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Case report

A CURE FOR RECENTLY ACQUIRED HEPATITIS C

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ABSTRACT

Chronic hepatitis C is a global health threat. Most individuals infected with the hepatitis C virus (HCV) will inevitably progress to chronic infection, leading to cirrhosis and hepatocellular carcinoma. The current use of direct-acting antiviral (DAA) agents has changed the outlook for the treatment resulting in a cure for a short time. Recently acquired hepatitis C, also known as acute hepatitis, should be treated with regimens similar to chronic hepatitis C. We report a case of recently acquired hepatitis C manifested with jaundice, confirmed by a positive HCV RNA result and seroconversion. The patient was referred to a gastroenterologist with his girlfriend with newly diagnosed chronic hepatitis C for further evaluation and treatment. Both underwent DAA treatment with glecaprevir/pibrentasvir for two months. Upon completion of the therapy and 12 weeks later, HCV PCR was undetected in both cases. We treated our patient long before the onset of chronic liver disease and long-term complications. The current case underscores the importance of asking about potential ongoing exposure to an HCV-infected person.

Keywords: Direct-acting antiviral therapy, exposure to an HCV-infected person, early HCV infection, sustained virological response,

INTRODUCTION

Hepatitis C is a global health threat that affects about 58 million people globally, with 1.5 million cases diagnosed each year [1]. Approximately 70-75% of individuals infected with the hepatitis C virus (HCV) will progress to chronic infection, leading to cirrhosis and hepatocellular carcinoma [2]. The advent of direct-acting antiviral (DAA) agents is the most significant advance in the clinical management of hepatitis C. This therapy markedly improved treatment efficacy and tolerability. Moreover, DAA medications provide an opportunity for hepatitis C not only to be treated but cured [3].

Despite this therapy, the number of new HCV infections has increased. Nearly all remain undiagnosed as they are usually asymptomatic. Thus, the actual number of those harboring HCV may be much more. A few recent studies indicate persistent HCV outbreaks [4, 5]. Most new cases are among special populations like intravenous drug users (IDUs), men having sex with men (MSM), and recently HIV-negative MSM, using pre-exposure prophylaxis for HIV (PrEP) [6]. Some pose an additional problem as they become re-infected after being cured. Several recent outbreaks of MSM, HIV-infected or uninfected, have redefined HCV as a potential sexually transmitted infection under specific conditions and risk factors [7].

Here we describe a case of recently acquired hepatitis C successfully cured with DAA therapy, and briefly overview the diagnosis and treatment of early HCV infection.

CASE PRESENTATION

A previously healthy 35-year-old male presented to an emergency department in mid-March 2020 with a 5-day history of mild fatigue and dark urine for one day. With suspicion of acute viral hepatitis, he was admitted to an infectious disease department. Additional history revealed that the patient's new girlfriend of 8 months was diagnosed with chronic hepatitis C in February 2020 while being evaluated for a connective tissue-like disorder. Her HCV RNA result was 12 000 000 IU/ml (genotype 1b), and liver tests were within the normal range (data not shown). At that time, the patient's anti-HCV antibody test was negative, as were the aminotransferases. He denied having known risk factors such as blood transfusion, tattoo, piercing, drug usage, or recent invasive procedure or operation. On admission, his oxygen saturation was 96% on room air among the other normal vital signs. The physical exam showed slight jaundiced skin and sclera and mild non-tender hepatomegaly. The remainder of his examination was unremarkable. Liver tests were notable for alanine transaminase (ALT) 1491 I/U, bilirubin 111 μmol/L, and an international normalized ratio 1.3. The patient's complete blood count was without changes. Abdominal sonography visualized liver enlargement without intra- and extrahepatic dilation. Testing for viral hepa-

