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CASE REPORT

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A 28-year-old male patient with asymptomatic and multi-drug-resistant HBV infection: a case report

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Abstract

Chronic hepatitis B virus (HBV) infection poses a significant global health challenge, impacting millions of individuals and elevating the risk of morbidity and mortality. Antiviral therapies are the primary treatment for chronic HBV infection, but treatment resistance can occur, leading to poor clinical outcomes and an increased risk of liver complications. This case report presents the clinical trajectory of a 28-year-old male diagnosed with asymptomatic HBV infection in 2016 under the auspices of the Hepatitis Control Program, Government of Azad Jammu and Kashmir, Pakistan. Over 6 years, persistent HBsAg, HBV, and HBeAg were observed, with absent acute markers and co-infections. Initial HBV DNA viral load was 1×10^4 copies/mL in 2016, escalating despite entecavir and pegylated interferons therapy, indicating multi-drug resistance. Tenofovir therapy initially reduced viral load but later exacerbated it, reaching 1.86×10^6 copies/mL in 2022. Liver function abnormalities and lipid profile irregularities persisted. Urine examination consistently showed abnormalities. Pending HBV DNA sequencing results may offer insights into treatment resistance. This case underscores the need for an adaptive approach in managing chronic HBV infections within public health programs. Continuous monitoring, integration of virological and biochemical data, and a tailored treatment strategy are essential for optimizing outcomes in similar cases, stressing the importance of refining therapeutic approaches against chronic HBV infection.

Introduction

Chronic hepatitis B virus (HBV) infection is a major global health burden, affecting millions of people and leading to significant morbidity and mortality [1]. Antiviral therapy serves as the primary treatment approach for chronic HBV infection. However, the emergence of treatment resistance poses a significant challenge, contributing to suboptimal clinical outcomes and heightened vulnerability to liver-related complications [2]. Recent research highlights the effectiveness of antiviral therapies like tenofovir and entecavir in significantly reducing HBV viral load and enhancing liver function in the majority of patients [3], while another study found that treatment with pegylated interferon can lead to a sustained virological response in a significant proportion of patients [4]. However, drug resistance can occur with prolonged use of these therapies [5].

Over the past two decades, oral antiviral agents have been introduced for the treatment of hepatitis B virus (HBV) infection [6]. Long-term antiviral therapy is often necessary for the majority of patients, with incomplete

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viral suppression and the emergence of drug resistance representing significant concerns [7].

In this case report, we describe a patient with asymptomatic HBV infection who developed resistance to two commonly used antiviral therapies, entecavir and pegylated interferon, and is currently being treated with Tenofo B according to the modified practice guidelines of Pakistan Society for the Study of Liver Diseases (PSSLD) under Hepatitis Control Program, Government of the AJK state, Pakistan. The treatment efficacy was monitored by detecting the viral load of HBV DNA using quantitative real-time PCR after each 6-month period. A decrease in viral load was considered responsive, whereas a constant or increased viral load was deemed non-responsive to the therapy. The degree of liver disease was assessed by measuring liver function tests (LFTs) including ALT, ALP, and total bilirubin. Several other diagnostic tests like complete blood profile (CBC), lipid profile, and urine routine examination were also performed to detect the patient health condition. This case highlights the challenges of managing treatment-resistant HBV infection and the importance of ongoing research to identify effective strategies for overcoming resistance and improving patient outcomes.

Case presentation

Basic demography and longitudinal assessment of hepatic viral markers

The case involves a 28-year-old male student from the Neelum Valley district of Azad Jammu and Kashmir, Pakistan. The patient was initially diagnosed with asymptomatic HBV infection in 2016. The diagnostic findings revealed positivity for HBsAg, HBV DNA, and HBeAg, indicative of an active infection. Moreover, the patient was tested negative for anti-HBc (IgM), anti-HBs, HCV RNA, and Hepatitis D, as outlined in Table 1. The longitudinal assessment demonstrated the persistence of positive HBsAg, HBV, and HBeAg over a 6-year period. However, the patient consistently tested negative for anti-HBc (IgM), anti-HBs, HCV RNA, and Hepatitis D, suggesting a chronic HBV infection with an absence of acute markers and co-infections.

