

## The importance of the dentist in the diagnosis of Cowden syndrome – Case report

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### ABSTRACT

Cowden Syndrome is an autosomal dominant disorder characterized by the development of several hamartomas in a variety of tissues, including the skin, gastrointestinal tract, adipose tissue, and bone and connective tissues. This syndrome is associated with a high risk of developing malignancies, especially breast, thyroid and endometrium cancers. This report presents a case of a 53-year-old patient who sought assistance at the Dentistry Department of the University Hospital of Brasilia (HUB) to receive basic dental treatment. The current and past medical history and oral and facial manifestations led to the diagnosis of Cowden syndrome. This case report aims to highlight the importance of a dental surgeon in the diagnosis of this syndrome, based on the observation of oral manifestations and medical history.

### KEYWORDS

Cowden Syndrome; Multiple Hamartoma Syndrome.

### RESUMO

A Síndrome de Cowden é uma desordem hereditária autossômica dominante, caracterizada pelo desenvolvimento de diversos hamartomas em vários tipos de tecidos, incluindo a epiderme, trato gastrointestinal, tecido adiposo e tecidos ósseo e conjuntivo. Essa síndrome é associada a um risco elevado de desenvolvimento de malignidades, especialmente câncer de mama, tireoide e endométrio. Esse relato apresenta o caso de um paciente de 53 anos de idade que procurou o Departamento de Odontologia do Hospital Universitário de Brasília (HUB) para tratamento dental básico. História médica atual e passada e manifestações orais e faciais levaram ao diagnóstico de síndrome de Cowden. Este relato de caso apresenta a importância do cirurgião-dentista no diagnóstico desta síndrome, com base na observação das manifestações orais e história médica.

### PALAVRAS-CHAVE

Síndrome de Cowden; Síndrome dos Hamartomas Múltiplos.

### BRIEF LITERATURE REVIEW

Cowden Syndrome is an autosomal dominant disease with a wide degree of penetration and variation of expressiveness. This syndrome is characterized by the formation of multiple hamartoma of the three embryonic tissue origins: endoderm, ectoderm and mesoderm.

The mucocutaneous manifestations are almost universal and evolve slowly [1].

It is a rare disorder that predisposes to the development of malignancies such as breast, thyroid and endometrial cancers as well as benign hamartomatous overgrowth of tissues, especially skin, colon and thyroid [2-5].

This syndrome, also known as Multiple Hamartoma Syndrome, was first described in 1963 by Lloyd and Denis, with reference to the patient Rachael Cowden [5,6]. The prevalence of Cowden Syndrome is estimated at 1/200.000 [4-6] and it is usually diagnosed during the third decade of life, although it can present its first signals between 4-75 years of age [5,7].

### CASE REPORT

A 53-year-old male came to the Dentistry Department of the University Hospital of Brasilia (HUB) to receive basic dental treatment. On physical examination multiple papules were observed on the face, especially in the area of lips, nose wing and neck, and armpits and abdomen, mostly measuring less than 1 mm (Figure 1A). Acral keratosis was also detected on the dorsal surface of the hands and keratosis pilaris throughout the length of the arms and forearms.

In clinical examinations, similar papular and nodular lesions were observed in the oral cavity, including oral mucosa, labial mucosa, jugal mucosa, tongue dorsal surface and buccal gingival margin (Figure 1B,1C,1D).

In the past medical history, the patient reported total thyroidectomy performed in

2011 due to thyroid cancer and the use of Levothyroxine Sodium for synthetic thyroid hormone replacement. He denied other alterations in his health and the occurrence of similar cases in his family. A biopsy was performed on two lesions: papule jugal mucosa and papule on the lower lip region. The collected material was sent for histopathological analysis at the Pathology Centre of HUB. The histopathological examination revealed sessile polypoid formation, epithelial lining of stratified squamous with acanthosis. There were no grainy or corneal layers. No viral cytopathic effect or dysplastic changes were found. The mucous corium shows usual cellularity, with evident collagen deposition and discrete congestion of the blood vessels. There is no significant inflammatory activity (Figure 1E,1F). The oral mucosal lesions were diagnosed as fibroepithelial hyperplasia.

After confirming the diagnosis based on established criteria, the patient was asked about the syndrome, referred for evaluation and conduct to the dermatology clinic. He continues to monitor his health condition with an oncologist to treat the thyroid cancer and track other possible malignancies.





**Figure 1** - A) Frontal view of the patient's nose reveals multiple papules. B) Intraoral examination showing multiple papular lesions on the gingiva. C) Multiple papules in the tongue. D) Jugal mucosa reveals multiple nodules. E) Photomicrograph (10x) of histological sections stained by hematoxylin-eosin. F) Photomicrograph (20x) of histological sections stained by hematoxylin-eosin.

## DISCUSSION

Cowden Syndrome is a rare autosomal dominant genodermatosis, with incomplete penetrance, variable expression and a gene mutation [8]. Mutations have been identified in phosphatase and tensin homolog (PTEN), a tumor suppressor gene located on 10q23 [9].

The mutation in the tumor suppressor gene PTEN and the loss of function of that protein occur in 80% of patients who meet the criteria diagnostic to Cowden Syndrome [10]. The other 20% of patients do not have identifiable genetic mutations [4,11].

The loss of cellular regulation of signaling pathways, the control of cell proliferation and apoptosis generated by mutation of this gene

increase the risk of developing cancer in different organs [3,12,13].

