Case Report

Cowden syndrome

Early presentation, late diagnosis

Sultan H. Al-Khenaizan, *FRCPC, DABD,* ***Khaled A. Mohajer,*** *MBBS.*

ABSTRACT

تعتبر متلازمة كاودن من الأمراض الوراثية النادرة التي تتميز بتكون أورام عابية في مختلف الأعضاء مع زيادة خطر الإصابة بالأورام السرطانية. يتميز هذا المرض بعلامات سريرية مختلفة حيث تظهر علامات جلدية غير مميزة يمكن تفويتها. نستعرض في هذا المقال حالة مريض سعودي يبلغ من العمر 39 عاماً تقدم مشتكياً من تقرنات طرفية تابعة لمتلازمة كاودن، وقد تم تشخيصها وعلاجها بالخطأ على أنها ثآليل فيروسية من قبل عدة أطباء جلدية. نهدف من هذا المقال إلى زيادة الوعي بمتلازمة كاودن بين العاملين في مجال الرعاية الصحية.

Cowden syndrome is a rare genodermatosis characterized by the formation of hamartomas in various organs and increased risk of malignancy. This disease has variable expression and often presents with subtle skin signs, which can be missed. We report a 39-year-old Saudi male who presented with acral keratoses of Cowden syndrome, and misdiagnosed and treated by many dermatologists as viral wart. We aim to increase awareness of Cowden syndrome among health care workers.

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From the Division of Dermatology, Department of Medicine, King Fahad National Guard Hospital, King Abdulaziz Medical City, Riyadh, Kingdom of Saudi Arabia.

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Address correspondence and reprint request to: Assistant Professor Sultan H. Al-Khenaizan, Consultant Dermatologist, Division of Dermatology, Department of Medicine, King Saud Bin Abdulaziz University for Health Sciences, King Fahad National Guard Hospital, PO Box 22490, Riyadh 11426, Kingdom of Saudi Arabia. Tel. +966 (1) 2520088 Ext. 14175. Fax. +966 (1) 2520088 Ext. 14229. E-mail: salkhenaizan@hotmail.com

Cowden syndrome (CS), also named multiple hamartoma syndrome, is an autosomal dominant (AD) disorder characterized by the formation of hamartomas in various organs, and by increased risk of malignancy.[1] Cowden syndrome is associated with hamartomas and tumors of all 3 embryonic germ layers: ectodermal; mesodermal; and endodermal origin affecting multiple organs.[1] The first case was reported in 1963 by Lloyd and Dennis who named the disease after their patient Rachel Cowden.[2] The disease occurs in approximately 1 in 200,000 individuals, but it is believed to be underdiagnosed, as CS has variable expression, and often presents with subtle skin signs, which can be missed.[3] Here, we present one patient with CS who was misdiagnosed as viral wart, and whose acral keratoses were treated by many dermatologists as such. We also review the current literature emphasizing the recent development of this rare disease.

Case Report. A 39-year-old Saudi male was referred to the dermatology clinic of King Fahad National Guard Hospital for treatment of multiple skin lesions on the face, hands, and feet. These lesions had been present for more than 6 years, and were treated as viral warts by many dermatologists in other hospitals. Examination of the skin revealed multiple smooth-surfaced skin-colored papules on the paranasal areas (**Figure 1**). Hyperkeratotic skin colored papules were seen on the dorsal hands and feet. Pitted keratoses were seen symmetrically on the palms and soles (**Figures 2a & 2b**). Multiple skin tags were seen in the neck and groin area. Head examination revealed large head circumference in the ninety-eighth percentile. Oral cavity examination showed high arched palate and multiple 1-3 mm smooth-surface whitish gingival papules. Multiple excisional skin biopsies taken from facial lesions consistently demonstrated trichilemmomas (**Figure 3**). The patient's past medical history was significant for lower gastro-intestinal (GI) bleeding due to arteriovenous malformation surrounding the cecum associated with Meckel's

