Genetic and developmental disorders of the oral mucosa: Epidemiology; molecular mechanisms; diagnostic criteria; management

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1 | INTRODUCTION

Oral mucosal lesions may appear as ulcers, color changes and alterations in size and configuration of oral anatomy. This review presents a broad overview of genetic and developmental disorders of the oral mucosa that might be recognized in children, adults and the elderly.1-3 A number of genetic disorders (Table 1) have specific manifestations of the oral mucosa caused by a derangement of one or several of the components of the tissue. Many of them follow the skin or systemic signs of the underlying genetic disease, but in a few cases, oral signs represent the first manifestation of the disorder. Disorders during embryonic development (Table 2) might lead to a wide range of abnormalities in the oral cavity; some of them are quite common but of negligible concern, whereas others are rare but serious, affecting not only the oral mucosa, but also other structures of the oral cavity (ie palate, tongue and gingiva).

2 | GENETIC DISORDERS

2.1 | Genodermatoses

2.1.1 | Chondro-ectodermal dysplasia

Chondro-ectodermal dysplasia, also termed Ellis-van Creveld syndrome, is a rare disease first described in 1940 by Ellis & van Creveld.4 Approximately 150 cases have been reported worldwide to date.5 The exact prevalence is unknown, but the syndrome seems more common among the Amish community. This rare condition is inherited as an autosomal recessive trait with a variable expression. Mutations of the Ellis van Creveld protein 1 and 2 genes, located in a head-to-head configuration on chromosome 4p16, have been identified as causative.6,7 The mutations of Ellis van Creveld belong to the short rib-polydactyly group and especially type III (Verma-Naumoff syndrome).

Chondro-ectodermal dysplasia is characterized by the presence of short ribs, polydactyly, growth retardation and ectodermal and cardiac defects. The most constant oral findings are fusion of the upper or lower lip to the gingiva and hypertrophy of the labiogingival fraenum, resulting in the disappearance of the mucolabial fold, or the presence of multiple fibrous bands. Oligodontia and small conical teeth with enamel hypoplasia are also present.8 The differential diagnosis from similar chondrodystrophies, such as Jeune dystrophy, McKusick-Kaufman syndrome, includes oro-facial-digital syndrome, and Weyers acrodental dysostosis.5,9-11 The oral dental management is quite complex and often requires a multidisciplinary approach to correct the dental defects. Orthodontics and maxillofacial oral surgery are often involved in the treatment; moreover, comprehensive restorative treatment is fundamental to manage enamel hypoplasia and to replace missing teeth.10

2.1.2 | Dyskeratosis congenita

Dyskeratosis congenita or Zinsser-Engman-Cole syndrome is a multisystem disorder,12 first described by Zinsser in 1906 and recognized...
as a clinical entity by Engman & Cole. Dykeratosis congenita is a rare disease with an estimated annual incidence of less than one per million population. The most common mode of inheritance is the X-linked recessive form, which affects mainly males and is caused by mutation of the DKC1 gene at the Xq28 site. It is characterized by hyperpigmentation, telangiectasias and atrophic areas of the skin (usually on the face, neck and chest), dystrophic nails, hyperhidrosis, by hyperpigmentation, telangiectasias and atrophic areas of the skin (usually on the face, neck and chest), dystrophic nails, hyperhidrosis, keratosis follicularis, pachyonychia congenita, multiple hamartoma syndrome, Peutz-Jeghers syndrome, tuberous sclerosis, and white sponge nevus.

2.1.3 | Ehlers-Danlos syndrome

Ehlers-Danlos syndrome is a group of connective tissue disorders inherited as an autosomal dominant, autosomal recessive or X-linked recessive trait. It was first described by Edvard Ehlers, a Danish dermatologist, in 1908 by Henri-Alexandre Danlos, a French dermatologist. The prevalence is between 1:5000 and 1:10 000, but the epidemiology of the specific types is largely unknown. The various types of the syndromes are clinically and genetically heterogeneous, resulting from defects in either the synthesis or the structure of fibrillar collagen.

Although the basic defect is not well known, the three fundamental mechanisms of disease include deficiencies of collagen-processing enzymes, dominant negative effects of mutant collagen chains and haploinsufficiency. Defects in either collagen-processing enzymes or collagen structure are ubiquitous in all subtypes of the disease, leading to collagen fragility throughout the body. The oral mucosa is excessively fragile and subject to bruising. Gingival bleeding and periodontitis are common.

Wound healing may only be slightly delayed. Tooth mobility is not increased, although a hypermobility of the temporomandibular joint may occur. Approximately 50% of patients have the ability to touch their nose with the tip of the tongue (Gorlin’s sign) compared with 10% of the normal population. The differential diagnosis includes cutis laxa, Marfan’s syndrome, Marfanoid hypermobility syndrome and osteogenesis imperfecta. Oral manifestations include periodontitis and oral mucosal ulceration. There is no definitive treatment for the syndrome.

2.1.4 | Hereditary benign intraepithelial dyskeratosis

Hereditary benign intraepithelial dyskeratosis is a rare autosomal dominant disorder that was first described by Von Sallmann & Paton in 1959. The disorder occurs almost exclusively in members of the Native American Haliwa-Saponi tribe (formerly referred to as Haliwa Indians) or descendants of them. Several additional cases were described in persons who reside in the northeastern part of North Carolina. Some cases were also reported in Italy, England, Germany and Brazil.