titis was as follows: HBsAg (–), anti-HAVIgM (–), ant-HEVIgM (–), ant-HEVIgG (–), HBsAg (–), and anti-HCV (+) (Table 1). The patient received intravenous fluid and improved rapidly, as did his liver function tests. He was discharged home markedly improved after 7 days of treatment. At a follow-up visit after two weeks, his liver tests returned to normal. The patient's HCV RNA (Abbott Molecular Inc., USA) obtained a few days was 44,306 IU / ml (genotype 1b). He was diagnosed with recently acquired hepatitis C and was referred to a gastroenterologist together with his girlfriend for further evaluation and treatment. When the medications were available after approval, they both underwent DAA treatment with glecaprevir/pibrentasvir for two months (3 tablets daily): for his girlfriend from October to November 2020, and for the patient from January to February 2021. Upon completion of the therapy and 12 weeks later, HCV PCR was undetectable in both patients.

Table 1. Table caption. Laboratory findings in the patient with recently acquired hepatitis C, on day 0 and day 7

Variable	On admission	Day 7	Reference range
Hemoglobin, g/l	151	-	140-160
WBC* x10^9/l	7,7	-	3.5-10.5
Tc† x10^9/l	219	-	150-350
INR‡	1,07	-	<1.2
Bilirubin, μmol/l	111	68	5-21
ALT§, U/l	1491	302	01-50
AST, ‖ U/l	513	177	10-60
Protein, g/l	65	-	60-82
Albumin, g/l	45	-	33-52
Glucose, mmol/l	4,5	-	3.4-6.1
HBs Ag ¶,	nonreactive		
AV IgM**	nonreactive		
HEV IgM ††	noreactive		
HEV IgG	nonreactive		
HCV Ab ‡‡,	reactive		
HCV RNA§	44 306 IU/ml		

Abbreviations:

*WBC, white blood cells, † Tc, thrombocytes, ‡ INT, international ratio, § AST, aspartate aminotransferase, ‖ ALT, alanine aminotransferase, ¶ HBsAg, hepatitis B surface antigen, **HAV IgM, IgM antibody to HAV

††HEV IgM, IgM antibody to HEV; HEV IgG, IgG antibody to HEV, ‡‡ HCVAb, antibodies to HCV

§HCV RNA, tested on day 7

DISCUSSION

Our patient was diagnosed with recently acquired hepatitis C manifested by jaundice, confirmed by a positive HCV RNA test and seroconversion. If it were not for jaundice, he would have remained unrecognized and likely become chronic. Nevertheless, he was treated with a pan-genotypic DAA regimen and achieved sustained virological response. Sexual contact was considered the most likely route of transmission.

HCV infection has been classified as acute or chronic. Acute HCV infection has been arbitrarily defined as the first 6 months after the acquisition of infection and chronic from 6 months onwards in the absence of spontaneous virus clearance [8]. However, recent insights into the natural history of HCV infection, emerging trends in transmission pattern (sexual route), and the advance of therapy question this classification.

Adapted terminology

Acute hepatitis C is benign and usually asymptomatic. When clinically manifested, jaundice occurs in a small proportion of patients. In addition, there is no definitive diagnostic assay which makes the diagnosis difficult [9]. Futhermore, several funding bodies have refused reimbursement treatment to patients considered to have acute C hepatitis because HCV DAA licensing was based on chronic infection [10]. Considering all this, to optimize the management and surveillance of HCV infection, there is a need to adapt this terminology.

The European AIDS Treatment Network (NEAT-ID) [11] defined the first 6 months of HCV infection as a recently acquired hepatitis C rather than acute, while from the 6th month onwards to the 12th month – early chronic hepatitis C and (any of) the following laboratory criteria for diagnosis: a/ a positive anti-HCV antibody test in the presence or absence of a positive HCV-RNA and a docu-

mented negative anti-HCV antibody test within the previous 12 months, or b/ positive HCV-RNA and a documented negative HCV-RNA and negative anti-HCV antibody test within the last 12 months. In real-world historical data are often missing, and alternate diagnostic criteria are applied: a positive HCV-RNA test regardless of the anti-HCV-antibody test result and an acute rise in ALT greater than three times the upper limits of normal with documented normal ALT within 12 months, with an association with ongoing risk behavior and exclusion of other causes of acute hepatitis.

