SEVERE BONE DEFORMITIES IN PRIMARY HYPERPARATHYROIDISM

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Abstract. *The classic description of primary hyperparathyroidism (PHPT) is as a disease of kidney stones and bones. However, the clinical manifestation of osteitis fibrosa cystica with severe bone changes is rare in modern medicine. We present a clinical case of a 30-year-old man with severe bone deformities of the long bones, scoliosis, brown tumors and severe osteoporosis. At the time of the diagnosis, he has the classic biochemical and hormonal picture of primary hyperparathyroidism: severe hypercalcemia, hypophosphatemia, and significantly elevated parathyroid hormone values. The changes were temporarily affected after surgical treatment of the parathyroid adenoma. After a four-year loss to follow-up, the patient presented with worsening symptoms and hypercalcemia, possibly due to incomplete tumor removal. The bone changes are debilitating and imply incomplete reverse development, considering their severity and duration. Comparison is made with other similar cases in the literature.*

Key words: *hyperparathyroidism, bone deformities, osteitis fibrosa cystica*

Introduction

Bone involvement in severe and persistent hyperparathyroidism was classically described as osteitis fibrosa cystica (OFC) in the late 19th century [1]. It includes pronounced subperiosteal bone resorption leading to the formation of cyst-like cavities and brown tumors, increased fracture risk, skeletal deformities, and disturbances in calcium-phosphate metabolism. OFC can develop with persistently elevated parathyroid hormone (PTH) levels in the settings of primary, secondary, and tertiary hyperparathyroidism [2].

Primary hyperparathyroidism (PHPT) is a disease of the parathyroid glands with increased production of PTH (autonomic hypersecretion) and high or high-normal calcium [3]. The most common are the sporadic forms, due to an adenoma of one of the parathyroid glands in 85-90% [4]. Multiple adenomas, parathyroid carcinoma, as well as familial forms within the syndromes of multiple endocrine neoplasia (MEN I and MEN IIA), etc., are rarer causes.

Primary hyperparathyroidism is more common in women and over the age of 50. In recent decades, there has been a change in the clinical manifestation of primary hyperparathyroidism with predominance of asymptomatic forms, including normocalcemic and normohormonal forms. The inclusion of serum calcium in the routine biochemical panel is thought to be a major reason for the shift in prevalence of PHPT from symptomatic to asymptomatic (early) forms. In Denmark, for example, for the period from 1977 until 1990 a relatively constant incidence of PHPT was reported, after which there was a 3-fold increase in men and a 5-fold increase in women by 2010 [5]. A Scottish study involving a population of 400,000 individuals (Tayside Cohort) showed a steadily increasing incidence of PHPT from 0.71% in 2007 to 1.02% in 2018 [6]. Another factor for the increasing prevalence is the more frequent testing of PTH, vitamin D, calcium and phosphorus in individuals with osteoporosis. Thus, normocalcemic forms with high levels of parathyroid hormone and normal calcium are often discovered [7]. These trends lead to much earlier detection and treatment of hyperparathyroidism in countries with developed health care. That is why severe forms of osteitis fibrosa cystica with skeletal deformities are an extremely rare finding nowadays.

Clinical Case Description

In the present clinical case, we present a 30-year-old man who was admitted to the University Hospital "Sv. Marina" Varna in 2020, with complaints of the appearance of a tumor-like formation in the right neck region, originating from the mandible and bone deformities. After a careful history taking, it turns out that the pain in the spine and the appearance of scoliosis dated back to the age of 15, when he also experienced a fracture of the left tibia. At the age of 25, a decrease in height was also recorded.

The patient reported joint pain since the age of 13 involving small and large joints of the upper and lower extremities, which necessitated the use

of non-steroidal anti-inflammatory drugs for a period of 6 months during adolescence. As a result, he had a hemorrhage from a gastric ulcer, for which he was operated in the same year.

On admission into the clinic of endocrinology, the physical status was striking, with a pronounced right maxillofacial deformity with bone hardness, painless on palpation. Scoliosis of the spine was evident with a pronounced gibbus, deformed knee and elbow joints, thickened wrist joints. A limited mobility was observed. The phalanges of both hands were deformed, the distal phalanges being shortened and thickened, with pseudoclubbing.

Laboratory tests showed a constellation characteristic of primary hyperparathyroidism (Table 1), and neck ultrasound demonstrated a visible lesion with a typical appearance of a parathyroid adenoma, 15/24 mm in size, most likely of the lower right parathyroid gland. (Figure 1). Additionally, the patient had evidence of nephrocalcinosis and chronic kidney disease stage II according to KDIGO. In view of the established diagnosis, confirmed also by a TC^{99m} SESTAMIBI scan, he was referred for surgical parathyroidectomy.

