Gingival squamous cell carcinoma in adolescence

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Squamous cell carcinoma (SCC) is a rare finding in the adolescent population, with most cases occurring in patients with underlying heritable diseases or immunologic conditions. Moreover, the incidence of oral SCC in this age group is extremely low. While isolated cases of adolescent oral SCC have been documented, most have been primary tongue or lip lesions. We report 4 cases of gingival SCC occurring in otherwise healthy adolescent patients. The preliminary clinical impressions ranged from factitial injury to inflammatory tissue. Microscopic similarities, including overlap with pseudoepitheliomatous hyperplasia and keratoacanthoma, were seen. Review of the literature indicates that adolescent gingival SCC is extremely rare and a challenging diagnosis for the clinician and pathologist alike. Diagnostic pitfalls, possible etiologic factors, and the prognostic outlook of this condition are discussed. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;107:92-99)**

Squamous cell carcinoma (SCC) is the most common neoplasm of the maxillofacial region and an infrequent finding in patients under the age of 40.[1] Oral SCC (OSCC) is likewise rare in patients younger than 40, with cited incidences of 0.4%[2] to 6.6%.[3] Intraorally, SCC of this younger population has a predilection for the tongue and lips[4-8] and gingival involvement is distinctly unusual.

SCC in patients under 20 years of age (which we herein refer to as the adolescent population) is exceptionally rare. Most reported cases have originated in the respiratory tract including the larynx, trachea, bronchi, and lungs; skin; and genital tract.[9]

In this study, we present 4 cases of gingival OSCC. All 4 cases occurred in otherwise healthy adolescent patients. We also review the current literature on OSCC affecting the younger population, with specific focus on diagnostic challenges faced by clinicians and pathologists, etiology, management considerations, and prognostic implications.

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CASE REPORTS

Case 1

A healthy 18-year-old white female was referred for evaluation of gingival lesions with associated teeth mobility. Her medical and family histories were noncontributory; however, a 3.5-pack-year history of cigarette smoking was disclosed. On intraoral examination, multiple white, nodular, and ulcerated growths were present upon the #22-27 facial and lingual gingiva. Radiographs of this region revealed 50% to 75% horizontal bone loss (Fig. 1). The clinical impression included an atypical epithelial proliferation versus traumatic or factitial injury. A biopsy was performed and read as "epithelial proliferation suggestive of squamous odontogenic tumor-like proliferation." Because of these equivocal findings, it was determined that a second biopsy was warranted. Microscopic examination of the second specimen showed a verrucous-appearing epithelial proliferation with a prominent endophytic growth pattern. The tumor was characterized by a central, keratin-filled crater with distinct lateral cupping and exhibited the overall architecture of a keratoacanthoma (Fig. 2). The epithelium was markedly dyskeratotic with mild cellular pleomorphism. Stromal invasion was identified toward the lesion base and several sections showed deep infiltration into the bone, prompting consideration of a carcinoma cuniculatum. A diagnosis of well-differentiated squamous cell carcinoma was ultimately rendered. The patient was subsequently treated with a hemimandibulectomy and bilateral supraomohyoid neck dissections. The final pathologic diagnosis was well-differentiated squamous cell carcinoma. Perineural and lymphovascular invasion were absent and excised lymph nodes were negative for carcinoma. She contin-

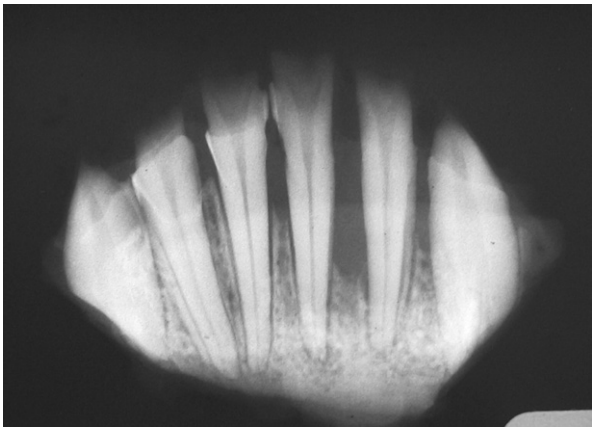

Fig. 1. Case #1. Radiograph showing at least 50% horizontal bone loss in the anterior mandibular region.

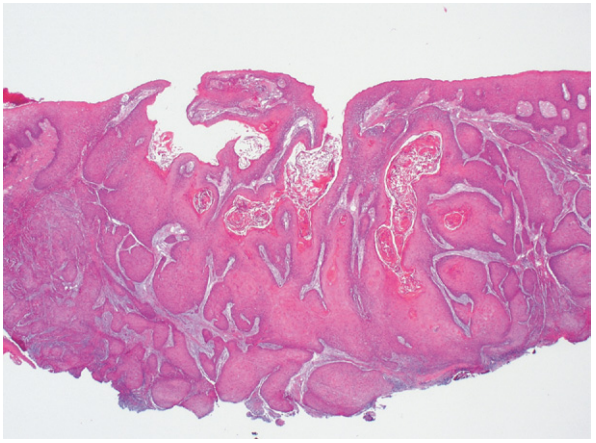

Fig. 2. Case #1. Histologic section of a well-differentiated squamous cell carcinoma with keratoacanthoma-like features, including a central, keratin-filled invagination and lateral cupping (hematoxylin-eosin stain, magnification ×20).

ues to be without evidence of disease 51 months postoperatively.