Therapy

The high rate of progression to chronic hepatitis, the absence of a vaccine, and pre-exposure or post-exposure prophylaxis is the motivation to consider early treatment of recently acquired hepatitis C.

Treatment is one of the most contentious issues, especially the timing and duration. Early therapy would achieve higher cure rates, but the precise time when to begin is a difficult choice. If therapy starts too early, there is a risk of treating those who will clear HCV spontaneously, as in 20-45% of cases [12]. In addition, excessive treatment will lead to increased toxicity and cost. However, delayed treatment initiation favours the spread of infection among a high-risk population and disease progression [13]. Studies of DAA therapy in recently acquired hepatitis C are limited by small sample sizes, selected populations, and genotype-specific regimens [14, 15]. Until more definitive data are available, the EASL and AASD/IDSA guidelines [10, 16] recommend immediate treatment initiation without waiting for possible spontaneous clearance ("treatment as prevention" concept). Scaling up DAA treatment can reduce HCV incidence and prevalence, particularly among people at the highest risk of ongoing transmission (e.g. HIV positive, IDUs and MSM) [6]. Due to the high safety and efficacy, DAA regimens for recently acquired hepatitis C should follow the current treatment guidelines for chronic hepatitis C [10, 16]. The regimens are short and well-tolerated. Even patients with decompensated cirrhosis and significant comorbidities can be treated. The main objective of DAA treatment is a sustained virological response (SVR), defined as undetectable HCV RNA 12 weeks (SVR12) or 24 weeks (SVR24) after completion of antiviral treatment, which is indicative of a cure. This response should be assessed by a sensitive molecular method with the lowest level of detection of ≤15 IU/ml. The achieved SVR rates range from 90% to 96%, depending on the stage of liver disease and viral genotype [10]. Regimens with high efficacy and the ability to avoid genotyping are recommended as diagnosis of recently acquired hepatitis C may be a diagnostic challenge. Of great significance is the development of pan-genotypic drug combinations, including sofosbuvir/velpatasvir and glecaprevir/pibrentasvir in a fixed-dose combination lasting for at least 8 weeks [10]. The latter regimen was successfully used in both cases. Despite the timely diagnosis of our patient, the DAA treatment start was delayed for 11 months because of the lengthy drug approval process. Monitoring should continue in patients with ongoing risk for reinfection. Immediate treatment of HCV reinfection with DAA drugs is required. Potential drug-drug interactions should be monitored during treatment and managed by discontinuing the drug for 8-12 weeks, changing the dose, or switching to an alternative medication [10].

Sexual intercourse is considered an inefficient way of HCV transmission, and its epidemiological role is controversial. A recent study reported a low HCV seroprevalence of 0.6% among monogamous heterosexual couples [17]. However, sexual transmission of HCV has increased recently [18]. Transmission may be more effective in the presence of other biological and behavioral factors like HCV-HIV coinfection, multiple sex partners, and high-risk sexual practices. A history of other sexually transmitted infections and blood exposure via partner violence should also be considered. Some studies indicated an ongoing sexually transmitted epidemic among HIV-positive MSM and recently in HIV-negative MSM, using PrEP [6].

In our patient, we found no risk factors. Likewise, the source of HCV acquisition has not been identified in a significant number of other reported patients [19]. However, the patient's sexual contact with a new partner with a high degree of HCV viremia merits special consideration. Though we cannot establish definitive causality, ongoing intimate exposure to an HCV-infected person raises a high suspicion of sexually acquired HCV infection. Phylogenetic analysis of HCV would help to clarify our assumption but during the study period, it had been not routinely performed in Bulgaria.

In **conclusion**, we present a case of recently acquired hepatitis Crarely manifested by jaundice. We managed to diagnose it timely, treat and cure it long before the onset of chronic liver disease and long-term complications. The current case underscores the importance of asking about potential ongoing exposure to an HCV-infected person.

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