Analysis of blood and urine parameters

The results of the patient, outlined in Table 2, offer a thorough examination of blood and urine parameters spanning 6 years. This sheds light on the complex relationship between virological and biochemical factors in asymptomatic HBV infections. The liver function parameters demonstrated a sustained elevation in alanine transaminase (ALT), indicating persistent liver inflammation. Alkaline phosphatase (ALP) levels remained within the normal range, signifying stability in bone and liver health, while total bilirubin levels stayed consistently within normal limits, indicating steady bilirubin metabolism. However, the lipid profile displayed a mixed pattern, with triglyceride (TG) and cholesterol levels generally within normal limits. High-density lipoprotein (HDL) cholesterol levels were consistently normal, while low-density lipoprotein (LDL) cholesterol occasionally exceeded the upper limit, suggesting potential cardiovascular risks. While, hematological parameters, such as total leucocyte count (TLC), platelet counts, red blood cell (RBC) counts, hematocrit (Hct), and hemoglobin (Hb), exhibited various fluctuations but generally stayed within normal ranges. Notably, the increase in platelet counts after 3 years may indicate a response to ongoing viral infection. Under routine urine examination every time, his urine was found with pus cells and epithelial cells, displaying a pale yellow color with a pH of nearly 6.0, constantly.

Table 1 Details of tested viral markers at various diagnostic stages of the patient

Viral markers	Results at various investigation stages						
	Initial stage (2016)	After 1 year (2017)	After 2 years (2018)	After 3 years (2019)	After 4 years (2020)	After 5 years (2021)	After 6 years (2022)
HBsAg (ICT)	Positive	Positive	Positive	Positive	Positive	Positive	Positive
HBV DNA (PCR)	Positive	Positive	Positive	Positive	Positive	Positive	Positive
HBeAg (ICT)	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Anti-HBc IgM (ICT)	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Anti-HBs (ICT)	Negative	Negative	Negative	Negative	Negative	Negative	Negative
HCV RNA (PCR)	Negative	Negative	Negative	Negative	Negative	Negative	Negative
HDV RNA (PCR)	Negative	Negative	Negative	Negative	Negative	Negative	Negative

Key: *HBsAg* Hepatitis B surface antigen, *HBV* Hepatitis B virus, *HBeAg* Hepatitis B envelope antigen, *Anti-HBc* Hepatitis B core antibody, *Anti-HBs* Hepatitis B surface antibody, *HDV* Hepatitis Delta virus

Table 2 Evaluation of multiple diagnostic parameters at various stages

Parameters	Normal ranges	Initial stage (2016)	After 1 year (2017)	After 2 years (2018)	After 3 years (2019)	After 4 years (2020)	After 5 years (2021)	After 6 years (2022)
Blood diagnostic results at various stages								
ALT	29 to 33 IU/L	41	53	48	55	57	49	52
ALP	44 to 147 IU/L	29	33	48	57	71	102	123
Total bilirubin	0.1 to 1.2 mg/dL	0.59	0.58	0.51	0.60	0.55	0.50	0.55
TG	Up to 199 mg/dL	78	69	75	68	74	81	79
Cholesterol	Up to 200 mg/dL	142	147	125	129	147	139	144
HDL	35 to 55 mg/dL	45	39	47	42	48	40	43
LDL	10 to 140 mg/dL	94	99	82	87	76	101	90
TLC	5000 to 10000 cells/µL	5900	6300	8500	7200	8100	6900	7400
Platelets	135,000 to 317,000 per µL	167,000	163,000	159,000	271,000	264,000	195,000	210,000
RBCs	4.7 to 6.1 million cells/µL	5.25	5.25	5.40	5.61	5.10	5.30	5.0
Hct	38 to 50%	51	49%	50%	42%	43%	49%	44%
Hb	14 to 18 g/dl	16.4	16.7	16.0	16.1	15.8	17.2	16.3
Urine examination results at various stages								
Color	Clear to pale yellow	Pale yellow	Pale yellow	Pale yellow	Pale yellow	Pale yellow	Pale yellow	Pale yellow
Specific gravity	1.005 to 1.030	1.010	1.007	1.025	1.015	1.020	1.015	1.015
PH	4.5 to 8.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
Sugar	0 to 0.8 mmol/L	Nil	Nil	Nil	Nil	Nil	Nil	Nil
Urobilinogen	Up to 1.0 mg/dL	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Puss cells	0–5/ HPF	0–1	2–3	1–2	0–1	1–2	1–2	4–5
RBCs	≤ 2 cells/ HPF	Nil	Nil	Nil	Nil	Nil	Nil	Nil
Epithelial cells	≤ 2–5 cells/HPF	1–2	0–1	1–2	0–1	2–3	0–1	1–2

