Oral manifestations of phosphatase and tensin homolog hamartoma tumor syndrome

Report of three cases

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ABSTRACT

Background. Phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome (PHTS) encompasses several rare disorders linked to mutations of the PTEN gene, including Cowden disease (CD) and Bannayan-Riley-Ruvalcaba syndrome (BRRS). The authors present a case series involving patients with characteristic periodontal features.

Case Descriptions. The authors assessed three patients, two of whom already had been diagnosed with BRRS, consisting of a 60-year-old man and his 33-year-old daughter, both of whom had pathognomonic oral and cutaneous manifestations, and a 26-year-old man affected by multiple micropapillomatous and keratotic periodontal lesions, through which the diagnosis of CD was made. All three patients were referred to the oral medicine unit of the authors' institution because of asymptomatic lesions of the oral mucosa, and ~~for~~ two of them underwent incisional biopsy.

Conclusions. This series of cases emphasizes that oral health care workers always should perform a more careful visual inspection of the oral cavity, without neglecting a macroscopic analysis of the gingival pattern. The knowledge of these diseases and their clinical features, associated with a multidisciplinary approach, allows clinicians to achieve remarkable diagnostic success.

Practical Implications. Gingival manifestations may represent one of the primary clinically detectable manifestations of these rare systemic diseases, in respect of which an early diagnosis could decrease the associated mortality and morbidity.

Key Words. Oral medicine; genetics; neoplasms; phosphatase and tensin homolog; PTEN hamartoma tumor syndrome.

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Germline mutations in the phosphatase and tensin homolog (PTEN) gene are linked to a spectrum of disorders known as "PTEN hamartoma tumor syndrome" (PHTS). These disorders are Cowden disease (CD), Bannayan-Riley-Ruvalcaba syndrome (BRRS), adult Lhermitte-Duclos disease (LDD) and autism spectrum disorders associated with macrocephaly. The bulk of the clinical data regarding these disorders comes from studies of patients with CD and, less commonly, with BRRS.[1]

Here, we present a case series of three patients: a 26-year-old white man affected by CD and a 60-year-old white man man and his 33-year-old daughter, both affected by BRRS and having the complaint of multiple oral papillomatous lesions and cutaneous trichilemmomas. The purpose of this study is to add new data to the current literature on the clinical findings of these rare diseases, considering that oral manifestations are identified as major diagnostic criteria of PHTS.

CASE DESCRIPTIONS

All three cases described here involve patients treated in the Oral Medicine Unit, Department of Head and Neck Diseases, University of Naples Federico II, Italy. The internal institutional review board at the University at Naples Federico II approved this study, and we obtained written informed consent from all participants before completing study assessments.

Case 1. In October 2013, a 26 year-old white man was referred to the oral medicine unit with the main complaint of asymptomatic keratotic lesions of the maxillary and mandibular gingiva (Figure 1). His medical history included a mild form of celiac disease, as well as multiple papillomatous lesions of the penis, hands and plantar skin. His dental history was negative for oral disease. He had never undergone endoscopy or colonscopy.

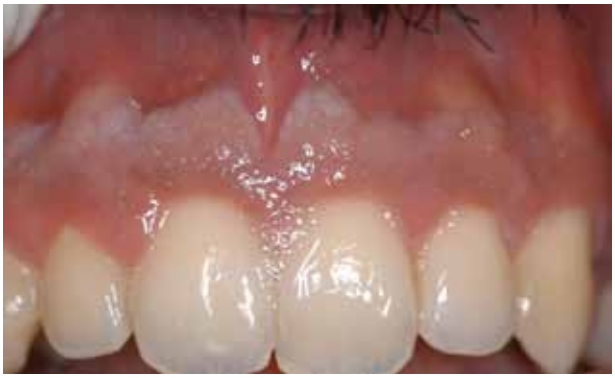

Figure 1. Clinical features of case 1: widespread keratotic lesions and micropapillomatosis of the maxillary gingiva.

