C A S E R E P O R T

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Brown tumor of the mandible – a possible clinical manifestation of primary hyperparathyroidism

Smeđi tumor mandibule – moguća klinička manifestacija primarnog hiperparatireoidizma

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Abstract

Introduction. One of the possible manifestations of primary hyperparathyroidism (PHPT) is the appearance of a benign bone tumor. We hereby present a case of a young woman whose first clinical manifestation of PHPT was a brown tumor of the mandible. **Case report.** A 27-year-old female patient was hospitalized at the Clinic for Endocrinology, Diabetes, and Metabolic Diseases due to problems occurring in the form of nausea, exhaustion, the feeling of suffocation, dysphagia, pain in the right ear and the right half of the cheeks, with suspected PHPT. Initial laboratory findings pointed out the high levels of parathyroid (PT) hormone (PTH) and calcium (Ca^{2+}) ions, low levels of vitamin D, and increased parameters of bone metabolism with signs of osteopenia. Cone beam computed tomography revealed the presence of bilateral radiolucent lesions of the mandible. Scintigraphy verified a retrosternal hot focus consistent with PT adenoma. After parathyroidectomy was performed, there was a normalization of PTH values, bone metabolism parameters, and the Ca^{2+} values. Four months after parathyroidectomy, a significant regression of the mandibular tumefaction was confirmed, clinically and radiologically. **Conclusion.** Brown tumors are rare first clinical manifestations of PHPT. Owing to their histological similarities with other giant-cell lesions (GCLs), definitive diagnosis is sometimes difficult and is based on a correlation of pathohistological, radiological, and laboratory findings. Due to the spontaneous regression of bone lesions after treatment of the basic cause of PHPT, brown tumors should be considered in the differential diagnosis of any GCLs in order to avoid unnecessary surgical procedures.

Key words:
bone diseases, endocrine; diagnosis; giant cell tumors; hyperparathyroidism, primary; mandible.

Apstrakt

Uvod. Jedna od mogućih manifestacija primarnog hiperparatireoidizma (PHPT) jeste pojava benignog tumora koštanog tkiva. Prikazana je mlada žena kod koje je prva klinička manifestacija PHPT bila smeđi tumor mandibule. **Prikaz bolesnika.** Bolesnica stara 27 godina bila je hospitalizovana na Klinici za endokrinologiju, dijabetes i metaboličke bolesti zbog tegoba u vidu mučnine, iscrpljenosti, osećaja gušenja, otežanog gutanja, bola u desnom uhu i desnoj polovini obraza, sa sumnjom na PHPT. Početni laboratorijski nalazi ukazivali su na visoke nivoe paratireoidnog (PT) hormona (PTH) i jona kalcijuma (Ca^{2+}), nizak nivo vitamina D, kao i povišene vrednosti parametara koštanog metabolizma, sa znacima osteopenije. Kompjuterizovanom tomografijom konusnog zraka utvrđeno je bilateralno rasvetljenje u donjoj vilici. Scintigrafijom je potvrđeno prisustvo promene, retrosternalno, koja je mogla odgovarati adenomu PT žlezde. Nakon sprovedene paratireoidektomije, došlo je do normalizacije vrednosti PTH, parametara koštanog metabolizma i vrednosti Ca^{2+}. Četiri meseca nakon paratireoidektomije, potvrđena je, klinički i radiološki, značajna regresija tumefakcije donje vilice. **Zaključak.** Smeđi tumori su retka prva klinička manifestacija PHPT. Zbog njihove patohistološke sličnosti sa drugim gigantocelularnim tumorima, postavljanje definitivne dijagnoze je nekada teško i zasniva se na korelaciji patohistološkog, radiološkog i laboratorijskog nalaza. S obzirom na to da nakon izlečenja PHPT dolazi do sponatne regresije lezija u kosti, smeđi tumori bi trebalo da budu razmotreni u diferencijalnoj dijagnozi svih gigantocelularnih lezija, kako bi se izbegao nepotreban hirurški tretman.

Ključne reči:
kosti, endokrine bolesti; dijagnoza; tumor gigantskih ćelija; hiperparatireoidizam; mandibula.

