Brown tumors of the oral cavity: presentation of 4 new cases and a systematic literature review

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Objective. The aim of this study was to obtain data from a review of cases of brown tumors (BT), which are benign lesions of bone characterized by giant cells that arise during hyperparathyroidism (HPTH). BTs may affect the maxillofacial area and manifest as a brownish, slow-growing swelling causing difficulty in the differential diagnosis.

Study Design. We present data from 4 new cases of oral BTs based on a systematic literature review conducted by searching EMBASE, Medline, and CENTRAL databases, according to the PRISMA guidelines. Only articles in English were considered. Individual patient data were analyzed to identify risk factors for multiple or extraoral maxillofacial BTs.

Results. In total, 167 cases (163 from 136 articles and 4 new cases; mean age 36.6 years; male-to-female ratio 1:2) were retrieved. The onset of extraoral maxillofacial BTs (odds ratio [OR] 176.3; 95% confidence interval [CI] 18.7−1657.8; $P < .05$) and maxillary BTs (OR 17.5; 95% CI 6.0−50.8; $P < .05$) were the risk factors for multiple oral BTs, whereas the presence of a BT in the mandible (OR 0.01; 95% CI 0.001−0.1; $P < .05$) was a negative predictor for the presence of other extraoral maxillofacial BTs.

Conclusions. The results of this systematic review suggested that the mandible is the most frequent oral location of BTs. Whenever a BT is detected in the maxilla or when multiple oral BTs are diagnosed, more BTs in the maxillofacial area should be suspected.
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Oral manifestations of brown tumors (BTs) commonly appear as exophytic, painful, slow-growing lesions that can reach large dimensions, are hard on palpation, are fixed to the tissues underneath, and have a considerable tendency to bleed. Depending on their location and size, these lesions can affect chewing, dentition, and nasal patency. Although they are benign, BTs often show focal malignancy, with a tendency to infiltrate nearby areas. Radiographically, they appear as well-defined unilocular or multilocular radiolucent areas; dental root resorption, tooth displacement, and the absence of the lamina dura can also be observed in areas affected by the disease.[1-5] The lesions are often difficult diagnostic challenges because it is mandatory to differentiate them from other types of oral swelling and other giant cell lesions that can affect the oral cavity.[3] This article presents 4 new cases of BTs of the oral cavity, as well as a systematic review of other cases of BTs reported in the literature; an individual patient data analysis was conducted to provide assistance to clinicians in the diagnostic process.

BTs generally represent the last stage of hyperparathyroidism (HPTH) bone disease, called *osteitis fibrosa cystica*, which was described for the first time in 1891 by Von Recklinghausen. HPTH causes imbalance between osteoclastic and osteoblastic activities, promoting osteoclasts and leading to widespread bone resorption. Long-lasting HPTH causes BTs, which are focal osseous lesions characterized by bone cortex thinning and replacement of bone marrow with fibrous tissue. The clinical appearance of a brown lesion, from which the term *brown tumor* is derived, is attributed to large areas of hypervascularization with hemorrhage and hemosiderin deposits, which are typical of the lesion.[6]

In the past, BTs were very common and appeared in 80% of patients with HPTH. Over the past 20 years, the incidence of BTs has decreased considerably (< 10%) as a result of early diagnosis and more accurate control of HPTH.[7] HPTH is a clinical syndrome caused by excessive production of parathormone (PTH). Four types of HPTH can be distinguished: (1) primary or primitive HPTH caused by a primary disease of the parathyroid glands (mainly adenoma); (2) secondary HPTH resulting from a

Statement of Clinical Relevance

Differential diagnosis of oral manifestations of brown tumors, including oral swelling, is often difficult. This article presents 4 new cases and a review of existing cases in the literature to help clinicians in diagnostic and management procedures.

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reactive condition to chronic hypocalcemia; (3) tertiary HPTH caused by disarrangement of the parathyroids; and (4) quaternary HPTH caused by ectopic PTH secretion (malignancies can produce a PTH-related peptide [PTHrP]).[8]

Persistent high PTH levels may be responsible for skeletal changes, consisting of fibrous osteoclastic reactions. Imbalance between osteoblastic and osteoclastic activities causes bone resorption, cortex thinning, and replacement of bone marrow with fibrous tissue. Subperiosteal bone resorption of the phalanges, the absence of the dentoalveolar lamina dura, the presence of focal areas of demineralization in the skeleton, and generalized osteoporosis are the main bone manifestations of HPTH.

BTs are part of a general bone disease called *cystic fibrous osteitis*, and they are focal lesions that occur within areas of resorption.[6]

The most commonly affected bones are the ribs, clavicles, and pubis, and it has been reported that in 4.5% of cases, the jaws (especially the mandible) are also involved.[1] Bone involvement is almost always present, whereas peripheral variants are very rare.[9]

Microscopic examination of the lesions reveals a giant cell granuloma, characterized by dense fibrous stroma with fibroblasts, mononuclear cells with a possible monocytic nature, focal areas of osteoid tissue, cystic degeneration, hemorrhage, macrophages with phagocytized deposits of hemosiderin, and osteoclasts as giant multinucleated cells.[2]

CASE SERIES

This article presents data from 4 new cases of BTs of the oral cavity and a systematic review of other cases reported in the literature, as well as findings from data analysis of individual cases. Because the features of oral BTs can mimic many benign and malignant diseases, the findings from the analysis of the cases presented in the literature can assist clinicians with the differential diagnostic process.

Case 1

A 62-year-old woman with a previous diagnosis of parathyroid adenoma made 2 years ago presented with an exophytic lesion in the right posterior mandibular edentulous ridge. The lesion was a 5-cm wide pedunculated swelling, which did not infiltrate the underlining tissues, was red-brown in color, and had a smooth surface, hard consistency, and an ulcerated central area. The lesion was slightly painful, especially during chewing movements (Figure 1A). Panoramic radiographs (Figure 1B) and computed tomography (CT) scans showed bone involvement with erosion of the cortical bone. Incisional biopsy revealed a giant cell lesion and laboratory tests showed HPTH, hypercalcemia, hypophosphatemia, and increased alkaline phosphatase. The final diagnosis was a BT with central and peripheral involvement. Further instrumental tests showed another 2-cm lesion located in the ischium. HPTH was treated with resection of the adenoma and medical therapy with bisphosphonates. The oral lesion was treated with surgical excision and bone curettage, and the 3-year follow-up was uneventful.

Case 2

A 47-year-old man presented with 2 oral lesions, one in the mandible and the other in the maxillary region. Both lesions were exophytic and pedunculated, with a hard consistency, dark red color, and ulcerated with a high tendency to bleed (Figures 1C and 1D).

