



THE ORAL IMPLICATIONS OF PRIMARY HYPERPARATHYROIDISM

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Accepted February 21, 2018

Primary hyperparathyroidism is a disease caused by excessive production of parathyroid hormone (PTH). The disease is generated usually by parathyroid solitary adenoma, multigland adenomas or carcinoma. In reduced cases the affection is a part of the syndrome of multiple endocrine neoplasia or genetic syndromes. Classical manifestations of primary hyperparathyroidism include: bone disease, kidney stones, nephrocalcinosis, gastrointestinal, cardiovascular, neuromuscular and neuropsychiatric symptoms. In severe forms of hyperparathyroidism oral lesions are widened to the level of: dental arches, mouth mucosa, salivary glands. Currently, due to the use of multichannel serum autoanalyzer patients with hyperparathyroidism are identified prior to previously described clinical manifestations. The diagnosis of the disease is based on biochemical, hormonal, imaging investigations and in selected cases genetic tests. The diagnosis of oral manifestations in primary hyperparathyroidism requires clinical examination, radiological and histopathology investigations. The treatment of overt primary hyperparathyroidism is surgical (parathyroidectomy). For asymptomatic and normocalcemic primary hyperparathyroidism the guidelines recommendations take into account conservative and surgical treatment approach. The management of oral lesions in hyperparathyroidism requires in some cases surgical resection of bone lesions and reconstruction, laser resection, lithotripsy procedures and interventional sialendoscopy. Diagnosis and treatment of oral manifestations in primary hyperparathyroidism requires a multidisciplinary team to include endocrinologist, nephrologist, stomatologist and maxillofacial surgeon.

Keywords: primary hyperparathyroidism, oral lesions, jaw tumor syndrome.

INTRODUCTION

Primary hyperparathyroidism is a disease caused by excessive production of PTH. The prevalence of primary hyperparathyroidism is estimated between 0.1% and 0.4% of the general population¹. In postmenopausal women, the prevalence of the affection varies according to the studies published between 2.1% and 6.7%^{2,3}.

The disease is generated usually by parathyroid solitary adenoma (80%), multigland adenomas (15%) or carcinoma (1%)⁴. In reduced cases (5%) the affection is a part of the syndrome of multiple endocrine neoplasia or genetic syndromes. Multiple endocrine neoplasia syndrome (MEN) is defined by the presence of multiple endocrine tumors. Initially, two types were described: MEN 1 characterized by presence of parathyroid, pancreatic islet cell, and anterior pituitary tumors and MEN 2 with two

subtypes: MEN 2A associate presence a medullary thyroid cancers, pheochromocytoma, parathyroid tumors and MEN 2B in which they are present medullary thyroid cancers, pheochromocytoma and neuromas⁵. Subsequently, subtype 2B was defined as MEN type 3. MEN 3 are characterized according to the statements of Nasir MA and colleagues by “*a marfanoid habitus, mucosal neuromas involving oral and ocular tissues, and a number of ophthalmologic findings including prominent corneal nerves, thickened eyelids, and subconjunctival neuromas*”⁶. In recent decades has been described MEN 4 that associate parathyroid, anterior pituitary, reproductive organs, kidneys and adrenal tumors⁷. MEN syndrome are autosomal dominant disorders. The mutations in specific genes identified in the syndrome are interested menin (MEN 1), tyrosine kinase receptor encoded by the rearranged during transfection protooncogene (RET-MEN 2 and 3), cyclin-dependent kinase inhibitor (MEN 4)^{7, 8, 9, 10, 11, 12}. Other genetic

conditions that associate primary hyperparathyroidism are represented by:

- familial hypocalciuric hypercalcemia,
- familial isolated hyperparathyroidism,
- autosomal dominant moderate hyperparathyroidism,
- neonatal severe hyperparathyroidism,
- hyperparathyroidism-jaw tumor syndrome^{13, 14, 15, 16, 17}.

Hereditary hyperparathyroidism is characterized by the appearance at young ages of the affection and can be generated by mutation of: the calcium-sensing receptor (familial hypocalciuric hypercalcemia, autosomal dominant moderate hyperparathyroidism and neonatal severe hyperparathyroidism), CDC73 stands of Cell division cycle 73, Paf1/RNA polymerase II complex component (hyperparathyroidism-jaw tumor syndrome). Further investigations are necessary to identify genes associated with familial isolated hyperparathyroidism^{18, 19, 20, 21}.

