Dermatologic manifestations of parathyroid-related disorders

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Abstract Dermatologic manifestations of parathyroid-related disorders, although rare in sporadic cases, are not uncommon in familial syndromes. Patients with familial hyperparathyroidism have several types of skin lesions. In multiple endocrine neoplasia 1, patients commonly have angiofibromas (85%) and collagenomas (70%), lesions that show loss of one 11q13 allele, the molecular abnormality in multiple endocrine neoplasia 1. They can also present with lipomas or café-au-lait spots. Cutaneous amyloidosis, an entity that can occur sporadically, has been described in multiple endocrine neoplasia 2a and is usually localized to the interscapular area. Metastatic calcification is an entity commonly encountered in patients with hyperparathyroidism and renal failure. It can be complicated by infections and necrosis. It is best treated by controlling hypercalcemia, hyperphosphatemia, hyperparathyroidism, antibiotics, and analgesia. Parathyroidectomy is reserved for refractory cases. Hypoparathyroidism presenting in the context of polyglandular failure type 1 is characterized by mucocutaneous candidiasis. Pseudohypoparathyroidism, an inherited disorder with end-organ unresponsiveness to parathyroid hormone, is characterized by Albright hereditary osteodystrophy. Patients present with short stature, round facies, brachydactyly, and short fourth or fifth metacarpals.

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Introduction

Parathyroid hormone (PTH) is one of the two major calciotropic hormones, the other being calcitriol, that regulate calcium and phosphate homeostasis.1-3 It is responsible for the minute-minute regulation of serum-ionized calcium, keeping it in a very narrow physiologic range, because of enhanced renal tubular calcium reabsorption and increased bone resorption in response to hypocalcemia. Changes in serum-ionized calcium are detected by the parathyroid gland through the calcium-sensing receptor, a G protein–coupled complex that is most heavily expressed in the parathyroid gland and kidney.4 Activation of the receptor secondary to increments in serum-ionized calcium suppresses PTH secretion and enhances renal calcium excretion, both actions resulting in normalization of serum calcium.

Skin manifestations of parathyroid-related disorders will be discussed in the context of syndromes of hyperparathyroidism, primary or secondary to renal failure, and syndromes of hypoparathyroidism.

Primary hyperparathyroidism may be sporadic or hereditary.5 Hereditary hyperparathyroidism includes familial...
isolated hyperparathyroidism including the jaw tumor syndrome, familial benign hypercalcemic hypocalciuria, and the multiple endocrine neoplasia syndromes. Hypoparathyroidism syndromes include sporadic hypoparathyroidism, hypoparathyroidism associated with polyglandular failure, pseudohypoparathyroidism, and autosomal dominant hypocalcemia.

**Hyperparathyroidism**

**Clinical presentation**

Hyperparathyroidism is a condition characterized by hypercalcemia with inappropriate suppression of PTH. The disease is more common in women, typically diagnosed in their mid-50s. Because of the widespread use of automated multichannel chemistries, many patients are asymptomatic and identified from their laboratory studies. Classic manifestations of the disease in patients not detected through blood testing include nephrolithiasis, low bone density, and fractures.\(^5,6\) The majority of cases of hyperparathyroidism are sporadic, the pathology being usually a single adenoma in 80% of cases, multiple adenomas in 2% to 4% of cases, four-gland hyperplasia in 10% to 15% of cases, and carcinoma in 1% to 2% of the cases. The molecular basis of sporadic cases is, in large part, unknown.

Familial isolated hyperparathyroidism, similar to most familial syndromes of hyperparathyroidism, presents in young adulthood, with a high penetrance (>80%); no other endocrine or nonendocrine organs are involved. Hyperparathyroidism–jaw tumor syndrome presents similarly, but a distinguishing feature of the syndrome is the presence of ossifying tumors of the maxilla or mandible, renal cysts, and neonatal severe hypercalcemia. The disease is more common in women, typically diagnosed in their mid-50s. Because of the widespread use of automated multichannel chemistries, many patients are asymptomatic and identified from their laboratory studies. Classic manifestations of the disease in patients not detected through blood testing include nephrolithiasis, low bone density, and fractures.\(^5,6\) The majority of cases of hyperparathyroidism are sporadic, the pathology being usually a single adenoma in 80% of cases, multiple adenomas in 2% to 4% of cases, four-gland hyperplasia in 10% to 15% of cases, and carcinoma in 1% to 2% of the cases. The molecular basis of sporadic cases is, in large part, unknown.

