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(CASE REPORT)

A case of hypercalcemia with hyperparathyroidsm on severe immunodeficiency stage 4 HIV infection, lung tuberculous infection, protein energy malnutrition treated with zolendronic acid

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Abstract

Introduction: Hypercalcemia referred as serum calcium level over two standard deviations above the average mean values. Clinical manifestations may be due to hypercalcemia or may be due to the causal disorder or may be due to both. Hypercalcemia disorders can caused by group of illness/abnormalities.

Cases Presentation: A-5 year-4 months old girl was taken to hospital with chief complaint fatigue and shortness of breath. Patient was also complained decrease of appetite since 6 months before hospital admission. Patient was diagnosed with Human Immunodeficiency Virus (HIV) infection and lung tuberculosis infection. On serial laboratory examination found hypercalsemia and increase of septic marker, increase of parathyroid hormone on normal vitamin D level. Patient showed rapid clinical improvement on the second day after administration of zolendronic acid. Antibiotics, Oral Antituberculosis Treatment (OAT) and supportive treatment were administrated due to comorbidities.

Summary: Hypercalcemia is a rare conditions in children with HIV infections. Zolendronic acid should be considered for patient with hypercalcemia.

Keywords: HIV; Biphosphonate; Zolendronic acid; OAT; Tuberculosis; Antibiotics

1. Introduction

Hypercalcemia can be defined as serum calcium greater than 2 standard deviations above normal mean. Hypercalcemia is less common in children than in adults, but is more likely to be clinically significant in younger patients[1].

Clinical manifestations may be due to hypercalcemia itself or may be due to the causal disorder or may be due to both. Hypercalcemia manifestations will vary depend on whether the hypercalcemia is acute onset and severe (greater than 12 mg/dL or 3 mmol/L) or whether it is chronic and relative mild. Patients may also tolerate higher serum calcium level if the onset is gradual, but at concentration above 14 mg/dL (3.5 mmol/L) most patients are symptomatic. In both acute and chronic cases, the major manifestations usually affect gastrointestinal, renal and neuromuscular function.

Hypercalcemic disorders can be broadly grouped into Endocrine Disorders, Malignant Disorders, Inflammatory Disorders, Medication-Induced Hypercalcemia, and Immobilization. Holistic approach is essential for diagnosis and management of patient with hypercalcemia, especially in patient with systemic commorbidites.

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Osteoclast are highly affected by HIV and tuberculous infection. HIV protein stimulates osteoclastogenesis and bone resorption activity and also increase of TRAP secretion by osteoclasts, leading to demineralization and degradation of larger bones. This study reports a very rare case of symptomatic hypercalcemia which incidentally found in children with comorbid HIV infection and with secondary Tuberculosis Infections.

2. Case report

A 5 year-4 months old girl was taken to hospital with multiple complaints, the chief complaint of patient was shortness of breath. Shortness of breath was preceded by cough and fever. Patient complained cough from 6 months before admission accompanied by intermittent fever. Cough got worsen in last 2 weeks, cough was said productive and accompanied by non-blood staining phlegm. Patient also complained watery stool from 9 months before admission. The frequency of defecation about 1-2 times per day. Watery defecation was not accompanied by abdominal pain, fluctuated during the day. These complaints have got better and worsened time by time without any intervention.

Patient also complained decrease of appetite since 6 months prior to hospital admission and got worsen daily. Due to decrease of food intake since 6 months before admission patient look thin, her face look older and older by time. Patient loss about 5 kg of body weight in last 6 months. Her chest bone looked more prominent and her clothes much looser time by time.

Before onset of this illness patient was very active and cheerful children. She actively plays with peers and her grandmother. From age 4 years old patient look less active but still can play with friends. Since 2 weeks ago patient looked fussier and prefer to hug her grandmother rather than play with her peers.

The patient's gait and ability to walk properly continues to decline. Since first day of admission patient refuse to walk nor stand up by herself. Patient looked more fatigue than before. There were no complaint of rapid or irregular heart beat nor chest pain.

