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REVEIW ARTICLE

Association of Human Cytomegalovirus with Hepatitis C Virus Infections

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INTRODUCTION

Once infected, an individual probably carries CMV for life. The infection usually remains latent. The sites of persistent or latent infection probably include multiple cell types and various organs [1].

However, CMV reactivation syndromes develop frequently when T lymphocyte-mediated immunity is compromised e.g. after organ transplantation, in association with lymphoid neoplasms and certain acquired immunodeficiencies, such as HIV infection and liver cirrhosis. CMV may contribute to further T lymphocyte hyporesponsiveness. Thus, according to some reports, occult infection may not have serious clinical consequences and may become injurious only when the virus is reactivated after immunosuppression [2].

Although the relationship between CMV IgG and CMV replication in tissues is not well understood, high CMV IgG levels are associated with increased incidence of subclinical atherosclerosis [3], coronary heart disease [4], and with cardiovascular and all-cause mortality [5] in the general population and also with subclinical carotid artery disease in HIV-infected individuals [6].

The association of chronic HCV infection with high CMV IgG levels is therefore interesting because it suggests a biologic mechanism through which HCV could contribute to the pathogenesis of a variety of chronic diseases. HCV contributes to liver disease and insulin resistance through well described pathways [7].

Recently, virus-virus interactions classified by organizing them into three main categories: (1) direct interactions of viral genes or gene products, (2) indirect interactions that result from alterations in the host environment, and (3) immunological interactions, unique to organisms equipped with an adaptive immune system [8].

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INCIDENCE OF CMV IN HCV PATIENTS:

Infection with human CMV may lead to liver damage in immunocompromised individuals. CHC is featured by impairment of innate and specific immunity as well apoptotic cell death. Active CMV replication was observed in only 18 out of polish 123 chronic HCV individuals (14.6%) [9].

In earlier study on dual viral infections HBV/CMV and HCV/CMV) it was demonstrated that CMV was detected in HBV or HCV patients mostly as a dual infection and that it can aggravate the course of the disease [10].

Recently, higher rate of CMV co-infection reported in chronic HCV Egyptian patients than those reported in other patient populations. Whether HCV predisposes patients to CMV infection or CMV predisposes patients to HCV is not clear [11].

In a recent study included a total of eighty four cases (48 females and 36 males) that were referred to blood banks for blood donation, Fifty three out of 84 cases (63%) were positive for HCV-RNA while 31 (37%) cases had negative HCV RNA. Forty six (87%) and 13 (25%) cases out of 53 HCV RNA positive patients were positive for HCMV IgG and immunoglobulin M (IgM) antibodies respectively. While 20 of 53 cases (38%) had detectable HCMV DNA [2].

In that study both HCMV IgM and CMV DNA were more frequently detected in healthy controls than in spontaneously cleared HCV subjects. However, virus-induced changes that may affect co-infecting viruses involve the innate immune mechanism induced by type I interferon known as the antiviral state [2]. The antiviral state consists of increased expression of a combination of enzymes, which if activated, shut down cellular translation [12].

In negative control group, CMV will replicate solely without the involvement of another virus i.e. HCV which explains the higher prevalence of CMV DNA in controls than spontaneously cleared HCV patients [2].

In HIV patients, HIV-infected women with chronic HCV have significantly higher CMV IgG levels than HIV-infected women without HCV RNA [13].

EFFECTS OF CMV/HCV COINFECTION:

Different studies reported that CMV causes hepatitis with inflammation and fibrosis of liver cells. That means CMV affects the liver and overall immunological status of the host body [14].

A study reported elevated liver enzymes and marked histological changes in the liver of HCMV/HCV co-infected patients. The serum levels of ALT and Aspartate Transaminase (AST) enzymes showed a highly significant (P value < 0.001) elevation in positive HCMV DNA than in negative subjects, thus suggesting a role of HCMV in liver pathogenesis, but though the histological changes were more marked in liver, replication HCV were inhibited in HCMV-positive cases [10]. This supports the results of another study [15].

Furthermore, one study reported that HCMV infection interacted with HCV and raised the influence on the liver enzymes and cause hepatitis [16].

Considering the fact that HCMV viruses exert an immunomodulatory effect resulting in enhanced immunosuppression [17], and cytokine dysregulation which could accelerate HCV pathogenesis in critically ill patients [18].

The findings of another study support the hypothesis that even low level of HCMV replication doesn't evolve into clinical disease it significantly influences HCV outcome, there is a general trend towards elevated levels of CMV IgG antibodies in HCV chronic patients than those in spontaneously cleared HCV patients in recent Egyptian study [2].

