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HEPATITIS C VIRUS SUPERINFECTION IN INDIVIDUALS WITH CHRONIC HEPATITIS B VIRUS INFECTION. A COMPARATIVE CASE STUDY

Anca Streinu-Cercel[1,2], Ileana Rebedea[1,2], Oana Streinu-Cercel[2], A. Streinu-Cercel[1,2], Liliana Preoțescu[1,2], Daniela Manolache[1]

[1.] *National Institute for Infectious Diseases „Prof. Dr. Matei Balş" Bucharest, Romania*
[2.] *Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, Faculty of Medicine*

Abstract. Hepatitis B virus (HBV) is known to infect over 500 million people worldwide while WHO estimates that there are more than 170 million chronic HCV carriers. A study conducted in 2009 in Romania revealed a seroprevalence of HBV infection of 5.59% and of 4.56% for HCV infection [ASRF, 2009]. HBV and HCV coinfection is one of the leading problematics in the area of infectious diseases. The National Institute for Infectious Diseases „Prof. Dr. Matei Balş", Bucharest is one of the excellence centers in Eastern Europe for diagnosing and treating hepatitis B and C. During 2009, the National Institute for Infectious Diseases „Prof. Dr. Matei Balş" monitored 3027 patients with chronic HBV hepatitis, out of which 402 patients presented chronic HBV HDV coinfection, 256 patients presented acute HBV hepatitis without comatose state and 3 presented acute HBV hepatitis with comatose state. In 2009, we also monitored 6012 patients with chronic HCV hepatitis and we admitted 26 cases of acute HCV hepatitis and 3 cases of HEV acute hepatitis. Out of the total number of patients monitored in our clinic almost 3% represent HBV and HCV coinfections.
This article compares the evolution of 5 cases of HCV superinfection in patients with chronic HBV infection. All of the patients were diagnosed within the National Institute for Infectious Diseases „Prof. Dr. Matei Balş" and 4 out of the 5 cases were treated with specific antiviral therapy. Patients 1 through 4 attained and maintained undetectability for HCV-RNA while patient 5, who refused antiviral treatment, developed a chronic HCV hepatitis with fluctuating viral load values. All patients treated with Peg IFN and ribavirin for HCV hepatitis responded well to therapy, with undetectability of viral load at 2 weeks of treatment. One treated patient positivated the HCV viral load 5 years after the initial HCV hepatitis. We suspect this may be associated with administration of hepato-toxic drugs.
We also present an illustrative case report of a patient with a particular evolution under HBV antiviral treatment with lamivudine and successive HCV treatment with Peg IFN and ribavirin, discussing the possible role of the chronology of HBV and HCV infection on the evolution of the hepatic disorder.
Keywords: HCV superinfection, chronic HBV infection

Introduction

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are two of the leading causes of chronic hepatitis, cirrhosis and hepatocellular carcinoma and account for more than one million deaths annually. Hepatitis B virus (HBV) is known to infect over 500 million people worldwide [Mandell, 2009]. A study conducted in 2009 in Romania revealed a seroprevalence of HBV infection of 5.59% and of 4.56% for HCV infection [ASRF, 2009]. By comparison, most European countries report a prevalence of HCV in the general population ranging between 0.5 and 2%. The CDC has estimated that at least two thirds of all community-acquired HCV infections are related to illicit injection drug use [Mandell, 2009]. WHO estimates that about 3% of the world's population has been infected with HCV and that there are more than 170 million chronic

Anca Streinu-Cercel
INBI "Prof. Dr. Matei Balş"
1, Dr. Calistrat Grozovici Str, Bucharest
Phone: 0040(21)318.61.00
email: anca_sc@yahoo.com

carriers who are at risk of developing liver cirrhosis and/or liver cancer.

HBV and HCV coinfection is one of the leading problematics in the area of infectious diseases. The National Institute for Infectious Diseases „Prof. Dr. Matei Balş", Bucharest is one of the excellence centers in Eastern Europe for diagnosing and treating hepatitis B and C. During 2009, the National Institute for Infectious Diseases „Prof.Dr. Matei Balş" monitored 3027 patients with chronic HBV hepatitis, out of which 402 patients presented chronic HBV HDV coinfection, 256 patients presented acute HBV hepatitis without comatose state and 3 presented acute HBV hepatitis with comatose state. In 2009, we also monitored 6012 patients with chronic HCV hepatitis and we admitted 26 cases of acute HCV hepatitis and 3 cases of HEV acute hepatitis. Out of the total number of patients monitored in our clinic almost 3% represent HBV and HCV coinfections.

