Simultaneous Occurrence of Nephrolithiasis, Fanconi Syndrome, and Nephro-osteopathy in a Patient on First-line Antiretroviral Therapy – A Case Report

Abstract

Tenofovir disoproxil fumarate is part of the first-line antiretroviral therapy and can lead to Fanconi syndrome, acute kidney injury, chronic kidney disease, and reduced bone mineral density. We report the first case of simultaneous occurrence of nephrolithiasis, urolithiasis, Fanconi syndrome, and bone fracture in a 54-year-old lady who presented with pain and inability to bear weight on the right lower limb following a trivial fall. She was diagnosed with human immunodeficiency infection in the year 2000 and was on tenofovir, lamivudine, and efavirenz for the past 6 years. On evaluation, she had azotemia, glycosuria, proteinuria, normal anion gap metabolic acidosis, multiple renal stones, and a proximal ureteric calculus causing right-sided hydroureteronephrosis. The patient developed sepsis following the double "J" stenting procedure. She was managed with intravenous bicarbonate therapy and the substitution of tenofovir to abacavir with a favorable outcome.

Keywords: *Antiretroviral therapy, case report, Fanconi syndrome, nephrolithiasis, nephropathy, osteopathy, simultaneous*

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Introduction

Tenofovir disoproxil fumarate (TDF) is part of the first-line antiretroviral therapy (ART) recommended by the latest National AIDS Control Organisation (NACO) guidelines along with lamivudine and efavirenz.[1] This nucleotide analog reverse transcriptase inhibitor was thought to have a good safety profile based on earlier studies;[2] however, recent studies have indicated the association between TDF and renal impairment and bone demineralization.[3,4] The long-term studies have reported incremental risk with cumulative exposure in 41% of the participants after 10 years of TDF-based regimen.[5] The spectrum of TDF-induced nephrotoxicity includes Fanconi syndrome, acute kidney injury, and chronic kidney disease.[1] The exact mechanism by which TDF causes nephropathy and osteopathy is not fully understood; however, tenofovir gets accumulated within the proximal tubular cells and leads to mitochondrial damage and subsequent Fanconi syndrome and hypophosphatemic osteomalacia.[6,7] A recent study showed that TDF influenced osteoblast differentiation and induced a significant dose-dependent decrease in mineralization in human osteoblasts.[8] The prevalence of renal and ureteral stones in patients with human immunodeficiency virus (HIV) infection is higher than in non-HIV individuals despite non-PI (protease inhibitor)-based ART regimens. The simultaneous occurrence of nephrotoxicity, Fanconi syndrome, and osteopathy is rare and infrequently reported.[9,10] We describe a case of ART-induced delayed Fanconi syndrome, osteomalacia, acute kidney injury, and nephrolithiasis who presented with fractured neck of femur 6 years after starting tenofovir-based ART regimen despite of living with HIV for the past 20 years.

Case Report

A 54-year-old lady with a history of HIV infection for last 20 years, now presented with complaints of pain over the right hip and inability to bear weight on the right lower limb following a trivial fall. She was on first-line ART, with a fixed-dose combination of TDF (300 mg), lamivudine (300 mg), and efavirenz (600 mg) once a day at bedtime

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for the past 6 years. On examination, she had tenderness over the right hip, shortening of the right lower limb, and restricted range of motion. The patient was initially evaluated by an orthopedic surgeon and diagnosed with a fractured neck of the right femur [Figure 1]. She was admitted and planned for hemiarthroplasty. On preliminary investigation, she was found to have azotemia, hypokalemia, anemia, glycosuria, proteinuria, raised serum alkaline phosphatase level, and normal anion gap metabolic acidosis. Lab parameters at admission are shown in Table 1. Urine routine and microscopic examination demonstrated glucose 3+, protein 1+, with few red blood cells. There was no evidence of any crystals. She was managed with oral potassium supplementation, and her ART was modified to abacavir 600 mg, lamivudine 150 mg once daily (OD), and efavirenz 600 mg OD because of acute kidney injury.

The diagnosis of renal Fanconi syndrome was established with the background of tenofovir use for the past 6 years and current evidence of hypokalemia, hypophosphatemia, glycosuria, proteinuria, hyperchloremic metabolic acidosis, and raised alkaline phosphatase levels. As the diagnosis of Fanconi syndrome was straightforward, the 24-hour urinary calcium, phosphorus, glucose, uric acid, and organic acids were not done.The serum 1,25-dihydroxyvitamin D level was 10 pg/mL (reference range: 15–60 pg/mL);however, iPTH (intact parathyroid hormone) levels were not available.