This is augmented by a recent study in which, patients with reactivated CMV had significantly higher fibrosis scores (72.7%) than those with undetectable CMV DNA (23.8%) [11].

Adding to the previous results, the prevalence of latent CMV infection paralleled the severity of liver disease of HCV patients. It was higher among patients with cirrhosis and HCC, and lower among patients with normal aminotransferases [19].

In contrary, there were no apparent correlations between HCV and CMV viral loads in polish patients. Coinfection with CMV has not influence on the laboratory biochemical parameters and injury of liver tissue. Active CMV infection did not influence inflammatory activity and fibrosis in liver tissue. Hemoglobin concentration, erythrocytes, leucocytes and platelet count, absolute neutrophil count and activity of ALT was similar in HCV and HCV/CMV-infected patients[9].

This is supported by previous study which showed that there are no significant unidirectional or bidirectional interactions between HCV and CMV operating at the level of viral replication in vivo following liver transplantation [20].

EFFECT OF CMV/HCV ON ANTI - HCV THERAPY

The early virologic response to anti-HCV therapy was independent on CMV infection [9]. On the other hand, human CMV infection inhibits response of chronic hepatitis-C-virus-infected patients to interferon-based therapy. Patients with positive CMV had higher rates of non-response and relapse (79.5%) than those with negative CMV DNA (19%). Chronic HCV patients with latent CMV had higher rates of response (81%) to treatment than those with reactivated CMV (20.5%). Therefore, HCV patients with reactivated CMV and advanced fibrosis were least likely to achieve a SVR following interferon therapy. This possibility is reduced to 50% of its original value in patients with reactivated CMV without fibrosis [11].

IL28B POLYMORPHISM AND CMV/HCV COINFECTION

In Egypt, several reports stated that approximately 50% of patients infected with genotype 4, the most common among Egyptian HCV patients, achieve a SVR to treatment regimen. Genome-wide association studies have recently revealed that single nucleotide polymorphisms (SNPs) within or adjacent to IL28B that codes for interferon-λ, predict spontaneous resolution of HCV [21], and a likely SVR to IFN-based treatment in CHC patients infected with genotypes other than type 4 [22].

Therefore, IL28B SNPs may have strong predictive value for the outcome of IFN-based therapy in the difficult to treat HCV genotype 4 patients, but it was estimated that IL28B variations account for about 15% of the inter-individual variability of SVR, thus supporting the necessity for additional predictors of the response to treatment. Recent predictors include vitamin D deficiency, IFN-inducible proteins serum levels, steatosis and insulin resistance [23], or IFN-stimulated genes (ISGs) such as oligo adynelate synthetase 1 (OAS1) [24].

The search for additional predictive factors for response is mandatory. Co-infection with other pathogens is, in some instances, an interfering factor against host genotypebased prediction. Recently two predictors for SVR in genotype 4 patients were reported; first, reactivation of CMV infection [11], and second, coinfection with HIV [25].

The dual analysis of both roles of IL28B SNP and CMV co-infection clearly showed that CHC carriers not infected with CMV have a 7-fold higher rate of SVR than those CHC patients co-infected with CMV, so CMV DNA testing may be of value at the moment to make better prognostication on response to IFN [26].

INTERPLAY BETWEEN HCV AND CMV MOLECULAR MECHANISMS

The association of HCV infection with CMV pathogenesis has been extensively studied in liver transplant patients [27], in HIV patients [13], and in patients receiving HCV antiviral therapy [11].

Coinfection of HCV with active CMV viremia induced severe failure to achieve acceptable rates of SVR, probably by inhibiting the JAK-STAT cascade [11].

CMV has evolved multiple mechanisms for disrupting the IFN-stimulated JAK/STAT signal transduction. It appears to inhibit IFN-α responsiveness by decreasing JAK1 protein, which is an essential component of IFN-α signaling [28].

It was reported that CMV blocks IFN-stimulated gene factor 3 (ISGF3)-dependent (MHC class I) and ISGF3-independent gene expression in infected cells. Moreover, the essential component of ISGF3, protein48 (p48), is significantly decreased by CMV. Therefore decreased JAK1 and p48 would inhibit IFN-α stimulated signal transduction, transcription factor activation, and gene expression, thus it is likely to globally block IFN-stimulated responses in CMV-infected patients [29].

Chronic HCV infection may influence the immune response against CMV in a similar fashion to old age and HIV infection [13]. Chronic infection with HCV leads to exhaustion and death of HCV-specific T-cells but may also cause defects in overall immune function [30].

