



## Spontaneous Negative Seroconversion of Both Hepatitis B and C in an Egyptian HD Patient

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### Authors' contributions

This work was carried out in collaboration among all authors. Research idea, study design and data acquisition done by author AFM. Providing intellectual content of critical importance to the work described by authors AMAE and ARY. Author RMFS data analyzed and interpreted the work. Author NSA supervised or mentorship the work. Author AFM takes responsibility that this study has been reported honestly, accurately and transparently and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

### Article Information

DOI: 10.9734/AJMAH/2021/v19i230300

Editor(s):

(1) Dr. Mohamed Salem Nasr Allah, Weill Cornell Medical College, Qatar.

Reviewers:

(1) Mouinga Ondeme Augustin Ghislain, Centre Interdisciplinaire de Recherches Médicales de Franceville (CIRMF), Gabon.

(2) Ishtiaq Ahmed, Isra University, Pakistan.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/66317>

Case Study

Received 30 December 2020

Accepted 06 March 2021

Published 19 March 2021

### ABSTRACT

**Background:** Hepatitis b virus infection (HBV) was recognized as an important hazard for patients and staff in Hemodialysis Units (HDU), and this issue was first recognized in the 1960s with a set of guidelines for the control of HBV in HDU. HCV is a blood-borne infection and is the most significant cause of viral hepatitis which is mainly transmitted by blood transfusion. Thus, it is reasonable to perform initial screening for HCV in HD patients. Patients admitted or re-admitted to an HD unit are recommended to be tested for HBsAg, HCV, and HIV antibodies and to be followed up monthly or at least every three months after admission to HDU. We aim to present this case of spontaneous clearance of HBV and HCV positive after being positive for more than twelve years on HD.

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**Case Presentation:** A 66 years old Egyptian male patient with Chronic Kidney Disease (CKD) from Alexandria had started HD 14 years ago while he tested positive for HCV-Ab and HBs Ag positive, although fared well with normal liver function, while the source of infection was not known. HCV-Ab turned into seronegativity after twelve years on HD. Astonishingly, after 13 years on HD; the test of HBs Ag became negative and hepatitis B surface antibody appears by Elisa testing. This was noticed or observed following the implementation of quality enhancement of the HD parameters in most of the HD services provided units according to the regulations of Ministry of Health (MOH), and this was accompanied by better anemia and more frequent utilization of high flux dialysis with a consequent reduction to the need for blood transfusion in the last four years. Previous publications advocated hypothetical mechanisms of HCV clearance during the process of HD: namely, filtration of the virus particles through the pores of the dialysis membrane and or their adsorption to the HD membrane. These welcome spontaneous clearances of the HBV and HCV in this patient could be attributable to the improvement of anemia state and use of high flux dialysis that might have improved the immunity of this patient.

**Conclusion:** Spontaneous clearance of HBV and HCV could potentially possible and could benefit from the improvement of both patients and HD states that could enhance the immune system or mechanical entrapment of the virus particles. Suggestions need further studies for confirmation.

*Keywords: Hepatitis B; hepatitis C; spontaneous clearance; negative seroconversion; Egyptian hemodialysis.*

## 1. INTRODUCTION

The prevalence of hepatitis viruses in HD patients is much greater than in the general population. Hepatitis outbreaks in hemodialysis (HD) patients and staff were reported in the late 1960s, and a number of hepatotropic viruses transmitted by blood and other body fluids have been identified. The incidence of HBV and HCV in dialysis units has been falling over the last 3 decades, although data from the USA showed that the incidence of HBV infection in dialysis units has become stable at 1% per year in the 10 years before 2002 [1]. The prevalence of hepatitis C virus antibody (anti-HCV) is high, between 3.4% and 32.1%, among HD patients [2]. Significant advances have been made in the prevention of hepatitis B and C virus transmission in these high-risk populations; however, the transmission risk is still present [3].

Hepatitis b virus infection (HBV) was detected as an important hazard for patients and staff in hemodialysis units (HDU) with a set of guidelines for the control of HBV in HDUs [4].

