Novel PTEN mutation in Cowden syndrome: case report with late diagnosis and non-malignant course

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Abstract

Cowden syndrome (CS) is an infrequent genodermatosis caused by mutations in the *phosphatase and tensin homolog* (*PTEN*) gene in the majority of cases. As such, it belongs to the PTEN hamartoma tumor syndrome spectrum. This disease has a variable clinical expression characterized by the development of multiple hamartomatous tumors in different organs, usually during the second and third decades of life, and a high cumulative risk of several malignancies. We present a case of Cowden syndrome with late diagnosis presenting with a florid dermatological expression and multiple benign tumors, but no malignancies. A novel *PTEN* mutation was identified.

Keywords: Cowden syndrome, multiple hamartoma syndrome, PTEN hamartoma tumor syndrome, PTEN, hereditary cancer syndromes

Introduction

Cowden syndrome (CS) is a rare genetic condition that belongs to a spectrum of diseases derived from *phosphatase and tensin homolog* (*PTEN*) gene mutations, which compose the PTEN hamartoma tumor syndrome (PHTS), [1]. Clinical presentation includes multiple benign lesions and several malignant neoplasms [1, 2]. Mucocutaneous lesions usually appear within the first couple of decades, allowing dermatologists to suspect this condition before malignant neoplasms develop [3].

The diagnosis is classically based on clinical criteria, periodically updated by the National Comprehensive Cancer Network (NCCN), [2], though confirmatory genetic testing is frequently used. Other criteria may serve as tools for selecting patients for genetic testing, such as the NCCN's *PTEN* testing criteria 2 and the Cleveland Clinic clinical scoring system for phenotype-based pre-test probability [4]. Multiple *PTEN* gene mutations have been identified, though the different types apparently do not indicate clinical variability [5].

Case Synopsis

A 52-year-old woman consulted for multiple warts of her hands and feet. She had been treated repeatedly with topical agents and cryotherapy. Her medical history included thyroidectomy for multinodular goiter, bilateral cholesteatoma, hysterectomy for uterine fibroids, trigeminal schwannoma, tracheal fibrotic nodules, and a finger fibroma. There was no family history of multiple neoplasms or hereditary syndromes.

Physical examination revealed keratotic, wart-like papules on the dorsum of hands and feet, and round, keratotic palmoplantar pits (**Figure 1**). Centrofacial and periorificial keratotic papules of 1-2 millimeters were also identified (**Figure 1**). Oral examination revealed a buccal polypoid papule and gingival papillomatosis (**Figure 2**). Head circumference was below the 97th percentile.

The histopathology of acral and facial papules was consistent with trichilemmoma. Gingival biopsy showed verrucous hyperplasia with no dysplasia. The buccal lesion was an oral fibroma. Breast cancer screening was negative. Gastrointestinal endoscopy revealed glycogenic acanthosis and ten colorectal inflammatory and hyperplastic polyps.

She met sufficient NCCN genetic testing criteria and scored 77% (52.7-91.3%) in the Cleveland Clinic scoring system. *PTEN* gene study revealed a heterozygous mutation: a four-nucleotide deletion (c.510_513del) resulting in a premature stop codon (p.Ser170Argfs*12). No reference of this mutation was found in published literature and genetic databases.

Case Discussion

We present a 'de novo' case of CS, with late diagnosis and atypical presentation, in which a novel *PTEN* mutation was identified.

Although our patient was diagnosed with CS at 52 years of age, the diagnosis is usually made earlier based on familial history and mucocutaneous findings, since the latter develop during the first decades of life [3]. Early diagnosis is important for correct management of the risk of malignancies, which typically develop before the sixth decade of life [2, 3]. Our patient has reached this age and fortunately remains malignancy-free.