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Multiple endocrine neoplasia (MEN) has been defined as “a case or family with hormone-secreting or hormone-producing neoplasia in multiple tissue types.”\(^8\)

There are six MEN syndromes, including McCune Albright, which is of mosaic origin. The other five are autosomal dominant: MEN1, MEN2, Carney complex, Von Hippel Lindau disease, and neurofibromatosis type 1.\(^8\) Hyperparathyroidism is a feature of MEN1 and MEN2a. Of all the neoplastic syndromes, MEN1 is associated with the largest number of tumor types. Tumors manifest at a young age in at least two of three tissue types: parathyroid, enterohpatic endocrine tissue, and anterior pituitary. The highest penetrance is for hyperparathyroidism occurring in 90% of cases; patients are diagnosed 20 to 30 years earlier than for sporadic cases. It is followed by pancreatic tumors, most commonly gastrinomas in 40% of cases, and pituitary tumors in 20% of cases; prolactinomas are the commonest. Other rarer hormone-secreting tumors include foregut carcinoid and adrenal neoplasms. In cases of a recognized MEN kindred, patients are likely to be asymptomatic and identified in the course of screening of members of known kindreds. Otherwise, patients may present with bone disease, fractures, kidney stones, gastrointestinal symptoms with recurrent multiple ulcers, and amenorrhea or hypogonadism most often caused by prolactinomas. Patients with MEN1 only represent 2% to 4% of cases of primary hyperparathyroidism.\(^5\) Non–hormone-secreting tumors include angiofibromas, collagenomas, lipomas, ependymomas, and meningiomas (see below). Menin is a classic tumor suppressor gene that contributes to cell-selective survival through bi-allelic inactivation. A loss of sequences at the same locus on chromosome 11 (11q13) has been found in approximately two thirds of parathyroid adenomas from patients with MEN1 and one fourth of adenomas from patients with sporadic primary hyperparathyroidism, suggesting that the same gene might be involved.

Multiple endocrine neoplasia 2a is an autosomal dominant disorder characterized by medullary thyroid cancer with an almost 100% penetrance, pheochromocytoma in 40% of patients, and primary parathyroid hyperplasia in 10% to 20% of patients. Multiple endocrine neoplasia 2b is also an autosomal dominant disorder characterized by MTC in almost all patients, pheochromocytoma, but not hyperparathyroidism. Medullary thyroid cancer, the dominant feature of MEN2a and MEN2b, is either picked up in the asymptomatic patient because of screening or because of a neck mass and/or lymphadenopathy. Less commonly, it may present because of symptoms of carcinoid such as flushing and diarrhea, symptoms of pheochromocytoma, namely, spells of anxiety, headaches, pallor, sweating, or hypertensive crises. Other features include intestinal ganglioneuromas and chronic constipation. The underlying abnormality in MEN2a and MEN2b is germline mutations in the RET protooncogene.\(^9\)

Patients with hyperparathyroidism in the setting of renal failure present with anemia, fatigue, decreased bone density and fractures, and hypogonadism, and in end-stage renal disease, intractable pruritus and metastatic calcifications. The calcification is frequently widespread and affects predominantly lungs, kidneys, stomach, and blood vessels. Skin and muscles may also be involved. The pathophysiology of parathyroid glandular hyperplasia in renal failure
includes decrements in ionized calcium levels stimulating parathyroid secretion and growth, a direct stimulation of the parathyroid cells by hyperphosphatemia, and a decrease in the number of calcium-sensing receptors.

Patients with any one of the familial hyperparathyroidism syndromes, or hyperparathyroidism secondary to renal failure, are more likely to harbor four-gland hyperplasia or multiple adenomatosis, with differing sizes of the parathyroid glands.