For example, peripheral blood dendritic and naı¨ve CD4+ T-cells are reduced in number and function in individuals with chronic HCV [31], and peripheral blood CD4+ T-cell levels are also reduced in individuals with HCV-associated cirrhosis, perhaps because CD4+ T-cells are sequestered in the tissues of these individuals [32].

CMV/HCV AND LIVER TRANSPLANTATON

Recurrence of HCV infection after liver transplantation is nearly universal and may lead to increased graft loss and mortality. The RNA of HCV may be detected as soon as 48 hours post transplantation. The recurrence of hepatitis C progresses to cirrhosis in a high percentage of liver transplant recipients. The impact of CMV infection post-liver transplantation in HCV-infected individuals has led to contradictory findings [33].

CMV infection not only causes direct effects in target organs (e.g., hepatitis), but it has also a number of indirect effects, including a general immunosuppressive syndrome. This enhanced immunosuppressive effect could influence the recurrence and/or the severity of HCV replication in the posttransplantation patients [34].

At least 3 studies have shown that CMV infection significantly increased the risk of fibrosis and allograft cirrhosis in liver transplant recipients undergoing transplantation because of HCV [35, 36, 37].

In the first study half of the CMV-viremic patients developed allograft cirrhosis as compared with 11% of the CMV-negative patients. CMV viremia was associated with significantly diminished cirrhosis-free actuarial survival in patients with hepatitis due to HCV. The authors concluded that after liver transplant for CHC, patients who develop CMV viremia have a significantly greater risk of severe hepatitis C recurrence [35]. Coincidentally, the second study studied the impact of CMV infection on patient and graft outcomes in 93 consecutive HCV-infected liver transplant recipients. Graft failure was significantly more common in CMV-positive compared with CMV-negative patients. The CMV infections examined in a time-dependent manner remained as a strong predictor of graft failure. The authors concluded that CMV infection is an independent risk factor for graft failure in these patients [36].

In the third study, fibrosis scores were higher and fibrosis of stage $\geqslant 2$, as determined by liver biopsy 4 months after transplantation, was more common in patients with CMV infection ($P = .01$ for each). Graft failure, defined as cirrhosis, relisting for liver transplantation, retransplantation, or death, was significantly more common among CMV-infected patients. Donor age, CMV infection, receipt of mycophenolate mofetil, and year of transplantation each independently predicted graft failure [37].

Notably, however, in another three studies in which preemptive therapy for CMV disease was instituted on detection of viremia by sensitive assays (PCR) a correlation between CMV infection and progression of hepatitis C could not be shown [38, 14, 20].

One study prospectively evaluated if CMV could be associated to hepatitis C recurrence in 66 liver transplant recipients. The recurrence of hepatitis C by biopsy was demonstrated in 62.1% of cases. The authors did not find an association between CMV infection or disease and hepatitis C recurrence; nevertheless, the mean fibrosis score at last follow- up was higher in patients with CMV disease versus those without CMV disease. The authors concluded that CMV infection and viral load were not associated with an increase in the overall rates of hepatitis C recurrence or HCV viral load after liver transplantation, but may be associated with more severe forms of recurrence. The limitations of this study are that they did not perform HCV genotyping and there was not a liver biopsy protocol [14].

A previous study did not find a relation between CMV viremia and recurrence of hepatitis C in liver transplant recipients. The authors performed a one-year follow-up of 39 liver transplant recipients for HCV-related cirrhosis. Differently to the previous authors, they gave preemptive treatment with ganciclovir when CMV PCR was detected. This early intervention on

CMV, that allowed only a transitory viremia, could be the reason why the authors did not document a bigger recurrence of hepatitis C in the group with CMV viremia. There was no difference either in the incidence or in the grade of acute rejection episodes [38].

The third study investigated a cohort of 69 HCV-infected liver transplant recipients and 188 HCV-negative liver transplant recipients and monitored them for CMV infection. The authors gave preemptive therapy when CMV viremia was detected by PCR. They did not either document a difference between the incidence and grade of acute rejection. In agreement with the previous two studies the authors concluded that a short CMV viremia does not correlate to more hepatitis C recurrence [20].

In summary, the data of different studies are not conclusive on the impact of CMV in liver transplantation for HCV-related cirrhosis. However, with the current evidence it seems that CMV infection and disease could have a negative impact on the liver allograft, generating more hepatitis C recurrence and organ rejection. An early detection of CMV viremia and an early intervention with preemptive therapy may avoid these deleterious effects [33].

