Chapter 8

Dental and Oral Complications

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Introduction

The oral phenotype of dyskeratosis congenita (DC) and related Telomere Biology Disorders (TBDs) is characterized by leukoplakia and developmental anomalies of the permanent teeth, such as decreased root/crown ratio and mild taurodontism (vertically enlarged pulp chamber and shortened roots) [1]. Individuals undergoing hematopoietic cell transplantation (HCT) at an early age are susceptible to disruptions in tooth development, as well as development of chronic oral graft versus host disease (GVHD), reduced salivary flow (xerostomia), and thrush (oral candidiasis), each of which require medical management.
Oral Leukoplakia

Oral leukoplakia associated with DC/TBDs manifests clinically as a heterogeneous mucosal lesion and may develop at any age, from childhood to later in adult life. Often localized to the dorsum (top) of the tongue, buccal mucosa (insides of the cheeks), palate (roof of the mouth) and/or gingiva (gums), the lesion(s) can present as a fine reticular or a plaque-like white area, with or without peripheral erythema (redness). The clinical presentation varies among individuals, with oral signs and symptoms developing at different rates. Very little is known about the clinical or histopathological features of oral leukoplakia in DC/TBDs; however, they are thought to contribute to an increased risk of developing head and neck squamous cell carcinoma (HNSCC).

Head and Neck Squamous Cell Carcinoma

Approximately 660,000 cases of HNSCC will arise globally each year, 54,000 of which will be in people in the United States [2, 3]. HNSCC risk factors in the general population include exposure to carcinogens, most notably tobacco smoking and alcohol consumption, infection with high-risk types of human papillomavirus (HPV), and genetic predisposition, such as in DC/TBDs.

HNSCC is considered a heterogeneous disease both at the molecular and clinical levels, with the existence of at least two genetic subclasses: HPV-positive and HPV-negative tumors [4]. Despite advances in diagnosis and treatment, the five-year survival rate for HNSCC continues to be approximately 50% [5, 6]. Most individuals who develop HNSCC had a clinically visible premalignant oral lesion (dysplasia) prior to developing cancer; early diagnosis and surgical management of oral dysplasia/HNSCC is extremely important in reducing patient complications.

Oral leukoplakia itself is not uncommon in the general population, with an estimated prevalence from less than 1% to more than 5% [7-10]. The rate of its malignant
transformation into HNSCC varies from near nil to about 20% over one to thirty years [11-13].

Individuals with DC/TBDs have a very high risk of developing cancer. Specifically, the ratio of observed to expected (O/E) cancers was 4-fold greater in DC/TBDs when compared with the general population (see Chapter 9, Solid Tumors). Forty percent of the most common solid tumors in DC/TBDs were found to be HNSCC, including an approximately 216-fold increase in the O/E ratio for cancer of the tongue [14]. While bone marrow failure continues to be the main cause of mortality in DC/TBDs, these numbers suggest an independent high risk of mortality arising from HNSCC.

It has been suggested that non-homogeneous oral leukoplakia carries a higher degree of malignant transformation risk compared with the homogeneous variants; however, there is no reliable method to identify which oral lesion will transform into cancer and which will not [15]. Clinical [16], histological [17], and molecular markers [18, 19] may aid in assessing the risk of an individual patient to develop cancer; however, currently there is no evidence-based and clinically useful predictor of malignant transformation in people with DC/TBDs or in the general population.

Oral Lichen Planus

Lichen planus (LP) is an autoimmune T cell-mediated mucocutaneous inflammatory disease of unknown etiology [23]. Occurring in approximately 1% of the general population and most frequently in women 30 to 60 years of age [24], LP can affect the oral mucosa, genitals, and skin. The clinical presentation of oral lichen planus (OLP) and the oral lesions associated with DC/TBDs is phenotypically identical.

As with oral leukoplakia in DC/TBDs, OLP has variable clinical characteristics and presentations. The most common type (reticular) is characterized by lacy white striae located bilaterally on the buccal mucosa, gingival, or tongue. The erosive (red or ulcerated), atrophic, and plaque-like versions of OLP are thought to have greater
malignant potential than the reticular type, perhaps because of chronic inflammation. Reticular OLP is often asymptomatic, but the atrophic and ulcerative forms can cause symptoms ranging from a burning sensation to severe, unremitting oral pain [25, 26].

