Hypophosphatemic osteomalacia due to tenofovir-induced Fanconi syndrome in chronic hepatitis B patient

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Summary

Tenofovir disoproxil fumarate (TDF) is an antiviral agent widely used in first-line treatment of chronic hepatitis B (CHB). Its use has been linked to side effects on kidneys and bones such as sporadic Fanconi syndrome, renal failure and bone disease, osteomalacia (OM) mostly reported in the literature occurring in HIV patients. There also have been few case reports about TDF related hypophosphatemic OM in CHB. We report a case of 55-year old female patient with CHB infection with complaints of diffuse pain, difficulty in walking, fatigue and nausea who was on TDF treatment diagnosed as hypophosphatemic OM. We performed a literature review of TDF related hypophosphatemic OM in CHB infection (Pub med 1995-2017 key words osteomalacia; tenofovir; Hepatitis B; Fanconi syndrome). This case based review aimed to increase awareness about tenofovir-related hypophosphatemic osteomalacia in CHB and to emphasize the importance of close renal function monitoring for early diagnosis to prevent pathologic fractures.

KEY WORDS: osteomalacia; tenofovir; hepatitis B; Fanconi syndrome.

Introduction

Tenofovir disoproxil fumarate (TDF) is an antiviral agent widely used in first-line treatment of human immunodeficiency virus (HIV) infection and also in chronic hepatitis B (CHB) infection. Its use has been linked to side effects on the kidneys and bones such as sporadic Fanconi syndrome, renal failure and bone disease (1-7).
Cases of OM associated with tenofovir use have been mostly reported in the literature occurring in HIV patients (3-8). There also have been few case reports about tenofovir related hypophosphatemic OM in CHB patients (1, 9-13).
We report a case of 55-year-old female patient with CHB infection with complaints of diffuse pain and difficulty of walking, fatigue and nausea who was on tenofovir treatment and developed hypophosphatemic OM. We also performed a literature review of published cases of tenofovir related hypophosphatemic OM in CHB infection [Pub med 1995-2017 keywords osteomalacia, tenofovir, Hepatitis B, Fanconi syndrome, osteomalacia].

Case report

A 55-year-old female patient with CHB infection was admitted to our clinic with complaints of diffuse bone pain and gait disturbance, fatigue and nausea for one year. She had low back pain, pain in the hips and lower extremities, chest and shoulders. She had lost approximately 5 kg in the last 6 months. CHB infection was diagnosed 8 years ago. She received lamivudin treatment at the beginning of her diagnosis. She was on TDF 245 mg treatment for 2 years when the symptoms developed.
She was diagnosed as osteoporosis and treated with several antiresorptive agents with no improvement before admission to our clinic. A DXA scan showed a L1-L4 lumbar spine BMD of 0.630 g/cm^2 (T-score= –3.46) and femur neck BMD 0.484 g/cm^2 (T-score= – 3.86).
To rule out malignancy, thorax and abdomen computed tomography (CT) has been done. There was no evidence for malignancy.
On the physical examination there was mild weakness in knee extensor and hip flexor muscles. Sensation was preserved and osteotendinous reflexes were normal. The musculoskeletal examination revealed diffuse pain to palpation over low back, thorax, arms and legs. She was unable to walk without assistance.
Hypophoshatemia (1.1 mg/dl), hypocalcemia (8.1 mg/dl), hypouricemia (1.3 mg/dl), elevated alkaline phosphatase (330U/L), low 25OH D vitamin (14.5 ng/ml) and normal parathyroid hormone (37 pg/ml) levels were observed. Serum creatinine, potassium and sodium levels were in normal ranges. 24 hour urine excretion of Ca (230 mg/24h) and P (0.5 g/24h) was in normal ranges. Glucosuria and proteinuria 1003 mg/24h (n range 0-300 mg) were detected. The patient has no diabetes. Blood glucose level was 81 mg/dl. Urinary spot Protein/ Creatinine (59 mg/dl /48 mg/dl) ratio was increased which shows renal impairment.
No abnormality was observed on electromyographic evaluation.

