with hematemesis,[6] and it is important to diagnose patients presenting with acute chest pain as inadvertent anticoagulation or anti platelet therapy may increase chances of enlarging hematoma formation, esophageal compression, and potentially life-threatening rupture.

Management is usually conservative, and includes measures such as withholding of oral feeds during acute phase with gradual re-initiation as symptoms resolve, cessation of drugs which can prolong bleeding, and anti–emetics for retching and vomiting. Surgery is usually reserved for cases with either massive bleeding or perforation. Shim et al reported treatment of a case with therapeutic angiography.[5] Most cases have favorable outcomes, with progressive resolution of lesion, which usually ulcerates before resolving.

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Acquired Fanconi's syndrome associated with tenofovir therapy in a patient with acute hepatitis B

Tenofovir, a nucleotide reverse transcriptase inhibitor was originally licensed for the treatment of human immunodeficiency virus (HIV) infection and approved in 2008 for the treatment of Hepatitis B Virus (HBV) infection. It is now increasingly recognized as a cause of acquired Fanconi's syndrome (FS) in HIV infected individuals, and rarely in patients with Hepatitis B on Tenofovir therapy of prolonged duration. However, development of FS soon after initiation of the therapy is very rare and has not been reported elsewhere. We describe a case of a patient with acute hepatitis B who developed refractory hypokalemia and profound electrolyte abnormalities compatible with features of FS within two weeks of starting Tenofovir therapy.

Case Report

A 29 year old female presented with prodromal symptoms for 4 days followed by jaundice for one week. She had no known comorbidities . On evaluation, her liver function tests were suggestive of acute hepatitis (serum total/ conjugatedbilirubin 5.3/2.8 mg/dL, AST 946 IU/L, ALT 1088 IU/L, serum albumin 3.6 gm/dL, total protein 7.2 gm/dL, ALP 112 IU/L, INR 1.11). Serologicaltests for HBsAg and IgM anti-HBc were positive, IgG anti-HBc was negative and Serum HBV DNA levels were 255 IU/ml. HBeAg was negative and other markers for acute viral hepatitis including IgM HAV, IgM HEV, IgM Dengue,

IgM Leptospira tridot, IgM scrub typhus, IgM CMV, IgM HSV 1 & 2, IgM EBV were negative. Serum HBsAg was negative during her antenatal work up two years priorto this episode. Her husband and child were negative for HBsAg and were vaccinated with Hepatitis B vaccine.

She was given symptomatic treatment and advised an enhanced follow up. Over a period of 3 weeks, her serum bilirubin levels increased from 5.3 mg/dL to 19.0 mg/dL, INR increased from 1.11 to 1.57 and she developed minimal hepatic encephalopathy. Based on the worsening of symptoms and lab parameters, the diagnosis of acute hepatitis B progressing to acute liver failure was considered. She was hospitalized, provided supportive treatment and tablet Tenofovir was started with once daily dosing. Following this, her serum bilirubin and serum transaminases started to decline. However, after two weeks of therapy her encephalopathy worsened and her serum bilirubin and INR values started to rise. Further investigation revealedhypokalemia (Serum potassium: 2.5meq/L) and overt hepatic encephalopathy. Non contrast-enhancedcomputerized tomography (NCCT) of brain was normal.

Her abdominal ultrasonogram was suggestive of acute hepatitis (without evidence of cirrhosis /portal hypertension or ascites) and upper GI endoscopy too was normal. Blood urea nitrogen, serum creatinine and serum alphafetoprotein levelswere normal. As her encephalopathy and hypokalemia were not responding to treatment with intravenous potassium chloride and anti-coma regimen, an extensive work up was done to evaluate and pin point the cause of hypokalemia.

Her serum creatinine levels were 0.9mg/dL, MDRD calculated eGFR was 78.8 ml/min/1.73 m2 and both kidneys appeared normal on ultrasonography. Serum magnesium levels were1.6 mg/dL (Range: 1.7-2.2mg/dL) and 24 hour urine potassium excretion was 32 mEq/24hrs. Also there was hypophosphatemia (2.2 mg/dL; Range: 2.5-4.5 mg/dL) which did not respond to oral phosphate supplementation, along with hypouricemia of 2.1mg/dL (Range: 2.4-6.0 mg/dL), non-nephrotic range proteinuria (0.6 gm/24 hrs; normal value being less than 30mg/24 hours) and glucosuria (3.2 gm/day; normal value being less than 100 mg/day) with normal blood glucose (112 mg/dl). A working diagnosis of tenofovir induced Fanconi's syndrome was considered and tenofovir was replaced with oral Entecavir 1mg once daily.