The World Health Organization (WHO) classifies OLP as a precancerous disease in the general population. However, this designation is controversial. The frequency of malignant transformation in the general population has been found to range anywhere from 0.4% to more than 6% [8, 9]. 1-5% of OLP lesions will undergo malignant change to squamous cell carcinoma (SCC) of the mouth [27-30]. Between 1 and 3% of vulvar lichen planus lesions in the general population may develop into SCC [31, 32] while a small but unknown percentage of penile lesions will transform [33, 34]. Chronic inflammation appears to play an important role in the promotion of malignant transformation of oral mucosa in some disorders. Both OLP with dysplasia and oral lesions of individuals with DC/TBDs show evidence of chronic inflammation coincident with a higher than normal rate of transformation to HNSCC. Therefore, OLP with dysplasia may serve as a unique disease model for studying the high rate of oral malignancy associated with DC/TBDs.

NCI Cohort Study

The National Cancer Institute (NCI) cohort study of inherited bone marrow failure syndromes (02-C-0052) evaluated 44 individuals with DC/TBDs between September 2003 and June 2012, and included detailed oral examinations, radiographs and clinical photos. The overall prevalence of oral leukoplakia was 64%: 75% in children and 50% in adults, with the youngest patient being 3 years old and the oldest 53. 93% of oral leukoplakia was localized to the dorsal tongue (plaque-like and reticular lichenoid white lesions with papillary atrophy). Of those with tongue lesions, 20 out of 26 (77%) had papillary atrophy. Only seven had oral ulcerations at the time of examination, and very few had accompanying erythema. The presence or absence of oral symptoms with DC/TBD-associated oral lesions is not known but may be underreported.
Variants in five DC/TBD-related genes were identified among 32 of the 44 individuals evaluated in this study: WRAP53, DKC1, TERC, TINF2, and TERT. The remaining patients did not have a known genetic cause of disease. Ninety percent (9/10) of patients with DKC1 variants but only 17% (1/6) of those with TERT variants had oral lesions, which suggests an association between development of oral leukoplakia and the specific DC/TBD gene variant (Table 1).

**Table 1.** Presence of oral lesions by gene in patients with DC/TBDs (unpublished data).

<table>
<thead>
<tr>
<th>Gene Mutation</th>
<th>n</th>
<th>Oral Lesions</th>
<th>No Oral Lesions</th>
<th>p value</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TERT</td>
<td>6</td>
<td>1 (17%)</td>
<td>5 (83%)</td>
<td></td>
<td>0.17</td>
<td>0.11-0.28</td>
</tr>
<tr>
<td>DKC1</td>
<td>10</td>
<td>9 (90%)</td>
<td>1 (10%)</td>
<td>&lt;0.0001*</td>
<td>0.28</td>
<td>0.18-0.44</td>
</tr>
<tr>
<td>TERC</td>
<td>3</td>
<td>2 (67%)</td>
<td>1 (33%)</td>
<td>&lt;0.0001*</td>
<td>0.28</td>
<td>0.18-0.44</td>
</tr>
<tr>
<td>TINF2</td>
<td>11</td>
<td>6 (55%)</td>
<td>5 (45%)</td>
<td>&lt;0.0001*</td>
<td>0.36</td>
<td>0.24-0.56</td>
</tr>
<tr>
<td>Unknown</td>
<td>12</td>
<td>8 (67%)</td>
<td>4 (33%)</td>
<td>&lt;0.0001*</td>
<td>0.28</td>
<td>0.18-0.43</td>
</tr>
<tr>
<td>WRAP53</td>
<td>2</td>
<td>2 (100%)</td>
<td>0</td>
<td>&lt;0.0001*</td>
<td>0.14</td>
<td>0.09-0.23</td>
</tr>
</tbody>
</table>

Eight subjects evaluated in the NCI cohort have had multiple oral biopsies with histopathological results that ranged from benign, chronic inflammation, pyogenic granuloma, and hyperkeratosis to moderate dysplasia and HNSCC.

**Clinical Implications: Patients**

Oral leukoplakia in DC/TBDs develops at an unusually young age and is characteristic in appearance and location. Since most leukoplakias are asymptomatic, the need for treatment is primarily based on the precancerous nature of the lesion, and this can only be determined by tissue biopsy. A region of the oral lesion may transform into oral cancer, but it is not currently known what that progression looks like in DC/TBDs. Early
diagnosis and surgical management of oral dysplasia and HNSCC is extremely important in reducing morbidity.