REFERENCES

1. Hara S, Hoshino Y, Naitou T, Nagano K, Iwai M, Suzuki K, et al. Association of virus infected-T cell in severe hepatitis caused by primary Epstein-Barr virus infection. J Clin Virol. Mar 2006; 35(3):250-6.
2. Tabll A, Shoman S, Ghanem H, Nabil M, El Din NG, El Awady MK. Assessment of human cytomegalovirus co-infection in Egyptian chronic HCV patients. Virol J. 2011; 8:343.
3. Nieto FJ, Adam E, Sorlie P, Farzadegan H, Melnick JL, Comstock GW, et al. Cohort study of cytomegalovirus infection as a risk factor for carotid intimal-medial thickening, a measure of subclinical atherosclerosis. Circulation. 1996; 94: 922–927.
4. Sorlie PD, Nieto FJ, Adam E, Folsom AR, Shahar E, Massing M. A prospective study of cytomegalovirus, herpes simplex virus 1, and coronary heart disease: the atherosclerosis risk in communities (ARIC) study. Arch Intern Med. 2000; 160: 2027–2032.
5. Roberts ET, Haan MN, Dowd JB, Aiello AE. Cytomegalovirus antibody levels, inflammation, and mortality among elderly Latinos over 9 years of follow-up. Am J Epidemiol. 2010; 172:363–371.
6. Parrinello CM, Sinclair E, Landay AL, Lurain N, Sharrett AR, Gange SJ, et al. Cytomegalovirus immunoglobulin G antibody is associated with subclinical carotid artery disease among HIV-infected women. J Infect Dis. 2012; 205:1788–1796.
7. Bugianesi E, Salamone F, Negro F. The interaction of metabolic factors with HCV infection: Does it matter? J Hepatol. 2012; 56 Suppl: S56–S65.
8. DaPalma T, Doonan BP, Trager NM, Kasman LM. A systematic approach to virus-virus interactions. Virus Res. Apr 2010; 149(1):1–9.
9. Lapiński TW, Kovalchuk O, Parfieniuk A, Flisiak R. Prevalence, clinical and therapeutical implications of active CMV infection in patients with chronic hepatitis C. Przegl Epidemiol. 2009; 63(2):305-9.
10. Bayram A, Ozkur A, Erkilic S. Prevalence of human cytomegalovirus coinfection in patients with chronic viral hepatitis B and C: A comparison of clinical and histological aspects. J Clin Virol. 2009; 45:212-217.
11. Bader El-Din NG, Abd El-Meguid M, Tabll AA, Anany MA, Esmat G, Zayed N, et al. Human cytomegalovirus infection inhibits response of chronic hepatitis-C-virus-infected patients to interferon-based therapy. J Gastroenterol Hepatol. 2011; 26(1):55-62.
12. Galligan CL, Murooka TT, Rahbar R, Baig E, Majchrzak-Kita B, et al. Interferons and viruses: signaling for supremacy. Immunol Res. 2006; 35(1-2):27-40.
13. Kuniholm MH, Parrinello CM, Anastos K, Augenbraun M, Plankey M, Nowicki M, et al. Hepatitis C viremia is associated with cytomegalovirus IgG antibody levels in HIV-infected women. PLoS One. Apr 2013; 17,8(4):e61973.
14. Humar A, Kumar D, Raboud J, Caliendo AM, Moussa G, Levy G, et al. Interactions between CMV, HHV-6, and the recurrence of hepatitis C after liver transplantation. Am J Transplant. 2002; 2:461-6.
15. Razonable RR, Burak KW, van Cruijsen H, Brown RA, Charlton MR, Smith TF, et al. The pathogenesis of hepatitis C virus is influenced by cytomegalovirus. Clin Infect Dis. 2002; 35:974-981.
16. Rafael E, de la Hoz A, Stephens G. Diagnosis and treatment approaches to CMV infections in adult patients. J Clin Virol. 2002; 25:S1-S12.
17. Lee SO and Razonable RR. Current concepts on cytomegalovirus infection after liver transplantation. World J Hepatol. 2010; 27,2(9):325-336.

