Oral cancer in a 5-year-old boy: a rare case report and review of literature

Nathan V. Lee, DMD,[a] Erh Tung Ben Kang, DMD,[b] Christof Senger, MD,[c] and Catherine F. Poh, DDS, PhD[d]

Oral cancer in children is rare. Diagnosis may be delayed as a result of confusion with reactive lesions. Furthermore, cancer staging, with or without bony invasion, can be complicated during tooth eruption. Literature on pediatric oral cancers is lacking, making determination of the possible etiopathology difficult. We describe an exceptional case of a 5-year-old male child who presented with anterior maxillary gingival pseudoepitheliomatous hyperplasia that progressed to carcinoma cuniculatum with invasive oral squamous cell carcinoma (OSCC). Because of the interesting timing of events, we hypothesize that human papillomavirus (HPV) inoculation through cutaneous squamous papilloma played a contributory role. A review of similar case reports in the literature is included. Biopsy of suspicious oral lesions should not be delayed because of the young age of the patient. Atypical hyperplasia should include squamous cell carcinoma (SCC) in the differential diagnoses. For surgical management of aggressive lesions during the mixed dentition, permanent successors should be included in the surgical margins to prevent recurrence. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;130:e10–e19)

Oral squamous cell carcinoma (OSCC) in children is rare. However, oral reactive lesions, such as trauma or infection, are common in the pediatric population and confusion between these and squamous cell carcinoma (SCC) may delay the diagnosis. Moreover, the literature on pediatric oral cancers is sparse, making determination of the possible etiopathology difficult. Recently, human papillomavirus (HPV) infection by subtypes 16 and 18 have been implicated in the development of oropharyngeal cancer, but elucidation of its association with oral cancer remains elusive.[1] We present a rare case of a 5-year-old patient with oral cancer, including its diagnosis as carcinoma cuniculatum, treatment, and follow-up. Literature review of similar pediatric oral cancer case reports, the challenges of diagnosis and management, and the possible etiopathology are discussed.

CASE REPORT

An otherwise healthy 5-year-old Caucasian male presented with sudden-onset swelling between the right deciduous maxillary central (#E) and lateral (#D) incisors, with a deep probing depth on the mesial area of #E. A periapical radiograph (Figure 1A) showed a radiolucency apical to #E and a mesiodens between the 2 permanent central incisors (#8 and #9). The swelling did not respond to a course of antibiotics. Extraction of #D and #E was performed. At the 1-week postextraction follow-up, the extraction site showed a painful swelling with some "whitish exudate" (Figures 1B and 1C). The lesion continued to increase in size at the extraction site, and the patient was then referred to an oral surgeon for biopsy. The initial biopsy was performed 6 weeks after the initial clinical presentation and showed sheets of proliferative squamous epithelium and occasional keratin formation, with bland cytology and absence of atypia or cellular pleomorphism (Figure 2A). In consideration of the patient's age and the lack of identifiable inflammatory etiologies or infectious agents, a diagnosis of primary pseudoepitheliomatous hyperplasia (PEH) was given, and the lesion was thought to be reactive.

After the initial biopsy, the lesion recurred rapidly. The subsequent excisional biopsy 6 weeks later showed anastomosing channels lined by squamous epithelium with hyperkeratosis and microcystic structures resembling "rabbit burrows" and areas with prominent nuclear pleomorphism, hyperchromasia, and numerous atypical mitotic figures (Figure 2B) as well as diffuse p16 positivity (Figure 2C). A diagnosis of carcinoma cuniculatum, a variant of OSCC, was made. Given the malignant characteristics, wider excision of the lesion was recommended. Considering the age of the patient, marginal resection of the anterior right maxilla was performed, with removal of the right permanent central and lateral incisors (erupted #8 and unerupted #7) as well as the right deciduous canine (#C) and right permanent canine (unerupted #6). This was performed 6 weeks after the second excisional biopsy (Figure 3A and pathology in Figure 2D). The labial mucosa, palatal mucosa, and periosteum were maintained to create an anatomic barrier around the tumor, and a full-thickness flap was raised beyond the margins of the planned resection (Figures 3B and 3C). The floor of the nasal cavity was reserved to avoid cosmetic defect in the alar

[a]Resident in Oral Medicine and Oral Pathology, Faculty of Dentistry, University of British Columbia, Vancouver, BC, Canada.
[b]Oral and Maxillofacial Surgeon, British Columbia Children's Hospital and Vancouver General Hospital; Clinical Assistant Professor, Faculty of Dentistry, University of British Columbia, Vancouver, BC, Canada.
[c]Anatomic Pathologist, British Columbia Children's Hospital; Clinical Assistant Professor, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada.
[d]Professor, Faculty of Dentistry, University of British Columbia; Oral and Maxillofacial Pathologist, Vancouver General Hospital, Vancouver, BC, Canada.
Received for publication Aug 1, 2019; returned for revision Oct 25, 2019; accepted for publication Dec 8, 2019.

