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# Cowden syndrome: clinical case and a brief review

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## Abstract

Cowden syndrome is a rare genodermatosis of autosomal dominant inheritance characterized by multiple hamartomas in several organs and an increased risk of malignancies. We present the case of a 53-year-old man with a history of benign and malignant thyroid disease, intestinal polyposis, and Chiari malformation. He had several trichilemmomas, papillomatosis of the oral cavity, macular pigmentation of the glans penis, among other clinical features suggestive of Cowden syndrome. Given the suspicion, genetic study was conducted and *PTEN* mutation was identified. Cowden syndrome affects 1:200,000 individuals. Mucocutaneous lesions are almost always present and there may be other typical features involving other organs, namely thyroid, colon, and brain. Mucocutaneous lesions may be the initial manifestation of this disorder and usually precede the onset of malignant lesions, making timely diagnosis essential for proper monitoring and screening.

**Keywords:** Cowden syndrome, genetics, *PTEN* mutation, trichilemmoma

## Introduction

Cowden syndrome (CS) is a rare genodermatosis of autosomal dominant inheritance and incomplete penetrance that most commonly results from the germline mutation of the phosphatase and tensin homolog gene (*PTEN*) deleted on chromosome 10 [1-6]. It is characterized by the presence of multiple hamartomas as well as an increased risk of certain types of cancer [1, 2, 6].

## Case Synopsis

A 53-year-old man was referred to our dermatology department owing to fibromas on the trunk and hyperkeratotic lesions on the hands evolving during the last 10 years (**Figure 1**). His medical history included multinodular goiter and total thyroidectomy owing to follicular variant of papillary thyroid carcinoma, intestinal polyposis, and Chiari malformation. The patient had no family history of genetic disorders. In addition to the fibromas and hyperkeratotic lesions on the dorsa of both hands, physical examination revealed facial papules suggestive of trichilemmomas, papillomatosis of the oral cavity in a cobblestone pattern, macular pigmentation of the glans penis, palmoplantar keratosis, macrocephaly (64.5 cm), and multiple lipomas (**Figures 2, 3, 4**). Past histological examinations of multiple intestinal polyps revealed the presence of hamartomatous lesions.



**Figure 1.** Hyperkeratotic lesions on the dorsa of the hands.



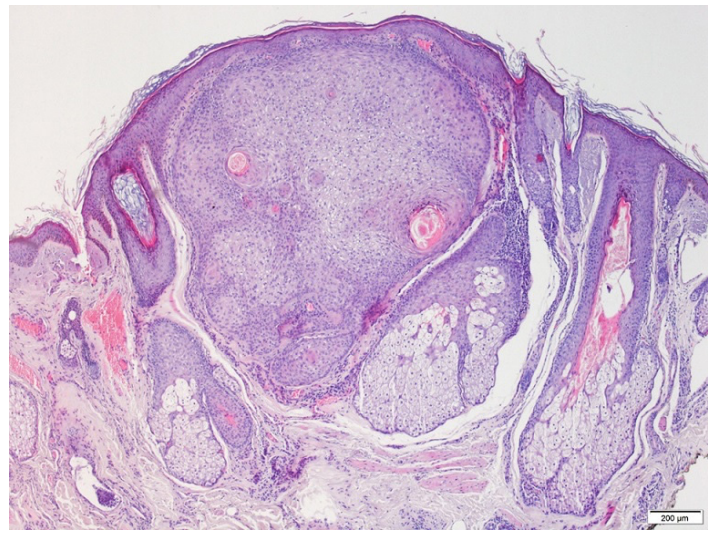
**Figure 2.** Trichilemmoma of the left hemiface.



**Figure 4.** Macular pigmentation of the glans penis.



**Figure 3.** Oral papillomas in a cobblestone appearance.



**Figure 5.** Solid lobule in the upper dermis, connecting with the epidermis, composed of small clear cells. A few squamous eddies are present.

Given this clinical presentation, the diagnostic hypothesis of CS was considered. Several biopsies were performed and confirmed facial trichilemmomas, inflammatory fibro-epithelial hyperplasia in the gingival mucosa, acral keratosis, and fibromas on the trunk (**Figure 5**).

Genetic study confirmed the *PTEN* mutation. Laboratory investigation and renal ultrasound showed no significant changes.

There was no family history of the disease. The study of the patient's offspring revealed a child with macrocephaly and all of the children are under investigation to screen for *PTEN* mutation.

## Case Discussion

CS was first recognized as a clinical entity in 1963 and first related to the mutation of the *PTEN* gene in 1997 [1, 2, 5-7]. *PTEN* is a suppressor gene responsible for the development of at least four distinct autosomal dominant syndromes, including CS presenting in adulthood, Bannayan-Riley-Ruvalcaba syndrome, a rare congenital disorder presenting in childhood, Proteus syndrome, and Proteus-like syndrome [1, 3, 4, 7, 8]. *PTEN* mutation is present in about 80% of the cases, whereas the remaining are associated with other mutations, leading to increased cell proliferation and survival [5, 9]. There is an associated risk of development of malignant tumors, such as brain, breast, endometrium, colon, thyroid, and

**Table 1.** Criteria used in the Cleveland Clinic Adult Clinic Scoring System.

PTEN Cleveland Clinic Score Calculator
Gender
Age
Head circumference
Age at date of measurement
Previous diagnosis of autism, developmental delay or mental retardation
Presence of suggestive skin lesions
Presence of suggestive mucosal features
Presence of arteriovenous malformations
Diagnosis of gastrointestinal polyps
History of thyroid cancer
History of germ cell tumors

kidney [1-3, 7], which may occur in at least 40% of the patients [5].

