

Autoimmune Hepatitis After Liver Transplantation

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1. Introduction

Autoimmune hepatitis (AIH) is a progressive, chronic inflammatory liver disease of unknown etiology that occurs in children and adults with a prevalence of female. This clinical syndrome is caused by an immune response that is misdirected against self or foreign antigens that resemble self-antigens, leading to a progressive inflammatory and fibrotic process of the liver (Krawitt, 2006; Czaja, 2001, 2007a, 2007b; Vergani et al, 2002; Manns & Vogel, 2006, Vergani & Mieli-Vergani, 2008). The complications of AIH are the same as any other progressive liver disease. Primary hepatocellular carcinoma is a known consequence; in some patients, chronic hepatitis progresses to cirrhosis and, ultimately, to carcinoma. Liver transplantation is required when end stage liver disease develops (Krawitt, 2006).

AIH has been widely described in liver transplant recipients with and without AIH before transplantation. In the first scenario the term of recurrent AIH has been proposed, while de novo AIH implies the development of AIH in the graft of a recipient who did not have the disease before. De novo and recurrent AIH develop in the clinical context of immune suppression. Consequently the diagnosis may depend more heavily on the exclusion of other causes for allograft dysfunction rather than on the presence of criteria for the diagnosis of classic AIH codified by the international scoring system. The careful analysis of these cases provides exiting and exceptional opportunities to study the pathogenesis of AIH in a human model. To understand the bases for recurrent and de novo AIH after liver transplantation, it is necessary to apply current hypotheses of pathogenesis for classic disease.

2. Pathogenic mechanism of AIH

The pathogenesis of AIH remains uncertain, but conditions that favor its emergence are becoming clearer. Environmental agents like viruses, toxins or drugs (Krawitt, 2006, Czaja et

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al, 1992, Czaja, 1999a) may trigger a cascade of T-cell mediated events against liver antigens in a context of genetic predisposition (Czaja & Manns, 1995; Alvarez, 1999, Molmenti et al, 2002; Sanchez-Urdazpal et al, 1992), leading to a progressive necroinflammatory liver disease.

Although multiple genes are probably involved in a predisposition to AIH, human leukocyte antigen (HLA) genes appear to play the dominant role (Donaldson et al 1998, Donaldson, 2002). Type 1 AIH, characterized by circulating antinuclear antibodies, smooth muscle antibodies, antiactin antibodies, atypical perinuclear antineutrophilic cytoplasmic antibodies and autoantibodies against soluble liver antigen and liver-pancreas antigen is associated with the HLA DR3 serotype, particularly among white patients. In Japan the most common associated HLA locus is HLA DR4; among white North Americans and northern Europeans, susceptibility relates to the alleles DRB1-0301 and DRB1-0401 (Hytiroglou et al, 2009; Hennes et al, 2008). Type 2 AIH, a rare disorder characterized by antibodies against liver-kidney microsomal 1 and liver cytosol 1 has been associated with the HLA DRB1 and HLA DQB1 alleles (Djilali-Saiah et al 2004).

Loss of self tolerance is the requisite for autoimmune disease, and it distinguishes autoimmune conditions from disorders associated with immunologic reactions to foreign antigens. The most promising considerations are defects in the negative selection of autoreactive immunocytes (Czaja, 2007c; Czaja & Carpenter, 2006) and clonal expansion of immunocytes cross-reactive to homologous antigens (molecular mimicry) (Hubscher, 2001; Prados et al, 1998; Ayata et al, 2000). The negative selection removes thymocytes that are capable of strongly binding with self peptides presented by major histocompatibility complex (MHC). This process is an important component of immunological tolerance and serves to prevent the formation of self reactive T cells. According to experimental evidences the risk of autoimmune disease probably relates to actions of genes that limit this process (Czaja & Carpenter, 2006; Banff Working Group, 2006). Molecular mimicry has been proposed as pathogenetic mechanism for AIH. This hypothesis has been substantiated in experimental models by showing that the immunocytes can be activated by diverse but similar epitopes, and they can be clonally expanded to show a broad cross-reactivity. Such cells then can be directed against self-antigens that mimic foreign antigens (Hubscher, 2001; Prados et al, 1998; Ayata et al, 2000). Molecular mimicry is a useful concept to explain how different viruses, drugs or unknown environmental agents might produce a self-perpetuating hepatic injury with the same clinical expression. It also may explain how AIH recurs or develops *de novo* after liver transplantation. In addition, experimental evidences suggest that genetic polymorphisms affecting the cytokine microenvironment (Gonzales-Koch et al, 2001; Donaldson et al, 1991), immune regulators (Czaja et al, 1993a) and the mechanism of apoptosis (Czaja et al, 1997) could influence the immunocyte activation and perpetuate the immune response.

The identification of CD4+ regulatory T cells has reinvoked the concept that failure of or escape from normal suppression of reactivity against the self has an essential role in the development of autoimmune disease. Recent experimental evidence suggests that immunoregulatory dysfunction characterized by decreased numbers of CD4+CD25+ regulatory T cells may occur in AIH (Longhi et al, 2004).

