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Multiple miliary osteoma cutis of the face associated with Albright hereditary osteodystrophy in the setting of acne vulgaris: a case report

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Abstract

Osteoma cutis is a condition characterized by the formation of bone within the skin. Such aberrant ossification of the skin and subcutaneous tissue is considered primary when it arises in the absence of underlying tissue damage or a preceding cutaneous lesion. Conversely, secondary osteoma cutis occurs when skin ossification is the result of a pre-existing skin lesion, trauma, or inflammatory process [1, 2]. Although rare, primary osteoma cutis has been associated with a number of different genetic disorders. Albright hereditary osteodystrophy (AHO), a condition first described in 1942 by Fuller Albright, is an autosomal dominant metabolic disorder caused by a mutation in the GNAS1 gene [3]. This disease is associated with a variety of phenotypic traits including cutaneous ossification, short stature, brachydactyly, obesity, and mental retardation. It should be noted that brachydactyly is the most specific feature of AHO [4]. However, owing to variable expressivity individuals may present only with a subset of these symptoms [5, 6]. The cutaneous ossification observed in patients with AHO may be seen in infancy or early childhood and is sometimes the earliest presenting symptom. Nonetheless, because clinical features of AHO can be seen in the absence of metabolic derangements (i.e. normal serum calcium, phosphorus, and PTH levels) an early diagnosis is often missed and delayed for many years. Herein, we present a case of miliary osteoma cutis of the face in a 68 year-old woman with phenotypic features of AHO and laboratory studies consistent with type 1a PHP.

Keywords: Albright hereditary osteodystrophy, osteoma cutis, pseudohypoparathyroidism, pseudopseudohypoparathyroidism, acne vulgaris, cutaneous ossification, case report

Introduction

Osteoma cutis is a condition characterized by the formation of bone within the skin. Such aberrant ossification of the skin and subcutaneous tissue is considered primary when it arises in the absence of underlying tissue damage or a preceding cutaneous lesion. Conversely, secondary osteoma cutis occurs when skin ossification is the result of a pre-existing skin lesion, trauma, or inflammatory process [1, 2]. Although rare, primary osteoma cutis has been associated with a number of different genetic disorders. Albright hereditary osteodystrophy (AHO), a condition first described in 1942 by Fuller Albright, is an autosomal dominant metabolic disorder caused by a mutation in the GNAS1 gene [3]. This disease is associated with a variety of phenotypic traits including cutaneous ossification, short stature, brachydactyly, obesity, and mental retardation. It should be noted that brachydactyly is the most specific feature of AHO [4]. However, owing to variable expressivity, individuals may present only with a subset of these symptoms [5, 6]. The cutaneous ossification observed in patients with AHO may be seen in infancy or early childhood and is sometimes the earliest presenting symptom. Nonetheless, because clinical features of AHO can be seen in the absence of metabolic derangements (i.e. normal serum calcium, phosphorus, and PTH levels) an early diagnosis is often missed and delayed for many years. Herein, we



Figure 1. Miliary osteoma cutis of the face. Multiple scattered one to three millimeter skin-colored, hard papules on the face and cheeks.

present a case of miliary osteoma cutis of the face in a 68-year-old woman with phenotypic features of AHO and laboratory studies consistent with type 1a PHP.

Case Synopsis

A 68-year-old woman with a history of mild acne vulgaris as a teenager presented to our clinic complaining of multiple facial lesions. She reported that the otherwise asymptomatic lesions first appeared at the age of 16 years but never regressed despite using multiple facial creams. Her past medical history was notable for hysterectomy because of uterine calcification in her 50s. On physical examination she was a normal appearing female with a BMI of 28.8, average height of 5 feet 6.5 inches, and normal cognition. Her face was typical shape but had

many scattered one to three millimeter skin-colored papules apparent on the face, cheeks, and forehead (**Figure 1**). The lesions were firm and non-tender to palpation and the patient denied any associated pain, itching, or bleeding. Notably, the fifth digits of both the right and left hands were significantly shortened (**Figure 2**). Punch biopsy of a lesion measuring 0.2 x 0.3 cm from the right cheek demonstrated ossified bone fragments within the dermis consistent with osteoma cutis (**Figure 3**).

A metabolic work-up was subsequently conducted and revealed an elevated PTH level of 109 pg/mL (reference range: 14-64 pg/mL), elevated thyroid stimulating hormone (TSH) of 5.11 μ U/mL (reference range: 0.4-4.5 μ U/mL), normal free-T4 index of 2.1



Figure 2. Brachydactyly of the fifth digits on both the right and left hand with both dorsal and ventral views.