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Introduction

The incidence of diagnosis of primary hyperparathyroidism (PHPT) has been substantially growing since the early 70s when a routine biochemical analysis began to determine the level of serum calcium (Ca) and diagnose asymptomatic patients (catch-up effect). Epidemiological studies suggest that the majority of patients (80%) have asymptomatic disease, while the classical clinical presentation, such as hypercalcemic syndrome, nephrolithiasis, osteoporosis, and gastrointestinal and mental disorders, is rarely seen [1, 2]. Due to its effect on bone metabolism, PHPT can also manifest itself as a type of pseudo-tumor – a brown tumor (BT) of bone – which appears in the advanced stages of the disease. We hereby present a case of a young woman whose first clinical manifestation of PHPT was BT of the mandible.

Case report

A 27-year-old female patient was hospitalized at the Clinic for Endocrinology, Diabetes, and Metabolic Diseases, University Clinical Center of Vojvodina, Serbia due to nausea, exhaustion, feeling of suffocation, dysphagia, and pain in the right ear and the right half of the cheeks, which appeared a month before. Five years earlier, the patient was followed up for a tumor on the left side of the mandible. Biopsy and excision of tumefaction were performed, and pathohistological findings determined that it was a giant-cell lesion (GCL). After the operation, hormonal testing was planned, but the patient did not show up for the follow-up exams. The family history was positive for nephrolithiasis.

Initial clinical examination found lower right facial deformity, with approximate dimensions 40 × 30 mm, without changes of the skin above. From the intraoral side, in the region of the right mandible, there was a tumefaction, with necrosis and granulation tissue, about 30 mm in diameter (Figure 1). In the diagnostic algorithm, X-ray and cone beam computed tomography were performed, and the presence of bilateral radiolucency in lateral segments of the mandible was observed. There was evidence of severe osteolysis of the right mandible, with root resorption of the first molar. In addition, there was a partial recurrence of the previous tumor in the left mandible, in the region beneath the lower left incisors and canines (Figures 2 and 3).

Laboratory findings pointed to PHPT with significantly increased bone turnover (Table 1). The performed bone densitometry discovered osteopenia (Z-score: L1–L4 -2.2,

Fig. 1 – The image on the left depicts the initial intraoral clinical finding. The image on the right shows the intraoral finding after the tumor biopsy.

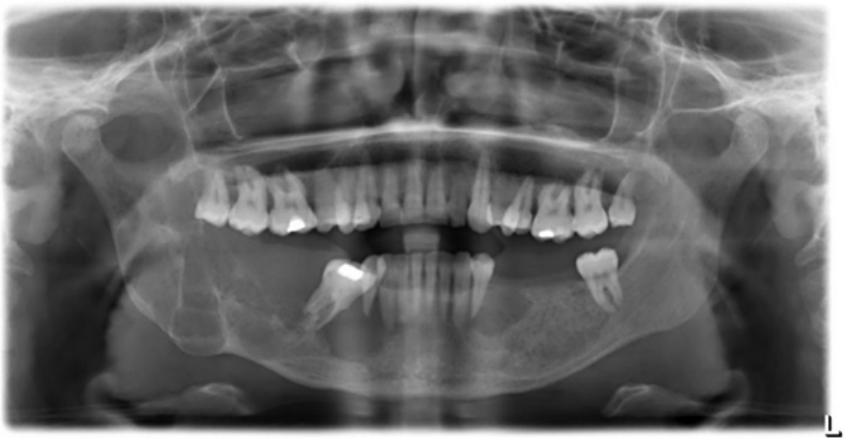

Fig. 2 – Initial state X-ray (orthopantomogram). On the right side of the mandible, tumefaction is poorly delineated, with a breach of cortical bone. There is no periosteal reaction, and there is dislocation of the right lower molar tooth with partial root resorption. On the left side, the osteolytic lesion is confined to the region beneath the lower incisors and canine. There is good delineation from the rest of the mandible. Laterally, there is evidence of previous cystic formation that has healed.

