Hair Follicle Bulb Region: A Potential Nidus for the Formation of Osteoma Cutis

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PRACTICE **POINTS**

- Understanding the pathogenesis of osteoma cutis (OC) can help physicians devise management of these disfiguring lesions.
- Small osteocalcific nodules in close proximity to the lower aspect of the hair bulb may be an important precursor to OC.

Osteoma cutis (OC) is an extraneous ossification of the skin. Heterotopic ossification can be either primary or secondary, depending on the presence of a preexisting lesion. Little is known about the morphogenesis of OC. During routine dermatopathologic examinations for unrelated conditions, small osteocalcific micronodules were noted in close approximation of the lower aspect of hair follicles. In most instances, osteocalcific lesions were found near a hair bulb and exceptionally within the hair bulb. Small osteocalcific nodules incidentally noted in close proximity to the lower aspect of the hair bulb may be a precursor to OC. They may form near or within the hair bulb, possibly under the influence of bone morphogenetic proteins (BMPs).

Cutis. 2021;107:E31-E34.

The term *osteoma cutis* (OC) is defined as the ossification or bone formation either in the dermis or hypodermis.[1] It is heterotopic in nature, referring to extraneous bone formation in soft tissue. Osteoma cutis was first described in 1858[2,3]; in 1868, the multiple miliary form on the face was described.[4] Cutaneous ossification can take many forms, ranging from occurrence in a nevus (nevus of Nanta) to its association with rare genetic disorders, such as fibrodysplasia ossificans progressiva and Albright hereditary osteodystrophy.

Some of these ossifications are classified as primary; others are secondary, depending on the presence of a preexisting lesion (eg, pilomatricoma, basal cell carcinoma). However, certain conditions, such as multiple miliary osteoma of the face, can be difficult to classify due to the presence or absence of a history of acne or dermabrasion, or both. The secondary forms more commonly are encountered due to their incidental association with an excised lesion, such as pilomatricoma.

A precursor of OC has been neglected in the literature despite its common occurrence. It may have been peripherally alluded to in the literature in reference to the miliary form of OC.[5,6] The cases reported here demonstrate small round nodules of calcification or ossification, or both, in punch biopsies and excision specimens from hair-bearing areas of skin, especially from the head and neck. These lesions are mainly observed in the peripilar location or more specifically in the approximate location of the hair bulb.

This article reviews a possible mechanism of formation of these osteocalcific micronodules. These often-encountered micronodules are small osteocalcific lesions without typical bone or well-formed OC, such as trabeculae formation or fatty marrow, and may represent earliest stages in the formation of OC.

Clinical Observations

During routine dermatopathologic practice, I observed incidental small osteocalcific micronodules in close proximity to the lower part of the hair follicle in multiple cases.

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The author reports no conflict of interest.
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doi:10.12788/cutis.0180

These nodules were not related to the main lesion in the specimen and were not the reason for the biopsy or excision. Most of the time, these micronodules were noted in excision or re-excision specimens or in a punch biopsy.

In my review of multiple unrelated cases over time, incidental osteocalcific micronodules were observed occasionally in punch biopsies and excision specimens during routine practice. These micronodules were mainly located in the vicinity of a hair bulb (Figure 1). If the hair bulb was not present in the sections, these micronodules were noted near or within the fibrous tract (Figure 2) or beneath a sebaceous lobule (Figure 3). In an exceptional case, a small round deposit of osteoid was seen forming just above the dermal papilla of the hair bulb (Figure 4).

Multiple osteocalcific micronodules were identified in a case of cicatricial alopecia. These micronodules were observed in sections taken at the levels of hair bulbs, and more or less corresponded to the size of the bulb (Figure 5A). Fortuitously, the patient was dark-skinned; the remnants of melanin within the micronodules provided evidence that the micronodules were formed within hair bulbs. Melanin staining confirmed the presence of melanin within some of the micronodules (Figure 5B).

