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Hepatic flares in chronic hepatitis C: Spontaneous exacerbation vs hepatotropic viruses superinfection

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Abstract

The hepatitis C virus (HCV) causes an acute infection that is frequently asymptomatic, but a spontaneous eradication of HCV infection occurs only in one-third of patients. The remaining two-thirds develop a chronic infection that, in most cases, shows an indolent course and a slow progression to the more advanced stages

of the illness. Nearly a quarter of cases with chronic hepatitis C (CHC) develop liver cirrhosis with or without hepatocellular carcinoma. The indolent course of the illness may be troubled by the occurrence of a hepatic flare, *i.e.*, a spontaneous acute exacerbation of CHC due to changes in the immune response, immunosuppression and subsequent restoration, and is characterized by an increase in serum aminotransferase values, a frequent deterioration in liver fibrosis and necroinflammation but also a high frequency of sustained viral response to pegylated interferon plus ribavirin treatment. A substantial increase in serum aminotransferase values during the clinical course of CHC may also be a consequence of a superinfection by other hepatotropic viruses, namely hepatitis B virus (HBV), HBV plus hepatitis D virus, hepatitis E virus, cytomegalovirus, particularly in geographical areas with high endemicity levels. The etiology of a hepatic flare in patients with CHC should always be defined to optimize follow-up procedures and clinical and therapeutic decisions.

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Key words: Chronic hepatitis C virus infection; Hepatic flares; Hepatic flares in immunocompromised patients; Immunocompromised patients; Hepatitis A virus superinfection

Core tip: Patients with chronic hepatitis C virus infection may experience hepatic flares due to an acute exacerbation of this disease that is frequently characterized by a significant increase in liver fibrosis and necroinflammation but by a high rate of sustained viral response to Peg-interferon plus ribavirin treatment. A hepatic flare may also be due to superinfection by other hepatotropic viruses, drug injury or a concomitant autoimmune disease. The aim of this review is to be of some help in identifying the cause of the flare in a single patient in order to optimize the follow-up and clinical and therapeutic decisions.

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INTRODUCTION

Hepatitis C virus (HCV) infection is a major global health problem with approximately 3% of the world's population infected^[1,2]. HCV is a small enveloped positive-strand RNA virus of the genus *hepacivirus* of the *flaviviridae* family^[3]. Phylogenetic analysis of HCV isolates has enabled the viral classification into six major genotypes (from 1 to 6) and more than 100 subtypes^[3].

HCV transmission follows percutaneous exposure to human blood, but more recently increasing evidence has highlighted the role of unsafe sexual intercourse^[4-6], particularly in human immunodeficiency virus-positive males who have sex with males^[1,7-9]. Worthy of note is the changing impact of various risk factors for HCV transmission in the last 20 years in several countries, consequent to variations in social and economic conditions and to the widespread use of invasive medical procedures, particularly in developing countries^[1,4,5,8,10,11].

HCV causes an acute infection that is frequently asymptomatic, but in its symptomatic form it is characterized by nausea, malaise and jaundice. A spontaneous eradication of HCV infection occurs in 15%-30% of patients, whereas in the remaining percentage the infection becomes chronic^[12-14].

Thus, the outcome of the infection is viral clearance or viral persistence, depending on certain, not fully recognized, host (sex, age at the time of infection, initial immune response, and more recently *IL28B* genotype)^[15-20] and viral characteristics (HCV genotypes, subtypes, quasi-species)^[21-23]. Today, chronic HCV infection is a leading cause of end-stage liver disease including liver cirrhosis and hepatocellular carcinoma (HCC)^[24-27]. For patients with HCV genotype 2 or 3, treatment is still based on a 24-wk administration of pegylated interferon (Peg-IFN) given once a week in combination with a daily oral dose of 800 mg of ribavirin, whereas for those with HCV genotype 1 a combination treatment with Peg-IFN, ribavirin and a protease inhibitor has been more recently introduced^[28-31]. These treatment schedules allow a sustained virological response in nearly 80% of patients with HCV genotype 2 or 3 and in 65%-75% of those with HCV genotype 1^[28,29,32,33]. At present interferon-free combination therapies with directly acting antivirals are under investigation, with excellent preliminary results^[34-38].

