原文題目(出處)：	Cowden syndrome—a case report emphasizing the role of the dental surgeon in diagnosis.Spec Care Dentist 2015;35: 51-4
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報告日期：	104/4/6

內文：

Introduction

Cowden syndrome (CS), also called multiple hamartoma syndrome, is a rare autosomal dominant genetic condition. This change is associated with mutations in the *phosphatase and tensin homologue* (*PTEN*) gene, a tumor suppressor located in chromosome 10q 22–33. These mutations may generate changes in derivative tissues of the three germinative layers of the human body, like the skin, astrointestinal tract, bones, central nervous system, eyes, genitourinary tract, and oral mucosa

The diagnosis of CS is based on the criteria defined by The International Cowden Consortium and are divided into pathognomonic, major and minor criteria (Table 1). Among these, mucocutaneous lesions like multiple facial verrucous papules (usually trichilemmomas), oral papillomatosis, and macrocephaly are easily detected by the dental surgeon. In addition, CS patients are also more prone to develop neoplasias, mainly in the thyroid, breast, and endometrium.

This case report describes an occurrence of CS diagnosed by a dental surgeon based on clinical history and oral cavity manifestations.

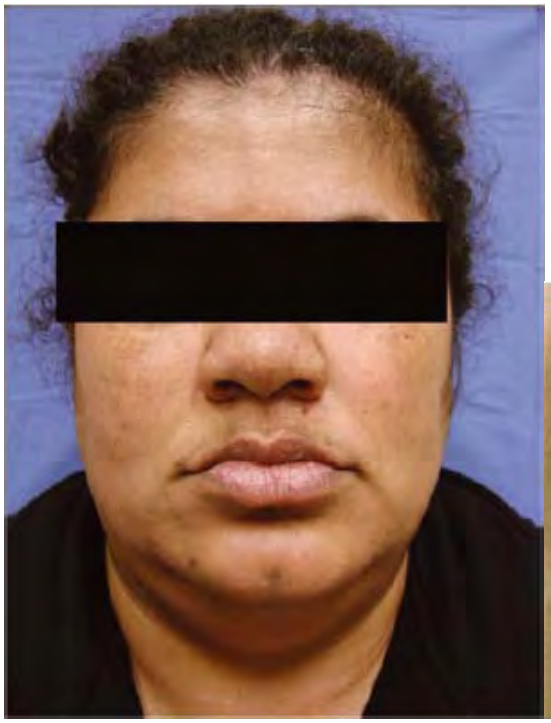
Table 1. Diagnostic criteria proposed by *the International Cowden Syndrome Consortium* (8).

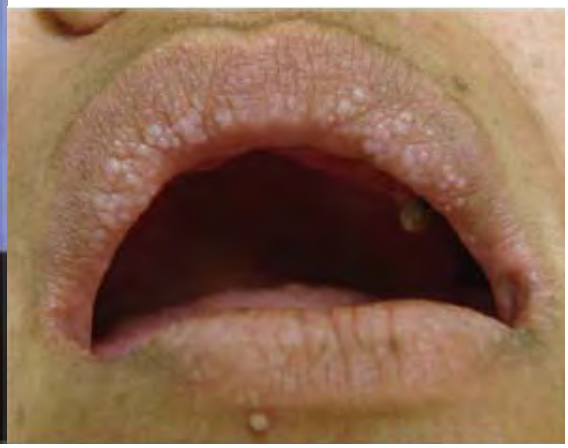
Pathognomonic Criteria
Mucocutaneous lesions alone if
• There are six or more facial papules of three or more must be trichilemmomas or
• Cutaneous facial papules and oral mucosal papillomatosis or
• Oral mucosal papillomatosis and acral keratosis or
• Palmoplantar keratosis, six or more
Major Criteria—Two criteria (one of which must be macrocephaly or Lhemitte–Duclos disease
Breast carcinoma
Thyroid carcinoma (nonmedullary), especially follicular thyroid carcinoma
Macrocephaly
Lhermitte–Daclos disease
Endometrial carcinoma
Minor criteria—Four criteria
Other thyroid lesions
Mental retardation
Gastrointestinal hamartomas
Fibrocystic disease of the breast
Lipomas
Fibromas
Genitourinary malformations or carcinoma
Or One major criterion an three minor criteria may also indicate diagnosis of CS