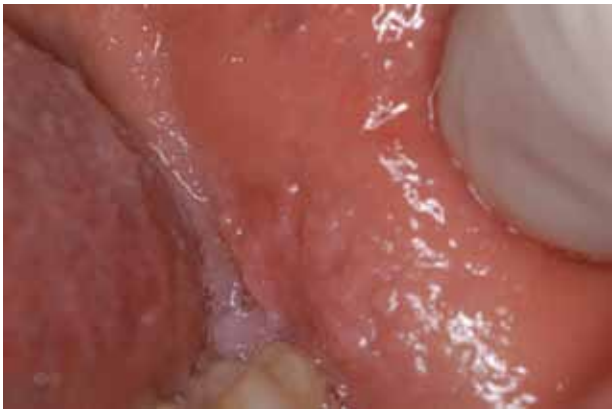

Figure 2. Clinical features of case 2: exophytic lesions of the left buccal mucosa with spongiotic aspect.

The patient, after providing his written informed consent, was hospitalized and examined by three of the authors (A.C., D.A., M.D.M.) by means of routine hematological tests, including glucose, sodium, potassium, chlorine, calcium, creatinine, albumin, hemoglobin, alanine aminotransferase, alkaline phosphates, aspartate aminotransferase, lactate dehydrogenase, creatine phosphokinase, hematocrit, red blood cell (RBC) count, mean corpuscular haemoglobin, mean corpuscular volume, platelet count, mean platelet volume, RBC distribution width, white blood cell count and differential, HIV, and hepatitis B and C viruses. All laboratory test values were normal.

The physical examination showed a widespread whitish papillomatosis of the maxillary and mandibular gingiva with a micropapillary, at times cobblestonelike, pattern and a mild keratosis. The same three clinicians performed an incisional biopsy of the maxillary gingiva, and the histopathological examination revealed a proliferation of multiple benign fibromas with overlying hyperkeratosis. This histopathological result, together with the widespread aspect of lesions in the mouth, the presence of multiple dermatological lesions and the absence of risk factors or inflammatory processes, led us to conjecture a different diagnosis than keratotic lesions.

Because we suspected CD, we conducted further investigations. A gastrointestinal endoscopy showed two gastric polypoid lesions, and, four weeks later, a gene study by means of direct sequencing established the diagnosis of CD caused by a germline mutation in exon 8. A close surveillance was established and, at press time, the patient continues to be monitored closely for manifestations of CD.

Case 2. In November 2013, a 33-year-old white woman was referred to the oral medicine unit with the main complaint of a one-year history of bilateral hamartomatous lesions of the buccal mucosa (Figure 2). Her medical history included moderate obesity (body weight, 103 kilograms; height, 1.75 meters; body mass index, 33.6), secondary amenorrhea (treated by means of ethinyl estradiol and drospirenone), diffuse gastric polyposis, osteoporosis and Hashimoto thyroiditis (treated by means of levothyroxin 125 micrograms per day). The patient has BRRS, diagnosed through genetic tests at the age of 25 years after the discovery of this disease in her father.

After providing her written informed consent, the patient was hospitalized and examined by means of routine hematological tests. All laboratory test values were normal.

Physical examination of the patient revealed bilateral exophytic lesions of the buccal mucosa (maximum diameter, about 1 centimeter) resulting from the confluence of multiple papillomas, widespread papillomatous lesions of the maxillary and mandibular gingiva (Figure 3) and micropapillomatosis of the tongue with a cobblestonelike pattern.

The three clinicians (A.C., D.A., M.D.M.) performed an incisional biopsy of the left buccal mucosa, and the histopathological examination revealed multiple fibropapillomas, with well-differentiated cells and parakeratosis, and an absence of inflammatory cells.