HBV infection has been effectively controlled by active vaccination, screening of blood donors, the use of erythropoietin, and segregation of HBV carriers. Staff should observe barrier precautions against exposure to blood and adhere strictly to infection control practices to prevent cross-infection between dialysis patients. Hepatitis C virus (HCV) is the most significant cause of viral hepatitis which is mainly transmitted by blood transfusion. The

introduction in 1990 of routine screening of blood donors for HCV contributed significantly to the control of HCV transmission. An effective HCV vaccine remains an unsolved challenge. Regular virology screening is the cornerstone of the effective control of chronic hepatitis in the setting of HD. Major recent advances in viral diagnosis technology and the development of new oral, direct-acting antiviral agents allow early diagnosis and better therapeutic response [5].

In 2002 a working party convened by the Public Health Laboratory Service (PHLS) on behalf of the Department of Health published an updated report [1] that include recommendations: Patients admitted or re-admitted to an HDU should be tested for HBsAg, HCV and HIV antibody every 3 months. Dialysis units should ensure that they have arrangements for obtaining test results rapidly before dialysis is carried out.

According to the Kidney Disease Improving Global Outcome (KDIGO) [6], HCV-Ab detection either initial testing with enzyme immunoassay (EIA) or with nucleic acid testing (NAT) is recommended, depending on the low or high prevalence of the virus in the country and in the particular hemodialysis unit. The 3rd generation EIA is the preferred immunologic assay and has proven high sensitivity also in dialysis patients [7]. In a large multicenter German study by [Hinrichsen et al 2002] [8] including 2796 dialysis patients, 0.8% of the entire study population was HCV-RNA positive but anti-HCV negative. There is no doubt that the detection of HCV-RNA by RT-PCR is the most sensitive and

specific assay for HCV detection. The natural history of chronic liver disease caused by HCV in HD patients remains unclear [9,10].

The Egyptian guidelines to control the spread of HBV, HCV, and HIV infections in HDU include the following: regular testing every three months, patient isolation, vaccination against hepatitis B, screening of blood donors, the use of erythropoietin to decrease the need for blood transfusion and later on direct antiviral drugs for management of HCV.

We present this case of spontaneous clearance of hepatitis B and hepatitis C in HD patient to raise the attention of the researchers and scientific committees for the possibility of spontaneous clearance and to look for factors that could improve the status quo.

## 2. CASE PRESENTATION

The presented case is of a 66-year-old Egyptian cigarette smoker male patient from Alexandria. He is married and has 3 offspring. He has hypertension, ischemic heart disease, and autosomal dominant polycystic kidneys that led to progressive chronic kidney disease (CKD). He started to receive HD on 26/11/2006, through a central HD catheter for few months then changed to right brachiocephalic A-V fistula. His height is 174 cm, while his last dry body weight was 65 kg. His hemodialysis details entail 3 sessions weekly, 4 hours each, with a blood flow rate of 250–300 ml/min, dialysate flow of 500ml/min, with an average fluid removal of 3-3.5 L/session. Heparin is utilized for anticoagulation during the sessions. The hemodialysis filter was based on a low flux polysulphone or helixon membrane with a surface area of at least 1.4 m<sup>2</sup>, which has been changed to high flux quality for the last 4 years. Apart from occasional intradialytic hypertensive episodes, the patient fared well on the HD sessions without any complications.

The patient started the journey of HD in 2006 with positive viral serology for HbsAg and HCV-Ab, which were followed up as a part of routine tests every 3 months, as the recommended guidelines for follow up in Egyptian HD units. The patient was isolated on a separate HD machine in a separate room. In 2018, HCV-Ab became negative; although he did not receive any anti HCV drugs. However, HBsAg remained positive; so, the patient stayed in isolation during his HD sessions. At the beginning of 2019, HBsAg became also negative. Repetition of all hepatitis B markers and HCV Ab every 3 months for one

year at different laboratories, confirmed by PCR testing for both HCV and HBV, were all negative, except for hepatitis B surface antibody relying on ELISA testing.

There were no manifestations denoting jaundice or ascites, and there were no other symptoms of hepatic disturbance. The patients did not have a history of any operations although there had been four admissions to Intensive Care Unit (ICU) due either to severe uncontrolled hypertension or acute coronary syndrome.