Cutaneous manifestations

Sporadic hyperparathyroidism is usually not associated with skin manifestations, except for metastatic calcifications. These present as small, firm, white papules or subcutaneous nodules that may overlie large joints. They may be associated with severe pruritus. Chronic urticaria has been described in a few case reports.

Multiple endocrine neoplasia 1

Nonendocrine features typically include facial angiofibromas (85%), truncal collagenomas (70%), and lipomas (30%). The first two are specific for MEN1, are of clonal origin, with loss of one 11q13 allele by in situ hybridization. They usually appear in the second decade of life. Angiofibromas in MEN1 are usually multiple, a few millimeters in size, skin-colored erythematous papules located mainly on the central face and lips. Collagenomas are skin-colored papules and nodules, they may be few or numerous, and are usually present on the neck and trunk (Fig. 1A and B). Lipomas may be single or multiple in MEN1. Other skin findings reported in MEN1 include café-au-lait and hypopigmented macules (Fig. 1C).

Multiple endocrine neoplasia 2a

Cutaneous macular/lichen amyloidosis can occur sporadically, as a familial disease, or in association with MEN2a. Cutaneous amyloidosis in MEN 2a is usually localized to the interscapular area. Lesions consist of pruritic scaly lichenoid papules with hyperpigmentation. Histopathologic features are similar to isolated lichen amyloidosis.
with altered keratin as the source of the deposits (Fig. 2). The presence of lichen amyloidosis in families with MEN2a has been associated with RET protooncogene mutation in codon 634. In one study, among family members with MEN2a and RET 634 mutations, the incidence of cutaneous lichen amyloidosis was 36%.15

Metastatic calcification

This type of calcinosis cutis arises in the setting of abnormal calcium or phosphate metabolism and has been observed in primary or secondary hyperparathyroidism, paraneoplastic hypercalcemia, milk alkali syndrome, sarcoidosis, and hypervitaminosis D. It is, however, most commonly seen in the setting of chronic renal failure. Precipitating factors for their occurrence include skin trauma or injections. Metastatic calcification in renal failure takes the form of either benign nodular calcification or calciphylaxis. Calcinosis cutis presents with firm, white dermal papules; nodules; plaques; or subcutaneous nodules typically at periarticular sites (Fig. 3). Lesions tend to resolve spontaneously when calcium and phosphate levels normalize. Calciphylaxis, on the other hand, is a rare and life-threatening condition of skin and soft tissue necrosis secondary to progressive calcification of cutaneous blood vessels. It is most commonly seen in end-stage renal disease in patients on dialysis or post renal transplant, and is usually associated with secondary and tertiary hyperparathyroidism. There have been reports, however, of its occurrence with primary hyperparathyroidism in the absence of renal abnormalities. Clinically, calciphylaxis begins as violaceous, mottled patches and plaques that resemble livedo reticularis (Fig. 4A). Occasionally, bullae are present. Lesions progress to painful, necrotic, indurated plaques and nodules that evolve to nonhealing ulcers covered with thick black eschars (Fig. 4B). Lesions most often involve the lower extremities and, less commonly, the upper extremities and trunk. It can also manifest as gangrene of fingers, toes, or penis. A meta-analysis of 155 patients with calciphylaxis between 1936 and 1996 revealed that diabetic patients are twice as likely as nondiabetic subjects in developing acral gangrene. Proximal location of the necrosis in thighs, buttocks, and trunks carried a mortality of 63%. Sepsis, secondary to infected ulcers, is the most common cause of death. Histologically, calciphylaxis is characterized by calcification of the wall of small- and medium-sized vessels in the dermis and subcutaneous fat. Fibroblast proliferation, giant cells, intimal hyperplasia, fibrosis, thrombosed vessels, and septal fat necrosis are also seen. The pathogenesis of calciphylaxis is still poorly understood. High PTH levels, vitamin D supplementation, hyperphosphatemia, and an elevated or normal plasma calcium concentration all play a role in calciphylaxis; but there seems to be no discrete calcium ×
phosphate product above which calciphylaxis would occur. Other triggering factors include immunosuppressive drugs, corticosteroids, human immunodeficiency virus disease, infections, protein C or S deficiency.18,22

