CASE REPORT

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A Case Report on rtQ215H Mutation in association with hepatocellular carcinoma among A Bangladeshi Hepatitis-B Chronic Carrier.

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Abstract

Background: *Hepatitis B virus (HBV) continues to pose a heavy burden in Bangladesh. Its high rate of natural mutations, such as rtQ215H, may influence not only drug resistance but also long-term health outcomes. Aim: To present a case highlighting the clinical impact of the rtQ215H mutation in an untreated chronic hepatitis B (CHB) patient.* ***Methods:*** *A 58-year-old Bangladeshi man with untreated CHB underwent HBV DNA quantification, serology, and sequencing of the polymerase gene. His clinical course was followed.* ***Results:*** *The rtQ215H mutation was found in the reverse transcriptase region. Though initially stable and with improved liver enzymes on lamivudine, the patient tragically developed hepatocellular carcinoma (HCC) within three years and died soon after.* ***Conclusion:*** *This case humanizes the risk behind HBV mutations. Even without prior therapy, rtQ215H may contribute to HCC development. Careful genetic monitoring of CHB patients is essential for early guidance and better outcomes.*

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Introduction

Hepatitis B virus (HBV) is a DNA virus from the Hepadnaviridae family. It is a major etiological agent of infectious hepatitis. Clinical pictures of this virus infection ranging from asymptomatic infection to complete resolution or acute fulminant to chronic hepatitis that may lead to life threatening condition, such as, liver cirrhosis (LC) and hepatocellular carcinoma (HCC) (1). Despite the availability of a safe, effective vaccine against HBV since 1982, infection still remains a major health problem. Globally, about 240 million people are chronic HBV (CHB) carrier and more than 780,000 people die due to acute and chronic consequences of infection in each year (2). Bangladesh belongs to the intermediate prevalence country of HBV infection.3 In this region, about 5%-6% of apparently healthy individuals are chronic carrier and most of them are unaware of their presence of infection (4,6). The lifetime risk of acquiring HBV infection is about 20% to 60% (7). Previous studies showed that HBV is responsible for 31.25% cases of acute hepatitis and 76.3% cases of chronic hepatitis, 61.15% cases of cirrhosis of liver and 33.3% cases of HCC in Bangladesh (8,10).

The rate of HBV replication among these chronic patients is considerable, about more than 108-1011 viral particles per day (11). As reverse transcriptase (RT) enzyme of HBV Pol gene lacks proof reading capacity, HBV replication is also associated with a high mutational rate of 105 substitutions /base /cycle (12). Thus, all possible single base changes in the HBV genome are generated daily and chance of antiviral resistant HBV mutant development in untreated CHB patients (8). There is a con¬cern that antiviral resistant HBV found up to 10% to 15% of untreated CHB patients (8,13). Besides that, different controlling approaches like vaccination and antiviral therapies create selective pressure on HBV genome result in antiviral resistant strains. The genomic changes are stable and these resistant viruses are transmitted to another individual (14).

Case Report

On 2014, we found a 58 years male untreated CHB patient at the department of Virology, BSMMU, when he came for his HBV DNA routine laboratory test. The patient was HBeAg negative and serum SGPT was 42 U/L. The viral load of this patient was 2.85×105 IU/ml. We did molecular study of this HBV DNA which showed rtQ215H mutation in the reverse transcriptase domain of the HBV Pol gene. This region is critical for antiviral action. After that, the patient was treated by lamivudine (Hepavir 100 mg/day, Square Pharmaceuticals Ltd., Bangladesh) from March 2014 to April 2017 and his SGPT became normal. In 2017, we again interviewed this patient and we found he diagnosed a case of HCC. After that, patient had expired within a month.