A segment of DNA localized at 4q35 is duplicated, resulting in triple alleles for two linked markers, suggesting that gene duplication is responsible for the disorder. The disease affects the oral mucosa and bulbar conjunctiva, with onset usually at birth or early childhood. The oral lesions usually appear as thick, soft, white, asymptomatic papules and plaques with varying sizes and can involve any part of the oral cavity. Milder cases may exhibit the opalescent appearance of leukoedema. Some of these appearances may be due to a superimposed Candida spp. infection. The differential diagnosis includes white sponge nevus due to the similarity of the clinical appearance of lesions. No treatment is recommended because of the nonmalignant nature of the disease.
2.1.5 | Keratosis follicularis

Keratosis follicularis, also known as Darier disease or dyskeratosis follicularis, is a rare keratinization disorder. It is an inherited autosomal dominant genodermatosis with complete penetrance. The disease was first described by Prince Marrow in 1886 and shortly after by Darier & White in 1889. The estimated prevalence is between 1:36 000 and 1:100 000 of the population, most often affecting males. It is caused by mutations in the ATP2A2 gene (12q23-q24.1) encoding a Ca\(^{2+}\) pump of the endoplasmic reticulum of the epithelial cells, resulting in abnormal organization or maturation of complexes responsible for cell adhesion. Mucosal lesions may affect the mouth, pharynx and female genitalia. The oral mucosae are affected in 13%-50% of cases. The typical oral lesions are small, whitish confluent papules of varying size with a central depression, which may occasionally coalesce into plaques and become hypertrophic, assuming a cobblestone appearance. The palate, gingiva, buccal mucosa and tongue are the most frequent sites of localization. The differential diagnosis includes acanthosis nigricans, papillary hyperplasia of the palate, warty dyskeratoma and familial benign pemphigus. The oral lesions of Darier disease are asymptomatic, thus no special dental management is required, and systemic retinoids used to treat severe cutaneous involvement do not improve oral disease.

2.1.6 | Lipoid proteinosis

Lipoid proteinosis, also known as Urbach-Wiethe syndrome or hyalinosis cutis et mucosae, is a rare autosomal recessive genodermatosis. It was first described by Urbach & Wiethe in 1929. Incidence and prevalence are not known. More than 300 cases (age range 6-67 years) have been reported worldwide. This condition is more common in Europe (the Netherlands or Germany) and South African regions, particularly among children of consanguineous marriages. The etiology remains uncertain. Mutations in the gene encoding for extracellular protein 1 on band 1q21 are found. The most common mutations are located on exons 6 and 7 of extracellular protein 1.

The mouth is extensively involved, most frequently affecting the palate, gingiva, buccal mucosa, lingual frenulum and tongue. The mucosa has a nodular and thick aspect and seems to be related to hyaline deposition, especially in the gingival tissues. The main differential diagnoses are hydroa vacciniforme and erythropoietic protoporphryia, but also include xanthomas, leposys and lichen amyloidosis. No specific treatment is available for this uncommon disorder.

2.1.7 | Multiple hamartoma syndrome

Multiple hamartoma syndrome, also known as Cowden disease, is a multisystem disorder inherited as an autosomal dominant trait showing a high degree of penetrance and a range of expressivity with a predisposition to cancer. Although the exact prevalence is unknown, it is estimated at 1:200 000. Mutation of the phosphatase and tensin homolog tumor-suppressor genes has been implicated in its pathogenesis. The chromosomal locus of this gene is on band 10q23.3. Inherited mutation in the phosphatase and tensin homolog gene has been found in about 80% of affected patients, whereas in the remaining 20% the etiology remains unknown. Oral findings are present in 80% of patients and are considered the major diagnostic criteria, especially for early clinical identification. Oral lesions usually consist of small multiple whitish or pink papules or nodules, around 1-3 mm, that affect the gingiva, dorsal tongue and buccal mucosa. These lesions may be isolated or coalesce in a characteristic cobblestone pattern, usually on the gingiva. Other possible oral findings include a high arched palate, periodontitis, extensive dental caries and xerostomia. The differential diagnosis includes tuberous sclerosis, juvenile polyposis syndrome, Peutz-Jeghers syndrome, Birt-Hogg-Dubé syndrome, Gorlin syndrome and neurofibromatosis type 1. As the malignancy of oral lesions is not described and the lesions are asymptomatic, no treatment of the oral lesions is generally required.

2.1.8 | Pachyonychia congenita

Pachyonychia congenita, or Jadassohn-Lewandowsky syndrome, is a rare group of genodermatosis usually inherited as an autosomal dominant trait. Since it was initially reported in 1906 by Jadassohn & Lewandowsky, approximately 1000 patients have been registered to date worldwide, but the prevalence is still not known. The disease is caused by the mutation of five keratin genes KRT6A (OMIM 148041), KRT6B (OMIM 148042), KRT6C (OMIM 612315), KRT16 (OMIM 148067) and KRT17 (OMIM 148069). Keratins play a key role in epidermal cell integrity and mechanical strength. These genes are expressed in the nail bed, palmpoplantar epidermis, oral and laryngeal mucosa and hair follicles. Disruption of the cytoskeletal system due to the keratin gene mutations leads to extreme fragility of the epithelial cells and tissues, which appears clinically as epidermolysis and compensatory hyperkeratosis at these sites. Onset is variable, with most cases manifesting soon after birth, others becoming clinically apparent only in late childhood and rarely in adulthood. It is characterized by symmetrical thickening of the nails, palmpoplantar hyperkeratosis with hyperhidrosis, blister formation and follicular keratosis.

The oral mucosal lesions appear as leukokeratosis, which are sometimes painful. These usually appear with a striated hyperkeratotic aspect and are present as thick and white or greyish-white areas that are usually located on the palate, dorsum of the tongue, the gingiva and the buccal mucosa. The differential diagnosis should include leukoplakia, lichen planus, white sponge nevus, dyskeratosis congenita, hereditary benign intraepithelial dyskeratosis and focal palmpoplantar and oral mucosa hyperkeratosis syndrome. No treatment is required for the oral lesions.
FIGURE 1 Cowden disease. Multiple lesions of the gums, which appears rounded, nodular and sessile. The gingivae look globally hyperplastic.