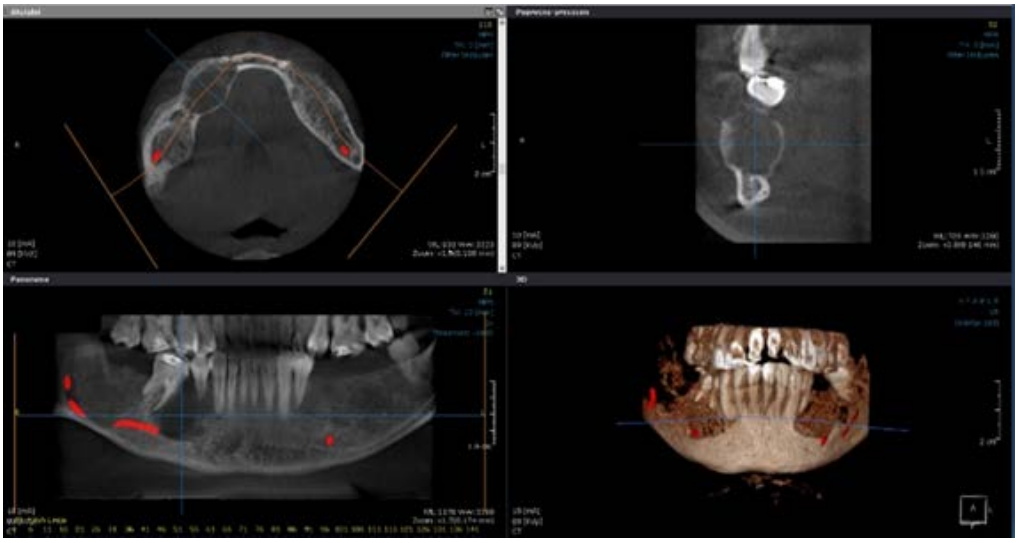

Fig. 3 – The initial appearance of the lesion on cone beam computed tomography in the region of the right side of the mandible.

Table 1

Laboratory findings before and after surgery

Parameters	Reference range	Before surgery	After surgery		
			5 days	2 months	6 months
Ca (mmol/L)	2.10–2.60	3.4	2.15	2.11	2.45
Ca^{2+} (mmol/L)	0.95–1.35	1.75	1.07	1.07	1.29
P (mmol/L)	0.74–1.52	0.78	1	1.24	0.97
ALP (U/L)	30–115	141	100	91	89
PTH (pg/mL)	14–72	1,290	126.3	43	83.2
Cross Laps (pg/mL)	162–436	2,911	707	692	399
P1NP (g/mL)	10–55.7	233.8	594.2	140.7	31.8
25(OH)-D total (nmol/L)	30–150	29	36	22.45	69

Ca – total calcium; Ca^{2+} – ionized calcium; P – phosphorus; ALP – alkaline phosphatase; PTH – parathyroid hormone; Cross Laps – cross-linked C-telopeptide of type I collagen; P1NP – procollagen type 1 N propeptide; 25(OH)-D – 25-hydroxy vitamin D.

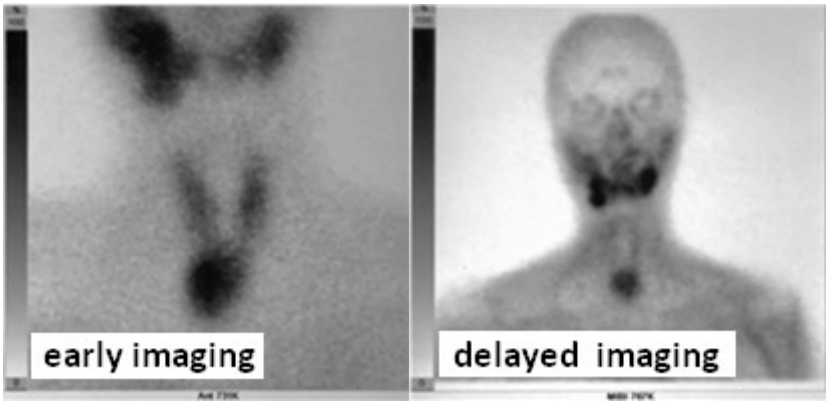

Fig. 4 – Scintigraphy of parathyroid glands (99mTc-MIBI). The early imaging shows the radioactive concentration at the site of the anterior mediastinum. The delayed imaging shows that it did not degrade.

femur: neck -2.0, total -2.2). Ultrasound examination of the abdomen verified nephrolithiasis in the right kidney. Moreover, the ultrasound examination of the thyroid and parathyroid (PT) glands discovered a focal, oval hypo-echogenic nodule near the inferior pole of the right thyroid lobe, at the superior entrance of the anterior mediastinum, measuring 32 × 13 mm (antero-posterior × latero-lateral diameter). Scintigraphy of the PT glands revealed more focal changes in the projection of the anterior mediastinum, which could match the localized ectopic adenoma/hyperplasia of the PT gland (Figure 4). PHPT was treated surgically by removing the upper and lower right PT glands. Laboratory findings

Fig. 5 – Clinical finding two months after parathyroidectomy. Significant regression of the tumor was noticed.