The natural history of chronic hepatitis C (CHC) may include the development of a spontaneous hepatic flare, *i.e.*, an acute exacerbation of CHC (ae-CHC), characterized by a substantial increase in the serum aminotransferase levels (usually 5 times or more the baseline

values)^[39-43], a frequent deterioration in liver fibrosis and necroinflammation of 2 or more scores in the Ishak scoring system but also a higher rate of sustained viral response (SVR) to Peg-IFN plus ribavirin treatment^[43]. Hepatic flares in patients with chronic hepatitis C may also be a consequence of the restoration of the immune system after pharmacological or spontaneous immunosuppression. In geographical areas where other viral infections of the liver are highly endemic, CHC patients may also develop hepatic flares due to hepatitis A virus (HAV), hepatitis B virus (HBV) or HBV plus hepatitis delta virus (HDV), hepatitis E virus (HEV) or cytomegalovirus (CMV) superinfection, particularly in groups of subjects at a greater risk of acquiring these viruses.

The aim of this review article is to analyze the pathogenesis, clinical course, difficulties in correctly diagnosing and possible treatment of flares of various origins, on the basis of our personal experience and published data.

SPONTANEOUS AE-CHC

This is a clinical event characterized by a substantial increase in the serum aminotransferase values compared to the previous levels, associated or not with an increase in serum bilirubin and with other symptoms characteristic of acute hepatitis^[39-48]. This acute exacerbation can occur spontaneously^[15-19,21-25] or due to the restoration of a deficient immune system, a clinical condition frequently observed in patients with onco-hematological diseases^[49-64] (Table 1).

Regarding spontaneous ae-CHC, most information comes from the studies carried out by Sheen *et al.*^[39], Rumi *et al.*^[41] and Sagnelli *et al.*^[43]. In 1996 Sheen *et al.*^[39] first described this clinical event observed during a follow-up of 5 or more years of 194 patients with CHC. This Author reported a hepatic flare in 78 (40.2%) patients, with an incidence of 11.9% per year.

Rumi *et al.*^[41] followed up 206 patients (106 with genotype 1 and 100 with genotype 2) for 71 mo (range 24-144) and observed spontaneous hepatic flares in 31 patients with genotype 2c and in 8 patients with genotype 1b (with a rate of 55.6 per 1000 persons/year for genotype 2c *vs* 15.0 for genotype 1b, $P = 0.001$). A second liver biopsy was available for a few patients, and those who experienced a hepatic flare more frequently showed a more than 2-point increase in the fibrosis score in the second biopsy, according to the Ishak scoring system (63% *vs* 19%, $P = 0.003$).

In 2013, Sagnelli *et al.*^[43] extensively analyzed the clinical presentation and clinical course of ae-CHC, and for the first time described the response to pegylated interferon plus ribavirin. In this study, 82 patients with a spontaneous symptomatic exacerbation of chronic HCV infection were pair-matched by age, sex and HCV genotype with 82 patients with chronic HCV infection who had not shown signs or symptoms of an acute exacerbation for at least 10 years. HCV genotype 2 was detected in 46.4% and genotype 1 in 43.9% of cases, and IL-

Table 1 Hepatic flares in patients with hepatitis C virus chronic infection: Main characteristics of published studies

