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FIELD OF VISION

Recurrent hepatitis C virus after transplant and the importance of plasma cells on biopsy

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Abstract

Hepatitis C virus (HCV) is the leading indication for liver transplantation in the United States. It recurs universally after transplant but the rate of fibrosis and the development of graft failure is variable. Different donor and recipient features have been demonstrated to impact fibrosis. Plasma cell hepatitis, a histologic finding, is one feature associated with poor graft and patient outcomes. The pathogenic mechanism resulting in plasma cell hepatitis is poorly understood, with evidence suggesting a role for both the HCV and the immune system.A recent publication described plasma cell hepatitis in a larger context of immune medicated graft dysfunction in transplant recipients receiving interferon based therapy. This manuscript will highlight the topic of plasma cell hepatitis and provide commentary on the lack of recognition, the data regarding pathophysiologic mechanisms and the potential management options.

Key words: Hepatitis C virus; Plasma cells; Biopsy; Sustained virological response

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INVITED COMMENTARY ON HOT ARTICLES

Hepatitis C virus (HCV) is the most common indication for liver transplantation in the United States. Recurrence of hepatitis C is nearly universal after transplantation and ensuing graft dysfunction occurs commonly. Ten percent of recipients progress to cirrhosis within 3 years of transplant[1] demonstrating that some patients develop aggressive recurrent HCV. Plasma cell hepatitis, diagnosed histologically, is one of a number of conditions associated with adverse outcomes and graft failure in patients with posttransplant HCV. Plasma cell hepatitis can develop in the context of interferon based therapy or in the absence of treatment with interferon. Levitsky *et al*[2] present a multicenter case-control study which included a large subset of patients found to have plasma cell hepatitis associated with interferon therapy for HCV.The manuscript should be read with interest by transplant hepatologists as it highlights important concepts regarding plasma cell hepatitis in patients with HCV after transplant. First, plasma cell hepatitis is under recognized. Second, the pathologic process resulting in plasma cell hepatitis is poorly understood. Finally, with a paucity of data, it is not possible to determine the best treatment for transplant recipients with this condition.

The case control series by Levitsky *et al*[2] reported that the incidence of any immune medicated graft dysfunction on interferon based therapy varied by center, ranging between 3.2%-16.3%. Persons found to have immune mediated graft dysfunction on HCV therapy had significantly worse survival, and more graft failure leading to higher rates of retransplantation. Plasma cell hepatitis was the most common manifestation of interferon induced immune mediated graft dysfunction. It is important to note that plasma cell hepatitis was also commonly identified prior to the use of interferon. The incidence of plasma cell hepatitis

Table 1 Generalized histologic and clinical features seen in post transplant patients with hepatitis C

Pathologic entity	Histologic features	Clinical and laboratory features
Plasma cell hepatitis	Plasma cells (often in sheets) Centrilobular necrosis	HCV PCR positive ANA or ASMA may be positive (often with low titers) Low level of immunosuppression Can be caused by interferon based therapy
De novo autoimmune hepatitis	Lymphoplasmacytic infiltrate Interface hepatitis	Positive ANA or ASMA Elevated immunoglobulins In persons on treatment HCV RNA often not detected (occurs in other settings in addition to HCV) Low level of immunosuppression Can be caused by interferon based therapy
Acute cellular rejection	Mixed inflammatory infiltrate Endotheliitis Nonsuppurative Cholangitis Centrilobular necrosis (variable)	Low level of immunosuppression Can be caused by interferon based therapy
Recurrent hepatitis C	Lymphocyte Aggregates Portal based fibrosis FCH is one variant (Cholestasis, Apoptosis, Fibrosis)	HCV PCR positive In FCH, markedly high viral load In FCH, high level of immunosuppression

HCV: Hepatitis C virus; FCH: Fibrosingcholestatic hepatitis; ANA: Antinuclear antibodies; ASMA: Anti-smooth muscle antibody; PCR: Polymerase chain reaction.

on pretreatment biopsies was much more common in persons who developed immune mediated graft dysfunction (36.5%) compared to the control group (7.7%, $P = 0.003$) on treatment[2]. Fourteen of the cases labeled as plasma cell hepatitis by the central pathologist were not recognized by the local pathologist who initially interpreted the liver biopsy[2]. The authors conclude that plasma cell hepatitis often predicts the development of immune mediated graft dysfunction occurring during interferon based treatment. In addition, the author's recommend that clinicians should not reduce immunosuppression doses and should not initiate interferon based therapy in those with immune features including plasma cell hepatitis on pretreatment biopsies.

The informative and interesting conclusions of this article deserve further comment. A main feature of the article from Levistky and colleagues is that plasma cell hepatitis is under recognized and is often mistaken for recurrent hepatitis C or other forms of rejection[2]. A histologic scoring system was developed in 2008[3]. Diagnostic features of plasma cell hepatitis include numerous plasma cells, often in sheets or clusters, accompanied by centrilobular necrosis. Despite the existence of standardized criteria, it is not surprising that plasma cell hepatitis is under recognized. With few publications describing plasma cell hepatitis, it is not topical to hepatologists and pathologists. Additionally, in post-transplant patients, other processes such as recurrent HCV, *de novo* autoimmune hepatitis and acute cellular rejection present alternative diagnoses. Table 1 highlights clinical and histologic features which might help distinguish the different diagnoses. It is important to realize significant overlap does exist between the pathologic process making a definite diagnosis impossible in some cases. The recent publication in a high profile journal will hopefully lead to better recognition of this disorder.

