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The Pivotal Pimpels: Collagenomas as Early Indicators of Cowden Syndrome in a Boy Collagenomas in Cowden Syndrome

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Abstract

Cowden syndrome (CS) is a rare autosomal dominant disorder predisposing to various extracutaneous benign and malignant tumors due to germline mutations in the PTEN gene. CS is characterized by highly variable expressivity and age-dependent penetrance. Mucocutaneous manifestations often represent important clinical clues to the diagnosis of CS and may precede the development of tumors in internal organs. We report on a boy in whom the presence of multiple collagenomas served as a clinical clue to the diagnosis of CS at the age of 4 years. Such early diagnosis enables the establishment of a screening programme years before malignant tumors develop.

Keywords: Cowden Syndrome; Collagenoma; Connective Tissue Nevi; Germline Mutation, Hamartoma, Macrocephaly; PTEN Phosphatase

Abbreviations: CS: Cowden Syndrome; PTEN: Phosphatase and Tensin Homolog; NCCN: National Comprehensive Cancer Network; BOS: Buschke–Ollendorff Syndrome; TS: Tuberous Sclerosis; MEN1: Multiple Endocrine Neoplasia Type 1; PHTS: PTEN Hamartoma Tumor Syndrome

Introduction

Cowden syndrome (CS) is an autosomal-dominant genetic disorder caused by germline phosphatase and tensin homolog (PTEN) mutations on chromosome 10, characterized by multiple hamartomatous lesions in the skin and various organs. PTEN is a phosphatase that acts as a tumor suppressor, inhibiting cell proliferation in various tissues. In CS, loss-of-function mutations in PTEN gene lead to overactivation of the PI3K/AKT/mTOR pathway, resulting in increased proliferation and survival of tissue cells. Mucocutaneous benign lesions most commonly develop much earlier compared with malignant tumors, making cutaneous lesions to important marker lesions for CS.

The most common skin lesions observed are trichilemmomas (6-38%), mucocutaneous neuromas (5–10%), oral papillomas (15–85%) and acral keratoses (10-82%) [1]. The most common extracutaneous manifestations include macrocephaly (80-100%) [2,3], gastrointestinal polyps (80-90%), and solid tumors such as breast (85% of female patients, with only anecdotal cases in male patients [4,5], thyroid (35%), endometrial cancer (28%) and renal cell carcinoma (34%) [6]. Early diagnosis is crucial for managing symptoms effectively, initiating cancer surveillance, improving outcomes and offering genetic counseling to affected families.

Diagnosis of CS is based on established clinical criteria, most commonly the revised criteria proposed by Pilarski et al. and incorporated into current National Comprehensive Cancer Network (NCCN) guidelines (Table 1) and is confirmed by PTEN genetic testing [7]. Differential diagnoses include Buschke–Ollendorff syndrome (BOS), isolated familial collagenomas [8], sporadic eruptive collagenomas [9], tuberous sclerosis (TS) and

multiple endocrine neoplasia type 1 (MEN1) [10], as detailed in Table 2. Early diagnosis of CS, however, can be particularly challenging in case of a negative family history, when a de-novo mutation must be suspected. In this situation, the recognition of suggestive skin lesions can be paramount as shown in our case.

Table 1: Clinical criteria according to NCCN (25) for the diagnosis of CS, (the right column indicates the criteria present in our patient at the age of 18 years)

	Present in our patient
Major criteria	
Breast cancer	-
Endometrial cancer (epithelial)	N/A
Thyroid cancer (follicular)	-
Gastrointestinal hamartomas (including ganglioneuromas, but excluding hyperplastic polyps)	-
Lhermitte-Duclos disease (adult)	-
Macrocephaly (≥97th percentile: 58 cm for women, 60 cm for men)	x
Macular pigmentation of the glans penis	-
Multiple mucocutaneous lesions (any of the following, biopsy proven OR dermatologist diagnosed):	x
- Multiple trichilemmomas (≥3, at least one biopsy proven)	
- Acral keratoses (≥3 palmoplantar keratotic pits and/or acral hyperkeratotic papules)	
- Mucocutaneous neuromas (≥3)	
- Oral papillomas (particularly on tongue and gingiva, multiple (≥3))	
Minor criteria	
Autism spectrum disorder	-
Colon cancer	-
Oesophageal glycogenic acanthosis (≥3)	-
Lipomas (≥3)	-
Mental retardation (intelligence quotient ≤75)	-
Renal cell carcinoma	-
Testicular lipomatosis	-
Thyroid cancer (papillary or follicular variant of papillary)	-
Thyroid structural lesions (e.g., adenoma, multinodular goitre)	-
Vascular anomalies (including multiple intracranial developmental venous anomalies)	-
At-risk individuals:	
Three or more major criteria (one of which must include macrocephaly, Lhermitte-Duclos disease, or gastrointestinal hamartomas) or	
Two major criteria and three minor criteria.	
Relatives:	
Any two major criteria with or without minor criteria; or	
One major and two minor criteria; or	
Three minor criteria.	