Based on the classification of HBV and HCV coinfections into: simultaneous HBV and HCV infection in acute hepatitis, HBV and HCV coinfection in patients with chronic liver diseases, HCV superinfection in individuals with chronic HBV infection, HBV superinfection in individuals with HCV infection and occult HBV infection in patients with HCV infection [Liu, 2006], this article aims to compare the evolution of 5 cases of HCV superinfection over chronic HBV hepatitis. All of the patients were diagnosed within the National Institute for Infectious Diseases „Prof.Dr. Matei Balş" and 4 out of the 5 cases were treated with specific antiviral therapy. We also present an illustrative case report of a patient with a particular evolution under HBV antiviral treatment with lamivudine and successive HCV treatment with Peg IFN and ribavirin, discussing the possible role of the chronology of HBV and HCV infection on the evolution of the hepatic disorder.

Material and methods

Selected cases

Out of the total number of cases of HCV superinfection in patients with chronic HBV hepatitis diagnosed within the National Institute for Infectious Diseases „Prof.Dr. Matei Balş" since 2002, we chose 5 representative cases, 4 of which were treated with specific antivirals (patients 1-4). The 5th patient (T.G.) refused specific treatment.

Four patients had documented chronic HBV hepatitis (patients 2-5) while one patient (M.L.D.) had a history of chronic HBV infection dating 4 years back, when she had negativated the HBV-DNA but had not displayed seroconversion.

Monitored parameters

All 5 patients were monitored according to the following parameters: TGO (aspartate aminotransferase), TGP (alanine aminotransferase), total seric bilirubin, prothrombin concentration, HBV and HCV viral loads, serological markers of HBV and/or HCV infection. These parameters were determined at baseline (hospital admittance for either HBV hepatitis or HCV hepatitis), at 2 weeks, at 8 weeks, at 12 weeks and at 24 weeks.

Treatment options

The acute HBV treatment for patient 1 (M.L.D) consisted of lamivudine 100 mg per day for 24 weeks. The patient was included in the National Institute for Infectious Diseases „Prof.Dr. Matei Balş" study on acute HBV hepatitis based on the following criteria: recent onset of jaundice (serum bilirubin > 5 mg/dL or >85 μmol/L), coagulopathy (international normalized ratio (INR): 1.40–1.60 within a week of onset); the presence of hepatitis B surface antigen in the serum; evidence of active viral replication (documented by measurable HBV DNA with 15 IU/mL or 104 copies/mL detection limit); hepatic cytolysis defined as serum alanine aminotransferase levels more than five times the upper limit of normal; detection of high-titer immunoglobulin M antibody to hepatitis B core antigen (IgM HBcAb), age over 18 years old, admittance for acute HBV hepatitis, time span since diagnosis <8 days and written informed consent of the patient.

The exclusion criteria were as follows: seropositivity of immunoglobulin G antibody to hepatitis B core antigen (IgG HBcAb); superinfection or coinfection with hepatitis A, C, D, E, Epstein–Barr virus, cytomegalovirus, and human immunodeficiency virus; other liver diseases such as drug-induced hepatitis, Wilson disease, alcoholic liver disease and autoimmune hepatitis; any sign of chronic liver disease (liver palm and spider angioma), cases displaying features of chronic liver disease at ultrasonography or computed tomography investigation (splenomegaly, atrophy of the right lobe with enlargement of the left lobe and varices or collaterals); malignant jaundice induced through obstructive or hemolytic mechanism; prolonged prothrombin time induced by blood system disease.

The chronic HBV treatment for patient 1 (M.L.D.) consisted of lamivudine 100 mg per day for 48 weeks. The patient was included in the National Institute

for Infectious Diseases „Prof.Dr. Matei Balş" study on chronic HBV hepatitis based on specific inclusion and exclusion criteria.

The treatment of HCV hepatitis for patients 1-4 consisted of Peg IFN 180 mg weekly and ribavirin 1200 mg daily over periods of time determined individually for each patient according to their biological parameters. Patients 1-4 were included in the National Institute for Infectious Diseases „Prof.Dr. Matei Balş" study on chronic HCV hepatitis based on specific inclusion and exclusion criteria.

Patient history

Patient 1. M.L.D., a 21 year-old female patient, was diagnosed in 2005 with acute HBV hepatitis. She was treated with lamivudine 100 mg per day for 24 weeks, she progressed to chronic HBV hepatitis and continued lamivudine treatment for another 48 weeks, when she discarded HBsAg but did not display seroconversion. Four years later, in 2009, she returned to our clinic for acute HCV infection with genotype 2 hepatitis C virus. She received treatment with Peg IFN 180 mg weekly and ribavirin 1200 mg per day over 24 weeks, along with symptomatic therapy when needed. She negativated HCV viral load after the first two weeks of therapy and was also undetectable for HBV-DNA.

Patient 2. C.C., a 32 year-old female patient, was diagnosed in 2002 with hepatitis B (intrafamilial transmission – husband positive for HBsAg). She developed chronic HBV hepatitis and two years later, at the age of 34, she was diagnosed with hepatitis C (i.v. drug use transmission). She received treatment with Peg IFN alpha 2b 180 mg weekly and ribavirin 1200 mg/day for 4 weeks. She negativated the HCV-RNA after 2 weeks of therapy. In 2007, at 37 years old, she displayed positivation of HCV-RNA, with 609519 IU/mL viral load and TGP value of 120. Given the patient's transmission history for HCV, we could not exclude hepato-toxic drugs from the list of possible HCV-RNA positivation reasons. This severe acute form of hepatitis C matched our criteria for treatment of chronic HCV hepatitis so she underwent a second course of therapy.