2.1 Pathogenesis of recurrent AIH

AIH recurs after liver transplantation in 11% to 83% of cases with considerable variation between studies depending on the diagnostic criteria applied. Many studies suggest that the

risk of recurrence increases with the time after transplantation (Birnabaum et al, 1997; Campsen et al, 2008; Prados et al, 1998; Sempoux et al, 1997). In an interesting study, Duclos-Vallee et al. suggest that the histological recurrence of AIH may develop 1-5 years before the laboratory manifestations (Duclos-Vallee et al, 2003).

The pathogenesis of recurrent AIH is uncertain, although it is widely accepted that a strong genetic predisposition may affect its occurrence, behavior and outcome (Czaja, 2008a), as well as its risk of recurrence (Czaja, 1999b, 2002, 2009). HLA mismatching between donor and recipient has been proposed as a factor in recurrent disease (Wright, 1992), but its importance continues to be disputed (Gonzales-Koch et al, 2001; Ayata et al, 2000; Milkiewicz, 1999, Reich, 2000, Devlin, 1995). Some authors suggest that matched rather than mismatched HLA may be a factor influencing the development and severity of the disease (Neumann et al, 2003; Futagawa & Terasaki, 2004). In this instance, it seems that similar class II MHC molecules between donor and recipient can intensify the autoreactive response.

HLA DRB1*03 is present in over 70% of the recipients who experience recurrence (Gonzales-Koch et al, 2001), and the DRB1*0301 allele may be a factor in promoting disease severity before transplantation (Czaja, et al, 1997) and disease recurrence after transplantation (Gonzales-Koch et al, 2001, Czaja, 2008b, Devlin et al, 1995). Other autoimmune promoters might include gene polymorphisms that alter the cytokine microenvironment (Czaja et al, 1999a) or involve polymorphisms of genes affecting immunocyte activation, such as those encoding cytotoxic T lymphocyte antigen-4 (Agarwal, 2000). Furthermore, the female predisposition for recurrent AIH suggests that an acquired preferential X chromosome inactivation (that has been described in primary biliary cirrhosis) may also be important (Miozzo et al, 2007). Potential associations with loci in other chromosomes are under investigation (Fukagawa et al, 2001; Vogel et al, 2002).

The donor liver may contain antigenic substrates against which the recipient-derived immunocytes can react, and these substrates could be normal components that share homologies with other self-antigens within the recipient (Czaja, 2002). The structural and conformational homologies between antigenic targets within the donor liver and those within the recipient might provoke a promiscuous T cell response through molecular mimicry.

Knowledge concerning antigenic targets responsible for initiating the cascades of events in recurrent AIH is still rudimentary. A leading candidate has been the asialoglycoprotein receptor, a surface membrane protein. Hepatocytic microsomal enzymes, such as CYP2D6, and cytosolic components, such as transfer ribonucleoprotein complexes, are also under investigation (Czaja, 2002). Professional antigen presenting cells exist outside the liver, and antigenic peptides can be presented and subsequently processed independently of the graft (Obhrai, 2006; Bell & Westermann, 2008; Vierling, 1999). T cell subsets, cross-reactive to homologous hepatic antigens, could be expanded by the presentation of donor antigens on recipient-derived antigen-presenting cells that replace those of the donor liver (Vierling, 1999). The rapidity of this replacement and the number of antigen-presenting cells in the recipient lymph nodes and spleen might affect the timing and severity of the recurrence (Czaja, 2002).

Promiscuous T cells that have been primed to react to molecular homologies are probably already present within the recipient (Sprent, 1993; Vierling, 1999), and the appearance and

severity of recurrent AIH simply reflect the dose of antigenic targets within the donor liver (Czaja, 2002). Alternatively, the immunological response may be newly created by protracted exposure to donor-derived hepatic antigens (Czaja 2002, 2009). This hypothesis suggests that recurrent AIH could reflect an immune response against donor liver antigens that is not HLA-restricted (Czaja, 2002). The class II MHC molecules within the donor liver could directly activate the immunocytes of the recipient and generate a response that is not dependent on the presentation of antigenic peptide or HLA matching (Vierling, 1999). In this instance, the MHC molecules of the donor liver would be the antigenic targets and HLA restrictions on immunocyte activation would be overridden.

Components of the Autoreactive Response	Putative Mechanisms
Class II MHC molecules	Present autoantigen to T helper lymphocyte Initiate immunocyte activation
HLA susceptibility alleles	Encode structure of the antigen binding groove of the class II MHC molecule Determine optimal autoantigen for presentation <i>DRB1*03</i> in white North Americans
Professional antigen presenting cells	Macrophages and dendritic cells Exist outside the liver within the recipient Re-populate the donor liver after transplantation
Donor liver autoantigens	Promote promiscuous T cell response against homologous targets in the donor liver, such as microsomal antigens (CYP2D6, UDG), cytosolic components (ribonucleoprotein complexes), surface membrane receptors (asialoglycoprotein receptor), class II MHC molecules, or superimposed viral antigens
Promiscuous T lymphocytes	Target multiple antigens in the donor liver that resemble the original activating epitope Retain long memories for the antigenic target Re-invigorate after long dormancy
Counter-regulatory cytokines or regulatory T cell populations	Facilitate autoreactivity by reduced suppressive actions

