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Case Report

Challenges in the diagnosis and treatment of brown tumors – Clinical radiological features in a case series and review of the literature

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Abstract

Introduction: brown tumors result from changes in bone metabolism due to primary, secondary, or tertiary hyperparathyroidism. Their significance lies in the increased risk of pathological fractures, pain, disability, and functional limitation they can cause.

Case reports and discussion: this case series report presents 3 patients with secondary hyperparathyroidism due to chronic kidney disease (CKD) who had not been diagnosed or treated and had sustained pathological fractures. These cases were presented at a referral hospital in southwestern Colombia. The clinical, radiological, and surgical characteristics are described. Additionally, a critical literature review is conducted on secondary CKD-related hyperparathyroidism to emphasize the importance of diagnostic suspicion, as nearly 1 in 3 patients with advanced-stage CKD will develop secondary hyperparathyroidism, leading to a high risk of pathological fractures associated with significant morbidity.

Keywords:
Brown tumors. Osteitis fibrosa cystica. Secondary hyperparathyroidism. Pathological fractures.

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INTRODUCTION

Brown tumors are the result of excessive osteoclastic activity and consist of accumulations of osteoclasts and giant cells within fibrous tissue. This phenomenon is the outcome of a metabolic bone disease triggered by primary, secondary, or tertiary hyperparathyroidism (HPT) (1).

They may be considered an enigmatic and infrequent clinical entity due to advances in the diagnosis of CKD and hyperparathyroidism since the beginning of the 21st century. Similarly, their early diagnosis is rare since there are no protocols for their detection in patients with CKD (2). The direct association between hyperparathyroidism and bone metabolism disease dates back to 1925 when Mandl performed the first parathyroidectomy described in the literature, demonstrating improvement of bone lesions in patients with osteitis fibrosa cystica, a disease of which brown tumors are a severe and localized sign (1,3).

Incidence rates are reported to be higher in men, with a ratio of 3:1 vs women, and are more common in patients older than 50 years (4). They can occur anywhere but are more common in the facial bones, ribs, clavicles, pelvis, and femur (5).

Clinically, most are asymptomatic but can cause swelling, a sensation of a mass, and even pain, especially when associated with pathological fractures. Depending on their location, they can cause radicular pain or, in some cases, have been reported to cause cauda equina syndrome and paraparesis (6,7).

The main focus of treatment revolves around identifying and addressing the underlying cause of hyperparathyroidism through surgical resection or pharmacological management aimed at restoring the function of the parathyroid glands responsible for the excessive production of parathyroid hormone (PTH) (8). In cases in which brown tumors cause pathological fractures, a surgical procedure is usually required to stabilize the affected bone.

Given the uniqueness of brown tumors, their clinical significance is notable. This case series presents 3 cases of brown tumors associated with secondary hyperparathyroidism due to chronic kidney disease, 2 of which cases showed that the initial clinical sign of hyperparathyroidism was the presence of a pathological fracture. The third case involves a patient who presented without fractures but with pain in the lower extremity, followed by a CT scan that revealed the presence of an osteolytic lesion, and later sustained an associated pathological fracture. These cases were managed at a referral hospital in southwestern Colombia in 2023.

CASE REPORTS

The patients included in this series met the following criteria:

1. Clinical documentation of hyperparathyroidism.
2. Documentation of the presence of brown tumors, excluding the possibility that these lesions were due to bone metastases.
3. Presence of an associated pathological fracture.

CASE REPORT #1

A 39-year-old man with a 10-year history of chronic kidney disease due to polycystic kidney disease, on renal replacement therapy for the past 9 years on a 3 times per week regimen, with nephrology follow-up every 4 months. However, he reports difficulty accessing health care due to remote residence and socioeconomic conditions. Additionally, he has a 15-year history of hypertension and left hip fracture due to high-impact trauma from a traffic accident, which was surgically treated with a short cephalomedullary nail.

He fell from his own height, sustaining a direct trauma to his left hemipelvis and leg, resulting in an inability to stand, left thigh pain, and deformity. Upon admission to the center, a biochemical profile was obtained, revealing significant hypercalcemia and markedly elevated PTH (2306 pg/mL).

An anteroposterior X-ray of the left femur showed the previously described hip osteosynthesis material, a large osteolytic lesion involving the middle and distal thirds of the femur with a displaced diaphyseal fracture of the distal third of the left femur (Fig. 1). These findings confirmed the presence of hypercaptation in the skull, mandible, axial, and appendicular skeleton, with absence of renal silhouettes, and lytic lesions in the left femur and right tibia with an associated pathological fracture in the left femur.

