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A Rare Case of Sagliker Syndrome in 16 Year-old Child: Complication of Untreated Hyperparathyroidism

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Abstract: ***Sagliker syndrome is a syndrome described in patients with chronic kidney disease (CKD) in the course of untreated or inadequately treated secondary hyperparathyroidism. We reported one patient male, 16 year-old with CKD stage V on regular hemodialysis, presented with change in facial feature overtime, characterized by uglifying face with enlarged upper and lower jaws, malformation of jaws, oral mass, abnormality of teeth, and deformity of legs. That manifestation was accompanied by history of bone fracture and other problems such as cardiomyopathy, mild tricuspid regurgitation, trivial mitral regurgitation. Laboratory examination found hyperparathyroid, vitamin D insufficiency, hypocalcemia, hyperphosphatemia, anemia, thrombocytopenia, and decreased glomerular filtration rate. Radiological imaging found osteodystrophy appearance on long bones, calvaria, and jaw bones. Patient had history of inadequately treated mineral disorder. Patient was treated by regular hemodialysis, antihypertensive medication, calcitriol, phosphate binder, folic acid, and erythropoeitin stimulating agent after recognition of the syndrome. Parathyroidectomy cannot be done in this patient. The early recognition of Sagliker syndrome would lead to safe and effective treatment by parathyroidectomy and medication which can decrease morbidity and longterm complication. The inability to correct all the morphologic changes can be catastrophic for those patients, hence appropriate treatment for CKD must begin early by the time of diagnosis in specialized centers.***

Keywords: bone-mineral disorder, chronic kidney disease, secondary hyperparathyroidism.

1. Introduction

Sagliker syndrome is a novel syndrome described in patients with chronic kidney disease (CKD) in the course of untreated or inadequately treated secondary hyperparathyroidism (SHPT), firstly described in 2004 as a new entity by Sagliker et al. [1],[2]. The incidence approximately just 0.5% in population of CKD patients currently undergoing hemodialysis treatment [2]. The age and sex predilection still unknown. Sagliker syndrome are particularly found in developing countries such as China, India, Pakistan, Bangladesh, Indonesia, Southeast Asia, South America, and Africa [3],[4]. Other case series found that 6.34% of the patients developed Sagliker syndrome, which is much higher compared to other countries [5].

Improper treatment in the early stages of CKD is the cause of retention of phosphorus, vitamin D deficiency and disorder in the calcium-phosphorus metabolism, hence causing renal osteodystrophy [5]. Sagliker syndrome is an exaggerated form of renal osteodystrophy, comprising CKD, SHPT, uglifying appearance to the face, short stature, irregularly scattered skull and facial bone alterations, destruction of maxillary and mandibular bones, irregularly shaped and located teeth, soft and innocent tissue accumulations in the upper oral cavities, class II malocclusion of malocclusion of the upper and lower jaws, upward curved fingertips, knee and scapula deformities, brown tumors, hearing loss, neuropsychiatric disorders, and depression, among other features [2],[5]-[8]. This syndrome usually starts and develops before puberty while CKD reaches late stage 3 right after phosphate levels start to increase [4].

Previous studies have shown the major manifestations of this syndrome, while its therapeutic response and prognosis are rarely mentioned.

2. Case Report

A 16 year-old boy suffered from chronic kidney disease stage V was referred to our center, with chief complaint swelling on left arm and chest since 6 months ago. He had been on regular hemodialysis since 4.5 years at regional general hospital due to chronic kidney disease stage V. He has been using brachialis arteriovenous (AV) shunt for hemodialysis twice a week. He was diagnosed with total occlusion of left subclavial proximal vein and collateral left innominate vein and venous hypertension of left upper extremity. He undergone percutaneous transmural angioplasty (PTA) and double lumen catheter insertion, but unfortunately PTA procedure was not success. He undergone shunt ligation surgery of left brachiocephalic vein on August 2018 and the complaint was resolved.

He also complained change in body feature since 3 years ago. Facial feature was changed in the form of upper and lower jaws bone enlargement and abnormal shape and lining of teeth resulting in eating difficulties (Figure 1). He was found with severely malocclusion of jaws. Bowing legs was complained since 3 years ago, worsen after the he suffered from bone fracture after trauma 2 years ago, open reduction internal fixation with plate and screw (ORIF PS) was done by orthopedist. Patient's gait was affected. Valgus deformation and limited active and passive range of movement was found on both knees and ankles. He complained of lump on palatum and under tongue since 9 months ago, not easily bleed. He also had a short stature, with genetic potential height was laid below the expected range. The body change progressively worsen overtime. No hearing problem and neurological deficit was found.

Previously patient had been treated by antihypertensive therapy such as telmisartan, bisoprolol, and amlodipin. Patient never had phosphate binder, vitamin D therapy, and calcium before admitted to our center.