Patient 3. S.P., a 43 year-old female patient, known with chronic HBV hepatitis for 10 years (transmitted probably through complications of Caesarean-section for Rh-negative twins pregnancy), presented for cytolytic syndrome (TGP value of 1587) in 2006. She mentioned dentist treatment dating 6 months back, with bleeding procedures, and was diagnosed with HCV hepatitis. She underwent Peg IFN 180 mg weekly and ribavirin 1200 mg daily for 3 months and she displayed favorable response to treatment. At follow-up visits after 3 years with no other antiviral therapy, she was HBsAg negative, HBsAb positive and undetectable for HCV-RNA.

Patient 4. A.P. a 26 year-old male patient with medical history of chronic HBV hepatitis presented in 2003 with intense jaundice, marked cytolysis, altered clinical status after a trip to Iraq for reporter work. He was diagnosed with acute HCV hepatitis and was treated with Peg IFN 180 mg weekly and ribavirin 1200 mg daily for 6 months with favorable evolution.

Patient 5. T.G. a 21 year-old female, married, with husband of Kuwaitian nationality, was diagnosed as HBsAg positive in 2007, upon requesting Kuwaitian residence. Her HBV-DNA was 256 IU/mL. After a 6 months visit, she returned to Romania (the Kuwaitian residence request was rejected so long as she was HBsAg positive). Upon returning to Romania, she developed acute HCV hepatitis, refused specific antiviral treatment and shortly progressed to chronic HCV hepatitis.

Patient admittance and evaluation data

The baseline is considered the admission date for each of the 5 patients presenting with acute HCV hepatitis over a chronic HBV hepatitis. The serological markers and viral loads at baseline are illustrated in table I.

Upon the 2nd visit (at week 2), 4 patients had undetectable HBV-DNA (patients 1, 2, 4 and 5). The HCV viral load determined through reverse-transcription polymerase chain reaction was undetectable for patients 1 through 4, while patient 5 displayed an HCV viral load of 11,657,324 IU/mL, All patients were positive for HCV Ab (table II).

At 8 weeks, all patients had undetectable HBV-DNA. The HCV viral load was undetectable for patients 1 through 4, while patient 5 displayed a decreasing HCV viral load of 6,587,432 IU/mL. All patients were positive for HCV Ab (table III).

At 12 weeks, all patients were undetectable for HBV-DNA. The HCV viral load was undetectable for patients 1 through 4, while patient 5 displayed a decreasing HCV viral load of 5,987,321 IU/mL. All patients were positive for HCV Ab (table IV).

At 24 weeks from baseline, all patients were undetectable for HBV-DNA. The HCV viral load was undetectable for patients 1 through 4, while patient 5 displayed an increasing HCV viral load of 7,654,897 IU/mL. All patients were positive for HCV Ab (table V).

BASELINE	Patient 1 (M.L.D.)	Patient 2 (C.C.)	Patient 3 (S.P.)	Patient 4 (A.P.)	Patient 5 (T.G.)
HBs Ag	negative	positive	positive	negative	positive
HBe Ab	positive	positive	positive	positive	positive
Hbe Ag	negative	negative	negative	negative	negative
HBcIgM Ab	negative	negative	negative	negative	negative
HBV-DNA	undetectable	743 IU/mL	2356 IU/mL	undetectable	256 IU/mL
HCV Ab	positive	positive	positive	positive	positive
HCV RT-PCR A	69900 IU/mL	36743 IU/mL	67543 IU/mL	179754 IU/mL	12765435 IU/mL

Table I. Baseline HBV and HCV parameters for all 5 patients

2nd visit (week 2)	Patient 1 (M.L.D.)	Patient 2 (C.C.)	Patient 3 (S.P.)	Patient 4 (A.P.)	Patient 5 (T.G.)
HBV-DNA	undetectable	undetectable	215 IU/ml	undetectable	undetectable
HCV Ab	positive	positive	positive	positive	positive
HCV RT-PCR M	<600 IU/mL	<600 IU/mL	<600 IUmL	<600 IU/mL	11657324 IU/mL

Table II. HBV and HCV parameters for all 5 patients at week 2

3rd visit (week 8)	Patient 1 (M.L.D.)	Patient 2 (C.C.)	Patient 3 (S.P.)	Patient 4 (A.P.)	Patient 5 (T.G.)
HBV-DNA	undetectable	undetectable	undetectable	undetectable	undetectable
HCV Ab	positive	positive	positive	positive	positive
HCV RT-PCR M	<600 IU/mL	<600 IU/mL	<600 IU/mL	<600 IU/mL	6587432 IU/mL