Patient was diagnosed with Human Immunodeficiency Virus (HIV) infection before admission in VCT division with laboratory examination result CD4 6 (1.7%), CD8 132 (37.18%). Patient was not administered antiretroviral therapy (ART) and OAT yet. Her mother was also diagnosed with HIV infection and extrapulmonary Tuberculosis, her mother is already on treatment with antiretroviral therapy (ART) and consume regular anti tuberculosis drug since 9 months ago. Laboratory examination at Prof. DR. I.G.N.G. Ngoerah Hospital on February 27th, 2022 revealed leukocytes 5.64x103/µL, neutrophils 4.2x103/µL (74%); lymphocytes 0.5x103/µL (10.5%), hemoglobin of 7.9 mg/dL; platelet 349x103/µL, mean corpuscular volume (MCV) 78 fL; and MCHC 30.90 pg; SGOT 270.8 U/L, SGPT 19.3 U/L, creatinin 0.73 mg/dL, BUN 20.9 mg/dL, GFR 77.6, Potassium 3.37 mmol/L, Sodium 134 mmol/L, Chlorida 99.4 mmol/L, Calcium 15 mg/dL.

Patient was given RLD5% fluid to correct hypercalcemia. Antibiotics with ampicillin 50 mg/kg/time every 6 hours and Gentamicin 7.5 mg/kg/day every 24 hours. Antipiretic was given as needed and management of severe energy malnutrition with special formula milk (density 1, high MCT and high PER).

On the third day of hospitalization no improvement of fatigue, patient still unable to walk and unwilling to communicate. Laboratory examination revealed hypokalemia and hypercalcemia with range 14.2-15.5, high ferritin (596), high CRP (35.4), nomal urine electrolytes and normal vitamin D (25-OHD) value, slightly decrease of serum phosphat (2.3), normal magnesium level and increase of intact PTH 66.65 (normal value according to age 9-59). Thyroid USG performed within normal result. Antibiotics, OAT and supportive treatment were continued. Then patient was decided to be administred zolendronic acid with dosage 0.03 mg/kg/dose.

On the second day after zolendronic acid administration patient able to stand by herself and start to communicate, patient can sit in the toilet for defecation. On the seventh days after zolendronic acid administration patient able to walk and have better communication with family. Patient can drink 30 % of enteral nutrition by oral and 70 % was administrated by Nasogastric Tube. Rapid progression of electrolyte imbalance was gradually seen on the third day after zolendronic acid administration. Laboratory examination revealed Potassium (3.99) mmol/L, sodium (141) mmol/L, Chloride (105) mmol/L, calcium was rapidly decrease without other intervention from 14.4 into 9.2 mg/dL, with nomal urine electrolyte reevaluation. No secondary dosage was given and no side effect of intravenous zolendronic acids administration was observed. Other supportive treatment was continued.

3. Discussion

Calcium as nutrient is most commonly associated with the formation and metabolism of bone. Over 99 percent of total body calcium is found as calcium hydroxyapatite ($Ca_{10}[PO_4]_6[OH]_2$) in bones and teeth[2]. Calcium in the circulatory system, extracellular fluid, muscle and other tissues is critical for mediating vascular contraction and vasodilatation, muscle function, nerve transmission, intracellular signal and hormonal secretion. Bone tissue serves as reservoir and source of calcium for critical metabolic needs through the process of bone remodeling[2,3].

Extracellular calcium concentrations are maintained remarkably stable, because of high sensitivity of cell systems or organs, including central nervous system, muscle and endocrine glands, to small variations of extracellular calcium concentrations[4]. Serum calcium levels are normal tightly controlled through regulated secretion of parathyroid hormone (PTH) by parathyroid glands and its subsequent actions on bone, kidney and intestine. Increase in serum calcium level can be sensed by calcium-sensing receptor (CaR) on the surface of the parathyroid cell. When stimulated by an increase of ionized Ca, the CaR responds by activating secondary messengers to diminish PTH production and secretion[5].

Hypercalcemia is an infrequent finding in children. In adults, the causes are most often from malignancy or hyperparathyroidism. In childhood the etiologies are diverse, may be age specific and many have an underlying comorbidity. Untreated hypercalcemia can have serious consequences, including renal failure[4]. The differential diagnosis for hypercalcemia includes extensive group of disorders. The most common disorders include Primary Hyperthyroid, Secondary Hyperparathyroidism due to granulomatous disease, inflammation, medication, vitamin D toxicity and feedback to vitamin D deficiency[6,7,8].

