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 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 medicated graft dysfunction in transplant recipients receiving interferon based therapy. 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.

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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[3]. 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[3]. 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 Levitsky and colleagues is that plasma cell hepatitis is under recognized and is often mistaken for recurrent hepatitis C or other forms of rejection[3]. 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 definitive 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[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[3]. 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[3]. 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[3]. Although graft failure and retransplantation occurred in some cases, five year survival was above 80% and similar to control subjects[3]. 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)[3]. 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[3]. It is additionally notable that SVR rates in series of patients with plasma cell hepatitis ranged between 40%-67%[3]. Given that poor outcomes are observed with plasma cell hepatitis in persons who never received interferon[3], 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[3] 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-

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### 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)            | HCV PCR positive                                     |
|                                   | Centrilobular necrosis                   | ANA or ASMA may be positive (often with low titers)  |
| De novo autoimmune hepatitis      | Lymphoplasmacytic infiltrate             | Low level of immunosuppression                        |
|                                   | Interface hepatitis                      | Can be caused by interferon based therapy            |
| Acute cellular rejection          | Mixed inflammatory infiltrate            | Positive ANA or ASMA                                 |
|                                   | Endothelitis                             | Elevated immunoglobulins                             |
|                                   | Nonsuppurative Cholangitis               | In persons on treatment HCV RNA often not detected   |
|                                   | Centrilobular necrosis (variable)        | (occurs in other settings in addition to HCV)        |
| Recurrent hepatitis C             | Lymphocyte Aggregates                    | Low level of immunosuppression                        |
|                                   | Portal based fibrosis                    | Can be caused by interferon based therapy            |
|                                   | FCH is one variant (Cholestasis, Apoptosis, Fibrosis) | 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.
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\(^3\) 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\(^3\). 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\(^3\) 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\(^2\).

With an immune predisposition, plasma cell hepatitis and de novo autoimmune hepatitis have overlapping features. They are nearly histologically indistinguishable\(^2\), and some refer to them interchangeably\(^2\). 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\(^6\). In addition, in transplant recipients for indications other than HCV, de novo autoimmune hepatitis has been shown to respond well to steroid therapy\(^7\), whereas plasma cell hepatitis in HCV infected recipients typically does not\(^8\).

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\(^4\). The recommendation by Levitsky et al\(^3\) 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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