Abbreviations: CYP2D6, cytochrome 2D6; HLA, human leukocyte antigen; MHC, major histocompatibility complex; UDG, uridine diphosphate glucuronosyltransferase

Table 1. Pathogenic Mechanisms of Recurrent Autoimmune Hepatitis

Viral infections are another source of antigenic homologies that may activate promiscuous T cells (Czaja, 2002) (Table 1). The genomic sequences of hepatitis C virus, herpes simplex virus, and cytomegalovirus have homologies with CYP2D6 (Manns et al, 1991; Ma et al, 2006), and other mimics between viral and self-antigens undoubtedly exist that can trigger recurrent AIH (Vergani et al, 2002; Bogdanos et al, 2001). Viruses may also produce an inflammatory process within the graft that may resemble the recurrent AIH. An anti-graft response against a viral antigen may be indistinguishable from an autoimmune response, and the recurrent AIH in this instance could represent a normal immune response against an unsuspected viral agent in an immunosuppressed host (Vierling, 1999). The complexity and inner connectivity of the counter-regulatory mechanisms that must be disrupted to cause recurrent AIH allows broad speculation about the triggering events and the factors which perpetuate the disease (Czaja 2002, 2008b).

Another factor related to the recurrence of AIH is represented by the net state of immunosuppression. Corticosteroid withdrawal, adjustments in the dose and nature of the immunosuppressive drugs (cyclosporine, tacrolimus, and mycophenolate mofetil), acute and chronic rejection, superimposed infection, and drug toxicities are post-transplantation events that have all been implicated in the recurrence of AIH (Hubscher, 2001; Neuberger, 2002; Schreuder et al, 2009). Recurrence has been associated with reduction in the doses of immunosuppressive medication, especially corticosteroids (Neuberger et al, 1984; Gonzalez-Koch et al, 2001; Prados et al, 1998; Khalaf et al, 2007). These observations indicate that the pathogenic mechanisms of AIH are perpetuated after liver transplantation and that they can be suppressed but not eradicated by treatment schedules that are properly dosed (Czaja, 1999b). Recent studies, however, have indicated that the requirement for corticosteroid suppression may not be permanent after liver transplantation and that corticosteroid therapy can be successfully withdrawn in 50-68% of patients (Campsen et al, 2008; Trouillot et al, 1999). There is evidence that AIH recurs in 35% of individuals withdrawn from corticosteroids, but the recurrence has not been associated with discontinuation of the medication by multivariate analysis (Campsen et al, 2008). These findings do not discount the earlier observations that corticosteroid withdrawal or dose reduction contributes to disease recurrence, but they suggest that successful withdrawal is possible if the effort is persistent, individualized and well-timed (Czaja, 1999b).

Patients transplanted for AIH have a higher frequency of acute and chronic rejection (81% versus 47%, $p < 0.001$) and corticosteroid-resistant rejection (38% versus 13%, $p = 0.003$) than patients transplanted for other conditions (Vogel et al, 2004; Hayashi et al, 1998), and in one series, the frequency of acute cellular rejection was higher (33% versus 14%) than in other transplanted patients from the same institution and from other institutions (33% versus 4%) (Czaja, 1999b; Trouillot et al, 1999). The propensity for acute and chronic cellular rejection may reflect an intrinsic immune hyper-reactivity within the patient with AIH (Czaja, 1999b). Alternatively, rejection may be the basis for releasing hepatic antigens that sensitize the susceptible individual and trigger the recurrence (Czaja, 2009). Patients with recurrent AIH have a higher frequency of rejection during the first 3, 6 and 12 months after transplantation than patients without recurrent disease, but previous rejection is not a requisite for recurrence (Molmenti et al, 2002). Another factor that has been implicated in recurrence has been the calcineurin inhibitors used in the immunosuppressive regimen after transplantation (Schreuder et al, 2009; Gautam et al, 2006). Cyclosporine and tacrolimus may have paradoxical effects which can promote the autoreactive response. Cyclosporine inhibits

signal transduction from the engaged T cell antigen receptor (Hess et al, 2001), and it may also have a direct toxic effect on the thymic stroma (Beschorner et al, 1988). These actions may alter the editing of T lymphocytes within the thymus and impair the negative selection of autoreactive cells. Furthermore, the impairment of T cell antigen receptor signaling can prevent the apoptosis of autoreactive lymphocytes which can in turn extend their survival (Lotem et al, 1999; Wang et al, 1999). Tacrolimus affects the thymic microenvironment in a fashion like cyclosporine, and it might also paradoxically enhance immune reactivity (Cooper et al, 1991). These theoretical considerations have not been established in human disease (Gautam et al, 2006), and both medications have been used successfully in the treatment of recurrent AIH (Hubscher, 2001). Nevertheless, the failure of recurrent AIH to respond to one calcineurin inhibitor might warrant institution of the other (Hurtova et al, 2001).