2.1.9 | Peutz-Jeghers syndrome

Peutz-Jeghers syndrome is an autosomal dominant condition characterized by the association of gastrointestinal polyposis, mucocutaneous pigmentation and cancer predisposition. The exact global prevalence is unknown, but is estimated to be in the range of 1:25,000 to 1:300,000 births in the USA. The syndrome is inherited in an autosomal dominant manner and is caused by a mutation of the LKB1/STK11 gene (19p13), which encodes for a serine/threonine kinase.

This syndrome is characterized by intestinal polyposis (hamartomas) and blue and/or dark brown mucocutaneous pigmented spots. Polyps, present from childhood, may lead to intussusception or gastrointestinal bleeding. The disease is associated with an increased risk of gastrointestinal cancer. In addition, extracolonic manifestations, both malignant and nonmalignant lesions, may also be present.

Orally, the pigmented maculae are typically placed in peri-oral and/or intra-oral areas, which could present at birth and become more extensive in early childhood. These constitute the most important diagnostic finding and appear as spots 1-10 mm in diameter, always found on the lower lip and the buccal mucosa, but rarely on the upper lip, tongue, palate and gingiva. The presence in childhood of pigmented spots on the lips, buccal mucosa and peri-oral tissues should alert the clinician to investigate for Peutz-Jeghers syndrome.

The differential diagnosis includes Addison’s disease, Albright’s syndrome, Gardner’s syndrome, simple freckles and normal pigmentation. The surgical excision of intestinal polyps is recommended. No treatment is required for the pigmented lesions, except for aesthetic reasons, and good results are reported with the use of potassium titanyl phosphate laser ablation.

2.1.10 | Tuberous sclerosis

Tuberous sclerosis, also known as epiloia or Bourneville-Pringle syndrome, is transmitted as an autosomal dominant neurocutaneous syndrome with high penetrance. The prevalence in the general population in Europe was estimated to be 8.8:100,000. Many patients die by the age of 20 years.

Two major mutation loci have been identified: one in TSC1 and the other in TSC2, tumor-suppressor genes located in chromosome 9q34 and 16p13. The TSC1 gene codes for hamartin protein and TSC2 gene is responsible for encoding for tuberin. The loss of the complex created by these proteins, an important inhibitor of neoplasia, promotes an uncontrolled cell proliferation and migration. It is characterized by epilepsy, mental handicap, paraventricular calcifications, multiple small gliomas, mucocutaneous manifestations, skeletal disorders and, rarely, ophthalmic tumors. Characteristic skin lesions occur on the face, principally along the nasolabial fold and cheeks (facial angiofibromas), peri-ungual fibroma (Koenen tumors) and fibrous plaques on the forehead and scalp. Other lesions include renal angiomyolipomas, subependymal nodules and retinal hamartoma.

The oral cavity is frequently involved. The oral mucosa may present fibromas, especially affecting the anterior gingiva. Other sites less frequently involved include labial mucosa, superior labial frenulum, palate and tongue. The gingiva or other parts of the oral mucosa may exhibit confluent nodules a few millimeters to less than 1 cm in diameter, which are of whitish or normal color. Enamel pits also occur. The differential diagnosis of oral lesions should include multiple fibromas, multiple condylomata acuminata, focal epithelial hyperplasia and neurofibromatosis. Frequent dental examinations are needed in order to eliminate potential irritative factors.

2.1.11 | White sponge nevus

White sponge nevus is rare autosomal dominant disorder with a high degree of penetrance and varied expressivity. It was first described in 1909 by Cannon and the prevalence is less than 1:200,000. Mutations of the keratin 4 or keratin 13 genes have been reported. Clinically, the disease is characterized by the presence of white, corrugated and diffuse plaques on the oral mucosa. The clinical manifestations tend to appear at an early age. The lesions are benign, asymptomatic and usually bilateral. The oral manifestations are found in the buccal mucosa and the ventral surface of the tongue mostly, but they may occur anywhere on the oral mucosa (Figure 2). Extra-oral sites, such as esophageal, laryngeal, nasal and anogenital mucosa, might also be affected.

The differential diagnosis includes oral leukoplasia and dyskeratosis congenita and, rarely other genodermatoses associated with white hyperkeratotic lesions of the oral mucosa. No standard treatment protocol is reported for this condition; nevertheless, partial remissions have been documented with the use of tetracycline mouth rinse; long-term low-dose treatment of systemic antibiotic therapy maintained the remission, suggesting that a bacterial overgrowth may be associated.

2.2 | Other genetic disorders

2.2.1 | Acanthosis nigricans

Acanthosis nigricans was first reported in 1890 by Pollitzer. The condition involves skin and mucosa, characterized by dark
discoloration and papillary lesions. There are two forms of acan-thosis nigricans, benign and malignant. The benign form is quite common, with a prevalence in the general population of 1%-13%; racial differences are reported (Figure 3). The malignant form is a rare disease of unclear origin. The disease seems to be most common in Native Americans, followed by African Americans, Hispanics and Caucasians. The disease is most commonly associated with disorders related to insulin resistance, including obesity, type 2 diabetes, and polycystic ovary syndrome. Elevated insulin concentrations result in direct and indirect activation of insulin-like growth factor-1 receptors on keratinocytes and fibroblasts, leading to proliferation. Some drugs, such as insulin, fusidic acid, nicotinic acid, systemic corticosteroids and estrogens, may precipitate the signs of this condition. The form associated with malignant neoplasms is less common, although the lesions themselves are not malignant.