2212-4403/$-see front matter
https://doi.org/10.1016/j.oooo.2019.12.005

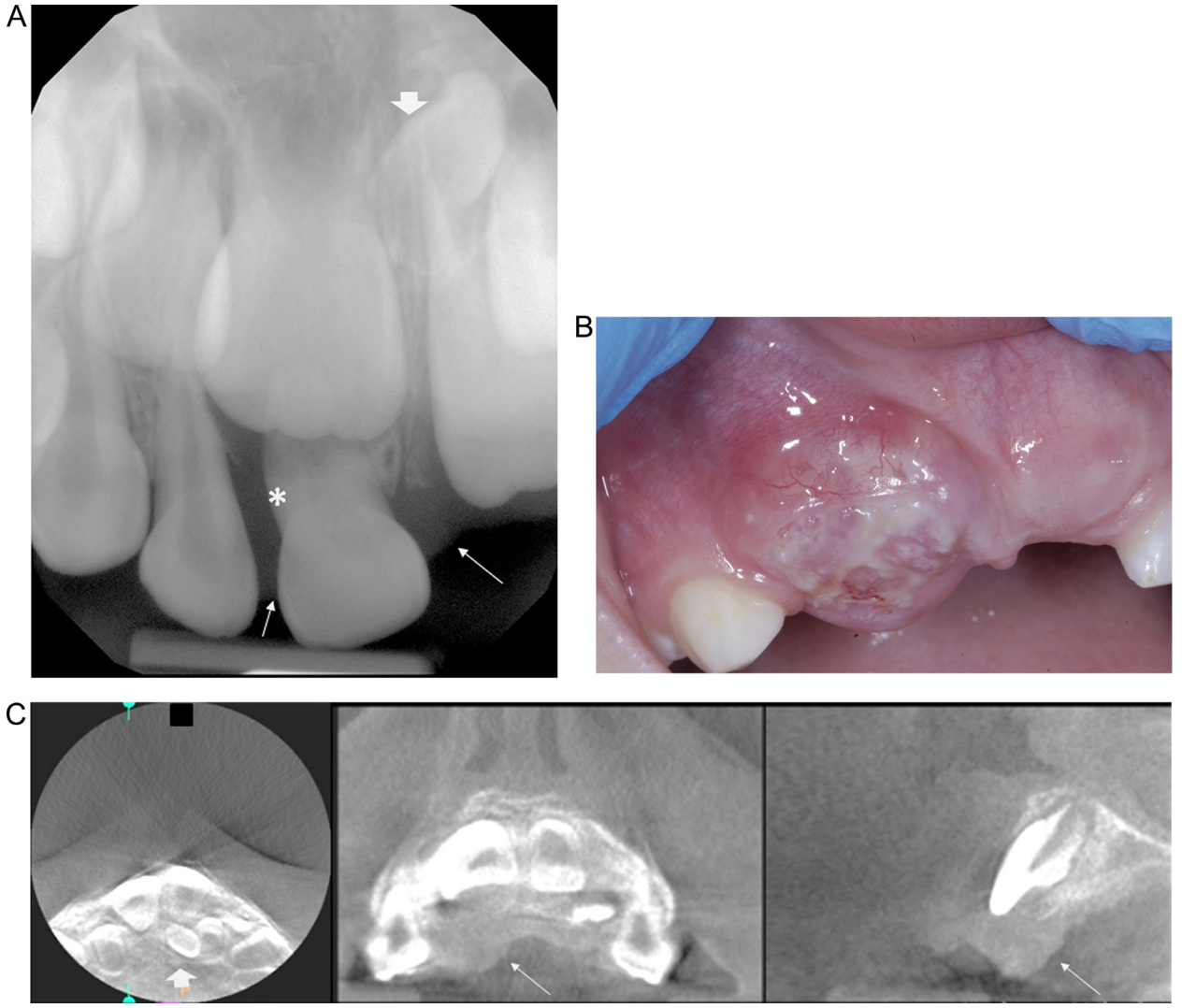

Fig. 1. Radiographs and clinical images. **A,** Periapical radiograph at the initial presentation showing a radiolucency distal to the right deciduous central incisor (#E) (*), soft tissue shadow around it *(arrows)*, and a mesiodens *(arrowhead)* apical to the left permanent central incisor (#8), between the roots of two permanent central incisors (#8 and #9). **B,** Clinical image showing a labial and palatal gingival mass at the right edentulous ridge with some whitish exudate 4 weeks after the initial presentation (see Figure 1A) and 1 week after extraction of the right deciduous central and lateral incisors (#E and #D). **C,** A cone beam computed tomography (CBCT) view showing significant palatal soft tissue swelling *(arrows)* and an impacted mesiodens *(arrowhead)* 4 weeks after the initial presentation (see Figure 1A) and 1 week after extraction of the right deciduous central and lateral incisors (#E and #D).

base (see Figure 3C). Primary closure of the soft tissue was performed with placement of iodoform ribbon gauze to minimize dead space (Figure 3D). Recovery was uneventful. At the 4-week postoperative follow-up, the surgical site was completely healed (Figure 4A). At the same visit, numerous 1- to 2-mm papules were noted on both hands, especially concentrated and confluent on the cuticles of the fingers/thumb and the back of hands (Figures 4B, 4C, and 4D). Numerous similar lesions of various sizes were also found on the chin, close to philtrum, and around and close to the right commissure of the mouth. These cutaneous lesions were seen to have resolved spontaneously at the 3-month postoperative follow-up (Figure 4F). A space maintainer was delivered at this appointment. At the last follow-up, 24-month after surgery, there was no locoregional recurrence (Figure 4E).

Retrospectively, according to the patient's mother, the patient had cutaneous warts that appeared on the dorsal surface of his fingers starting at age 2 years when older siblings—his brother (age 5 years) and sister (age 8 years)—had also presented with similar cutaneous