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Table 2: Differential diagnoses of Cowden syndrome.

	Gene mutation	Skin manifestations	Organ manifestations	Malignant tumors	Onset of skin lesions	Onset of extracutaneous manifestations
Buschke Ollendorf syndrome	LEMD3 gene	Elastomas and collagenomas	Osteopoikilosis	Osteosarcoma	Adolescence	Childhood
Familial collagenomas	LEMD3 gene	Multiple isolated collagenomas	-	-	Adolescence	-

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Cowden syndrome	PTEN gene	Collagenomas, trichilemmomas, oral papillomas, acral keratoses, sclerotic fibromas, mucocutaneous neuromas	Gastrointestinal hamartomatous polyps, hypothyroidism, macrocephaly, neurodevelopmental delay	Breast, thyroid and endometrial cancers	Childhood	Adulthood
Tuberous sclerosis	TS1/TS2 gene	Facial angiofibromas, periungual fibromas (Koenen tumors), hypomelanotic macules (Ashleaf spots), Shagreen patches on the lower back	Renal angiomyolipomas, seizures, cognitive impairment	Renal cell carcinoma	Infancy	Childhood
MEN1	MEN1 tumor-suppres-sor gene	Collagenomas, angiofibromas, gingival papules and lipomas, café au lait macules, confetti-like hypopigmen-tations	Tumors of parathyroidglands, endocrine pancreas, neuroendocrine tumors and anterior pituitary.	Malignant degeneration of neuroendocrine tumors	Adolescence	Adoles-cence

Table Abbreviations: NCCN: National Comprehensive Cancer Network; CS: Cowden Syndrome; MEN1: Multiple endocrine neoplasia.

Case Report

A 4-year-old boy was referred from his pediatrician due to multiple, firm, dome-shaped papules located on the neck, scalp, back, armpits, and left hand, each measuring approximately 0.5 to 1 cm in diameter (Figure 1). These lesions were asymptomatic but had increased in number since early childhood. The child had remarkable macrocephaly without symptoms. Initially, the cutaneous lesions were suspected to be connective tissue nevi, leading to a provisional diagnosis of BOS. However, genetic testing for the LEMD3 mutation, associated with this condition, was negative. The patient's family history was unremarkable, with no reported cases of CS, associated cancers, or related syndromes. A larger lesion located on the left hand was surgically removed after a mechanical trauma.

