

Herbal supplement-induced nipple and areolar melanosis

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Introduction

Melanosis is the abnormal or excessive production of melanin in the skin or other tissues. Melanosis of the areola/ nipple has been rarely reported and is thought to be less common than mucosal melanosis of the vulva, penis, or oral mucosa. Melanosis of the areola/nipple can clinically mimic melanoma and pigmented mammary Paget's disease as all three are characterized by asymmetric lesions with irregular shape and color [1]. Here we report a case of areola/nipple melanosis likely induced by the herbal supplement, Curcumin Plus.

Case report

A 59-year-old Caucasian woman with a past medical history of Hashimoto's thyroiditis, rheumatoid arthritis, and uterine polyps presented with several months of bilateral darkening of her areolae and nipples. She denied any preceding erythema, pruritus, nipple discharge or bleeding. She was post-menopausal and had no history of breast cancer. Her only medications included levothyroxine and four capsules daily of the supplement Curcumin plus for joint pain.

Clinical examination revealed hyperpigmented patches without scale of both nipples and lower areolae (Figure 1a and 1b). The patient was evaluated by gynecology and endocrinology to rule out underlying hormonal causes. Laboratory test results (complete cell count, basic biochemical analyses, thyroid function, hormone panel including total testosterone, free testosterone, estrogen, estradiol, prolactin, progesterone, follicle stimulating hormone, luteinizing hormone, dehydroepiandrosterone sulfate, cancer antigen 125, hemoglobin A1c, insulin like growth factor-1 and random cortisol level) were normal. Her iron studies were normal except for an increased ferritin level, which was attributed to her rheumatoid arthritis. Ultrasounds revealed slight thyroid enlargement and no ovarian masses, and her mammogram was normal. A 2mm punch biopsy was obtained from each areola. Histopathology of the areola (Figure 2) revealed increased amount of melanin pigment and prominent macromelanosomes in the lower portion of the epidermis, without increased number of melanocytes, consistent with benign melanosis of the areola and nipple.

Two months after initial presentation, the patient discontinued her Curcumin plus supplement. Within one month of discontinuation, her nipples began to lighten and the hyperpigmentation resolved (Figure 1c). One year later, the patient reported that her husband started taking Curcumin Plus and developed nipple hyperpigmentation that resolved after discontinuation of the supplement. However, he was not evaluated by a physician. The timing of onset and resolution of the pigmentation and the absence of any other potential causes, suggest the Curcumin Plus supplement as the inciting cause of the patient's nipple and areolar melanosis.



Figure 1. Right (a) and left; (b) breast showing hyperpigmentation of the lower areolae; c) the left breast after discontinuation of Curcumin plus supplement.

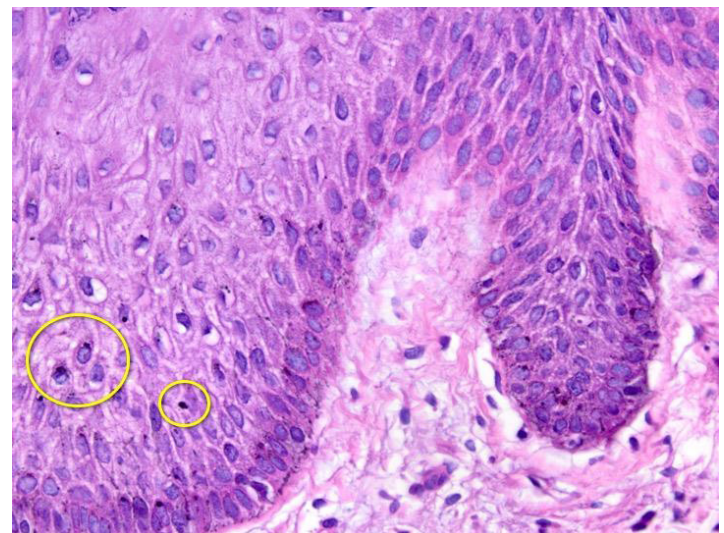


Figure 2. Haematoxylin and Eosin sections (40x magnification) of the areolar biopsy showing increased amount of pigment in the lower portion of the epidermis. Yellow circles indicate macromelanosomes.

Discussion and conclusion

Melanosis of the areola was first described in 1990 by Pittis and Barber within the spectrum of benign melanosis which includes: melanosis of the vulva; penile lentigo; labial melanotic macule and primary acquired melanosis of the conjunctiva [2,3]. Histologic confirmation is required to rule out other diagnoses such as melanoma, pigmented mammary Paget disease, pigmented epidermotropic metastasis from breast carcinoma and unilateral nevoid hyperkeratosis of the nipple and areola [2].

To date there have been limited reported cases of melanosis of the areola. Most documented reports are of young women aged 25 to 40 years. The majority of these women were pregnant when the pigmentation developed or changed, suggesting that melanocytes in the areola may have a higher sensitivity to hormonal stimulation during pregnancy [1,2,4]. While the histopathologic features could be seen in post inflammatory epidermal hyperpigmentation, our patient did not have any preceding inflammation insults and the overall clinical context is more consistent with melanosis. Our patient did not have any known hormonal abnormalities and the dyspigmentation resolved with the discontinuation of the herbal supplement Curcumin Plus. The main ingredients of this supplement are curcumin, *Boswellia serrata*, nattokinase and phenylalanine. Review of the literature did not reveal any cases of areola or nipple melanosis in conjunction with the ingestion of any of these ingredients.

The components of this supplement have limited reported side effects. Curcumin is the active ingredient of the dietary spice turmeric and is extracted from the rhizomes of *Curcuma longa*, a plant in the ginger family [5]. It has been used for inflammatory diseases, diabetes, and Alzheimer's disease [5]. Its benefits are attributed to its antioxidant properties [6]. Therapeutic potential of oral curcumin is thought to be limited due to rapid metabolism [5,6]. Adverse effects are rare and include diarrhea, nausea, yellow stool, increased alkaline phosphatase, headache, rash, increased risk of bleeding, hypoglycemia and allergic contact dermatitis [7]. *Boswellia serrata* is processed from the Burseraceae tree and has anti-inflammatory properties. Adverse effects include nausea, diarrhea, gastrointestinal upset, and increased menstrual flow [8].

Nattokinase is an enzyme contained in the sticky component of natto, a cheese-like food made of soybeans fermented with *Bacillus subtilis* [9]. It has strong fibrinolytic activity and carries a theoretical risk of hemorrhage [9]. Phenylalanine is an essential amino acid and a precursor to melanin and has been reported to improve vitiligo in combination with UVA. Adverse effects include exacerbation of tardive dyskinesia, anxiety, hyperactivity, and headaches [10].

An informal google search revealed that curcumin and *Boswellia serrata* are marketed as skin lightening agents and are used in cosmeceutical products. No reports of hyperpigmentation due to any ingredients of Curcumin plus were found. To our knowledge there have not been any other reported associations between these substances and melanosis of the nipple and areola. While we cannot prove causality, the timing of the patient's and her husband's hyperpigmentation relative to use and discontinuation of Curcumin plus is most suggestive of this.

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