Subsequently she required 250 meq of potassium chloride daily for 5 days to keep the serum potassium levels above 3.5 mEq/dL. Hypophosphatemia and hypomagnesemia were corrected with intravenous magnesium and oral phosphate solution respectively. Over next two weeks, her liver function testsshowed improvement and she became symptomatically better. Subsequently her sensorium improved and she was sent home on oral potassium supplementation. During follow up there was further improvement in LFT and serum electrolyte levels were within normal limits.

Discussion

Fanconi's syndrome was first described by Lignac in 1924 and further defined by Fanconi in 1936 in children presenting with rickets, growth retardation, and glucosuria. It is a generalized proximal tubulopathy. In its complete form it associates renal tubular acidosis, glycosuria with normoglycemia, aminoaciduria, hypophosphatemia, hypouricemia, and tubular proteinuria.

The main clinical presentations of tenofovir nephrotoxicity are (a) proximal tubular dysfunction with preserved renal function and (b) proximal tubular dysfunction associated with decreased renal function, i.e. a partial or complete Fanconi syndrome with or without reduction in GFR.[1] Decreased renal function may be classified as AKI, CKD, or a glomerular filtration rate (GFR) that is decreased when compared with baseline values, albeit within normal limits.Currently available information suggests that all of them share a basic common pathogenesis.

Tenofovir is an acyclic nucleotide inhibitor of HBV polymerase and HIV reverse transcriptase. It is eliminated unchanged in the urine by a combination of glomerular filtration and proximal tubular secretion.[2] 20–30% of the drug is actively transported into renal proximal tubule cells by organic anion transporters (hOAT1, and to a lesser extent, OAT3) in the basolateral membrane. Subsequently the drug is secreted to the tubular lumen by the apical membrane transporters MRP-4 and MRP-2 (multidrug resistance proteins,

encoded by ABCC4 and ABCC2 genes, respectively).

On a cellular level, it has been proposed that disruption of the Na-K-ATPase pump on the basolateral membrane of the proximal tubular cell could inhibit active transport into the peritubular capillaries. Another theory is that active transport may remain intact but the permeability of the proximal tubule is increased, thereby significantly enhancing back-diffusion of solutes. In the case presented in this article, the most likely factor causing the patient's FS was a drug. A search of the literature reveals that several drugs apart from tenofovir have been implicated in causing FS, among them aminoglycosides, ifosfamide, cisplatin, streptozocin, mercaptopurine, tetracycline, and valproic acid.Certain antiretrovirals have been implicated in causing FS, namely cidofovir, adefovir, and 1 case of didanosine.

A National Institutes of Health sponsored clinical workshop on hepatitis B proposed that persons with acute viral hepatitis complicated by an increase in INR above 1.5 and deep jaundice persisting for more than four weeks should receive antiviral therapy.[3] Antiviral treatment of patients with fulminant hepatitis B is recommended in the AASLD guidelines because of the safety of nucleos(t)ide analog therapy and the need for liver transplantation in many of these patients.[4]

Therefore, considering fulminant hepatitis B our patient was started on tenofovir, which was given for a period of two weeks after which the patient developed FS. With the discontinuation of tenofovir, her metabolic abnormalities gradually resolved. Some observational cohort studies describing low rates of renal dysfunction with tenofovir use were of short duration.[1,5] Similarly our patient may have had a lesser degree of renal damage so that her electrolyte abnormalities were not associated with any decline in GFR value.

This case and the other cases reported to date suggest that tenofovir should be used with caution in patients with evidence of pre-existing renal tubular dysfunction and in those taking concomitant nephrotoxic agents. Caution should be exercised in the elderly and in those with reduced GFR as well. The possibility of irreversible renal damage also suggests that patients given this drug should be followed more closely in the 12- to 18- month period after initiation of tenofovir therapy and should have a urinalysis, serum creatinine, and potassium performed on a regular basis following initiation of therapy. Raising the awareness of clinicians with regard to the potential for this side effect is important so that it can be discovered early and the patients can be switched to an alternate antiviral therapy.

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