Table III. HBV and HCV parameters for all 5 patients at week 8

4th visit (week 12)	Patient 1 (M.L.D.)	Patient 2 (C.C.)	Patient 3 (S.P.)	Patient 4 (A.P.)	Patient 5 (T.G.)
HBV-DNA	undetectable	undetectable	undetectable	undetectable	undetectable
HCV Ab	positive	positive	positive	positive	positive
HCV RT-PCR M	<600 IU/mL	<600 IU/mL	<600 IU/mL	<600 IU/mL	5987321 IU/mL

Table IV. HBV and HCV parameters for all 5 patients at week 12

5th visit (week 24)	Patient 1 (M.L.D.)	Patient 2 (C.C.)	Patient 3 (S.P.)	Patient 4 (A.P.)	Patient 5 (T.G.)
HBV-DNA	undetectable	undetectable	undetectable	undetectable	undetectable
HCV Ab	positive	positive	positive	positive	positive
HCV RT-PCR M	<600 IU/mL	<600 IU/mL	<600 IU/mL	<600 IU/mL	7654897 IU/mL

Table V. HBV and HCV parameters for all 5 patients at week 24

Conclusions

Patients 1 through 4 attained and maintained undetectability for HCV-RNA while patient 5, who refused antiviral treatment, developed a chronic HCV hepatitis with fluctuating viral load values.

All patients treated with Peg IFN and ribavirin for HCV hepatitis responded well to therapy, with undetectability of viral load at 2 weeks of treatment. Patient 1 positivated the HCV viral load 5 years after the initial HCV hepatitis. Given the patient's relevant epidemiologic context, we suspect this may have been associated with administration of hepato-toxic drugs.

Case report

We selected the case report of patient number 1 (M.L.D.) due to its particularities and the interesting evolution that the patient displayed over the course of both acute and chronic HBV hepatitis and acute HCV hepatitis.

21 year-old female patient, presents at the National Institute for Infectious Diseases „Prof. Dr. Matei Balş", Bucharest, Romania in 2005 for severe asthenia, inappetence and jaundice. The symptomatology had developed over 5 days, but was initially ignored by the patient. The patient also presented hyperchrome urine and acholic stool.

a potential preexisting hepatic disorder or an obstructive pathology of the biliary ducts)

- biochemical tests for the evaluation of a cytolysis syndrome and of possible coagulation disorders
- markers for the evaluation of the hepatic function and the serology for acute viral hepatitis
- given the patient's epidemiological context, the HIV serology was also determined (the results were negative for HIV infection)

In the absence of pertinent data on the patient's HBV vaccine status, the **epidemiologic investigation** was of utmost importance as it revealed data on the patient's husband, aged 20, diagnosed with chronic HBV and HDV hepatitis 5 years back. Their official marriage had taken place 6 months back (the patient's habit and lifestyle data are synthesized in table VI, together with the epidemiologic report).

The epidemiologic investigation, correlated with the clinical exam, gave rise to the suspicion of an acute HBV and HDV hepatitis. We ordered viral load tests for the two potential viruses: HBV-DNA and HDV-RNA at admittance. The delta hepatitis virus load was negative, which refuted the presumptive diagnosis of HBV and HDV coinfection.

The laboratory tests ascertained the acute HBV hepatitis **diagnosis**: positive HBc IgM Ab, positive HBsAg, negative HDV Ab, negative HDV IgM Ab.

M.L.D., female 21 years old	
Transmission	Sexual transmission, 6 months back
Habit and lifestyle, epidemiology	Married for 6 months. Husband with chronic HBV+HDV hepatitis diagnosed 5 years back.

Table VI. Epidemiologic report, habit and lifestyle for patient M.L.D.

The **clinical exam** revealed sensitivity to palpation in the right hypochondrium and jaundice. The intensity of the jaundice was quite difficult to assess due to the dark skin tone of the patient (both as natural feature and as result of intensive artificial tanning over the past 3 months).

The clinical exam data oriented the diagnostic process towards severe acute HBV hepatitis. The **differential diagnosis** excluded acute HAV or HEV hepatitis and biliary ducts' pathology which would have justified both the jaundice and the hyperchrome urine and acholic stools.

In order to diagnose the patient, we ordered the following paraclinical investigations:

a complete blood count

- abdominal ultrasound ecography (for excluding

The serology results indicated the need for differential diagnosis with severe acute exacerbation of a chronic HBV hepatitis.

We evaluated the patient's alcohol intake level through a study form (figure 1) since alcohol could constitute a significant risk factor in the progression of the hepatic disease.

The biochemistry and serology results at acute HBV hepatitis admittance (baseline) are illustrated in table VII.

The patient matched the International Institute for Infectious Diseases "Prof.Dr. Matei Balş" acute HBV hepatitis study's inclusion criteria. As such, she was distributed to the lamivudine treatment group according to the study's randomization algorithms.