Risk Factor	Theoretical Consequences
Long duration after transplantation	Activated "memory immunocytes" re-charge Corticosteroids are withdrawn Immunosuppressive regimens are reduced Acute or chronic cellular rejection occurs Drug toxicity develops Viral infection superimposed
Corticosteroid withdrawal	Facilitates autoimmune response
Reduced immunosuppression	Facilitates autoimmune response
Acute or chronic rejection	Releases hepatic antigens Invigorates promiscuous lymphocytes
Calcineurin inhibitor	Reduces thymic negative selection of immunocytes Impairs apoptosis of activated immunocytes Provokes paradoxical autoreactive response
HLA matching or mismatching	Intensifies autoreactive response
Female gender	Acquired preferential X chromosome inactivation Impairs mechanisms that protect self-tolerance
Severity of original disease	Immune reactivity persists post-transplant Genetic predisposition for severe disease facilitates recurrence

Table 2. Risk Factors Associated with Recurrent Autoimmune Hepatitis After Transplantation

The severity of the original liver disease may also be a factor in disease recurrence after liver transplantation. Patients with recurrent AIH have higher serum levels of immunoglobulin G and histological findings of plasma cell infiltration and severe inflammatory activity more often immediately prior to transplantation than patients without recurrence (Montano-Loza et al, 2009). These observations suggest that recurrent AIH is a continuum of the original disease or a newly created process in a susceptible host with a propensity for severe immune reactivity (Czaja, 2009). They imply that aggressive disease suppression immediately prior to transplantation might alter the consequences after transplantation (Montano-Loza et al, 2009) or that an vulnerable individual may be identified early who warrants close surveillance after transplantation (Czaja, 2009). Most likely, the intrinsic bases for recurrent AIH interact with the extrinsic factors to define the true risk.

2.2 Pathogenesis of de novo AIH

De novo AIH is a late complication that develops in patients undergoing transplantation for nonautoimmune liver disease (Czaja, 2002, 2007b). Since its first description by the King's College group (Kerker et al, 1998), it has been widely reported in both adult and child recipients after deceased or living liver donor (Hernandez et al, 2001; Gupta et al, 2001; Henegan et al, 2001; Salcedo et al, 2002; Aguilera et al, 2001; Miyagawa et al, 2004; Inui et al, 2005; Venick et al, 2007; Di Cocco et al, 2008). The frequency of de novo disease may be increased because the population at risk is exposed to a great number of risk factors. Children seem to have a predilection for the syndrome (Birnbaum et al, 1997; Campsen et al, 2008; Duclos-Valle et al, 2003; Yao et al, 2007; Czaja & Freese, 2002) and immunosuppression with cyclosporine is a common feature (Birnbaum et al, 1997; Pappo et al, 1995; Czaja & Freese, 2002).

Pathogenic mechanisms involved in the de novo AIH probably are the same as those responsible for the disease before transplantation. Impaired negative selection of autoreactive immunocytes and molecular mimicry are still the principal pathogenic considerations, but their emergence as initiators of disease must be analyzed within the context of the clinical setting. Immunosuppressive therapy and exposure to diverse pathogens after transplantation may severely compromise the ability of an immune system already weakened by chronic illness and/or immaturity to preserve self tolerance.

Cyclosporine inhibits signal transduction from the engaged T-cell antigen receptor (Ayata et al, 2002) and also may have a direct toxic effect on the thymic stroma (Seyam et al, 2007). These actions may alter the editing of T lymphocytes within the thymus and impair the negative selection of autoreactive cells. Impairment of T cell antigen-receptor signaling can prevent the apoptosis of class II MHC-restricted autoreactive lymphocytes, which in turn may leak into the peripheral compartment and be intolerant of self. Cyclosporine inhibits the calcineurin-mediated pathway in the signaling of the apoptosis, and in this fashion, it may extend the survival of autoreactive cells (Czaja, 1999b, 2007b; Khalaf et al, 2007). Active immune mediated lesions within the colon, liver, stomach, and pancreas have been described in an animal model treated with cyclosporine, and the findings constitute cyclosporine-induced autoimmune disease (Trouillot et al, 1999).

A T-cell-dependent autoaggressive disease also has been reported after syngenic and/or autologous bone marrow transplantation in recipients treated with cyclosporine (Hayashi et

al, 1998), and it may reflect cyclosporine-induced failure of T-lymphocytes to recognize class II MHC antigens as self (Gautam et al, 2006; Hess et al, 2001). Pretreatment of animal models of bone marrow transplantation with monoclonal antibodies against class II MHC determinants prevents adoptive transfer of syngenic graft-versus-host disease, whereas antibodies against class I MHC antigens are unable to prevent this outcome (Beschorner et al, 1988; Lotem et al, 1999). Tacrolimus affects the thymic microenvironment in a fashion like cyclosporine, and it also can induce a graft-versus-host-like reaction after syngenic bone marrow transplantation in rats (Cooper et al, 1991). These observations suggest that such immunosuppressive drugs (cyclosporine and tacrolimus) may have paradoxical effects in some liver transplant patients. Immunosuppression is the desired primary action, but enhanced autoreactivity may be a secondary consequence in some individuals. Young patients with immature immune system would logically be most vulnerable for the autoimmune response and most instances of de novo AIH have been reported in the pediatric group. An active thymus, immature T-cell-antigen receptor repertoire and repeated exposure to multiple homologous infectious and/or drug-related antigens would be likely additional requisites for de novo disease.

