Tenofovir Disoproxil Fumarate Related Metabolic Syndrome and Steatohepatitis in a Case of Chronic Hepatitis B

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Introduction

- Tenofovir disoproxil fumarate (TDF) is a nucleotide analog used in the treatment of chronic hepatitis B virus infection (HBV).
- TDF is considered to have no direct hepatotoxicity.
- Here we present a patient with HBV developing liver test abnormalities and biopsy-proven steatohepatitis (SH) after starting TDF, and the resolution of liver test abnormalities and SH after switching TDF to entecavir (ETV).

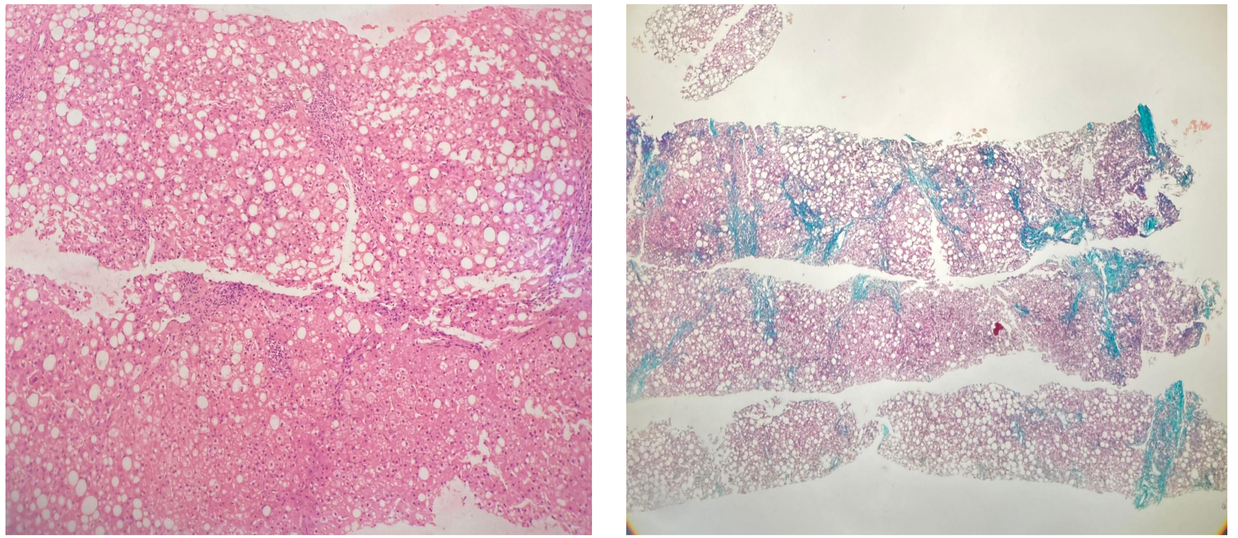
Case presentation

- A 48-year-old female patient was admitted to our clinic with positive HBsAg and HBV-DNA level of 21600 copies/mL. Her Anti-HBe was positive and Anti-HDV was negative.
- Abdominal ultrasonography revealed 2 cm hepatomegaly; her AST was 74 U/L (5-40 U/L) and ALaT 125 U/L (10-40 U/L). Her BMI was within normal limits, she had no comorbidities and was not on any medication.
- Her lipid panel was within the normal range. She was prescribed 245 mg/day TDF, and was scheduled for regular clinical follow-up. Six months later, her AST was 113 U/L, ALT 148 U/L, and her HBV-DNA was negative.
- The patient was advised to follow-up closely. Eighteen months after the initiation of TDF, her AST level increased to 211 U/L and ALT to 216 U/L.
- Her HbA1c was 6.1% and HOMA-IR was 4.0. MRI showed fat accumulation in the liver, and a liver needle biopsy was performed.

Case presentation-continued

- Histological evaluation revealed grade 2 steatosis with moderate ballooning degeneration and stage 3/4 fibrosis (Figure 1).
- Autoimmune serologies including antinuclear antibody and anti-smooth muscle antibody were negative, and ceruloplasmin phenotype was normal.
- The causation of TDF was hypothesized. TDF was stopped, and ETV 0.5 mg/day was initiated.
- Her follow-up at month 3 revealed a decreased trend in transaminase levels.
- At year two, a control abdominal ultrasonography showed no fat accumulation and HbA1c was 5.6%.

Figure 1.



A: Hematoxylin-eosin staining shows 50% steatosis (grade 2), portal and lobular inflammation and moderate hepatocyte ballooning. **B:** Masson-trichrome staining shows portocentral and pericellular fibrosis (stage 3/4).

Discussion

- While it is known that TDF co-administration with other nucleotide analogs (e.g., didanosine, stavudine) can cause fatty infiltration of the liver, we present a rare case of metabolic syndrome and SH with TDF monotherapy.
- Despite some reports suggesting tenofovir, specifically tenofovir alafenamide, might be associated with adverse metabolic changes in HIV patients, our patient with HBV developed these changes while she was on TDF.
- We show that hepatic steatosis associated with TDF can be reversible with the medication change to ETV.

References

1. Patel V, Sanyal AJ. Drug-Induced Steatohepatitis. Clin Liver Dis. 2013 Nov;17(4):533–46, vii.
2. LiverTox: Clinical and Research Information on Drug Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Tenofovir. [Updated 2020 Oct 20].
3. Zhang Y, Li Z, Luo Q, Xu W, Wang L, Zhu S, et al. Changes in blood lipids in patients with chronic hepatitis B after 48 weeks of tenofovir alafenamide treatment: A prospective real-world clinical study. Antivir Ther. 2022 Apr 1;27(2):13596535221082400.