The diagnosis of CS relies heavily on its clinical diagnostic criteria. According to the latest updates in the NCCN guidelines these include breast, endometrial (epithelial), and thyroid (follicular) cancer. Additional associations include ≥3 gastrointestinal hamartomas (including ganglioneuromas, but excluding hyperplastic polyps), Lhermitte-Duclos disease (dysplastic gangliocytoma of the cerebellum), macrocephaly (≥97th percentile), macular pigmentation of the glans penis, and mucocutaneous lesions as major criteria. The latter is fulfilled when presenting any of the following: ≥3 trichilemmomas (at least one biopsy proven), ≥3 acral keratoses (palmoplantar keratotic pits and/or acral hyperkeratotic papules), ≥3 mucocutaneous neuromas, and/or ≥3 oral papillomas. Minor criteria include autism spectrum disorder, colon cancer, ≥3 esophageal glycogenic

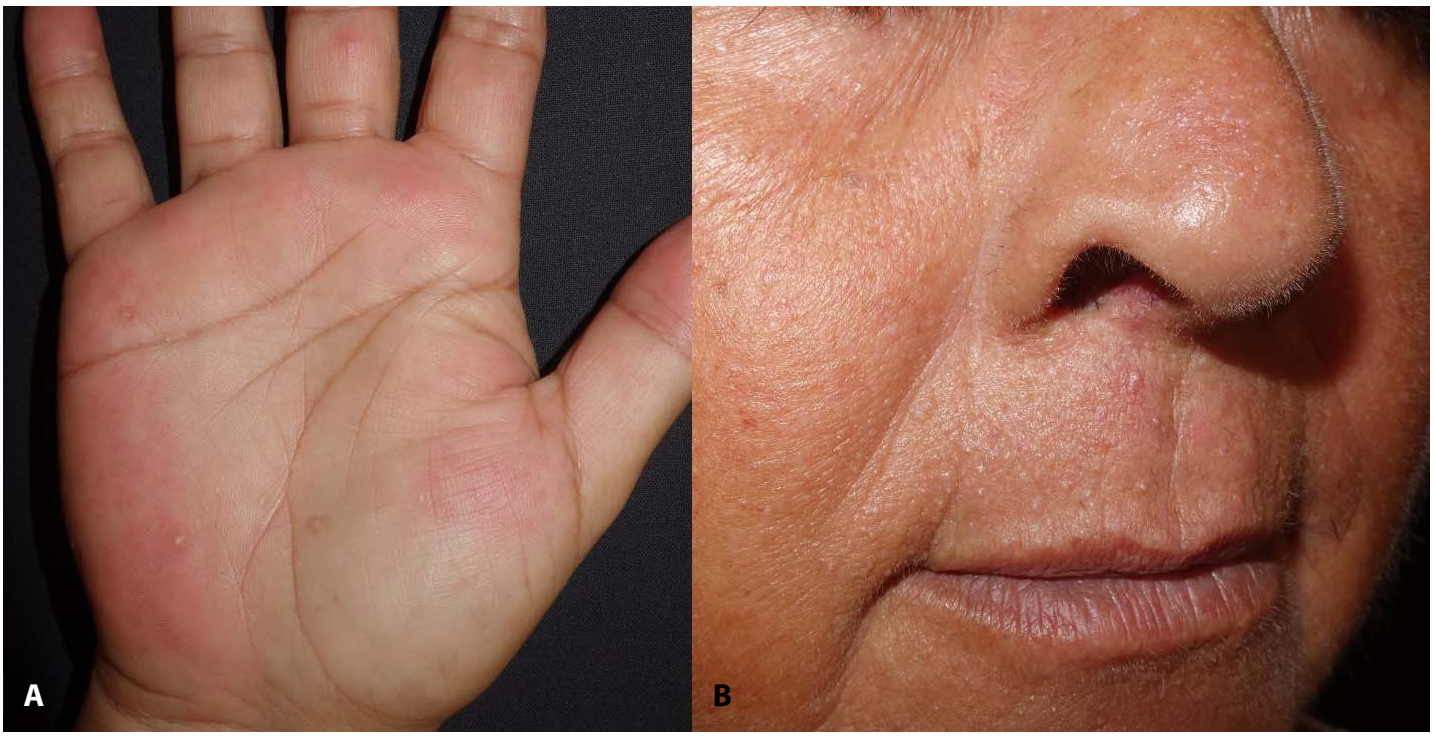

Figure 1. *Cutaneous lesions.* ***A)*** *Round keratotic palmar pits.* ***B)*** *Millimetric keratotic papules with centrofacial and periorificial distribution.*

