Osteitis Fibrosa Cystica; A Forgotten Manifestation of Secondary Hyperparathyroidism Due to End-Stage Renal Disease: A Case Report

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Introduction: Osteitis fibrosa cystica is a rare complication of secondary hyperparathyroidism. Even though it is thought to be a disease of the past, it still continues to be seen in this modern era in the setting of undiagnosed or untreated chronic kidney disease.

Case Presentation: A 26-year-old married Ethiopian women presented with 4 year history of progressive proximal weakness of extremities and diffuse bone pain. Physical examination revealed diffuse bone tenderness and features consistent with myopathy. Blood work up showed raised creatinine, markedly elevated PTH, borderline low calcium, and vitamin D in severe deficiency range. X-Ray findings were consistent with classical skeletal lesion of severe secondary hyperparathyroidism.

Conclusion: Osteitis fibrosa cystica is a rare but still frequent complication of secondary hyperparathyroidism, which may be the initial presentation of chronic kidney disease. This case report emphasizes the importance of considering secondary hyperparathyroidism in patients presenting with weakness and bone pain to allow for early diagnosis, treatment, and improvement of overall prognosis.

Keywords: osteitis fibrosa cystica, secondary hyperparathyroidism, end-stage renal disease, Ethiopia, case report

Introduction

Hyperparathyroidism (HPT) is the excess production of PTH by the parathyroid glands, and classified into three forms: primary, secondary, and tertiary. Primary HPT is typically due to an adenoma or hyperplasia of the parathyroid glands. Secondary HPT is a common complication of CKD; it is defined by elevated levels of PTH, and it is associated with abnormalities in mineral and bone metabolism. It results from changes in calcium, phosphorus, and vitamin D metabolism that develop during early stages of CKD. The two major consequences of SHPT are renal osteodystrophy and progressive vascular calcifications.

Osteitis fibrosa cystica (OFC) is a rare complication of untreated secondary hyperparathyroidism in patients with end-stage renal disease. A disease which was once a common form of renal osteodystrophy has become rare due to early biochemical screening and optimal management. Nonetheless, classical OFC can still occur, due to delay in diagnosis and in resource-limited settings such as ours in which renal management is suboptimal.

OFC is characterized clinically by bone pain and radiographically by sub-periosteal bone resorption, osteolysis of the distal clavicles, a “salt and pepper” appearance of the skull, bone cysts, and brown tumors of the bones. Although bone histology remains the best method for differentiating between the forms of renal osteodystrophy, elevated serum levels of PTH, low calcium, phosphorus, elevated ALP, and classic findings on skeletal X-ray are commonly used for diagnosing SHPT and OFC.

We report a case of a 26-year-old Ethiopian woman who presented with progressive proximal limb weakness and diffuse bone pain. Laboratory screening and additional diagnostic work up led to unexpected diagnosis. This case also emphasis treatment challenges in resource-limited settings.
Case Presentation

A 26-year-old married Ethiopian women presented to renal clinic with 4 year history of progressive proximal symmetric weakness described as inability to get up from chair, walk upstairs, and comb hair, which eventually led to inability to ambulate without aid. She also complained of generalized bone pain, and easy fatigability. She also had a history of shortness of breath, palpitation, dizziness, tinnitus, and loss of appetite. Also gave a history of poor sunlight exposure. She did not provide history of urinary incontinence or retention, fecal incontinence, sensory loss, visual disturbance, headache, and loss of consciousness. She denied having fever, weight loss, night sweating, skin or facial rash, oral lesion, joint pain or swelling and other systemic symptom. Four years before current presentation she was evaluated for weakness, undergone blood work up and imaging, and told to have muscle disease. She was born and raised in the eastern part of Ethiopia; she is married and delivered a dead fetus because of prolonged labour. She did not use alcohol or tobacco. Family history was negative for any disorders of calcium or tumors. Her social functioning and activities of daily living were markedly affected which resulted in significant psychological distress.