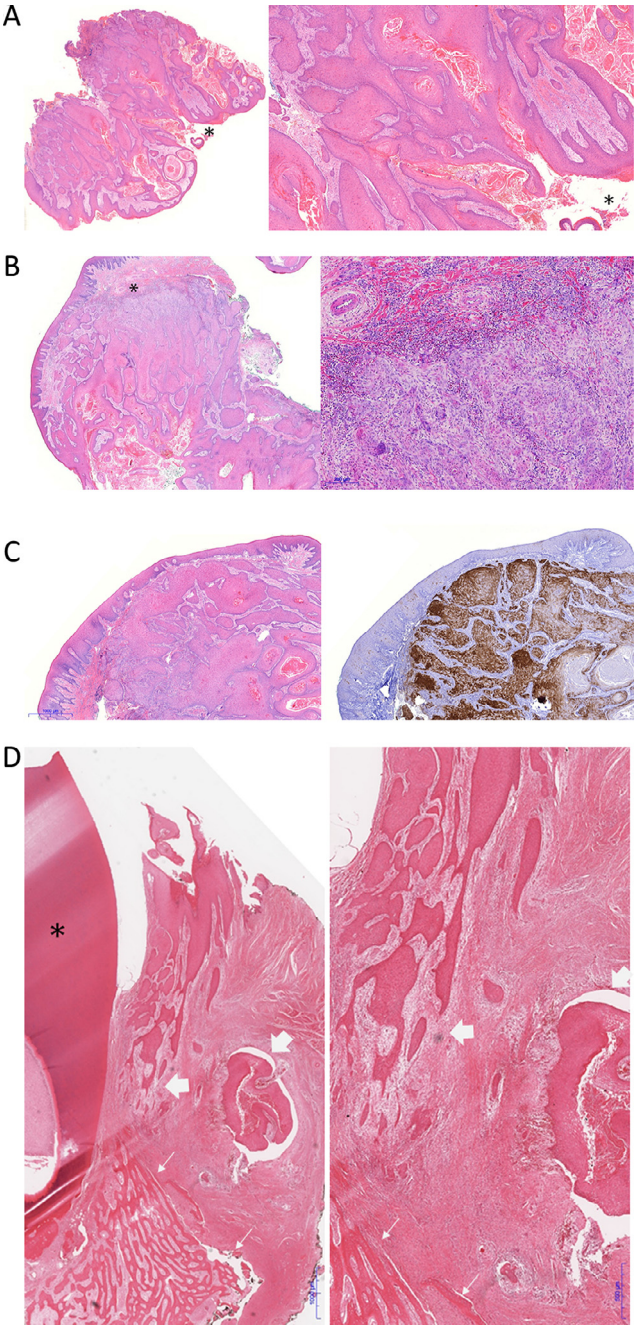

Fig. 2. Histopathology of the 3 specimens. **A,** Initial biopsy of the soft tissue swelling in Figure 1B (hematoxylin and eosin ([H&E] staining; original magnification: left, × 10, and right, × 25) showing a well-differentiated squamous proliferation with minimal cellular atypia surfaced by slightly hyperplastic epithelium with no epithelial dysplasia. This was diagnosed as primary pseudoepitheliomatous hyperplasia (PEH). *A high-resolution version of the image is available as eSlide: VM05694.* **B,** The second excisional biopsy of the soft tissue swelling 6 weeks after the first biopsy (H&E staining; original magnification: left, × 10, and right, × 35) showing a complex endophytic architecture, anastomosing channels, keratin-filled cystic structures resembling "rabbit burrows", and peripheral areas (*) with prominent nuclear pleomorphism, hyperchromasia, and numerous atypical mitotic figures. This was diagnosed as invasive squamous cell carcinoma (SCC) with features of carcinoma cuniculatum. *A high-resolution version of the image is available as eSlide: VM05695.* **C,** Another view of the second excisional biopsy (original magnification, × 15; left, H&E staining and right, p16 immunohistochemistry staining) showing strong positivity for p16 staining at the areas of carcinoma cuniculatum. **D,** After the completion of decalcification, the marginal maxillectomy specimen showing the right central permanent incisor (#8) (*), tumor invasion along the gingival socket and into the attached gingiva *(arrowheads)* with intact alveolar bone *(arrows).* (H&E staining after decalcification; original magnification: left, × 10, and right, × 20). *A high-resolution version of the image is available as eSlide: VM05696.*