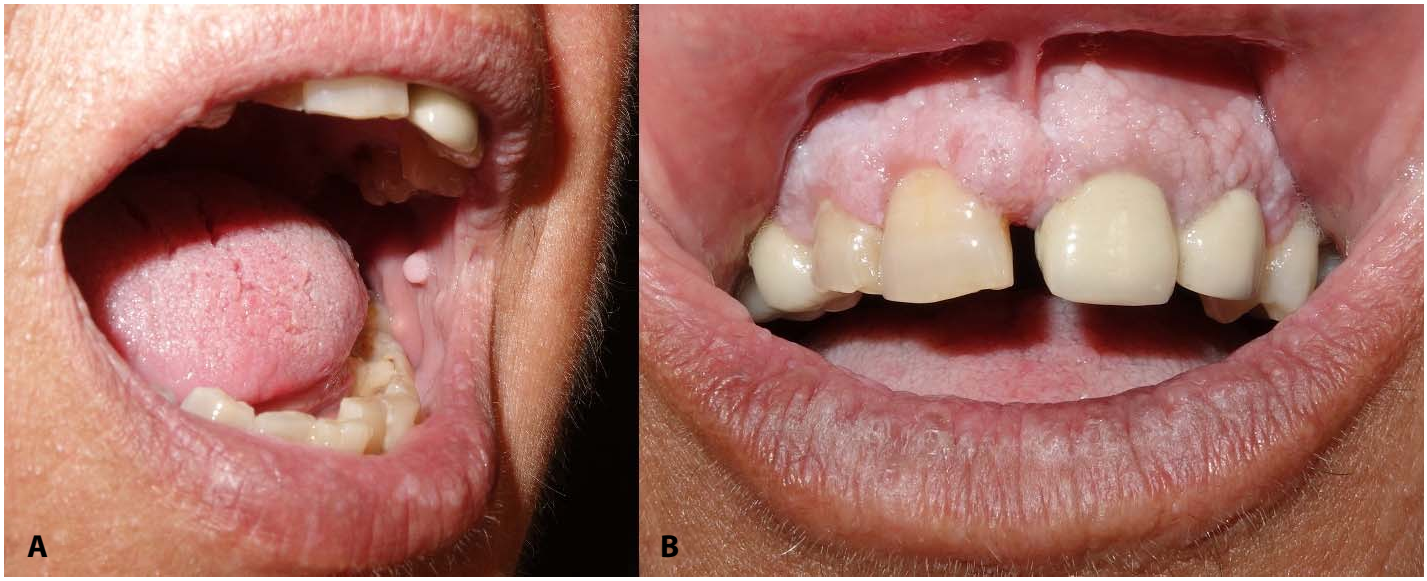

Figure 2. *Oral lesions.* ***A)*** *Polypoid lesion on the buccal mucosa.* ***B)*** *Gingival papillomatosis.*

acanthoses, ≥3 lipomas, intellectual disability, renal cell carcinoma, testicular lipomatosis, thyroid cancer (papillary or follicular variant of papillary), thyroid structural lesions (including adenoma and multinodular goiter), and vascular anomalies. Among individuals without a family history of CS/PHTS, clinical diagnosis can be made when meeting ≥3 major criteria or by meeting two major and three minor criteria. Our patient only met one major criterion (mucocutaneous lesions) and two minor criteria (glycogenic acanthosis and thyroid structural lesions). Therefore, despite presenting with multiple mucocutaneous lesions and a high clinical suspicion from a dermatological perspective, she did not meet sufficient NCCN criteria for the operational clinical diagnosis [2]. However, the NCCN criteria for PTEN testing [2] includes these items but requirements are less rigorous. The CC Cleveland Clinic system [5] also takes into account a wider range of manifestations. The latter two are useful tools supporting genetic testing.

Study of the *PTEN* gene identified a novel mutation that was considered pathological owing to the presumed deleterious effect on the PTEN protein. It is unclear whether this particular mutation is related to our patient's clinical features and non-malignant course.

Conclusion

This case underlines the importance of dermatological evaluation in the diagnosis of CS/PHTS and the usefulness of developing testing criteria, which take into account this spectrum's significant clinical variability. This highlights the need for continued revision of clinical diagnostic criteria and study of possible mutation-phenotype associations.

Potential conflicts of interest

The authors declare no conflicts of interests.

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