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Gingival Papillomatosis as the Oral Sign of Cowden Syndrome: A Case Report

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ABSTRACT Cowden syndrome (CS) is a rare autosomal dominant, hereditary, multiorgan disease with higher risk for malignancies (breast, thyroid, endometrium). Mucocutaneous lesions occur in 90% of cases and are characterized by facial trichilemmomas, oral mucosal papillomas, and benign acral keratoses. We present the case of a 39-year-old female patient with the chief complaint of "white spots" on the upper and lower attached gingiva accompanied with skin changes on the face, hands, and soles. The patient's family medical history revealed that her mother had an endometrial polyp and the sister had thyroid cancer. In the patient's medical personal history she reported follicular thyroid adenoma, thyroid abnormalities (i.e. lymphocytic thyroiditis), fibrocystic changes and juvenile breast papillomatosis, lipoma, multiple fibromas, and genitourinary tumors. Based on extensive family and personal medical history, physical examination and histopathological findings, diagnostic criteria were fulfilled for the diagnosis of Cowden syndrome.

KEY WORDS: Cowden syndrome, gingival papillomatosis, multiple hamartoma syndrome

INTRODUCTION

Cowden syndrome (CS) is a rare autosomal dominant, hereditary, multisystem disease with higher risk for malignancies, particularly in the breast, thyroid, and endometrium (1). It can also be found under the names Cowden's disease and multiple hamartoma syndrome (MHS). It rarely appears with colorectal cancer, renal cell carcinoma, melanoma, macrocephaly, delayed development, and intellectual disability (2). Cowden syndrome is more common in women in the second and third decades of life. According to the available literature, less than 500 cases have been reported in the literature worldwide (3-6). Mucocutaneous lesions occur in 90% of cases and are characterized by facial trichilemmomas, oral mucosal

papillomas, and benign acral keratoses (7). Most cases of CS result from mutations in the phosphate and tensin homolog (PTEN) suppressor gene, located on chromosome 10q23.3. Furthermore, PTEN encodes a dual phosphatase protein that negatively regulates the PI3K-Akt-mTOR pathway (8). We present a case of a 39-year-old female patient with CS.

CASE REPORT

A 39-year-old woman was referred to the Department of Oral Medicine, School of Dental Medicine, University of Zagreb with the chief complaint of "white spots" on the upper and lower attached gingiva. The patient also complained about skin changes on the face, hands, and soles of the feet.

The patient's family medical history was relevant as follows: the mother had an endometrial polyp, the father had hypertension, and the sister had undergone thyroidectomy due to thyroid cancer. In the patient's personal medical history, she reported juvenile breast papillomatosis that has been regularly controlled since 1996. She had several operations and aspirational punctures on her breasts from 1996 to 2015. During regular breast surveillance, one cytological puncture showed fibrocystic changes with the atypia of the ductal epithelial cells, but repeated cytological puncture was in favor of fibrocystic changes.

The patient's medical history revealed a liver hemangioma a few years earlier as well as a left side neck lipoma and left foot hemangioma. She had undergone a surgery of a cavernous left ovary lymphangioma and leiomyomas of the uterus in 2014. The last gynecological ultrasound finding had shown a polyp in the endometrium and multiple myomas of the myometrium. The patient had thyroid surgery (lobectomy of the right lobe and removal of the isthmus) due to follicular adenoma in 2017. The last ultrasound cytological finding of the remaining thyroid tissue corresponded to chronic inflammatory thyroid disease, i.e. lymphocytic thyroiditis. In the same year, cardiological examination revealed the presence of a small stationary circular pericardial effusion with no hemodynamic significance. The findings of eosinophilia (8.4, reference interval 0-7) in the peripheral blood and positive serology (anti-SS-A/Ro=57) were detected and monitored. She was currently taking levothyroxine (Euthyrox®) and analgesics as needed and had been smoking up to ten cigarettes a day for the past five years.

Extraoral examination revealed small papillomas on the upper lip (Figure 1). Intraoral examination showed papillomatosis of the upper and lower attached gingiva, mostly affecting the interdental papillae (Figure 1, Figure 2). Clinically, a firm nodule on the left retromolar region was histologically confirmed as a fibroma. In the histopathological picture, a loose connective tissue with lobules of mature fat was covered by stratified squamous epithelium. Focal lymphocyte infiltrate was found subepidermally (Figure 3).

Routine laboratory investigations were noncontributory. Panoramic imaging was performed and showed no pathological changes. Oral mucosa sampling for HPV DNA molecular analysis PCR was not performed because our patient fulfilled the diagnostic criteria for CS (1), given the family and personal medical history and physical findings.