Postoperatively, there was a significant decrease in the values of parathyroid hormone (PTH), total and ionized calcium, presented in table 1, corresponding to the so-called “hungry bone syndrome” or recalcification crisis, suggesting successful treatment.

Initial improvement in biochemical parameters would suggest complete cure and correction of hyperparathyroidism with regression of biochemical abnormalities. After surgery, the patient was lost to follow-up for a period of four years. In 2024 he was admitted again to the endocrinology clinic with progression of complaints and skeletal deformities in comparison to those from 2020, worsening renal function with eGFR 29 ml/min/1.73 m^2 (stage IV according to KDIGO).

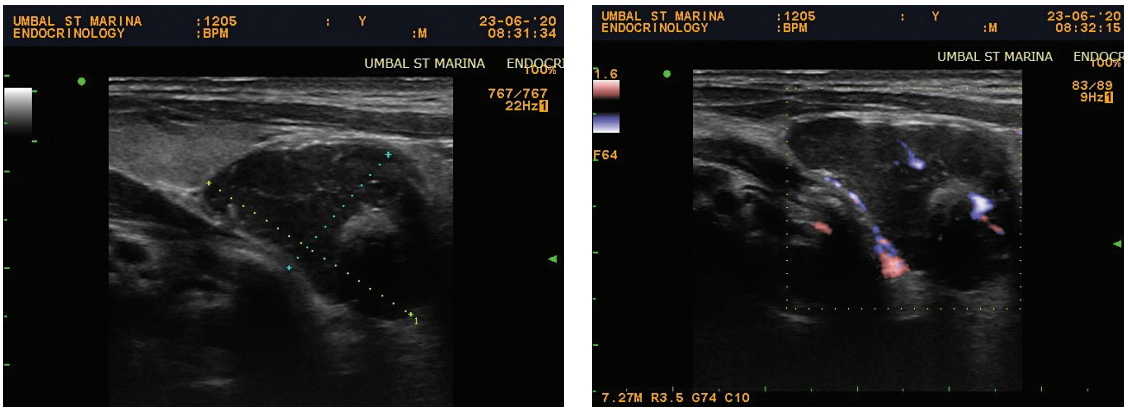


Fig. 1. Neck ultrasonography. A hypoechoic vascularized formation is visible, 15/24 mm in size, with an irregular shape and heterogeneous structure, localized below the lower pole of the right thyroid lobe, in the typical location of the right inferior parathyroid gland

Table 1. Laboratory results during follow-up

Parameter	In 2020 At diagnosis	In 2020 Postoperatively	In 2024	Unit of measurement/ reference range
PTH	2049	71	2376	pg/ml (0-87)
β -cross laps	3.63	-	> 6	ng/ml (0.093-0.580)
alkaline phosphatase	1246	1117	682	U/l (< 150)
25-OH-Vitamin D	12.3	12.27	27.9	ng / ml
Ionized Ca2+	1.9	1.08	2.19	mmol/l (1.12-1.23)
Total calcium	3.57	2.03	4.06	mmol/l (2.12-2.62)
Phosphate	0.93	0.56	0.7	mmol/l (0.77-1.56)
Calciuria	6.10	-	8.62	mmol/24 h (2.5-7.5)
Phosphaturia	15.2	-	21.11	mmol/24 h (13-32)
Creatinine	137	141	250	mcmol/l
eGFR (CKD-EPI)	61	56	29	ml/min/1.73 m^2
Uric acid	496	408	777	mcmol/L

As a new finding, a gouty tophus on the first finger of the right hand was also established without accompanying joint crisis (Figure 2). The X-ray studies performed demonstrate the severe changes in the bone anatomy (Figure 3, Figure 4).

Radiographs showed osteolytic lesions in all long bones corresponding to brown tumors (Figure 2). The radius and ulna have a valgus deformity at their distal end and a varus deformity at the proximal end. X-rays of the hands show acroosteolysis and subluxations of the distal phalanges. DEXA bone mineral measurement was also performed, although it was difficult to interpret due to severe deformations of the spine and long bones. Pronounced osteoporosis is visible with dominant involvement for cortical bone: Z-score L1-L4 (-1.2); L2 (-1.6); femoral neck: Z-score total: (-2.2); Z-score femoral neck (-2.2); Z-score distal radius: (-4.2).

From the biochemical and hormonal indicators, there is persistent hypercalcemia with increased PTH values, hypophosphatemia and ultrasound data of a persistent/recurrent parathyroid formation under the lower pole of the right thyroid lobe. A therapeutic attempt was made to influence the high-grade hypercalcemia with rehydration, forced diuresis, administration of denosumab and the calcimimetic cinacalcet in preparation for reoperation. The result was a short-term and insufficient improvement – on the fifth day after the application of denosumab, a drop in ionized calcium to 1.52 mmol/l from the initial 2.19 mmol/l was registered. Additionally, a uric acid inhibitor (allopurinol) was initiated along with short-term low-dose colchicine (0.5 mg every other day for a 10-day period).