Case 2

A healthy 17-year-old white male was referred for evaluation of a white, nodular mass of the left posterior maxillary buccal gingiva, extending through the interproximal area to palatal tissues. His medical and family histories were noncontributory. His social history was negative for tobacco and alcohol products. Radiographic evidence of bone loss was noted between the involved molars. The clinical impression from the referring clinician was an abscess with granulation tissue. The initial biopsy revealed a squamous proliferation characterized by focal epithelial detachment, individual cell keratinization, and mild atypia (Fig. 3). After examination of multiple sections, the biopsy was read as "epithelial proliferation suspicious for well-differentiated squamous cell carcinoma." It was further stated that distinction from pseudoepitheliomatous hyperplasia (PEH) was difficult in this case. A second biopsy was performed and revealed features diagnostic of a well-differentiated squamous cell carcinoma. The patient underwent a left hemimaxillectomy with left supraomohyoid neck dissection and a final pathologic diagnosis of well-differentiated squamous cell carcinoma was rendered. Perineural and lymphovascular invasion were absent and the excised lymph nodes were negative for carcinoma. Interestingly, the patient returned 6 months postoperatively complaining of pain in the malar region. CT imaging revealed mucosal thickening in the left maxillary sinus. Another biopsy was performed and showed the presence of atypical epithelium with one detached epithelial island. In conjunction with an outside consultant's opinion, it was decided that definitive evidence of recurrent carcinoma was not present in this specimen. Both the primary and consulting pathologist agreed that the histologic interpretation was extremely challenging and follow-up was strongly recommended. The patient is without disease 46 months postoperatively.

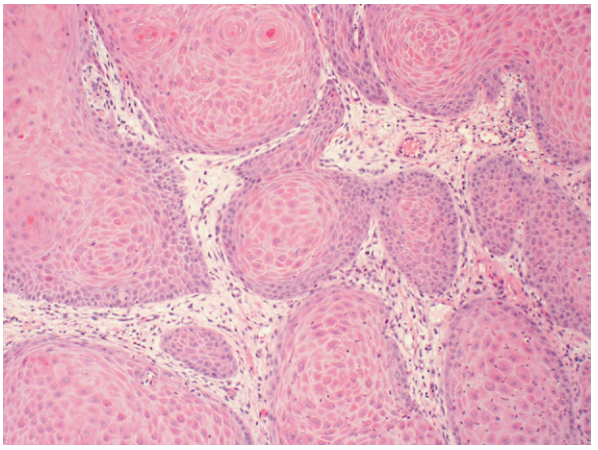

Fig. 3. Case #2. Histologic section of a well-differentiated squamous cell carcinoma composed of squamous islands with focal evidence of dyskeratosis and keratin pearl formation, reminiscent of pseudoepitheliomatous hyperplasia (hematoxylin-eosin stain, magnification ×100).

Case 3

A healthy 11-year-old white female presented for evaluation of a nodulo-papillary growth of the right maxillary facial gingiva, noted by her parents after spontaneous exfoliation of the primary canine. Her medical, family, and social histories were noncontributory. The biopsy was diagnosed as well-differentiated squamous cell carcinoma. A right hemimaxillectomy was performed (Fig. 4) and also read as well-differentiated squamous cell carcinoma with keratoacanthoma-like features (Fig. 5). The patient continues to be without disease 6 months postoperatively.

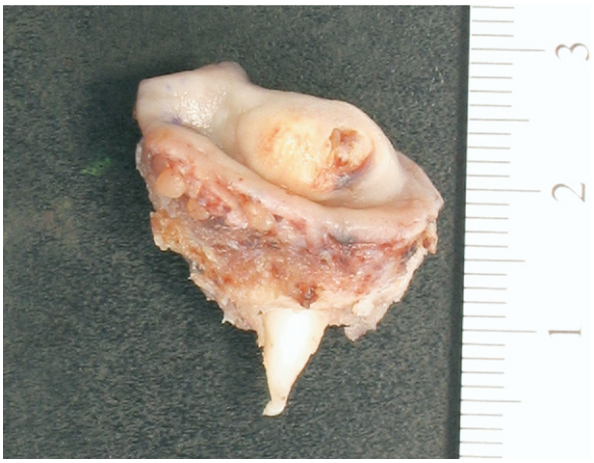

Fig. 4. Case #3. Hemimaxillectomy specimen demonstrating a yellow-white, nodular mass with a central crater.