Ref.	Type of study	Patients (flare/total)	Patients with flare	Etiology of flare
Sheen <i>et al</i> ^[39]	Prospective	78/194	40%	Spontaneous ae-CHC
Tsuji <i>et al</i> ^[47]	Prospective	28/120	23.30%	Spontaneous ae-CHC
Rumi <i>et al</i> ^[41]	Prospective	39/206	19%	Spontaneous ae-CHC
Ferri <i>et al</i> ^[64]	Prospective	1/31	3.20%	ae-CHC due to anti-TNF alfa
Pitini <i>et al</i> ^[53]	Prospective	10/10	/	ae-CHC due to anti-CD20
Coppola <i>et al</i> ^[50]	Prospective longitudinal	7/7	/	ae-CHC due to anti-CD20
Grebely <i>et al</i> ^[83]	Prospective	5/136	3%	HCV-superinfection
Sagnelli <i>et al</i> ^[43]	Cross-sectional	82/82	/	Spontaneous ae-CHC
Coppola <i>et al</i> ^[48]	Cross-sectional	57/57	/	Spontaneous ae-CHC
Sagnelli <i>et al</i> ^[67]	Cross-sectional	8/8	/	HAV superinfection
Biliotti <i>et al</i> ^[80]	Cross-sectional	14/14	/	HBV superinfection
Sagnelli <i>et al</i> ^[81]	Cross-sectional	29/29	/	HBV superinfection
Pritchard ^[65]	Case report	1/1	/	ae-CHC due to anti-TNF alfa
Deterding <i>et al</i> ^[84]	Case report	1/1	7%	HBV/HDV superinfection
Sagnelli <i>et al</i> ^[86]	Case report	1/1	/	HCV-superinfection
Accapezzato <i>et al</i> ^[90]	Case report	1/1	/	HCV-superinfection
Hiraga <i>et al</i> ^[40]	Retrospective	22/1760	1.25%	Spontaneous ae-CHC
Ennishi <i>et al</i> ^[51]	Retrospective	36/131	27.40%	ae-CHC due to anti-CD20
Mahale <i>et al</i> ^[62]	Retrospective	33/308	11%	ae-CHC related to chemotherapy
Li <i>et al</i> ^[66]	Retrospective	1/8	12.50%	ae-CHC due to anti-TNF alfa
Marignani <i>et al</i> ^[52]	Retrospective	2/3	66.60%	ae-CHC due to anti-CD20

HCV: Hepatitis C virus; HBV: Hepatitis B virus; ae-CHC: Acute exacerbation chronic hepatitis C; TNF: Tumor necrosis factor; HAV: Hepatitis A virus; HDV: Hepatitis delta virus.

28B CC genotype was more frequent in patients with ae-CHC than in those without (40.2% *vs* 24.4%, $P < 0.05$). A second liver biopsy was available for 23 patients with ae-CHC and for 31 patients without, the first performed at enrolment and the second during the follow-up. These patients were naïve for anti-HCV therapy. A deterioration in liver fibrosis > 2 scores (Ishak) was observed in 78.3% of patients with ae-CHC and in 35.5% of those without ($P < 0.005$); a deterioration in necroinflammation > 2 scores occurred in 60.9% of patients with ae-CHC and in 9.6% of those without ($P < 0.005$). In this study 32 (46.4%) patients with ae-CHC and 38 without (52%) received pegylated interferon plus ribavirin, with an SVR in 81.2% of the patients in the first group and in 60.5% of those in the second, a difference not significant to the statistical analysis but of substantial clinical importance.

Other authors have described episodes of ae-CHC: Tsuji *et al*^[47] reported ae-CHC in 27.4% of 120 patients with CHC with persistently normal alanine aminotransferase levels; Coppola *et al*^[48] described 57 consecutive HCV-RNA-positive patients with a hepatic flare hospitalized because of the severity of symptoms and found a high prevalence of cases with HCV genotype 2a, whereas Hiraga *et al*^[40] reported a prevalence of less than 1.5% of flares in a follow-up study of 1760 patients with CHC.

To conclude on this point, patients with a spontaneous ae-CHC frequently show HCV genotype 2, IL28-B CC genotype and an unfavorable outcome. The more rapid progression to liver cirrhosis and the risk of developing HCC strongly warrant an early initiation of anti-HCV therapy, also considering that about 80% of subjects obtain an SVR with standard Peg-IFN plus ribavirin treatment. The high frequency of HCV genotype 2 and of IL28-B CC genotype and the reactivation of a cell-mediated immune response favoring HCV clearance

may be among the reasons for this favorable response to treatment.

Hepatic flares in chronic HCV infection may also occur during interferon-based antiviral treatment, but with no increase in HCV viral load in the case of drug-related toxicity^[54,55] and interferon-induced autoimmune disorders^[56-60] and with viral rebound in the case of treatment failure. A hepatic flare in patients who have achieved a sustained viral response with interferon-based treatment can be considered rare since in a 4-year follow-up study of more than 1300 such patients this event never occurred^[61].