Bone health appears to be compromised in HIV-infected patient. A recent meta-analysis reported the prevalence of osteoporosis and osteopenia in HIV patients respectively as 15 and 67%. Altered bone was three times more prevalent in HIV-infected individuals compared with HIV-uninfected controls[8-10].

In HIV-infected patients, bone loss is primarily enhanced by two pivotal factors: HIV infection with its direct consequences and HAART. HIV-infected adults exhibit an increased risk of osteoporosis and factures. Bone health appears to be compromised in HIV-infected children and adolescents too, although the long-term outcomes are largely unknown[10].

The evidence of reduced bone mass in treatment-naive patients indicates that the virus directly affects bone homeostasis. The bone as part of the skeletal system interacts with immune cells in the bone marrow, interacting with each other in a significant mutual influence. Recently, the molecular mechanisms involved in the homeostatic interactions between bone and immune cells has been elucidated[9].

Among many of the viral pathogenic mechanisms, HIV regulatory, auxiliary and structural proteins play critical roles during cell-host interaction and thus have shown significant impacts on bone in experimental studies. It is important to highlight that the HIV-induced detrimental effects on cells are not only consequence of active viral replication and role of infectious virions but also caused by several HIV proteins that are released to extracellular media which could induce harmful effects, such as apoptosis, oxidative stress, mitochondrial dysfunctions, or autophagy alterations, on surrounding cells[9].

To command the balance of bone resorption and formation, osteoblast produces receptor activator factor of nuclear factor-kB ligand (RANKL) that controls the differentiation of osteoclasts[13]. Osteocytes the terminally differentiated form of osteoblast also produce RANKL to regulate osteoclast activity[3]. Under physiological conditions, osteoclastogenesis involves RANKL and macrophage colony-stimulating factor (M-CSF) produced by osteoblast and bone marrow stromal cells[14]. M-CSF prompts the expression of RANKL receptor (RANK), on osteoclast precursor which then interacts with RANKL to initiate osteoclasts' differentiation. As a counterpart, osteoprotegerin (OPG), a neutralizing soluble, trap receptor expressed by bone marrow stromal cells and osteoblasts able to inhibit the RANKL-RANK interaction.

HIV protein Tat is an 86–104 residue protein essential for HIV-1 replication as it acts as a potent activator of viral gene expression. Its interaction with Nef protein enhances peripheral blood monocyte-derived osteoclast differentiation and RANKL activity, which increases both the mRNA transcription of specific osteoclast differentiation markers, such as cathepsin K and calcitonin receptor, and the tartrate-resistant acidic phosphatase (TRAP) expression and activity. may be considered a viral factor that stimulates osteoclastogenesis and bone resorption activity[15].

Lymphocytes B and T in HIV patient have exhibited several signs of dysfunction with impact on bone homeostasis. They are sources of OPG and consequently, their dysfunction contributes to viral-induced bone loss. Hence, there is a higher frequency of RANKL-expressing B cells (resting memory and exhausted tissue-like memory B cells) expanded as consequence of inflammation and lower frequency of OPG-expressing B cells (resting memory B cells) in HIV-infected compared to HIV-uninfected individuals, thus resulting in increase RANKL/OPG ratio that correlates with decrease total hip BMD, T- and Z-scores in the HIV-infected patient[18,19].

Other mechanism could explained increased hypercalcemia risk and reduced bone mineral density in naive treatment HIV patient are direct infection to osteoclasts precursors. HIV infects osteoclast precursors at different stages of osteoclastogenesis, either via cell-free viruses or, more efficiently, through transfer from infected T cells. These infected precursor cells have been proposed as HIV reservoirs that display greater migratory capacity and exhibit the enhanced ability to recruit and concentrate in the bones which the virus alters bone resorption machinery[16,17]. HIV can enlarge podosomes and enhance the osteolytic activity of the bone resorption apparatus, also known as the “sealing zone” (SZ). The virus is also able to increase the TRAP secretion by osteoclasts, leading to demineralization and degradation of larger bone extensions [10,17].

Other probability cause of hypercalcemia in this patient is systemic immune disturbance of granulomatous disease. The most common granulomatous disorders causing hypercalcemia are sarcoidosis and tuberculosis[20].