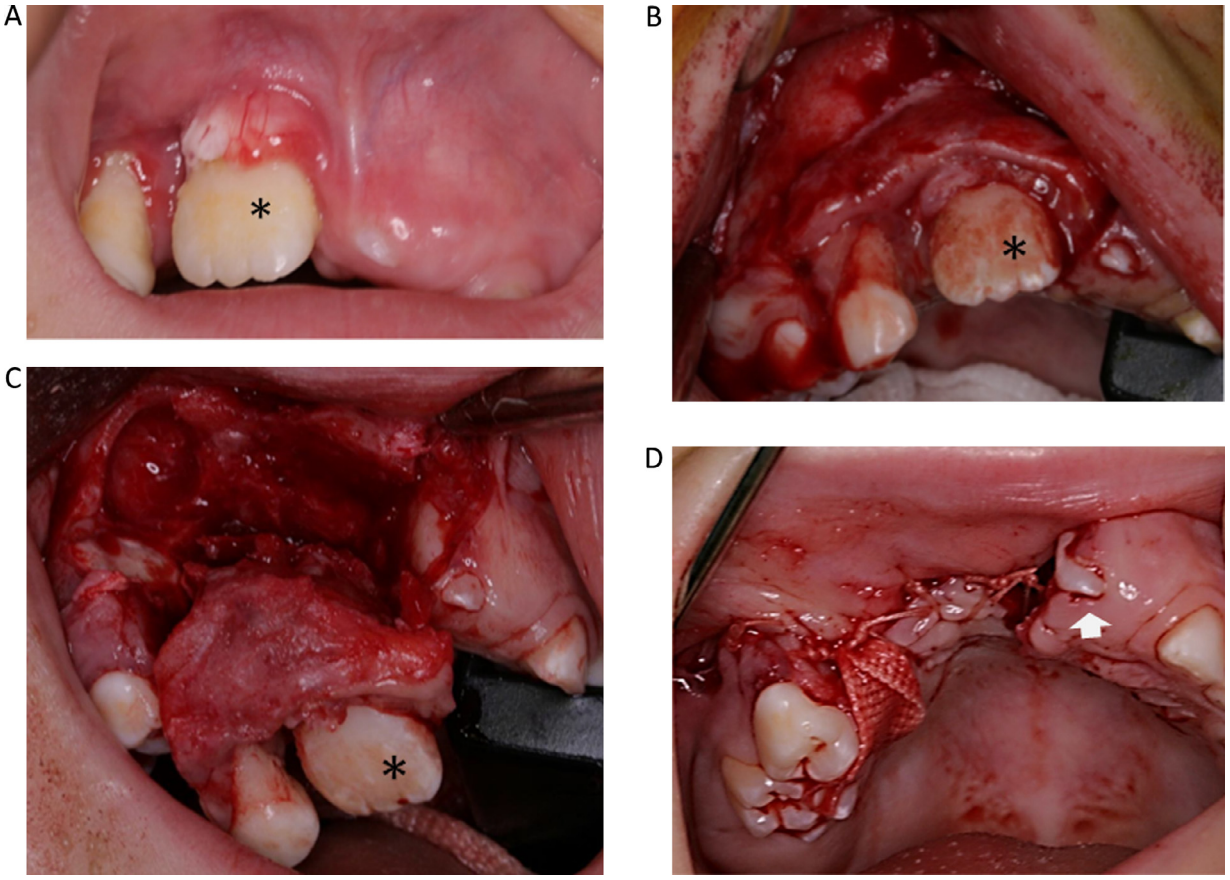

Fig. 3. Intraoperative images during marginal resection (the third pathology specimen) 6 weeks after the excisional biopsy. **A,** Clinical image showing a white lesion at the labial gingiva of the erupting right permanent central incisor (#8) (*). **B,** A full-thickness flap was raised around the planned margins of resection. The labial mucosa, palatal mucosa, and periosteum were maintained as an anatomic barrier. **C,** Marginal maxillectomy involving the right permanent central incisor (erupted #8), and lateral incisor (unerupted #7) as well as the deciduous canine (#C) with maintenance of the nasal cavity. **D,** Closure of the surgical site and placement of iodoform ribbon gauze. The erupting left permanent central incisor (#9) can be seen *(arrowhead)*.

lesions. The mother reported that the lesions affecting the patient's siblings resolved spontaneously within 6 to 12 months' time but that those on the patient persisted and lasted for over 4 years until age 6 years (see Figures 4B, 4C, and 4D). Coincidently, the patient had had a fall, resulting in trauma to the upper deciduous anteriors with "sliced open gums" around age 2 years, and the left deciduous central incisor (#F) had been removed because of mobility 1 year after the fall, 30 months before the onset of the swelling around #D and #E.

DISCUSSION

Oral squamous cell carcinomas (OSCCs) in the pediatric population (age $\leq$ 16 years) remain infrequent.[2] Studies have shown that OSCC in children is typically associated with congenital syndromes,[3] such as Fanconi anemia or Li-Fraumeni syndrome, as children have less exposure to the conventionally known risk factors, such as tobacco use and alcohol consumption.[4] Genetic syndromes or immunocompromised status may leave children vulnerable to tumorigenesis.[5] OSCCs tend to involve the tongue, which is an anatomic region associated with greater genetic instability.[6] Incidences of nonsyndromic pediatric oral cancers are limited to those described in case reports. A literature search for OSCC affecting the oral cavity proper, including the gingiva, alveolus, and/or palate, in nonsyndromic patients age 16 years or less, yielded 25 reported cases, including the present (Table I).[2,7-25] The average age of patients was 10.4 $\pm$ 3.6 years (median 10 years); there was a slight male predilection (16 males vs 9 females); and the majority (18 cases [72%]) involved the maxilla or the palate, which is different from cases associated with syndromes. Seventeen (85%) of the 20 cases with lesional descriptors had rapid-onset mucosal swelling, whereas the other 3 cases had gingival bleeding, ulceration, or mobile teeth. Reactive gingival lesions that are common in children, such as parulis, pyogenic granuloma, peripheral ossifying fibroma, peripheral giant cell granuloma, and fibroepithelial polyp, were higher on the clinical differential diagnosis. Radiographically, there was poorly defined