Diagnosis

The diagnosis of primary hyperparathyroidism, be it sporadic or familial, is made in the presence of hypercalcemia and elevated or inappropriately normal intact PTH levels, measured with an immuno-radiometric assay. In sporadic cases, PTH is frankly elevated in more than 85% of cases, and in the remainder it is in the upper range of normal.5 In younger individuals with any of the familial hyperparathyroidism syndromes, the intact PTH levels may be closer to the middle range of normal, but are still inappropriate for the hypercalcemia. This is because PTH levels are lower in younger subjects than in older ones, but the normative range for PTH does not take such age effect into consideration.5 Low urinary calcium expressed as Ca/Cr clearance ratio (UCaXSCr/SCaXUCr) of less than 0.01 distinguishes cases, PTH is frankly elevated in more than 85% of cases, measured with an immuno-radiometric assay. In sporadic cases, PTH is frankly elevated in more than 85% of cases, and in the remainder it is in the upper range of normal.5 In younger individuals with any of the familial hyperparathyroidism syndromes, the intact PTH levels may be closer to the middle range of normal, but are still inappropriate for the hypercalcemia. This is because PTH levels are lower in younger subjects than in older ones, but the normative range for PTH does not take such age effect into consideration.5 Low urinary calcium expressed as Ca/Cr clearance ratio (UCaXSCr/SCaXUCr) of less than 0.01 distinguishes familial benign hyperparathyro...
of an autoimmune disorder, secondary to infiltrative disorders or surgery. Familial hypoparathyroidism with autosomal dominant, autosomal recessive, and X-linked transmission has been described. Congenital hypoparathyroidism may be inherited as an autosomal dominant or recessive disorder, with described mutations in the signal peptide gene of prepro-PTH, interfering with normal processing of PTH. Congenital hypoparathyroidism has also been associated with other developmental defects. A form of autosomal dominant hypoparathyroidism, the molecular basis for which is unknown, has been reported in association with renal dysplasia and sensorineural deafness. DiGeorge syndrome is characterized by defective development of the third and fourth pharyngeal pouches, resulting in thymic absence or hypoplasia, cardiac defects, and parathyroid hypoplasia with hypocalcemia. Most cases of DiGeorge syndrome are sporadic, but approximately 90% of familial cases have deletions or microdeletions of 22q11.2. In rare cases, hypoparathyroidism is due to an inherited activating mutation of the calcium-sensing receptor (autosomal dominant hypocalcemia), suppressing PTH secretion despite hypocalcemia. Hypoparathyroidism may also present as part of polyglandular autoimmune syndrome type 1, otherwise known with the acronym HAM (hypoparathyroidism, Addison’s disease, chronic mucocutaneous candidiasis). It is caused by mutation in a single gene named the autoimmune regulator gene located on chromosome 21. Pseudohypoparathyroidism is an inherited disorder with end-organ unresponsiveness to PTH, due to abnormalities in the gene encoding the stimulatory Gs-α-one protein of the adenyl cyclase (GNαS1) complex. GNαS1 is imprinted (imprinting means activation or deactivation of genes) in a tissue-specific manner, resulting in three different syndromes. Renal expression of GNαS1 is determined from the maternal allele, and inheritance of the maternal but not the paternal allele leads to hypocalcemia.

Regardless of its cause, clinical manifestations of hypoparathyroidism are in large part due to low serum-ionized calcium levels and include paresthesias, muscle cramps, tetany, laryngo- and bronchospasm, extrapyramidal signs, and seizures. Others are cataracts, abnormal dentition, and personality disorders. On physical examination, patients

Fig. 5  A, Albright hereditary osteodystrophy with short stature, round facies, short neck (courtesy of Dr Serge Jabbour, Thomas Jefferson University, Philadelphia, PA). B, Brachydactyly in a patient with Albright hereditary osteodystrophy: often there is shortening of the fourth and fifth metacarpals (courtesy of Dr Serge Jabbour).