Skin alterations are one of the most characteristic features of this disease; they are thick with small velvety papillary lesions, tags and dark pigmentation. The most common sites of involvement are the axillae, neck, groin, umbilicus, peri-anal area and the genitalia. The genetic type of benign acanthosis nigricans involves the oral mucosa in about 10%-15% of cases. The tongue and lips are very often involved, but rarely the gingiva, buccal mucosa or palate. The lips may be enlarged and covered by papillomatous growths, particularly at the commissures. There is hypertrophy and elongation of the filiform papillae, resulting in a shaggy appearance of the tongue. Hyperplasia of the interdental papilla and pseudo-pocket formation have also been described. The differential diagnosis includes hairy tongue. No treatment is required for the benign form and oral cavity manifestations. The malignant form is a rare condition associated with neoplasms. Eight cases of malignant acanthosis nigricans have been reported globally.

2.2.2 | Angio-osteo-hypertrophic syndrome

Angio-osteo-hypertrophic syndrome, also known as Klippel-Trénaunay-Weber syndrome, is a rare congenital vascular bone syndrome first described by Klippel & Trénaunay in 1900 and later confirmed by Weber. The incidence is unknown but around 1000 cases have been reported in the literature. The etiology remains unknown; however, it has been suggested that the syndrome may result from a mesodermal abnormality between the third and sixth weeks of gestation during vascular differentiation, probably due to an intrauterine insult.

The syndrome consists of a classical triad of clinical features represented by cutaneous hemangiomas, such as nevus flammeus, lymphangiomas, arteriovenous fistulas or varicosities (or both), cutis marmorata and unilateral hypertrophy of hard and soft tissues with different localizations.

In the oro-facial region, patients with this condition may present a unilateral increase of facial dimensions in both the hard and soft tissues, especially in the lips, cheeks, tongue, teeth and periodontal tissues. Sometimes, there is also a unilateral increase of the dimensions of fungiform papillae and palate anomalies like petechiae. The oral hemangiomas are usually located on the lips, buccal mucosa, soft and hard palates and gingiva and oropharynx. Premature tooth eruption, marked displacement of teeth on the affected side and jawbone overgrowth may produce asymmetry, malocclusion and anterior open bite. The differential diagnosis includes Sturge-Weber syndrome, Maffucci's syndrome and large isolated hemangiomas. Dental management is supportive, but severe asymmetry of the face requires an interdisciplinary approach, including corrective surgery.

2.2.3 | Encephalotrigeminal angiomatosis

Encephalotrigeminal angiomatosis, also known as Sturge-Weber syndrome, Sturge-Weber disease, Sturge-Weber-Dimitri syndrome and meningofacial angiomatosis, is a rare, congenital, neuro-oculo-cutaneous dysplasia. It was initially described by Schirmer in 1869 and later in much more detail by Sturge & Weber. In Europe, the birth prevalence is estimated to be around 1:20 000 and 1:50 000. No ethnicity predilection is described. It has been theorized that the disease originates from a somatic mutation in GNAQ gene.
(9q21), during the early stages of cerebral vascularization, as a developmental anomaly of embryonic origin because of errors in mesodermal and ectodermal development. There is failure of regression of a vascular plexus around the cephalic portion of the neural tube that is destined to become facial skin.

The common clinical features are angioma of the leptomeninges, dermal angiomas resulting in port wine stains, due to the deep purple hue that they leave on the skin or mucosa, abnormal findings in skull radiographs, mental retardation, epilepsy, ocular involvement and hemiplegia. Hemangiomas of the oral mucosa have a bright red or purple color and are placed unilaterally, rarely cross the midline and may involve the upper gingiva, buccal mucosa, lips, tongue and floor of the mouth. In gingivae, these lesions present as unilateral hyperplasia due to an increased vascular component. Other oral abnormalities reported are pyogenic granulomas, unilateral hypertrophy of the alveolus, ipsilateral premature eruption or delayed eruption of teeth and malocclusion (Figure 4A,B). The differential diagnosis includes large disseminated hemangiomas and Klippel-Trenaunay-Weber syndrome. Treatment is variable and depends on the nature or intensity of the clinical features; dentists and oral surgeons need to be aware of serious bleeding risks.

2.2.4 | Familial adenomatous polyposis

Familial adenomatous polyposis is an autosomal dominant disorder characterized by the development of hundreds to thousands of intestinal adenomatous polyps, mainly of the colon and rectum. Extra-intestinal manifestations are frequently observed, involving a variety of systems, including the skin, skeleton and soft tissues. This combination has been called Gardner’s syndrome. Worldwide, this disorder is a major cause of cancer-associated morbidity and mortality. Its prevalence varies considerably among different populations, with the highest reported from Western and industrialized countries; it is quite rare: 1:10,000 subjects in the USA and 1:11,300 to 1:37,590 in Europe. It is caused by a mutation in the adenomatous polyposis coli gene (APC) of the X chromosome (Xp11.23). It is a multigene disorder characterized by dermatologic, skeletal, ocular, urinary, gastrointestinal, neurological and oral abnormalities. The skin and the skeleton are the most common sites affected; oral findings are less frequently reported. The frequently observed oral mucosal manifestations are multiple papillomas on the tongue, buccal mucosa, palate, gingiva or lips and are considered characteristic. Similar papillomas may be found at junctions between the mucosa and the skin on the vulva, peri-anal and peri-oral areas. Other oral manifestations are oligodontia or hypodontia of both deciduous and permanent dentitions; dysplastic enamel, microdontia, taurodontism and malocclusion are not rare. The differential diagnosis of oral lesions should include multiple papillomas and condylomata acuminata due to human papillomaviruses, focal epithelial hyperplasia andcontinentia pigmenti. Oral papillomas typically require surgical excision, especially in the gingiva if they limit the normal tooth eruption.