On general examination the patient appeared to be chronically sick looking and walking with the aid of a stick. Vital signs were stable. There was conjunctival pallor; skeletal examination revealed diffuse bony tenderness which was more prominent at pelvic and proximal tibia, chest wall deformity, and scoliosis. Nervous system examination revealed a hypotonic muscle tone, a proximal muscle power of 3/5 (both upper and lower extremity bilaterally) and a distal muscle power of 5/5 (both upper and lower extremity bilaterally), deep tendon reflex of +2, and down-going plantar reflex. Cranial nerve and sensory examination was normal. She initially presented as an outpatient to the neurology clinic for evaluation of weakness and later linked to renal clinic after blood work up revealed raised serum creatinine. With impression of SHPT further blood work up and imaging was undertaken.

Skeletal X-ray revealed sub-periosteal erosion of radial border of middle phalanx of second and third digits associated with acro-osteolysis of distal phalanx (Figure 1); generalized osteopenia, cystic lesion of distal metaphysis of both femur and proximal metaphysis of both tibia and insufficiency fracture diaphysis of left tibia (Figure 2A, 2B and 2C); bilateral displaced femoral neck fracture (Figure 3); resorption and end plate sclerosis of lumbar vertebra with compression fracture (Figure 4); and osteopenia, lytic lesion, and sub-periosteal erosion of left humeral head, and lytic lesion of distal end of clavicle (Figure 5).

Laboratory test was performed (Table 1). It showed; ionized calcium: 1 mmol/L, intact PTH: 1604 pg/mL, vitamin D: 10.2 ng/mL, creatinine: 3.8 mg/dL, ALP: 1780 iu/mL. Abdominal ultrasound revealed bilaterally shrunken echogenic kidney (right=6.7 cm and left=6.9 cm) with loss of cortico-medullary differentiation. Electromyography finding was consistent with proximal myopathy. Whereas, nerve conduction test and muscle biopsy results were normal. Laboratory investigations were carried out using the following kits and assays: hematology (HumaCount 30, Human,
Germany), biochemistry (Humalyzer 3000, Human, Germany), and the assay method used for PTH was immunometric (IMA).

With the above findings a diagnosis of OFC due to secondary hyperparathyroidism associated with CKD was reached. Additional diagnosis was severe vitamin D deficiency, metabolic myopathy, and anemia.

The patient was started on dietary phosphate restriction, calcium carbonate 1 g/day with meal, vitamin D3 50,000 IU by mouth weekly for 8 weeks, ferrous sulphate 325 mg po tid, and paracetamol 1 g per need for pain control. Alfacalcidol 0.25 µg/day was prescribed, but it was not available in the city. She was counselled on prognosis, need for renal replacement therapy (RRT), and nephrologist evaluation. However, because of financial reason she declined referral and RRT. At 2 month follow up visit, she had some improvement in bone pain and weakness. On laboratory test (Table 2), vitamin D level returned to normal (34 ng/mL), serum ionized calcium had risen to 4.8 mg/dL, and PTH became 58 pg/mL (this was due to laboratory error). At this point vitamin D and calcium dose was reduced to 800 iu/day and 500 mg/day respectively. At 5 months of follow up the patient developed severe symptomatic hypocalcemia and hyperkalemia, ECG revealed prolonged QT interval. Subsequently the patient was admitted and received intravenous infusion of calcium gluconate and potassium shift therapy. She was discharged on oral calcium 2 g/day and alfacalcidol 0.25 µg/day.

Figure 2 (A) PA X-ray of tibia; cystic lesion of distal metaphysis of femur and lytic lesion of proximal metaphysis of tibia. (B and C) Lateral X-ray of tibia; osteopenia, and lytic lesion of right tibia, and Insufficiency fracture of mid-diaphysis of left tibia.