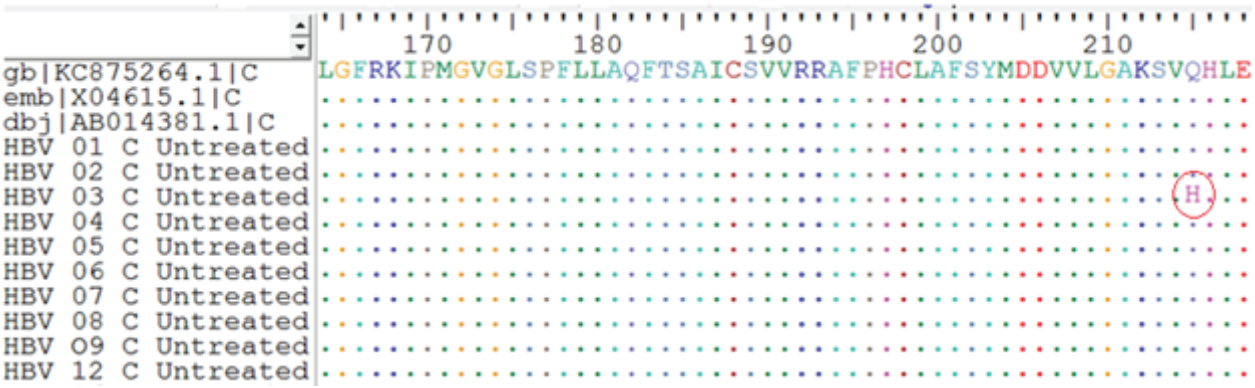

Figure 1: Mutation prediction of antiviral resistance mutation in HBV genotype C*.

Note: Circle in figure indicates mutation. Mutations were identified by the alignment of all obtained HBV Pol protein with respective genotype positive reference sequences from NCBI gene bank through BioEdit software. Figure 1 shows mutation as rtQ215H in the reverse transcriptase domain of HBV the Pol gene.

Discussion

The emergence of natural mutations in the HBV genome should be expected due to characteristics of its genome. The major causes of mutations in association with antiviral resistance include some viral factors, such as, high kinetics of viral replication and clearance, and the lack of a proofreading mechanism during reverse transcription by RT enzyme, which creates many mutants of HBV (15). Antiviral resistance designates the presence of a unique nucleotide and the corresponding amino acid mutations in the antiviral target gene that have been previously reported as associated with antiviral resistance (16). These genomic mutations are stable and resistant viruses can be transmitted to another individual which is a significant public health risk (7). Thus, our study strongly demands to document the antiviral resistance mutations of HBV among untreated Bangladeshi CHB patients. Antiviral resistance mutations present as primary and compensatory or secondary type of mutations. Primary resistance mutations decrease sensitivity to antivirals agents (17). While, the compensatory mutations restores the functional defects in viral polymerase activity that gains replication capacity of that resistant virus and increases resistance to antiviral agents (16,17). Commonly reported primary resistance mutations are A181V, A181T, T184G, A194T, S202I, N236T, M204V, M204I and M250V. The major secondary/compensatory mutations are L80V, L80I, L180M, rtI169T, V173L, rtQ215H/S (18,19, 20). Other proposed compensatory mutations are rtV84M, rt214, rtL217P, rtL229M, rtI233V, rtN238H (21).

We found that HBV showed single antiviral resistance mutation as rtQ215H in an untreated patient. Sayan et al showed that compensatory mutations at rtQ215A/H/P/S found as naturally developing mutations in untreated CHB patients (22). Further researches reported that frequent mutations had found at rtQ215 in both untreated and lamivudine/adefovir treated patients.23, 24 Earlier published data also suggested that these amino acid changes at codons: rt214, rt215, rt221 and rt238 reduce efficacy to adefovir and lamivudine, and these mutation are marked as adefovir secondary/-compensatory resistance mutations (25,26,27). A case report by Micco et al. also reported that polymorphism in rtQ215H causes primary resistance to adefovir found in a lamivudine resistant and adefovir non-re-

sponsive CHB patient (28). This finding suggests that mutation at rtQ215H could be responsible for primary resistance to adefovir, or reduced sensitivity to adefovir. On the contrary, Olyaee et al. reported that HBV Pol gene mutations in the rtQ215 locus are frequently found in the untreated CHB patients (24). This author suggested that the rtQ215 changes do not affect HBV replication and do not causes antiviral resistance to adefovir or lamivudine but poses higher risk liver disease progression and it may be represents as the polymorphisms rather than resistance mutations (24). When we interviewed this rtQ215H mutation positive patient, we found the patient was further treated by lamivudine and his SGPT became normal. However, we do not know if this mutation is responsible for adefovir resistance or not. Interestingly, this patient developed HCC in the year of 2017 and died soon after. Therefore, it is suggested that polymorphisms and mutations of codon 215 should be carefully monitored by physicians for their relevance to therapy failure and disease progression.

Limitations Of Study

We observed this patient by interviewed over phone call and not take opportunity for direct supervision.

Conclusion

In conclusion, HBV could be shown rtQ215H mutation among the untreated patients. This mutation may not be responsible for antiviral resistance rather it could be complicated with HCC. Therefore, mutations in the 215 region of the RT domain HBV Pol gene among the CHB patients should be carefully monitored by physicians for their relevance to therapy failure and disease progression.

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