Therefore, it is recommended that a dentist or dental specialist (oral medicine or oral and maxillofacial surgeon) screen individuals with DC/TBDs for oral lesions every six months, in addition to an otolaryngologist (ears, nose, and throat doctor, ENT) evaluation every six to 12 months. The frequency of follow-up may increase to visualization of oral lesions every 2 months if it is clinically indicated.

Fiber optic examinations are recommended from the age of 10 years to visualize the posterior oropharynx. The frequency of follow-up may be increased in the presence of histologically confirmed oral dysplasia, or a history of oral cancer. Clinical photos are recommended longitudinally to follow the progression of oral lesions. Persistent oral lesions should be biopsied when clinically indicated. Surgical removal of oral lesions in the absence of a precancerous histological diagnosis is not recommended since it may compromise surveillance efforts.

Oral leukoplakia associated with DC/TBDs is similar in appearance to oral lichen planus. When symptomatic, it may present as ulcerations on the tongue or buccal mucosa that do not resolve within two weeks or recur over time.

Topical steroids used to manage ulcerative oral lichen planus may be helpful in reducing the size and duration of the oral ulcerations in DC/TBDs, and may include fluocinonide, dexamethasone rinse 0.5mg/5mL, and clobetasol cream or ointment (0.05%). Frequency of application should be determined by the prescriber. Associated pain is managed primarily via topical anesthetics. It is not known whether treatment of symptomatic oral leukoplakia in DC/TBDs will alter the risk of malignant transformation.

Clinical Implications: Clinicians

In relation to lesions seen in the general population, oral leukoplakia of DC/TBDs tends to occur in patients younger than 50 years of age and in the absence of risk factors, like
smoking or alcohol use. Leukoplakia may be the first manifestation of DC/TBDs and can be easily identified during routine dental and medical examinations.

The gold standard for oral cancer diagnosis remains tissue biopsy with histological assessment; however, there are adjunctive clinical diagnostic tools that aid in early detection, including toluidine blue dye (TB) and fluorescent visualization imaging systems.

**Toluidine Blue**

TB is a member of the thiazine group of metachromatic dyes. These dyes bind to DNA and are partially soluble both in water and alcohol. Theoretically, dysplastic and malignant cells have higher nucleic acid content than normal, and thus staining of suspicious lesions with this dye can aid recognition of mucosal changes. Used since the early 1980s, lesions that take up the TB dye are six times more likely to become oral cancers [35]. The TB test appears to be highly sensitive (97.8% – 93.5%) but less specific (73.3% - 92.9%), mainly because of high false positive results [36, 37]. TB has been shown in single- and multicenter studies to be useful in identifying OLPs and OSCC and can provide information about lesion margins and so aid in biopsy site selection [38-42].

Recently, molecular studies on TB stained lesions demonstrated a link between carcinoma and loss of heterozygosity (LOH). This concept refers to deletion of regions of chromosomes (for example 3p, 17p, and 9p) known to be frequently lost in head and neck cancers and dysplasia. LOH occurs early in oral carcinogenesis, but the patterns of such loss can be predictive of the risk of progression. Oral lesions that stained positive with the TB dye were much more likely to have LOH [35, 43]. The loss of heterozygosity has not been evaluated in dysplastic DC/TBD lesions.
Tissue Autofluorescence

The value of tissue autofluorescence in the screening and diagnosis of precancerous lesions of the lung, uterus, cervix, and skin is well documented. In the past decade, several forms of autofluorescence technology have been developed to inspect the oral mucosa, including VELscope R (LEDDental, Inc., of White Rock, British Columbia, Canada). This U.S. Food and Drug Administration- and Health Canada-approved technology uses blue/violet light (400-460nm) to illuminate oral tissue. By visualizing these oral tissues through a light filter, normal tissue appears pale green, while abnormal tissue has a “loss of fluorescence” and appears dark brown or black. Like TB, autofluorescence may aid in choosing tissue biopsy sites, as well as visualizing surgical margins [44, 45].

There is general consensus that the clinical stage at time of diagnosis of HNSCC is the most important predictor of recurrence and mortality in oral cancer patients. The time to diagnosis is influenced by multiple clinical and sociodemographic variables, including patient reluctance to consult a health-care professional due to lack of access to health care, especially in patients with low socioeconomic status.