Importantly, no conclusive data show that cyclosporine or tacrolimus induce AIH in humans, and both medications have been used successfully to treat classic AIH in adults and children (Cooper et al, 1991; Hurtova et al, 2001; Czaja, 2008; Wright et al, 1992; Reich et al, 2000; Devlin et al, 1995). Furthermore, animal models of cyclosporine-induced AIH have been highly perturbed models that may have no clinical relevance (Trouillot et al, 1999).

3. Clinical features and diagnostic criteria

AIH is an inflammatory process of unknown cause that is characterized by increased serum aspartate (AST) and alanine (ALT) aminotransferase levels, hypergammaglobinemia, autoantibodies, and interface hepatitis on histological examination (Krawitt, 2006; Czaja & Freese, 2002). Immunoglobulin G is the predominant serum γ -globulin component that is abnormally increased, and the typical autoantibodies associated with the disease are antinuclear antibodies (ANA), smooth muscle antibodies (SMA), and antibodies to liver kidney microsome type 1 (anti-LKM1) (Czaja, 2007b).

Antinuclear antibodies and SMA tend to cluster together, and they are not commonly expressed in association with anti-LKM1 (Homberg et al, 1987; Czaja et al, 1992; Czaja, 1999a). This mutual exclusivity has justified the designations of type 1 AIH to identify the disease associated with ANA and SMA and type 2 AIH to identify the disease associated with anti-LKM1 (Czaja & Manns, 1995). These terms have not been endorsed by the International Autoimmune Hepatitis Group (IAIHG) since the serological types may not be distinct pathological entities (Alvarez et al, 1999). Nevertheless, the designations have been useful descriptors in clinical practice and in research studies, and they have become entrenched in the terminology of the disease. The same basic features of AIH in the native liver have characterized recurrent AIH in the transplanted liver.

Transplant recipients with AIH are younger and more commonly women than other transplant recipients (Molmenti et al, 2002), and they have HLA DRB1*03 more frequently (Sanchez-Urdazpal et al, 1992; Gonzalez-Koch et al, 2001). HLA DRB1*03 and DRB1*04 are the principal susceptibility factors for AIH in white North American and northern European

patients (Donaldson et al, 1991), and HLA DRB1*03 has been associated with early age of disease onset and a higher frequency of treatment failure than patients with other HLA (Czaja et al, 1993, 1997; Czaja & Carpenter, 2006). The same clinical phenotype that has typified AIH in native patients also characterizes the patients who develop recurrent disease after transplantation (Gonzalez-Koch et al, 2001; Hubscher, 2001). In de novo AIH, Salcedo et al. found a significant increase in the prevalence of HLA DR3 and a trend to higher frequencies for HLA-B8, -DR15, -DR51 and -Q6 (Salcedo et al, 2002). Symptoms may vary from none to severe (jaundice and hepatic failure), and the presence of disease must be actively sought in asymptomatic patients by the regular monitoring of liver indices (serum AST, ALT, bilirubin, and γ -globulin levels) and protocol liver biopsies (Pappo et al, 1995; Duclos-Vallee et al, 2003; Yao et al, 2007).

Type	Feature	Frequency
Clinical	Female	Common
	Young	Common
	Asymptomatic	Common
	Jaundice	Rare
Laboratory	Increased Serum AST/ALT	Required
	Increased Serum γ -globulin	Usual
	Increased Serum immunoglobulin G	Usual
	HLA DRB1*03	Common (ethnic dependent)
	No viral markers	Required
Serological	ANA/SMA	Common
	Anti-LKM1	Possible
Histological	Interface hepatitis	Required
	Plasma cell infiltration	Common
	Lobular hepatitis	Rare
	Acidophil bodies	Rare
	Mixed features	Possible
	Non-specific hepatitis	Possible

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ANA, antinuclear antibodies; anti-LKM1, antibodies to liver/kidney microsome type 1; HLA, human leukocyte antigen; SMA, smooth muscle antibodies

Table 3. Clinical Features of Recurrent Autoimmune Hepatitis After Liver Transplantation

The importance of autoantibodies in the diagnosis of recurrent and de novo AIH is still debated. The majority of patients in whom a diagnosis of recurrent AIH is made have positive autoantibodies. However, several studies have shown that autoantibodies persist in the majority of patients who undergo transplantation for AIH, generally at lower titers than before liver transplantation, irrespective of other features suggestive of disease recurrence (Ahmed et al, 1997; Prados et al, 1998; Gotz et al, 1999; Reich et al, 2000). This is analogous to

the situation that exists for patients undergoing liver transplantation for primary biliary cirrhosis; most remain positive for antimitochondrial antibodies without necessarily having other features to suggest disease recurrence (Esquivel et al, 1988; Mattalia et al, 1997). One study suggested that the presence of autoantibodies in titers exceeding pretransplantation levels may be the manifestation of recurrent AIH (Reich et al, 2000) but this observation, based on small number of cases requires further confirmation. It is possible as suggested by Gonzales-Koch et al., that the formation of autoantibodies may be impaired in the setting of immunosuppression (Gonzales-Koch et al, 2001). Impaired antibody formation after liver transplantation is well recognized in hepatitis C virus (HCV)-positive patients, many of whom have high viral RNA levels without detectable anti-HCV antibodies (Poterucha et al, 1992; Hsu et al, 1994).