2.2.6 | Focal palmoplantar and oral mucosa hyperkeratosis syndrome

Focal palmoplantar and oral mucosa hyperkeratosis syndrome was first described by Gorlin in 1936. It is inherited as an autosomal dominant trait and is also referred to as hyperkeratosis palmoplantaris and attached gingival hyperkeratosis and by many other names. It is a very rare disease and belongs to the heterogeneous group of inherited palmoplantar keratoderm with associated ectodermal manifestations. The prevalence is unknown. Only a few
cases have been reported in the literature, including some families affected by the disease in several consecutive generations.\textsuperscript{100,123}

Palms, soles and attached gingiva, areas bearing mechanical pressure or friction, are the most common sites where the disorder appears as focal painful hyperkeratosis.\textsuperscript{121} Adult patients additionally demonstrate hyperhidrosis, hyperkeratosis, slight peri-ungual keratoses at several toe- and fingernails and thickening of the nails.\textsuperscript{100,121,124} Marked hyperkeratosis of the attached gingiva presenting as leukoplakia is a constant finding.\textsuperscript{121} However, other oral sites, such as the palate, alveolar mucosa, lateral border of the tongue, retromolar pad mucosa and the buccal mucosa along the occlusal line may be involved due to mechanical stress during normal oral function.\textsuperscript{100,121}

The differential diagnosis should include pachyonychia congenita, dyskeratosis congenita, Papillon-Lefèvre syndrome and oral leukoplakia and esophageal carcinoma syndrome. Regarding the treatment, unfortunately, no reliably successful treatment exists, but aromatic retinoids, usually topical keratolytics, such as 6% salicylic acid in white soft paraffin or a gel of 6% salicylic acid in 70% propylene glycol, may occasionally be helpful. Dental management is only supportive.

2.2.7 | Gingival fibromatosis

Gingival fibromatosis, first reported by Goddard & Gross in 1856,\textsuperscript{125} is a rare disease characterized by proliferative fibrous overgrowth of the gingival tissue caused by an increase in the subepithelial connective tissue elements.\textsuperscript{118} The prevalence is unknown; the incidence is 1:750 000 in live births.\textsuperscript{126} It is transmitted as an autosomal dominant or autosomal recessive trait and can occur in either dominant (common) or recessive forms.\textsuperscript{127} Clinically it is a slowly progressive disease involving excessive collagen deposition. There is generalized enlargement of the gingiva, which is usually firm, smooth and occasionally nodular, with minimal or no inflammation and normal or pale in color.\textsuperscript{126} The upper gingiva is more severely affected and may prevent the eruption of the teeth (Figure 6).

The enlarged tissues result in both functional and esthetic problems: it may partially or totally cover the dental crowns, pseudo-pocketing, delay or impede tooth eruption and can cause diastemas, malpositioning of teeth, cross and open bites, prominent lips and open lip posture.\textsuperscript{126,128} The differential diagnosis should include gingival hyperplasia due to phenytoin, nifedipine and cyclosporine and gingival fibromatosis, which may occur as part of other genetic syndromes. Treatments vary according to the degree of severity of gingival enlargement and different types of treatment modality could be employed for the excision, including conventional surgery, electrosurgery, apically positioned flap and lasers.\textsuperscript{129,130} The maintenance of good oral hygiene and plaque control is fundamental. Attempts at improving oral hygiene are of limited benefit in severe gingival enlargement; in this case, surgical gingival resection is indicated.

2.2.8 | Maffucci’s syndrome

Maffucci’s syndrome is a rare congenital nonhereditary mesodermal dysplasia, first reported by Angelo Maffucci in 1881.\textsuperscript{131} The prevalence is unknown. About 250 cases have been reported so far in the world literature. The exact etiology is still unknown. No familial pattern, sexual or racial predilection has been reported.\textsuperscript{132,133} However, somatic mosaic mutations in isocitrate dehydrogenase 1 and 2 genes have been identified.\textsuperscript{134} The syndrome is characterized by multiple enchondromas, principally in the small bones of the hands and feet. These abnormalities are usually asymmetric and can cause secondary fractures and lead to significant deformity.\textsuperscript{133,135} Other findings are multiple hemangiomas localized on the skin, mucosae and viscera including the oropharynx, intra-abdominal and gastrointestinal tract.\textsuperscript{135,136} They are typically located in the subcutaneous tissues and appear as blue nodules, which can be emptied by manual compression.\textsuperscript{137} Due to these clinical signs, some authors consider the disease as a variant of Ollier’s disease, which has only enchondromatosis.\textsuperscript{138} Thrombi may form, calcify and give a characteristic appearance of phleboliths on plain X-rays.\textsuperscript{135}

**FIGURE 5**  Focal dermal hypoplasia. A, Polysyndactyly of the hand in a child with focal dermal hypoplasia. B, Enamel hypoplasia of an inferior incisor from the same patient.
The oral mucosa is rarely affected and the oral lesions are usually multiple hemangiomas.\textsuperscript{139} The tongue is the most frequent site of hemangiomas, but the buccal mucosa, lips, soft palate and other oral regions can also be involved. This disease is associated with an increased risk of malignant transformation, especially chondrosarcomas and hemangiosarcomas.\textsuperscript{133,137,140} The overall prevalence of malignancies associated with Maffucci’s syndrome is 23%-100% in different studies.\textsuperscript{135,137} The differential diagnosis includes hemangiomas, Ollier’s disease, the blue rubber bleb nevus syndrome and Klippel-Trenaunay-Weber syndrome. Overall management aims at the relief of symptoms, early detection of malignancies and long-term follow-up. Management of the oral lesions is usually surgical and depends on the size and location of the lesions.