The patient underwent open reduction, biopsy, and internal fixation of the fracture (Fig. 1). Immunohistochemical staining confirmed the suspected diagnosis. Subsequently, a parathyroidectomy was performed. However, the patient developed hungry bone syndrome with a fatal outcome.

CASE REPORT #2

A 66-year-old woman with a 15-year history of chronic kidney disease due to diabetic nephropathy, on a 10-year regimen of renal replacement therapy. Additionally, she had a history of hypertension, dyslipidemia, osteopenia, and moderate dependency

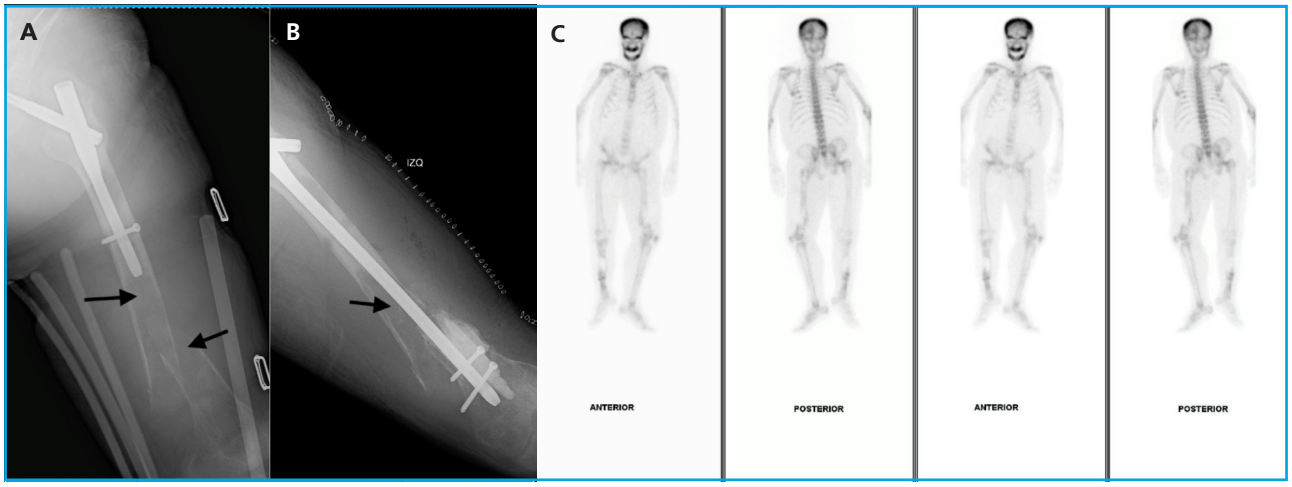

Figure 1. A. Plain X-ray of the left femur in an anteroposterior projection showing a diaphyseal fracture and osteolytic lesions at the fracture site. B. Plain X-ray of the postoperative femur. C. Bone scan performed with technetium showing hypercaptation in the skull, jaw, axial, and appendicular skeleton.

for activities of daily living (Barthel index, 65 points; Lawton and Brody scale, 6 points) due to sequelae from a fall 5 years prior with trauma to the left hemibody. However, she reports not seeking hospital care due to socioeconomic difficulties. Her family notes that after 1 year of being bedridden, she was gradually able to walk with a walker.

She fell from her own height, sustaining trauma to the right hemibody, resulting in right groin pain, inability to stand, and inability to mobilize the right lower limb.

She was admitted to the ER with a 2 cm shortening of the right lower limb vs the contralateral limb, and the affected limb was externally rotated. An anteroposterior X-ray of the pelvis revealed an old untreated fracture in the left femur with signs of callus formation and varus deformity, and a Garden III intracapsular transcervical fracture of the right hip with an osteolytic lesion in the greater trochanter of the left femur (Fig. 2A). Afterwards, due to the osteolytic lesion, the contrast-enhanced CT scan of the hip revealed the above-mentioned fracture with callus formation in the left hip and the transcervical fracture of the right hip (Fig. 2A). Given the patient's past medical history, further tests were performed, revealing PTH levels of 1560 pg/mg.