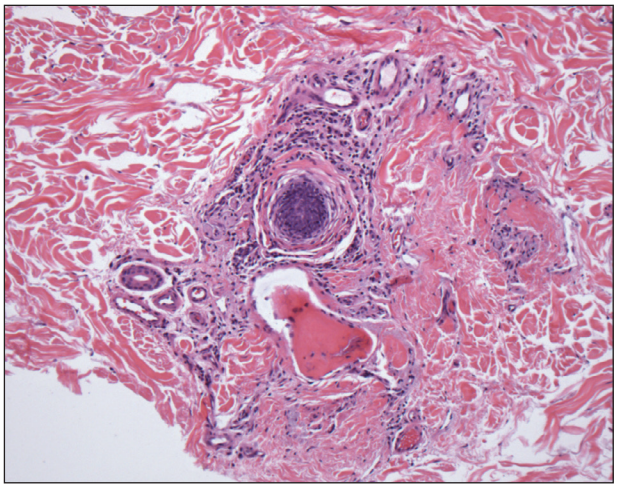

FIGURE 1. Micronodule of osteoid without mineralization next to a hair bulb with an osteoblastic rim (H&E, original magnification ×10).

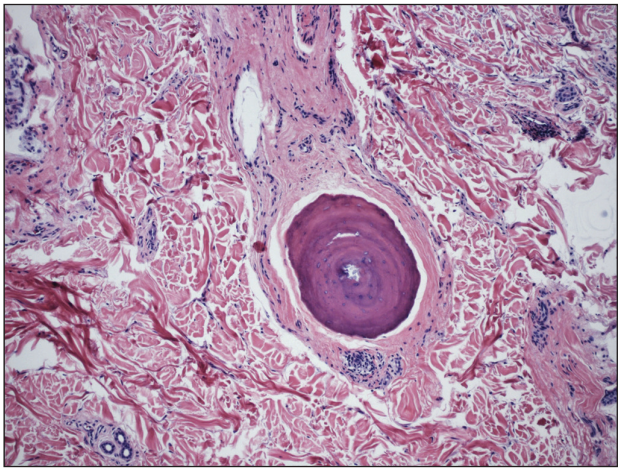

FIGURE 2. Osteocalcific micronodule within the fibrous sheath of the hair follicle (H&E, original magnification ×10).

Comment

Skeletogenesis in humans takes place by 2 methods: endochondral ossification and intramembranous ossification. In contrast to endochondral ossification, intramembranous ossification does not require a preexisting cartilaginous template. Instead, there is condensation of mesenchymal cells, which differentiate into osteoblasts and lay down osteoid, thus forming an ossification center. Little is known about the mechanism of formation of OC or the nidus of formation of the primary form.

Incidental micronodules of calcification and ossification are routinely encountered during histopathologic review of specimens from hair-bearing areas of the skin in dermatopathology practice. A review of the literature, however, does not reveal any specific dermatopathologic term ascribed to this phenomenon. These lesions might be similar to those described by Hopkins[5] in 1928 in the setting of miliary OC of the face secondary to acne. Rossman and Freeman[6] also described the same lesions when referring to facial OC as a "stage of pre-osseous calcification."

When these osteocalcific micronodules are encountered, it usually is in close proximity to a hair follicle bulb. When a hair bulb is not seen in the sections, the micronodules are noted near fibrous tracts, arrector pili muscles, or sebaceous lobules, suggesting a close peripilar or peribulbar location. The micronodules are approximately 0.5 mm in diameter—roughly the size of a hair bulb. Due to the close anatomic association of micronodules and the hair bulb, these lesions can be called *pilar osteocalcific nodules* (PONs).