On the basis of the results of blood tests, which showed HPTH, hypercalcemia, hypophosphatemia, and increased alkaline phosphatase, the final diagnosis was primary HPTH. HPTH was treated with resection of the adenoma and medical therapy with bisphosphonates. In this case, the BTs were the first manifestations of HPTH caused by an undiagnosed parathyroid adenoma. Because the lesions did not show any radiographic bone involvement (peripheral types), they were treated with simple excision and curettage of the cortical bone. The 5-year follow-up was uneventful.

Case 3

A 68-year-old totally edentulous man who was undergoing dialysis for chronic renal failure caused by nephrocalcinosis presented with an exophytic lesion, 4 × 2 cm in diameter. The lesion was located on the mandibular ridge, was red-brown in color, and had a smooth surface (Figure 1E). Laboratory tests showed HPTH, hyperphosphatemia, and increased alkaline phosphatase, consistent with secondary HPTH. Radiographic examination showed no signs of bone involvement (Figure 1F). The lesion was treated with surgical excision and curettage only. The 4-year follow-up was uneventful.

Case 4

A 35-year-old female with a history of papillary and follicular thyroid carcinoma that had been treated unsuccessfully with total thyroidectomy and radioiodine therapy presented with a residual parathyroid mass. Panoramic radiographs showed multiple osteolytic lesions of the mandible, consistent with central BTs with no peripheral component (Figure 1G). Blood tests confirmed the hypothesis of HPTH, hypercalcemia, hypophosphatemia, and an increase in alkaline phosphatase. A bone biopsy confirmed clinical suspicions of a BT. The lesions were treated with surgical excision and bone curettage. The 3-year follow-up was uneventful.

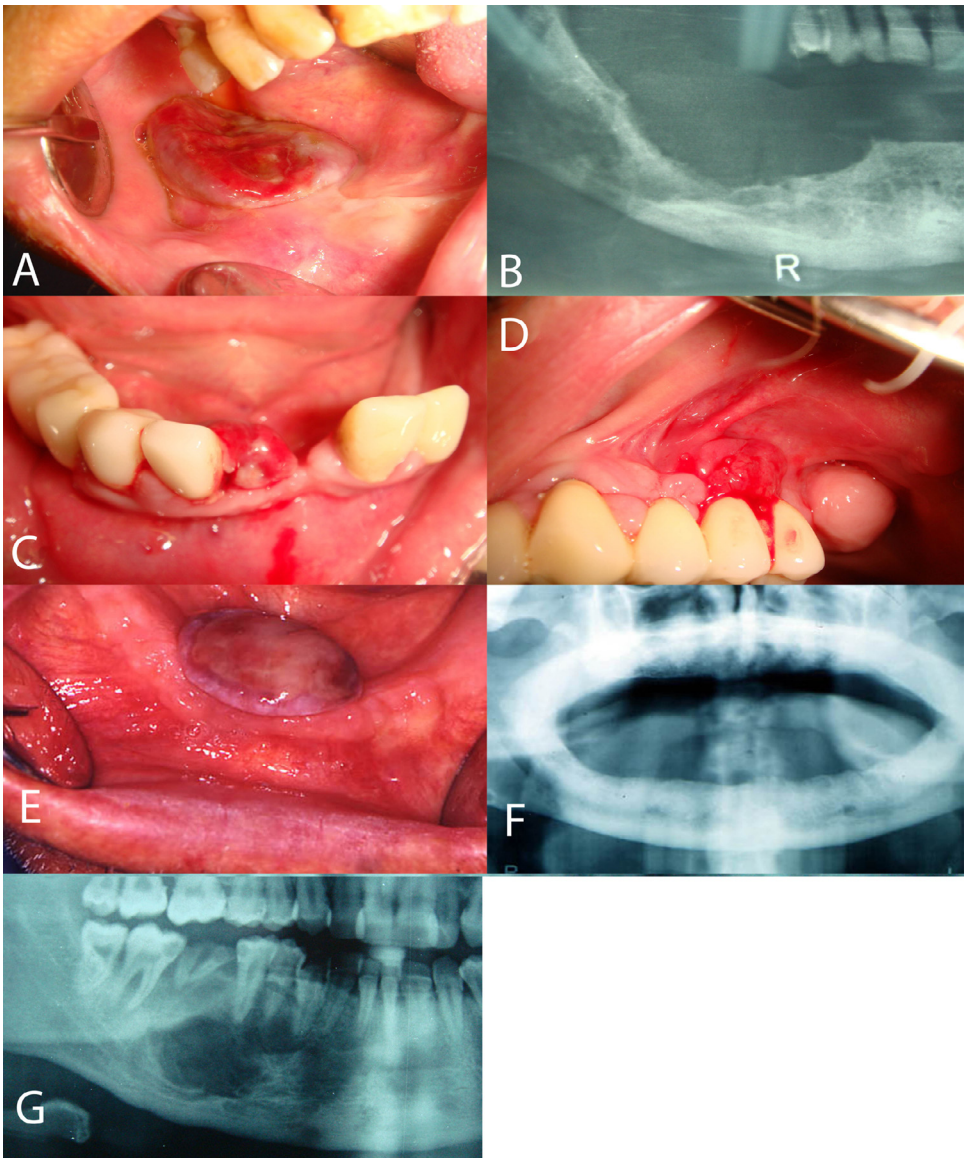

Fig. 1. *Patient 1:* **A**, Clinical appearance of the lesion during intraoral examination. **B**, Orthopantomography in the pretreatment phase. Even if the lesion is exophytic in nature, it damages the underlying bone. *Patient 2:* **C**, Clinical appearance of the lesion involving the lower jaw during intraoral examination. **D**, Clinical appearance of the lesion involving the upper jaw during intraoral examination. Multiple lesions were present in this subject. *Patient 3:* **E**, Clinical appearance of the lesion involving the lower jaw during intraoral examination. **F**, Orthopantomography at the time of diagnosis. The lesion was exophytic in nature and a normal cortical bone was detected via panoramic radiographs. *Patient 4:* **G**, Orthopantomography in the pretreatment phase showed an altered bone structure of the jaw, but no swallowing of the mandible could be clinically noted.

The clinical and laboratory features of the presented cases are summarized in Table I.