### 2.2.9 Neurofibromatosis (type 1)

Neurofibromatosis, also known as von Recklinghausen’s disease, is a group of genetic disorders inherited as an autosomal dominant trait, characterized by multiple cutaneous lesions and tumors of the central and peripheral nervous system.\textsuperscript{141} Neurofibromatosis type 1 is the most common, affecting approximately 1:3500 individuals worldwide.\textsuperscript{141} It is due to a mutation of the neurofibromatosis type 1 gene, which is a tumor-suppressor gene located in the long arm of chromosome 17q11.2.\textsuperscript{142} and rarely by 17q11 microdeletion (only 5%).\textsuperscript{143} The cardinal features of the disease are the “cafe-au-lait” spots (more than six spots, >5 mm in diameter in children or >15 mm in adults) and the skin neurofibromas.\textsuperscript{144} Other clinical signs are nervous system manifestations, skeletal disorders, iris Lisch nodules (melanocytic hamartomas that appear as well-defined, dome-shaped elevations projecting from the surface of the iris) and multiple neurofibromas.\textsuperscript{145}

Neurofibromatosis type 1 may present oral symptoms in up to 72% of affected patients, who exhibit multiple or, rarely, isolated nodular neurofibromas that vary in size.\textsuperscript{146} Common sites include the tongue (26%), buccal mucosa (8%), alveolar ridge (2%), labial mucosa (8%), palate (8%), gingiva (2%), nasopharynx, paranasal sinuses, larynx, floor of the mouth and salivary gland. Oral neurofibromas usually present as firm, uninfamed, submucosal discrete masses. Tumors generally tend to grow slowly and patients are usually asymptomatic. However, symptoms may arise due to trauma to the swellings, especially depending on the oral location (eg tongue, palate).\textsuperscript{147,148} The most commonly reported finding is enlargement of the fungiform papillae of the tongue.\textsuperscript{142} Gingival neurofibromas can enhance periodontal disease, as tissue growth limits routine oral hygiene measures.\textsuperscript{149}

Patients may present with absent, impacted and/or malpositioned teeth.\textsuperscript{150} Tumors may also arise within the jaws and other bones.\textsuperscript{151} Individuals with neurofibromatosis type 1 demonstrate an increased incidence of benign tumors, with the risk of malignant transformation being 3%-5%.\textsuperscript{152} The differential diagnosis should include multiple mucosal neuromas, multiple endocrine neoplasia type III syndrome and Klippel-Trenaunay-Weber syndrome. Oral neurofibromas, especially when accessible and a small size, are most frequently treated by surgical excision.\textsuperscript{147} A good oral health status in patients with neurofibromatosis type 1 must be achieved through oral hygiene maintenance and regular dental check-ups.\textsuperscript{145}

### 2.2.10 Oro-facial-digital syndrome (type 1)

Oro-facial-digital syndromes constitute a heterogeneous group of embryonic development disorders first described by Mohr in 1941.\textsuperscript{153} Thirteen types of this syndrome have been described based on clinical manifestations and inheritance patterns, characterized by malformations of the face, oral cavity, hands and feet.\textsuperscript{154,155} Oro-facial-digital syndrome type 1, also known as the Papillon-League-Psaume syndrome, or oro-facio-digital dysostosis, was first described in 1954.\textsuperscript{156} and it is the most common among all types. The other types are extremely rare.\textsuperscript{157} The prevalence of oro-facial-digital syndrome type 1 is unknown, but the annual incidence is estimated to be between 1:250 000 and 1:50 000 live births.\textsuperscript{158} It is transmitted as an X-linked dominant trait, which occurs mostly in females; the disease has lethal effects in males.\textsuperscript{159,160} The other types of oro-facial-digital syndrome show autosomal recessive inheritance.\textsuperscript{159} Oro-facial-digital syndrome type 1 is caused by mutations in the CXORF5 gene, later renamed oro-facial-digital syndrome I, which is found on the short arm of X-chromosome (Xp22.2-Xp22.3).\textsuperscript{161,162} This is characterized by a number of heterogeneous clinical features involving malformations of the digits, face and oral cavity. The cardinal clinical manifestations are digital malformations of hands (50%-70%) and feet (25%), such as clinodactyly, brachydactyly or syndactyly of the hands and polydactyly of the feet.\textsuperscript{162,163} Other common conditions are polycystic kidney disease, which can be the most determining feature in this syndrome, cutaneous lesions, such as milia, xeroderma, alopecia, sparse hair and dermatoglyphic abnormalities.\textsuperscript{161,164} Central nervous system disease occurs in 40% of oro-facial-digital syndrome type 1 individuals, with

![FIGURE 6](image-url) Gingival fibromatosis. A 20-year-old female patient with gingival overgrowth without displacement of teeth. The gingiva is pink, firm, nodular, painless and nonhemorrhagic.
mental retardation, seizures, hydrocephalus, cerebellar anomalies, porencephaly and agenesis of corpus callosum.\textsuperscript{165,166} Facial features include frontal bossing, facial asymmetry, hypertelorism and a broadened nasal bridge.\textsuperscript{167} Regarding the intra-oral lesions, constant oral mucosal findings are multiple hyperplastic frenula traversing the upper and lower gingivalabial folds; accessory gingival frenula are common.\textsuperscript{168,169} The tongue appears multilobed or bifid and often exhibits multiple hamartomas and ankylosis. Clefts of the lips and the soft and hard palate are common. Mandibular lateral incisors are often missing, supernumerary teeth are common and upper canines are often malpositioned.\textsuperscript{168-170} The differential diagnosis should include oro-facial-digital syndrome type II (Mohr syndrome), chondro-ectodermal dysplasia and oculo-dento-digital syndrome. A multidisciplinary approach is necessary in the treatment of this syndrome. Maxillofacial surgery and orthodontics are often needed to treat the oral manifestations.