The skin inspection revealed a trichilemmoma localized on the left nasolabial fold, multiple cutaneous papillomas of the left hemithorax and the homolateral abdominal skin, skin-colored scars on the site of an inframammary incision on the right side (results of a surgical removal performed four months previously) and a hemangioma on the elbow. A yearly follow-up protocol has been established.

Case 3. In November 2013, a 60-year-old white man visited the oral medicine unit, initially not as a patient but rather to accompany the woman described in case 2, who was his daughter, on her visit.

His medical history included hypertension, colon cancer (in 2005) and a series of surgical removals of multiple cutaneous trichilemmomas. Physical exami-

ABBREVIATION KEY. **BRRS:** Bannayan-Riley-Ruvalcaba syndrome. **CD:** Cowden syndrome. **LDD:** Lhermitte-Duclos disease. **PHTS:** PTEN hamartoma tumor syndrome. **PTEN:** Phosphate and tensin homolog. **RBC:** Red blood cell.

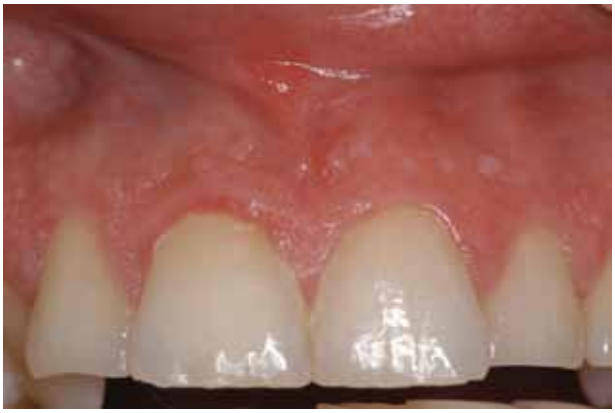

Figure 3. Clinical features of case 2: widespread papillomatous lesions of the maxillary gingiva.

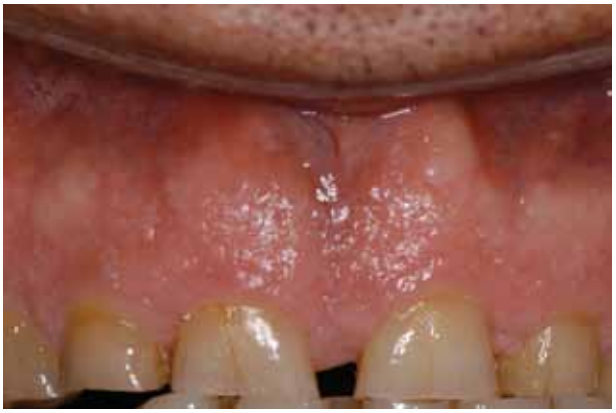

Figure 4. Clinical features of case 3: widespread papillomatosis of the maxillary gingiva.

nation revealed widespread papillomatous lesions of the maxillary and mandibular gingiva with the same clinical periodontal pattern as in case 2, as well as multiple papillomas of the dorsum of the tongue, all of which had a cobblestonelike pattern (Figure 4). Skin inspection revealed multiple papillomas of the abdomen and some macular pigmentations of the glans penis.

Follow-up for all three patients. Three of the authors (A.C., D.A., M.D.M.) properly informed the patients about the need to undergo a regular follow-up for gastric and colon polyps, thyroid nodules, and breast and cutaneous diseases because these conditions usually are symptomatic of PHTS and also are associated with higher cancer risk.