An orthopedic oncology consultation was requested due to the presence of osteolytic lesions that posed a risk of pathological fractures, and given the patient's age, bilateral total hip arthroplasty was recommended. However, due to surgical risk and multiple comorbidities, a decision was made to perform right hip arthroplasty in the first surgical act. Postoperatively, with contralateral hip pain, an X-ray was revealed the presence of a well-positioned right hip prosthesis and a transcervical refracture of the left hip associated with an osteolytic lesion in the ipsilateral proximal metaphysis that had gone unnoticed (Fig. 2B). Left hip arthroplasty was performed uneventfully, and the postoperative X-ray revealed well-positioned bilateral hip prostheses (Fig. 2B).

The femoral heads were sent for histopathological examination, which reported renal osteodystrophy, confirming the suspected diagnosis of a brown tumor. Four days after surgery, the patient began experiencing intense pain in her left knee without associated trauma, which prompted a femur X-ray that revealed the presence of a fracture in the distal metaphysis of the ipsilateral femur (Fig. 2B). A left knee X-ray revealed the presence of an osteolytic lesion in the left femur distal metaphysis with an associated pathological fracture (Fig. 2B). The CT scan of the left knee revealed multiple lytic lesions in the distal femoral metaphysis and diaphysis (Fig. 2B).

The primary pathology was prioritized, and the patient was evaluated by endocrinology and head and neck surgery, who considered her eligible for parathyroidectomy. However, the patient refused surgical treatment and signed a voluntary hospital discharge form.

CASE REPORT #3

A 33-year-old woman with an 8-year diagnosis of chronic kidney disease due to lupus nephropathy, on a 4-year regimen of renal replacement therapy, with

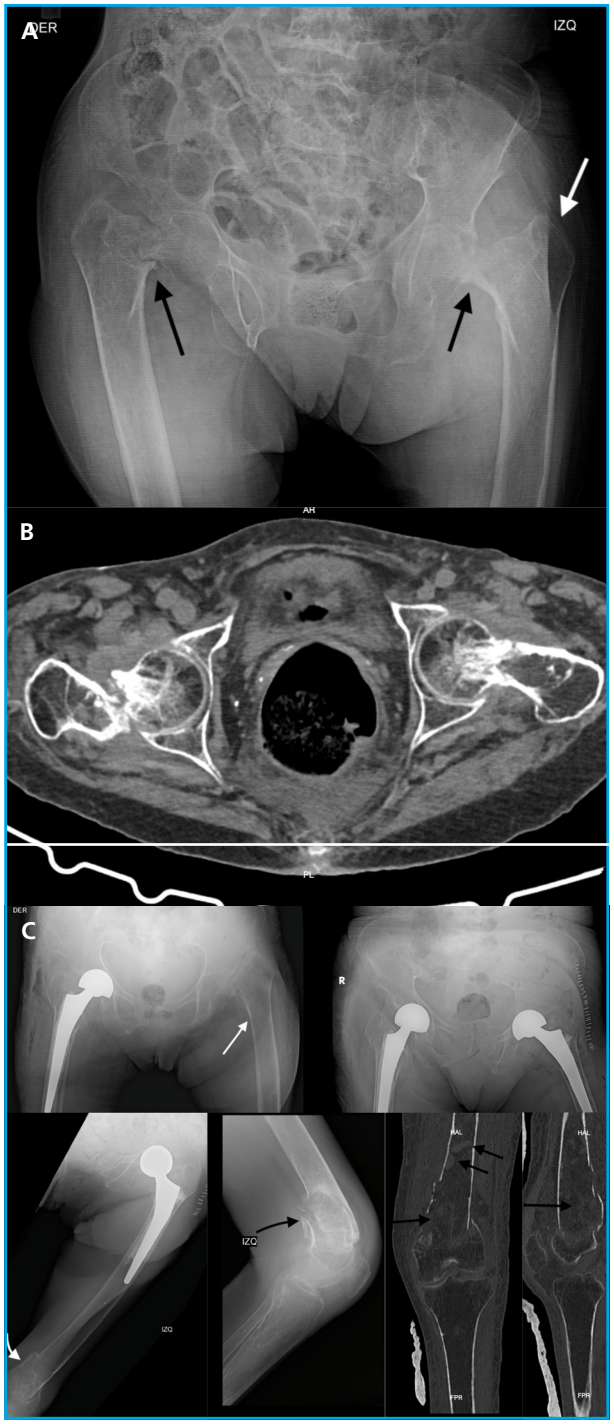

Figure 2. Panel A (upper): anteroposterior plain X-ray of the pelvis. Old fracture in the left femur and signs of callus formation with varus deformity. Transcervical intracapsular fracture of the right hip (Garden III) with an osteolytic lesion in the greater trochanter of the left femur. Panel A (lower): axial CT scan of the hip. Transverse section. Panel B (upper left): plain X-ray of the pelvis with a total right hip replacement. Transcervical refracture of the left hip. Panel B (upper right): bilateral hip replacement. Panel B (lower left): lateral plain X-ray of the knee showing lytic lesions. Panel B (lower right): transverse section of an axial CT scan of the knee.

the last lupus flare 5 months prior to the clinical presentation.