diverticulum. The patient has 2 sons and 4 daughters, and one daughter cannot walk, but was unavailable for examination. Two other daughters were deaf-mute. His 13-year-old son had multiple skin-colored small papules over forehead and cheeks, multiple palmo plantar pits, and white small papules on the anterior surface of the upper gingival. Based on the presence of facial trichilemmomas, acral keratoses, mucosal lesions and macrocephaly, a diagnosis of Cowden syndrome was rendered in our patient. Investigations included upper GI endoscopy, which showed diffuse nodularity in lower esophagus and gastric antrum with normal duodenum. Lower GI endoscopy showed nodular mucosa with multiple small polyps. Blood investigations including complete cell count, renal function tests, liver function tests, thyroid stimulating hormone (TSH) were normal. The patient had appointments for follow-up with the dermatology and gastroenterology clinics.

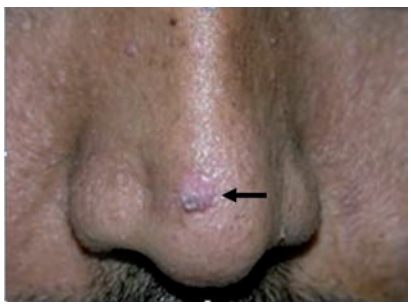

Figure 1 - Multiple warty skin-colored papules on the nose and paranasal areas, later confirmed as trichilemmomas.

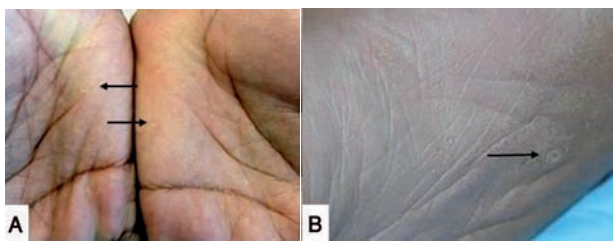

Figure 2 - Pitted keratoses distributed symmetrically on the **a**) palms, and **b**) soles.

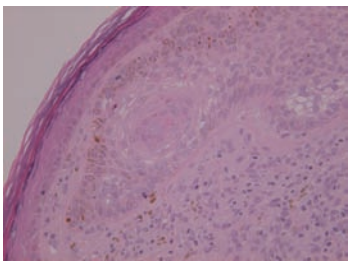

Figure 3 - Histopathological appearance of facial small papules confirming the diagnosis of trichilemmoma (Hematoxylin and Eosin, x20)

Discussion. Cowden syndrome is a rare genodermatosis with over 150 cases reported in the literature.[1] Most patients with CS manifest the phenotype by the age of 20 years, which includes facial trichilemmomas, acral keratoses, papillomatous papules, and mucosal papillomas.[4] Facial trichilemmomas are the most frequent lesions, and can be seen in 86% of patients, preferentially localized in the periorificial regions.[1] Acral keratoses are skin colored, warty papules on the dorsum of hands and feet, while palmoplantar keratoses are translucent punctuate keratoses on palms and soles.[1] Mucosal papillomas are present in 80% of patients and can impart cobblestone appearance.[1] Squamous cell carcinoma, basal cell carcinoma, malignant melanoma, Merkel cell carcinoma, and trichilemmal carcinoma have also been reported.[5]

Thyroid, breast, GI, skeletal, and genitourinary findings are the most frequent systemic manifestations of CS.[4] One of the most frequently reported internal manifestation is thyroid disease, occurring in approximately two-thirds of patients.[1] This includes multinodular goiter, thyroidal dysfunction, and thyroiditis.[1] The risk for thyroid cancer, typically follicular is approximately 10%.[1] In women with CS, the lifetime risks of breast cancer is estimated to be 25-50% in contrast to the 11% in the general population, and is bilateral in one-third of patients.[5,6] Fackenthal et al[7] reported breast cancer in male patients. Another common benign breast lesion is fibrocystic disease.[1] The most frequent changes in the female genitourinary tract are functional menstrual irregularities and ovarian cysts.[4] The risk of endometrial carcinoma has been estimated to be 5-10%.[8] Renal cell carcinoma, carcinoma of the bladder, hepatocellular carcinoma, and cervical cancer have been previously reported.[4]