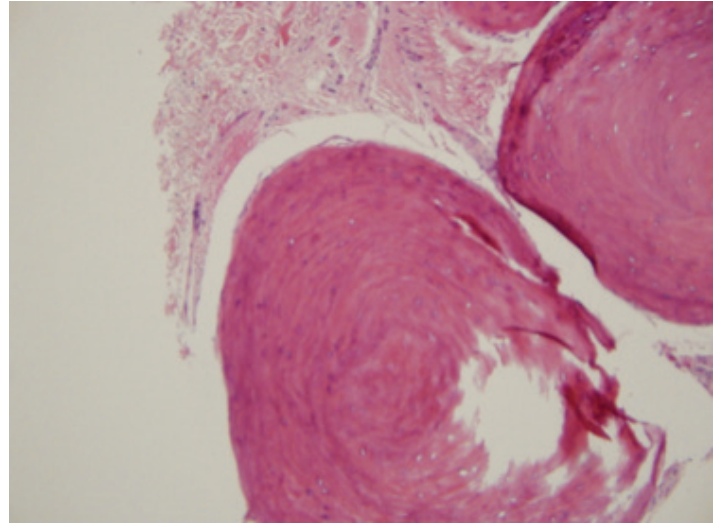
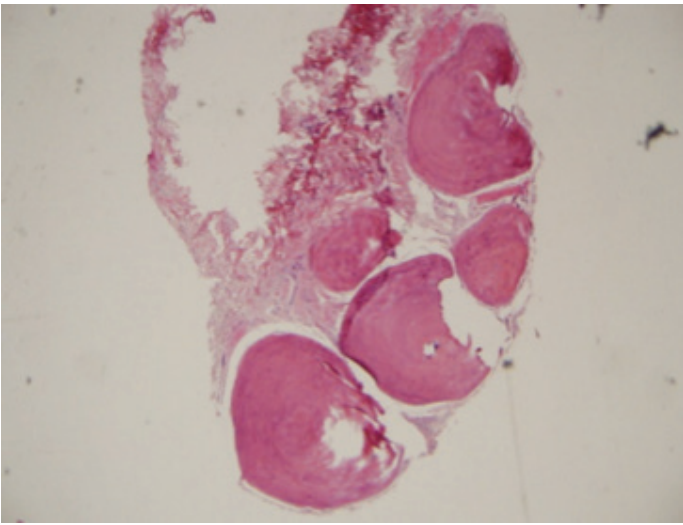


Figure 3. Punch biopsy of a lesion from the right cheek measuring .2 x .3 cm demonstrating ossified bone fragments within the dermis, a picture consistent with osteoma cutis. Left: H&E, 100x; right: H&E, 300x.

(reference range: 1.4-3.8), low 25-hydroxyvitamin D level of 21 ng/mL (reference range: 30-100 ng/mL), normal 1,25-dihydroxyvitamin D level of 53 pg/mL (reference range: 18-72 pg/mL), normal calcium level of 10.1 mg/dL (reference range: 8.6-10.4 mg/dL), and normal phosphate level of 4.2 mg/dL (reference range: 3.0-4.5 mg/dL). Because the work-up was consistent with subclinical hypothyroidism and subclinical pseudohypoparathyroidism, the patient was actively followed on an outpatient basis. To address the hypovitaminosis D, treatment with 50,000 units per week of ergocalciferol was initiated. Follow-up labs revealed a PTH level of 103 pg/mL, 25-hydroxyvitamin D level of 27 ng/mL, calcium level of 9.5 mg/dL, and phosphate level of 3.7 mg/dL. The patient's facial lesions were treated with needle incision and curettage and healed well with no post-procedural complications.

Case Discussion

Osteoma cutis refers to the abnormal development of bone tissue within the dermis and hypodermis of the skin. This condition is considered primary when it is associated with an underlying genetic disorder or an absence of preexisting cutaneous pathology and secondary when it arises due to inflammatory, neoplastic, or traumatic processes [1, 2]. Secondary osteoma cutis occurs more commonly and is associated with a variety of lesions in which bone formation may occur including pilomatricomas, intradermal nevi, basal cell carcinomas, scars, dermatomyositis, and scleroderma [1, 7].

Cutaneous ossification typically presents as multiple, small, superficial, skin-colored papules that are only a few millimeters in diameter [8]. Larger plaques may form when the small papules coalesce. The lesions have a predilection for the scalp, face, hands, feet, abdomen, and periarticular regions but can occur in any region of the body [9].