Repeated clinical examination revealed a well-looking conscious, oriented, and cooperative patient who attended the HDU by himself. He is known to be a compliant as regards medications and HD team instructions and advice. His average blood pressure was around 140/90. He used to have pallor, but no congested neck veins and no lower limb edema. The right brachiocephalic fistula was functioning well. Chest examination showed bilateral fine basal crepitation and chest x-ray showed increased bronco-vascular markings while abdominal examination showed no abdominal scars, no organomegaly, and no ascites. Abdominal ultrasound demonstrated normal size and echogenicity of the liver with no focal lesions; the portal vein is patent with the normal caliber and the gall bladder had normal wall thickness with no intraluminal stones or masses. The kidneys were echogenic with bilateral multiple cortical cysts. Patient was followed up monthly by routine laboratory investigation, and We have calculated the average of the 12 months as illustrated in Table 1. At 3/6 /2020: the cellular immune function of the patient was performed and results showed normal CD4 610(43%), normal CD8 369 (26%), normal CD4/CD8 1.6 l (low normal) Differential leucocyte counts was 5.26{neutrophil 2893 (55%) and lymphocyte 1420 (27%)}

The patient received the following medications: Nifedipine 20 mg/12hours, alpha methyl dopa 250mg/8hours, aspirin 81 mg once/day, valsartan 160 mg/12 hours, famotidine 20 mg once/day, vitamin B12 tablets once/day, calcium carbonate 600 mg/8 hours, L-carnitine amp once / week, B-comp ampoule once / week. Before the previous 4 years, he used to receive one unit packed red blood cells every 3-4 months whenever serum hemoglobin dropped below 8 gm/dl due to unavailability of adequate ESA dose. In the last few years; the monthly ESA dose has increased to 8000 IU/week with no need for further blood transfusion. Parenteral iron 100 mg was received once weekly.

**Table 1. Routine laboratory data (average values of the last 12 months)**

<b>Routine lab for patient on HD</b>	<b>Average laboratory data of the last 12 months</b>	<b>SD</b>
Pre dialytic Blood urea	118.536	17.022
Post dialytic Blood urea	44.418	7.497
Serum creatinine	9.22	1.275
Urea Reduction Ratio	62.935	3.513
Hemoglobin	8.21	0.494
Serum albumin	4.358	0.225
Serum calcium	7.27	0.765
Serum phosphorus	4.27	1.254
Serum iron	66.76	4.703
Parathyroid hormone (PTH)*	295	
Uric acid	5.21	0.687
Serum sodium	136.5	5.1555
Serum potassium	4.775	0.498

\*PTH testing was performed only once during the last 12 months

### 3. DISCUSSION

The presented case is a 66-year-old Egyptian cigarette smoker male patient from Alexandria, who has been on regular HD for 14 years and has positive viral serology for HCV-Abs and HBs Ag. The patient started the use of high flux dialyzers and experienced an increase in the regular dose of erythropoietin in the last four years. Interestingly, he firstly showed HCV negative seroconversion after staying 12 years on HD and continued to be so thereafter until now, with regular 3-monthly assessment by routine antibody testing, and confirmation by PCR-HCV once, which revealed negative results. Clearance of HCV in HD patients has been reported by some previous studies which investigated HCV viral kinetics before, during, and after a regular 4-h hemodialysis session. Most studies revealed a significant decrease in HCV viral load during HD sessions with a return to basal levels after 48 h, prior to the next session [11,12]. When the effect of the type of dialysis membrane on viral load kinetics was examined, it was found to decrease with hemophan and polysulfone membranes but not with cuprophan [13]. The potential mechanisms explaining the intradialytic reduction of HCV are the passage of the virus through the membrane into the dialysate or the ultra-filtrate and possibly adsorption of the virus or viral particles by the dialysis membrane. The former mechanism seems insufficient to explain viral load reduction during HD since HCV virions are larger (30-40 nm) than the pores of the dialysis membrane (10-20 nm). Three studies failed to detect HCV-RNA in the dialysis ultra-filtrate [14,15,16]. On the other hand, adsorption of the virus or viral particles by the dialysis membrane was

