Oral presentation of 10 patients with Cowden syndrome

Isadora Luana Flores, DDS, MSc,[a] Saray Aranda Romo, DDS, MSc, PhD,[b] Francisco Javier Tejeda Nava, DDS, MSc, PhD,[b] Alan Roger dos Santos Silva, DDS, MSc, PhD,[a] Pablo Agustin Vargas, DDS, MSc, PhD,[a] Oslei Paes de Almeida, DDS, MSc, PhD,[a] and Márcio Ajudarte Lopes, DDS, MSc, PhD[a]

University of Campinas, Piracicaba, São Paulo, Brazil; Autonomous University of San Luis Potosí, San Luis Potosí, Mexico

Cowden syndrome (CS) is an autosomal dominant genodermatosis that frequently affects several tissues with hamartomatous growth. The oral cavity is quite commonly involved with papillomatous lesions, which can be crucial to early diagnosis of this disease. In this series, 10 patients with a great diversity of manifestations associated with CS are presented, in whom oral papillomatosis was a constant and relevant finding to establish the diagnosis of CS. The role of the dentist in recognizing the oral lesions, the other diagnostic criteria, the risk for the development of malignancies, and the importance of lifetime follow-up are discussed. (Oral Surg Oral Med Oral Pathol Oral Radiol 2014;117:e301-e310)

Cowden syndrome (CS), or multiple hamartomatous syndrome, is a genodermatosis described in 1940 by Costello in a Mexican young woman.[1] In 1963, Lloyds and Dennis reported a 20-year-old woman with mucocutaneous lesions and abnormalities in the thyroid, breasts, and gastrointestinal tract. Her surname was Cowden, which became the name of this disease.[2] CS is included in the large family of hereditary gastrointestinal polyposis, with an autosomal dominant trait and incomplete penetrance.[1-4] The prevalence is about 1:200 000, making it a rare disease.[3,4] The causes remain unclear, but mutation in the *PTEN* gene (phosphatase and tensin homolog gene) has been strongly considered, which affects the proliferation of the epidermis, thyroid, breast, gastrointestinal tract, and oral mucosa tissues. CS shows high penetrance in both sexes, and the differences in the clinical manifestations can be observed within and between families.[5] Hamartomatous lesions, defined as an overgrowth of epithelial and stromal cellular components with normal features, are the classic manifestations of CS.[3,5] Nevertheless, the presence of these hamartomatous mucocutaneous lesions in multiple organs and systems significantly increases the predisposition for the development of malignant neoplasms and contributes greatly to morbidity if not detected early.[3,4]

The diagnostic criteria standardized in 2000 by the International Cowden Consortium[6] and revised in 2004 by Pilarski and Eng[7] are based on major and minor clinical factors, as shown in Table I. Among the broad clinical spectrum, mucocutaneous manifestations are considered the most important characteristics of this syndrome, because 99% of the patients will have some of these lesions during the course of the disease.[7,8] Therefore, a careful mucocutaneous examination is crucial to early recognition of CS, contributing to patient management.[8-10] Thus, the aim of this article is to describe 10 patients (1 family with 4 members and 6 individuals sporadically) affected by CS, in all of whom oral lesions contributed along with other extraoral manifestations to the diagnosis of this syndrome.

CASE REPORTS

Eight patients were attended at the Orocentro of the Piracicaba Dental School, State University of Campinas (UNICAMP), Piracicaba, Brazil, and 2 patients were assisted at the Faculty of Stomatology, Autonomous University of San Luis Potosí (UASLP), San Luis Potosí, Mexico. After the presumptive diagnosis of CS, the patients were referred to specialist physicians for systemic assessment. Nevertheless, complete compliance was not reached in all cases.

Familial cases

Demographic aspects and patient history. Patient 1 was a 48-year-old white man who was referred by a physician to the Orocentro at Piracicaba owing to swelling on the palate. His medical history was not contributory, and he described his health as good. Patient 2 (his son) and patients 3 and 4 (his siblings) were referred by him for investigation of the same condition. Patient 2 was a 23-year-old white man with mild intellectual disability who denied any lesion. Patient 3 was a 63-year-old white woman with a remarkable medical history including surgical treatment for cataract and benign nodules in the thyroid, 30 and 22 years ago, respectively. In addition, she underwent cornea transplant for glaucoma, but she became blind in the right eye. The patient also reported a hyperplastic colonic polyp that after 3 years was diagnosed as tubular adenoma with mild dysplasia. Patient 4 was a 64-year-old white man with no complaint and no relevant medical history.

Extraoral clinical findings. A mild motor coordination disorder and goiter were observed in patient 1. His son

[a]Department of Oral Diagnosis, Piracicaba Dental School, University of Campinas.
[b]Faculty of Stomatology, Autonomous University of San Luis Potosí.
Received for publication Nov 11, 2013; returned for revision Dec 18, 2013; accepted for publication Jan 7, 2014.