AE-CHC IN PATIENTS WITH SPONTANEOUS OR DRUG-INDUCED IMMUNOSUPPRESSION

Some authors have recently demonstrated HCV reactivation during or after drug-induced immunosuppression, but the knowledge of ae-CHC in these immunosuppressed patients is scanty^[49] (Table 1). Coppola *et al*^[50] described an increase in HCV RNA of at least 1.5 log IU/mL in plasma and of at least 1.1 log IU/mL in peripheral blood mononuclear cells of 7 patients receiving rituximab and corticosteroid-based chemotherapy; these patients developed a hepatic flare 3-5 mo after treatment was discontinued. In a retrospective study Ennishi *et al*^[51] described a hepatic flare in 27% of 131 patients with non-Hodgkin's lymphoma (NHL) and HCV infection treated with rituximab and prednisone-based chemotherapy. Marignani *et al*^[52] described 3 patients with NHL and HCV infection treated with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) therapy, two of whom experienced HCV reactivation and

a subsequent hepatic flare after chemotherapy was discontinued. Pitini *et al*^[53] described HCV reactivation with a hepatic flare in 10 anti-HCV-positive patients treated with R-CHOP for NHL.

In a retrospective study on 308 patients with cancer and HCV infection, Mahale *et al*^[62] described a hepatic flare in 11% of cases, 73% in those with hematological malignancies and 29% in those with solid cancer ($P < 0.001$); in the multivariate analysis, the underlying hematological malignancy ($P = 0.02$, OR = 3.2, 95%CI: 1.2-8.7) and the use of rituximab ($P = 0.004$, OR = 4.2, 95%CI: 1.6-10.9) were the only independent predictors of ae-CHC.

Also the relationship between anti-TNF- α agents and HCV infection needs further investigation. These biological agents are effective therapy for a wide spectrum of chronic inflammatory diseases such as psoriasis, rheumatoid arthritis and inflammatory bowel disease and have been demonstrated to be safe in CHC^[63]. In fact, Ferri *et al*^[64] reported that of 31 patients with rheumatoid arthritis and HCV infection treated with anti-TNF- α agents only one developed a hepatic flare but without an elevation in the HCV viral load. Pritchard^[65] described a patient with rheumatoid arthritis treated with the anti-TNF- α agent etanercept who experienced a 3-fold increase in the serum aminotransferase levels together with an increase in HCV viral load and who reverted to the previous values once etanercept treatment was discontinued. Li *et al*^[66] also described a patient who developed a hepatic flare under etanercept and showed remission once this drug was replaced with infliximab.

To conclude on this point, in patients with an onco-hematological disease, rituximab-based chemotherapy, and to a lesser degree rituximab-sparing chemotherapy, favors HCV replication in hepatocytes, which, once the treatment is discontinued and the immunological conditions restored, may be a target for enhanced cell-mediated activity. In these patients, ae-CHC may have a further unfavorable clinical impact since the hepatic flare frequently requires the discontinuation of life-saving chemotherapy. Thus, the HCV load and serum aminotransferases should be closely monitored in onco-hematological patients receiving chemotherapy, particularly if therapy is rituximab-based and/or includes high-dose corticosteroids.

VIRAL SUPERINFECTION IN PATIENTS WITH CHRONIC HEPATITIS C

In patients with chronic CHC a hepatic flare may also be the clinical manifestation of HAV, HBV, HBV plus HDV, HEV or CMV superinfection (Table 1) or of lifestyle factors such as alcohol intake or the consumption of hepatotoxic drugs.

HAV superinfection in patients with CHC has been documented by several authors^[67-74]. Sagnelli *et al*^[67] described 21 patients with chronic hepatitis who developed hepatitis A, 13 with an underlying chronic HBV infection and 8 with a chronic HCV infection. In all cases HAV

always had a self-limiting clinical course, associated with a marked inhibition of HBV and HCV genomes; no patient had clinical, laboratory or ultrasound evidence of liver cirrhosis in this study and the underlying chronic hepatitis showed a regular clinical course. These data are in contrast with those from a previous study reporting a high rate of fulminant hepatitis due to acute hepatitis A occurring in patients with pre-existing chronic hepatitis^[68], but are in complete agreement with those reported in numerous other studies^[69-74].