18. Varani S and Landini MP. Cytomegalovirus-induced immunopathology and its clinical consequences. Herpesviridae. 2011; 7,2(1):6.
19. Gerakari S, Zouboulis-Vafiadis I, Chrysos G, Daikos G, Themeli-Digalaki K, Papadopoulos S, et al. The effect of coinfection by hepatotropic and hepatomimetic viruses in physical evolution of HCV hepatitis. Internet Journal of Infectious Diseases. 2011; Volume 9 Number 2.
20. Nebbia G, Mattes FM, Cholongitas E, Garcia-Diaz A, Samonakis DN, Burroughs AK, et al. Exploring the bidirectional interactions between human CMV and HCV replication after liver transplantation. Liver Transpl. 2007; 13:130-5.
21. Rauch A, Kutalik Z, Descombes P, Cai T, Di Iulio J, Mueller T, et al. Genetic variation in IL28B is associated with chronic hepatitis C and treatment failure: a genomewide association study. Gastroenterology. 2010; 138:1338-145.
22. Zeuzem S, Berg T, Moeller B, Hinrichsen H, Mauss S, Wedemeyer H, et al. Expert opinion on the treatment of patients with chronic hepatitis C. J Viral Hepat. 2009; 16:75-90
23. Thompson AJ, Muir AJ, Sulkowski MS, Ge D, Fellay J, Shianna KV, et al. Interleukin-28B polymorphism improves viral kinetics and is the strongest pretreatment predictor of sustained virologic response in genotype 1 hepatitis C virus. Gastroenterology. 2010; 139:120-9.
24. El Awady MK, Anany MA, Esmat G, Zayed N, Tabll AA, Helmy A, et al. Single nucleotide polymorphism at exon 7 splice acceptor site of OAS1 gene determines response of hepatitis C virus patients to interferon therapy. J Gastroenterol Hepatol. 2011; 26: 843-850.
25. Fabris C, Falleti E, Cussigh A, Bitetto D, Fontanini E, Bignulin S, et al. IL-28B rs12979860 C/T allele distribution in patients with liver cirrhosis: role in the course of chronic viral hepatitis and the development of HCC. J Hepatol. 2011; 54: 716-722
26. El Awady MK, Bader El Din NG, Tabll A, El Hosary Y, Abdel Aziz AO, El Khayat H, et al. IL28B and CMV predict response to combined therapy. World J Gastroenterol. Jan 2013; 14,19(2): 290-298.
27. Razonable RR. Cytomegalovirus infection after liver transplantation: current concepts and challenges. World J Gastroenterol. 2008; 14: 4849–4860.
28. Miller DM, Cebulla CM, Sedmak DD. Human cytomegalovirus inhibition of major histocompatibility complex transcription and interferon signal transduction. Curr Top Microbiol Immunol. 2002; 269:153-170.
29. Miller DM, Zhang Y, Rahill BM, Waldman WJ, Sedmak DD. Human cytomegalovirus inhibits IFN-alpha-stimulated antiviral and immunoregulatory responses by blocking multiple levels of IFN-alpha signal transduction. J Immunol. 1999; 162: 6107-6113.
30. Thimme R, Binder M, Bartenschlager R. Failure of innate and adaptive immune responses in controlling hepatitis C virus infection. FEMS Microbiol. Rev. 2012; 36:663–683.
31. Yonkers NL, Sieg S, Rodriguez B, Anthony DD. Reduced naive CD4 T cell numbers and impaired induction of CD27 in response to T cell receptor stimulation reflect a state of immune activation in chronic hepatitis C virus infection. J Infect Dis. 2011; 203:635–645.
32. McGovern BH, Golan Y, Lopez M, Pratt D, Lawton A, Moore G, Epstein M, Knox TA. The impact of cirrhosis on CD4+ T cell counts in HIV-seronegative patients. Clin Infect Dis. 2007; 44: 431–437.
33. Medina J, Pérez-Sartori G, Aguado JM. Interactions between CMV and other viruses (HHV6, HHV7, HCV and EBV) in transplantation. Review. Trends Transplantation. 2007; 1:129-36.
34. Mocarski ES Jr. Immune escape and exploitation strategies of cytomegaloviruses: impact on and imitation of the major histocompatibility system. Cell Microbiol. 2004; 6: 707-717.
35. Rosen HR, Chou S, Corless CL, Gretch DR, Flora KD, Boudousquie A, et al. Cytomegalovirus viremia. Transplantation. 1997; 64:721-6.
36. Burak KW, Kremers WK, Batts KP, Wiesner RH, Rosen CB, Razonable RR, et al. Impact of cytomegalovirus infection, year of transplantation, and donor age on outcomes after liver transplantation for hepatitis C. Liver Transpl. 2002; 8:362-9.
37. Chopra KB, Demetris AJ, Blakolmer D, Dvorchik I, Laskus T, Wang LF, et al. Progression of liver fibrosis in patients with chronic hepatitis C after orthotopic liver transplantation. Transplantation. 2003; 76:1487-91.
38. Teixeira R, Pastacaldi S, Davies S, Dhillon AP, Emery VC, Rolles K, et al. The influence of cytomegalovirus viraemia on the outcome of recurrent hepatitis C after liver transplantation. Transplantation. 2000; 70:1454-8.