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Cowden syndrome presenting with trichilemmomas

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Abstract

Cowden syndrome (CS) is a genetic cancer predisposition syndrome that is associated with germline mutations in the phosphate and tensin homologue deleted on chromosome ten (PTEN) tumor suppressor gene. It is characterized by the formation of benign and malignant tumors. Characteristic benign tumors include trichilemmommas, acral keratoses, mucocutaneous neuromas, and oral papillomas. The most common malignant condition include breast, thyroid, and endometrial cancers. We present a case of a 30-year-old woman with CS, who initially presented with trichilemmomas that were misdiagnosed as comedonal acne. Recognition of the presenting features of CS is important to ensure proper referral, management, and treatment for these patients.

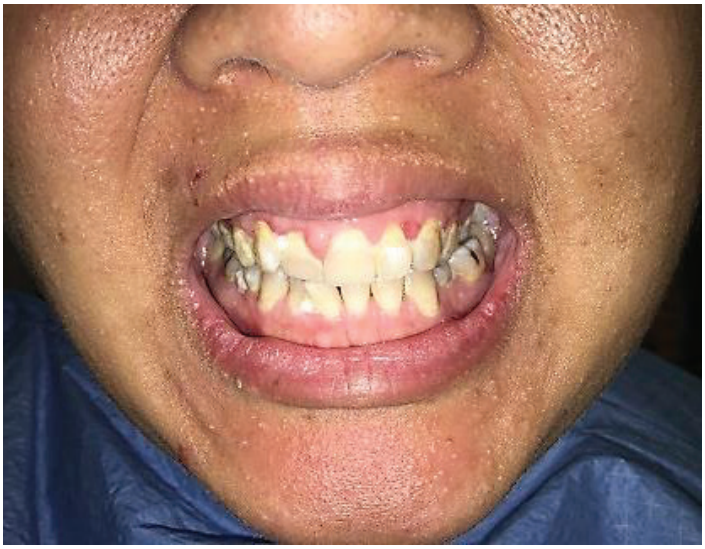

Figure 1. On the upper gingiva, there were several pink cobblestone-like papules.

Case Presentation

PATIENT: 30-year-old-woman
DURATION: Many years
DISTRIBUTION: Face

HISTORY: A 30-year-old woman was referred to Bellevue Hospital Center Dermatology Clinic for the evaluation of bumps on her face, which had been present for many years. When she was younger, a dermatologist had diagnosed the bumps as acne, and she received laser treatments for them. The bumps improved slightly with the laser treatments, but they always returned. She has continued to develop more. The lesions were asymptomatic; they did not itch, hurt, or bleed. There was no family history of similar lesions or skin cancer.

The patient had a history of invasive breast cancer that had been treated with chemotherapy and bilateral mastectomy, and she was undergoing an evaluation for thyroid nodules. She reported that the lesions appeared to diminish in size while she was receiving chemotherapy but subsequently returned after the completion of treatment.

PHYSICAL EXAMINATION: On the upper gingiva, there were several pink cobblestone-like papules (**Figure 1**). On the face and ears, there were many 1-to-3-mm, skin-colored papules, some slightly keratotic in appearance (**Figure 2**).

LABORATORY DATA: On genomic testing, the patient was found to have a c.388 C>T mutation in the PTEN gene.