Figure 1: Clinical picture of the case showing severe cephalometric maxillary and mandibulary changes, irregularly shaped and placed dental abnormalities, brown tumors, and legs and gait abnormality

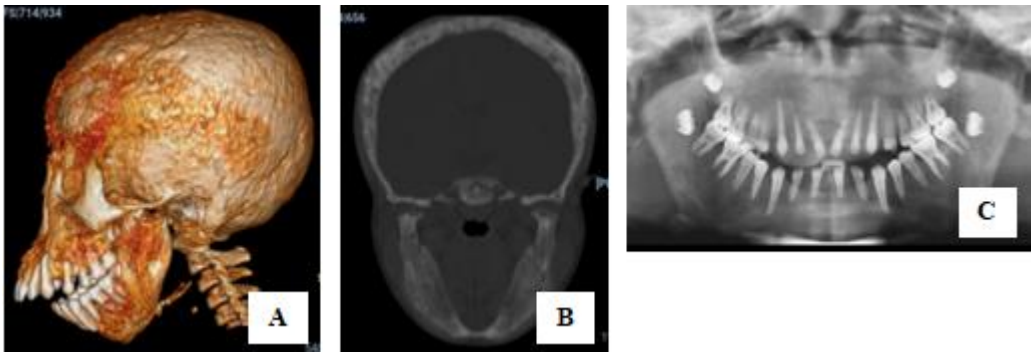

Figure 2: Imaging of the case: severe cephalometric maxillary and mandibulary changes and severe malocclusion (A, B), CT scan: salt and pepper appearance in calvaria and hypodensity of maxillofacial bones (C), panoramic photo: enlargement of mandibula with erosion and decreased trabeculation of mandibula and maxilla and stricture of most teeth pulpae (D)

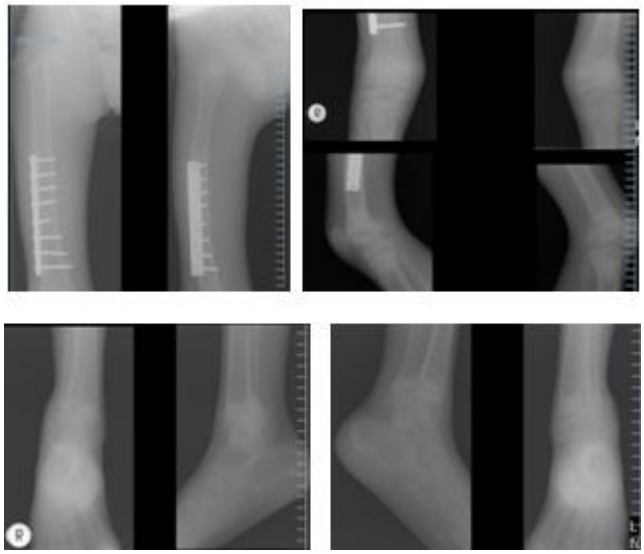

Figure 3: Bilateral femur, genu, ankle AP/lateral showed bowing fracture with internal fixation on 1/3 medial right and left femur, valgus alignment on both ankles

Complete blood count found normochromic normocytic anemia (8.44 g/dL) with mild thrombocytopenia (147.60 x 103/µL), serum iron 50.43 ug/dL, TIBC 136 ug/dL, ferritin 1488 ng/mL, transferin saturation 37%, BUN 25 mg/dL, creatinin 4.84 mg/dL, glomerular filtration rate (GFR) 14.7 ml/min/1.73 m2, alkaline phosphatase (ALP) 137 U/L, calcium 8.8 mg/dL, anorganic phosphor 4.71 mg/dL. Increased intact parathyroid hormone 2319 pg/mL and Vitamin D insuficiency (20.5 ng/mL) was found.

Noncontrast CT scan midface and colli showed tumor in maxilla and hard pallatum region, suspected brown tumor, with salt and pepper appearance in calvaria and hypodensity of maxillofacial bones suspected renal osteodystrophy, compression and destruction in vertebral corpus C6 with rugger jersey sign in cervical thoracal vertebrae. Panoramic photo found enlargement of mandibula with erosion and decreased trabeculation of mandibula and maxilla and

stricture of most teeth pulpae (Figure 2). Bilateral femur and genu AP/lateral showed bowing fracture with internal fixation on 1/3 medial right and left femur, with good alignment and oposition, no fracture and dislocation of knee. Bilateral ankle AP/lateral showed valgus alignment (Figure 3). Thyroid USG found bilateral colli lymphadenopathy, no abnormality in thyroid, isthmus, parotid and submandibular glands. Thorax PA showed cardiomegaly with aortosclerosis (ASHD).

Patient was treated by regular hemodialysis, telmisartan 1x80 mg, bisoprolol 1x5 mg, amlodipin 1x10 mg, calcitriol 0,5 mg three times a week, calcium carbonate 3x250 mg, folic acid 2x2 tablets, and erythropoietin 2000 IU subcutaneous on hemodialysis. Patient was consulted to pediatric surgery division, parathyroidectomy could not be done due to small size of the parathyroid glands.