M.L.D., female, 21 years old		
Baseline	TGP 6761 TGO 4532 BILT 7 TP% 67%	positive HBsAg positive HBeAg negative HBe Ab negative HBcIgM Ab negative HDV Ab negative HCV Ab negative HIV Ab HBV-DNA 6830000 IU/mL

TGP – alanine aminotransferase, TGO – aspartate aminotransferase
BILT – total bilirubin, TP% - prothrombin concentration

Table VII. Acute HBV infection baseline biochemistry and serology results

Alcohol: No Yes * Stopped
(How long ago have you stopped the alcohol intake? :.....days/ weeks/ months/ years)
.....2.....Beers (per day / per week/ per month/ per year)
.....2.....Glasses of wine (per day / per week/ per month/ per year)
.....2.....Glasses of strong alcohols (whisky, vodka, etc) (per day / per week/ per month/ per year)

Figure 1. Study form for the evaluation of alcohol intake filled out by patient 1

She received 100 mg of lamivudine per day over a period of 6 months, along with symptomatic therapy, when needed.

Under treatment and close monitoring, the patient showed an initially favorable evolution but at the end of the 6 months of lamivudine therapy (our study's maximum admitted therapy span), the patient had displayed neither HBV viral load negativation nor HBsAg – HBsAb seroconversion.

As such, we switched the patient into monitoring of the chronic HBV hepatitis and she continued the lamivudine treatment for another 48 weeks. At the end of therapy, after a course of 18 months of lamivudine treatment, the patient displayed negativation of the viral load, but did not show HBsAg – HBsAb seroconversion. Seroconversion did not occur over the yearly monitoring visits after cessation of treatment, either. After completion of therapy, the patient stopped regularly showing up for follow-up visits. Table VIII depicts the dynamics of the hepatic markers and the acute HBV hepatitis serology.

The normalization of TGP over antiviral therapy is depicted in figure 2.

The TGP values dramatically decreased between baseline and the 2nd week of treatment and continued on a descending scale up to normalization, present at week 24.

The pattern of total bilirubin value decrease under specific antiviral treatment is dynamically illustrated in figure 3, according to the laboratory findings at each of the 5 medical visits. The values

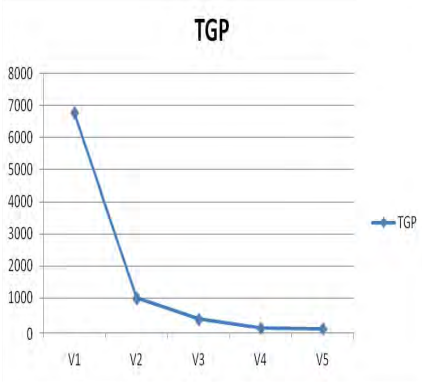

Figure 2. TGP dynamics over 24 weeks of lamivudine treatment

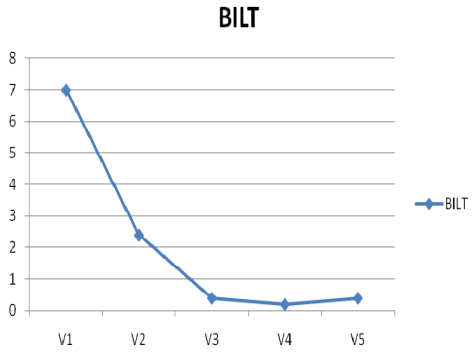

Figure 3. Total bilirubin dynamics over 24 weeks of lamivudine treatment

of total bilirubin dramatically decreased between admittance and the 2nd week of treatment and continued on their descending trend up to normalization, evident at week 24.

M.L.D., female, 21 years old		
2nd visit (week 2)	TGP 987	positive HBs Ag
	TGO 122	positive HBe Ag
	BILT 2,4	positive HBe Ab
	TP% 80%	positive HBcIgM Ab
		HBV-DNA 8658 IU/mL
3rd visit (week 8)	TGP 331	positive HBs Ag
	TGO 96	negative HBe Ag
	BILT 0,4	positive HBe Ab
	TP% 93,8%	negative HBs Ab
		HBV-DNA 6430 IU/mL
4th visit (week 12)	TGP 56	negative HBs Ag
	TGO 52	negative HBe Ag
	BILT 0,2	positive HBe Ab
	TP% 91,2%	positive HBs Ab
		HBV-DNA 2930 IU/mL
5th visit (week 24)	TGP 34	negative HBs Ag
	TGO 23	negative HBe Ag
	BILT 0,4	positive HBe Ab
	TP% 95,1%	positive HBs Ab
		HBV-DNA 1978 IU/mL

TGP – alanine aminotransferase, TGO – aspartate aminotransferase
BILT – total bilirubin, TP% - prothrombin concentration

Table VIII. Dynamics of the hepatic markers and acute HBV hepatitis serology

Figure 4 depicts the dynamics of the prothrombin concentration (PT%), with a mostly constant ascending trend over the 24 weeks of lamivudine therapy.