Key: *Hb* Hemoglobin, *Hct* Hematocrit, *TLC* Total leucocytes count, *ALT* Alanine transaminase, *RBCs* Red blood cells, *ALP* Alkaline phosphatase, *TG* Triglycerides, *LDL* Low-density lipoproteins, *HDL* High-density lipoproteins

Progression of viral load and treatment response

The progression of the patient's viral load, as depicted in Table 3, reveals a concerning trend over the course of multi-drug treatments. Calculating the fold-change from the initial inactive stage (viral load = 1×10^4 copies/mL) to subsequent treatment phases highlights the magnitude of viral replication despite therapeutic interventions.

After 1 year with entecavir, the viral load increased modestly from 1×10^4 to 1.3×10^4 copies/mL, suggesting a limited response. However, after 2 years of entecavir treatment, the viral load further escalated to 1.5×10^4 copies/mL, and after 3 years, this reached up to 1.3×10^5, indicating a suboptimal suppression of viral replication. Similarly, the shift to pegylated interferons also demonstrated an increase in viral load, reaching 1.1×10^6 copies/mL after 2 years with pegylated interferons.

The subsequent transition to Tenofo B therapy initially resulted in the decrease (1.9×10^5) of the viral load after 6 months of the therapy. But later, this therapy resulted in a marked increase in viral load, reaching 1.86×10^6 copies/mL after just 1 year. This drastic surge indicates a concerning scenario of multi-drug resistance, with the virus exhibiting reduced susceptibility to various antiviral agents. The consistent rise in viral load despite sequential treatment attempts underscores the urgent need for a comprehensive understanding of potential drug-resistant mutations through the pending results of HBV DNA sequencing. This information is crucial for devising a tailored and more effective therapeutic strategy to curb the persistent viral replication in this complex case of chronic HBV infection.

Table 3 Treatment management and the viral load of the patient

Viral load at inactive stage	Viral load (copies/mL) of the patient after treatment					
	After 1 year with entecavir (Jul, 2017)	After 2 years with entecavir (Aug, 2018)	After 3 year with entecavir (Sep, 2019)	After 1 year with pegylated interferons (Oct, 2020)	After 2 years with pegylated interferons (Nov, 2021)	After 1 year with Tenofo B (Dec, 2022)
1×10^4 copies/mL	1.3×10^4	1.5×10^4	1.3×10^5	1.7×10^5	1.1×10^6	1.86×10^6

Conclusion

The presented case report details the intricate and challenging management of a 28-year-old male diagnosed with asymptomatic HBV infection. Despite initiation of treatment under the Hepatitis Control Program, Government of AJ&K, Pakistan, the patient exhibited resistance to entecavir (after 3 years) and pegylated interferons (after 2 years). Moreover, the viral load data revealed a concerning trend of escalating replication, reaching 1.86×10^6 copies/mL after 1 year with Tenofo B, indicating a scenario of multi-drug resistance. The ALT demonstrated persistent abnormalities, emphasizing the ongoing impact of the viral infection on hepatic health. Pending results of HBV DNA sequencing hold the potential to unveil specific viral mutations contributing to treatment resistance, guiding future therapeutic interventions. This case report underscores the necessity for a nuanced and adaptive approach in managing chronic HBV infections, recognizing the dynamic nature of the virus and the potential emergence of resistance. Ongoing monitoring, integration of virological and biochemical data, and a personalized treatment strategy are imperative in navigating the intricate landscape of chronic HBV infections to optimize patient outcomes within the framework of the Hepatitis Control Program, Government of AJ&K, Pakistan.