DISCUSSION

CD is a rare, multisystem disease that causes an increased risk of malignancies (breast, thyroid and endometrial) as well as a benign hamartomatous overgrowth of tissues (such as skin, colon and thyroid). CD was first described in one family in 1963,[2] a description then extended by Weary and colleagues[3] in 1972, who added an additional set of five patients and expanded the spectrum of component features. Germline PTEN mutations first were reported in people with CD in 1997.[4,5]

BRRS is a rare congenital disorder whose primary clinical features include macrocephaly, hamartomatous intestinal polyps, lipomas and pigmented macules on the penis. Other features include developmental delay, vascular anomalies, large birth weight and joint hyperextensibility.[6] Diagnoses are based on the presence of several of the primary clinical features. BRRS has been shown to be allelic to CD, with approximately 60 percent of patients with a clinical diagnosis of BRRS having PTEN mutations.[7,8] There are relatively few data regarding the clinical features of BRRS patients with documented PTEN mutations, however; only 30 published cases have been identified (in a 2003 review[9]).

The National Comprehensive Cancer Network, Fort Washington, Pa., has established testing criteria denoting when PTEN testing is indicated, which are based on the clinical features present in a patient.[10] It also has established management and screening recommendations for people who have been found to have a PTEN mutation. However, in clinical practice, it often is necessary to provide treatment for patients on the basis of their clinical diagnosis alone, either because testing is not possible or because it has been done but no mutation has been found. Thus, accurate clinical diagnostic criteria are a necessary adjunct to genetic testing.

Box 1 presents a summary of the diagnostic criteria for PHTS proposed by Pilarski and colleagues.[1]

Patients affected by PHTS require lifelong follow-up, and family members should be screened for the disease. For example, mammography at regular intervals and monthly breast self-examination are of great importance for the early diagnosis of breast cancer. Some authors even suggest bilateral prophylactic mastectomy for patients with PHTS.[11]

Thyroid function tests, thyroid ultrasonography, complete blood count, complete urine analysis, Papanicolau (Pap) test and abdominopelvic ultrasonography should be performed with all patients at the first stage and repeated at regular intervals. If thyroid nodules are present, fine-needle biopsy or surgical biopsy should be performed.[12]

Box 2 presents a brief summary of the management of CD.[10]

As is well known from the literature and also confirmed by our experience, alterations in the oral mucosa and skin usually are present in patients with PHTS.[1] Starink and colleagues[13] reported that 100 percent of patients with PHTS developed oral papillomatosis by the second decade of life, and, for this reason, in the majority of cases such features may precede malignancy in other sites.

A differential diagnosis of oral papillomatous lesions includes multiple traumatic fibromas, oral fibromas in tuberous sclerosis, Darier-White disease, Heck disease, lymphangioma, pyogenic granuloma, fibroepithelial polyps, lipoid proteinosis, oral florid papillomatosis, oral

BOX 1

Revised clinical diagnostic criteria for PTEN* hamartoma tumor syndrome.†

MAJOR CRITERIA
Breast cancer
Endometrial cancer (epithelial)
Thyroid cancer (follicular)
Gastrointestinal hamartomas (including ganglioneuromas, but excluding hyperplastic polyps; three or more gastrointestinal hamartomas total)
Lhermitte-Duclos disease (adult)
Macrocephaly (an occipital-frontal head circumference in the 97th percentile or higher): 58 centimeters for females, 60 cm for males)
Macular pigmentation of the glans penis
Multiple mucocutaneous lesions (any of the following), proven by means of a biopsy or diagnosed by a dermatologist: ▬ Multiple trichilemmomas (three or more, at least one of them proven by means of a biopsy) ▬ Acral keratoses (three or more palmoplantar keratotic pits, acral hyperkeratotic papules or a combination of the two) ▬ Mucocutaneous neuromas (three or more) ▬ Oral papillomas (particularly on tongue and gingiva), multiple (three or more)
MINOR CRITERIA
Autism spectrum disorder
Colon cancer
Esophageal glycogenic acanthosis (three or more lesions)
Lipomas (three or more)
Intellectual disability (that is, an intelligence quotient test score of 75 or lower)
Renal cell carcinoma
Testicular lipomatosis
Thyroid cancer (papillary or follicular variant of papillary)
Thyroid structural lesions (for example, adenoma, multinodular goiter)
Vascular anomalies (including multiple intracranial developmental venous anomalies)
OPERATIONAL DIAGNOSIS IN AN INDIVIDUAL: EITHER OF THE FOLLOWING
Three or more major criteria, but one must be macrocephaly, Lhermitte-Duclos disease or gastrointestinal hamartomas
OR
Two major and three minor criteria
OPERATIONAL DIAGNOSIS IN A FAMILY IN WHICH ONE PERSON MEETS REVISED CLINICAL DIAGNOSTIC CRITERIA FOR PTEN HAMARTOMA TUMOR SYNDROME OR HAS A PTEN MUTATION
Any two major criteria with or without minor criteria
OR
One major criterion and two minor criteria
OR
Three minor criteria