The role of bone morphogenetic protein (BMP) signaling in the maintenance of the hair cycle is well established. Bone morphogenetic proteins are extracellular cytokines that belong to the transforming growth factor β family. The hair bulb microenvironment is rich in BMPs, which are essential in cross-talk between hair matrix cells and follicular dermal papilla (FDP) cells in the maintenance of the hair cycle, especially during cytodifferentiation.[7] Follicular dermal papilla cells lose their hair follicle inductive properties in vitro in the absence of BMP signaling. Introducing BMP to the in vitro niche restores these molecular properties of FDP cells.[8]

As the name implies, BMPs were discovered in relation to their important role in osteogenesis and tissue homeostasis. More than 20 BMPs have been identified, many of which promote bone formation and repair of bone fracture. Osteoinductive BMPs include BMP-2 and BMP-4 through BMP-10; BMP-2 and BMP-4 are expressed in the hair matrix and BMP-4 and BMP-6 are expressed in the

FDP.[8,9] All bone-inducing BMPs can cause mesenchymal stem cells to differentiate into osteoblasts in vitro.[10]

Overactive BMP signaling has been shown to cause heterotopic ossification in patients with fibrodysplasia ossificans progressiva.[8] Immunohistochemical expression of BMP-2 has been demonstrated in shadow cells of pilomatricoma.[11] Calcification and ossification are seen in as many as 20% of pilomatricomas. Both BMP-2 and BMP-4 have been shown to induce osteogenic differentiation of mouse skin–derived fibroblasts and FDP cells.[12]

Myllylä et al[13] described 4 cases of multiple miliary osteoma cutis (MMOC). They also found 47 reported cases of MMOC, in which there was a history of acne in 55% (26/47). Only 15% (7/47) of these cases were extrafacial on the neck, chest, back, and arms. Osteomas in these cases were not associated with folliculosebaceous units or other adnexal structures, which may have been due to replacement by acne scarring, as all 4 patients had a history of acne vulgaris. The authors postulated a role for the *GNAS* gene mutation in the morphogenesis of MMOC; however, no supporting evidence was found for this claim. They also postulated a role for BMPs in the formation of MMOC.[13]

Some disturbance or imbalance in hair bulb homeostasis leads to overactivity of BMP signaling, causing osteoinduction in the hair bulb region and formation of PONs. The cause of the disturbance could be a traumatic or inflammatory injury to the hair follicle, as in the case of the secondary form of MMOC in association with chronic acne. In the primary form of osteoma cutis, the trigger could be more subtle or subclinical.

Trauma and inflammation are the main initiating factors involved in ossification in patients with fibrodysplasia ossificans progressiva due to ectopic activity of BMPs.[9]

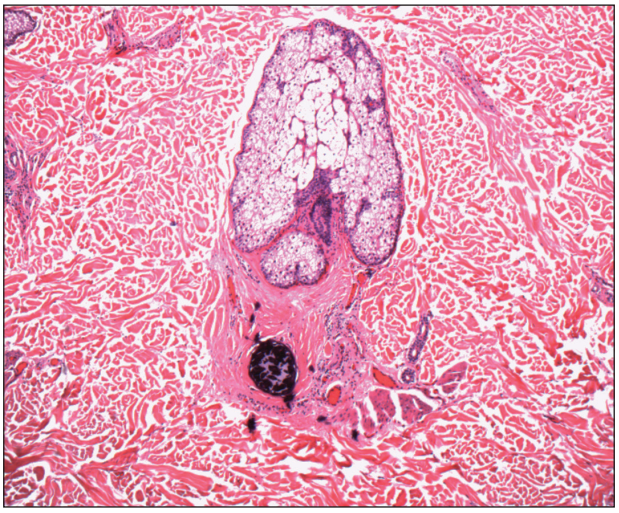

FIGURE 3. Calcific micronodule beneath a sebaceous gland (H&E, original magnification ×10).