Several studies have been published on HBV superinfection in HCV chronic carriers and an inhibition of the HCV genome, temporary or persistent, has always been documented^[75-83]. Biliotti *et al*^[80] in 2008 described 14 patients with an underlying chronic HCV infection who developed acute hepatitis B of mild clinical course that suppressed HCV replication. To this regard Sagnelli *et al*^[81] in 2009 described the clinical and virological impact of hepatitis B virus superinfection in 29 patients with chronic HCV infection and compared the data obtained with those from a control group of 29 normal subjects who developed acute hepatitis B in the same period, pair-matched by age, sex, and risk factors for the acquisition of HBV infection. Acute hepatitis B showed a severe course more frequently in patients with a pre-existing chronic HCV infection (34.5% *vs* 6.9%, $P < 0.05$). HCV RNA was undetectable in all patients during HBV superinfection: one-third eradicated the HCV chronic infection and two-thirds became HCV-RNA-positive during a follow-up of 4-6 years; HCV clearance was more frequent in patients with acute hepatitis B with a severe course (83.3% *vs* 22.2%, $P < 0.05$). Some published case reports are in good agreement with these data^[75-77].

Hepatic flares due to superinfections by other viruses such as HDV, heterologous HCV strains, HEV and CMV in patients with chronic hepatitis C have been poorly investigated.

There is little information on the outcome of chronic HCV infection after HBV/HDV superinfection. To this regard Deterding *et al*^[84] described a patient with chronic hepatitis C who cleared HCV infection during an acute self-limiting HBV/HDV superinfection.

Patients with chronic HCV infection may also develop a superinfection by a heterologous HCV strain if they continue to be at risk of acquiring HCV infection^[85-90]. Grebely *et al*^[85] described 6 patients with chronic HCV infection and a history of intravenous drug addiction who became superinfected with a different HCV strain; 5 of these 6 developed a new episode of acute hepatitis C. In a patient with chronic hepatitis C and a history of intravenous drug addiction, Sagnelli *et al*^[86] documented a second episode of HCV infection associated with a hepatic flare and with the replacement of HCV subgenotype 2c with subgenotype 2b.

Accapezzato *et al*^[90] described a patient with chronic hepatitis C who developed a second episode of acute hepatitis C after colonoscopy, and the replacement of HCV genotype 1b with genotype 4. Thus, this might sug-

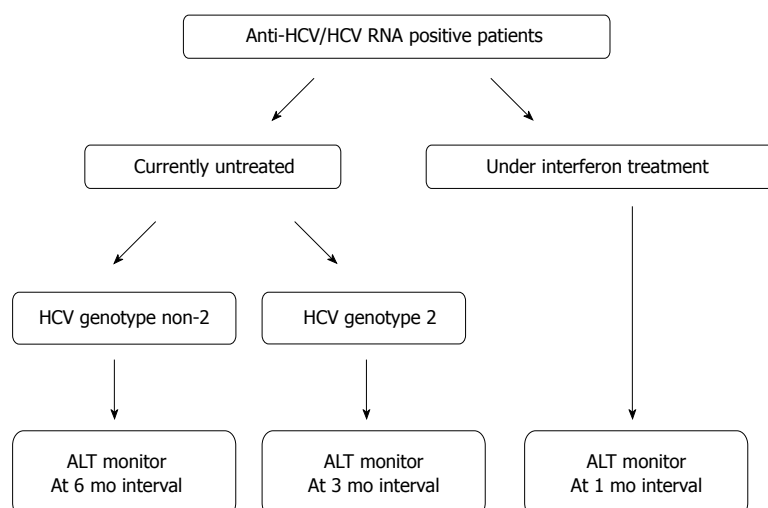


Figure 1 Monitoring schedule for the identification of a spontaneous hepatic flare in immunocompetent anti-hepatitis C virus/hepatitis C virus-RNA-positive patients. HCV: Hepatitis C virus; ALT: Alanine aminotransferase.