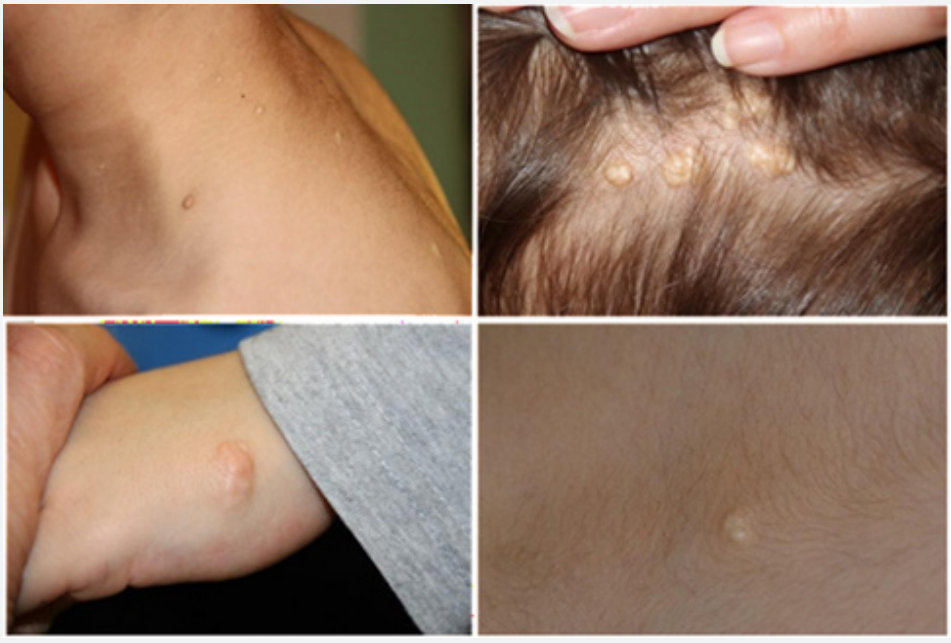

Figure 1: Collagenomas that developed up to the age of 4: a) neck; b) scalp; c) left hand; d) trunk.

The resulting histopathology revealed tightly packed collagen bundles in a storiform pattern [11], consistent with a sclerotic fibroma- a specific subtype of collagenomas. This finding together with the important macrocephaly raised suspicion of CS. Subsequent gene testing by PCR and Next-Generation Sequencing confirmed a heterozygous germline mutation (c.289C>T) exon 5 of the PTEN gene, establishing the diagnosis of CS. Thereafter, the patient underwent baseline evaluation in accordance with

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current NCCN guidelines and expert recommendations, including thyroid ultrasound. Additional investigations, such as abdominal ultrasound and skeletal imaging, were performed to exclude differential diagnoses but revealed no pathological findings [12]. As the child grew older, oral papillomatosis (Figure 2) developed which is a typical feature of CS.

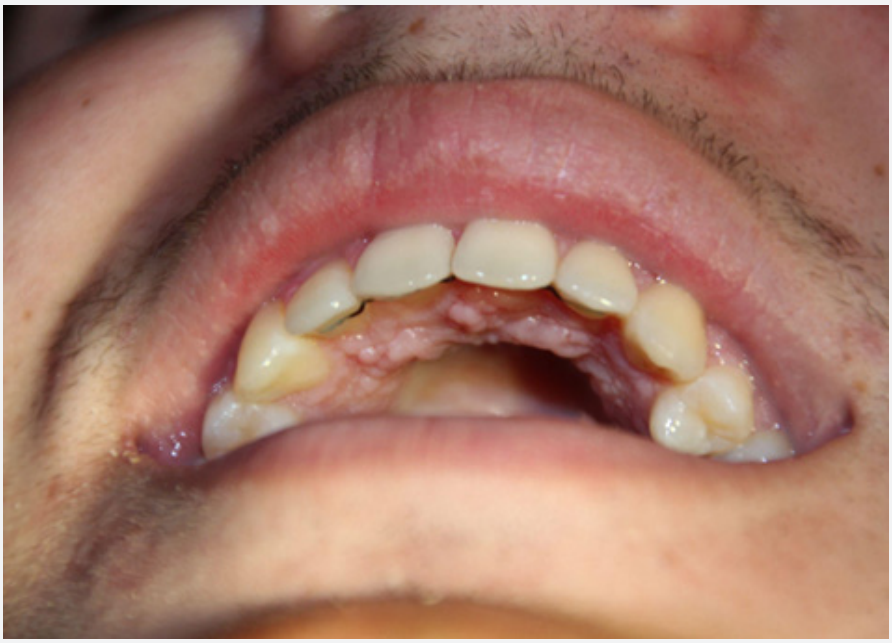

Figure 2: Oral papillomatosis (developed during adolescence).

Results & Discussion

Collagenomas are rare benign connective tissue nevi first described in 1972 by Weary et al. [13]. They usually present as asymptomatic, localized, flesh-colored, waxy papules or nodules and can occur at any site; however, the head and neck are most commonly affected [14]. Histopathologically, a sharply defined hypocellular dermal nodule with hyalinized dense collagen arranged in a wavy or plywood pattern can be observed [11]. Immunohistochemistry is positive for CD34, vimentin, mucin, and also shows sporadic positivity for factor XIIIa; however, embryonic membrane antigen, S-100, and neuron-specific enolase are negative [15]. Although the collagenomas in our patient were initially misinterpreted as connective tissue nevi associated with BOS, their confirmation by histopathology raised the suspicion of CS which was confirmed by gene testing.