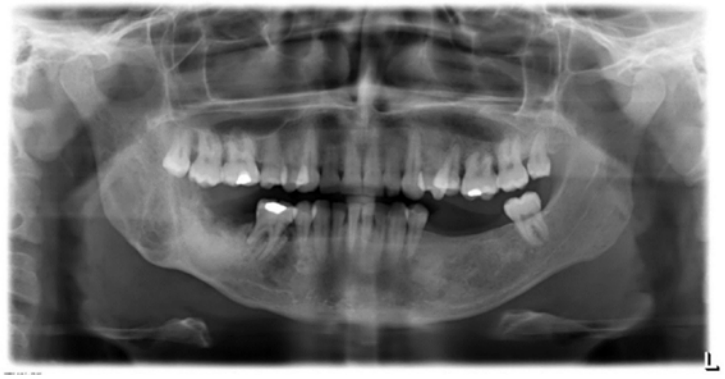

Fig. 6 – Control X-ray (orthopantomogram) four months after parathyroidectomy. There are signs of new bone formation and almost complete resolution of cystic tumefaction on both sides of the mandible.

were taken in different time periods – a couple of days, two months, and six months postoperatively, and they are shown in Table 1. Due to low levels of vitamin D, replacement therapy was introduced, followed by normalization of bone turnover. Two months after parathyroidectomy, there was significant regression of the tumor (Figure 5). Despite the significant reduction in the tumor masses, six months following parathyroidectomy, the oral surgeon decided to remove part of the tumor tissue that protruded beyond the borders of the alveolar ridge. Pathohistological findings reaffirmed that it was a GCL. Even though the lesion was large at the beginning, after treating the cause of PHPT, there was almost complete resolution of the lower jaw lesion with slight residual deformity of the alveolar ridge (Figure 6) that did not require any further operative corrections. The patient was absolutely satisfied with the functional and aesthetic outcomes.

Discussion

PHPT is a common endocrine disorder that affects one out of 500 women in the third and after the sixth decade of life. In 85% of cases, it is caused by a PT adenoma; in 15% of cases, it is caused by multiple gland disease (multiple adenomas or hyperplasia), while it is rarely a result of PT carcinoma. Familial cases may occur as a part of multiple endocrine neoplasia (MEN) 1, MEN 2a, hyper-PT jaw tumor syndrome, or familial isolated hyperparathyroidism [1–3]. Due to the rare occurrence of bone manifestations of PHPT, especially as the first sign [4], it is hard to distinguish PHPT bone changes from other osteolytic lesions. We describe a case of PHPT in which the first clinical manifestation of the disease was BT of the mandible. GCL in the jaws includes several types of lesions whose common microscopic characteristic is the presence of gigantic multinucleate cells in the vascular stroma. These lesions exhibit different behaviors, from benign to malignant and locally aggressive behavior, and sometimes, it is quite difficult to classify them only based on the microscopic findings. We are familiar with the pathohistological description of GCLs since the 1940s, and nowadays, they include peripheral giant-cell granuloma, central giant-cell granuloma, giant-cell tumor, BT in hyperparathyroidism, aneurysmal bone cysts, and cherubism [5]. Histological features of a BT are characterized by the replacement of bone marrow with loose, richly vascularized connective tissue. In the remaining cancellous bone, there is increased osteoclast activity. Due to the weakening of the bone, there are on-site microfractures, with consecutive hemorrhage and abundant hemosiderin pigment deposits that give the tumor its characteristic brown color [6]. Purely based on the pathohistological examination, the distinction between BT and giant cell tumor

is extremely difficult, and the key issue for a correct diagnosis is the correlation of clinical, laboratory, and radiological findings, as was in our case.