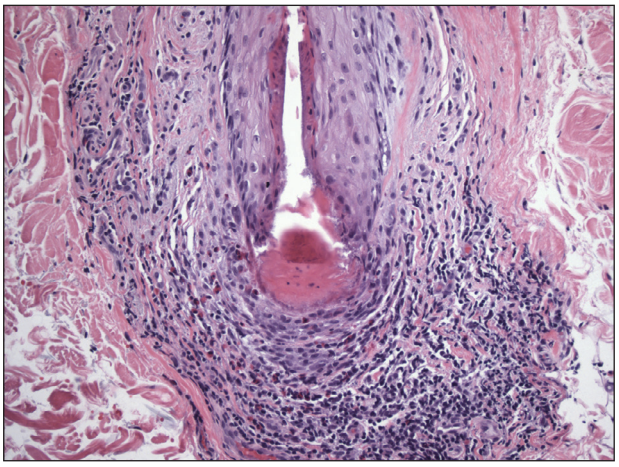

FIGURE 4. An exceptional observation demonstrated the beginning of osteoid formation at the junction of matrix epithelium and papilla, where bone morphogenetic protein–assisted cross-talk aimed at regulating the hair cycle transpires (H&E, original magnification ×20).

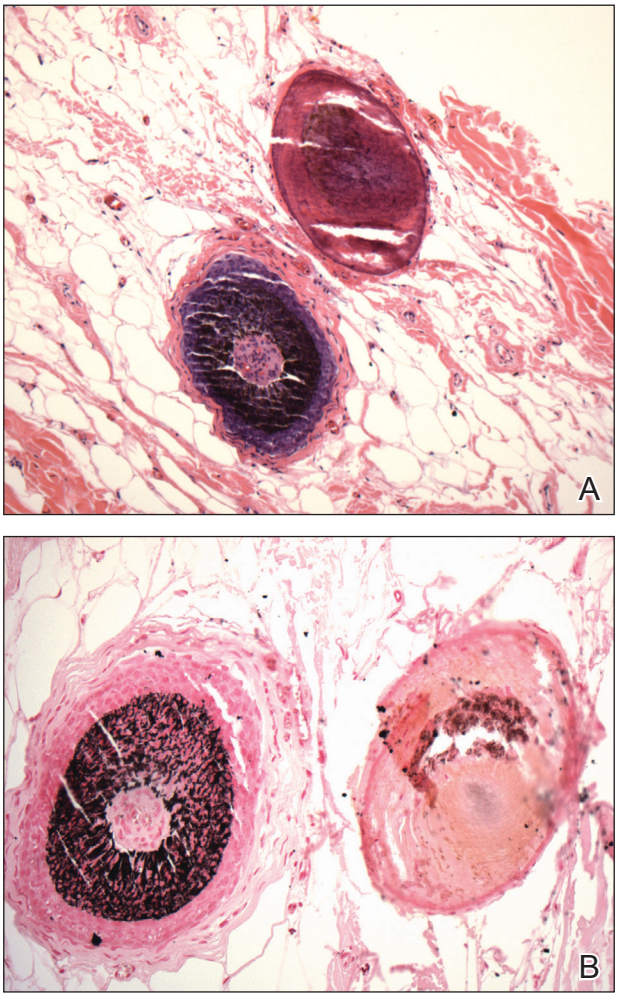

FIGURE 5. A, A section from subcutaneous tissue revealed an osteocalcific micronodule and an adjacent hair bulb with similar size and shape (H&E, original magnification ×20). B, Melanin stain of the osteocalcific micronodule and adjacent hair bulb (Fontana-Masson, original magnification ×40).

The primary form of ossification appears to be similar to the mechanism by which intramembranous ossification is laid down (ie, by differentiation of mesenchymal cells into osteoblasts). In the proposed scenario, the cells of FDP, under the influence of BMPs, differentiate into osteoblasts and lay down osteoid, forming a limited-capacity "ossification center" or pilar osteocalcific nodule.

It is difficult to know the exact relationship of PONs or OC to the hair bulb due to the 2-dimensional nature of histologic sections. However, considering the finding of a rare case of osteoid forming within the bulb and in another the presence of melanin within the osteocalcific nodule, it is likely that these lesions are formed within the hair bulb or in situations in which the conditions replicate the biochemical characteristics of the hair bulb (eg, pilomatricoma).