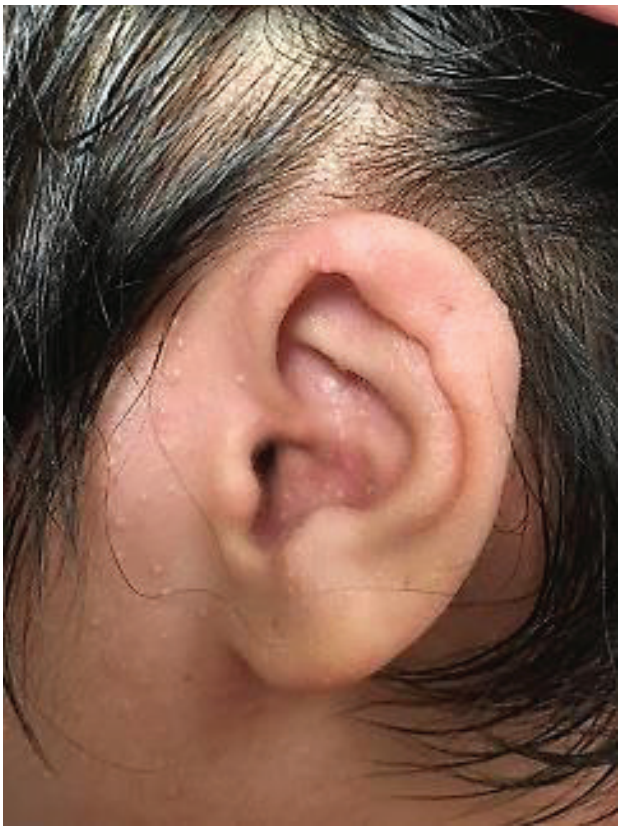

Figure 2. On the face and ears, there were many 1-to-3-mm, skin-colored papules, some slightly keratotic in appearance.

HISTOPATHOLOGY: There is an endophytic, well-circumscribed proliferation of large keratinocytes with pale cytoplasm (**Figure 3**).

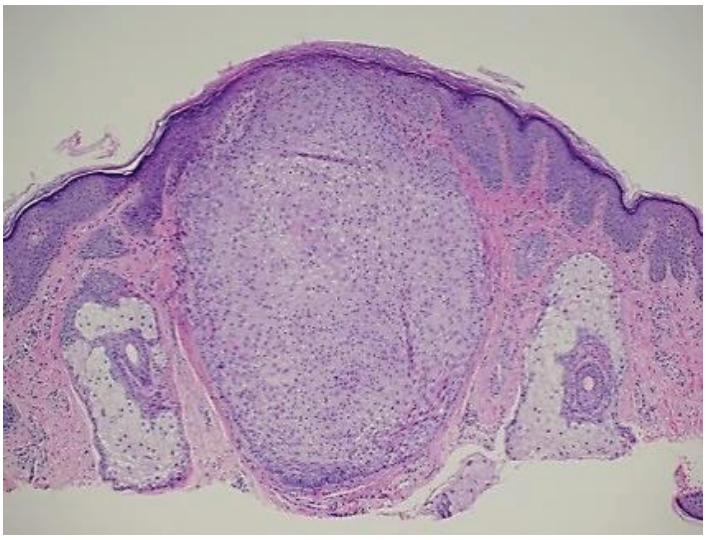

Figure 3. An endophytic, well-circumscribed proliferation of large keratinocytes with pale cytoplasm.

DIAGNOSIS: Cowden syndrome

Discussion

PTEN hamartoma tumor syndrome (PHTS) is a term that is used to describe a group of rare syndromes, which are associated with germline mutations in the tumor suppressor phosphate and tensin homologue deleted on chromosome ten (PTEN). The four major syndromes are Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome, Proteus syndrome, and Proteus-like syndrome. PTEN is a lipid phosphatase that negatively regulates the PI3K-AKT-mTOR pathway, which mediates cell growth and survival. Loss of functional mutations may lead to unregulated cellular proliferation and tumorigenesis. Somatic PTEN mutations are frequently found in cancers of the breast, prostate cancer, and melanoma. In patients with PHTS, germline mutations manifest phenotypically with the formation of hamartomas. In addition to benign tumors, patients with Cowden syndrome, specifically, also are at increased for malignant tumors, which include tumors of the breast, thyroid, and endometrium [1-3].