Autoantibodies arising *de novo* after liver transplantation have also been noted in association with episodes of rejection (Duclos-Valle et al, 2000). Classic autoantibodies are commonly present in the serum of these patients but atypical serum autoantibodies are characteristically observed (Alvarez et al, 1999; Hubscher, 2001). Among these atypical antibodies, one antibody type seems to be direct against the cytosolic enzyme glutathione S-transferase T1. Interestingly GSTT1 mismatch between the donor and the recipient has been reported as a prerequisite for the development of *de novo* AIH after liver transplantation (Aguilera et al, 2001; Inui et al, 2005). In addition the early detection of anti-GSTT1 antibodies may help to identify a subset of patients at risk of developing *de novo* AIH (Salcedo et al, 2009).

Several studies have shown the important role of the routine liver biopsies in the diagnosis of AIH without biochemical evidence of hepatitis (Ahmed et al, 1997; Prados et al, 1998; Gotz et al, 1999). Interface hepatitis is the histological hallmark of recurrent AIH after transplantation, and plasma cell infiltration is a feature of the disease (Gonzalez-Koch et al, 2001; Hubscher, 2001; Ayata et al, 2000; Banff Working Group et al, 2006) Concurrent immunosuppressive therapy can modify the nature and severity of the inflammatory infiltrate, and the histological diagnosis may be based on more subtle changes than those observed in the native disease (Gonzalez-Koch et al, 2001; Hubscher, 2001). Plasma cell infiltration is neither specific nor required for the diagnosis of recurrent AIH (Banff Working Group et al, 2006). Acidophil bodies in conjunction with lymphoplasmacytic infiltrates are seen in early recurrent AIH (Ayata et al, 2000), and an acute lobular hepatitis is also compatible with the diagnosis (Ayata et al, 2000; Sempoux et al, 1997). The histological changes of acute or chronic rejection may occur simultaneously with those of AIH, and concurrent pathological processes must be considered when confusing mixed and atypical histological features are present (Pappo et al, 1995; Hytioglou et al, 2009).

The histological findings of *de novo* AIH may differ from the interface hepatitis usually found in the classic AIH (Gupta et al, 2001). In *de novo* AIH there is histological evidence of portal and periportal hepatitis with or without centrilobular necrosis and lymphoplasmacytic portal tract infiltrate with a variable degree of plasma cells. Histological features of bile ductular proliferation and markedly increased serum concentrations of gamma glutamyl transpeptidase suggest the likelihood of treatment failure and probably indicate a variant syndrome of AIH (Campsen et al, 2008; Berg et al, 2002). *De novo* disease in some adults has been associated with severe centrilobular necrosis that may confound diagnosis and adult patients have been reported to express an atypical antiliver/kidney

cytosolic antibody of uncertain pathogenic significance (Czaja, 2007b). This antibody reacts to rat hepatocyte cytoplasm, chiefly in the centrilobular area, and also shows indirect immunofluorescence in distal and proximal tubules of rat kidney (Czaja, 2007b).

The diagnostic guidelines (Alvarez et al, 1999), not tested in patients receiving immunosuppressive therapy, cannot be used with confidence in the post-transplantation setting (Hubscher, 2001; Li & Neuberger, 2009; Neuberger, 2002; Duclos-Valle, 2005; Schreuder et al, 2009). As stated before, the diagnosis of recurrent and de novo AIH requires the presence of compatible clinical, laboratory and histological findings, and it depends mainly on the exclusion of other conditions that can resemble it (Milkiewicz et al, 1999).

Acute or chronic cellular rejection is the main diagnosis that must be excluded (Banff Working Group et al, 2006; Lefkowitz, 2002). The key clinical distinctions between AIH after liver transplantation and acute cellular rejection are time to disease onset, HLA DRB1*03 status, and autoantibody production. Recurrent autoimmune hepatitis develops after a median interval of 2 years (Czaja, 2002, 2009; Gonzalez-Koch et al, 2001), whereas acute cellular rejection typically develops within 6 weeks after transplantation with a median interval of 8 days (Wiesner et al, 1998). Patients with recurrent AIH commonly have HLA DRB1*03, and they have autoantibodies of substantial titer (Sanchez-Urdazpal et al, 1992; Gonzalez-Koch et al, 2001). The major histological distinctions between recurrent AIH and acute cellular rejection are the moderate-severe interface hepatitis and plasma cell infiltration that characterize AIH, and the eosinophils, endotheliitis, and cholangitis that characterize acute cellular rejection (Lefkowitz, 2002).