She presented to the orthopedic outpatient clinic with a 4-month history of persistent pain in the proximal region of her right thigh, with increased volume vs the contralateral side, but without limitation in passive or active range of motion. The comparative hip CT scan revealed the presence of an osteolytic lesion in the proximal right femur (Fig. 3), with high suspicion of secondary hyperparathyroidism due to chronic kidney disease given her history. However, due to the patient's age and low risk of pathological fractures

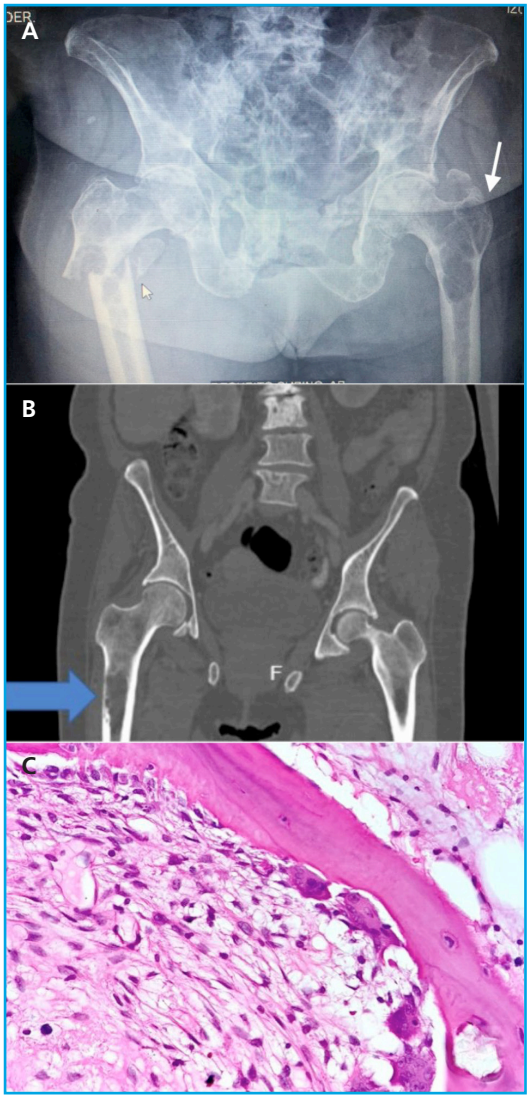

Figure 3. A. Anteroposterior plain X-ray of the pelvis showing a subtrochanteric fracture of the right femur and an osteolytic lesion in the greater trochanter of the contralateral femur. B. Comparative hip CT scan showing an osteolytic lesion in the right proximal femur. C. Histological section of hip bone stained with hematoxylin and eosin, compatible with renal osteodystrophy.

calculated by extrapolation of the Mirels scale—originally used for bone metastases—surgery was initially deemed unnecessary.

However, given the patient's socioeconomic condition, which hindered periodic follow-up, she was admitted through the ER, evaluated by Nephrology and Head and Neck Surgery, where parathyroidectomy was recommended. While awaiting the procedure, 30 days later, the patient sustained a fall from her own height with trauma to her right hip. A new X-ray confirmed the presence of a subtrochanteric fracture of the right femur, along with an osteolytic lesion in the greater trochanter of contralateral femur (Fig. 3).

She was admitted through the ER, and the next day, she underwent open reduction and internal fixation of her right femur (Fig. 3). Subsequently, parathyroidectomy was performed uneventfully. She continued with a normal rehabilitation program and follow-up by Nephrology and Endocrinology. After 6 months, new images were obtained showing adequate fixation and consolidation of the fracture without signs of loosening or increased lytic lesions (Fig. 3).

DISCUSSION

Brown tumors constitute a severe and localized manifestation of osteitis fibrosa cystica (OFC). They result from elevated levels of parathyroid hormone (PTH), leading to increased bone resorption rates. This bone is replaced by fibrous tissue and vascular spaces filled with hemosiderin-laden macrophages, giving the lesion its characteristic brown color (2,9).