Figure 3 AP pelvic X-ray showing bilateral displaced pathologic femoral neck fracture, the so called “protrusio acetabuli”. Compression fracture of lumbar vertebra and osteopenia of pelvic bone is also seen.
Discussion

OFC is an uncommon high turnover bone lesion that is induced by severe hyperparathyroidism, irrespective of its cause. In CKD, the development of SHPT and the consequent OFC is associated with abnormal mineral metabolism through the following events: 1) decreased glomerular filtration results in phosphate retention and decreased activation of vitamin D; 2) consequently the hyperphosphatemia and decreased calcitriol results in low serum ionized calcium; and 3) these 3 abnormalities result in increase in PTH secretion. Without early detection and treatment, persistent SHPT leads to altered osseous metabolism with resorption of bone and tissue change collectively known as OFC.

OFC which was once a common manifestation of renal osteodystrophy has become rare given early diagnosis and optimal control of abnormal mineral metabolism. However, this classical bone lesion still occurs, mostly in the face of uncontrolled CKD or in resource-limited areas in which routine biochemical screening and treatment of SHPT remains inadequate.

OFC clinically presents as bone pain and may be associated with other manifestation of HPT such as muscle weakness and pathologic fracture. Radiographically it is characterized by sub-periosteal bone resorption, osteolysis of the distal clavicles, a “salt and pepper” appearance of the skull, bone cysts, and brown tumors of the bones. Concomitant vitamin D deficiency often results in more severe skeletal disease. Our patient presented with gradually
progressive proximal muscle weakness and diffuse bone pain. We believe that failure to consider SHPT as a possible underlying cause resulted in significant disability due to extensive skeletal destruction and multiple pathologic fractures.

The multiple bony lesions of SHPT are often misdiagnosed as malignant neoplasm such as metastatic carcinoma, bone cysts, osteosarcoma, giant-cell tumors, and multiple myeloma. Because these radiological features (eg, cyst-like radiolucency) overlap and can be characteristic of these other diseases, making diagnosis difficult.

The most important way to distinguish skeletal manifestations of advanced SHPT from malignancy is by biochemical analysis. As in our case, elevated serum PTH along with low serum calcium and high serum phosphorus in patients with CKD establishes the correct diagnosis.

Treatment of OFC requires definitive control of HPT. This is achieved through dietary phosphate restriction, phosphate binders, calcium, vitamin D analogue, and calcimimetics. Parathyroidectomy is indicated in patient with refractory SHPT and tertiary HPT.

| Table 1 Summary of Investigation on Initial Evaluation |
|------------------------------------------------------|
| **Variables**                          | **Reference Range** | **2/7/2021** |
| White cell count (per µL)                | 4000–10,000         | 8290         |
| Hemoglobin (mg/dL)                       | 11–16.5             | 7.4          |
| MCV (fL)                                | 80–99               | 68           |
| MCH (pg)                                | 26.5–33.5           | 24           |
| Platelet count (per µL)                  | 100–300             | 912          |
| ESR (mm/hr)                              | 0–20                | 45           |
| AST (IU/L)                               | 12–38               | 38           |
| ALT (IU/L)                               | 7–42                | 12           |
| ALP (IU/L)                               | 60–306              | 1780         |
| Creatinine (mg/dL)                       | 0.5–1.2             | 4.25         |
| Blood urea nitrogen (mg/dL)              | 7–20                | 94           |
| Sodium (mmol/L)                          | 136–146             | 135          |
| Potassium (mmol/L)                       | 3.5–5               | 4            |
| Chloride (mmol/L)                        | 98–107              | 98           |
| Total calcium (mg/dL)                    | 8.4–10.4            | 7.4          |
| Ionized calcium (mg/dL)                  | 4.4–5.2             | 4            |
| Phosphorus (mg/dL)                       | 4.5–5.5             | N/A*         |
| Vitamin D (ng/mL)                        | >20                 | 10.2         |
| Intact PTH (pg/mL)                       | 15–68.3             | 1604         |

**Urinalysis**

| Variables            | Reference Range | 2/7/2021 |
|----------------------|-----------------|----------|
| Specific gravity     | 1.010           |          |
| pH                   | 6.6             |          |
| Albumin              | Negative        |          |
| Blood                | Negative        |          |
| WBC                  | 5–8             |          |
| RBC                  | 0               |          |
| Cast                 | –               |          |
| 24 hour urine protein| N/A*            |          |
| UPCR/UACR            | N/A*            |          |