She underwent ultrasonography (USG) of the abdomen, which revealed gross dilatation of the right kidney's pelvicalyceal system and multiple calculi involving both the kidneys. On non-contrast computed tomographic imaging of the lower abdomen, findings of USG were confirmed; the right kidney measured 9.8 cm with a normal contour and attenuation pattern. Four calculi were noted in the right kidney's lower polar region, the largest measuring 2.1 cm × 1.6 cm. A few air pockets were noted in the lower pole calyces in nondependent location suggestive of emphysematous pyelitis. A 6-mm calculus was noted in the proximal right ureter (4 cm distal to pelvic ureteric junction), causing upstream hydroureteronephrosis. The left kidney measured 8.3 cm with normal contour and attenuation pattern. A calculus measuring 3 mm was noted in the lower polar calyx of the right kidney.

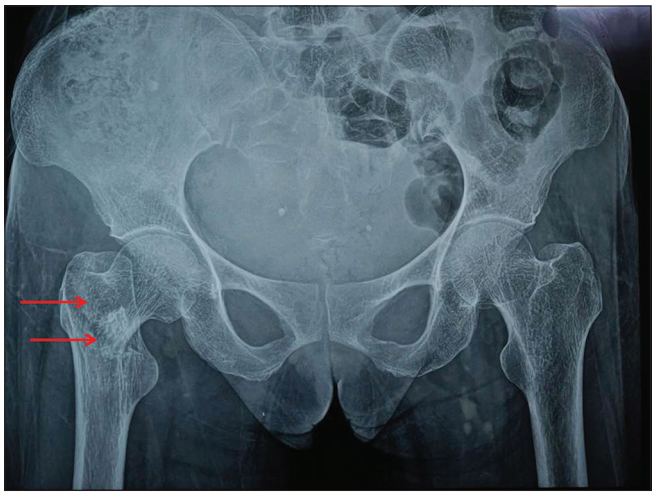

Figure 1: Anteroposterior radiograph of pelvis. The red arrows show fractured neck of right femur

She underwent cystopanendoscopy and right double "J" stenting with 5 F and 26 cm stent. Three days after the procedure, her clinical condition deteriorated. She developed tachycardia, tachypnea, and hypotension. Clinical diagnosis of pulmonary thromboembolism was considered because of recent surgery and immobilization, and she was started on unfractionated heparin. Over the next 6 hours, her condition further deteriorated, and the patient was shifted to intensive care unit. She was intubated and put on mechanical ventilation. Her repeat laboratory parameters revealed neutrophilic leucocytosis, worsening azotemia, and arterial blood gas analysis showed severe metabolic acidosis [Table 1]. Her urine culture had grown *Escherichia coli* and *Enterobacter aerogenes* sensitive to ciprofloxacin, piperacillin plus tazobactam. She was managed as a postoperative urinary tract infection and started on culture-sensitive injectable antibiotics in renal-modified doses, and bicarbonate infusion. The patient's condition improved over the next 72 hours, and she was extubated. Her serum creatinine gradually improved to 1.4 mg/dL. No orthopedic intervention was done, and the patient was discharged with advice to follow up after 1month.

Discussion

The prevalence of HIV in India is 0.22%. Despite this low prevalence, India has the third-highest cases of HIV infection in the world in terms of absolute numbers with an estimated 2.14 million people living with HIV, 87,000 estimated new infections, and 69,000 AIDS (acquired immune deficiency syndrome)-related deaths annually.[1] TDF, along with lamivudine and efavirenz (TLE), is the first-line ART regimen recommended for ART-naive persons living with HIV, with HIV-1 infection, age >10 years, and body weight >30 kg. A single pill of TLE should be taken at bedtime, 2 to 3 hours after dinner.[1]

TDF causes toxic acute tubular necrosis of varying severity and Fanconi syndrome in persons exposed to TDF-based regimen. Nephrotoxicity can occur at any time during tenofovir therapy, both early and delayed, with the median duration of presentation ranging between 16 months and 5 years.[11] Discontinuation of TDF can lead to significant renal recovery; however, many patients never achieve baseline renal function and develop chronic kidney disease. About 20% to 30% of the total excretion of TDF occurs through tubular secretion. TDF enters the proximal tubule from the basolateral side using organic anion transporter (OAT) 1 and is assisted by OAT3. It is