This syndrome affects 1:200,000 individuals [8, 9]. The great phenotypical variability makes the disease a diagnostic challenge [1, 2].

Skin manifestations are present in almost all patients [5, 6]. Trichilemmomas, acral keratosis, and palmoplantar pits are examples of cutaneous findings that may raise the suspicion of CS [2]. Oral papillomas are frequently observed and generally coalesce giving a "cobblestone appearance" [5, 6]. Macular pigmentation of the glans penis is also a major diagnostic criterion and may present in almost half of the male patients [7].

The frequency of gastrointestinal polyps is high in patients with CS [4, 6-9]. Histologic types include hamartomatous, hyperplastic, inflammatory, lipomatous, ganglioneuromatous, and adenomatous polyps [2, 4, 9]. The lifetime risk of colorectal carcinoma is 16% [5].

Thyroid pathologic findings encompass both benign and malignant features. Benign thyroid disease is expected in 50-70% of the patients [2, 5], whereas malignant tumors emerge in about 14% of the cases [4]. The most common histologic subtype of thyroid carcinoma is papillary carcinoma, followed

by follicular and anaplastic carcinomas [4].

Brain manifestations of CS include macrocephaly, one of the most consistent features of CS, as well as Lhermitte-Duclos disease (LDD), a dysplastic gangliocytoma of the cerebellum that typically occurs in adulthood [2, 6, 7]. Some studies suggest that individuals with CS may have varying degrees of cognitive impairment [2, 7]. In our patient, there is a history of Chiari malformation that has never been linked to the syndrome in the literature. We need more data to suggest a possible relationship between the two entities.

There are several ways to screen CS in suspected patients. The Cleveland Clinic adult clinical scoring system is able to calculate the risk probability of *PTEN* mutation for adult patients with no family history of the syndrome [3, 10], (**Table 1**). There are also screening recommendations of the National Comprehensive Cancer Network (NCCN), revised in 2015, that help with the diagnosis [4]. In the latter, features are divided into major and minor criteria, as shown in **Table 2** [1, 2, 7].

According to NCCN guidelines, our patient presented 4 major and 3 minor criteria for the diagnosis of CS.

**Table 2.** Adapted National Comprehensive Cancer Network guidelines for the diagnosis of Cowden syndrome.

Major criteria	Minor criteria
Breast, endometrial or follicular thyroid cancer	Autism spectrum disorder
Lhermitte-Duclos disease (adult-onset)	Colon, papillary thyroid cancer (papillary or follicular variants) or renal cell carcinoma
Macrocephaly	Esophageal glycogenic acanthosis ( $\geq 3$ )
Macular pigmentation of the glans penis	Intellectual disability (IQ $\leq 75$ )
Mucocutaneous lesions including at least three: trichilemmomas; or palmoplantar pits; or acral hyperkeratotic papules; or oral papillomas (or one proven by biopsy); or mucocutaneous neuromas	Lipomas (at least three) Testicular lipomatosis
Three or more GI hamartomas/ganglioneuromas	Thyroid abnormalities, including adenoma, goiter or nodules Vascular abnormalities, including cerebral developmental venous anomalies
Criteria for diagnosis Three or more major criteria, one being macrocephaly, Lhermitte-Duclos disease, or GI hamartomas OR Two major and three minor criteria	

One previous study, suggests that mucocutaneous lesions respond promptly to acitretin but may recur after discontinuation of the therapy [11]. Other treatment options have been used to remove skin lesions, including surgical excision, curettage, and laser therapy [12]. Targeting the dysregulated signaling pathway with rapamycin, an (mTOR) inhibitor, may be a therapeutic alternative in the future that may work by causing a functional compensation of the decontrolled cell growth [5].

Since this syndrome is associated with several malignancies, it is crucial to diagnose early and monitor these patients closely. There are screening guidelines also developed by NCCN that help the physician to timely monitor the most affected organs in patients diagnosed with CS [2]. Screening and surveillance should be started at the age of 18 with an annual physical examination and annual thyroid ultrasound [5]. In females, breast examination is recommended after the age of 25 every 6-12 months, including imaging tests after the age of 35 [2]. With regard to colorectal and endometrial cancer, the recommendations suggest that screening begins at the age of 35, with colonoscopy every 5 years and annual endometrial examination [2, 5]. Skin checkup should also be encouraged [2, 5]. Renal ultrasound

every 1-2 years may be recommended starting at the 5th decade [2].

Genetic counseling and screening of the relatives is recommended as assisted reproductive technologies may be used to avoid CS in future offspring of these individuals [2].

## Conclusion

In closing, this case reveals the importance of recognizing this uncommon syndrome, particularly given that mucocutaneous manifestations usually emerge early in the clinical course and may contribute to an adequate surveillance of associated malignancies.

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