The dermatological examination revealed the presence of white and yellowish papules located on the forehead, upper eyelids, and retroauricular area (Figure 4). Multiple pendular fibromas were seen in the inguinal region along with the punctate keratoses on the palms and soles. Keratotic papules were observed on the dorsal aspects of the hands, and there was follicular hyperkeratosis on the upper arms. The patient reported the focus of alopecia in the occipital region and also reported spontaneous regrowth of the hair. Based on the extensive family and personal medical

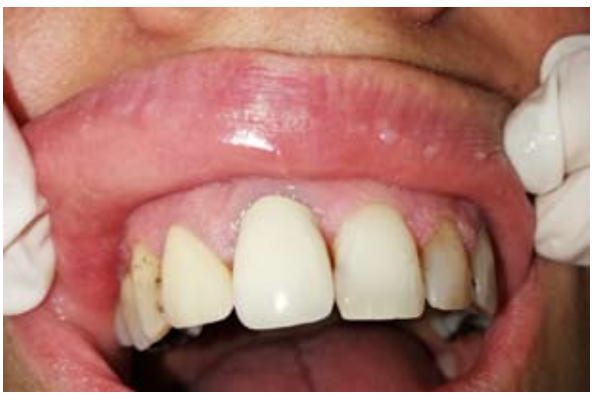

Figure 1. Papillomas on the upper lip and upper attached gingiva.

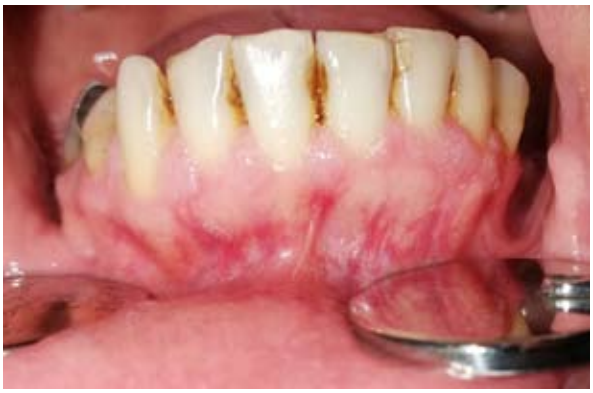

Figure 2. Papillomatosis of the lower attached gingiva.

Acta Dermatovenerol Croat
2019;27(4):260-264

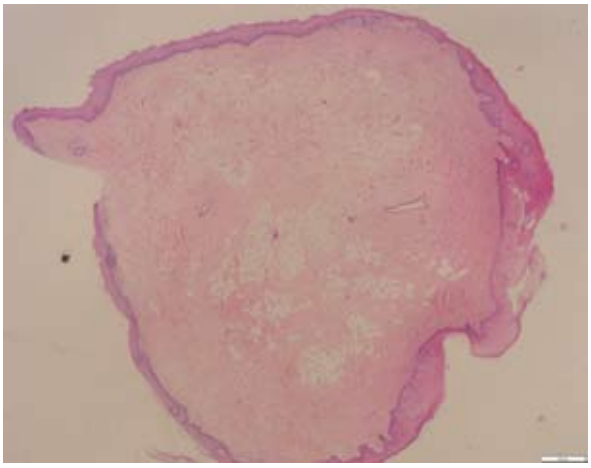

Figure 3. Microphotograph showing fibroma (×20).

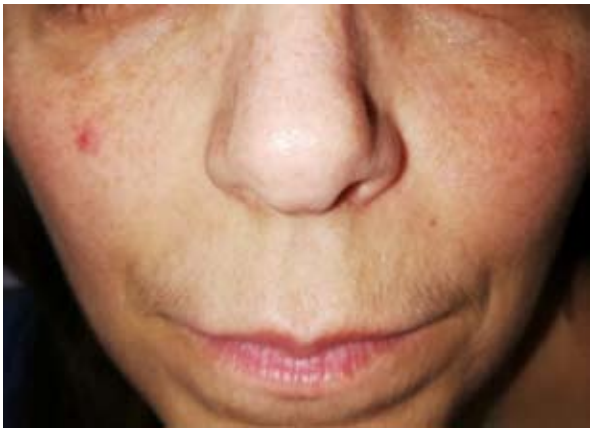

Figure 4. Multiple facial trichilemmomas.

history, physical examination, and histopathological findings, a diagnosis of CS was established.

DISCUSSION

Cowden syndrome is a rare autosomal disease which affects many organs and has mucocutaneous manifestations. Neoplasia risk ranges from 3% to 10% (4,9). The thyroid is the most commonly affected extracutaneous site, as confirmed in our patient who had follicular adenoma of the thyroid and lymphocytic thyroiditis.

Cowden syndrome exhibits mucocutaneous features which include multiple papules on the gingiva, labial mucosa, and tongue, giving them a cobblestone-like appearance. Multiple fibroepithelial polyps, oral papillomatosis, nodular gingival hyperplasia, fissuring, and lobulations of the tongue, and multiple facial trichilemmomas and acral keratosis can be found (10). Oral papillomas represent a pathognomonic criterion and can be observed in abundance on the gingiva and labial mucosa (1), as was the case in our patient.