Discussion

The patient presented by us has a classical for the distant past course of primary hyperparathyroidism, with severe bone and joint changes, exceptional for our time. Although the case does not present a di-



Fig. 2. Multiple skeletal deformities on physical examination

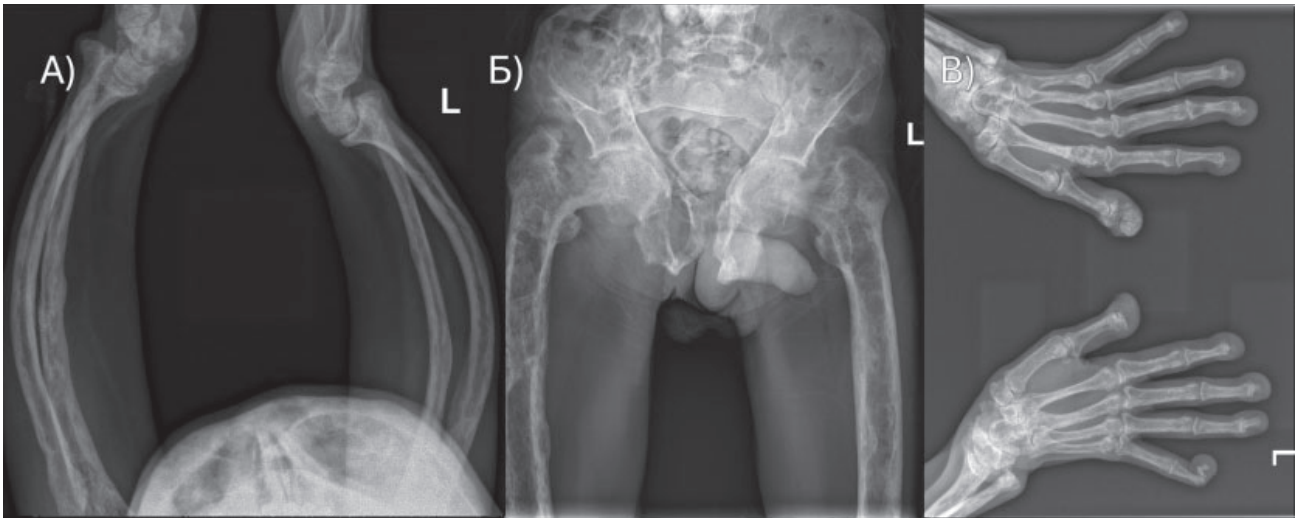


Fig. 3. X-Ray of A) radius and ulna bilaterally; B) femoral bones and pelvis; C) wrists and hands

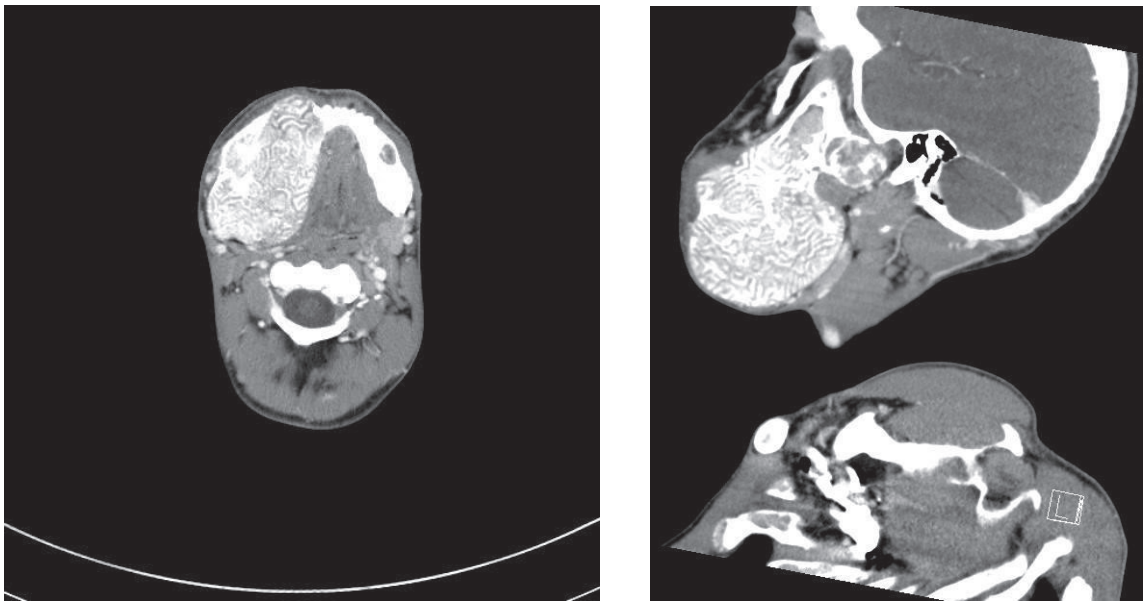


Fig. 4. CT imaging of a bone formation, originating from the right half of the lower jaw. Its bone structure is a point of interest. Osteolytic lesions of the type of osteitis fibrosa cystica are also visible contralaterally in the mandible

agnostic problem, it is of interest to the clinician due to the wide spectrum of pathologic changes and the unexpected recurrence after initial parathyroidectomy.