The cause of these tumors is hyperparathyroidism, which can be categorized as primary when due to hyperactivity of ≥ 1 parathyroid glands, often explained by a benign tumor (adenoma) or glandular hyperplasia; secondary when they are the result of chronic kidney disease (CKD) or vitamin D deficiency (due to reduced calcium absorption leading to increased PTH secretion); and tertiary when they develop in patients with long-standing secondary hyperparathyroidism, characterized by autonomous hypersecretion of PTH even after correction of the underlying cause (10).

Several risk factors are associated with an increased risk of developing these conditions, including age, sex, comorbidities, and certain drugs. Epidemiologically, they are more frequent in elderly patients, particularly those older than 50 years, with peak incidence rates in the 6th and 7th decades of life. This may be explained by age-related renal function impairment, which comprehensively impacts all kidney functions, including the ability to regulate calcium and phosphorus metabolism (11).

A study by Jat et al. (2016) stated that the prevalence of OFC in CKD was 32 %. Some studies have suggested that PTH production and other factors, such as activation of the renin-angiotensin-aldosterone system, cytokine production, and increased growth factor expression may play a role in the pathogenesis of these conditions (12).

Core needle biopsy is the gold standard for diagnosing brown tumors, in which the typical histological finding is clustered osteoclasts on a hemorrhagic fibrotic background (13). Diagnosis is crucial, as differential diagnoses include giant cell tumor, giant cell reparative granuloma, or aneurysmal bone cyst, each with a different prognosis and treatment plan (13).

The etiology of hyperparathyroidism should always be established to define the best therapeutic plan. Parathyroidectomy is considered the gold standard to control primary cases. However, hypocalcemia is a common postoperative complication. Sometimes, it occurs rapidly, profoundly, and lasts more than 4 days, and is associated with hypophosphatemia and hypomagnesemia, a presentation known as hungry bone syndrome (14).

As an alternative to reduce the incidence of the post-parathyroidectomy hungry bone syndrome, the use of bisphosphonates prior to surgery has been proposed. This intervention appears to reduce bone remodeling and attenuate hypocalcemia. Observational descriptive studies have been conducted with preoperative IV zoledronic acid, showing that it significantly reduces the need for IV calcium therapy and the length of postoperative hospital stay, making it a promising option to reduce the rate of hungry bone syndrome in patients with primary hyperparathyroidism (14). Additionally, in 2021, Pal et al. conducted a meta-analysis of observational descriptive studies, finding that preoperative zoledronic acid may be a viable and cost-effective option for reducing hungry bone syndrome in patients with primary hyperparathyroidism, potentially reducing the risk by up to 88 % (15).

However, since the focus of this article is patients with secondary hyperparathyroidism due to chronic kidney disease, it is noted that zoledronic acid is contraindicated in patients with this condition. The use of a single preoperative dose of denosumab is proposed as a great alternative; however, further studies are needed to explore this option (15).

In this article, 3 cases documented in 2023 at a referral hospital in southwestern Colombia were presented, where, in 2 of them, the cardinal presentation that led to the diagnosis of hyperparathyroidism was the presence of a pathological fracture, and in another, an osteolytic lesion was identified at the clinical follow-up, which led to a pathological fracture while awaiting parathyroidectomy. The aim is to emphasize

the importance of this disease, recognize that in some countries, follow-up of CKD patients is not exclusively performed by nephrologists due to socioeconomic factors, which involves a whole group of primary care physicians. The importance of systematically evaluating diagnostic images and suspecting brown tumors in patients presenting with musculoskeletal disease with a history of chronic kidney disease is highlighted to increase prevention, diagnosis, and treatment of hyperparathyroidism in early stages, thereby reducing the incidence of pathological fractures and associated morbidity.

CONCLUSIONS

Brown tumors are a rare clinical sign of prolonged hyperparathyroidism. Despite their potential consequences, this condition is not well-known due to its rare prevalence and clinical variability. Therefore, it is suggested that patients with chronic kidney disease should be evaluated for associated bone abnormalities. Management should be led by a nephrologist; however, in developing countries, the availability of specialists is limited. Thus, it is important to raise awareness among primary care physicians about the thorough investigation of this condition in at-risk populations.