SYSTEMATIC REVIEW

The present systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A comprehensive and systematic electronic search in Medline (via PubMed), EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) from database inception to February 2019 was conducted. The date of the last search was March 10, 2019. The database search was conducted by using a combination of the following MeSH terms and free text words: "hyperparathyroidism," "osteitis fibrosa cystica," "brown tumor," "brown tumour," "mandible," "maxilla," "jaw," "skull," "mandibular," "maxillary," "oral cavity," and "face." These terms were connected with the Boolean operator "OR" or, in cases of interceptions of concepts, with the operator "AND." A

Table I. Clinical and laboratory features of the presented cases

Case	Gender	Age (years)	Number	Dental arch	Bone involvement	Other locations	Examinations to diagnosis	Source of HPTH	HPTH therapy	Lesion therapy	Follow-up
1	F	62	Single	Lower	Mixed	Ischium (2 cm)	PTH = 945 pg/mL Ca = 12.3 mg/dL P = 2.3 mg/dL Alk.Ph. = 450 IU/L	Parathyroid adenoma	Adenoma resection and bisphosphonates	Excision and curettage	Uneventful for 3 years
2	M	47	Multiple	Lower and Upper	Peripheral	NR	PTH = 845 pg/mL Ca = 11.7 mg/dL P = 2.2 mg/dL Alk.Ph. = 550 IU/L	Parathyroid adenoma	Adenoma resection and bisphosphonates	Excision and curettage	Uneventful for 5 years
3	M	68	Single	Lower	Peripheral	NR	PTH = 876 pg/mL Ca = 8.7 mg/dL P = 4.6 mg/dL Alk.Ph. = 340 IU/L	Chronic renal insufficiency due to nephrocalcinosis	Dialysis	Excision and curettage	Uneventful for 4 years
4	F	35	Multiple	Lower	Central	Numerous osteolytic lesions (pelvic and ribs)	PTH = 460 pg/mL Ca = 12.1 mg/dL P = 2.2 mg/dL Alk.Ph. = 1500 IU/L	Follicular thyroid carcinoma	Total thyroidectomy	Excision and curettage	Uneventful for 3 years

Alk.Ph, alkaline phosphatase; *Ca*, calcium; *IU*, international unit; *NR*, not reported; *P*, phosphorus; *PTH*, parathyroid hormone.

supplementary manual search was conducted in the following journals: *Oral Oncology; Clinical Oral Investigations; Journal of Oral Pathology & Medicine; Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology; Head & Face Medicine*; and *Oral Diseases* for articles published from the journals' inception dates and February 2019. In addition, the bibliographies of all of the selected articles were reviewed.

All of the articles reporting new cases of oral BTs were included in this review. The articles included had to report a microscopic diagnosis of BT along with findings from laboratory tests to identify the type of HPTH. In addition, in cases of duplicate publications, those with the most recent data were selected. The following exclusion criteria were applied: no oral involvement of BTs, absence of microscopic examination of lesions, absence of HPTH diagnosis, inadequate patient information, and concurrence of systemic pathologies that could interfere with the diagnosis of HPTH.

Two reviewers (R.P. and C.L.) conducted the screening, independently and in duplicate, by using specially designed data extraction forms. For each lesion, the variables collected included year of publication; number (single or multiple), localization (intraoral or extraoral), bone involvement (central or peripheral) of tumors; age and gender of patients; mandibular or maxillary involvement; and type of HPTH. Supplementary information regarding extraoral localization was also retrieved. Any disagreements were resolved by a third reviewer (M.G.). In the case of studies that did not clearly meet the inclusion criteria or reports that had too little information in the title and abstract to make a clear decision, the reviewers obtained and reviewed the full article.

STATISTICAL ANALYSES

Information on the age and gender of patients, HPTH type, and clinical presentation of lesions (i.e., number of lesions, maxillary and/or mandibular lesions, only oral lesions and/or other maxillofacial lesions, and bone and/or mucosal involvement) was collected from the selected articles. The association between the clinical variables and the HPTH type, number of lesions, and localization was tested by using the χ^2 test for the discontinuous variables. The continuous variable (age) was tested for normal distribution by using the Shapiro-Wilk test, and if there was a normal distribution, it was tested with analysis of variance (ANOVA) between groups. All of the statistically significant variables were introduced into a multiple logistic regression model to determine the independent predictors for the HPTH type, number of lesions, and localization. $P < .05$ was used to determine statistical significance. Statistical analysis was performed by using data

analysis software (Intercooled Stata 8.0; StataCorp, College Station, TX).

RESULTS OF THE SYSTEMATIC REVIEW

The initial search of the electronic databases yielded 1238 articles , and the manual search yielded 9 additional articles. After independent elimination of duplicate articles, 1070 articles were considered for possible inclusion. In total, 652 articles were removed on the basis of review of their titles and abstracts; thus, 282 full-text articles were selected. Of these studies, 136 reporting data on 163 patients (Figure 2) were included in the review. Data from the 4 cases reported here by us were added to the results, for a total of 167 cases of oral BT.

The demographic and clinical data gathered from all of the cases, stratified by HPTH type, are shown in Table II. In 24% of the cases, the lesions were located in maxilla and the mandible, whereas in 29.9% of the cases, they involved only the maxillary region; the mandible was the most affected bone, accounting for the 70.1% of the cases. From the analysis of the reported literature, only 4 cases (2.4%) of peripheral BTs were found, and of these, 2 cases (1.2%) did not present bone involvement. The tibia, maxillary sinus, and pelvis were the most frequent extraoral locations involved by BTs.

Detailed characteristics of all of the included studies are reported in Table III (see additional material online).

Considering the association between the number of intraoral BTs and the other clinical variables, the presence of multiple oral lesions was a risk factor for other extraoral maxillofacial localizations (odds ratio [OR] 16.8; 95% confidence interval [CI] 4.7−59.4; $P < .05$)