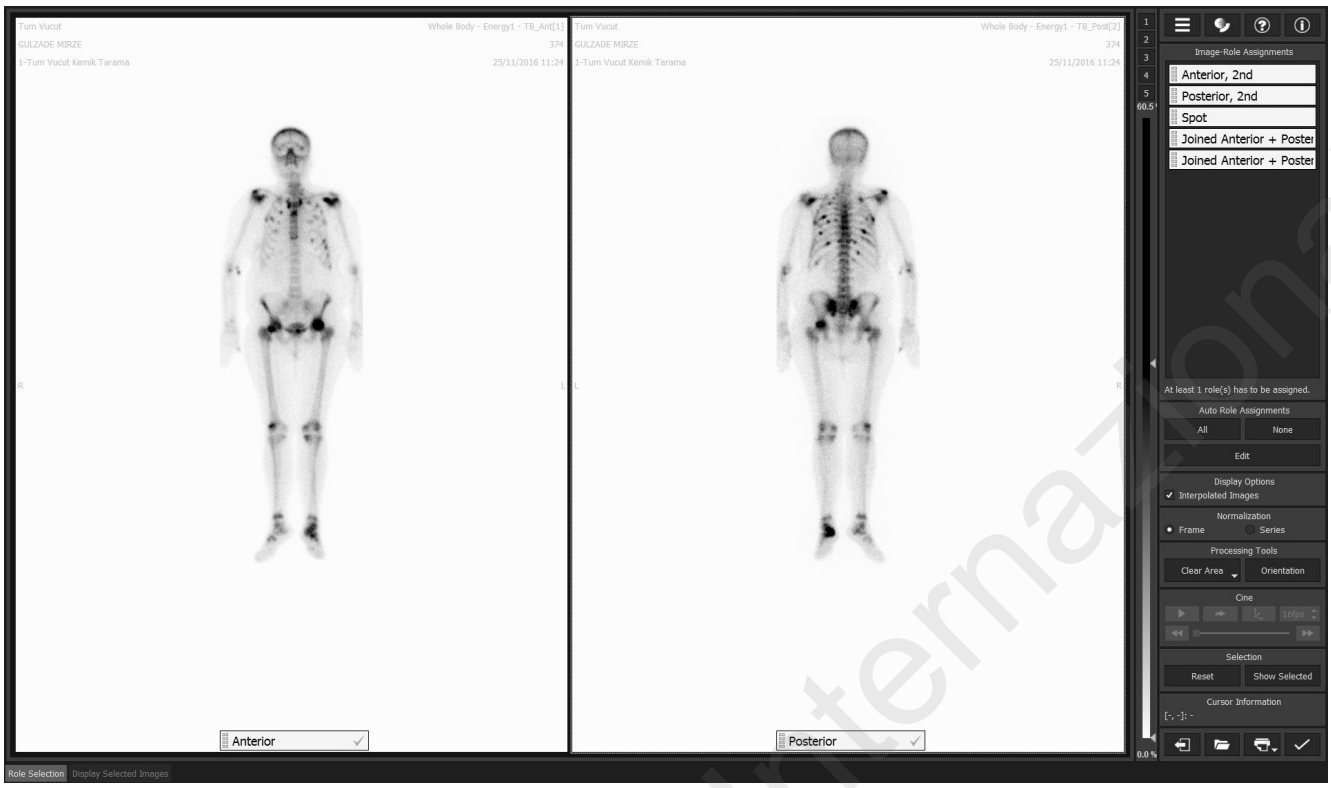

Figure 1 - Whole body 99mTc-MDP bone scintigraphy (anterior and posterior), at clinical presentation: increased focal uptake in the lumbar/thoracic spine, sacroiliac regions, hip, shoulder and ankle joints consistent with multiple pseudo fractures.

The whole body 99mTc-methylene diphosphonate (99mTcMDP) bone scintigraphy showed an increased uptake at the lumbar and thoracic spine, multiple ribs, clavicle, sacroiliac region, ankle, shoulder and hip joints, consistent with multiple pseudo-fractures (Figure 1).

Because of the relationship between TDF therapy and OM-related symptoms, and absence of other explanations, we made a diagnosis of hypophosphatemic TDF-induced OM. TDF was discontinued and switched to telbivudin 600 mg. Oral cholecalciferol 300000IU /month for 3 months and phosphate replacement was started. Because of increased viral load, telbivudin 600 mg was switched to Entakavir 0.5 mg tablets. A month after discontinuation of TDF and switching to another antiviral agent, bone pain and gait disturbances began to disappear and patient was able to walk unassisted after 2 months.

Blood tests performed 3 months after discontinuation of TDF and switching to another antiviral agent showed recovery in all parameters. Laboratory values at presentation and during follow-up are summarized in Table 1. A DXA scan performed 5 months after TDF cessation showed a rapid improvement in bone mineral density.

Discussion

Chronic hepatitis B (CHB) is a condition that may need to be treated lifelong thus the drugs used must be both efficacious and safe (2, 4). The renal and bone complications in patients using TDF were reported mostly in studies from HIV-infected patients (3, 14-17).

Renal dysfunction, hypophosphatemia, and Fanconi like syndrome have also been reported in CHB-infected persons on TDF (1, 9-13). The characteristics of CHB infected patients with hypophosphatemic OM induced by tenofovir in literature are seen in Table 2. The most common symptom was widespread bone pain. Pain sites were low back, abdomen, both arms, both legs and throracic region. The other symptoms were weakness, fatigue, and poor oral intake, difficulty in walking, nausea, weight loss and osteoporosis, hip fractures (9-13). Hypokalemia was present in the case reported by Hamnvick et al. (11). Tenofovir treatment duration until toxicity ranged between 10 months to 4 years (9-13).

It is not known whether the coexistence of presence of liver disorder and several factors related to disease and adverse drug effects make a difference in applying the knowledge of TDF in HIV to that of CHB patients. There is a need to further study the TDF bone toxicity specifically in CHB patients and determine the disease specific risk factors for bone toxicity.

