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Syringocystadenoma papilliferum developing over hyperkeratosis of the nipple in a pregnant woman

To the Editor: Syringocystadenoma papilliferum (SCAP) is usually a solitary lesion that most commonly occurs on the scalp.¹ Rarely, lesions have been described on the breast.¹ It usually presents at birth or develops in childhood as a warty crusted papule. Although there is increasing evidence for apocrine histogenesis, eccrine origin could also be a possibility as well as derivation from pluripotent cells.¹ In approximately one third of cases, it is associated with organoid nevus²; it has also been described in association with nevus comedonicus.³ Here we report, to the best of our knowledge, the first case of SCAP developing over hyperkeratosis of the nipple.

A 27-year-old woman in her thirty-fifth week of first pregnancy presented with a 5-week history of enlarging asymptomatic skin lesion on the nipple of her right breast (Fig 1, A). She had had an asymptomatic verrucous hyperpigmented plaque diffusely involving the right nipple for 5 years that was diagnosed as hyperkeratosis of the nipple (HNA) based on biopsy findings of hyperkeratosis, keratotic plugging, acanthosis, papillomatosis, and a sparse perivascular lymphocytic infiltrate (Fig 1, B). The HNA was stable until a new 0.5-cm skin-colored papule developed over the HNA starting in her thirtieth week of gestation. The

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patient was otherwise healthy. Shave excision of the newly developed lesion revealed papillary foci in continuity with the surface squamous epithelium. These papilla had a bilayered epithelium of inner columnar cells showing decapitation secretion and outer flattened cells as well as a fibrovascular core containing abundant plasma cells (Fig 1, C and D). These findings were consistent with SCAP.

First described in 1923, HNA is a benign condition of unknown origin.^{4,5} It is usually bilateral, affecting young adult women and occurring as a hyperpigmented verrucous lesions on the nipple (17%), areola (25%), or both (58%).^{4,5} Although HNA shares clinical and histopathologic features of epidermal nevus, it is usually acquired after puberty and is not associated with systemic disease. In 1938, Lévy-Franckel classified HNA into 3 types. Type 1 is an extension of epidermal nevus. Type 2 is usually associated with several other dermatoses including ichthyosis, Darier disease, or lymphoma. Type 3 is the isolated nevoid variant. Hormonal factors may contribute to its etiopathogenesis in that lesions appear or worsen in pregnancy or with hormonal therapy.⁵

There are yet no reports of an association of HNA with SCAP or other tumors. The fact that HNA shows features of an epidermal nevus and may theoretically be an extension of epidermal nevus makes the development of different neoplasms, including SCAP, within it possible, similar to what has been reported with nevus sebaceous and nevus comedonicus. The basic defect producing the hamartomatous process in epidermal nevi that may result in immature cells capable of differentiating into follicular and glandular cells and tumors could also be playing a role in SCAP development over HNA. This is especially true given that a recent study demonstrated that SCAP could itself be a hamartomatous tumor arising from pluripotent cells.¹

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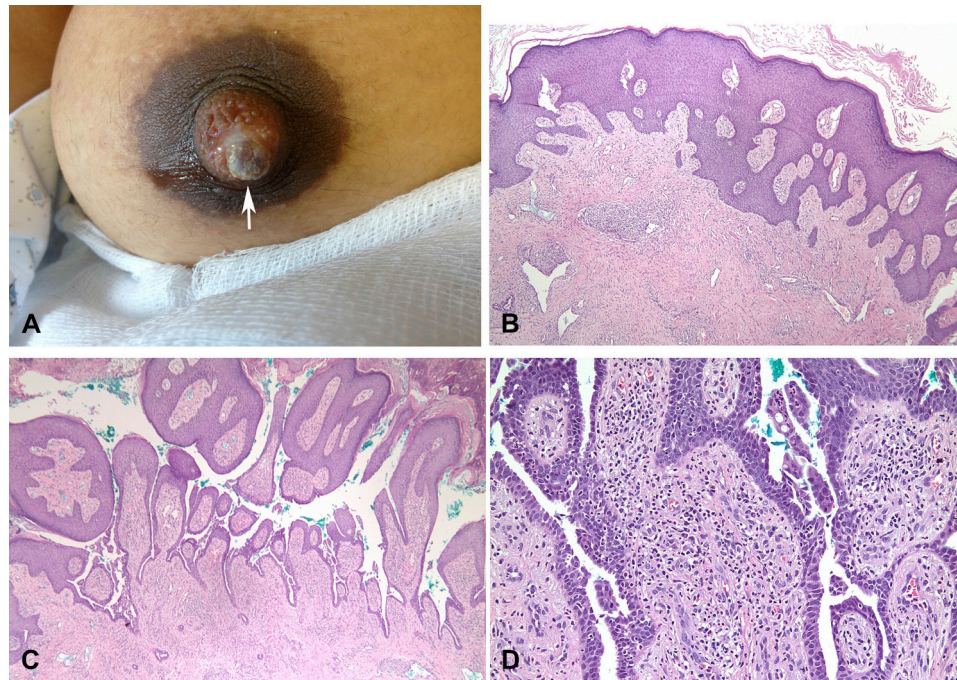


Fig 1. **A**, Syringocystadenoma papilliferum (arrow) developing over hyperkeratosis of the right nipple. **B**, Nevoid hyperkeratosis of the nipple. Orthokeratotic hyperkeratosis, acanthosis, papillomatosis, and a sparse superficial perivascular lymphocytic infiltrate (Hematoxylin-eosin stain; original magnification: $\times 40$). **C** and **D**, Syringocystadenoma papilliferum. Papillary foci in continuity with the surface squamous epithelium. These papilla had a bilayered epithelium of inner columnar cells showing decapitation secretion and outer flattened cells as well as a fibrovascular core containing abundant plasma cells. **C** and **D**, Hematoxylin-eosin stain; original magnifications: **C**, $\times 40$; **D** $\times 200$.

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Ipilimumab-associated Sweet syndrome in a patient with high-risk melanoma

To the Editor: Ipilimumab is a biologic anticancer therapy used in the treatment of advanced melanoma. Ipilimumab's antitumor effect stems from CTLA-4 blockade, which results in the non-specific activation of T cells. Rash is a common side

effect of ipilimumab, with all-grade rash occurring in approximately 25% of patients and high-grade rash in 2.4%.¹ Cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and DRESS have been reported after ipilimumab exposure.^{2,3}

We present what, to our knowledge, is the first reported case of Sweet syndrome associated with ipilimumab therapy. The patient was a 70-year-old white woman with a history of stage IIIB nodular melanoma. Six months before admission, she underwent wide local excision and lymphadenectomy with no evidence of residual disease. Because of her high risk for recurrence, she elected to enroll in a clinical trial for adjuvant chemotherapy and was randomized to receive infusions of high-dose ipilimumab (10 mg/kg) every 3 weeks. Nineteen days after receiving her fourth ipilimumab infusion, she presented to the hospital with a painful rash (Fig 1) and fever, with temperature of 38.4°C. Cutaneous examination revealed multiple erythematous and tender papules and nodules on her face and upper extremities, as well as pseudovesicular lesions on the lips and oral mucosa. Multiple skin biopsies showed similar histopathologic features of a