Two cases of treatment with aromatase inhibitors and development of miliary osteoma cutis—Is there an association?

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INTRODUCTION

Osteoma cutis is a benign condition characterized by extra-skeletal bone formation within the dermis and subcutaneous tissue. The condition commonly occurs in late- to middle-age women and can be primary or secondary. Secondary causes include iatrogenic, traumatic, metabolic, inflammatory, and cutaneous neoplasms such as basal cell carcinoma, pilomatricoma, and hemangiomas.[1] Of the secondary causes, acne vulgaris is one of the most common historical elements.[2] The condition can also be a feature of a genetic syndrome: fibrodysplasia ossificans progressiva, Albright hereditary osteodystrophy, progressive osseous heteroplasia, and platelike osteoma cutis.[3] Here we discuss 2 unique cases of miliary osteoma cutis.

Abbreviation used:

AI: aromatase inhibitor

CASES

Case 1 was a 71-year-old woman who presented to our dermatology clinic with a progressive facial rash of 1-month duration. Skin examination found numerous 2- to 5-mm bland, skin-colored, dermal papules symmetrically distributed on the chin, cheeks, and forehead (Fig 1). On palpation, lesions were firm, dome shaped, and nontender. Her medical history included rosacea, basal cell carcinoma of the lip, and breast cancer treated with mastectomy, chemoradiation, and exemestane, 25 mg/d for the last 3 months. Punch biopsy was performed at the initial office visit.

Case 2 was a 61-year-old woman who was referred to our clinic for a full skin examination. On examination, multiple skin-colored, firm, papules on a background of erythema were distributed on her cheeks. Lesions were 1 to 3 mm in size, nontender, and asymptomatic. No other areas were involved. Her medical history included hyperlipidemia, osteopenia, migraines, and breast cancer treated four years prior with bilateral mastectomy, chemotherapy, and letrozole, 2.5 mg/d for the last 3 years. She had a family history of melanoma but denied any history of skin cancer herself. The patient was started on azelaic acid 15% twice a day for suspected granulomatous rosacea. At her 3-month follow-up, a punch biopsy was performed because of lack of improvement.

Histologic examination for both cases found bone fragments within the dermis leading to the diagnosis of miliary osteoma cutis (Fig 2). Computed tomography scan without contrast was consistent with that diagnosis, showing innumerable punctate subcutaneous hyperdensities (Fig 3).

Interestingly, both patients noted a temporal relationship between initiating the aromatase inhibitor and the condition. The patient in case 1 quickly recognized the onset of lesions within the initial months of starting exemestane and presented to clinic within 3 months of drug initiation. The temporal course is less clear in case 2 because of the extended period between drug initiation and visit to the clinic.

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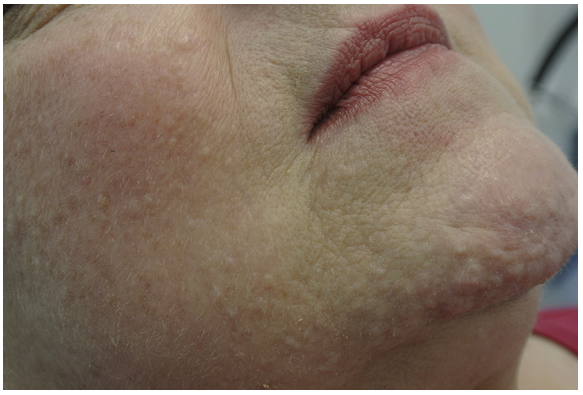

Fig 1. Miliary osteoma cutis, clinical image. Numerous skin-colored, firm papules were present in a symmetric distribution

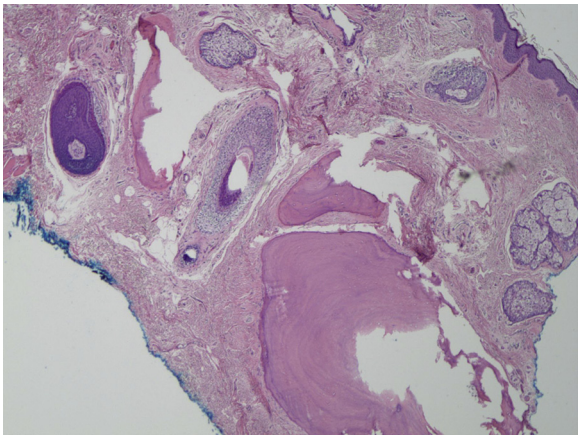

Fig 2. Miliary osteoma cutis, histologic image. Bone fragments in the dermis. (Hematoxylin-eosin stain; original magnification: ×4)