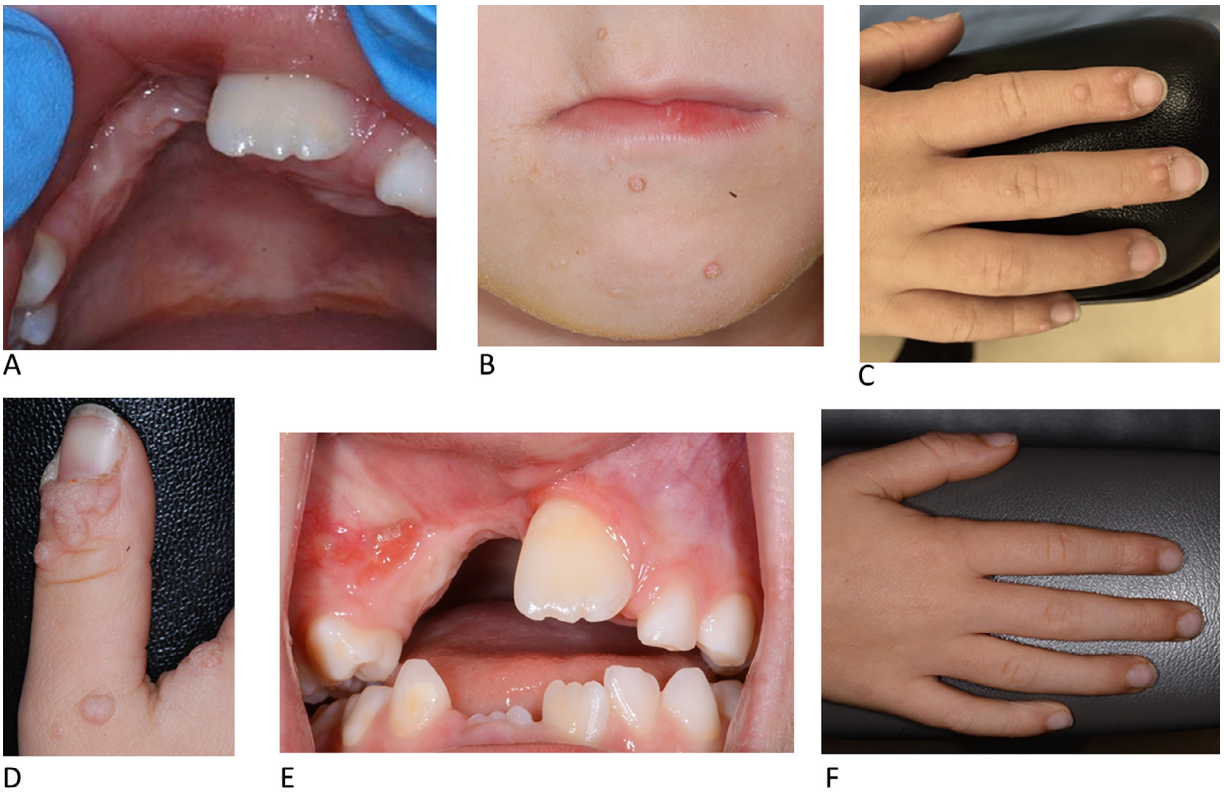

Fig. 4. Clinical images after resection. **A,** Five-week postoperative follow-up image showing the completely healed surgical site. At the same time, numerous cutaneous squamous papillomata, 1 to 2 mm in diameter, were identified on the patient's lower face around the mouth and chin areas **(B)** and on the fingers of both hands (only showing right hand in **C** and right thumb in **D**). **E,** Three-month postoperative follow-up image showing the completely healed surgical site; at the same time, the cutaneous squamous papillomata had completely resolved (showing right hand in **F**).

bony erosion at the invading front, but this may only be evident in advanced lesions. Of the 15 case reports with radiologic findings (see Table I), 12 (80%) described radiolucencies with irregular borders or osteolysis associated with the clinical lesion.[7,9,11,14-16,18,20-22,24,25] The other 3 (20%) cases had nonspecific findings or no radiographic changes.[13,19,23] To our knowledge, our patient is the youngest reported nonsyndromic OSCC case.

Carcinoma cuniculatum, a rare variant of SCC, is histologically characterized by endophytic anastomosing squamous epithelial proliferation, with formation of small keratin cysts[26] and ramifying proliferated epithelium without overt atypia (Figure 2).[27] This lack of pronounced dysplasia on histology can lead to an erroneous diagnosis of benign PEH, especially in pediatric patients, such as ours. Clinically, carcinoma cuniculatum often presents as a nonspecific swelling, with a relatively smooth surface that expresses a keratin-like material, which is often mistakenly believed to be pus (see Figure 1B). Most of the reported carcinoma cuniculatum cases were patients in their fifth and sixth decades and had a history of tobacco consumption. These lesions were not related to human papillomavirus (HPV) infection and were located on the gingiva or the alveolar ridge mucosa.[23] Of the 24 other case reports (see Table I), 11 presented pathology images, and 9 of them were pathologically similar, if not identical, to our current case, suggestive of carcinoma cuniculatum.[10,13,15,16,18,20-22]

The current American Joint Committee on Cancer staging system classifies all tumors invading through the cortical bone as T4; hence, stage IV represents late-stage disease.[28] These staging criteria, which stratify lesions into groups with or without bony invasion, are critical in the decision for the need for adjuvant therapy but can be confusing and challenging for patients in mixed dentition, as in our case. During exfoliation of a deciduous tooth, the resulting loss of the mucosal barrier may provide an unimpeded pathway for adjacent invasive cells to reach the alveolar bone. The gubernacular canal that connects the developing permanent dental follicle with the oral mucosa may also provide an uninhibited path of invasion.[29] In our case, the rapid recurrence after the first excision may have resulted from a residual lesion left at the gubernacular canal or at the follicular space of the right permanent central incisor (#8). As there is no true bony invasion of

Table I. Summary of post-1970 English language case reports/series of oral squamous cell carcinoma (SCC) affecting the gingiva, alveolus, or palate in nonsyndromic pediatric patients 16 years of age and younger