Autoimmune hepatitis and chronic rejection each occur months after transplantation, but this is their only point of resemblance. Each condition should be easily distinguished from the other as cholestasis, portal ductopenia, centrilobular fibrosis, and foam cell arteriopathy characterize chronic rejection (Banff Working Group et al, 2006; Lefkowitz, 2002). The principal pathogenic distinctions between the recurrent AIH and the rejection responses probably relate to the origin of the antigen-presenting cells that initiate the immune response and the nature of the antigens that are targeted by the activated immunocytes. The autoimmune response requires re-population of the donor liver with antigen-presenting cells (such as dendritic cells and macrophages) from the recipient. The presentation of self-antigens common to both the donor and recipient can initiate the autoimmune response in the donor liver. In contrast, the rejection response is based on the reactivity of promiscuous cytotoxic T lymphocytes from the recipient against foreign antigens presented by the donor liver, including class II MHC molecules, viral proteins, and novel donor organ antigens (Czaja, 2002; Vierling, 1999).

Plasma cell hepatitis and isolated central perivenulitis can also confuse the diagnosis of recurrent AIH. Each condition is probably a variant of rejection. Plasma cell hepatitis does not improve with corticosteroid treatment; it may develop as immunosuppressive therapy is reduced; and it improves as the immunosuppressive regimen is intensified (Demetris & Sebagh, 2008; Fiel et al, 2008). Isolated central perivenulitis can be found in 28% of allografts, and it can lead to de novo autoimmune hepatitis or chronic liver injury, especially if it occurs late after transplantation (Krasinskas et al, 2008). Typically, perivenulitis is untreated, but this approach is debated and anti-rejection therapy has been proposed.

Diagnosis	Distinctive Features
Recurrent autoimmune hepatitis	Late onset (median, 2 years) Interface hepatitis Plasma cell infiltration Autoantibodies (serum titer $\geq 1:320$) HLA DRB1*03 (ethnic dependent)
Acute cellular rejection	Early onset (median, 8 days) Endotheliitis Cholangitis (histological finding) Eosinophilic infiltrates
Chronic cellular rejection	Late onset (range, 3-8 months) Cholestasis (histological finding) Portal ductopenia Centrilobular fibrosis Foam cell arteriopathy
Plasma cell hepatitis	Rejection variant Associated with reduced immunosuppression Unresponsive to corticosteroids Improves with increased immunosuppression
Isolated central perivenulitis	Rejection variant Progressive if late occurrence May result in autoimmune hepatitis
Hepatitis C virus infection	Portal lymphoplasmacytic response possible Serological markers of active viremia
De novo AIH	Late onset (median, 2 years) Children predilection Interface hepatitis Portal and periportal hepatitis with or without centrilobular necrosis and lymphoplasmacytic portal tract infiltrate Autoantibodies (classic and atypical) Response to prednisone and azathioprine

Table 4. Differential Diagnosis of Recurrent and De Novo AIH After Transplantation

Superimposed viral infections, especially HCV, must always be excluded in patients with graft disruption after transplantation because may elicit a pronounced lymphoplasmacytic response within the portal tract that can be difficult to distinguish from recurrent AIH (Banff Working Group et al, 2006; Demetris & Sebagh, 2008). Furthermore, recurrent AIH and HCV infection may occur together in the same allograft (Pappo et al, 1995). A comprehensive virological assessment is warranted to exclude infection in all patients with features of recurrent AIH after transplantation.

The absence of reliable diagnostic markers for recurrent AIH has compelled reliance on the histological findings to support the diagnosis, and the features of nonspecific chronic hepatitis have been the minimal bases for the diagnosis in some cases (Hubscher, 2001). Seronegative AIH has been described in native patients (Czaja et al, 1993; Gassert et al, 2007; Heringlake et al, 2009), and there is an emerging experience that suggests that it may be a relevant consideration in patients with graft dysfunction after liver transplantation (Nakhleh et al, 2005; Berg et al, 2002; Ayata et al, 2002; Seyam et al, 2007). Most patients who undergo liver transplantation for cryptogenic chronic hepatitis can be classified into conventional diagnostic categories after review of their liver tissue specimens before and after liver transplantation, but 15% remain cryptogenic and at risk for disease recurrence and progression (Ayata et al, 2002).

Cirrhosis may develop after transplantation in seronegative patients with recurrent histological features of chronic hepatitis, especially in those patients transplanted for seronegative fulminant hepatitis, and the possibility of recurrent seronegative AIH cannot be excluded in these individuals (Seyam et al, 2007). Consequently, recurrent AIH should be considered in all patients with acute and chronic graft dysfunction after liver transplantation. The diagnostic criteria must accommodate the atypical manifestations encountered after transplantation that may reflect superimposed medication effects and diverse other diseases associated with the transplantation.

4. Outcome

Recurrent AIH is typically a mild inflammatory process in an asymptomatic individual who has been inadequately immunosuppressed after transplantation or prematurely withdrawn from corticosteroids (Gonzalez-Koch et al, 2001; Prados et al, 1998; Neuberger, 2002; Khalaf, 2007). Recurrent disease usually responds to the re-introduction of corticosteroid therapy or adjustments in the doses of the original immunosuppressive agents (Gonzalez-Koch et al, 2001; Faust, 2000, 2001). The frequency of recurrence does not correlate with the frequency of graft loss, and patient and graft survivals after recurrence have been similar to those of other transplanted diseases (Li & Neuberger, 2009; Schreuder, 2009). Survival in patients with recurrent disease has ranged from 78-89% (Vogel et al, 2004; Yusoff et al, 2002).

