most adequate treatment needs to be tailored according to each patient's clinical history and situation.

In the near future antiviral treatments for post-LT HCV recurrence will hopefully be fully based on potent new direct-acting antiviral agents in all-oral, interferon-free regimens. However, *de novo* AIH has been widely observed to develop in LT recipients with etiologies other than HCV. Therefore, given the complexity of the follow-up of liver allografts, strict awareness is needed in this setting for the detection and correct interpretation of liver enzymes increase, particularly during but not limited to long-term post-LT follow-up.

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