Osteoma cutis that arises in the absence of a genetic disease has been well-documented and can be divided into four categories based on both location and progression: platelike, isolated, widespread, and multiple miliary facial osteomas [10, 11]. Metabolic abnormalities such as alterations in calcium and phosphate levels are not typically seen in this group of conditions. Miliary osteoma cutis of the face is thought to be the most common cause of osteoma cutis and typically occurs in women with a history of acne vulgaris [12]. Platelike osteoma cutis is an interesting variant characterized by large skin-colored plaques ranging from 1-15 cm that are often single and located on the scalp [13]. Isolated osteoma cutis is usually seen in adulthood and presents as a single nodule, whereas the widespread variant typically presents in early life as multiple, solid nodules and papules. Interestingly, some authors believe that the widespread variant is actually osteoma cutis associated with pseudopseudohypoparathyroidism and AHO. The lack of distinguishing biochemical abnormalities (i.e. normal calcium, phosphorus, and PTH) is thought to lead to the erroneous diagnosis [14].

Table 1. Genetic diseases associated with primary osteomas cutis.

	Pathogenesis	Clinical Manifestations	Genetic Mutation
Fibrodysplasia ossificans progressiva	Endochondral ossification of skeletal muscle and deep connective tissue	Baldness, deafness, dystrophic great toes, mental retardation, early death due to restricted chest movement [8].	ACVR1 (ALK2)[23]
Progressive osseous heteroplasia	Intramembranous ossification of skin and soft tissues	Often presents in first month of life; females preferentially affected. Small papules and large plaques in random bodily distribution, may be unilateral. ALP, LDH, and CPK may be elevated (increased bone production or muscle destruction). Lesions may become ulcerative, infected, and painful [8].	GNAS1 [24]
Platelike osteoma cutis	Intramembranous ossification of skin and soft tissues	Newborns and young children. No dysmorphic features or abnormal calcium or phosphorus metabolism. Non-progressive [8].	GNAS1 [25]
Albright hereditary osteodystrophy	Intramembranous ossification of skin and subcutaneous tissue	Dysmorphic features. May have large subcutaneous masses which disrupt underlying tissue. PHP or PPHP [8].	GNAS1 [15]

*ALP – alkaline phosphatase; LDH – lactate dehydrogenase; CPK – creatine phosphokinase; PHP – pseudohypoparathyroidism; PPHP – pseudopseudohypoparathyroidism.

Four genetic diseases have been associated with the development of primary osteoma cutis: fibrodysplasia ossificans progressiva, progressive osseous heteroplasia, platelike osteoma cutis, and Albright hereditary osteodystrophy which are summarized in **Table 1** [8].

In addition to osteoma cutis, most patients with AHO also present with type 1a or 1c PHP or PPHP [15, 16]. GNAS1, a gene that codes for the alpha subunit of the stimulatory G-protein adenylate cyclase, is mutated in both PHP and PPHP. The difference between these two inherited disease processes is rooted in genomic imprinting. Inheritance of the mutated allele from an affected mother leads to the development of both PTH end-organ resistance and atypical somatic features (i.e. PHP 1a). Conversely, paternal inheritance confers a normal hormonal response but still leads to the somatic symptoms characteristic of AHO, a picture consistent with PPHP. The variability in phenotypes seen among different patients with AHO and PPHP is likely the result of tissue-specific combinations of paternal imprinting and haploinsufficiency [17].

This case of miliary osteoma cutis of the face and history of uterine calcification in our 68-year-old patient with a history of acne vulgaris and diagnosis of AHO proves unique, as it brings to light the importance of a thorough diagnostic work up in patients presenting with osteoma cutis. The relationship between multiple miliary osteomas of the face and chronic acne vulgaris has been reported in a variety of cases [12, 18, 19, 20, 21]. However, had we attributed our patient’s biopsy proven osteoma cutis solely to her history of mild acne vulgaris, we would have failed to uncover the underlying diagnosis: Albright hereditary osteodystrophy. Conducting a thorough physical exam and a careful metabolic workup including serum levels of calcium, phosphorus, PTH, 1,25-OH vitamin D, and TSH is, therefore, of importance when evaluating a patient presenting with cutaneous ossification. Classically, lab values in type 1a PHP will reveal hypocalcemia, hyperphosphatemia, hyperparathyroidism, hypothyroidism, and hypovitaminosis D. If these laboratory abnormalities are seen in combination with the somatic features (short stature, round face, brachydactyly, obesity, mental retardation, and

cutaneous ossification), a diagnosis of AHO should be suspected. Owing to the variable expressivity of AHO, expression of both the somatic features and metabolic abnormalities may vary from person to person [5, 6, 22]. This appeared to be true in our 68-year-old patient who presented with miliary osteoma cutis, bilaterally shortened fifth digits of the hands, elevated PTH and TSH, and low vitamin D levels.

Conclusion

Although AHO is a very rare disorder, it should be considered in the differential diagnosis of any patient presenting with cutaneous ossification. Awareness of the clinical presentation and associated metabolic derangements of AHO can aid in the earlier diagnosis of this disease and help decrease patient morbidity.

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