Dyskeratosis Congenita and Oral Cavity Squamous Cell Carcinoma: Report of a Case and Literature Review

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Summary: Dyskeratosis congenita is a rare genetic condition of telomerase dysfunction in which patients are at an increased risk of squamous cell carcinoma (SCCa) of the oral cavity. We present here the youngest patient in the literature with a diagnosis of SCCa. We discuss the literature and management of this advanced presentation of SCCa in a child, stressing the importance of palliative care involvement in facilitating medical decision making.

Key Words: tongue cancer, pediatric palliative care, oral tumor

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Dyskeratosis congenita (DC) is a rare, inherited bone marrow failure syndrome, originally described by Zinsser in 1906.[1–4] Resulting from abnormally short telomeres and mutations in telomere biology genes, DC is characterized by 3 main features: nail dystrophy, abnormal skin pigmentation, and oral leukoplakia.[5,6] Individuals with DC are also at risk for developing bone marrow failure, aplastic anemia, myelodysplastic syndrome, leukemia, and other cancers, including squamous cell carcinoma (SCCa) of the oral cavity.[7,8] Here, we report a case of a young patient with DC who presented with oral symptoms and lesions and was found to have oral cavity SCCa. Equally important, we discuss the advantages of early involvement of the palliative care team in facilitating difficult decision making and symptom management.

CASE REPORT

Case reports are exempt from institutional review board approval at our hospital.

A 10-year-old boy with spastic diplegic cerebral palsy and recurrent aspiration pneumonitis secondary to aspiration of secretions presented in consultation for sialorrhea. He was born prematurely at 33 weeks gestation and at approximately age 1.5 years, he received a diagnosis of DC with associated chronic lung disease and aplastic anemia. Genetic testing showed that he was heterozygous for the p.w272x mutation in the TINF2 gene. This result is consistent with a diagnosis of DC. Parental studies indicated that the mutation is very likely a de novo event. This mutation is located in exon 6 of the TINF2 gene and results from a G to A substitution at nucleotide position 815. This changes the amino acid from a tryptophan to a stop codon within exon 6. He received a bone marrow transplant for aplasia at 27 months of age. He also had bilateral cystic periventricular leukomalacia and gastric reflux, status postgastric tube with Nissen fundoplication. Therapy for his sialorrhea included salivary gland botulinum toxin (Botox, Allergan, Dublin, Ireland) injections and scopolamine patches with diminishing effect. Two months before presentation, he underwent bilateral parotid duct ligation and bilateral submandibular gland excision, at which time the oropharyngeal examination results were normal. At postoperative follow-up visits, the family reported better salivary control with reduced but thickened saliva. He then presented 2 months after surgery with increasing oral pain and firm white nodular tongue lesions.

Clinical Findings

Examination findings included well-healing submandibular incisions, nontender enlarged parotid glands bilaterally, a firm and tender submandibular and anterior superior cervical neck, and a tender tongue with firm nodular irregular lesions along with patchy white plaques. On the right anterolateral tongue, examination revealed a friable area. Contrast-enhanced computed tomography revealed a tumor involving the intrinsic tongue musculature with an irregular nodular contour of the left floor of the mouth, mass effect on the left genioglossus muscle, and fullness of the left tongue base protruding into the oropharynx. There were several enhancing lymph nodes with central necrosis seen in levels 1B, 2A, and 2B bilaterally and in right level 3. The largest conglomerate of nodes was in the right submandibular space measuring $4.3\times2.3\times3.9\ cm^3$.

Evaluation of neck magnetic resonance imaging with gadolinium enhancement revealed an ill-defined enhancing mass along the entirety of the tongue with enhancement along the inferior alveolar ridge and mandible suspicious for malignant infiltration (Fig. 1). As in the computed tomography scan, magnetic resonance imaging showed numerous enlarged and necrotic lymph nodes.

Operative endoscopy and biopsies were then performed, finding a diffusely nodular tongue with several friable regions of nodular change with leukoplakia. The most prominent areas of friable nodularity were at the right anterolateral tongue and the left dorsal mid-lateral tongue, from which biopsies were taken (Fig. 2).