Year[Ref]	*Age/Gender*	*Ethnicity**	*Anatomic site*	*Clinical presentation*	*Related history*	*Treatment and stage, if known*	*Follow-up years and prognosis*
1970[7]	15/M	Caucasian	Gingiva/alveolus (anterior mandible)	Loose lower anterior teeth	–	Segmental resection and adjuvant radiotherapy	~4 years, no recurrence
1985[8]	10/M	NS (Connecticut, USA)	Gingiva/alveolus (anterior mandible)	Unknown	–	Segmental resection	~23 years, no recurrence
1985[9]	13/M	African American	Gingiva/alveolus (right maxilla)	Rapidly swelling gums	Sickle cell trait	Segmental resection	2 years, no recurrence
1988[10]	7/M	NS (Ohio, USA)	Gingiva/alveolus (right maxilla central and unerupted lateral incisors)	Rapid growth	–	Subtotal maxillectomy with obturator	~3 years, no recurrence
1998[11]	6/F	NS (Brazil)	Gingiva/alveolus (right maxilla, lateral incisor)	Persistent painless lump	–	Subtotal maxillectomy with obturator (T1 N0 M0)	~11 years, no recurrence
1998[11]	14/M	NS (Brazil)	Gingiva/alveolus (maxilla)	2 month oral ulceration	–	Segmental resection and a comprehensive neck dissection (T4 N2 bM0)	6 months, died of distant metastasis
1998[11]	15/F	NS (Brazil)	Soft palate (left)	2.5 year raised painless lesion	–	Subtotal maxillectomy with obturator (T1 N0 M0)	~9 years, no recurrence
1999[12]	6.5/F	NS (Texas, USA)	Gingiva/alveolus (maxilla)	Unknown	–	Segmental resection	6 years, no recurrence
2001[13]	14/M	NS (Virginia, USA)	Gingiva/alveolus (left posterior mandible)	Gingival bleeding	Orthodontic treatment	Segmental resection	3 years, no recurrence
2007[14]	10/F	NS (Ontario, Canada)	Gingiva/alveolus (left maxilla, canine/premolars)	Progressive swelling	–	Segmental resection and elective neck dissection (T1 N0 M0)	2 years, no recurrence
2008[15]	11/M	NS (The Netherlands)	Gingiva/alveolus (right anterior maxilla)	Progressive swelling	Orthodontic treatment	Segmental resection (T4 aN0 M0)	Unknown
2009[16]	6/M	NS (California, USA)	Gingiva/alveolus (right maxilla)	Persistent swelling after extraction	Removal of deciduous teeth	Segmental resection	Unknown
2009[17]	10/M	NS (England)	Gingiva/alveolus (right mandible canine/first premolar)	Progressive swelling	–	Subtotal mandibulectomy, elective neck dissection and adjuvant chemoradiotherapy (T4 N0 M0)	1 year, no recurrence
2009[18]	16/F	Chinese	Gingiva/alveolus (anterior mandible)	Painless swelling	–	Segmental mandibulectomy and elective neck dissection	1.5 years, no recurrence
2009[19]	11/F	Caucasian	Gingiva/alveolus (right mandible)	Nodulopapillary growth	Spontaneous exfoliation of deciduous canine	Hemimaxillectomy	0.5 years, no recurrence

(*continued on next page*)

Table I. Continued

Year[Ref]	*Age/Gender*	*Ethnicity**	*Anatomic site*	*Clinical presentation*	*Related history*	*Treatment and stage, if known*	*Follow-up years and prognosis*
2010[20]	7/F	NS (England)	Gingiva/alveolus (right maxilla central incisor and primary lateral incisor	Persistent swelling	–	Maxillectomy with obturator	2 years, no recurrence
2011[21]	7/M	Brazilian	Gingiva/alveolus (left maxilla canine/ premolars)	Progressive gingival swelling	–	Segmental resection (T3 N0 M0)	1.5 years, no recurrence
2012[22]	10/M	East Indian	Gingiva/alveolus (right maxillary canine/ premolar)	Progressive swelling	–	Subtotal maxillectomy (T2 N0 M0)	1 year, no recurrence
2012[23]	16/F	East Indian	Gingiva/alveolus (right mandible)	Toothache and ulcerated gingival lesion	–	Radiation only (T3 N0 M0)	0.5 year, no recurrence
2014[24]	6/M	African-American	Gingiva/alveolus (left mandibular premolars)	Toothache with swelling	–	Segmental mandibulectomy and neck dissection	Unknown
2015[2]	10/M	NS (India)	Mandible (retromolar trigone)	–	–	Segmental mandibulectomy and modified neck dissection (T4 N1 M0)	Lost to follow-up
2015[2]	12/F	East Indian	Soft palate	–	–	Wide excision with supra-myohyoid neck dissection (T3 N1 M0)	8 years, no recurrence
2015[2]	15/M	East Indian	Gingiva/alveolus	–	–	Neoadjuvant chemoradiation (T4 N2 bM0)	Lost to follow-up
2016[25]	8/M	NS (Ontario, Canada)	Gingiva/alveolus (left maxilla, deciduous molars to first molar)	2-week left facial swelling	–	Partial maxillectomy (T3 N0 M0)	2 years, no recurrence
Current case	5/M	Caucasian	Gingiva/alveolus (right maxilla incisors)	Persistent gingival swelling	Trauma (fall with gingival laceration)	Segmental maxillectomy	2 years, no recurrence

*Authors' state, province, and/or country stated in brackets.NS, not specified.

adjacent structures but, rather, tumor extension within the already existing gubernacular canal or follicular space, it is imperative that this should not be staged as T4 or categorized as stage IV. The latter scenario with T4 or stage IVA disease often requires aggressive treatment, and consequently, there are significant post-treatment complications. It is recommended that such complex cases be reviewed at multidisciplinary conferences involving oral and maxillofacial pathologists, radiologists, and surgeons because this approach has been shown to improve patient outcome.[30] For surgical management of these lesions, extraction of the involved primary teeth along with the permanent successors is recommended to ensure a clear margin and to prevent recurrence.[31]

In the 25 cases (see Table I), the most common treatment was surgery with or without neck dissection, with 23 (92%) of the cases receiving this treatment. Excluding the 5 cases without follow-up information, only 1 patient who had lymph node metastasis at the time of presentation died of distant metastatic disease.[11] In most of the cases reported, patients were successfully managed with surgical resection alone; 16 (94%) of 17 cases with reported follow-up were only treated with surgery and showed relatively good prognosis (see Table I). Of the cases listed in Table I, 4 received primary (n = 1)[23] or adjuvant (n = 3)[2,7,17] radiation therapy; this treatment is generally reserved for unresectable tumors, taking into consideration the significant long-term comorbidities in the pediatric population. Bony invasion and lymph node involvement are indicators for adjuvant radiotherapy, chemotherapy, or both. Because of the rarity of reported pediatric cases and pathology showing minimal atypical change (i.e., a diagnosis of PEH at initial biopsy), the diagnosis of these lesions may be delayed, and malignancy may be missed, leading to undertreatment. OSCC mimicking benign gingival enlargement should always be considered in younger patients, and both clinical and pathologic information is required to make a definitive diagnosis of carcinoma cuniculatum.