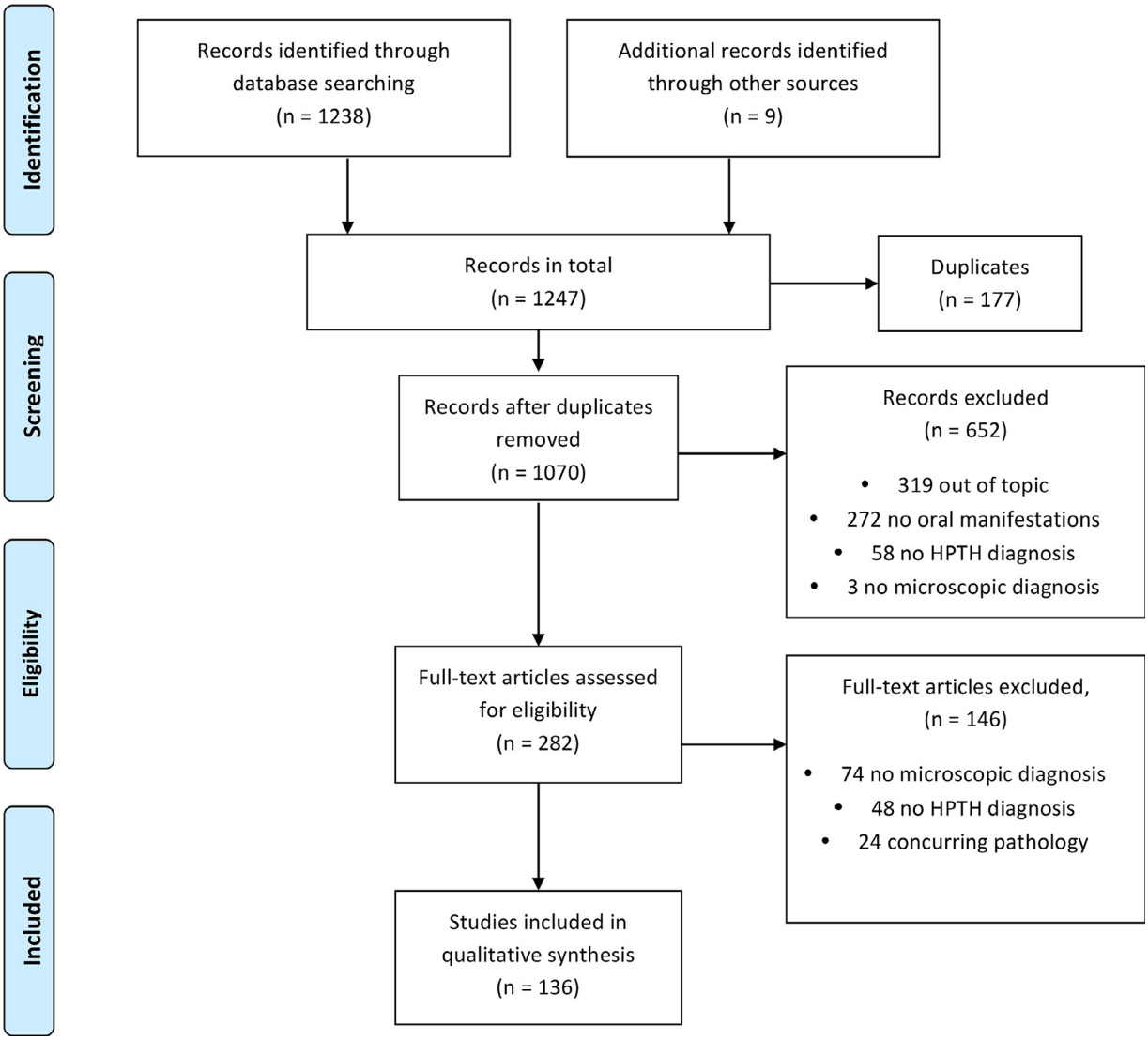

Fig. 2. Flow diagram of selected studies.

Table II. Demographic and clinical data stratified by HPTH type

	Total		*Primary HPTH*		*Secondary HPTH*		*Tertiary HPTH*	
	N = 167	*% = 100*	*N = 74*	*% = 44.3*	*N = 86*	*% = 51.5*	*N = 7*	*% = 4.2*
Age (years ± SD; maximum−minimum)	36.7 ± 17.4; 1−83		39.7 ± 17.3; 7−83		33.9 ± 16.7; 1−77		39.3 ± 23.5; 12−68	
Gender (male; female)	56; 111	33.5%; 66.5%	23; 51	31.1%; 68.9%	28; 58	32.6%; 67.4%	5; 2	71.4%; 28.6%
Localization (intraoral only; also extraoral)	144; 23	86.2%; 13.8%	58; 16	78.4%; 21.6%	79; 7	91.9%; 8.1%	7; 0	100%; 0%
Jaw involvement (one jaw; both jaws)	127; 40	76%; 24%	60; 14	81.1%; 18.9%	62; 24	72.1%; 27.9%	5; 2	71.4%; 28.6%
Number (single; multiple)	106; 61	63.5%; 36.5%	44; 30	59.5%; 40.5%	57; 29	66.3%; 33.7%	5; 2	71.4%; 28.6%
Bone involvement (central; peripheral)	163; 4	97.6%; 2.4%	71; 3	96%; 4%	85; 1	98.8%; 1.2%	7; 0	100%; 0%
Maxillary involvement	89	53.3%	39	52.7%	48	55.8%	2	28.6%
Mandibular involvement	117	70.1%	49	66.2%	61	70.9%	7	100%

HPTH, hyperparathyroidism; *SD,* standard deviation.

because only 3 of the 103 patients who presented a single BT had maxillofacial lesions, whereas 20 of the 41 who presented multiple tumors had maxillofacial lesions with. Considering the distribution of lesions in the jaws, 106 patients had only a single lesion in one jaw, whereas 61 presented with multiple lesions. Although the mandible was the most affected jaw (117 cases vs 89 in the maxilla), the maxilla was the most frequently involved jaw when multiple lesions were found, demonstrating a risk factor for the presence of multiple lesions (OR 7.8; 95% CI 3.6−16.7; $P < .05$).

The onset of both extraoral maxillofacial BTs (OR 176.3; 95% CI 18.7−1657.8; $P < .05$) and maxillary BTs (OR 17.5; 95% CI 6.0−50.8; $P < .05$) remained positively associated, in a multiple regression model, with the presence of multiple oral lesions.

Considering the possibility of detecting other extraoral maxillofacial BTs, the presence of a maxillary BT was associated with an increased risk of other maxillofacial lesions (19 of 89 patients; OR 5; 95% CI 1.6−15.5; $P < .05$), whereas mandibular involvement was correlated in a negative way (9 of 117 patients; OR 0.2; 95% CI 0.09−0.5; $P < .05$).

The variables that were positive in the univariate analysis for the presence of extraoral maxillofacial lesions were introduced into a multiple regression model, and the presence of BT in the mandible (OR 0.01; 95% CI 0.001−0.1; $P < .05$) was confirmed as a negative predictor of extraoral maxillofacial lesions.

DISCUSSION

The uncommon clinical presentation and difficulties encountered in diagnosing the 4 new cases described here led us to perform a systematic review. Furthermore, because BTs are becoming more rarely encountered entities because of the greater attention to early diagnosis of HPTH, it is important to highlight some clinical information to make the diagnostic process easier.

The results of the systematic analysis of the reported cases highlight that BTs seem to mostly affect females and rarely occur in patients with tertiary HPTH. Half the cases reviewed had a single oral manifestation, and the other half had multiple oral manifestations. A clinically relevant finding is that the most frequent localization of BTs is the mandible, but when the maxilla is affected or when multiple oral BTs are found, there is a high probability of multiple, extraoral maxillofacial BTs. The CIs of the statistical analyses are quite wide; thus, these results have to be considered with caution. Furthermore, it would be interesting to perform a systematic review on all cases of BTs (not only oral BTs) to investigate the current rate of frequency of this disease and how it has changed in the last decades.