3. Discussion

Almost every patient with CKD eventually develops SHPT unless they are treated with proper management at early phase of the disease [2],[9],[10]. Secondary hyperparathyroidism cause tremendous changes that start to occur throughout the body and include all organs but particularly the long bones, vertebral bones, and these facial bones: skull, bones in the head, maxillary and mandibulary jaw bones, and teeth, known as osteitis fibrosa/renal osteodystrophy (OF/RO) [6],[11],[12]. Clinical manifestation such as unique and serious facial deformities which is unrecognizably uglifying human face appearance, irregularly formed round or oval accumulations in skull bones, short stature, extremely severe destructional nasal, maxillary and mandibular protuberance, irregularly located teeth and dental abnormalities such as pointed x- or o-shaped teeth, type 2 malocclusion of the maxillary bones (frontal forward and upward malformation of the upper jaws), curved fingertip changes, x- or o-type knee deformities and crippled walking in particularly left legs, large deformed scapulas [2],[4]-[7]. There is no significant sex predilection, and adult patients are the most affected. The pathologic process often involves the jaws diffusely, possibly leading to severe facial asymmetries and disfigurement.

Imaging aspects of OF/RO typically revealed demineralization, loss of lamina dura and trabecular bone, that looks like frosted glass or ground glass feature, which may be useful to recognize the disease, usually confined to a single bone or to 1 quadrant (in its polyostotic or craniofacial presentation), not diffusely affecting both maxilla and mandible [5],[11],[13]. Microscopically, histologic samples collected from patients with OF/RO usually reveal an increased osteoclastic resorption of the bone trabeculae and a higher proliferation of osteoblasts present on the bone surfaces. Interspersed with these altered osseous components, an increased accumulation of fibrous tissue is noted. Moreover, scattered multinucleated giant cells may also be found, but this is not as a prominent microscopic feature as in BTH [11],[13].

Both mandible and maxilla can be affected individually or simultaneously when CKD-BMD manifests [14],[15]. Painful exophytic mass or as an asymptomatic swelling occur in the gnathic bones is known as brown tumor of hyperparathyroidism (BTH). BTH are bone lesions caused by rapid osteoclastic activity and peritrabecular sclerosis, result of hyperparathyroidism [5],[11]. It cause a well-defined radiolucent or hypodense image on radiographic and CT examinations but usually not producing cortical disruptions and periosteal reactions [11]. Microscopically, BTH is characterized by vascular fibroblastic stroma, and several osteoclast-like multinucleated giant cells are often interspersed within hemorrhagic infiltrates and hemosiderin deposits [15].

The exact mechanism underlying SS is not sure. Because not all patients with CKD and severe SHPT develop Sagliker syndrome, there may be genetic predisposition in these patients to develop this syndrome. An international study suggested that GNAS1 genes missense mutations rather than chromosomal abnormalities or calcium-sensing receptor gene abnormalities would be considered for the genesis of Sagliker syndrome [1],[4]. Screening for mutations in GNAS1 can be done by polymerase chain reaction (PCR) amplification and DNA sequencing of 13 exons [4]. Sagliker syndrome patients had typical biochemical serum calcium values averaging 6–7 mg/dL, phosphate levels of 7–8 mg/dL, increased levels of alkaline phosphatase (ALP) (120–240 U/L), and at least 3.5 times greater values than normal for intact PTH levels (180–240 pg/mL by immunoradiometric assay) before entry to HD treatments. Laboratory text, such as thyroid function, growth hormone levels and sex hormone levels showed no striking differences in SS [1],[2].

Although the process of musculoskeletal changes stops with kidney transplantation, deformities occurred due to SS are not reversible and this leads to a poor quality of life for the affected patients [7]. Body changes particularly in children and adolescents become irreversible-disastrous not only for anatomical and pathophysiologically, but also for appearance, spiritual, and psychological issues. Proper treatment must begin as early as possible with renal replacement therapy, calcium containing medications, vitamin D, or similar products. Non metal containing phosphate and lipid lowering agents such as Sevelamer HCl, calcium-sensing-receptor inhibitors such as Cinacalcet HCl, non metal containing phosphate binders such as Lanthanum carbonate can be administered [16]. Surgical modality such as kidney transplantation for advanced cases to reestablish normal renal function is also a possibility. Parathyroidectomy also seem to be effective for whom pharmacological treatment failed to adequate regulation of parathyroid function. In time parathyroidectomy may control and partially ameliorate bone changes shown in SS. However, relapses of SHPT caused by residual parathyroid tissue left in the neck, hyperplastic grafted tissue, undetected supernumerary gland during surgery or the multiple ectopic glands are relatively frequent in HD patients. Parathyroidectomy should not be put off when patients failed to respond to pharmacological therapy [1],[11]. In this case, parathyroidectomy could not be done due to small size of the parathyroid glands and lack of experience.

Additionally, there were no data established about the longterm prognosis and survival of Sagliker syndrome worldwide.

4. Conclusion

We reported a case of Sagliker syndrome to emphasize the importance of early therapy of bone and mineral disorder. The early recognition of Sagliker syndrome would lead to safe and effective treatment by parathyroidectomy and medication which can decrease morbidity and longterm complication. Though it is possible that such patients could survive long-term with regular dialysis, the inability to correct all the morphologic changes can be catastrophic for those patients. Appropriate treatment for CKD must begin early by the time of diagnosis in specialized centers.

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