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Review

De Novo Autoimmune Hepatitis After Liver Transplantation: Natural History and Diagnosis

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Simple Summary: De novo autoimmune hepatitis is a rare form of late graft dysfunction and rejection that can result in loss of graft requiring re-transplantation or causing death. Prompt identification and treatment are essential to a favorable outcome for the patient.

Abstract: De novo autoimmune hepatitis (dnAIH) refers to autoimmune hepatitis manifesting in post-liver transplant patients for whom liver transplant was performed for pathologies other than autoimmune hepatitis. dnAIH, also called plasma cell-rich hepatitis though rare, is a form of graft rejection and is one of the causes of late graft dysfunction. This paper reviews the literature on the subject, focusing on the treatment and outcomes of dnAIH in both pediatric and adult populations. Diagnosis of dnAIH relies on serological and histological examinations however dnAIH should not be ruled out in seronegative patients.

Keywords: Liver Transplant; De Novo Autoimmune Hepatitis; Outcomes; Cirrhosis; Plasma Cell-rich Hepatitis;

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1. Introduction

De novo autoimmune hepatitis (dnAIH), first described in 1998 [1], refers to autoimmune hepatitis manifesting in post-liver transplant patients for whom liver transplant was performed for pathologies other than autoimmune hepatitis. In recent years, "plasma cell-rich hepatitis" has been preferred to dnAIH. dnAIH has also been considered a form of rejection that can result in graft loss [2]. As is the case with recurrent autoimmune hepatitis, dnAIH is also one of the causes of late graft dysfunction. dnAIH has been reported to occur in up to 7% of post-liver transplant patients. Glutathione S-transferase T1 (GSTT1) mismatch [3–7] has been reported to play a role in dnAIH with antibodies against glutathione S-transferase being found in 100% of patients with dnAIH [4], however, not enough research has been done on the subject provide a more detailed understanding of its role in the pathogenesis of dnAIH.

Other reports have reported monocyte/macrophage-derived cytokines of the IL-12 - IFN-γ as well as the IL-6 - IL-17 clusters in the perpetuation of the chronic inflammation in dnAIH [8,9]. Over the years, several studies have reported on the treatment and outcomes of de novo autoimmune hepatitis with various degrees of success, however, dnAIH remains relatively unknown to clinicians.

2. Diagnosis

De novo autoimmune diagnosis may be made based on serological examination, histological examination, and clinical manifestations. It is usually marked by findings similar to those of autoimmune hepatitis. Including elevated levels of aminotransferases, hypergammaglobulinemia, elevated serum immunoglobulin G, positive anti-nuclear antibody

(ANA), anti-smooth muscle antibody (ASMA) or anti-liver kidney microsomal antibody (anti-LKM) [10,11]. Typical histological findings include periportal and portal hepatitis with lymphocyte and plasma cell infiltration; hence plasma cell-rich hepatitis [10]. In some cases, de novo autoimmune hepatitis diagnosis has been without positive results for the autoantibodies or without elevated IgG levels. In such cases, diagnosis considered the presence of plasma cell infiltrates as well as responsiveness to treatment [12]. Therefore, even for patients who are seronegative for autoantibodies, de novo autoimmune hepatitis must be ruled out by biopsy [13]. Patients who have experienced one or more episodes of rejection have more of a risk of developing de novo autoimmune hepatitis than those who have not.

3. Treatment

The treatment plan for de novo autoimmune hepatitis follows the standard protocol for the management of autoimmune hepatitis with Prednisone alone or combined with Azathioprine being used as the first line. Mycophenolate Mofetil may be used in place of Azathioprine [14]. 30mg prednisone and 1-2mg per kg azathioprine per day for adult patients [15]. In pediatric patients, 2mg per kg per day of prednisolone (maximum daily dose of 60mg per day) and azathioprine 1.5 - 2mg per kg per day may be administered [1]. Typically, the steroid dose is tapered depending on the patient's responsiveness to the treatment until a maintenance dose of 5-10 mg per is achieved [6]. Treatment protocol for autoimmune hepatitis must be started immediately as soon as the patient presents with graft dysfunction in association with autoimmune features. Anti-rejection treatment should be maintained. Either tacrolimus or cyclosporin may be used. In patients experiencing pronounced prednisone adverse effects, budesonide has been proposed as a replacement since it has a less pronounced adverse effect profile [16]; Budesonide has a 90% fast pass hepatic clearance rate. Withdrawal of immunosuppressive agents can be considered after serological and histological remission have been both attained. Serological remission is attained when both serum IgG and transaminases are normal. Histological remission which takes longer than serological remission is attained when interface hepatitis disappears. If immunosuppressants are withdrawn prematurely, the patient faces a risk of remission. Treatment should be maintained for at least 3 years, and for at least 2 years after complete normalization of serum transaminases and IgG levels [17], After which withdrawal can be considered based on the clinical situation.