GENERAL CONSIDERATIONS

PTH is secreted by the parathyroid glands as a polypeptide containing 84 amino acids; the biologically active fraction is represented by 34-N-terminal amino acids. PTH regulates serum calcium through direct actions on bone (bone resorption by stimulating of osteoclasts) and kidney (increase renal calcium reabsorption, conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D-3 active form forme of vitamin D3) and indirect action on the intestine (PTH stimulates calcium absorption via active vitamin D).

Classical manifestations of primary hyperparathyroidism include: bone disease (osteitis fibrosa cystica, which is characterized by subperiosteal bone resorption, bone cysts and brown tumors), kidney stones, nephrocalcinosis, gastrointestinal, cardiovascular, neuromuscular and neuropsychiatric symptoms²².

In severe forms of hyperparathyroidism oral lesions are widened to the level of:

- dental arches,
- mouth mucosa,
- salivary glands.

Dental arcades changes include loss of bone density, decalcification of the alveolar with alteration of the alveolodental ligament and to the expulsion of the teeth, brown tumor.

Brown tumor are bony lesions characterized by "erosive bony lesions caused by rapid osteolysis and peritrabecular fibrosis, resulting in a local destructive phenomenon. Facial skeleton is involved in about 2% of all cases of which the mandible is frequently affected"²³. In most cases is interested the mandible especially in the area of molars and premolars and and the incidence determination are low in the maxilla^{24, 25}.

Lesions to the level of oral mucosa are represented by isolated lesions-epulis (benign tumor situated on the gingival or aveolar mucosa), regional and generalized gingival enlargements. Epulis is considered to be a reactive lesion characterized by gingival lesions with inflammatory process, cellular hyperplasia and granulation tissue proliferation. The manifestation can represent first lesion of primary hyperparathyroidism^{26, 27}.

Hyperparathyroidism is associated with salivary stones. Sialolithiasis usually affect the submandibular and parotid glands and can be generated by electrolyte alterations, stasis or chronic infections. Persistence of hypercalcemia predispose to salivary calculi²⁸.

Oral lesions in patients with severe hyperparathyroidism are shown in Table 1.

Table 1

Oral lesions in patients with severe hyperparathyroidism

Oral lesions in patients with severe hyperparathyroidism	
Lesions to the level of dental arches	<ul style="list-style-type: none"> • loss of bone density, • decalcification of the alveolar with alteration of the alveolodental ligament and to the expulsion of the teeth, • brown tumor
Lesions to the level of mouth mucosa	isolated lesions (epulis), regional and generalized gingival enlargements
Lesions to the level of salivary glands	sialolithiasis

Currently, due to the use of multichannel serum autoanalyzer patients with hyperparathyroidism are identified prior to previously described clinical manifestations. Asymptomatic primary hyperparathyroidism describe patients with hyperparathyroidism presenting the biochemical and hormonal picture characteristic of the disease in the absence of classical symptoms and signs²⁹.

A new entity, normocalcemic primary hyperparathyroidism is defined by elevated PTH, in the present of normocalcemia³⁰.

Hyperparathyroidism jaw tumour syndrome is a autosomal dominant affection characterized by adenomas or carcinomas of parathyroid, ossifying fibromas of the jaw, renal and uterine tumours. Ossifying fibromas of the maxilla and mandible are a benign fibro-osseous lesion composed of fibrous tissue mature bone, osteoid and cementum³¹. The affection affect particulare the mandible and ossifying fibroma are the tendency for recurrence and malignant transformation³².

DIAGNOSIS OF PRIMARY HYPERPARATIROIDISM

The diagnosis of the disease is based on biochemical, hormonal, imaging investigations and in selected cases genetic tests. The biochemical investigations include levels of PTH in the presence of elevated/normal serum calcium levels. The PTH measurement is required to be achieved through second (optimal range: 10–65 pg/ml) or third-generation (optimal range: 5–35 pg/ml) PTH assays^{33, 34}. It is important to monitor renal function and assessed the level of 25-hydroxyvitamin D. Parathyroid imaging methods used in the diagnosis of primary hyperparathyroidism include: technetium-99m-labelled sestamibi scanning (standard preoperative localizing test), single photon emission computed tomography, ultrasound, computed tomography scan (CT) and magnetic resonance imaging (MRI)³⁵.