Histopathologic evaluation of the biopsies showed ulcerated squamous mucosa with invasive keratinizing SCCa. In addition, large pleomorphic hyperchromatic nuclei were identified. Adjacent stroma appeared fibrotic with moderate chronic lymphocytic reaction. These findings were consistent with SCCa, grade T4 N2c M0, stage IV. The human papilloma virus (HPV) in situ hybridization studies for HPV DNA were negative for both high-risk and low-risk HPV types. NUT immunohistochemical stain for NUT midline carcinoma was negative.

Management

Presentation of this patient's case at an interdisciplinary tumor board included involvement of pediatric oncology and adult and pediatric otolaryngology, including facial plastic and reconstructive

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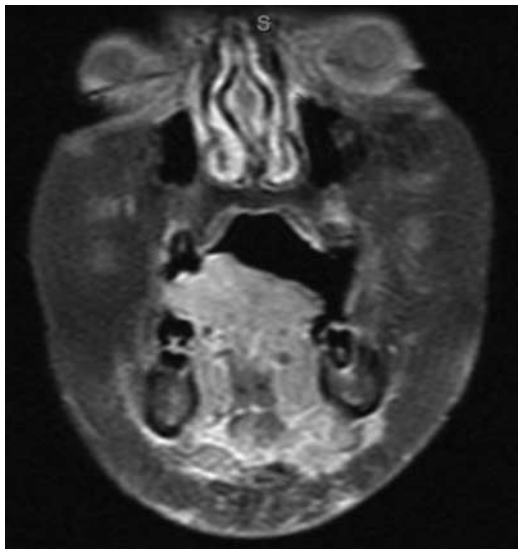

FIGURE 1. Coronal magnetic resonance imaging with contrast, demonstrating nodular tongue showing tumor involving the intrinsic musculature of the tongue bilaterally.

surgeons, as well as radiation therapy and pediatric palliative care specialists. Therapy for SCCa typically involves surgery and radiation. The child's underlying diagnosis of DC meant that radiation therapy carried an increased risk of future malignancy. Surgical extirpation of the primary site would have required extensive reconstruction with loco-regional or free-tissue transfer. Tissue transfer was relatively contraindicated by his DC. The overall prognosis for this child was felt to be very poor at best.

The prospect of morbidity materially out of proportion to a chance of success led to a frank discussion of optimal means of palliating symptoms for this child. Palliation needed to focus on managing pain and the prospect of progressive asphyxiation. Unfortunately, tracheostomy—the means by which asphyxiation could be best prevented and aspirated secretions managed—would be likewise complicated by skin breakdown in the peristomal region of the tracheostomy site.

All options, including surgery with curative intent, radiation therapy, and palliative choices, were presented to the family in a multidisciplinary team meeting. After extensive discussion, the family chose to forgo life-prolonging measures, including intubation, and instead chose to focus upon optimizing symptom management in the home setting for their son. The palliative care team coordinated home hospice care through a community hospice organization, and the patient was discharged home per the family's request, with ongoing outpatient support of our pediatric palliative care service.

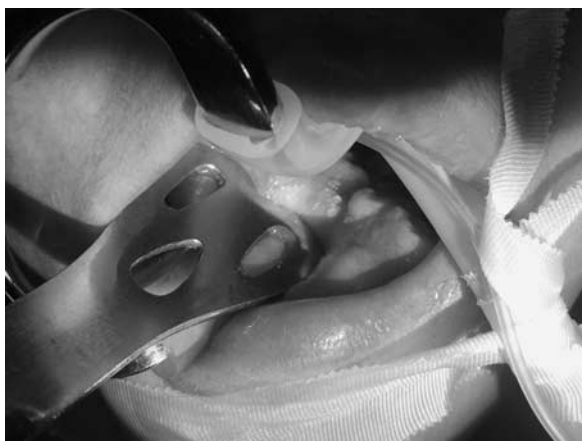

FIGURE 2. Nodular tongue lesions.

On arrival home, the patient was described as "happy, singing songs with his family." His parents, aware of the rapidly progressive nature of this tumor, focused on their son's comfort and enjoyment. He required progressively increasing levels of supplemental oxygen because of hypoxemia related to underlying chronic lung disease, morphine via a continuous ambulatory delivery device to control pain, and diazepam for anxiety. In addition, dexamethasone was used to minimize oropharyngeal and facial edema. Because of his previous salivary gland excision, oral secretions were minimal, so no medication for this was required. The palliative care team spoke with the patient's home hospice team or the patient's parents nearly every day and conducted a home visit 2 weeks after hospital discharge to aid with pain and symptom management and care coordination. The patient remained awake and alert intermittently throughout his time at home, enjoying visits with friends and family, and he continued to take small amounts of oral intake for pleasure even on the day before he died.