3 | DEVELOPMENTAL DISORDERS

3.1 | Oral mucosa

3.1.1 | Cysts of the oral mucosa in newborns

Nodules or cysts of the oral mucosa occur with a high incidence (about 80%) in infants.\textsuperscript{171} These cysts can be classified as gingival cysts (dental lamina cysts) and median palatal mucosal cysts (Epstein’s pearls).\textsuperscript{171} Epstein’s pearls are considered to be the result of the entrapment of the epithelial cells in the median palatal raphe. Pearls are small white or yellow vesicles (1-3 mm diameter) in the median area of the palate, but these disorders can also affect other structures of the oral cavity, the tongue and lips. They do not require treatment as they resolve spontaneously over the first few weeks of life.

3.1.2 | Fordyce’s granules

Fordyce’s granules, also termed Fordyce’s spots or disease, are heterotopic/ectopic sebaceous glands that are considered to be a normal variation of the oral mucosa. These spots were first described by Kölliker in 1861, but are named after Fordyce, who reported on them in 1896.\textsuperscript{172,173} They appear as multiple, small, milia-like, yellowish structures with a 1-2 mm diameter that occasionally might form confluent plaques. Granules are also described on the genital mucosa and on the skin of the face. They are found in the majority of adults, with an estimated prevalence of about 80%, which increases with age.\textsuperscript{173} In the oral cavity, the granules are found on the vestibular mucosa, but the upper lip, gingiva and anterior pillars of fauces may also be involved (Figure 7). The composition of granules is identical to that of sebaceous glands on the skin and about 50% of the sebum composition is triglycerides.\textsuperscript{174} They appear to be a more frequent finding in people with greasy skin types, with some rheumatic disorders and in hereditary nonpolyposis colorectal cancer.\textsuperscript{67} No treatment is required.

3.1.3 | Leukoedema

Leukoedema is a benign and asymptomatic condition that probably represents a variation of normal mucosa. Sandstead & Lowe first described this exclusively in adults. However, Martin & Crump also recognized it in children and young adults.\textsuperscript{175,176} Leukoedema appears as a grayish-white lesion located on the buccal mucosa, frequently bilaterally. Analogous mucosal changes have been found on vaginal and laryngeal mucosae. The etiology is unknown, but associations with tobacco use, local irritation from sodium lauryl sulphate-containing toothpaste\textsuperscript{177} and malocclusion have been suggested. The prevalence differs in adults depending on the population examined: very high in Black adults (almost 90%) and quite frequent in White adults, who show much less pronounced forms (prevalence rate: 3:1000 in White adults).\textsuperscript{176} Histologically, the lesions show hyperparakeratosis and are frequently elongated with irregular rete-pads and intracellular edema of the Malpighian layer.\textsuperscript{176} Leukoedema differs from leukoplakia as there is no loss of pliability or flexibility of the involved tissues (Figure 8). Differential diagnosis from lichen planus is realized by stretching the mucosa: leukoedema will either disappear or persist, whereas lichen planus will become more evident. Leukoedema should also be differentiated from white sponge nevus and habitual cheek-biting.\textsuperscript{176} Fordyce’s spots do not require any treatment. However, anxious patients require reassurance.

3.1.4 | Retrocuspid papilla

Retrocuspid papilla was first described in 1947 by Hirschfeld\textsuperscript{178}; it is a 2-4 mm nodule located, more commonly, bilateral on the lingual attached gingiva in proximity of mandibular canines. It is considered a developmental anomaly as it appears bilaterally and in a predictable location. It is observed more frequently in young children and seems to regress or disappear during their growth.\textsuperscript{179} Histologically,
the lesions are composed mainly of loosely arranged delicate fibrous connective tissue with occasional mature, dense collagenous areas; papillae could be classified into two different types by the presence or absence of stellate and occasionally multinucleated fibroblasts.\textsuperscript{180} It should be differentiated from pyogenic granuloma, peripheral giant cell granuloma, irritation fibroma, gingival cyst or a metastatic neoplasm to the gingiva.\textsuperscript{181} No treatment is required.

3.1.5 Geographic tongue

Geographic tongue, or benign migratory glossitis, is a disorder of unknown etiology and pathogenesis, although an inherited pattern has been suggested with a polygenic mode of transmission. Changes in the lingual microbiota profiles were noted; however, it remains unknown if this finding is a consequence of the lesions or of factors associated with the initiation and progression of the disease.\textsuperscript{182} The prevalence ranges from 1.0% to 2.5% and it is more frequent in adults than in children.\textsuperscript{183} Clinically, the lesions appear as a central atrophic area bounded by a raised white circinate line with multiple tongue sites affected. The circinate, irregular erythematous lesions are caused by loss of filiform papillae, whereas the fungiform papillae remain unchanged. The most common locations are the lateral margins and tip of the tongue. Lesions vary in size from several millimeters to several centimeters. These lesions persist for a short time in an area of the tongue and then disappear and reappear in another area (Figure 9). The finding of an association between fissured tongue and geographic tongue supports a genetic basis for the two conditions.\textsuperscript{184} The fissures may act as stagnation areas on the tongue surface in which glossitis may begin. Geographic tongue presents with clinical, histological and genetic patterns similar to those of psoriasis, suggesting that it may represent an oral manifestation of the disease.\textsuperscript{184} Geographic tongue typically does not require any medical treatment. Geographic tongue can sometimes cause tongue discomfort; to manage this it is possible to treat patients with pain relievers and mouth rinses with an anesthetic and/or antihistamine and/or corticosteroid ointments or rinses.

3.1.6 Fissured tongue

After geographic tongue, fissured or “scrotal” tongue is the second most common developmental malformation of unknown cause of the tongue, even if in recent years a polygenic mode of transmission was proposed. Many authors have observed a relationship between scrotal tongue and geographic tongue, as a genetic association between these lesions was supposed.\textsuperscript{184} Its prevalence

FIGURE 8 Leukoedema. The buccal mucosa is characterized by a grayish-white, opalescent pattern and a slightly wrinkled surface is present.