Progression to cirrhosis and graft loss can occur (Milkiewicz et al, 1999; Ratziu et al, 1999; Rowe et al, 2008), and recurrent AIH with graft loss after the second transplantation has been reported (Reich et al, 2000). Furthermore, not all patients with recurrent AIH are inadequately immunosuppressed at the time of presentation (Ratziu et al, 1999) or responsive to the re-institution of corticosteroid therapy (Prados et al, 1998; Neuberger, 2002). Patients with severe, aggressive recurrent AIH have not been fully characterized, and the individuals at risk for a dire outcome cannot be reliably identified. The serological type of the original disease may affect the need for transplantation (Cattan et al, 2002), but it does not correlate with prognosis after transplantation (Vogel et al, 2004). Similarly, the severity of the disease at transplantation does not predict outcome after the procedure (Montano-Loza et al, 2009). Patients transplanted for fulminant AIH have lower frequencies of recurrence after transplantation and better survivals than patients transplanted for chronic AIH (Reich et al, 2000; Nunez-Martinez et al, 2003), but most patients who develop recurrent AIH do not have fulminant presentations. The outcome of de novo AIH remains largely unknown, but several cases with severe liver damage

and hepatic failure leading to death have been described (Hernandez et al, 2001), indicating the need for specific management of this complication.

5. Treatment

The first course of action is to establish the correct diagnosis, reassess the adequacy of the immunosuppressive regimen, and determine the compliance of the patient. Measurement of the drug metabolites in blood may be necessary to ensure the adequacy of dosing and the compliance of the individual (Rumbo et al, 2004). The second course of action is to optimize the doses of the conventional immunosuppressive medication and to re-introduce corticosteroids if they have been withdrawn (Neuberger, 2002). Treatment with prednisone and azathioprine is typically effective in recurrent (Birnbaum et al, 1997; Pappo et al, 1995; Duclos-Vallee et al, 2003; Czaja & Freese, 2002; Czaja, 2007b) and de novo AIH (Salcedo et al, 2002). Failure to respond or disease progression despite compliance with therapy justifies a closely monitored empiric trial with alternative immunosuppressive agents. The calcineurin inhibitor could be changed to another drug in this same category (Hurtova et al, 2001); a purine antagonist (azathioprine or mycophenolate mofetil) could be added or its dose optimized (Rumbo et al, 2004); or rapamycin, which is a mTOR (mammalian target of rapamycin) inhibitor, could be introduced (Kerkar et al, 2005). These agents have been reported as effective salvage therapies in small single-center case reports, but none have been established by large multicenter experiences or organized clinical trials. Patients in whom therapy fails have worsening fibrosis and possible graft loss (Vogel et al, 2004; Campsen et al, 2008) and those not administered corticosteroids progress to cirrhosis, require re-transplantation or die of liver failure (Czaja, 2007b). Re-transplantation must be considered if the disease continues to progress with the understanding that the disease could recur in the second graft and again jeopardize its survival (Reich et al, 2000).

6. Summary

AIH commonly recurs after liver transplantation, and asymptomatic histological recurrence may precede clinical recurrence by 1-5 years. Acute and chronic cellular rejection, drug toxicity, and viral infection must be confidently excluded, and treatment typically requires adjustment in the doses of immunosuppressive medication or the re-institution of corticosteroid therapy. Empiric treatments with another calcineurin inhibitor, purine antagonist (azathioprine or mycophenolate mofetil), or mTOR inhibitor (rapamycin) are available for refractory disease, and re-transplantation may be necessary.

Future studies are needed to codify diagnostic criteria, define risk factors that are predictive of recurrence and its progression, standardize surveillance schedules after transplantation, develop a uniform management algorithm, and elucidate mechanisms of disease.

Insights into the pathogenesis of recurrent and de novo AIH may elucidate a similar behavior in the native disease. Native AIH also exacerbates frequently after corticosteroid withdrawal, and this flare may occur after long intervals of quiescence. The concepts that activated immunocytes can trigger the same disease after a long dormancy or that a susceptible host with a genetic predisposition can develop newly created episodes of the same disease may apply to both conditions. The experiences in liver transplantation have

much to teach about AIH, and future investigations that clarify the mechanisms of recurrent and of de novo AIH will have broad implications for autoimmune diseases in general, not only for classical AIH. Future investigations must continue to utilize the human transplantation experience to elucidate the key mechanisms of the autoimmune response in the native liver.

7. References

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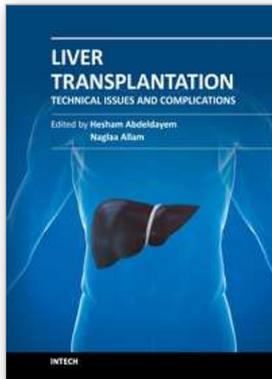
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