In order to exclude the possibilities of primary hyperthyroid Thyroid USG was performed and found no sign of structural and vascularization of thyroid and parathyroid gland. Imaging modality like CT-Scan and MRI of brain and thyroid gland was planned to exclude PTH Dependent Primary Hiperthyroidism, but postponed due to efficacy of resources used. For explaining increase of calcium in correlation of inflammation, septic marker study was performed, and laboratory examination showed increased of CRP as marker of inflammation. Probability of combination of PTH dependent and independent hypercalcemia in this patient is still in considered and need further examination.

To date, advanced therapy for hypercalcemia in adults is combination of biphosphonate followed by therapeutic calcitonin (extracted from salmon) and calcium restricted diet. In our facilities, biphosponate is the only modalities available for hypercalcemia therapy.

In HIV infection adult biphosponate treatment is routinely initiated to prevent secondary osteoporosis. With the consideration of hypercalcemia and risk for decrease bone density in this children patient was initiated with intravenous biphosphonates. Bisphosphonates have been used extensively to treat some bone disorders such as postmenopausal and glucocorticoid-induced osteoporosis, malignancy-induced hypercalcemia and Paget’s disease[23]. Structurally, bisphosphonates are chemically stable derivatives of inorganic pyrophosphate. Like their natural analogue PPi, bisphosphonates have a very high affinity for bone mineral because they bind to hydroxyapatite crystals. A critical pharmacological feature of all bisphosphonates is their extremely high affinity for, and consequent deposition into, bone relative to other tissues. This high affinity for bone mineral allows bisphosphonates to achieve high local concentration throughout the entire skeleton. Bisphosphonates inhibit osteoclastic bone resorption and are effective in the treatment of hypercalcemia due to conditions causing increased bone resorption.

The effect of bisphosphonates on osteoclast activity is the result of their potency as inhibitors of the enzyme farnesyl pyrophosphate synthase, a key branch point enzyme in the mevalonate pathway. Farnesyl pyrophosphate synthase generates isoprenoid lipids utilized in sterol synthesis and for the posttranslational modification of small GTP-binding proteins essential for osteoclast function. As a consequence of the inhibition of osteoclast activity, recruitment and apoptosis, suppression of bone turnover occurs[23,24]. Accordingly, bisphosphonates have become the primary therapy for skeletal disorders characterized by excessive or imbalanced skeletal remodeling, in which osteoclast and osteoblast activities are not tightly coupled, leading to excessive osteoclast-mediated bone resorption.

The potential adverse effects of bisphosphonates on the growing skeleton have been the main limiting factor to their usage in pediatric patients. However, experience in recent years has suggested that bisphosphonates treatment is safe in pediatric patients. Other study by Felix et al found, in a dose-dependent manner, the RANKL/OPG ratio, elevated by zoledronate could suggest an anabolic effect on osteoclasts via osteoblasts’ secretion after application of bisphosphonates at high concentrations. Lower bisphosphonate concentrations, however, seemed to cause an OPG gene expression in osteoblasts that exceeds the RANKL gene expression[7].

4. Conclusion

A 5 year-4 months-old girl was diagnosed with Human Immunodeficiency Virus (HIV) infection and lung milliary tuberculosis infection. Patient was incidentatlly found imbalance electrolyte, potassium (3.48) mmol/L, sodium (132) mmol/L, chloride (101) mmol/L, high ferritin (596), high CRP (35.4), calcium (13.6-15.2) mg/dL, with nomal urine electrolyte and normal vitamin D (25-OHD) value, slightly decrease of serum phosphat (2.3), normal magnesium level and increase of intact PTH 66.65 (normal value according to age 9-59). Antibiotics, OAT and supportive treatment was administrated with no significant improvement of electrolyte imbalance and patient was administered zolendronic acid with dosage 0.03 mg/kg/dose. Patient showed rapid improvement especially fatigue on the second day after zolendronic acid administration.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

If studies involve use of animal/human subject, authors must give appropriate statement of ethical approval. If not applicable then mention 'The present research work does not contain any studies performed on animals/humans subjects by any of the authors'.

Statement of informed consent

Informed consent was obtained from participant included in the report.

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