The formation of PONs might act as a terminal phase in the hair cycle that is rarely induced to provide an exit for damaged hair follicles from cyclical perpetuity. An unspecified event or injury might render a hair follicle unable to continue its cyclical growth and cause BMPs to induce premature calcification in or around the hair bulb, which would probably be the only known quasiphysiological mechanism for a damaged hair follicle to exit the hair cycle.

Another interesting aspect of osteoma formation in human skin is the similarity to osteoderms or the integumentary skeleton of vertebrates.[14] Early in evolution, the dermal skeleton was the predominant skeletal system in some lineages. Phylogenetically, osteoderms are not uniformly distributed, and show a latent ability to manifest in some groups or lay dormant or disappear in others. The occurrence of primary osteomas in the human integument might be a vestigial manifestation of deep homology,[15] a latent ability to form structures that have been lost. The embryologic formation of osteoderms in the dermis of vertebrates is thought to depend on the interaction or cross-talk between ectomesenchymal cells of neural crest origin and cells of the stratum basalis of epidermis, which is somewhat similar to the formation of the hair follicles.

Conclusion

Under certain conditions, the bulb region of a hair follicle might provide a nidus for the formation of OC. The hair bulb region contains both the precursor cellular element (mesenchymal cells of FDP) and the trigger cytokine (BMP) for the induction of osteogenic metaplasia.

REFERENCES

1. Burgdorf W, Nasemann T. Cutaneous osteomas: a clinical and histopathologic review. *Arch Dermatol Res.* 1977;260:121-135.
2. Essing M. Osteoma cutis of the forehead. *HNO.* 1985;33:548-550.
3. Bouraoui S, Mlika M, Kort R, et al. Miliary osteoma cutis of the face. *J Dermatol Case Rep.* 2011;5:77-81.
4. Virchow R. *Die krankhaften Geschwülste*. Vol 2. Hirschwald; 1864.
5. Hopkins JG. Multiple miliary osteomas of the skin: report of a case. *Arch Derm Syphilol.* 1928;18:706-715.
6. Rossman RE, Freeman RG. Osteoma cutis, a stage of preosseous calcification. *Arch Dermatol.* 1964;89:68-73.
7. Guha U, Mecklenburg L, Cowin P, et al. Bone morphogenetic protein signaling regulates postnatal hair follicle differentiation and cycling. *Am J Pathol.* 2004;165:729-740.
8. Rendl M, Polak L, Fuchs E. BMP signaling in dermal papilla cells is required for their hair follicle-inductive properties. *Genes Dev.* 2008;22:543-557.
9. Shi S, de Gorter DJJ, Hoogaars WMH, et al. Overactive bone morphogenetic protein signaling in heterotopic ossification and Duchenne muscular dystrophy. *Cell Mol Life Sci.* 2013;70:407-423.
10. Miyazono K, Kamiya Y, Morikawa M. Bone morphogenetic protein receptors and signal transduction. *J Biochem.* 2010;147:35-51.
11. Kurokawa I, Kusumoto K, Bessho K. Immunohistochemical expression of bone morphogenetic protein-2 in pilomatricoma. *Br J Dermatol.* 2000;143:754-758.
12. Myllylä RM, Haapasaari K-M, Lehenkari P, et al. Bone morphogenetic proteins 4 and 2/7 induce osteogenic differentiation of mouse skin derived fibroblast and dermal papilla cells. *Cell Tissue Res.* 2014; 355:463-470.
13. Myllylä RM, Haapasaari KM, Palatsi R, et al. Multiple miliary osteoma cutis is a distinct disease entity: four case reports and review of the literature. *Br J Dermatol.* 2011;164:544-552.
14. Vickaryous MK, Sire J-Y. The integumentary skeleton of tetrapods: origin, evolution, and development. *J Anat.* 2009;214:441-464.
15. Vickaryous MK, Hall BK. Development of the dermal skeleton in *Alligator mississippiensis* (Archosauria, Crocodylia) with comments on the homology of osteoderms. *J Morphol.* 2008;269:398-422.