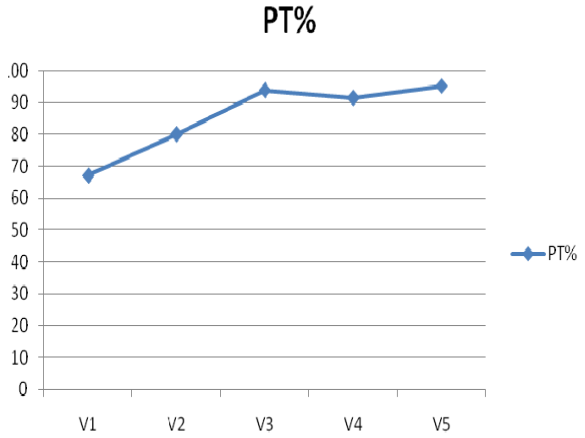

Figure 4. Prothrombin concentration dynamics over 24 weeks of lamivudine treatment.

Figure 5 illustrates the descending slope of the HBV-DNA viral load over the 24 weeks of antiviral therapy. The viral load decreased dramatically between baseline and the 2nd week of treatment and continued on a descending slope up to week 24. The patient did not achieve HBV-DNA viral load non-detectability over the acute hepatitis treatment of 24 weeks. As such, we switched the patient into monitoring of the chronic HBV hepatitis and she

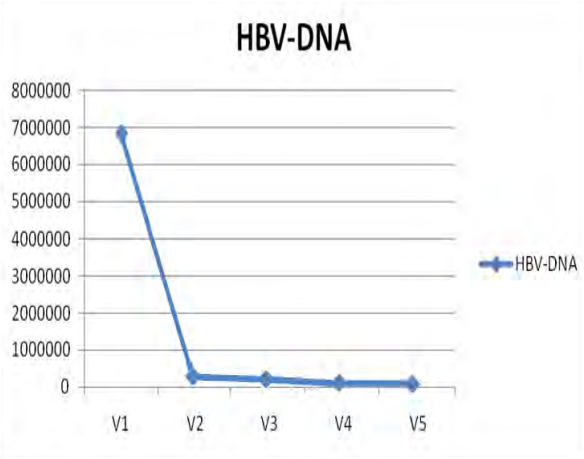

Figure 5. HBV-DNA dynamics over 24 weeks of lamivudine treatment

continued the lamivudine treatment for another 48 weeks. At the end of therapy, after a course of 18 months of lamivudine treatment, the patient displayed negativation of the viral load, but did not show HBsAg – HBsAb seroconversion.

After completing the 48 weeks chronic hepatitis B lamivudine therapy, the patient intermittently showed up for follow-up visits. In 2009, the patient presented with symptomatology similar to the previous episode. As such, our initial putative diagnosis was that of HBV hepatitis reactivation.

The laboratory findings once again refuted the epidemiologic assumption, diagnosing an acute HCV hepatitis with parenteral transmission due to

contaminated needles for i.v. drug use (HCV-RNA 12780000 IU/mL, negative HCV Ab). The patient, aged 25, was positive for i.v. drug abuse.

The biochemistry and serology results at acute HCV hepatitis admittance (baseline) are illustrated in table IX.

HCV genotype 2 was identified and the patient matched the International Institute for Infectious Diseases "Prof. Dr. Matei Balş" acute HCV hepatitis study's inclusion criteria. Therefore, she received treatment with Peg IFN 180 mg weekly and ribavirin 1200 mg per day over 24 weeks, along with symptomatic therapy, when needed.

Table X. depicts the dynamics of the hepatic markers and the acute HCV hepatitis serology.

The normalization of TGP over specific HCV antiviral therapy is depicted in figure 6. The TGP values dramatically decrease between baseline

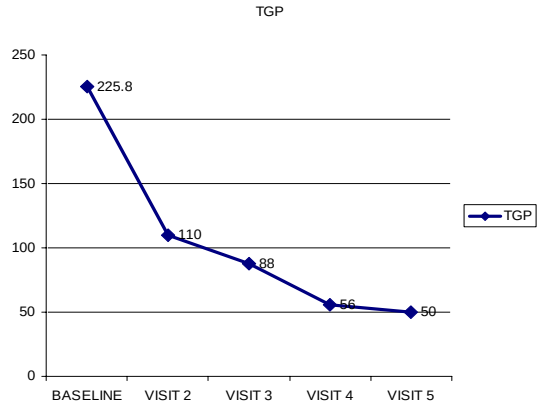

Figure 6. TGP dynamics over 24 weeks of Peg IFN and ribavirin treatment

and the 2nd week of treatment and continue on a descending scale up to normalization, present at week 24.

