Title
Two cases of secondary cutaneous ossification arising in lower abdominal keloids

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Conflicts of interest
The authors declare no conflicts of interest associated with this manuscript.
Abstract

Cutaneous ossification is a rare, benign dermatological condition where bone forms in the dermis or subcutaneous tissue. It is classified as primary when it emerges without a pre-existing condition and secondary when it associates with an underlying condition such as trauma, scars, inflammation, and neoplastic disease. The secondary form accounts for most cases of cutaneous ossification. The pathogenesis of cutaneous ossification is not clear. Keloids are benign fibroproliferative skin disorders that are characterized by chronic inflammation. Their pathogenesis is also not fully understood. We report two cases of secondary ossification arising in postoperative lower abdominal keloids and review the literature on secondary ossification of the skin. We speculate that the intense chronic inflammation in keloids may drive the osteoblastic transformation of either mesenchymal stem cells, endothelial cells, or fibroblasts in the keloids.

Key words: cutaneous ossification, keloid, secondary ossification, inflammation
**Introduction/Background**

Cutaneous ossification (also known as osteoma cutis) and cutaneous calcification (calcinosis cutis) are rare conditions that both involve the deposition of calcium salts in the skin and subcutaneous tissues. However, unlike cutaneous calcification, cutaneous ossification associates with dystrophic deposits of bone\(^1\). This benign condition occasionally presents as primary skin lesions but is mostly secondary to another skin condition such as trauma, scars, inflammation, and malignant and benign neoplastic lesions\(^1\). The etiology of cutaneous ossification is still unclear.

Keloids are benign recalcitrant fibroproliferative skin disorders that arise from damage to the dermis. Surgery on its own associates with 40–70% recurrence rates but these rates drop to <10% when surgery is accompanied by adjuvant treatments such as postoperative radiotherapy\(^2,3,4\). There are no specific drugs for this condition because of the lack of suitable animal models. To our knowledge, there are no detailed reports of secondary ossification associated with keloids.

We describe here two cases of cutaneous ossification that associated with postoperative lower abdominal keloids and review the literature on secondary ossification of the skin.

**Case 1**

Four years previously, a 42-year-old woman visited our outpatient clinic with the chief complaint of scar pain after gynecological surgery for uterine fibroids. A clinical examination revealed a hard, red, elastic, and raised 3 × 2.5-cm mass in the lower part of the postoperative scar (Fig. 1a). The patient had no history of skin cancer in this area and had no personal or family history of bone or metabolic disorders. She was diagnosed with postoperative keloid and underwent complete surgical extirpation followed by electron beam therapy. Histopathology revealed a nodular lesion in the dermis that consisted of excessive numbers of so-called “keloidal collagen bundles”, namely, thick, haphazardly arrayed, glassy, and eosinophilic collagen bundles that formed nodular and whorled masses. The lesion also had elevated fibroblast numbers (Fig. 2a). Notably, the lower part of the lesion contained some small nodules of bone tissue (Fig. 2b). These clinical and pathological findings yielded a diagnosis of postoperative keloid associated with secondary cutaneous ossification. Two years after the operation, recurrence has not been observed (Fig. 1b). The patient continues to be followed up.

**Case 2**

A 32-year-old woman visited our outpatient clinic with the chief complaint of scar pain
after dermatological surgery for an epidermal cyst six years ago. The clinical examination revealed a hard, red, elastic, and raised 3 × 11-cm mass in the postoperative scar (Fig. 3a). The patient had no history of skin cancer in this area and had no personal or family history of bone or metabolic disorders. She was diagnosed with postoperative keloid and underwent complete surgical excision followed by electron beam therapy. Histopathology revealed similar findings to those in Case 1 (Fig. 4a, b), namely, keloidal collagen, elevated fibroblast numbers, and small ossified nodules in the lower part of the lesion (Fig. 4c). The patient was diagnosed with postoperative keloid associated with secondary cutaneous ossification. Three years after surgery, recurrence was not observed (Fig. 3b).

**Discussion**

Cutaneous ossification involves the deposition of bone in the skin due to the production of osteoblast tissue. To date, three large case series on secondary cutaneous osteoma have been published. Thus, in 1963, Roth et al. summarized the causes of secondary cutaneous ossification in the 120 cases they experienced and the 305 cases they found in the literature: they detected 153 skin conditions that arose prior to secondary cutaneous ossification, including acne vulgaris, acne, scleroderma, dermatomyositis, basal cell carcinoma, scarring, venous stasis, calcified epithelioma, and folliculitis. In 1997, Burgdorf and Nasemann described the 10 primary and 25 secondary cutaneous ossification cases that they had found in 20,000 skin biopsy materials: they observed that the secondary causes were epithelioma, basal cell carcinoma, melanocytic nevus, appendageal and fibrous proliferations, inflammation, and trauma. In 2002, Conlin et al. reported 74 cases of primary and secondary cutaneous osteomas and found that benign neoplasms, especially melanocytic nevus, were the most common cause of the secondary cases. In 2014, Ishida et al. summarized these reports and showed that secondary cutaneous ossification accounted for 83% of all cutaneous ossification cases and that the most common causes of the secondary cases were pilomatricoma (21%), melanocytic nevus (19%), and inflammation or trauma (10%) (Table 1). To the best of our knowledge, cutaneous ossification that associates with keloid scarring has not yet been reported.