* PTEN: Phosphatase and tensin homolog.
† According to the diagnostic criteria for PHTS proposed by Pilarski and colleagues.[1]

papillomas in Goltz syndrome, mucosal neuromas of multiple endocrine adenomatosis, acanthosis nigricans, pseudoepitheliomatous hyperplasia and squamous cell carcinoma.[14]

BOX 2

Management of Cowden disease.

WOMEN
▬ Breast self-examination starting at age 18 years
▬ Clinical breast examination starting at age 25 or five to 10 years before the earliest breast cancer in the family occurred, whichever comes first
▬ 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 years or five years before the youngest age at which cancer occurred in family history, whichever comes first
▬ Thyroid ultrasound at age 18, then once per year
▬ Colonoscopy, starting at the age of 35 years, then every five to 10 years
▬ Annual dermatologic examination
RISK TO RELATIVES
▬ Explanation of possible inherited cancer risks to relatives, as well as of options for risk assessment and management (the parents of an affected proband must be examined clinically and genetically; if a parent is affected, his or her family members are at risk)
▬ Genetic counseling

CLINICAL IMPLICATIONS

The purpose of this article is to stimulate general dental practitioners to perform an accurate oral examination focusing mainly on the periodontal mucosa and to investigate the differential diagnosis of widespread oral papillomatous lesions carefully. These can represent one of the primary clinical features of this diagnostic challenge, even in young people.

Early diagnosis is the most important element in the management of PHTS: affected people have a lifetime risk of up to 50 percent for breast cancer, 10 percent for thyroid cancer and 5 to 10 percent for endometrial cancer. Over 90 percent of affected people will show some clinical manifestations by their 20s.[15-19]

Dental practitioners who suspect the presence of a PTEN-related syndrome, or more generally of a multiple hamartoma syndrome, should request from specialists a better screening of their patients to meet major and minor diagnostic criteria before resorting to genetic investigation, which is expensive. The important diagnostic steps after the oral examination are an accurate anamnestic evaluation, an accurate total-body dermatological examination, a breast and thyroid ultrasound imaging, a genitourinary screening, gastroscopy and colonoscopy.

Establishing a clear diagnosis means giving these patients the opportunity to undertake an earlier self-surveillance, thereby decreasing the mortality and morbidity associated with these conditions. Once again, dentists may play an important role in the diagnosis and management of rare systemic diseases.

CONCLUSIONS

Our experience highlights that oral health care workers could represent the first line of defence in early diagnosis of rare disorders. In the patients in ur three cases, gingival clinical features and a widespread oral papillomatosis led us to suspect PHTS or, in the already diagnosed patients, PHTS-related lesions.

Three cases of PHTS, two of them in patients of relatively young ages, are not a small amount to be seen in a single center, and this aspect stresses the importance of intercepting disease early.

Nowadays, the visual inspection of the oral cavity requires higher standards, commensurately greater time, and a wider knowledge of these diseases and their main clinical features. A multidisciplinary approach is key in these diagnostic challenges and allows clinicians to achieve a remarkable diagnostic success. If physicians are able to provide an early diagnosis, people with rare disorders can achieve an adequate quality of life, reducing the systemic complications of their conditions. ■

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