investigated evaluating this potential mechanism of HCV reduction that revealed conflicting results [17,18]. In the current case; the hemodialysis was previously based on a low flux polysulphone or helixon membrane with a surface area of at least 1.4 m<sup>2</sup> that has been changed to high flux quality for the last 4 years. Whether the pores of high flux dialyzers could result in more adsorption of HCV particles, needs further studies. Furthermore, the impact of the dialysis membrane or the dialysis procedure (hemofiltration, hemodiafiltration) on HCV viral kinetics requires further investigation. Another interesting hypothesis is the possibility of HCV reduction via host-mediated factors; the basis of this interesting concept is that the contact of the patients' blood with extracorporeal circulation may lead to the release of pro-inflammatory cytokines such as IL-2 and TNF- $\alpha$  as well as IFN- $\alpha$  and hepatocyte growth factor (HGF); factors with potential antiviral properties [12,19]. In line with this, the presented case showed a CD4/CD8 ratio of 1.6 that is accepted as a marker of immune potency; however, this finding is not supported by Haussuna et al. [20] who reported that T-regulatory lymphocyte cells count has no significant difference between HCV-negative and HCV-positive hemodialysis patients.

Surprisingly, the patient of the current case presentation has also been cleared from hepatitis B virus, and has become negative for HBsAg and developed hepatitis B surface antibodies by ELISA testing, after 13 years on HD. This finding is in contradiction to the well-known belief that spontaneous hepatitis B clearance rarely happens in hemodialysis patients, owing to their immunodeficient state [21]. However, some

authors Jeon and Ha [21]; Patel [22] published a few cases reports documenting hepatitis BV clearance followed by the development of hepatitis B surface antibodies, years after starting HD. The latter authors ascribed this clearance to the potential immunopotential that could have occurred with long-term HD. In our experience in looking after and supervising many hemodialysis patients and units in different areas in Egypt, we have come across a quite few cases that were spontaneously cleared from HBV in the last few years, although they were not published. The clearance of these few cases from hepatitis B virus in our locality might, putatively, be attributable to the recent trend of implementing better dialysis prescription in Egypt in the last few years, including the availability of high flux dialyzers, widespread implementation of better dialysis prescription and proper erythropoietin dosage. It is now well known that high flux hemodialysis, which is known to induce a significantly higher clearance rate of macromolecular toxins compared with the HD, has the potentials to improve the cellular immune function in maintenance HD patients, and thus it could reduce the incidence of infection and tumor, and improve the survival rate and quality of life of the patients [23,24,25]. In this context, [Xing] [19] found that High Flux Hemodialysis (HFHD) was associated with an increase in CD4+, CD4+/CD8+, IL-2, and mIL-2R (CD25+), and a decrease in SIL-2R, at 4, 24, and 48 hours after, compared with that before, HFHD indicating that the cellular immune function of the patients can be improved to a certain extent through this modality of renal replacement therapy.

In spite of the presence of HCV-Ab positivity for more than 12 years in the presented case, there was no abnormality in liver morphology by abdominal ultrasound. In addition, serum liver enzymes and albumin remained normal during the whole duration of HD. This observation was similar to that of Trevisoli et al. [26], who studied the effects of chronic uremia and HD on HCV-related liver disease, and on the progression of liver fibrosis, in HCV-infected patients with End Stage Renal Disease (ESRD). They reported that the biochemical and inflammatory activities in hemodialysis patients afflicted with HCV were generally lower than that observed in non-uremic HCV patients; a finding that persuaded the authors to hypothesize that hemodialysis and uremia might have a protective role against the progression of the disease caused by HCV [26]. In contrast, Barril [27] reported that the

progression time to cirrhosis can be much shorter in HCV-infected HD patients than in patients with normal renal function. However, many other studies suggested that HCV-infected HD patients presented a lower degree of inflammatory activity and a lower stage of liver fibrosis compared to HCV-infected patients with normal renal function [28,29,30]. The natural history of HCV in dialysis patients remains controversial because the course of HCV extends over decades, whereas dialysis patients have higher morbidity and mortality rates than those of the general population [2,31]. On the other hand, low aminotransferase levels in HCV-infected HD patients had also been ascribed to factors related to the dialysis procedure itself, and/or to the impact of dialysis on disease severity through reduction of viremia, and increased production of hepatocyte growth factor (HGF) and IFN- $\alpha$ , and through lymphocyte activation [32].

#### 4. CONCLUSION

Spontaneous clearance of HBV and HCV is potentially possible and might probably gain benefit from the improvement of both patients' states and HD characteristics that could enhance the immune system or induce mechanical entrapment of the virus particles. Further studies are needed to substantiate these observations and support these suggestions.

#### CONSENT

Informed consent was obtained verbally from the study participant.

#### ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

#### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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