The frequency of GI involvement in CS range from 65.6-93%.[9] Multiple polyps may be found anywhere throughout the GI tract, but most commonly in the colon with variable histopathologic features with low malignant potential.[4] Esophageal glycogenic acanthosis is a characteristic clinical manifestation of CS, and is used to distinguish CS from other polyposis syndromes.[4] Abnormalities of the central nervous system (CNS) are seen in approximately one-fifth of patients.[1] The pathognomonic feature within the CNS is the presence of Lhermitte-Duclos disease (LDD) (dysplastic gangliocytoma of the cerebellum), which is

a rare, slow growing, and non-malignant hamartoma.[5] Symptoms initially include headaches, cerebellar ataxia, and visual problems, while advancing disease leads to increased intracranial pressure.[5] Macrocephaly, defined as a head circumference greater than the ninety-seventh percentile, is present in approximately 80% of patients with CS.[5]

Cowden syndrome is inherited as an AD trait, with variable age-dependent penetrance, and may occur as de novo mutation.[1] The CS is caused by germ-line mutation in the phosphatase and tensin homolog (PTEN) gene, which is located on chromosome 10q23.3.[1] The PTEN mutation frequency range from 34-80% in individuals meeting the diagnostic criteria of CS.[3,10] The protein PTEN is a dual-specificity lipid phosphatase with enzymatic activity that removes phosphate groups from several intracellular signaling molecules.[3] It regulates cellular processes including cell cycling, translation, and apoptosis.[3] The PTEN has been associated with other disorders, often referred to collectively as the PTEN hamartoma tumor syndrome (PHTS).[6] The PHTS includes CS and Bannayan-Riley-Ruvalcaba (BRR) syndrome, which is characterized by macrocephaly, developmental delay, multiple lipomas, vascular malformation, and speckled penis.[6] The highest PTEN mutation frequencies (>92%) are consistently obtained in CS-BRR overlap families.[1]

The International CS Consortium Operational Criteria proposed a set of diagnostic criteria.[1] Pathognomonic criteria include facial trichilemmomas, acral keratoses, papillomatous lesions, and mucosal lesions.[1] Major criteria include breast cancer, thyroid cancer (non-medullary), macrocephaly, LDD, and endometrial cancer.[1] The most recent guidelines consider adult-onset LDD as pathognomonic for CS.[5] Thyroid lesions, mental retardation, GI hamartomas, fibrocystic disease of the breast, lipomas, fibromas and genitourinary tumors, or malformations are defined as minor criteria.[1] The diagnosis of CS is established when a patient has: 1) pathognomonic lesions alone, if there are 6 or more facial papules, of which 3 or more must be trichilemmoma, or cutaneous facial papules and oral mucosal papillomatosis, or oral mucosal papillomatosis and acral keratoses, or 6 or more palmoplantar keratoses; 2) 2 major criteria, one of which must be macrocephalia or LDD; 3) one major criterion and 3 minor criteria; 4) 4 minor criteria.[1]

Management of the patient with CS is multidisciplinary.[4] Baseline studies should include full blood count, urine analysis, TSH, thyroid scanning, chest radiography, and should be repeated as clinically indicated.[4] Further studies should be based on symptoms or abnormalities found in a thorough physical examination.[3] Due to increased risk of colorectal cancer, baseline screening colonoscopy at age 35 years, or at the time of diagnosis, and then proceed with interval testing as needed is recommended.[9] The PTEN testing as a molecular diagnostic tool has recently become available.[6] Treatment of facial papules and oral lesions have included surgical excision, curettage, oral isotretinoin, topical 5-fluorouracil, or laser ablation.[4] Education regarding the signs and symptoms of cancer is important.[3] A life-long follow up is necessary.[4] Patients should also be advised regarding the risk to relatives, and genetic testing should be suggested.[1]

In conclusion, we report an interesting case of Cowden syndrome where diagnosis was delayed. Dermatologists and gastroenterologists need to be aware of the cutaneous and internal features of this rare disease. This will facilitate early diagnosis, and hopefully, prevention of potential complication.

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