Clinicians can improve patient survival rate if a cancerous lesion is detected at an early stage, or if a precursor lesion (dysplasia) is discovered and treated prior to malignant progression. To this end, studies have shown that health-care providers would benefit from system-wide educational updates on oral cancer prevention and early detection.

Treatment of HNSCC

Treatment options are limited to the surgical removal of regions of oral dysplasia (moderate and severe), carcinoma in situ, and HNSCC. The extent of surgical resection depends upon the size and location of the tumor, so early detection is paramount to reduce morbidity and mortality. Laser ablation of regions of lichenoid striae in the absence of dysplasia is not recommended as the lesions are likely to recur. In addition, surgical alteration of normal oral architecture may compromise surveillance efforts.
Dental Manifestations

In addition to oral leukoplakia, DC/TBD patients may exhibit alterations in tooth development. Short dental roots resulting in unfavorable root/crown ratios may affect dental restorative considerations. Root/crown ratios are a non-specific finding and normally vary between different races, genders and arch (maxillary versus mandibular teeth) [46]. Short roots may complicate treatment planning in orthodontics and must be considered in prosthodontic anchorage and estimating the ability of a tooth to carry masticatory forces. In Atkinson et al’s study of 17 individuals with DC/TBDs, a decreased root/crown ratio was found in 75% of patients with sufficient tooth development to permit evaluation [1].

Taurodontism affects the molars and is characterized by vertical enlargement of the pulp chamber and reduced root size. It is a frequent finding in early humans and is found in some developmental syndromes. While the exposed portion of the teeth may look overtly normal without any characteristic anomaly on visual inspection, the floor of the pulp and furcation of the tooth may be shifted apically toward the root.

This occurs from failure or late invagination of Hertwig's epithelial root sheath, which is responsible for root formation and shaping.

Mild taurodontism was reported in Atkinson et al’s study (57% with radiographs and sufficient tooth development to permit evaluation) [1]. The clinical implication of taurodontism is increased risk of pulp exposure because of decay and dental procedures, endodontic treatment challenges, and with the shorter roots, prosthodontic and orthodontic issues as mentioned above [47].

Other oral findings, such as aggressive periodontal disease, hypodontia, increased dental decay, and thin enamel, have been reported, but do not appear to be more common in DC/TBDs than in the general population.
Post Hematopoietic Cell Transplantation Oral Manifestations

Individuals with DC/TBDs who undergo HCT may develop chronic conditions such as oral GVHD, reduced salivary flow (xerostomia), and thrush (oral candidiasis), which may require medical management. Those transplanted at an early age (<10 years) are more likely to experience disruptions in permanent tooth development. To a significant degree, the oral problems associated with HCT can be prevented or minimized with careful management. Consultation with a dental team experienced in caring for patients undergoing HCT procedures should be completed before the start of therapy.

Oral Graft Versus Host Disease

Signs and symptoms of oral GVHD are similar to autoimmune disorders like LP and may present as sensitivity of the lining of the mouth to acidic foods and mint flavored toothpaste. There may also be mucosal ulcerations, erythema and lichenoid striae. Treatment of oral GVHD is only recommended when symptomatic and can often be managed with topical steroid rinses or creams, or systemic immunosuppression. GVHD can also involve the salivary glands, resulting in xerostomia.

Xerostomia

Saliva serves many critical functions in the homeostasis of the oral ecosystem, in the oropharynx and larynx, and in speech and swallowing functions. Diminished saliva either from medications or oral GVHD results in an increased risk of dental demineralization and decay and oral infections such as candidiasis. A chronically dry mouth can also lead to an altered sense of taste, difficulty speaking, halitosis, oral pain, and difficulty chewing and swallowing, culminating in decreased quality of life. Without saliva, teeth do not remineralize, and there is gradual softening of the tooth matrix. The
teeth bend and dentin may fracture and cavitate, and the coronal structure fractures from the supporting root.

In patients with residual salivary gland function, sugarless gum or lozenges may stimulate salivary secretion. Sugar-free popsicles, plain ice cubes, or ice water may be used to keep the mouth moist. Systemic sialogogues may increase production of natural saliva from functional glands. Medications that may be beneficial in stimulating salivary glands include pilocarpine (Salagen), cevimeline (Evoxac), anethole trithione (Sialor), and bethanechol (Urecholine). Saliva replacements like Oral Balance Gel may offer some relief. There is no ideal substitute for saliva when salivary glands are nonfunctional.