Discussion

Recent advancements have transformed the treatment landscape for chronic hepatitis B (CHB), with notable progress in addressing HBeAg-negative disease. Pegylated interferon alpha (IFN-α) and nucleoside/nucleotide analogues such as entecavir and tenofovir represent potent options, boasting high efficacy and minimal resistance rates. Long-term use of these agents shows potential for sustained HBV DNA suppression, potential cirrhosis reversal, and reduced risk of hepatocellular carcinoma development [6]. Treating chronic hepatitis B is challenging, aiming to halt liver disease progression. Long-term antiviral therapy is essential due to viral persistence, but incomplete suppression and drug resistance are concerns. Choosing potent first-line therapies like entecavir and tenofovir is vital to prevent treatment failure and resistance. Effective management of failure requires precise monitoring and early intervention. Ongoing surveillance for efficacy and resistance is crucial for patients receiving sequential treatments. Discovering new treatment targets is key for improving therapy efficacy [7]. Interferon alpha shows limited efficacy, but in selected patients, it can achieve sustained viral suppression and even seroconversion. However, side effects limit its use [8]. Another study highlighted the long-term efficacy and safety of tenofovir disoproxil fumarate (Tenofovir DF) in nucleos(t)ide-naive, HBeAg-positive chronic hepatitis B patients. Over 96 weeks of treatment, tenofovir DF demonstrated consistent and potent viral suppression, leading to an increase in HBeAg loss. Although HBsAg loss was not observed, the treatment was well-tolerated with stable renal safety profiles [9]. In the present study, we are addressing a case of chronic HBV infection in which the patient exhibits resistance to three major and potent antiviral agents: entecavir, pegylated interferons, and Tenofo B. Despite this resistance, the patient remains asymptomatic for the infection.

For patients with drug-resistant HBV, a combination of tenofovir disoproxil fumarate (TDF) and entecavir (ETV) is considered potent, but concerns arise regarding long-term tolerance and cost. Recent trials highlight that TDF monotherapy offers similar antiviral efficacy, minimal resistance risk, lower cost, and enhanced safety, suggesting its viability for treating drug-resistant CHB patients [10]. The HBV polymerase lacks a proofreading function, leading to a substantial presence of mutant viral genomes in infected individuals. Studies estimate that the daily rate of de novo HBV production in chronically infected patients can reach 10^{11} virions, with a mutation frequency estimated at 1.4×10^{-5}–3.2×10^{-5} nucleotides [11]. However, in the current study, combined drug therapy has not been administered to the patient, and genome analysis to identify mutant genes is currently underway.

Individuals exhibiting a multi-drug-resistant profile necessitate more frequent monitoring through both direct sequencing and line probe assay. This is crucial for identifying potential novel HBV variants and low-level mutants within the viral population, particularly in instances of abrupt drug resistance emergence [12]. Emerging treatment targets, including core (capsid) inhibitors, siRNA targeting protein translation, entry inhibitors, and immune modulators, are envisioned to enhance the effectiveness of antivirals with the ultimate goal of achieving a strong cure for hepatitis B [13]. In our study, we conducted whole-genome sequencing of the multi-drug-resistant HBV case and submitted the data to GenBank, NCBI, and currently, the data is under analysis. Moreover, as a treatment support, we administered hepatoprotective agents Silymarin (200 mg) and Liv-52 Syrups to support liver regeneration and digestive functioning of the patient.

Various studies suggest that treatment resistance is a common occurrence in HBV infection and that it can occur with various antiviral therapies. Factors such as advanced liver disease and certain HBV genotypes may increase the risk of developing treatment resistance. Therefore, it is essential to consistently monitor HBV-infected patients undergoing antiviral therapy, assessing both the HBV viral load and indicators of liver injury, such as elevated alanine aminotransferase (ALT) activity [14]. Ongoing research is needed to identify effective strategies for overcoming treatment resistance and improving patient outcomes in HBV infection.

In our study, a 28-year-old male diagnosed with asymptomatic HBV infection received entecavir treatment consistently for three consecutive years. However, resistance to the therapy emerged for reasons yet to be determined. In contrast to our findings, De Socio et al. [15] documented the case of a 62-year-old patient treated with entecavir, noting no significant adverse effects. They observed rapid clinical and laboratory improvements, with subsequent clearance of hepatitis B surface antigen (HBsAg). Entecavir therapy continued until the 17th week, coinciding with the appearance of anti-HB antibodies. Additionally, Lok and McMahon [16] highlighted the favorable resistance profile of long-term entecavir treatment in clinical trials for chronic hepatitis B, indicating a low rate of resistance compared to other antivirals.