The etiology and pathogenesis of SCC in children is not well understood, considering its rarity and the fact that genetic alterations caused by conventional risk factors can occur in a short amount of time. Elucidation of the role of HPV in head and neck SCC has delineated a relatively younger patient population.[32] Childhood is a time of greater HPV exposure, especially those subtypes (HPV-1, 2, and 6) associated with benign cutaneous lesions.[33] HPV transmission in children can occur directly between carriers or by autoinoculation, or indirectly through exposure to fomites.[34] It is accepted that the host immune system normally can defend against 70% to 90% of HPV infections such that the virus becomes undetectable in 6 to 10 months but may not necessarily be fully cleared.[35] On the basis of the presence of cutaneous warts on our patient's hands at a young age (2 years) and the coincidental trauma to the affected site, we hypothesized that the etiology is related to an HPV infection via autoinoculation from cutaneous lesions on the hands and the infection then transmitted to the oral wound site after a fall and subsequent extraction of the deciduous left central incisor (#F). Because of the patient's young age at exposure to HPV and his less established immune system compared with that of his siblings, after an almost 3-year latent period, the lesion presented as an "abscess" clinically. The lesion from the second excisional biopsy showed diffuse positivity for p16 (see Figure 2C), a surrogate marker for HPV-induced cervical cancer most commonly associated with HPV-16 and -18.[36] Other HPV subtypes with sufficient evidence for causative factors in cervical cancer include HPV-31, -33, -35, -39, -45, -51, -52, -56, -58, and -59, which also have the ability to cause genetic and malignant transformation in the mucosal epithelium.[37,38] We tested for the presence of HPV DNA within the biopsy tissue by using polymerase chain reaction (PCR),[39] but our results were not positive for high-risk HPV subtypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, or 68 or low-risk HPV-6 or -11. Although the high-risk subtypes listed above, including the more uncommon non-16 and -18 subtypes, have been detected in OSCCs at a reported rate of 0% to 5%,[40] it is difficult to establish an etiologic link, given the low incidence.[41] The absence of HPV DNA may be explained by the "hit and run" hypothesis;[42] however, we cannot rule out the contribution of other unusual types of HPV to oral epithelial carcinogenesis in this case.

CONCLUSIONS

We presented here a rare case of gingival carcinoma cuniculatum in a 5-year-old boy, with possible association with HPV infection. Biopsy of suspicious oral lesions should not be delayed because of a patient's young age. In the presence of any atypical hyperplasia, differential diagnosis should include SCC. For surgical management of aggressive lesions during the mixed dentition stage, it is very important to include the permanent successors within the surgical margins to prevent recurrence.

ACKNOWLEDGMENT

We would like to thank Dr. Garry Gill and Dr. Matt Francisco for providing clinical information and images; Dr. Curtis Chen for radiologic interpretation;

and Mr. David Lu for the analysis of HPV status of the presented case. The study was supported by the Dr. Michele Williams Education and Research Fund, BC Cancer Foundation.

FUNDING

The study is supported by the Dr. Michele Williams Education and Research Fund, BC Cancer Foundation.