Fig. 6  Thickened, dystrophic, and brownish fingernails and toenails in a patient with chronic mucocutaneous candidiasis (courtesy of Dr Shukrallah Zaaynoun, American University of Beirut Medical Center).
have abnormal dentition, cataracts, and a positive Chvostek sign. Studies reveal a prolonged QT interval on electrocardiogram and calcifications of the basal ganglia. The clinical presentation is pseudohypoparathyroidism, which is similar to hypoparathyroidism (ie, hypocalcemia and hyperphosphatemia), and, in addition, patients have a characteristic body habitus, known as Albright hereditary osteodystrophy (type 1a pseudohypoparathyroidism). Albright hereditary osteodystrophy is characterized by short stature, round facies, short metatarsal and metacarpal bones (Fig. 5A and B). Because of end-organ resistance at the level of the kidney but not the skeleton, patients with pseudohypoparathyroidism present with osteitis fibrosa cystica and bony deformities from fractures. Patients with type 1b pseudohypoparathyroidism have metabolic abnormalities but not the Albright phenotype, presumably because PTH resistance is confined to the kidney only. Conversely, inheritance of the mutated GNXL1 allele from the paternal side results in the phenotype of Albright hereditary osteodystrophy but no metabolic abnormalities, otherwise known as pseudopseudohypoparathyroidism.

**Cutaneous manifestations**

The classic skin findings of hypoparathyroidism include a dry, rough, keratotic, and puffy skin. Nails may be ridged, lusterless, and distally split; hair is course and brittle. Chronic mucocutaneous candidiasis describes several clinical syndromes characterized by persistent and recurrent candidal infections of the skin, mucous membranes, and nails with little propensity for systemic involvement. Chronic mucocutaneous candidiasis may be associated with endocrinopathies, thymoma, or multiple autoimmune conditions. Skin lesions are characterized by erythematous, scaly, hyperkeratotic, or granulomatous plaques with serpiginous borders. In infants, a persistent candidal diaper dermatitis may be seen. The oral mucosa shows white adherent plaques of thrush and angular cheilitis. The esophagus, vulva, vagina, and anus may also be affected. Nails become thickened, discolored, and dystrophic with often edematous erythematous perungual skin (Fig. 6).

Many patients with pseudohypoparathyroidism have Albright hereditary osteodystrophy, which is characterized by short stature, short neck, round facies, brachydactyly, short fourth and fifth metacarpals, and subcutaneous ossifications (Fig. 5A and B). Extensive calcification of the skin and subcutaneous tissue has also been reported in a neonate with congenital hypoparathyroidism. Hypocalcemia secondary to hypoparathyroidism may induce generalized psoriasis, pustular psoriasis, and impetigo herpetiformis. Correction of the hypocalcemia usually results in clearing of the skin disease.

**Diagnosis**

In hypoparathyroidism, the diagnosis is made in the presence of low calcium, high serum phosphate, and normal or low intact PTH levels. In contrast, intact PTH levels are high in pseudohypoparathyroidism, but unable to correct the hypocalcemia. Patients with pseudopseudohypoparathyroidism have normal calcium, phosphate, and PTH levels, but the typical phenotype is Albright hereditary osteodystrophy.

**Brief overview of treatment**

Patients with hypoparathyroidism and pseudohypoparathyroidism are treated with calcium and, preferably, the active metabolites of vitamin D, calcitriol, or alphacalcidol, the effects of which are rapidly reversible in case patients develop vitamin D intoxication. Periodic monitoring of serum and urinary calcium levels, and kidney ultrasound are indicated to rule out nephrolithiasis or nephrocalcinosis. The goal of therapy is to minimize symptoms of hypocalcemia, to keep serum calcium levels at the low end of normal, and to avoid hypercalcuria, to minimize the risk of kidney stones. Studies have demonstrated the safety and efficacy of subcutaneous PTH injections in patients with hypoparathyroidism. Such therapy would control the hyperphosphatemia and minimize or avoid the risk of kidney stone, and although approved for the treatment of osteoporosis, it has not received Food and Drug Administration approval for the indication of hypoparathyroidism.

Chronic mucocutaneous candidiasis requires prolonged and repeated courses of systemic antifungals (mainly azole derivatives) like fluconazole, itraconazole, and ketoconazole to control the disease. Doses higher than the ones usually recommended are often needed.

Immunomodulatory agents like candida-specific transfer factor proteins as well as cimetidine have been used alone or in combination with systemic antifungals.

**References**