Systemic features include thyroid abnormalities in 75% cases, such as benign multinodular goiter, lymphocytic thyroiditis, and adenomas. Multiple intestinal polyps can be found in 50% cases. Various malignant tumors like breast cancer (25-50%), thyroid cancer (3-10%), endometrial cancer (5-10%), melanoma (6%), and renal cell carcinoma (10-13%) occur. Our patient reported recurrent juvenile breast papillomatosis, benign genital tumors, lymphocytic thyroiditis, and follicular adenoma of the thyroid.

Cowden syndrome can manifest with various clinical features, which makes it difficult for clinicians to establish a timely correct diagnosis. Consequently, the National Comprehensive Cancer Network proposed revised diagnostic criteria in 2008 (Table 1) (10,11,14).

Table 1. Diagnostic criteria proposed by the International Cowden Syndrome Consortium (ICSC) (Adopted from: (15))

PATHOGNOMONIC LESIONS (1 required)	**MAJOR CRITERIA** (2 required, one must be macrocephaly or Lhermitte-Duclos disease)	**MINOR CRITERIA** (4 required)
Six or more facial papules (≥3 trichilemmomas)	Breast carcinoma	Thyroid lesions (other than carcinoma)
Facial cutaneous papules + papillomatosis of the oral mucosa	Thyroid carcinoma	Learning difficulties or delayed development
Papillomatosis of the oral mucosa + acral keratosis	Macrocephaly (>97%)	Gastrointestinal hamartomas
≥ 6 palmoplantar keratoses	Endometrial carcinoma	Fibrocystic disease of the breast
	Lhermitte-Duclos disease (cerebellar dysplastic gangliocytoma)	Lipomas
		Fibromas
		Genitourinary malformations or carcinoma

Table 2. Management of Cowden syndrom (Adopted from: NCCN (16))

Management of Cowden syndrome
Women
Breast self-examination starting at age 18.
Clinical breast exam starting at age 25 or 5-10 years before the earliest breast cancer in the family occurred.
Patient education about endometrial cancer symptoms and clinical screening.
Discussion of prophylactic mastectomy and hysterectomy.
Men and women
Annual physical examination starting at age 18 or 5 years before the youngest age of cancer in family history.
Annual thyroid ultrasound starting at time of CS diagnosis.
Colonoscopy, starting at the age of 35, then every 5-10 years.
Consider renal ultrasound starting at age 40, then every 1-2 years.
Risk to relatives
Explain possible inherited cancer risk to relatives, options for risk assessment and management.
Provide genetic counseling.

The diagnosis of CS is usually established according to the following criteria:

1) The presence of pathognomonic criteria alone, if there are six or more facial papules, three of which must be trichilemmomas, or orofacial papillomatosis and acral keratosis, or identification of six or more palmoplantar keratosis lesions;
2) Two major criteria with one being Lhermitte-Duclos disease or macrocephaly;
3) One major and three minor criteria;
4) Four minor criteria (10,11,14).

Our patient fulfilled all pathognomonic and minor criteria (thyroid lesions, fibrocystic disease of the breast, lipoma, fibromas, genitourinary tumors).

Differential diagnosis of CS includes Bannayan-Riley-Ruvalcaba syndrome, Proteus syndrome, tuberous sclerosis, fragile X syndrome, Heck's disease, Darier's disease, epidermolysis bullosa, Goltz syndrome, and juvenile polyposis syndrome (11).

There is currently no specific and targeted therapy for Cowden syndrome. Management of CS includes regular surveillance, patient education, surgical removal of hamartomas, precancerous lesions, and malignant neoplasms, and genetic counseling of the patient and family members. The mucocutaneous lesions can be treated with 5-fluorouracil, retinoids, electrosurgery, cryosurgery, dermabrasion, laser abrasion, interferon-2α, bleomycin, and surgical excision (14). The National Comprehensive Cancer Network (NCCN) regularly provides updated guidelines that outline a cancer surveillance program for men and women with CS (15,16). Our patient has been referred to all recommended regular surveillance according to the latest NSCC guidelines.

CONCLUSION

Cowden syndrome is difficult to diagnose in a timely manner due to numerous clinical presentations. We described oral and systemic manifestations of Cowden syndrome in a 39-year-old woman to inform dentists and physicians on various clinical presentations of this rare syndrome, but also to encourage them to adopt unique and precise diagnostic criteria. The importance of detailed family and personal medical history in the diagnostic procedure has also been emphasized. Patients with CS require a comprehensive multidisciplinary approach with regular follow-up by various specialists, which is especially important for early detection and successful treatment of malignant tumors, thereby improving quality and prolonging the patient life.

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