The pattern of total bilirubin value decrease under HCV specific antiviral treatment is dynamically illustrated in figure 7, according to the laboratory findings at each of the 5 medical visits. The values of total bilirubin dramatically decrease between admittance and the 2nd week of treatment and continue

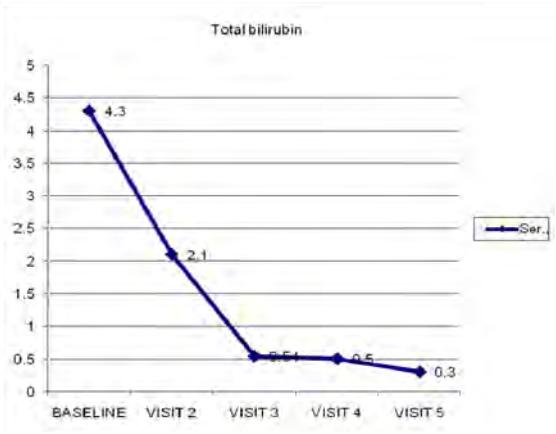

Figure 7. Total bilirubin dynamics over 24 weeks of Peg IFN and ribavirin treatment

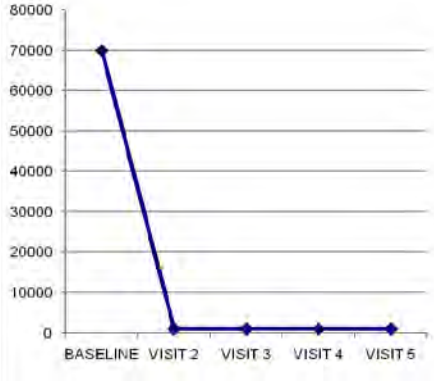

Figure 8. HCV-RNA dynamics over 24 weeks of Peg IFN and ribavirin treatment

on their descending trend up to normalization, evident at week 8.

Figure 8 illustrates the descending slope of the HCV-RNA viral load over the 24 weeks of specific HCV therapy. The viral load decreases dramatically between baseline and the 2nd week of treatment, when the patient displayed negativation of the viral load

The HCV hepatitis' evolution was favorable, the patient being undetectable for HCV-RNA at

M.L.D., female, 21 years old		
Baseline	TGP 2258 TP% 96,4% BILT 4,3	positive HCVAb negative HBs Ag positive HBe Ab negative Hbe Ag negative HBcIgM Ab negative AcHVA IgM HCV RT-PCR A 69900 IU/mL HBV-DNA undetectable

Table IX. Acute HCV infection baseline biochemistry and serology results

M.L.D., female, 21 years old		
2nd visit (week 2)	TGP 88 TP% 99,9% BILT 2,1	HCV RT-PCR M <600 IU/mL positive HCVAb
3rd visit (week 8)	TGP 110 TP% 93,8% BILT 0,54	HCV RT-PCR M <600 IU /mL positive HCVAb
4th visit (week 12)	TGP 56 TGO 52 BILT 0,5 TP% 91,2%	HCV RT-PCR M <600 IU/mL positive HCV Ab HBV-DNA undetectable
5th visit (week 24)	TGP 50 TP% 94,2% BILT 0,3	HCV RT-PCR M <600 IU/mL positive HCVAb HBV-DNA undetectable

TGP – alanine aminotransferase, TGO – aspartate aminotransferase
BILT – total bilirubin, TP% - prothrombin concentration

Table X. Dynamics of the hepatic markers and acute HCV hepatitis serology

the SVR (sustained virological response) follow-up evaluation. The patient continued on methadone treatment.

Discussions

We chose to present this clinical case due to its multiple particularities. As such, we mention the epidemiologic investigation report: the patient's husband known with chronic HBV and HDV hepatitis yet our patient only contracted the HBV infection.

Once the HBV serology was confirmed, this case underwent differential diagnosis with the severe acute exacerbation of chronic hepatitis B, M.L.D. being part of the category of patients with possible HBV chronic neo-natal infection with mother-to-child transmission, with slow-paced evolution and rare periods of exacerbation. Severe acute exacerbation of chronic HBV hepatitis is a unique clinical presentation of chronic hepatitis B characterized by very high alanine aminotransferase level accompanied by jaundice and hepatic decompensation [Wong, 2009]. In countries with intermediate to high endemicity for HBV, exacerbations of chronic hepatitis B may be the first presentation of HBV infection. A study has shown that about 50% of cases diagnosed as acute HBV infections in endemic areas are actually acute exacerbations of chronic HBV infection [Orenbuch-Harroch, 2008]. The patient's laboratory findings contributed to eliminating the severe acute exacerbation of the chronic HBV infection from the list of diagnostic hypotheses.

The patient's HBV hepatitis evolution under lamivudine therapy, 100 mg/day is interesting. Although in the beginning the treatment appeared to be efficient, the patient did not show negativation of the viral load and did not reach HBsAg –HBsAb seroconversion over the 24 weeks of therapy, requiring switch to chronic hepatitis monitoring. The patient was eventually responsive to lamivudine treatment (after 18 months), displaying undetectable HBV-DNA, but still without HBsAg –HBsAb seroconversion.