Treatment involves addressing the underlying cause through parathyroidectomy, though this procedure carries significant risks, including the potential for developing hungry bone syndrome. The use of bisphosphonates in the perioperative period has been described, but the evidence is limited and mostly focused on primary hyperparathyroidism. We hope this article encourages further research, particularly in the study of drugs approved for patients with chronic kidney disease.

REFERENCES

1. Flores R, Lopes J, Caridade S. Secondary hyperparathyroidism presenting as a brown tumor: A case report and review of the literature. Cureus 2023;15(1):e33820. DOI: 10.7759/cureus.33820
2. Demay MB, Rosenthal DI, Deshpande V. Case 16-2008. N Eng J Med. 2008;358(21):2266-74. DOI: 10.1056/NEJMcpc0802020
3. Niederle BE, Schmidt G, Organ CH, Niederle B. Albert J and His Surgeon: A historical reevaluation of the first parathyroidectomy. J Am Coll Surg 2006;202(1):181-90. DOI: 10.1016/j.jamcollsurg.2005.03.036
4. Messina L, Garipoli A, Giordano FM, Ferrari U, Grippo R, Sarli M, et al. A patient with multiple brown tumors due to secondary hyperparathyroidism: A case report. Radiol Case Rep 2021;16(9):2482-6. DOI: 10.1016/j.radcr.2021.06.015
5. Selvi F, Cakarer S, Tanakol R, Guler S, Keskin C. Brown tumour of the maxilla and mandible: a rare complication of tertiary hyperparathyroidism. Dentomaxillofacial Radiology 2009;38(1):53-8. DOI: 10.1259/dmfr/81694583
6. Kampschreur LM, Hoogeveen EK, op den Akker JW, Beutler JJ, Beems T, Dorresteijn LDA, et al. A haemodialysis patient with back pain: brown tumour as a cause of spinal cord compression under cinacalcet therapy. Clin Kidney J 2010;3(3):291-5. DOI: 10.1093/ndtplus/sfq052
7. Messina L, Garipoli A, Giordano FM, Ferrari U, Grippo R, Sarli M, et al. A patient with multiple brown tumors due to secondary hyperparathyroidism: A case report. Radiol Case Rep 2021;16(9):2482-6. DOI: 10.1016/j.radcr.2021.06.015
8. Bellorin-Font E, Vasquez-Rios G, Martin KJ. Controversies in the management of secondary hyperparathyroidism in chronic kidney disease. Curr Osteoporos Rep 2019;17(5):333-42. DOI: 10.1007/s11914-019-00533-x
9. Kalathas T, Kalatha T, Boultoukas E. Brown tumors; a possible pitfall in diagnosing metastatic disease. Hell J Nucl Med 2010;13(1):15-7.
10. Seyedzadeh A, Tohidi MR, Golmohamadi S, Omrani HR, Seyedzadeh MS, Amiri S, et al. Prevalence of renal osteodystrophy and its related factors among end-stage renal disease patients undergoing hemodialysis: report from Imam Reza Referral hospital of medical university of Kermanshah, Iran. Oman Med J 2022;37(1):e335-e335. DOI: 10.5001/omj.2021.120
11. Jervis L, James M, Howe W, Richards S. Osteolytic lesions: osteitis fibrosa cystica in the setting of severe primary hyperparathyroidism. BMJ Case Rep 2017:2017:bcr2017220603. DOI: 10.1136/bcr-2017-220603
12. Jat JA, Mal P, Kumar D. Renal osteodystrophy in end stage renal failure patients on maintenance haemodialysis. J Clin Exp Nephrol 2016;01:04.
13. Misiorowski W, Czajka-Oraniec I, Kochman M, Zgliczyński W, Bilezikian JP. Osteitis fibrosa cystica—a forgotten radiological feature of primary hyperparathyroidism. Endocrine 2017;58(2):380-5. DOI: 10.1007/s12020-017-1414-2
14. Witteveen JE, van Thiel S, Romijn JA, Hamdy NAT. therapy of endocrine disease: Hungry bone syndrome: still a challenge in the post-operative management of primary hyperparathyroidism: a systematic review of the literature. Eur J Endocrinol 2013;168(3):R45-53. DOI: 10.1530/EJE-12-0528
15. Pal R, Gautam A, Bhadada SK. Role of bisphosphonates in the prevention of postoperative hungry bone syndrome in primary hyperparathyroidism: A meta-analysis and need for randomized controlled trials. Drug Res 2021;71(02):108-9. DOI: 10.1055/a-1325-0351