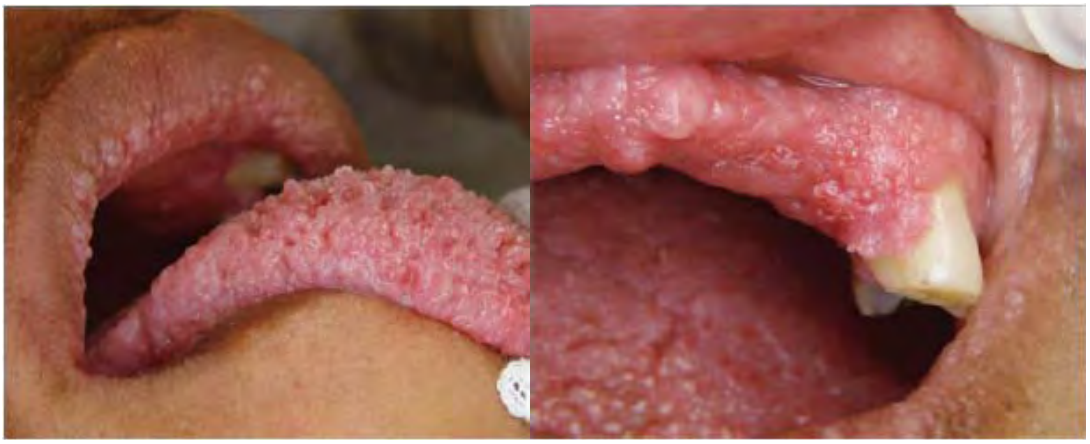
Case report

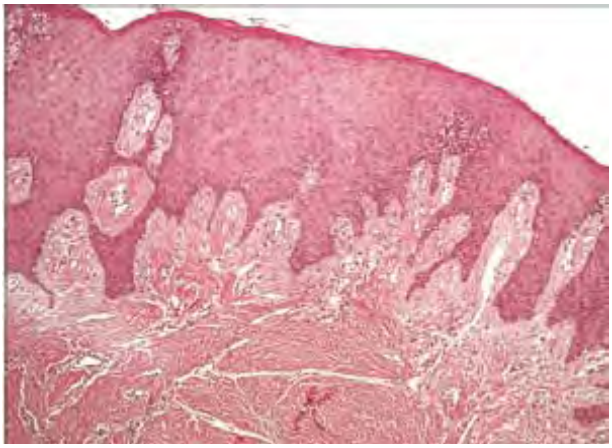
A 36-year-old female patient, with no children, looked for service in the Reference Teaching Hospital of the Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil, due to a gingival growth that hindered the use of a dental removable prosthesis.

Clinical history revealed a previous thyroidectomy carried out 15 years before (follicle carcinoma and follicle adenoma). The patient reported having had Hashimoto's thyroiditis and papules removed from hands and stomach, and was under medical follow-up for gastritis, arthrosis, depression, fibromyalgia, and breast nodules diagnosed as ductal ectasia. Extraoral examination revealed macrocephaly (Figure 1). The presence of papules in the perilabial and labial regions was detected (Figure 2). Papules were also noticed in hands and in the perinasal, periorbital and preauricular regions. Intraoral examination revealed papules also on the tongue and oral cavity floor, (Figure 3), as well as a single vegetative nodule with verrucous surface located on the upper alveolar ridge anteriorly to the canine (Figure 4). All these findings suggested CS or Heck's Disease. Biopsy of the nodular lesion was carried out, and histopathologic evaluation showed the presence of epithelial hyperplasia (Figure 5). The diagnosis of CS was established considering these intra- and extraoral findings and the patient's previous medical history. The patient was referred to specialized genetics and dermatology services, which confirmed the diagnosis. Since then, the patient has been under transdisciplinary follow-up for 2 years.









Discussion

CS is a rare genetic condition, with estimated one case in every 200,000 to 250,000 people. Eighty percent of cases are associated with mutations in *PTEN*, a gene that regulates cell cycle, migration and apoptosis, and affects the proliferation of the disease. It has been hypothesized that mutations in *PTEN* are the reason behind the abnormal proliferation of tissues and the higher chances of carriers to develop neoplasias. This syndrome has varied genetic expression that often manifest as subtle signs on the skin, which makes it go by misdiagnosed.

Diagnosis is based on the presence of multiple clinical signs. The International Cowden Consortium has stipulated parameters for the diagnosis of CS (Table 1), according to which the confirmation of one major criterion and of three minor criteria are enough to produce a positive diagnosis. In the present case, the patient presented more than six facial papules, apart from papules in the oral mucosa and on hands (pathognomonic criteria), thyroid carcinoma, macrocephaly (major criteria), and other lesions on the thyroid and papules in the stomach (minor criteria). However, in spite of all these characteristics and of the fact that the patient was under different specialties of medical follow-up, the diagnosis of CS had not been produced before her consultation with a dental surgeon. Ravi Prakash *et al.* underline that mean age of CS patients is 22 years. Therefore, early diagnosis and periodical follow-ups affords to identify the manifestations of CS, which develop gradually with time. Similarly to the present case, Mukamal *et al.* reported a similar delay in diagnosis, possibly due to the lack of a proper cross-link of the clinical conditions of the patient with CS.

The lesions observed in the oral cavity were papillomatous, and located mainly on the lips, gums and tongue. According to the diagnosis criteria, when six or more papillomatoses are observed, the suspicion of CS should be considered. Here, the

dental surgeon considered these findings in light of the other manifestations of the disease in other organs, and thus proposed the diagnosis of CS. Other manifestations in the head and neck region associated with CS are carcinomas in the parotid and submandibular glands. Therefore, when lesions as those described above are observed upon clinical examination, the dental surgeon should review information pertaining to the patient's clinical history and conduct a transdisciplinary investigation in search for other lesions, like papules on the skin, thyroid changes, macrocephaly, and gastrointestinal polyps to confirm or rule out the diagnosis of CS. This clinical case underlines the importance of the role of the dental surgeon in the diagnosis of CS, and of diseases that affect multiple organs.