The family received extensive anticipatory guidance from both the palliative care team and home hospice team regarding the risk of sudden asphyxiation, hemorrhage, or other sudden, life-ending event as the tumor progressed. The family agreed to an emergency palliative sedation plan but otherwise chose to avoid palliative sedation in favor of allowing the patient to be awake and alert as much as possible. After 20 days at home, he developed sudden-onset chest pain, hypoxia, and altered mental status. The family used the emergency medication plan as previously discussed. He died 3 hours later surrounded by family, and despite suffering in his final hours, his family was thankful that they had a "good day" before his sudden decline.

DISCUSSION

DC is inherited either in x-linked, autosomal dominant, or autosomal recessive fashion. Multiple genes have been identified in which mutations led to alterations of the telomere complex, leading to shortened telomeres.[5,9,10] Dysfunction of telomeres leads to premature cell death and chromosome instability, which affects stem-cell reserves, and eventually leads to bone marrow failure.[4] The symptoms that compose the classic triad of associated findings in DC may not manifest themselves in a predictable pattern in each case.[9] However, clinical findings are often observed in childhood with abnormal skin and nail changes appearing before age 10 years and bone marrow failure occurring before age 20.[9]

Compared with the general population, patients with DC are at an 11-fold increased risk of developing cancer of the upper aerodigestive tract.[11] The crude rate of cancer presentation in patients with DC is roughly 7% to 10%; 40% of those cancers are head and neck squamous cell carcinoma. The median age of DC patients with head and neck squamous cell carcinoma in the literature is 29 to 37 years,[9,11] which must be considered when examining young patients with DC.

In patients with DC, erosive oral leukoplakia has a propensity to develop into SCCa of the oral cavity and oropharynx, generally between ages 20 and 30 years.[11,12] The risk of degeneration of leukoplakia into SCCa is roughly 30% over 10 to 30 years.[10] Leukoplakia will occur in as many as 90% of patients with DC and commonly manifests between ages 5 and 14 years. In a 2008 review of oral phenotypes in DC, the authors noted that oral leukoplakia in any young individual is potentially indicative of DC or other inherited bone marrow failure syndromes and should warrant further evaluation.[13] We do not know why our patient presented at this young age with his SCCa.

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The role of oral manipulation because of a recent surgery has been considered; radiation was not a part of his previous bone marrow transplant conditioning. He was not exposed to oral toxins or irritants.

Current oral cancer surveillance guidelines of patients with DC include monthly self-examination of the oral cavity and head and neck and an annual screening by an otolaryngologist.[9,11,14] This will allow for timely detection of potential areas of concern with the goal of early identification and intervention of carcinoma. Specific areas of discussion in DC should involve consideration of pulmonary and hematologic factors as well as potentially adverse effects of radiation treatment.

Palliative care involvement early in the disease course of cancer patients, and in children with chronic unrelenting disorders such as DC, allows for "anticipating, preventing, and treating suffering."[15–18] Palliative care should be incorporated into existing programs, as we did here through engagement of the palliative care team into our tumor board discussions.

Surgical palliation was declined by the family secondary to concerns of post-surgical morbidity; however, the family actively embraced aggressive pain management and responsive symptom management. The pediatric palliative care service facilitated clear communication between the treatment team and the family. The patient died in familiar surroundings and with minimal suffering.

CONCLUSION

This case report demonstrates the youngest patient with DC to develop SCCa in the literature. This emphasizes the need for serial oral examination and increased clinical suspicion for carcinoma in young patients with DC who present with oral symptoms and lesions. Surgical, chemotherapeutic, and radiation treatment options must be tailored to each patient with awareness of increased treatment toxicities due to telomerase dysfunction. Physicians are frequently tempted to pursue all medical means of therapy. This case is an invaluable reminder that there are times in which the best therapy is the therapy that preserves dignity without pain. The early involvement of the palliative care team, before disfiguring surgery, and a frank and honest (albeit difficult) discussion with the family gave the family greater autonomy, decreased paternalism, and preserved the therapeutic alliance. Aggressive pain management and symptom relief allowed the patient to die in a manner which let the family spend the most time possible with their child in the environment most comfortable for their child: his home.

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