FIGURE 9 Geographic tongue. Left side of the dorsum of the tongue with typical appearance of geographic tongue. There is a map-like aspect with small red patches, surrounded by a serpiginous, white, hyperkeratotic border.

FIGURE 10 Fissured tongue. Fissured tongue characterized by grooves that vary in depth and are noted along the dorsal and lateral aspects of the tongue. Fissured tongue and geographic tongue (see Figure 5) have been reported in association with chronic granulomatous disease.
ranges from 0.5% to 5%. It has been associated with more advanced ages, whereas the prevalence of geographic tongue was higher in younger subjects. Clinically fissured tongue is characterized by multiple fissures or grooves on the dorsal surface varying in depth, size and number; usually, the fissures have a symmetrical distribution (Figure 10). The condition is asymptomatic. Local irritation of the fissures might occur if food debris, microorganisms and fungi are retained in the deeper fissures. Fissured tongue is a characteristic of Down’s syndrome and Melkersson-Rosenthal syndrome (also noted as “Miescher-Melkersson-Rosenthal syndrome”), a rare neurological disorder characterized by recurring facial paralysis and swelling of the face and lips. Treatment is not required.

3.1.7 | Median rhomboid glossitis

Median rhomboid glossitis was commonly referred to as a developmental defect with a starting point during embryogenesis, caused by the failure of the tuberculum impar to be covered completely by the lateral processes of the tongue. It is found anterior to the circumvallate papillae. As this defect is not observed in children, a developmental etiology has largely been discounted; furthermore, median rhomboid glossitis is also described as a form of hyperplastic candidiasis and the term is only used when lesions are found on the central portion of the tongue. Other predisposing factors include smoking, denture wearing, use of corticosteroid sprays or inhalers and HIV infection. The prevalence of this lesion was reported as 2.4% in the Israeli population. This tongue disorder is sometimes not clearly diagnostic to the clinician. Hyperplastic candidiasis may be present in other areas of the mouth as well, such as the commissures and the hard and soft palate (Figure 11). Associations with Actinomyces spp. have also been proposed.

3.1.8 | Hairy tongue

Hairy tongue is a relatively common disorder affecting the filiform papillae. Its prevalence varies geographically, ranging from 0.6% to 11.3%. The etiology is not clear, although several predisposing factors are advocated, such as oral antibiotics, oxidizing agents, metronidazole, smoking, radiation, poor oral hygiene and Candida albicans infection. Clinically, it is characterized by hypertrophy and elongation of the filiform papillae of the dorsum of the tongue, which take on a hairy appearance (Figure 12). Papillae, which normally are about 1 mm in length, may become as long as 12 mm. Papillae may vary from yellowish-white to brown or black when pigments produced by oral bacteria colonize them. Hairy tongue should not be confused with oral hairy leukoplakia, a condition characterized by vertical white striations typically affecting the lateral tongue bilaterally and caused by Epstein-Barr virus, occurring usually in immunocompromised patients. Hairy tongue is usually asymptomatic, but it may cause significant distress to the patient for esthetic reasons. Brushing of the tongue may promote desquamation and reduce the length of the papillae. In severe cases, with very long filiform papillae, topical application of keratolytic agents such as 30%-50% trichloroacetic acid or salicylic acid in alcohol or 40% urea in water destroys the elongated papillae.

3.1.9 | Lingual varices

Lingual varices, also referred to as lingual or sublingual varicosities, are dilated veins on the ventral surface of the tongue. These lesions may appear as part of the normal aging process. It is normal for there to be veins visible underneath the tongue, partly because the mucous membrane is so thin and translucent in this region, but where these vessels become dilated and tortuous, they may appear round and black like caviar. Age and an increase in venous pressure are predisposing factors; prevalence is quite large (20%-80% of the population) in the elderly population.

3.1.10 | Lingual thyroid nodule

The prevalence of ectopic thyroid tissue ranges between 7% and 10%. Lingual thyroid nodule is the most common ectopic thyroid, accounting for 90% of all cases with a prevalence between
1:100 000 and 1:300 000. The molecular mechanisms involved in thyroid dysgenesis are not fully known; nevertheless, mutations in regulatory genes expressed in the developing thyroid are speculated. Clinically, an enlargement of the posterior base of the tongue is evident as a firm, midline mass. The color can range from light pink to bright red and the surface may be smooth or irregular. Ectopic thyroid can be associated with clinically evident thyroid dysfunction, which can be either hypofunction or hyperfunction. Benign or malignant neoplastic changes can also occur in ectopic thyroid nodules. Nodules are often asymptomatic, but symptoms may be related to size and location as well as associated endocrine dysfunction. Symptoms of lingual thyroid nodules include cough, pain, dysphagia, dysphonia, dyspnea and hemorrhage. Asymptomatic nodules do not require therapy but they must be kept under observation. For those with symptoms, treatment depends on the size, nature of symptoms, thyroid function status and histological findings.

4 | CONCLUSIONS

Oral medicine and pathology is a clinical specialty encompassing the diagnosis and treatment of patients with a wide spectrum of disorders involving the oral cavity. Dentists, dental hygienists, general internists, pediatricians and so on need to broaden their knowledge bases and practice their clinical skills. A large variety of disorders affect the oral cavity, including genetic diseases, infections, cancers, blood diseases, skin diseases, endocrine and metabolic disorders, autoimmune and rheumatologic diseases, local lesions, to name a few. The oral mucosa shows considerable variation in its normal structure and can be affected by a wide range of conditions. They can be harmless, minor primary conditions and secondary indications of systemic disease. Several of them are quite rare and their diagnosis not easy.

5 | SUMMARY

The review describes the main oral mucosa disease manifestations. The review may be useful to the oral care specialties in the development of a differential diagnosis. In several circumstances, the severity or prognosis of the disease needs to be monitored.

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REFERENCES