REFERENCES

1. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med*. 2007;356:1944-1956.
2. Bhanuprasad V, Mallick S, Bhasker S, Mohanti BK. Pediatric head and neck squamous cell carcinoma: report of 12 cases and illustrated review of literature. *Int J Pediatr Otorhinolaryngol*. 2015;79:1279-1282.
3. Sarode GS, Batra A, Sarode SC, Yerawadekar S, Patil S. Oral cancer-related inherited cancer syndromes: a comprehensive review. *J Contemp Dent Pract*. 2016;17:504-510.
4. Bodner L, Manor E, Friger MD, van der Waal I. Oral squamous cell carcinoma in patients twenty years of age or younger—review and analysis of 186 reported cases. *Oral Oncol*. 2014;50:84-89.
5. Dombrowski ND, Wolter NE, Irace AL, et al. Squamous cell carcinoma of the head and neck in children. *Int J Pediatr Otorhinolaryngol*. 2019;117:131-137.
6. Zienolddiny S, Aguelon A-M, Mironov N, et al. Genomic instability in oral squamous cell carcinoma: relationship to betel-quid chewing. *Oral Oncol*. 2004;40:298-303.
7. Jones BJ. Oral carcinoma in the young patient: with a report of two cases. *Br J Oral Surg*. 1970;8:159-164.
8. Son YH, Kapp DS. Oral cavity and oropharyngeal cancer in a younger population. Review of literature and experience at Yale. *Cancer*. 1985;55:441-444.
9. Sacks HG, Holly R, Blum B, Joy ED. Case 58: maxillary alveolar mass in a 13-year-old boy. *J Oral Maxillofac Surg*. 1985;43:958-963.
10. Earle AS, Park CH, Vlastou C. Oral squamous cell carcinoma in children. *Ann Plast Surg*. 1988;20:148-152.
11. de Carvalho MB, Sobrinho Jde A, Rapoport A, et al. Head and neck squamous cell carcinoma in childhood. *Med Pediatr Oncol*. 1998;31:96-99.
12. Jin Y-T, Myers J, Tsai S-T, Goepfert H, Batsakis JG, El-Naggar AK. Genetic alterations in oral squamous cell carcinoma of young adults. *Oral Oncol*. 1999;35:251-256.
13. Bill TJ, Reddy VR, Ries KL, Gampper TJ, Hoard MA. Adolescent gingival squamous cell carcinoma: report of a case and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2001;91:682-685.
14. Binahmed A, Charles M, Campisi P, Forte V, Carmichael RP, Sándor GKB. Primary squamous cell carcinoma of the maxillary alveolus in a 10-year-old girl. *J Can Dent Assoc*. 2007;73:715-718.
15. Stolk-Liefferink SA, Dumans AG, van der Meij EH, Knegt PP, van der Wal KGH. Oral squamous cell carcinoma in children; review of an unusual entity. *Int J Pediatr Otorhinolaryngol*. 2008;72:127-131.
16. Sidell D, Nabili V, Lai C, Cheung G, Kirsch C, Abemayor E. Pediatric squamous cell carcinoma: case report and literature review. *Laryngoscope*. 2009;119:1538-1541.
17. Mehanna P, Patel J, Bailey BMW. Mandibular SCC in a 10 year old child—a clinical rarity. *Br J Oral Maxillofac Surg*. 2009;47:148-150.
18. Alsharif MJ, Jiang WA, He S, Zhao Y, Shan Z, Chen X. Gingival squamous cell carcinoma in young patients: report of a case and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2009;107:696-700.
19. Woo VL, Kelsch RD, Su L, Kim T, Zegarelli DJ. Gingival squamous cell carcinoma in adolescence. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2009;107:92-99.
20. Hutton A, McKaig S, Bardsley P, Monaghan A, Parmar S. Oral carcinoma cuniculatum in a young child. *J Clin Pediatr Dent*. 2010;35:89-94.
21. Ribeiro CMB, Gueiros LAM, Leon JE, do Carmo Abreu e Lima M, de Almeida OP, Leão JC. Oral squamous cell carcinoma in a 7-year-old Brazilian boy. *Int J Oral Maxillofac Surg*. 2011;40:994-997.
22. Solanki MC, Gandhi S, Koshy G, Mathew GC. Squamous cell carcinoma of maxilla in 10 year old boy: a rare case report. *Int J Pediatr Otorhinolaryngol Extra*. 2012;7:33-35.
23. Dhull A, Kaushal V, Narwal A. Unusual presentation of squamous cell carcinoma of alveolus in a young female. *Indian J Dent Sci*. 2012;4:64-66.
24. Smith A, Petersen D, Samant S, Ver Halen JP. Pediatric mandibular reconstruction following resection of oral squamous cell carcinoma: a case report. *Am J Otolaryngol*. 2014;35:826-828.
25. Magalhaes MAO, Somers GR, Sikorski P, et al. Unusual presentation of squamous cell carcinoma of the maxilla in an 8-year-old child. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2016;122:e179-e185.
26. Padilla RJ, Murrah VA. Carcinoma cuniculatum of the oral mucosa: a potentially underdiagnosed entity in the absence of clinical correlation. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2014;118:684-693.
27. Datar UV, Kale A, Mane D. Oral carcinoma cuniculatum: a new entity in the clinicopathological spectrum of oral squamous cell carcinoma. *J Clin Diagn Res*. 2017;11:ZD37-ZD39.
28. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin*. 2017;67:93-99.
29. Brown J. Mechanisms of cancer invasion of the mandible. *Curr Opin Otolaryngol Head Neck Surg*. 2003;11:96-102.
30. Wright FC, De Vito C, Langer B, Hunter A. Expert Panel on Multidisciplinary Cancer Conference Standards. Multidisciplinary cancer conferences: a systematic review and development of practice standards. *Eur J Cancer*. 2007;43:1002-1010.
31. Sahara N, Okafuji N, Toyoki A, et al. A histologic study of the exfoliation of human deciduous teeth. *J Dent Res*. 1993;72:634-640.
32. Majchrzak E, Szybiak B, Wegner A, et al. Oral cavity and oropharyngeal squamous cell carcinoma in young adults: a review of the literature. *Radiol Oncol*. 2014;48:1-10.
33. West LJ. Defining critical windows in the development of the human immune system. *Hum Exp Toxicol*. 2002;21:499-505.
34. Syrjänen S, Puranen M. Human papillomavirus infections in children: the potential role of maternal transmission. *Crit Rev Oral Biol Med*. 2000;11:259-274.
35. Shew ML, Fortenberry JD. HPV infection in adolescents: natural history, complications, and indicators for viral typing. *Semin Pediatr Infect Dis*. 2005;16:168-174.
36. Volgareva G, Zavalishina L, Andreeva Y, et al. Protein p16 as a marker of dysplastic and neoplastic alterations in cervical epithelial cells. *BMC Cancer*. 2004;4:58.

37. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens—Part B: Biological agents. *Lancet Oncol*. 2009;10:321-322.
38. Kreimer AR, Villa A, Nyitray AG, et al. The epidemiology of oral HPV infection among a multinational sample of healthy men. *Cancer Epidemiol Biomarkers Prev*. 2011;20:172-182.
39. Lu XJD, Liu KYP, Soares RC, et al. Potential clinical implications of HPV status and expressions of p53 and cyclin D1 among oropharyngeal cancer patients. *J Oral Pathol Med*. 2018;47:945-953.
40. Kim SM, Kwon IJ, Myoung H, Lee JH, Lee SK. Identification of human papillomavirus (HPV) subtype in oral cancer patients through microarray technology. *Eur Arch Otorhinolaryngol*. 2018;275:535-543.
41. Bouda M, Gorgoulis VG, Kastrinakis NG, et al. "High risk" HPV types are frequently detected in potentially malignant and malignant oral lesions, but not in normal oral mucosa. *Mod Pathol*. 2000;13:644-653.
42. McLaughlin-Drubin ME, Munger K. Viruses associated with human cancer. *Biochim Biophys Acta*. 2008;1782:127-150.

Reprint requests:

Catherine Poh
Faculty of Dentistry
University of British Columbia
2199 Wesbrook Mall Vancouver
British Columbia
V6T 1Z3
Canada
Cpoh@dentistry.ubc.ca