Bones, along with the kidneys and the gastrointestinal tract, are the main target organs affected in PHPT and leading to the clinical symptoms. PTH damage in target organs and tissues is mediated by the binding of PTH to its specific receptor PTH receptor type 1 (PTHR1), expressed on the cell surface of a large number of cells. The catabolic effect of PTH in bone is evident in patients with classical PHPT and have been demonstrated with continuous infusion of PTH in rodents8. Conversely, intermittent administration of PTH (1-34) has an anabolic effect and is used during the so-called “anabolic window” for osteoporosis treatment [9].

Of interest is the fact that despite the major expansion of osteoclasts in PHPT, leading to bone resorption, fractures, deformities and the formation of brown tumors, osteoclasts themselves do not express a receptor for PTH. The latter exerts its action mediated by osteoblasts on the surface of which there is PTHR1. PTH-PTHR1 binding in bone results in increased osteoblastic expression of RANKL (receptor activator of nuclear factor κappa-B ligand). RANKL binds to its receptor RANK on osteoclast precursors, stimulating their fusion, differentiation and activation resulting in bone resorption [8, 10].

The disease in the presented case had started already in adolescence with scoliosis, bone pain and fractures. Other authors also report similar severe skeletal deformities in cases with onset during childhood and adolescence [11, 12]. The nonspecific initial presentation and symptoms overlapping with rickets with low 25-OH-vitamin D levels could delay the correct diagnosis.

Usually, at the time of diagnosis of primary hyperparathyroidism, it is an asymptomatic or oligosymptomatic disease. This applies mostly to Europe and the USA [13]. In contrast, symptomatic forms with marked bone changes and deformities are more typical of health systems with poorer coverage, which lack universal serum calcium screening [14].

In general, the presence of target organ involvement (bone or kidney) and the early age of presentation require surgical treatment and removal of the parathyroid adenoma. In the presented case, there are all indications for operation [15]. After removal of the overproducing parathyroid tumor, an improvement in bone density and bone changes is expected, including reversal of “brown tumors”. In a case series, Agarwal et al. [16] followed 51 patients after parathyroidectomy. Their results demonstrated remineralization as early as the first week postoperatively, and an improvement in bone density during the first 3 months. In serial radiographs, the authors show an initial abnormal increase in the density of the brown tumors during the first 3 months, with subsequent “lightening” and partial regression in the size of the bone formations. This was accompanied by correction of bony deformities in 6 of 27 patients (22%).

Considering the extremely severe bone and joint changes in the case presented by us, a significant

improvement in bone density could probably be expected. On the other hand, reverse development of the gibbus, bony deformities and large jaw lesion seems unlikely in view of their severity and duration.

Another important point in the described case is the postoperative recalcification crisis, which should occur after successful removal of the parathyroid adenoma. In our clinical case, such a sharp drop in calcemia as well as in PTH levels postoperatively was reported. The rapid decrease in serum calcium is the result of the functional inhibition of the remaining healthy parathyroid glands. In cases of severe hyperparathyroidism, the development of this "hungry bone syndrome" can be expected. For this reason, replacement with active vitamin D and calcium is essential [17]. These initial changes suggest complete cure of the tumor, but the subsequent evolution of the disease in our patient points to incomplete removal.

Undertaking reoperation requires a certain preparation of the patient. It is essential that severe (in our case > 4 mmol/l) and even moderate hypercalcemia is a risk factor for the development of cardiac arrhythmias and a correspondingly higher operative risk. The calcium-lowering strategy undertaken with rehydration, loop diuretic, calcimimetic, and denosumab may be only partially effective until complete cure is achieved by surgery.

Conclusion

Modern and widespread diagnostic methods of conditions associated with hypercalcemia suggest easy and timely diagnosis of primary hyperparathyroidism. However, isolated cases with severe bone and joint changes occur in clinical practice. The present case highlights the importance of bone symptoms as the first, although sometimes nonspecific, manifestation of the disease. Primary hyperparathyroidism should be part of the differential diagnosis in radiographic evidence of osteolytic and cystic bone lesions.

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Постъпил за печат: 31.01.2025 г.

Submitted: 31.01.2025

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