Oral BTs clinically manifest as exophytic, slow-growing lesions, hard on palpation, fixed to the tissues underneath (mixed lesions), and having a considerable tendency to bleed, but sometimes, they are located in the jaws (central lesions) (Figure 3A). They are rarely peripheral (only 4 cases were reported in the literature, 1 by Whiteman and Schneider[9] and 3 by us), so the differential diagnosis can be very difficult, ranging from lymphomas[10] to radiolucent bony lesions,[11] making biopsy mandatory. Pathology reveals giant cells in a dense fibrous stroma, mononuclear cells (of a monocytic nature), focal areas of osteoid tissue, cystic degeneration, hemorrhage, macrophages with hemosiderin deposits, and osteoclasts as giant multinucleated cells (Figure 3B). Giant cell lesions of the oral cavity can result from a broad spectrum of diseases. In the last update of the World Health Organization (WHO) classification, giant cell lesions were classified under "giant cell lesions and bone cysts" as follows: central giant cell granulomas (CGCGs), peripheral giant cell granulomas (PGCGs), BTs, cherubism, aneurysmal bone cysts (ABCs), and simple bone cysts (SBCs).[12]

CGCGs are intraosseous osteolytic lesions mainly located in the mandible and often occurring in young patients age 10 to 20 years. The pathogenesis of CGCGs remains unclear. Some aspects cause them to appear as reactive lesions and some others as neoplastic lesions. A correlation between the occurrence of these abnormalities and the altered expression of certain

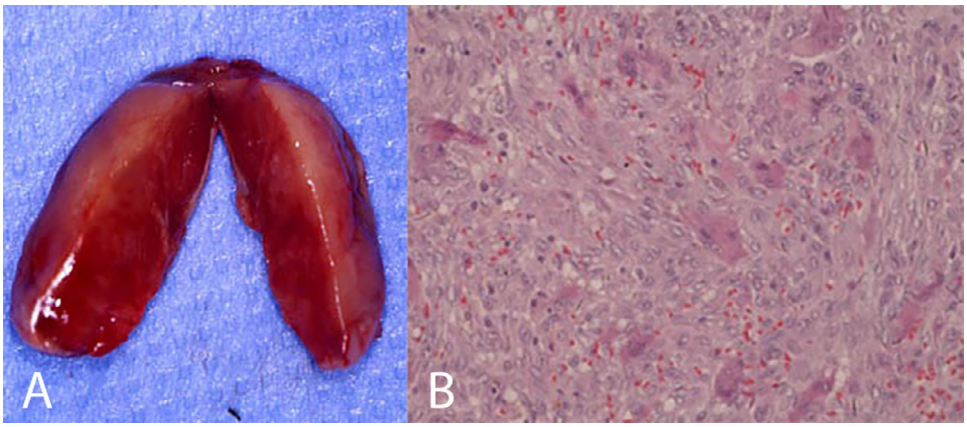

Fig. 3. **A**, Gross pathology generally revealing an exophytic mass with a dark red/brown color resulting from large areas of hypervascularization with hemorrhage and hemosiderin deposits. **B**, Pathology revealing a multinucleated giant cell within a dense fibrous stroma with fibroblasts, mononuclear cells with a possible monocytic nature.

markers (Ki-67, MMP, WWOX, cellular cannibalism, TGF-α, and TNF-β) has been investigated, and a possible neoplastic nature has been suggested; nevertheless, a reactive response to trauma cannot be excluded.[13-15] The lesions have a variable clinical course and histologic appearance. CGCGs are generally benign, but sometimes may show aggressive behavior, along with pain, rapid growth, root resorption, cortical perforation, and recurrence.

PGCGs are exophytic soft tissue formations adhering to the periodontium or the mucoperiosteum. PGCGs are generally reactive lesions caused by local irritative factors, such as plaque, calculus, or incongruous prostheses, and often appear red-brown in color. PGCGs do not generally relapse after surgical removal and elimination of the irritative factor.[13-14,16]

Cherubism is an autosomal dominant condition with high penetrance but variable expression, determined by genetic alterations in the *SH3 BP2* gene located on chromosome 4 p16.3. The genetic mutation determines upregulation of intracellular calcium, which promotes constant displacement of NFATc1 factor in the nucleus. This protein is activated by RANKL binding on osteoclast precursors and is considered the main transcription factor for osteoclast genesis and, thus, for osseous resorption.[17] Cherubism occurs in childhood and determines a deforming expansion of the cortical bones of the jaws, along with replacement of bone with fibrous tissue. Substantial improvements can occur in puberty. Osteolytic multilocular lesions can be observed on panoramic radiographs, and laboratory test results are negative. Familial history and age at onset can help establish the diagnosis. Cherubism may be associated with other rare syndromes, such as Ramon, Jaffe-Campanacci, and Noonan syndromes.[18]

ABCs are reactive lesions (more correctly pseudocysts) that may be correlated with hemodynamic alterations or poor healing after post-traumatic intrabony bleeding. ABCs are occasionally found in young patients. They appear as unilocular or multilocular radiolucent lesions in the premolar region of the mandible and can be found alone or in association with other diseases, such as Langerhans cell histiocytosis.[19,20] They generally have well-defined margins, ranging from 1 to 10 cm, and can appear near the dental roots without causing root resorption or pulpal necrosis. The lower jaw is the most affected craniofacial bone, but the long bones may also be affected. Microscopic examination shows blood-filled pseudocyst cavities containing fibrous septa and reactive bone; the cavities are bound by aligned macrophages. A biopsy may be necessary to reach the correct diagnosis, even if surgical intervention revealing null content is considered diagnostic.[20]

Once a giant cell lesion is suspected, the first diagnostic hypothesis can be suggested by the patient's medical history, if the HPTH condition is already recognized; however, when HPTH is unknown, diagnosis can be difficult. The unspecific clinical and radiographic oral features and the possibility of finding giant cells in many other oral lesions make clinicopathologic correlation difficult.[21] Blood tests (complete blood count, serum PTH, serum and urine calcium, serum and urine phosphorus, and alkaline phosphatase) or neck imaging (parotid and neck ultrasonography and parotid scintigraphy with double sestamibi indicator and technetium-99m [^{99m}Tc]) are often necessary to reach the correct diagnosis. Once HPTH is confirmed, complementary tests are required to assess organ damage (bone mineral density, renal ultrasonography, and ^{99m}Tc-sestamibi single-photon emission CT [SPECT/TC]) and the possible presence of other BTs or lesions in different skeletal sites.