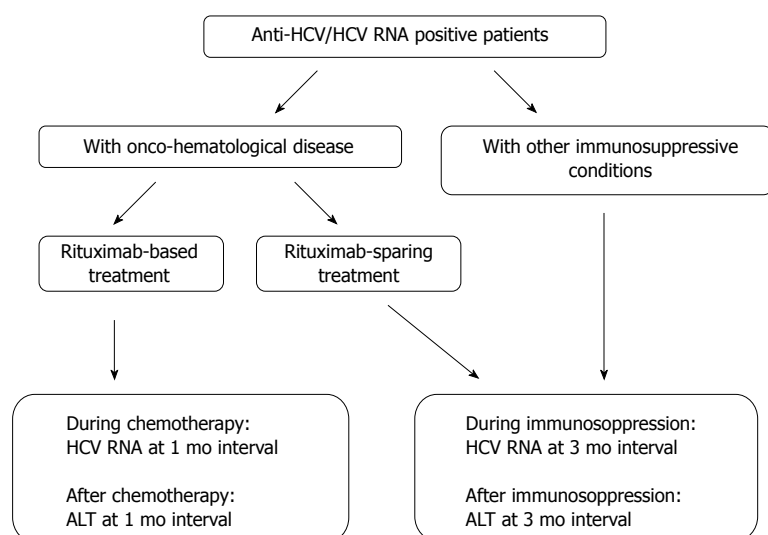


Figure 2 Monitoring schedule for the identification of a hepatic flare in anti-hepatitis C virus/hepatitis C virus-RNA-positive patients with spontaneous or drug-induced immunosuppression. HCV: Hepatitis C virus; ALT: Alanine aminotransferase.

gest re-determining the HCV subgenotype in the case of a hepatic flare in patients with CHC who continue to be at risk of acquiring HCV infection.

HEV infection is endemic in Southeast Asia and some studies have suggested that HEV superinfection in patients with an underlying chronic liver disease can cause severe hepatic decompensation^[91-94]. This event should be considered for a differential diagnosis even in geographical areas where HEV infection is infrequent^[95].

Cytomegalovirus can also cause liver damage and hepatic flares in the context of a systemic infection^[96,97]. Reactivation of CMV infection is a frequent complication after solid-organ transplantation^[99], but it may occur also in immunocompetent patients^[98-105] and, consequently, it should be considered among the possible causes of hepatic flares in patients with CHC.

Concluding on this point, HAV or HBV superinfection in patients with a pre-existing chronic HCV infection can cause acute viral hepatitis that may induce a strong inhibition of HCV replication and lead in some cases to a long-term HCV eradication. Viral superinfection, however, may be life-threatening in HCV chronic carriers at an advanced stage of the disease. Therefore,

efforts should be made to extend HAV and/or HBV vaccination to patients with CHC, a practice recommended by several international and national healthcare institutions but which remains poorly applied^[28,29]. The data on the clinical impact of HEV and CMV superinfection in patients with underlying chronic hepatitis C are scanty, but there is enough evidence to conclude that these two viruses should be considered in the differential diagnosis of flares.

CONCLUSION

The hepatic flare is a frequent and well-known event that may occur during the clinical course of CHC and may be due to different causes and have different outcomes. Apart from *IL28B-CC* aplogotype and HCV genotype 2, the risk factors for the development of a hepatic flare are still somewhat obscure, but a possible role of the metabolic disorders and endocrine derangements, such as liver steatosis, diabetes and insulin resistance should be investigated. The clinician treating a patient with chronic HCV infection should monitor for hepatic flares during the follow-up since an increase in the serum amino-

transferase values may be asymptomatic. To this regard, suggested monitoring schedules for immunocompetent and immunocompromised HCV patients are shown in Figures 1 and 2, respectively. When a hepatic flare occurs, the cause of this event or the etiologic agent should be identified and, when possible, appropriate treatment administered. The influence of the flares on the course of the underlying CHC should be monitored in order that the best clinical and therapeutic decisions be made.

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