**Serology**

| Variables | Reference Range |
|-----------|-----------------|
| Hepatitis B | Negative     |
| Hepatitis C | Negative     |
| HIV        | Negative       |
| VDRL       | Negative       |
| ANA        | Negative       |

Abbreviation: *N/A, not available.
In low and middle income countries such as ours, ESRD is associated with high rate of morbidity and mortality due to limited availability and affordability of treatment options. The management of CKD complications are suboptimal due to gaps in knowledge and limited resources. Treatment of CKD-MBD in resource-limited setting includes dietary phosphate restriction, phosphate binding usually with calcium carbonate, and vitamin D steroid. However, unavailability of diagnostics and therapeutic agents is the key challenges physicians face when caring for patients with such complication. Additionally, very few have access to RRT. Given these limitations, early disease detection and preventive measures remain the best options of management in resource-limited settings.

Unavailability of a laboratory capable of doing CKD-MBD panel in the region resulted in suboptimal laboratory monitoring, lack of access to essential drugs like active vitamin D analogue and calcimimetics led to persistence of SHPT and development of symptomatic severe hypocalcemia, and lack of access to RRT services and financial issues were limitations in management of this patient.

Conclusion
OFC is a rare but still frequent complication of SHPT, which may be the initial presentation of CKD. Delay in diagnosis of SHPT often leads to extensive skeletal destruction associated with significant disability. This case report highlights the significance of entertaining SHPT in patients presenting with weakness and bone pain to allow for early diagnosis, treatment, and improvement of overall prognosis.

Abbreviations
ALP, alkaline phosphatase; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–mineral bone disease; OFC, osteitis fibrosa cystica; PTH, parathyroid hormone; HPT, hyperparathyroidism; SHPT, secondary hyperparathyroidism; RRT, renal replacement therapy.

Ethical Approval
Institutional approval is not required to publish the case details.

Consent
Written informed consent was obtained from the patient for the publication of this case report and accompanying image.

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Table 2 Timeline of the Patient's Serial Laboratory Investigation

| Variables            | Normal Range | Initial Value | 22/9/2021 | 14/12/2021 | 22/12/2021 |
|----------------------|--------------|---------------|-----------|------------|------------|
| ALP (IU/L)           | 60–306       | 1780          | N/A*      | 965        | N/A*       |
| Creatinine (mg/dL)   | 0.5–1.2      | 4.25          | 4.3       | 5.3        | 5.4        |
| Blood urea nitrogen (mg/dL) | 7–20  | 94            | N/A*      | 138        | 138        |
| Sodium (mmol/L)      | 136–146      | 135           | 138       | 138        | 137        |
| Potassium (mmol/L)   | 3.5–5        | 4             | 4.3       | 6.8        | 4.1        |
| Chloride (mmol/L)    | 98–107       | 98            | 99.3      | 104        | 102        |
| Total calcium (mg/dL)| 8.4–10.4     | N/A*          | 5.9       | 3.92       | 5.72       |
| Ionized calcium (mg/dL) | 4.4–5.2    | 4             | 4.8       | 2.08       | 3.04       |
| Phosphorus (mg/dL)   | 4.5–5.5      | N/A*          | N/A*      | N/A*       | N/A*       |
| Vitamin D (ng/mL)    | >20          | 10.2          | 34        | 69.5       | N/A*       |
| Intact PTH (pg/mL)   | 15–68.3      | 1604          | 58.1      | 1377       | N/A*       |

Abbreviation: *N/A, not available.
Author Contributions
All authors made a significant contribution in the acquisition of data, analysis and interpretation; took part in drafting and writing of manuscript, revising and reviewing the article, gave final approval of the version to be published, have agreed to which journal the article has been submitted, and agree to be held accountable for all aspects of the work.

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