The main complication of CS is the high prevalence of breast, thyroid, and endometrium neoplasias, since the disease is the manifestation of changes in the *PTEN* gene, a tumor suppressor. Changes in the thyroid are present in between 40% and 60% of the cases, and manifest as hyperthyroidism, benign adenomas, and adenocarcinomas. In the present case, the patient developed Hashimoto's thyroiditis and follicle adenoma followed by follicle carcinoma. Therefore, CS carriers should be periodically followed-up so as to make it possible to diagnose malignant tumors as early as possible, allowing less invasive treatment approaches. Here, the thyroid neoplasias might have been diagnosed earlier, if the first clinical signs presented by the patient, such as papillomatoses in the mouth, had been observed more carefully.

Another neoplasia often observed in CS patients is breast cancer. Thus, women over 25 years of age with CS should carry out the breast self-examination, while women over 30 years old should have mammograms once a year. Polyps in thegastrointestinal tract is also very common, present in 35% to 40% of CS cases. Therefore, it is important to prescribe regular endoscopy to these patients. In this case report, the patient had been submitted to stomach polyp removal surgery before diagnosis of CS was defined.

The differential diagnosis of CS may be carried out together with that of other diseases or syndromes (Table 2). The Lhermite-Duclos disease is characterized by hamartomatous nodules in the cerebellum, and was first considered a separate disease, though today it is seen as a manifestation of CS. The symptoms of the Bannayan-Riley-Ruvalcaba syndrome are very similar to those of CS, and include facial papules. However, the difference between the two diseases lies in the fact that gingival hyperplasia is observed in the Bannayan-Riley-Ruvalcaba syndrome, not in CS. The Proteus syndrome and Juvenile Polyposis present a series of clinical manifestations that are similar to CS, though papillomatosis in the mouth are not reported.

Among the diseases that cause by mouth papillomatous lesions, the main disease that should be included in the differential diagnosis of CS is Heck's Disease, characterized by diffuse whitish papules in the oral cavity, which, in this case report, were initially considered to be the disease presented by the patient. However, this disease does not cause changes in other organs like breast, thyroid and endometrium. The multiple endocrinal neoplasia type 2B also is characterized by multiple oral papules and high prevalence of thyroid carcinomas; however, those papules characterize neuromas histopathologicaly, not epithelial hyperplasia, as in CS. Moreover, this condition presents other skeletal characteristics, and the manifestations in head and neck include marfanoid facies, the presence of neuromas on the eyelids (which causes eversion), and swollen lips.

Patients with CS require strict medical follow-up to diagnose and treat likely manifestations, as early as possible. The International Cowden Consortium

recommends that CS patients undergo comprehensive annual medical examinations from the 18th year of age on, with special care taken to detect any changes in skin and in the head and neck region.

The treatment of CS is defined by the severity of clinical manifestations of the syndrome. The patients are considered at high risk for neoplasias. If these patients are followed up at short intervals, the prognosis becomes more favorable, since neoplasias can therefore be diagnosed at their early stages, improving the chances of success in the treatment.

Muccocutaneous papillomatous lesions may be treated with carbon dioxide, laser, surgical removal, electrosurgery, cryosurgery and interferon 2-alpha and 5-fluorouracyl.

The case presented in this report emphasizes the role of the dental surgeon in the diagnosis of CS based on a crossexamination of clinical history and the identification of oral lesions during examination.

Table 2. Main differential diagnosis with oral manifestations CS.

	Similarities with Cowden Syndrome	Differences with Cowden Syndrome	References
Bannayan-Riley-Ruvalcaba	• Acral Keratoses • Facial papules • Lipomas • Macrocephaly	• Slanting palpebral fissures • Macrosomia at birth • Persistent drooling	Wilson *et al.*
Heck's disease	• Multiple papules or nodules on the oral mucosa	• No systemic manifestations	Borborema-Santos *et al.*
Multiple endocrinal neoplasia type 2B	• Thyroid cancer • Multiple papules or nodules on the oral mucosa	• Pheochromocytoma, • Marfanoid body habitus, • Ganglioneruomatosis of the gastrointestinal tract	Callender *et al.*

Conclusions

The dental surgeon should know systemic diseases that manifest in the oral cavity, like CS, to carry out the early diagnosis of its manifestations, implement efficacious therapeutic measures to ensure a better prognosis

題號	題目
1	下列特徵中哪一項不屬於 cowden syndrom 的主要特徵?? (A) Breast carcinoma (B) Thyroid carcinoma (C) Microcephaly (D) Lhermitte–Daclos disease
答案(C)	
題號	題目
2	下列對於 cowden syndrome 的敘述哪一項錯誤? (A) 發生機率為 1/200,000~250,000 (B) 好發年齡為 22 歲 (C) 口腔內與嘴唇上會產生多個突起 (D) 除口腔外其他地方不會有病變發生
答案(D)	