Table 1: Laboratory parameters during the hospital stay

Lab Parameters	On admission	Postoperative	At discharge	Reference range
Hemoglobin(g/dL)	9.5	8.2	9.6	12-16 g/dL
Total leucocyte count(cells/µL)	10,820	21,200	8200	4,000 to 11,000/µL
Platelets(cells/µL)	291,000	447,000	386,000	150,000-450,000/µL
Blood Urea (mg/dL)	58	112	24	8-20 mg/dL
Serum Creatinine (mg/dL)	3.31	3.46	1.5	0.50-1.10 mg/dL
Serum Sodium (mEq/L)	139	132	132	136-145 mEq/L
Serum Potassium (mEq/L)	2.4	5.8	3.7	3.5-5 mEq/L
T Bilirubin (mg/dL)	0.8	0.3	0.4	0.3-1 mg/dL
AST(U/L)	26	37	35	10-40 U/L
ALT(U/L)	21	70	32	10-40 U/L
ALP(U/L)	201	248	256	30-120 U/L
Serum Calcium(mg/dL)	7.5	7.8	8.2	8.6-10.2 mg/dL
Phosphorus(mg/dL)	2.2	2.4	3.0	3-4.5 mg/dL
Total Protein(g/dL)	6.8	7.2	7.6	5.5-9 g/dL
Albumin(g/dL)	2.8	2.5	2.8	3.5-5.5 g/dL
Globulin(g/dL)	4.0	4.7	4.8	2.5-4.0 g/dL
Urine Glucose	3+	3+	Nil	Negative
Urine Protein/creatinine ratio (mg/g)	1256.8	-	356.4	<200mg/g
Urine pH	6.6	-	>9.0	4.6-8.0
Arterial blood gas analysis				
pH	7.218	7.021	7.421	7.35-7.45
$PaCO_2$ (mm Hg)	24.6	9.8	30.9	35-45 mmHg
Bicarbonate (mEq/L)	10.1	2.6	20.3	21-27 mEq/L
Chloride(mEq/L)	114	119	101	98-106 mEq/L
Lactate(mEq/L)	0.1	1.3	0.5	0.7-1.8 mEq/L

AST=Aspartate tranaminase, ALT =alanine transaminase, ALP =alkaline phosphatase

subsequently extruded into the tubular lumen by multidrug resistance proteins (MRP) mainly MRP-4 and MRP-2. The polymorphisms in the genes encoding for MRP have been implicated in tenofovir toxicity.[12] Our patient presented with acute kidney injury with elevated blood urea nitrogen and creatinine after 6 years on TDF-based regimen.

The reabsorption of glucose, amino acids, uric acid, phosphate, and small proteins (e.g.,β2-microglobulin and vitamin D–binding protein); the secretion of hydrogen ions; and the synthesis of calcitriol are the primary functions of the proximal tubule. The accumulation of TDF in the proximal tubules results in the inhibition of mitochondrial DNA polymerase. Subsequently, it leads to glycosuria, phosphaturia, aminoaciduria, normal anion gap metabolic acidosis, and vitamin D deficiency, all of which may be a part of the tubular dysfunction described with partial or complete Fanconi syndrome. The impact on vitamin D and phosphate accounts for the bone manifestations seen with TDF.[9] Our patient had glycosuria, normal anion gap metabolic acidosis, proteinuria, and hypophosphatemia; thus, the diagnosis of Fanconi syndrome was considered. Hypercalciuria is characteristic of renal Fanconi syndrome; however, nephrolithiasis is rather uncommon. Presumably, this is because of polyuria and increased luminal concentration of citrate, which are inherent in Fanconi syndrome. Some of the investigations like 24-hour urinary calcium, phosphate, uric acid, and organic acids can aid in the diagnosis of Fanconi syndrome whenever the diagnosis is not clear. The above investigations were not done in this case as the diagnosis was established on the basis of clinical presentation, biochemical parameters, and history of tenofovir use. Once suspected, the diagnosis of renal Fanconi syndrome is easily confirmed, as was the case in our patient.

Historically PIs, specifically indinavir, have been implicated as a cause of nephrolithiasis. Although nephrolithiasis among HIV patients receiving indinavir is well-known, there is a paucity of data describing the prevalence of nephrolithiasis with non-indinavir-based ART regimens. Despite the recent shift toward less lithogenic HIV therapy, the prevalence of nephrolithiasis in persons living with HIV on non-PI-based ART regimens is 11%[13] compared with 5.2% in non-HIV population.[14] And the average time to nephrolithiasis diagnosis while receiving ART was 13.5 months (range 9–18 months).[13] The most common non-PI drug associated with nephrolithiasis is efavirenz, with a few case reports documented in the literature.[15]Our patient had bilateral nephrolithiasis, with a proximal ureteric calculus leading to hydroureteronephrosis. She went into sepsis following the removal of stone and double "J" stenting procedure. *Efavirenz could have contributed to these multiple stones in our patient; however, the stone analysis was not done.*

TDF affects osteoblast genes, suggesting a direct mechanism for bone alteration. Moreover, TDF is associated with parathyroid hormone (PTH) increase and changes in bone turnover biomarkers. Chronic phosphaturia as part of renal tubular dysfunction could be the putative mechanism associated with decreased bone mineral density. Our patient also presented with a fractured neck of the femur following a trivial fall.

Conclusion

TDF is part of the most commonly used ART regimen. The regular monitoring of renal function tests is required for the patients on TDF as it leads to nonoliguric renal failure, which is reversible following the discontinuation of the drug. Hypophosphatemic osteomalacia is increasingly identified in patients on TDF, and regular serum alkaline phosphatase levels and bone mineral density evaluation should be done in patients on TDF-based ART regimens.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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