Cowden syndrome is an autosomal dominant cancer predisposition syndrome that was first described in 1963. It remains the most well-characterized PHTS and is considered the prototype PHTS. Presentation is highly variable, and the diagnosis is based primarily on clinical criteria. The most recently proposed diagnostic criteria were developed in 2013 and have now been adopted by the National Comprehensive Cancer Network (NCCN). These criteria include major and minor diagnostic criteria, and a combination of features is required for diagnosis. Major criteria include mucocutaneous lesions, such as facial trichilemmomas, acral keratosis, mucocutaneous neuromas, and oral papillomas; breast cancer; follicular thyroid cancer; gastrointestinal hamartomas; Lhermitte-Duclos disease; macrocephaly; and macular pigmentation of the glans penis. Minor criteria include autism spectrum disorder, colon cancer, esophageal glycogenic acanthosis, lipomas, mental retardation, renal-cell carcinoma, testicular lipomatosis, papillary thyroid cancer, other thyroid lesions, and vascular anomalies [4].

The mucocutaneous findings of CS are the most distinctive and prevalent and occur in nearly all

patients by their third decade of life. Age of onset ranges from birth to 46 years, with an average age of 22 years. Trichilemmomas, which are benign follicular tumors with outer root sheath differentiation, usually measure 1-to-5 mm and occur on the face and neck [1]. Their pathogenesis is poorly understood, but one study found that most trichilemommas, which are associated with underlying CS, demonstrated loss of PTEN expression by immunohistochemistry while sporadic trichilemommas usually did not, which suggested that immunohistochemical staining could be a useful tool to help identify patients at risk for CS [5]. Oral mucosal lesions are present in up to 90% of patients with CS and present as small white or pink papules that measure about 1-to-3 mm and that may coalesce in a cobblestone pattern. Histopathologic examination may yield a non-specific diagnosis, such as non-specific keratosis, papilloma, or fibropapilloma. These lesions occur most commonly on the gingival, lingual, and labial mucosae and tend to develop after the onset of facial lesions [6, 7]. Acral keratoses demonstrate foci of orthokeratosis on histopathologic examination and may present as pits or verrucous papules on the palms and soles. Lipomas, which fall under minor criteria, occur in more than 30% of patients [1, 4, 8].

Screening for a malignant condition is critical in patients with CS, owing to the increased risk for breast, thyroid, and endometrial cancers. An increased susceptibility to colorectal cancer, kidney cancer, and melanoma also has been found [9]. Of these, breast cancer is the most common, followed by thyroid cancer. Lifetime risk of breast cancer in women with CS has been estimated at 25 to 50%, compared to approximately 12% for the general population. The average age at diagnosis is between 36 and 46 years of age, which is earlier than that for sporadic breast cancers. The lifetime risk for thyroid cancer among patients with CS of both genders has been reported to be 3 to 10% and is usually of the nonmedullary subtype—most commonly follicular or papillary. Benign thyroid disease affects up to 75% of patients with CS. Thyroid anomalies that are associated with CS include multinodular goiter, adematous nodules, and follicular adenomas. The lifetime risk for endometrial cancer is estimated at 5 to 10%, and women with CS also are more likely to develop uterine fibroids. According to NCCN guidelines, screening for malignant conditions should include clinical breast examination every six to 12 months starting at age 25, annual mammography and breast MRI starting at age 30 to 35 years or 5 to 10 years before the earliest known breast cancer in the family, baseline thyroid ultrasound at 18 years and annually thereafter, and colonoscopy at age 35 and every five years thereafter or more frequently if polyps are noted [1, 2, 8].

Recognition of the mucocutaneous features of CS is important, owing to the implications of the diagnosis. Because the cutaneous lesions of CS may be found in the general population, the diagnosis of CS may be overlooked as was the case in this patient, whose trichilemmomas were treated as acne for years. As a result, it is important to maintain a high index suspicion of CS in patients with multiple, characteristic, mucocutaneous lesions. Three or more of any one specific type, among trichilemmomas, acral keratoses, mucocutaneous neuromas, and oral papillomas, is sufficient to satisfy one major criteria. If a diagnosis of CS is considered, referrals to appropriate specialists and consideration for genetic testing should be pursued.

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