As a result of hyperparathyroidism, BT occurs in the incidence rate range from 1.5 to 4.5%, three times more frequently in females, especially after 50 years of age [7, 8], and in less than 2% of patients with PHPT [9]. According to the literature, common structures affected by BT are facial bones, long bones, ribs, clavicle, and pelvis. BT can develop in any bone and any stage of PHPT; however, it rarely appears as the initial sign of the disease [10]. In our case, BT was the first sign of PHPT at the moment when other extra-skeletal manifestations were not verified.

The treatment of choice for GCL depends on its etiology. GCL that is not associated with PHPT requires surgical excision of the lesion itself. On the other hand, for the giant cell tumor associated with PHPT, primary treatment is focused on the diagnosis and treatment of the basic cause of PHPT. In most cases, adenoma of PT glands is found as a source of PHPT and is treated by parathyroidectomy [11]. After normalization of hormonal changes, complete resolution of bone lesions can be expected. Since the regression rate of tumor changes depends on the scope of the change, which is proportional to the length of PHPT, it is necessary to diagnose PHPT in the shortest period of time [8, 12].

Based on our knowledge, this is a rare case of a young person having a large tumor of the mandible as a first clinical manifestation of PHPT, especially nowadays, when serum Ca^{2+} levels are routinely measured and PHPT has evolved into a typically asymptomatic disease.

Conclusion

GCLs, such as BTs, associated with PHPT are a non-typical clinical manifestation of the disease. Because of their microscopic similarities, histological differentiation between BTs and GCLs is very difficult, and definitive diagnosis is based on radiological findings of typical localization of the bone lesion, as well as laboratory findings of elevated Ca and PTH levels. Due to their spontaneous regression after treatment of the basic cause of PHPT, BTs should be considered in the differential diagnosis of any GCLs to avoid unnecessary surgical procedures in the mandible.

REFERENCES

1. *Kim LT*. Hyperparathyroidism [Internet]. 2020. Available from: https://emedicine.medscape.com/article/127351-overview#a3 [accessed 2022 July 22].
2. *Rai S, Rattan V, Bhadada SK*. Giant Cell Lesions Associated with Primary Hyperparathyroidism. J Maxillofac Oral Surg 2015; 14(4): 930–4.
3. *Bojković G, Caparević Z, Stojanović D, Lalosević D, Stojanović M*. Case report: parathyroid gland adenoma. Med Pregl 2003; 56(7–8): 377–80. (Serbian)
4. *Mahfoudhi M, Khamassi K, Battikh AG, Lahiani R, Sami T, Salah MB*. Brown tumor of the maxilla revealing primary hyperparathyroidism. Int J Clin Med 2015; 6(4): 252.
5. *Vera L, Dolcino M, Mora M, Oddo S, Gualco M, Minuto F,* et al. Primary hyperparathyroidism diagnosed after surgical ablation of a costal mass mistaken for giant-cell bone tumor: a case report. J Med Case Rep 2011; 5(1): 1–6.
6. *Ohi LG, da Cunha IW, Santini-Araujo E, Kalil RK.* "Brown Tumor" of Hyperparathyroidism. In: *Santini-Araujo E, Kalil RK, Bertoni F, Park YK,* editors. Tumors and Tumor-Like Lesions of Bone. London: Springer; 2015. p. 815–25.
7. *Thomas S, Nair P, Hegde K, Neelakantan S*. A bilaterally recurring exophytic mass on the lower jaw. BMJ Case Rep 2011; 2011: bcr0920103362.
8. *Zhong Y, Huang Y, Luo J, Ye Y*. Misdiagnosis of brown tumour caused by primary hyperparathyroidism: a case report with literature review. BMC Endocr Disord 2022; 22(1): 66.
9. *Walker MD, Bilezikian JP*. Primary Hyperparathyroidism. 2021. In: *Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E,* et al, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com Inc; 2000.
10. *Xu B, Yu J, Lu Y, Han B*. Primary hyperparathyroidism presenting as a brown tumor in the mandible: a case report. BMC Endocr Disord 2020; 20(1): 6.
11. *Stefanović D, Petrović M, Dugonjić S*. The accuracy of ultrasonography for detection of enlarged parathyroid glands in patients with different forms of hyperparathyroidism. Vojnosanit Pregl 2020; 77(12): 1277–88.
12. *Mittal S, Gupta D, Sekhri S, Goyal S*. Oral manifestations of parathyroid disorders and its dental management. J Dent Allied Sci 2014; 3(1): 34–8.

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