Considering the physiology of PTH, its production follows a circadian rhythm with a peak at night. The

ionized calcium level is the main PTH secretion regulation factor, with a negative feedback mechanism: An increase in calcium corresponds to a reduction in PTH secretion, and vice versa.[22]

PTH acts on 3 target organs: (1) kidneys, inhibiting phosphate and bicarbonate reabsorption, increasing calcium and magnesium reabsorption, and stimulating the activity of 1-α-hydroxylase; (2) bone, stimulating calcium and phosphorus reabsorption through the indirect mobilization of osteoclasts; and (3) intestine, with indirect effects on the absorption of dietary calcium, which stimulates the synthesis of active vitamin D (calcitriol).[23]

Four types of HPTH can be distinguished: primary or primitive HPTH caused by a primary disease of the parathyroid glands, and PTH hypersecretion that is associated with hypercalcemia, hypophosphatemia, hypercalciuria, and hyperphosphaturia. In 85% of cases, it is caused by one or more parathyroid adenomas, whereas in 1% of cases, it is caused by parathyroid carcinoma; in the remaining cases, it is caused by diffused parathyroid hyperplasia.[3] Primary HPTH is rarely associated with hyperparathyroidism–jaw tumor syndrome and type 1 and type 2-A multiple endocrine neoplasia. At present, the diagnosis of primary HPTH is frequently the result of a chance observation of hypercalcemia that precedes the onset of secondary symptoms. Laboratory examinations show hypercalcemia, elevated serum PTH values, and hypercalciuria. Imaging techniques, such as parathyroid and neck ultrasonography, double indicator sestamibi scintigraphy, and ^{99m}Tc can also help establish the final diagnosis. In cases of symptomatic HPTH, therapy consists of parathyroidectomy. If surgery is contraindicated or if HPTH is asymptomatic, medical therapy (hydration, nonthiazide diuretics, and reduction of dietary calcium) is recommended. Bisphosphonates are also variably used to treat primary HPTH.[24]

The clinical characteristics of primary HPTH have changed dramatically over time as a result of improvements in diagnostic methods. Elmslie et al., in 1933, first observed that skeletal disorders, such as giant cell granulomas, loss of lamina dura, and demineralization of the mandible, were often signs of HPTH.[25] More recently, Mundy et al., in a study of 207 patients with primary HPTH, found that 57% were asymptomatic, kidney stones were present in only 7%, and no bone involvement was detected.[26] At present, diagnosis is commonly made with the chance finding of hypercalcemia in asymptomatic patients when serum calcium evaluation is included in routine blood tests. However, despite the current trend, in a small number of patients, the diagnosis may be delayed and bone manifestations can be observed later.[27]

Secondary HPTH is established as a reactive condition to chronic hypocalcemia resulting from malabsorption syndromes or vitamin D deficiency. In most cases, hypocalcemia is the result of chronic renal failure caused by renal osteodystrophy, a side effect appearing in 50% of patients on dialysis for greater than 10 years. If the glomerular filtration rate falls below 60 mL/min, renal excretion of phosphate is reduced, resulting in hyperphosphatemia. Excessive chelate calcium phosphates and the consequent hypocalcemia stimulate PTH secretion. In these patients, the risk factors for the development of BTs are (1) HPTH present for greater than 3 years, (2) glomerular filtration rate less than 15 mL/min/1.73 m^2, and (3) PTH greater than 500 pg/mL.[23] Primary and secondary HPTH conditions can be distinguished on the basis of serum concentration evaluations of calcium and phosphorus.[24]

Tertiary HPTH is caused by disarrangement of the parathyroid glands. When these glands are stimulated for a long time by hypocalcemia, they undergo secondary hyperplasia and can become less sensitive to the negative feedback exerted by calcium. Thus, they become autonomous, establishing a type of (primary) HPTH, which is defined as tertiary HPTH.[28]

Quaternary HPTH is caused by ectopic hypersecretion of PTH that can occur in patients with malignant tumors, such as multiple myeloma, renal cell carcinoma, and gynecologic and respiratory tumors, or as a consequence of paraneoplastic syndrome. These tumors produce a peptide similar to PTH, called *parathyroid hormone-related peptide* (PTHrP). PTH and PTHrP are encoded by different genes but have the same sequence of the first 13 amino acids and the same tertiary configuration.[29]

There has been an increase in the number of reports of cases of BTs. The present analysis revealed that over the past 10 years, more new cases have been reported since the first study in 2009. This is notable because BTs represent the last stage of HPTH, and it is expected that improvements in care access could result in a decrease in the incidence of late stages of chronic diseases. It should also be noted that in the past, the differential diagnosis between BTs and other giant cell lesions was based on the levels of hormones, and it is likely that such analyses were not routinely performed. This may have led to the misdiagnosis of many BTs as CGCGs or PGCGs.

BT treatment first involves resolution of primary or secondary HPTH via medical or surgical therapy. Spontaneous regression is slow and occurs only in small lesions, in young patients, and in short-lasting HPTH conditions. Some studies have reported tumor regression, although not complete, after HPTH treatment; however, other studies have reported persistence of the tumor despite treatment. For small lesions in young people, the simple "wait and see" approach may be a prudent strategy. In cases of nonregression, the lesions must be treated surgically. Different surgical approaches have been described, with curettage or

radiotherapy being the more conservative approaches. In cases of large lesions, surgical excision is required. Other authors have reported initially treating these lesions with intralesional cortisone injections to reduce their size and then proceeding to enucleation. In cases of very large lesions that require extensive resections, reconstructions with bone grafts are necessary.[30]

The clinical manifestations of the 4 cases in this report varied and were of mixed types (both central and peripheral). One was of a central form only, 2 were of peripheral types only; and in 2 of the 4 cases, osteolytic lesions were found in other skeletal sites. In 3 of the 4 cases, the lesions were the result of primary parathyroid disease. The last case was related to chronic kidney failure that caused secondary HPTH. In all of the cases, in addition to specific HPTH therapy, surgical excision of the lesions and bone curettage were performed, and no recurrence or appearance of new lesions were observed in the follow-up period.

CONCLUSIONS

BTs represent the late systemic manifestations of hyperparathyroidism, and in the past, they occurred with a higher incidence. In the past 35 to 40 years, there has been an increase in secondary types of HPTH, mainly linked to renal failure in dialysis patients. However, although rare, BTs may be the first manifestation of undiagnosed hyperparathyroidism.

Histologically, BTs do not present pathognomonic features. Therefore, the finding of giant cell lesions mandates a very accurate differential diagnosis and should always induce suspicion of hyperparathyroidism, which must be resolved or ruled out with blood tests.

Generally, these lesions have a favorable prognosis. For small lesions that appeared recently and in young patients, adopting the "wait and see" approach is recommended. However, large lesions present for a long time and in older patients require surgical enucleation and curettage.