Hur et al. [17] successfully treated a patient with chronic hepatitis B using PEG-IFN alpha-2a after experiencing virologic and biochemical breakthroughs during lamivudine therapy. The emergence of YMDD mutants 48 months into lamivudine therapy prompted the switch to PEG-IFN alpha-2a. After 12 months of PEG-IFN alpha-2a treatment, HBV DNA became undetectable, hepatitis resolved, and the virologic response lasted for 16 months post-treatment cessation. While, He et al. [18] reported that the initial peg-IFN therapy yielded higher HBsAg serological response (SR) rates but lower virological and biochemical response rates compared to entecavir (ETV) at week 48. Peg-IFN showed comparable HBeAg SR results to ETV in univariate analysis but proved superior after adjusting for baseline factors. In contrast to these studies, our study participant's initial HBV DNA viral load in 2016 was 1×10^4 copies/mL. Despite 3 years of entecavir and 2 years of pegylated interferon therapy, the viral load increased, signaling multi-drug resistance. Liver function abnormalities and lipid profile irregularities persisted throughout the treatment period.

The transition from ETV to tenofovir disoproxil fumarate (TDF) did not lead to a significant reduction in HBsAg levels overall, but HBeAg-positive patients exhibited a more pronounced decrease in HBsAg after the switch [19]. A phase 3 clinical trial conducted in Japan demonstrated a notably greater decline in HBsAg levels among TDF-treated individuals compared to those treated with ETV, particularly among treatment-naïve patients [20]. In our study, spanning 6 years, we observed persistent HBsAg, HBV, and HBeAg presence in a 28-year-old male patient, with no acute markers or co-infections detected. Despite entecavir and pegylated interferons therapy, there was an escalation in HBV DNA viral load, indicating multi-drug resistance. Although Tenofovir initially reduced viral load, it later exacerbated it. Furthermore, liver function abnormalities and lipid profile irregularities persisted, and consistent abnormalities were noted in urine examinations.

Conclusion

This case report illustrates the complex clinical course of a 28-year-old male with chronic hepatitis B virus (HBV) infection, highlighting the challenges of treatment resistance and the potential emergence of multi-drug resistance. Despite initial management under the Hepatitis Control Program, Government of Azad Jammu and Kashmir, the patient's viral load exhibited suboptimal suppression with entecavir and pegylated interferons therapies. The transition to Tenofo B initially showed promise but ultimately resulted in a concerning surge in viral load, indicative of multi-drug resistance. The persistent abnormalities in liver function tests and lipid profile underscore the systemic impact of chronic HBV infection. Additionally, routine urine examinations consistently revealed notable findings, emphasizing the need for holistic patient assessment. Pending HBV DNA sequencing results hold the promise of shedding light on the mechanisms behind treatment resistance.

This case underscores the imperative for an adaptive and vigilant approach in managing chronic HBV infections within public health programs. Continuous monitoring, integration of virological and biochemical data, and a tailored treatment strategy are paramount for optimizing outcomes. The challenges presented in this case emphasize the critical importance of refining therapeutic approaches against chronic HBV infection, especially in the context of potential multi-drug resistance scenarios. The insights gained from this case contribute to the broader understanding of the complexities involved in chronic HBV management and underscore the necessity for ongoing research and advancements in therapeutic strategies.

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Authors' contributions
S.A.K and A.R. contributed in the study as equal contributors for study design, laboratory testing, and result analysis. S.A.K and M.Z.L. contributed in the result analysis and manuscript revision. S.A.K., B.S., S.K., and Z.A. contribute in the result analysis, results writing, and manuscript review writing. All authors have read and agreed to the submitted version of the manuscript.

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Availability of data and materials
The data is available, and further research is underway.

Declarations

Ethics approval and consent to participate
The University of Azad Jammu and Kashmir, Muzaffarabad's Board of Advanced Studies and Research (BASR) authorized the project for this study as mentioned in the study of Kazmi et al. [21] under the project number F-BASR/(41st M)/16- 40/1669–71.

Competing interest
The authors declare that they have no competing interests.

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