The pathogenesis of plasma cell hepatitis has yet to be defined. It has been described both as a manifestation of hepatitis C[4,5] and as a form of rejection[3]. Evidence exists for both possibilities. Prior series have shown that HCV plays a role. A two subject case series examined plasma cell hepatitis as a lymphoproliferative disorder[5]. Both patients in this series had serum or urine protein electrophoresis demonstrating a monoclonal protein and RNA probes for hepatitis C were positive within the plasma cell infiltrate[5]. An association between plasma cell hepatitis and mixed cryoglobulinemia has not been studied. In the current article, patient survival with plasma cell hepatitis was improved with a sustained virologic response to treatment for HCV[2]. Although graft failure and retransplantation occurred in some cases, five year survival was above 80% and similar to control subjects[2]. Additionally, there was a trend toward improved graft survival in cases of immune mediated graft dysfunction when hepatitis C was eradicated. In Kaplan-Meier analysis, the majority of graft loss occurred early after transplant with approximately 60% graft survival and no further graft loss occurring after two years in the group that achieved a sustained virological response (SVR)[2]. In contrast, the group that did not achieve an SVR continued to develop graft loss during the entire period of follow up and graft survival was less than 40% at five years[2]. It is additionally notable that SVR rates in series of patients with plasma cell hepatitis ranged between 40%-67%[2,3]. Given that poor outcomes are observed with plasma cell hepatitis in persons who never received interferon[3,6], prospective, randomized data are needed to compare outcome of interferon treatment versus no interferon treatment with respect to HCV eradication.

Other studies suggest the development of plasma cell hepatitis is an immune mediated event. Explanted livers of post transplant patients who later develop plasma cell hepatitis were more likely to have extensive plasma cell infiltrates[6] suggesting that immunologic predisposition exists even prior to transplant. However, not all persons with plasma cell infiltrates on explant will develop plasma cell hepatitis, and additional factors after transplant appear to play a role. There are data describing the development of plasma cell hepatitis in the setting of lowered immunosup-

pression[2,3]. In a series including 38 subjects with plasma cell hepatitis, 31 had either recently lowered immunosuppressant dosing or subtherapeutic drug levels[3]. In the series by Levitsky *et al*[2] significantly more patients with immune mediated graft dysfunction had a reduction in immunosuppression prior to interferon based therapy. Additionally, more subjects with immune mediated graft dysfunction had immunosuppression reduced during therapy[2]. One would expect interferon would have a role in the development of an immune mediated event and the contribution of interferon to the development of plasma cell hepatitis is not quite clear. In a retrospective series, interferon was not associated with the development of plasma cell hepatitis and its use did not impact outcome once plasma cell hepatitis developed[3]. In the series published by Levitsky *et al*[2] persons with existing plasma cell hepatitis had worsened immune mediated graft dysfunction after their immunosuppression was reduced and interferon was started. Increasing baseline immunosuppression prior to initiating interferon in patients with plasma cell hepatitis should be considered for future study, especially given data showing improved outcomes with augmenting immunosuppression alone[3].

With an immune predisposition, plasma cell hepatitis and *de novo* autoimmune hepatitis have overlapping features. They are nearly histologically indistinguishable, and some refer to them interchangeably[7]. A few subtle clues suggest that these processes have a different underlying pathophysiology. Case series have described *de novo* autoimmune hepatitis developing in conjunction with interferon based therapy with elevated autoimmune titers, undetected HCV RNA levels and pretreatment biopsies showing no plasma cells[8]. In addition, in transplant recipients for indications other than HCV, *de novo* autoimmune hepatitis has been shown to respond well to steroid therapy[9], whereas plasma cell hepatitis in HCV infected recipients typically does not[3].

Plasma cell hepatitis represents an important entity which is likely under reported as the result of poor recognition. Agreement on standardized nomenclature distinguishing plasma cell hepatitis from *de novo* autoimmune hepatitis in the post transplant setting may improve recognition. Plasma cell hepatitis best refers to plasma cell infiltration in the setting of post transplant hepatitis C. *De novo* autoimmune hepatitis best refers to plasma cell infiltration that occurs commonly with positive autoimmune titers, steroid responsiveness and, in the setting of interferon based therapy, may be best reserved when in a lymphoplasmacytic infiltrate develops without active viremia. As shown in Table 1, it must be recognized that overlap between the two conditions in both pathology and pathophysiologic mechanisms exist such that diagnostic certainty will not always occur.

Currently, the best management of plasma cell hepatitis that develops independent of HCV therapy is unclear. Limited data showed that augmentation of immunosuppression without the addition of prednisone may be of benefit[3]. Once on interferon based therapy, achieving an SVR was also shown to benefit patient survival[2]. The recommendation by Levitsky *et al*[2] that interferon should not be initiated in patients with plasma cell hepatitis may be overreaching based on the data presented. It also would suggest an alternate option with better outcomes existed. A practical approach may be augmenting baseline immunosuppression and a repeat liver biopsy. If the liver biopsy shows decreased immune features than interferon based therapy might be attempted. Ultimately, until there is better prospective data, responses to this entity will likely be reflective of single center experiences.

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