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APPENDIX

Table III. Characteristics of the included studies

First author	*Year*	*SL*	*ML*	*INT*	*EX*	*C*	*P*	*Age (years)*	*Gender*	*Man*	*Max*	*Type of HPTH*	*OL*	*Notes*
Lajolo	2019		X	X	X	X	X	62	F	X		Primary	Ischium	4 cases
Lajolo	2019		X	X			X	47	M	X	X	Primary		
Lajolo	2019		X	X		X		35	F	X		Primary		
Lajolo	2019	X		X			X	68	M	X		Secondary		
Singhal	2018	X		X		X		12	M	X		Secondary		
Popovik-Monevska	2018	X		X		X		60	F	X		Primary		
Satpathy	2017	X		X		X		15	F	X		Primary		
Lim	2017	X		X		X		21	F		X	Primary		
Zou	2018		X	X	X	X		26	F	X	X	Primary	Pelvic bone Rib	
Mellouli	2018	X		X		X		45	F	X		Secondary		
Dos Santos	2018	X		X		X		33	M	X		Tertiary		
Bralyn	2017		X	X		X		42	F	X	X	Primary		
Queiroz	2016		X	X		X		53	F	X	X	Secondary		
Aghaghazvini	2016	X		X	X	X		35	F		X	Primary	Max. sinus	
Nunes	2016		X	X		X		37	F	X	X	Primary		
Yucesoy	2018		X	X		X		24	M	X		Primary		
Pontes	2018	X		X		X		29	M	X		Secondary		13 cases
Pontes	2018	X		X		X		56	M		X	Secondary		
Pontes	2018	X		X		X		18	M	X		Secondary		
Pontes	2018	X		X		X		63	M	X		Secondary		
Pontes	2018	X		X		X		45	F	X		Secondary		
Pontes	2018		X	X	X	X		21	M	X		Secondary	Skull Ethmoid Vertebrae Lower extremities	
Pontes	2018	X		X		X		21	F		X	Secondary		
Pontes	2018	X		X		X		23	F		X	Secondary		
Pontes	2018	X		X		X		41	F		X	Secondary		
Pontes	2018	X		X		X		13	F		X	Secondary		
Pontes	2018	X		X		X		30	F		X	Secondary		
Pontes	2018	X		X		X		46	F	X		Secondary		
Pontes	2018	X		X		X		68	M	X		Tertiary		
Talukder	2017		X	X		X		45	F	X		Primary		
Azzi	2017		X	X		X		58	F	X		Primary		Rec. at 3 and 6 months
Jalali	2016		X	X		X		47	F	X		Secondary		
Pinto	2006	X		X		X		12	F	X		Tertiary		
Selvi	2009		X	X		X		19	M	X	X	Tertiary		
Magalhaes	2010		X	X		X		58	F	X	X	Tertiary		
Dorigatti	2012	X		X		X		21	M	X		Tertiary		
MacDonald	2012	X		X		X		64	M	X		Tertiary		
Bereket	2000	X		X		X		3	F	X		Secondary		
Arunkumar	2012	X		X		X		12	F	X		Secondary		
Nilesh	2014	X		X		X		17	M		X	Secondary		
Yadav	2014	X		X		X		12	M	X		Secondary		
Pace	2010		X	X		X		27	F	X	X	Secondary		
Andrews	2014		X	X		X		14	M	X		Secondary		
Nair	2011	X		X		X		35	F	X		Secondary		
Thomas	2011	X		X		X		27	F	X		Secondary		
Weiss	1980	X		X		X		18	F		X	Secondary		
Michiwaki	1996		X	X		X		42	M	X	X	Secondary		
Keyser	1996	X		X		X		35	F	X		Secondary		
Chang	2007		X	X		X		37	M	X	X	Secondary		
Adachi	2007		X	X		X		39	F	X	X	Secondary		
Bakathir	2008	X		X		X		21	F		X	Secondary		
Nabi	2010		X	X		X		24	F	X	X	Secondary		
Jakubowski	2011	X		X		X		49	M	X		Secondary		
Lopes	2015		X	X		X		44	F	X	X	Secondary		2 cases
Lopes	2015		X	X		X		23	F	X	X	Secondary		

(*continued*)

Table III. Continued

First author	Year	SL	ML	INT	EX	C	P	Age (years)	Gender	Man	Max	Type of HPTH	OL	Notes
Qaisi	2015	X		X		X		43	M	X		Secondary		
Youssef	2016	X		X		X		13	F	X		Secondary		
Aggunlu	2004		X	X		X		19	M	X	X	Secondary		
Biomakis	1976	X		X		X		27	F		X	Secondary		
Rao	1978	X	X	X		X		53	F	X	X	Secondary		2 cases
Rao	1978	X		X		X		53	F	X		Secondary		
Gurumurthy	1982	X		X		X		1	F		X	Secondary		
Goultschin	1982	X		X		X		16	M	X		Secondary		
Kaffee	1982	X		X		X		19	F	X		Secondary		
McWorther	1989	X		X		X		6.5	F	X		Secondary		
Korzets	1992	X		X		X		73	F		X	Secondary		
Fasanelli	1992		X	X	X	X		19	F		X	Secondary	Pelvic bone	
Marini	1992	X		X		X		26	M	X		Secondary		
Nadimi	1993		X	X		X		28	F	X	X	Secondary		
Balon	1998	X		X		X		37	F		X	Secondary		
Okada	2000	X		X		X		60	M		X	Secondary		
Asaumi	2001		X	X		X		47	M	X	X	Secondary		2 cases
Asaumi	2001		X	X		X		33	M	X	X	Secondary		
Jeren-Strujic	2001	X		X		X		23	F	X		Secondary		
Morrone	2001		X	X	X	X		57	M		X	Secondary	7th right rib	
Shang	2003	X		X		X		45	F	X		Secondary		
Taskapan	2004	X		X		X		27	F		X	Secondary		
Throndson	2004	X		X		X		24	M	X		Secondary		
Andreades	2004	X		X		X		57	M		X	Secondary		
Pinar Sumer	2004		X	X		X		44	F	X	X	Secondary		
Trantafillidou	2006	X		X		X		76	F		X	Primary		5 cases
Trantafillidou	2006	X		X		X		21	F	X		Secondary		
Trantafillidou	2006	X		X		X		70	F	X		Secondary		
Trantafillidou	2006	X		X		X		68	F	X		Secondary		
Trantafillidou	2006	X		X		X		71	M	X		Primary		Rec. at 1 year
Prado	2006	X		X		X		45	F	X		Secondary		
Leal	2006	X		X		X		31	F		X	Secondary		
Benjelloun	2007	X		X		X		17	F		X	Secondary		
Tarrass	2008	X		X		X		18	F	X		Secondary		
Di Daniele	2009	X		X		X		40	F	X		Secondary		
Fatahzadeh	2011		X	X		X		40	M	X	X	Secondary		
Lerman	2012	X		X		X		23	F	X		Secondary		2 cases
Lerman	2012	X		X		X		33	M	X		Secondary		
Praveen	2012		X	X	X	X		21	F	X	X	Secondary	Knee	
Artul	2013		X	X	X	X		46	F		X	Secondary	Max. sinus Frontal bone	
Pechalova	2013		X	X		X		19	M	X	X	Secondary		2 cases
Pechalova	2013	X		X		X		49	F		X	Secondary		
Altay	2013	X		X		X		59	M		X	Secondary		
Tayfun	2014		X	X	X	X		26	F	X		Secondary	Spinal cord	
Haroyan	2015		X	X		X		28	F	X	X	Secondary		
Verma	2014		X	X		X		31	F	X	X	Secondary		
Gadhia	2014		X	X	X	X		34	F	X	X	Secondary	Cervical spine	
Thankappan	2015	X		X		X		42	F		X	Secondary		
Jafari-Pozve	2014		X	X		X		29	M	X	X	Secondary		
Baracaldo	2015		X	X		X		27	F	X	X	Secondary		
Moon	2005	X		X		X		77	F	X		Secondary		
Reidy	1998	X		X		X		37	F		X	Secondary		
James	2014		X	X		X		28	F	X	X	Secondary		
Unlu	2003	X		X		X		7	F	X		Primary		2 cases
Unlu	2003	X		X		X		9	M	X		Primary		
Masson	1993	X		X		X		27	M	X		Primary		
Pahlavan	2006	X		X		X		21	M	X		Primary		
Whiteman	1978		X	X		X	X	35	F	X	X	Primary	Gingival	
Slem	1983		X	X	X	X		44	F	X	X	Primary	Orbit	