While the pathogenesis of secondary cutaneous ossification has not yet been elucidated, Burgdorf and Nasemann suggested that cutaneous ossification in general is due to either the transformation of primitive mesenchymal cells into osteoblasts or the metaplastic transformation of other, as yet undetermined, dermal cells as a result of stimulation by particular cellular environments. With regard to the latter theory, Schumachers and Worret suggest that the undetermined dermal cells may be fibroblasts:
they postulated that cutaneous ossification may involve an intracellular signaling pathway that induces skin fibroblasts to proliferate abnormally and then differentiate into bone tissue. There is evidence, albeit limited, that one or more of these possibilities could mediate keloid ossification, as follows. Thus, it has been shown that mesenchymal stem cells in keloid lesions give rise to abnormal fibroblasts and myofibroblasts. Since mesenchymal stem cells can readily differentiate into osteoblasts, it is also possible that the mesenchymal stem cells in keloids give rise to osteoblasts. This is further supported by the association between GNAS mutations and cutaneous ossification. GNAS regulates adipose-derived mesenchymal progenitor cell commitment and inactivating mutations in this gene induce osteoblast differentiation.

With regard to the possibility that undetermined dermal cells differentiate into osteoblasts, it has been shown that tissue injury such as trauma or infection that generates local hypoxia can induce endothelial cells to express BMPs, which causes them to convert into osteoblasts. Since keloids arise from trauma, associate with chronic inflammation, and are known to have dysregulated endothelial cells, it is possible that this mechanism drives keloid ossification. This is supported by the rare condition called Nanta's nevus, which is characterized by ossification of the intradermal nevus. Chronic inflammation is thought to be one of the triggers of ossification in this condition since cell infiltration is observed around the osteoma and around the hair follicles. Interestingly, our ossified keloid cases occurred in the pubic area and the histological findings indicated peri-follicular inflammation and calcification. This supports the notion that the chronic inflammation in keloids led to local calcification and ossification.

Finally, the other possibility is that the fibroblasts in keloids, which are abundant, abnormal, and proliferate vigorously, differentiate into osteoblasts, possibly as a result of the chronic inflammation in keloids. This possibility is supported by the fact that cutaneous ossification lesions not only contain osteoblasts and bone, they are surrounded by type I collagen and osteonectin-positive fibroblasts.

Notably, there are two types of normal bone ossification: endochondral ossification, where hyaline cartilage is replaced by bony tissue, and membranous bone formation, where bone forms directly without cartilage analogs. It is likely that ossification in keloids is due to membranous bone formation since the lesions in both of our cases did not have cartilage tissue.

In conclusion, it is possible that chronic inflammation, which is pronounced in keloids, may drive local mesenchymal stem cells, endothelial cells, or fibroblasts to differentiate into osteoblasts that then generate bony nodules in keloids. Further studies...
on the mechanisms that induce bone formation in keloids are warranted.

**Conflict of Interest:** The authors declare no conflicts of interest.

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**Figure legends**

Fig. 1 Preoperative (a) and postoperative (b) images showing the clinical findings in Case 1. The patient had a keloid in the lower part of the postoperative scar. Two years after surgical extirpation followed by radiotherapy, recurrence was not observed.

Fig. 2 Histological findings of Case 1. (a) Low-power image showing a nodular lesion in the dermis. The lesion consisted of large numbers of collage bundles that formed nodular and whorled masses and associated with increased fibroblast numbers. The lower part of the lesion contained small nodules of bony tissue. (b) Higher-power image showing the bony tissues in the lower part of the keloid.

Fig. 3 Preoperative (a) and postoperative (b) images showing the clinical finding of Case 2. The patient had a keloid in the pubic area. Three years after surgery, recurrence was not observed.

Fig. 4 Histological findings of Case 2. (a) Low-power image showing a nodular lesion in the dermis. The lesion consisted of nodule-forming, whorled collage bundles and high fibroblast numbers. The lower part of the lesion bore some small nodules that consisted of bony tissue. (b and c) Higher-power images showing the thick, glassy, eosinophilic collage bundles (b) and the bony tissue in the lower part of the keloid (c).
Table 1. Summary of the causes of cutaneous osteoma (modified with permission from Ishida et al., 2014).

| Cause                      | Percentage |
|----------------------------|------------|
| Epidermal                  | 50%        |
| Neural                      | 25%        |
| Connective tissue           | 20%        |
| Other                      | 5%         |
Fig. 1
Fig. 2
Fig. 3
Fig. 4

(a)

(b)

(c)
Table 1. Summary of the causes of cutaneous osteoma (modified with permission from Ishida et al., 2014 (under the “Creative Commons Attribution Noncommercial License”))

| Primary Cause | Secondary Cause |
|---------------|-----------------|
| Primary       | Secondary       |
| 47 (17.3%)    | 224 (82.7%)     |
| Common cause of secondary |  |
| Pilomatricoma | 56 (20.7%)     |
| Melanocytic nevus | 51 (18.8%) |
| Inflammation or trauma | 26 (9.6%) |
| Basal cell carcinoma | 19 (7%) |