This highlights the importance of collagenomas as early indicators of CS as previously reported [14-16]. This is particularly true in case of multiple collagenomas, as single lesions can also occur sporadically [14,15]. Thus, the occurrence of multiple collagenomas in a patient with macrocephaly, potentially intellectual disability, overgrowth, or tumors early in life should raise suspicion of CS [14-16]. Apart from CS, collagenomas have also been described in other genodermatoses, such as BOS, familial collagenomas, MEN1, TS, sporadic eruptive collagenomas, as well as in non-CS conditions within the umbrella term PTEN hamartoma tumor syndrome (PHTS), including Bannayan-Riley-Ruvalcaba syndrome and Proteus syndrome [6].

Other important cutaneous indicators of CS are trichilemmomas, benign tumors derived from the outer root sheath epithelium of hair follicles, most commonly presenting as small, flesh-colored papules on the facial skin, especially around the mouth, nose, and ears. The presence of multiple facial trichilemmomas is even considered pathognomonic for CS, usually preceding the development of internal tumors [1,17]. Histologically, trichilemmomas show lobular proliferation of pale-staining cells with clear cytoplasm, peripheral palisading, and connection to the epidermis. In comparison to sporadic trichilemmomas, in CS they show a loss of PTEN expression [18].

CS is also differentiated from other genodermatoses by the presence of a pathognomonic distinctive mucocutaneous triad [6,7]: multiple facial trichilemmomas, acral keratoses, and oral papillomas. Acral keratoses appear on palms, soles, or dorsal hands/feet; oral papillomas are small papules on lips, tongue, gingivae, or buccal mucosa, often with a cobblestone appearance (Figure 2). BOS presents with elastomas or collagenomas and osteopoikilosis but lacks this mucocutaneous triad. Skin

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lesions are typically firm, skin-colored papules or plaques, often appearing in childhood. BOS is caused by mutations in the LEMD3 gene and does not confer increased cancer risk. The presence of osteopoikilosis on radiographs is a hallmark finding, and cognitive delays or shortened stature may be present in some cases [19].

TS complex is caused by mutations in TSC1 or TSC2 and is characterized by facial angiofibroma's, hypomelanotic macules, shagreen patches, and ungual fibromas [20]; however, it does not feature the mucocutaneous triad. Non-Cowden variants of PHTS such as Bannayan-Riley-Ruvalcaba syndrome may present lipomas, pigmented penile macules, and intestinal hamartomas, but not the CS-specific triad [6]. While clinical features such as trichilemmomas and collagenomas are not exclusive to CS, loss of PTEN expression on immunohistochemistry represents a sensitive and specific marker for Cowden-associated lesions [21]. Individuals with suspected PHTS can be diagnosed clinically using the revised diagnostic criteria for PHTS published by Pilarski et al. in 2013 [22].

In most cases, the diagnosis is subsequently confirmed by PTEN genetic testing, which identifies pathogenic variants in the PTEN gene and allows differentiation of CS from other PHTS subtypes and genodermatoses [23]. The management of the mentioned skin lesions focuses on local therapies. These include topical 5-fluorouracil, cryotherapy, laser or excision [6]. Targeting the mTOR pathway represents a promising approach: In a pilot study involving 18 patients, sirolimus (oral loading dose of 6 mg sirolimus, followed by 2 mg daily for 8 weeks) demonstrated good overall tolerability, suppression of mTOR signaling in benign skin and gastrointestinal lesions, and preliminary clinical improvement in 67% of the participants.

Regression of cutaneous and gastrointestinal lesions was observed, and cerebellar function improved after one month. These findings suggest potential disease-modifying effects, although the therapy remains experimental [24]. Lifelong, organ-specific surveillance-including thyroid and renal ultrasound, breast imaging, and routine dermatologic and gastrointestinal assessments remains essential for early detection and reduction of morbidity and mortality [6]. Future research should focus on elucidating the genetic and molecular mechanisms underlying the development of CS lesions to gain deeper insights into their pathogenesis and to identify novel therapeutic targets.

Conclusion

Skin lesions such as collagenomas, trichilemmomas, oral papillomas and mucocutaneous neuromas are important indicators of CS that should be recognized by clinicians to enable timely diagnosis, appropriate patient management including implementation of cancer screening protocols.

Acknowledgment

The authors would like to thank our patient and his family for consenting to the publication of his clinical details.

Conflicts of Interest

The authors declare no conflicts of interest related to this case report.

Data Availability Statement

The data supporting the findings of this study are not publicly available due to patient privacy considerations but are available from the corresponding author upon reasonable request.

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Patient consent

Written informed consent for publication of clinical details and images was obtained from the patient's legal guardians.

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