(*continued*)

Table III. Continued

First author	*Year*	*SL*	*ML*	*INT*	*EX*	*C*	*P*	*Age (years)*	*Gender*	*Man*	*Max*	*Type of HPTH*	*OL*	*Notes*
Robinson	1988		X	X		X		40	M	X	X	Primary		
Scott	1999	X		X		X		23	F		X	Primary		
Goshen	2000	X		X		X		27	F	X		Primary		
Martinez-Gavidia	2000		X	X	X	X		62	M		X	Primary	Pubic ramus Right tibia Femur	
Fernandez-Bustilio	2000	X		X		X		43	M		X	Primary		
Kar	2001		X	X		X		35	F	X	X	Primary		
Guney	2001		X	X	X	X		56	F		X	Primary	Pelvic bone 5th cervical vertebra. 2nd thoracic vertebra Right humerus Right femur Both tibial bones	
Merz	2002	X		X		X		45	M		X	Primary		
Yamazaki	2003		X	X		X		72	F	X	X	Primary		
Corbetta	2003	X		X		X		36	M	X		Primary		2 cases
Corbetta	2003	X		X		X		42	M	X		Primary		
Alvarado	2003	X		X		X		39	F	X		Primary		
Suarez-Cunqueiro	2004		X	X	X	X		26	M	X		Primary	4th and 5th thoracic vertebrae	
Emin	2004		X	X	X	X		62	F	X		Primary	Tibia	
Daniels	2004		X	X	X	X		25	F		X	Primary	Pelvic bone	
Walsh	2005		X	X	X	X		13	F	X	X	Primary	Spine Knees Clavicles	
Grulois	2005	X		X		X		57	F	X		Primary		
Dinkar	2007	X		X		X		36	F	X		Primary		
Jebasingh	2008		X	X		X		68	M		X	Primary		
Venkatesh	2009	X		X		X		42	F	X		Primary		
Proimos	2009	X		X	X	X		42	F		X	Primary	Max. sinus	
Sutbeyaz	2009		X	X		X		53	M	X	X	Primary		
Angadi	2010	X		X		X		38	F	X		Primary		
Alhusban	2011	X		X		X		45	F	X		Primary		
Soundarya	2011		X	X	X	X		60	M		X	Primary	Right index finger	
Gouldfred	2012	X		X	X	X		34	F		X	Primary	Max. sinus	
Gangidi	2012	X		X		X		83	F	X		Primary		
Mori	2013		X	X	X	X		52	F		X	Primary	Max. sinus Iliac bones Pelvic bone	
Sia	2012	X		X		X		29	F		X	Primary		
Mantar	2012		X	X		X		23	M	X	X	Primary		
Wilson	2013	X		X		X		26	F		X	Primary		
Rafizadeh	2013	X		X		X		43	M		X	Primary		
Mendes	2014	X		X		X		39	F	X		Primary		
Chowdhury	2013		X	X		X		20	F	X	X	Primary		
Di Fede	2013	X		X		X		71	M	X		Primary		
Bindal	2013		X	X		X		38	F	X	X	Primary		3 cases
Bindal	2013	X		X		X		32	F	X		Primary		
Bindal	2013	X		X		X		40	F		X	Primary		
Pati	2014	X		X		X		34	M		X	Primary		
Qari	2014	X		X		X		55	F		X	Primary		
Kunte	2015	X		X		X		19	F	X		Primary		
Shetty	2015	X		X		X		22	F	X		Primary		
Huang	2015	X		X		X		42	M	X		Primary		
Olsen	2015	X		X		X		34	F	X		Primary		
Rai	2015	X		X		X		35	F	X		Primary		3 cases
Rai	2015		X	X	X	X		42	M		X	Primary	Frontal bone	

(*continued*)

Table III. Continued

First author	*Year*	*SL*	*ML*	*INT*	*EX*	*C*	*P*	*Age (years)*	*Gender*	*Man*	*Max*	*Type of HPTH*	*OL*	*Notes*
Rai	2015	X		X		X		38	F		X	Primary		
Kocer	1994	X		X		X		7	F	X		Primary		
Yapar	2005	X		X		X		50	F	X		Primary		
Hannah	2011	X		X		X		62	M		X	Primary		
Zhang	2013		X	X	X	X		55	F		X	Primary	Left chest wall Left malar	
Corrado	2015		X	X	X	X		10	F		X	Primary	Metaphysis and diaphysis of left tibia Right femur Left humerus	
Fernandez-Sanroman	2005	X		X		X		16	F	X		Primary		

C, central; *EX,* extraoral; *F,* female; *HPTH,* hyperparathyroidism; *INT,* intraoral; *M,* male; *MAN,* mandible; *MAX,* maxilla; *ML,* multiple localization; *OL,* other localizations; *P,* peripheral; *Rec,* recurrence; *SL,* single localization.