DIAGNOSIS OF ORAL MANIFESTATIONS OF PRIMARY HYPERPARATIROIDISM

The diagnosis of the brown tumors in the jaws requires clinical examination, ultrasound sonography test, radiological (intraoral and panoramic radiographing), CT, MRI and histopathology investigations. Extra- and intraoral oral examination can highlight facial deformities, buccal and lingual expansion of tumors, changes in occlusion. Radiographically, the brown tumors in the jaws appear as well-demarcated radiolucent osteolytic lesion³⁶. Altay C and coworkers reported that *“On multislice CT, the most common manifestation of Brown tumor is expansive and radiolucent bone lesion. CT may also show erosion of adjacent bone tissue. On MRI, Brown tumor shows expansile behavior with low to iso- signal intensity on the T1- and T2-weighted images. CT is the first-step imaging modality in defining and*

*evaluating effect of maxillofacial Brown tumors, while MRI is the problem solving imaging modality”*³⁷. Histologically investigations showing population of mononuclear stromal cells, multinucleated giant cells, hemorrhagic infiltrates and hemosiderin deposits and are non-specific³⁸.

The diagnosis of lesions to the level of mouth mucosa requires clinical and in selected cases histopathological examination.

Ultrasonography is the first stage in diagnosis of sialolithiasis. Sialo-MRI is a investigation that offers better definition of anatomical state of glandular parenchyma and duct³⁹.

The diagnosis of tumour hyperparathyroidism jaw syndrome requires clinical examination (ossifying fibromas can generate facial asymmetry by deforming of the jaw, extension in adjacent structures and secondary tooth displacement), CT, MRI, histopathological examination. Preez M *et al.* supported that on CT ossifying fibromas *“demonstrate internal soft tissue density, which reflects the fibrous component. On MR T1-weighted imaging they return low to intermediate signal, the low signal areas reflecting the osseous component. On T2-weighted imaging, they contain a mixture of low and high signal components reflecting the osseous and fibrous components, respectively”*³¹. Chen JD *et al.* reported that typical histopathological aspect are *“relatively avascular fibroblast-rich stroma and irregular spicules of woven bone, some of which show at least a focal rim of osteoblasts”*⁴⁰.

TRATMENT OF PRIMARY HYPERPARATIROIDISM

The treatment of overt primary hyperparatiroidism is surgical (parathyroidectomy). For asymptomatic hyperparatiroidism the guidelines recommendations take into account surgical treatment and conservative approach. The Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism published in 2014 in The Journal of Clinical Endocrinology & Metabolism recommends surgery in the following situations: age less 50 years, serum calcium >1.0 mg/dl upper limit of normal, alteration of bone mineral density evaluated by dual-energy x-ray absorptiometry (DEXA, T-score less -2.5) or previous fragility fracture, alteration of estimated glomerular filtration rate, hypercalciuria, presence of nephrolithiasis or nephrocalcinosis. Conservative management of asymptomatic hyperparatiroidism

consists of monitoring of calcium, creatinine, vitamin D, bone turnover markers annually or biannually. Medical therapy includes vitamin D; the Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism recommends 800 to 1000 IU as starting dose. Pharmacological therapy such as bisphosphonates and calcimimetics have not been approved by regulatory agencies. In patients with normocalcemic primary hyperparathyroidism, the above mentioned guide recommends monitoring of serum calcium and PTH annually, DEXA annually or biannually and in case of progression of the disorder (reduction of bone mineral density or fracture, nephrolithiasis or nephrocalcinosis) surgical treatment⁴¹.

MANAGEMENT OF ORAL LESIONS IN HYPERPARATHYROIDISM

Surgical treatment of primary hyperparathyroidism generates partial or completely regression of small osteolytic jaw. In some cases the regression of the jaw tumors is not due to the normalization of PTH what it requires surgical resection of bone lesions^{36,42}. Giant cell epulis and giant cell hyperplasia of the oral mucosa requires surgical excision or laser resection⁴³. The management of sialolithiasis comprises surgical treatment, lithotripsy procedures (extra-corporeal, intra-cannular lithotripsy) and interventional sialendoscopy³⁹. Due to the increased risk of malignancy in case of jaw tumour surgical excision lesions with bone grafting and reconstruction is recommended³¹.

CONCLUSIONS

The most common oral manifestations of primary hyperparathyroidism are represented by brown tumor, lesions to the level of mouth mucosa, sialolithiasis. In reduced cases may be present tumour hyperparathyroidism jaw syndrome. The management of oral lesions in primary hyperparathyroidism requires in some cases surgical resection of bone lesions and reconstruction, laser resection, lithotripsy procedures and interventional sialendoscopy. Diagnosis and treatment of oral manifestations in primary hyperparathyroidism requires a multidisciplinary team to include endocrinologist, nephrologist, stomatologist and maxillofacial surgeon.

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