4. Outcomes

For the evaluation of outcomes of de novo autoimmune hepatitis, 9 papers reporting treatment and outcomes for post-liver transplant de novo autoimmune hepatitis with at least data of patients being reported were considered (Table 1) with a total of 116 patients. Outcomes of interest were responsiveness to treatment, progression to cirrhosis, re-transplantation, or death. 19 of the patients had been diagnosed with Hepatitis C virus infection prior to transplantation and 97 had pathologies other than HCV (Table 2). None of the patients had autoimmune hepatitis prior to transplantation. 5 of the 9 papers reported a mean time of onset of de novo autoimmune hepatitis from transplantation (Table 3). The report's mean times ranged from 20 to 77.3 months. The mean time of dnAIH onset was longer in pediatric cases than in adult cases.

Reference	dnAIH Patients	Pediatric / Adult
Kwon et al (2018) [18]	30	A
Aguilera et al (2001) [19]	4	A
Aguado-Dominguez et al (2018) [20]	12	A
Andries et al (2001) [21]	11	P
Choudhary et al (2018) [22]	4	A
Ekong et al (2017) [23]	29	P
Gupta et al (2001) [24]	6	P
Kerkar et al (1998) [1]	7	P
Miyagawa-Hiyashiro et al (2004) [25]	13	A

Table 1. Articles reviewed indicating number of patients and population category; A: Adult; P: Pediatric

Reference	HCV	nHCV
Kwon et al (2018) [18]	11	19
Aguilera et al (2001) [19]	2	2
Aguado-Dominguez et al (2018) [20]	6	6
Andries et al (2001) [21]	0	11
Choudhary et al (2018) [22]	0	4
Ekong et al (2017) [23]	0	29

Table 2. Data indicating patients diagnosed with hepatitis c virus infection prior to live transplantation; HCV: Hepatitis C Virus; nHCV: Non-Hepatitis C Virus

Reference	T
Kwon et al (2018) [18]	20
Aguilera et al (2001) [19]	24
Miyagawa-Hiyashiro et al (2004) [25]	38
Gupta et al (2001) [24]	77.3
Ekong et al (2017) [23]	63

Table 3. Articles that reported the mean time (T) from liver transplantation to onset of de novo autoimmune hepatitis in months.

4.1. Responsiveness to treatment

Of the 116 patients, 89 were responsive to standard autoimmune hepatitis treatment regimens and 27 were not responsive (Table 2). Patients who had hepatitis c virus (HCV) infections tended to have a poorer response to treatment. To my knowledge, no clear linkage between HCV infection and de novo autoimmune hepatitis has been reported in the literature.

4.2. Progression to cirrhosis, Re-transplantation, or death

Some studies reported data of patients that progressed to cirrhosis, overall, 17 patients progressed to cirrhosis. Not enough data was reported in the meantime from dnAIH onset to progression to cirrhosis. Kown et al reported a mean time of 37 months from dnAIH onset to progression to cirrhosis [18]. Patients who progress to cirrhosis are more likely to need re-transplantation as remission may not be attained.

Of the 27 patients that were not responsive to treatment, gift dysfunction worsened resulting in loss of graft and necessitated re-transplantation or caused death of the patient, often due to liver failure.

5. Conclusion

De novo autoimmune hepatitis or as more recently known, plasma cell-rich hepatitis is a rare form of rejection and graft dysfunction in liver transplant patients. A favorable outcome of de novo autoimmune hepatitis is dependent on early detection and treatment. While the involvement of GSTT1 and monocyte/macrophage-derived cytokines in the pathogenesis of dnAIH have been reported, more room remains for research to provide a better understanding of the pathogenesis and long-term outcomes. Furthermore, since de novo autoimmune hepatitis affects the graft, it is more accurate to refer to it as alloimmune hepatitis mimicking autoimmune hepatitis.

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