Another element particular to this clinical case is drug abuse accompanied by an acute HCV genotype 2 hepatitis, 4 years apart from the initial HBV infection, with favorable evolution under Peg IFN and ribavirin treatment for 6 months.

It is also a matter of interest that over the course of acute HCV hepatitis, viral load evaluations showed undetectable HBV-DNA with replicating HCV-RNA. As such, we need to consider whether the patient was undetectable 4 years after the lamivudine treatment due to maintaining a sustained virological response to treatment or due to the HCV, both present and replicating, which would vanguard the hepatic disease. In 1994 Liaw et al. suggested that HCV may usurp the role of HBV in chronic hepatitis and act as the major cause of continuing hepatitis or ALT elevation after HBV/HBsAg clearance [Liaw, 1994]. Unfortunately, during these 4 years, our patient skipped most of the follow-up visits and as such we do not have accurate monitoring of HBV viral loads.

The field literature is abundant on the subject of HBV and HCV coinfection, offering a potential explanation to our patient's particular evolution.

In 1993 Shih et al. demonstrated the suppression of HBV expression and replication by hepatitis

C virus core protein. The study was performed on human hepatoma cell lines (HuH-7), through the cotransfection of HCV structural genes (core and envelope 1) simultaneously with cloned HBV DNA. The results of the study showed a marked suppression of HBV viral replication by HCV [Shih, 1993]. Another study on HBV HCV cotransfection confirmed this suppression of HBsAg and of HBeAg, the studied HCV core protein acting as multifunctional negative regulator of transcription critically involved in the molecular interactions between HBV and HCV, and between HCV and the cell [Wang, 1997].

On the same type of cell lines (HuH-7), Bellecave et al. applied a superinfection algorithm and concluded that HBV and HCV are capable of *in vitro* replication within the same cell without overt interference. The studied cell lines were stable HuH-7 cell lines inducibly replicating HBV and they were transfected with selectable HCV replicons or infected with cell culture-derived HCV. Bellecave et al. also postulated that the viral interference noticed in patients coinfected with HBV and HCV can be due to indirect mechanisms of the adaptive or innate host immunity [Bellecave, 2009].

These studies suggest a possible role of the chronology of HBV and HCV infection on the evolution of the hepatic disorder. We can therefore hypothesize that a simultaneous HBV + HCV infection may lead to the suppression of HBV expression and replication [Shih, 1993] while an HCV superinfection over a chronic HBV hepatitis can allow simultaneous replication of HBV and HCV [Bellecave, 2009].

Our hypothesis has also been discussed by Liaw et al., which confirmed the reciprocity of our theory: acute HBV superinfection in patients with chronic HCV hepatitis may increase the risk for severe HBV hepatitis as the newcomer may suppress the pre-existing HCV [Liaw, 2004]. Together with Liaw's earlier observation that acute HCV superinfection suppresses pre-existing HBV [Liaw, 1994], it seems that the timing or sequence of infection is a factor influencing the outcome of viral interactions.

Sagnelli et al. have also tried to evaluate the virological and clinical impact of HCV superinfection in chronic HBV carriers by studying the viral interaction, clinical presentation and course of the disease in 4 HBsAg/HBV-DNA positive chronic hepatitis patients who developed acute HCV infection. In all cases, plasma HBV-DNA, which had been detectable prior to the HCV infection, was no longer detectable when the acute HCV infection occurred. The inhibition exerted by HCV on HBV-DNA persisted throughout the follow-up period in three patients, but was temporary in the one patient who experienced an acute exacerbation of chronic HBV infection. HCV-RNA became persistently undetectable in two patients and reduced to low levels in the other two. Sagnelli et al. conclude that HCV superinfection in the monitored chronic HBV carriers resulted in a reciprocal inhibition of HBV–HCV genomes [Sagnelli, 2006].

The study performed by Cacciola et al. endorses our hypothesis on the role played by the chronology of HBV and HCV infection. Cacciola et al. documented the detection of frequent occult HBV infection in patients with chronic hepatitis C. PCR (polymerase chain reaction) techniques have led to identification of sequences characteristic to HBV genome in 66 out of 200 HCV positive patients. Out of these 66 patients, 46 had positive HBcAb and 20 had negative HBcAb. As for the clinical relevance of the HBV HCV superinfection, 33% of the patients with serologically positive HCV infection and occult HBV infection developed cirrhosis, compared to 19% evolution towards cirrhosis in the group of HCV infected patients without occult HBV infection [Cacciola, 1999].

Our conclusion based upon the results of this field literature review is that there is further need for investigation of the HBV HCV coinfection and superinfections, respectively, in order to determine the precise evolution of the hepatic disease generated by the two hepatitis viruses, either together or by themselves. There is suggestive clinical evidence that the interactions of HBV and HCV, together with the chronology of the viral infections can be determinants of the liver disease's progression.

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