Buti et al. reported that in patients using TDF for CHB Infection, the incidence of renal and bone events for up to 7 years of treatment was low, with 1.7% showing elevated serum creatinine, hypophosphatemia in 1.3% of patients and no significant change in bone mineral density between years 4 and 7 (18).

A recent study of 53,500 chronically CHB-infected persons showed generally low risk (below 2%) for renal and bone side effects (19). The duration of follow-up was short (<2 years) in most of the studies.

Mitochondrial toxicity leading to proximal renal tubular dysfunction (PRT) was suggested as a common pathogenic mechanism for TDF related bone and renal complications (6). The PRT may result in phosphate wasting only or may

Table 1 - Laboratory investigations at presentation and during follow-up.

Laboratory tests	During Tenofovir Treatment	Three months after Tenofovir discontinuation	Normal range
Glucose (mg/dL)	81	101	70-105
Phosphate (mg/dL)	1.1	3.5	2.3- 4.7
Calcium (mg/dL)	8.1	9.1	8.4- 10.2
Uric acid (mg/dl)	1.3	2.9	2.6-6
Alkaline phosphatase (IU/L)	303	177	40-150
25-OH vitamin D (ng/mL)	14.5	116	>30 ng/mL
Parathyroid Hormone (ng/L)	37	27	12-65
Creatinine (mg/dL)	0.94	0.87	0.6-1.1
Urinary calcium (mg/24h)	230	486	100-300
Urinary phosphorus (g/24h)	0.5	1	0.4-1.3
Urinary spot protein/ Creatinine ratio	59 mg/dl /48 mg/dl =1.22	28 mg/dl /98 mg/dl =0.28	0.1-0.2
Urinary protein	+++	Negative	Negative
Urinary glucose	++	Negative	Negative

Table 2 - The characteristics of chronic hepatitis B patients with hypophosphatemic osteomalacia induced by tenofovir in literature.

Author, year (ref)	Age, Male/ Female	Clinical presentation	Pain	TenofovirTreatment duration until toxicity	ALP U/L	P (mg/dL)	Ca (mg/dL)	25OHDvit (ng/mL)w	PTH
Hoe AKC et al., 2017 (1)	51,M	Pain	Back pain	1 year	↑	↓	N	NA	NA
Kim D et al., 2016 (10) [Article in Korean]	47,M	Fanconi syndrome, multiple bone pain	NA	NA	NA	NA	NA	NA	NA
Magalhaes-Costa P, 2015 (11)	40,M	Progressive chronic kidney disease, bone pain, multiple bone fractures	Hip pain	3 years	217 ↑	1.3↓	NA	26.4 ↓	N
Hamnvik OP et al., 2014 (12)	40,F	Pain, weakness, fatigue, poor oral intake. Difficulty in walking Nausea Osteopenia Weight loss Femoral neck fracture	Lower back, abdomen, both arms, both legs, Thorax	10 months	242↑	0.5↓	8.2↓	33 N	34.1pg/ml N
Gomez Martinez MV et al., 2014 (13)	49,F	Pain	Widespread bone pain mostly in thoracic region	1 year	438↑	1.7↓	NA	NA	NA

M: Male, F: Female
NA: Not available
N: Normal; ↑= Elevated; ↓ = Decreased

progress to complete proximal tubular damage (Fanconi syndrome), with impaired reabsorption and urine wasting of phosphate, calcium, magnesium, potassium, sodium, urate, amino acids, glucose and bicarbonate, resulting in hypophosphatemic OM and metabolic acidosis (5-7).

PRT may be assessed by measuring tubular protein excretion, fractional urinary excretion of phosphate, urinary protein-creatinine [Up/c] ratio and glycosuria (20). Pseudo fractures in OM can be misdiagnosed as disseminated bone malignancy. Malignancy should be ruled out before making diagnosis of osteomalacia induced by TDF (5).

25OH vitamin D was low and serum PTH level was normal in our patient. The normal level of PTH, in the presence of low vitamin D, associated with hypophosphatemia maybe consistent with hypophosphatemia as the prevalent metabolic alteration in our patient.

TDF discontinuation and oral phosphate supplementation is the most common approach for management. Some cases were treated only with calcium and vitamin D (3).

The American Association for the Study of Liver Diseases [AASLD] (16) recommends screening patients prior to starting TDF with renal safety measurements, including serum creatinine, phosphorus, urine glucose and protein, and periodically. This guideline recommends considering bone density study at baseline and during treatment in persons with history of fracture or risks for osteopenia (16).

Conclusions

This case based review aimed to increase awareness about hypophosphatemic osteomalacia as the clinical manifestation of tenofovir-induced Fanconi syndrome in patients with chronic hepatitis B infection. Clinical presentation was mostly diffuse bone pain predominantly in the lower limbs and vertebrae indicating multiple stress fractures. Multidisciplinary approach and close monitoring of proximal renal tubule function is important for early diagnosis to prevent occurrence of pathologic fractures.

Conflict of interest

There are no conflicts of interest.

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