2212-4403/$ - see front matter
http://dx.doi.org/10.1016/j.oooo.2014.01.015

Table I. Diagnostic criteria of CS according to the International Cowden Consortium,[3,5,6] as revised by Pilarski and Eng[7]

Pathognomonic lesions	*Major criteria*	*Minor criteria*
Mucocutaneous lesions - Facial trichilemmomas - Acral keratoses - Papillomatous lesions - Mucosal lesions	- Breast carcinoma - Thyroid carcinoma (follicular thyroid cancer) - Macrocephaly (occipital frontal circumference $\geq$ 97th percentile) - Lhermitte-Duclos disease (cerebellar dysplastic) - Endometrial carcinoma	- Other thyroid lesions - Mental retardation (IQ $\leq$ 75) - Hamartomas intestinal polyps - Fibrocystic disease of the breast - Lipomas and fibromas - Genitourinary tumors (uterine fibroids, renal cell carcinoma) or malformations

Any one the following items should be considered as diagnosis criteria for an individual without familial history of CS:

(1) Pathognomonic mucocutaneous lesions:
Six or more facial papules, of which 3 or more must be trichilemmoma, or
Cutaneous facial papules and oral mucosal papillomatosis, or
Oral mucosal papillomatosis and acral keratoses, or
Six or more palmoplantar keratoses
(2) Two major criteria
(3) One major and 3 minor criteria
(4) Four minor criteria

Diagnostic criteria for relatives in cases of 1 individual in the family with the diagnosis of Cowden syndrome:

(1) A pathognomonic mucocutaneous lesion
(2) Any one major criterion with or without minor criteria
(3) Two minor criteria

One of which must be macrocephaly or Lhermitte-Duclos disease.

(patient 2) had a significant motor coordination disorder, an adenoid face, thoracic kyphosis, and difficulty keeping his head normally positioned. Macrocephaly was observed in patients 1, 2, and 4, but not in patient 3. Additionally, a careful clinical examination of the skin found coalescent verrucous papillomatous lesions distributed on the forehead and around the nose, periorbital region, and external ear in all patients; nevertheless, patients 1 and 3 had a higher number of these scattered lesions on the head and neck. Flattened hyperkeratotic papules resembling flat warts on the back of the hands were observed in patients 1 and 3 (Figure 1), and a discrete translucent keratosis on the palmar region was also found in patient 1. Table II shows the extraoral manifestations observed in these patients.

Intraoral clinical findings. Intraoral examination of the 4 patients found multiple papillomatous, sessile, white-pink papules distributed in different anatomic sites. All lesions were asymptomatic and appeared predisposed to coalesce. Figures 2 and 3 show alveolar ridge involvement in patients 1 and 3. Multiple central deep folds were observed on the dorsum of the tongue in patients 1, 2, and 3. The complete distribution of oral lesions is presented in Table III.

Clinical management. Owing to high suspicion of CS diagnosis, all patients were informed about the clinical implications of this syndrome and the necessity of additional investigations in other organs. Moreover, lifelong, regular (periodic) assessment by an endocrinologist, gastroenterologist, and gynecologist was recommended. Patient 1 is the only member of the family who remains in follow-up with our service.

Excisional biopsies were performed on the periorbital region, soft palate, and bilateral commissures of patient 1. Histopathologic analysis of the periorbital specimen found papillomatous features with intense hyperparakeratosis consistent with

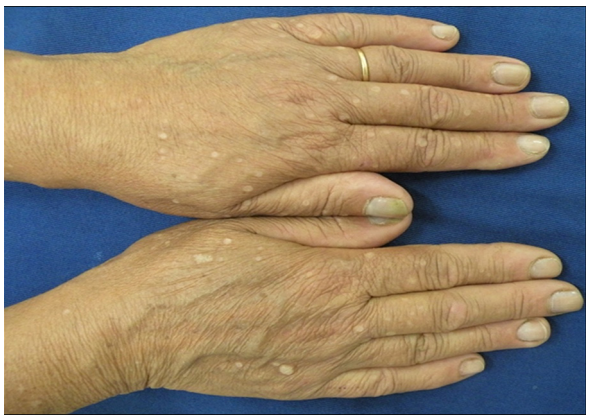

Fig. 1. Acral keratosis lesions with aspect of warty papules were found covering the dorsum of the hands.

trichilemmoma. Areas of soft palate and bilateral commissures of the same patient had hyperkeratosis and acanthosis of stratified squamous epithelium with papillomatous aspect and had connective tissue hyperplasia and mild inflammation consistent with papillomatous inflammatory fibrous hyperplasia (Figure 4).

Colonoscopy was requested for all 4 patients. Patient 1 had rectal polyps, which were microscopically diagnosed as tubular adenoma with mild dysplasia (Figure 5). Colonoscopy results for patients 3 and 4 were normal; patient 2 did not have a colonoscopy performed. Serologic tests to assess α-fetoprotein, cancer antigen 19-9, and carcinoembryonic antigen were also performed for patient 1, and the results showed normal values of 3.06 ng/mL, 5.01 IU/mL, and 4.57 ng/mL, respectively.