For the prevention of rampant dental demineralization and caries in a xerostomic mouth, patients should apply a 1.1% neutral sodium fluoride gel daily (for at least 5 minutes), using a custom-fitted vinyl tray if possible. This practice should be continued daily as long as the mouth remains dry because of low salivary flow rates. High-potency fluoride brush-on gels and toothpastes may be considered in those who are unable or unwilling to comply with the use of fluoride trays.

To prevent dental damage associated with a lack of saliva, patients with xerostomia should increase oral hygiene efforts and avoid foods and medications (like Nystatin Rinse, Mycelex Oral Troches) with high sugar content.

**Thrush/Oral Candidiasis**

Candida albicans is a yeast-like fungus naturally present in the oral cavity. It may overgrow in xerostomia, when there is disruption of oral bacteria (as caused by systemic antibiotics), or with the use of topical steroids. Infection presents as creamy white plaques on mucosal surfaces and can be wiped off.
Individuals may experience an increase in sensitivity localized to the lining of the mouth. Oral candidiasis may also present as cracking and redness at the angles of the mouth (angular cheilitis).

Topical anti-yeast medications such as nystatin rinse and clotrimazole (Mycellex) oral troches have a high sugar content and should generally be avoided in patients with xerostomia since they can promote tooth decay. Patients using these medications should be warned of the risk and increase oral hygiene efforts accordingly. Amphotericin B (available as a topical suspension [100mg/mL] 1mL up to 4 times daily) and fluconazole are effective systemic antifungals.

Tooth Development

Dental abnormalities have been reported among survivors of childhood cancer. These include dental hypoplasia or agenesis, root stunting, and enamel hypoplasia. The severity of the problem is dependent upon the timing of chemotherapy and radiation, with the greatest impact occurring when treatment is between the ages of three and five [48, 49].

Clinical Management

Helping patients understand how cavities develop assists in preventing them.

Having DC/TBDs does not confer genetic susceptibility to developing cavities (caries); rather, dental decay is a multifactorial problem. Diet, oral bacteria (which form plaque), a decrease in the quality and quantity of saliva, and other factors are implicated. It has been shown that dental decay will not develop in the absence of fermentable dietary carbohydrates [50]. All dietary carbohydrates are cariogenic (dental decay causing) to some degree, and this is influenced not only by the composition of carbohydrate-containing foods but by the sequence and frequency with which they are consumed. Sucrose appears to have the greatest cariogenic potential, and its frequency
The composition and rate of saliva flow can impact development of dental decay in several ways. Saliva can act as a buffer, neutralizing bacterial acid byproducts found on tooth surfaces and in carious lesions. The high concentrations of calcium and phosphorus and the low level of fluoride found in saliva may facilitate remineralization of early carious lesions and form caries-resistant surface enamel [54]. Saliva also contains several potentially bacteriostatic agents, including lysozyme, lactoferrin, and secretory immunoglobulins, which may inhibit the metabolism and growth of cariogenic bacteria [55-57].

Reduction in salivary quantity may be a side effect of various medications, including antidepressants, anti-anxiety medications, and antihistamines, or may be a component of post-transplant oral GVHD. Having a dry mouth can accelerate the rate of dental decay and significantly increased oral hygiene efforts are required. Patients should work with their general dentist and hygienist for strategies to prevent dental decay.

Fluoride is the most effective dietary component to exhibit a protective effect against root and surface caries. The mechanism by which it does so is not well understood but is thought to be related to its presence in enamel and dentin, and presumed role in
promoting remineralization of early demineralized areas of the tooth [58]. By exerting an antimicrobial effect, it suppresses cavity-causing oral bacteria [59].

General hygiene recommendations include brushing teeth two to three times a day with fluoridated toothpaste and flossing once a day at a minimum to help prevent tooth decay. Some dentists recommend using prescription strength fluoride toothpaste or antibacterial mouth rinse to aid in reducing oral disease. Biannual dental checkups and cleanings are recommended to monitor for the presence of oral pathology and prevent the development of significant dental decay and gum disease. Precautions during routine dental treatment may be necessary in the presence of low platelet counts and white blood cell levels.

Access to quality dental care for medically compromised patients may be challenging outside of large urban centers. Regional dental schools offer clinics with multidisciplinary dental specialty practitioners and may provide economical dental treatment or be able to recommend a community dentist.

References


41. Portugal LG, Wilson KM, Biddinger PW, Gluckman JL. The role of toluidine blue in assessing margin status after resection of squamous