Although clinical manifestations of the syndrome are different, the diagnosis has been facilitated since 2000, when members of the International Consortium Diagnostic Criteria for Cowden Syndrome organized the main features into three categories: pathognomonic criteria, major criteria and minor criteria [14].

The pathognomonic criteria include facials trichilemmomas, acral keratosis, papillomatous papules and mucosal lesions. In the major criteria are included breast, endometrial, and thyroid cancers, macrocephaly and Lhermitte-Duclos disease. As for minor criteria, it is reported other thyroid disease, mental retardation,

hamartomas intestinal polyps, fibrocystic breast disease, lipomas, fibroids, tumors, and urogenital malformations [14-17].

Once diagnosis of Cowden Syndrome is made, these patients should be considered at high risk for the development of malignancies [18].

Mucocutaneous manifestations are present in 99% to 100% of patients [15]. In the facial region, follicular hamartomas, which are called trichilemmomas, are the most common lesions. They are characterized by small and multi-colored normochromic papules distributed mainly around the eyes, nose and mouth [7,19]. This is very important because oral mucosal findings may make an early diagnosis of the syndrome possible and be a marker of the risk of developing malignancies [9]. The oral mucosal and dental stigmata are frequently associated with specific clinical phenotypes. The oral and maxillofacial manifestations of these syndromes may become visible several years before the malignant lesions [9].

The acral keratosis, located on the dorsal surface of the hands and feet, is another common injury in these patients, occurring in approximately 70% of them. The palmoplantar keratosis is also an important finding that occurs in 40% of patients with this syndrome [20]. Furthermore, lipomas, xanthomas, neurofibromas and hemangiomas are reported [21].

The extracutaneous manifestations, on the other hand, occur in approximately 90% of patients, involving more often the thyroid gland. These changes include colloid goiter, thyroglossal duct cysts, thyroiditis, hypo/ hyperthyroidism, adenoma and carcinoma [21]. Thyroid cancer occurs in 3-10% of patients and is the second most common cancer in patients with the syndrome [1,6,22]. Pathologic findings involve follicular cells, including multinodular goiter, multiple adenomatous nodules, follicular adenoma, follicular carcinoma, and less frequently, papillary thyroid carcinoma [23-26].

Thyroid function tests, ultrasonography and complete blood count should be performed routinely. If thyroid nodules are present, fine needle aspiration biopsy or surgical biopsy should be performed [6].

The occurrence of variations in the breast is also common, about 75% of patients, who are mostly affected with fibroadenomas and fibrocystic disease, the latter linked the development of tumors [7]. Breast cancer is the most common malignant tumor in patients with the syndrome. The lifetime risk of developing this type of cancer is up to 81% [27]. Performing breast self-exam and mammography at regular intervals is essential for early diagnosis of breast cancer. Furthermore, Canadas et al. [21], Hartmann et al. [28] and Lee et al. [29] suggested bilateral prophylactic mastectomy. Endometrial cancer occurs in 5% to 10% of all women with Cowden Syndrome [1]. In approximately 85% of patients are found polyps by performing gastrointestinal endoscopy, especially colorectal polyps [30]. They are mostly hamartomas polyps. However, it is estimated that 16% of these patients will develop colorectal carcinoma [30,31]. Bone changes are manifested in one third of patients, macrocephaly was observed in 80% of cases [6]. In the differential diagnosis oral papillomatosis injury should be considered multiple trauma fibroids, fibroma by oral Tuberous Sclerosis, White-Darier Disease (follicular dyskeratosis), Heck's disease (focal epithelial hyperplasia), lymphangioma, pyogenic granuloma, fibroepithelial polyps, Urbach-Wiethe disease (lipoid proteinosis), florida oral papillomatosis, papilloma by Goltz syndrome, mucosal neuromas of multiple endocrine adenomatosis, acanthosis nigricans, pseudoepitheliomatous hyperplasia and squamous cell carcinoma [32].

There is no specific treatment for Cowden Syndrome. The management includes early detection of malignancies, patient education, genetic counseling and regular monitoring [33]. Thus, it is extremely important that the patient take regular tests for investigation of colorectal

polyps, thyroid nodules, breast diseases and perform at intervals defined pelvic-abdominal ultrasound, and Papanicolau test [6,34].

The treatment can be symptomatic or aesthetic after the complete screening of the patient and the diagnosis of the syndrome. Mucocutaneous lesions present good response with the use of systemic acitretin. However, they may recur after cessation of drug treatment [7].

The management of facial papules include different treatment modalities including topical 5-fluorouracil, oral retinoids, curettage, electrosurgery, cryosurgery, laser ablation and surgical excision [35]. Larger oral lesions managing patient discomfort can be surgically removed [19].

Treatments aimed at reestablishing the molecular pathways associated with the PTEN gene have been studied and can eventually represent an alternative for those patients [18]. Moreover, Ni et al. [36] in their study confirmed the role of vitamin E as an anticancer agent in patients with Cowden Syndrome.

The case presented in this report shows the importance of a dentist in the diagnosis of Cowden Syndrome, based on the medical history and in the identification of oral lesions during the clinical examination. For this, the dentist should know the oral manifestations of systemic changes like Cowden Syndrome.

## CONCLUSION

Cowden Syndrome, a rare hamartoma syndrome, can lead to the development of malignancies in various organs. Most patients have merely aesthetic management, conducted by dermatologists. However, with proper screening and diagnosis defined, it is essential that the patient have regular follow-up with different health professionals. The dentist plays a key role in the diagnosis and implementation of therapeutic measures in these patients.

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