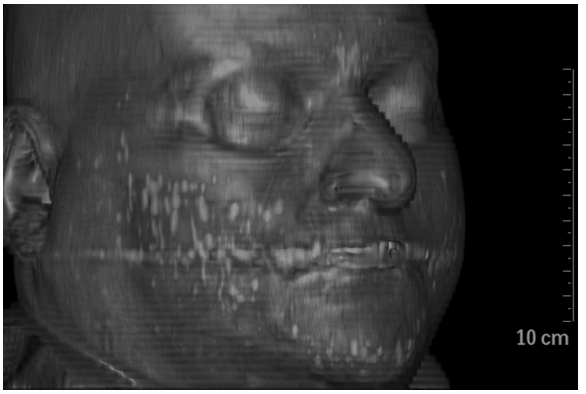

Fig 3. Miliary osteoma cutis, radiographic image. Three-dimensional reconstruction shows distribution of lesions. Artifact at the level of the mouth is from prior dental work.

Both patients elected for no further treatment of their condition. Despite this lack of therapy, at a five-year follow-up appointment the patient presented as case one demonstrated significant improvement. The patient from case two was lost to follow-up after diagnosis.

DISCUSSION

The pathogenesis of miliary osteoma cutis remains unknown, and current literature is limited to small case reports of the condition. Theories suggest that either osteoblastic metaplasia of mesenchymal cells or migration of normally developed osteoblasts may result in ectopic bone formation.[4] Regardless, bone formation and metabolism involve a complex interplay between osteoblasts, osteoclasts, and signaling molecules, many of which are affected by aromatase inhibitors (AIs).

AIs have a central role in adjuvant treatment of estrogen or progesterone receptor−positive breast cancers. They function by decreasing the peripheral conversion of androgens to estrogen by inhibiting the aromatase enzyme—the primary source of estrogen in postmenopausal women.[5] Common side effects depend on the specific AI but often include musculoskeletal toxicities, loss of bone minerals, and postmenopausal symptoms. Additionally, reports of hypercalcemia have been identified after initiation of the drug.[6-8] In the literature, there are no reports of AIs resulting in development of miliary osteoma cutis.

Osteoma formation likely occurs in predisposed individuals, such as those affected by chronic inflammation or trauma. In patients with a predisposition, exposure to a trigger may ultimately precipitate formation of ectopic bone. The patients in these cases both experienced a state of chronic inflammation secondary to rosacea. After initiation of an AI for treatment of their breast cancers, both patients noticed formation of firm, stable papules. We suggest the AI may have served as a trigger of localized calcification. This transition from inflammation to calcification is not a foreign concept. Previous studies of calcinosis cutis have suggested that chronic inflammation with elevations in inflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor-α, result in tissue damage, which serves as a nidus for dystrophic calcification.[9] Similarly, these cytokines have been found to be increased in patients with rosacea as a result of an aberrant innate immune system and toll-like receptor activation.[10] In our cases, initiation of the aromatase inhibitor may have disrupted the calcium homeostasis and, in the setting of ongoing inflammation, precipitated the formation of small calcifications. This course from inflammation, trigger exposure, calcification, and finally ossification requires further investigation.

Treatment of miliary osteoma cutis is cosmetic and often difficult. Medical management using topical

retinoids have been used but with limited success.[4] Surgical options include scalpel excision, but are not feasible with large burden of lesions. Fortunately, the condition may improve in the absence of treatment as seen in case 1.

CONCLUSION

AIs are an important therapeutic component of care given the high incidence of breast cancer. It is unclear if an association between AIs and miliary osteoma cutis exists; however, continued observation is important. Because patients may not see the need to consult a dermatologist, oncologists may be the ones to find additional cases and identify an association.

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