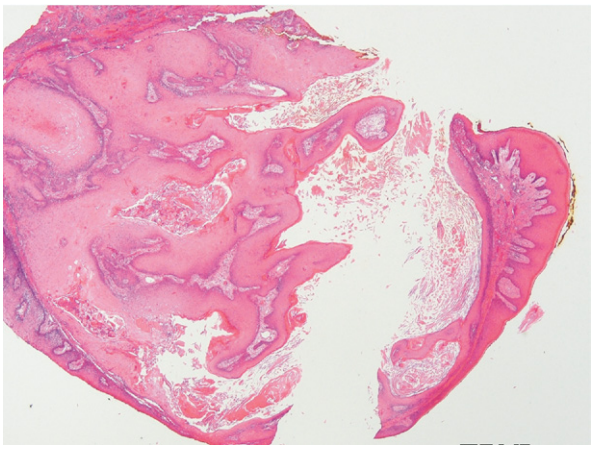

Fig. 5. Case #3. Histologic section of a well-differentiated squamous cell carcinoma with keratoacanthoma-like features (hematoxylin-eosin stain, magnification ×20).

Case 4

A healthy 11-year-old white female presented for evaluation of a white lesion of the right mandibular buccal gingiva. Her medical, family, and social histories were noncontributory. An excisional biopsy was performed and diagnosed as "fibroepithelial hyperplasia with multiple foci of retained odontogenic epithelial rests," most consistent with a PEH-like process. Three years later, the patient returned with a similar lesion at the same site. A follow-up incisional biopsy revealed histologic features of a well-differentiated squamous cell carcinoma. The biopsy was reviewed by several oral and surgical pathologists, all of whom agreed with the diagnosis. The patient was treated with a marginal mandibulectomy and continues to be without disease 24 months postoperatively.

DISCUSSION

Literature review

Thompson et al.[5] performed a retrospective review at the Armed Forces Institute of Pathology (AFIP) over a 30-year period and documented only 20 cases of OSCC in patients younger than 20 years of age. Although the total number of OSCCs was not stated, this review was an extension of a previous AFIP study,[4] in which 14,253 OSCCs accessioned before 1970 were studied. In the Thompson series, the most common sites of involvement were the tongue (9 cases) and the lips (6 cases); 4 patients had confirmed ipsilateral cervical metastases. The histologic grading ranged from well- to poorly differentiated and several tumors exhibited a papillary growth pattern. These patients had no reported hereditary or genetic predisposing factors. We performed a literature review and identified 63 published cases of adolescent OSCC in the English language, as summarized in Table I.[3-5,7,9-25] Of note, we also reviewed several papers that examined OSCC in patients under the age of 40.[6,26-32] However, specific information regarding adolescent patients was often difficult to extrapolate from these studies: consequently, they are not included in Table I.

Adolescent OSCC originating in the gingiva is exceptionally rare. To our knowledge, only 4 cases have been previously published. These cases are highlighted in Table I and summarized in Table II with our present 4 cases. Of these 8 cases, the affected patients ranged from 4 to 18 years in age and a slight predilection for the maxillary gingiva was seen. Clinically, most tumors were described as white, nodular or exophytic, sometimes granular or papillary-appearing proliferations. The most common clinical impression was that of an inflammatory lesion. There was often difficulty in microscopic interpretation of the biopsy specimens, with distinction from PEH posing a recurrent problem in several cases.[21,23] The final pathologic reading in 7 of the 8 cases was well-differentiated SCC.[20-21,23]

Clinical and histopathologic challenges

Diagnosing OSCC in the very young patient can be challenging, both on a clinical and microscopic level. On the gingiva, clinically white lesions may be mistaken for a wide array of benign epithelial proliferations such as a squamous papilloma, verruca vulgaris, and nonspecific epithelial hyperplasia. Lesions of traumatic origin such as frictional hyperkeratosis, chemical burns, or factitial injury may also be considered. Exophytic lesions may be misdiagnosed as reactive proliferations such as a pyogenic granuloma,[33] fibroma, peripheral ossifying fibroma, or peripheral giant cell granuloma; or inflammatory entities such as an abscess or parulis.[21] Granular-appearing lesions may raise the possibility of

Table I. Summary of reported adolescent oral squamous cell carcinoma cases

Author	*Year*	*No. of cases*	*Age in years*	*Gender*	*Site*
Frank et al.[10]	1936	1	Newborn	M	Tongue
Saleeby et al.[11]	1940	11	Newborn (2)	NS	Tongue
			⩽15 (4)		
New and Hertz[12]	1940	1	13	M	L margin and base of tongue
Merrifield et al.[13]	1955	1	5	F	FOM
Frazell and Lucas[14]	1962	1	19	F	Lateral tongue
Venables and Craft[15]	1966	1	17	F	R border of tongue
Pichler et al.[16]	1972	1	19	M	R lateral tongue
Turner and Snitzer[7]	1974	1	12	M	R dorsal, lateral, ventral tongue
Byers[17]	1975	4	17	NS	NS
			19		
			19		
			19		
Patel and Dave[18]	1976	5	<20		Anterior tongue
Krolls and Hoffman[4]	1976 (?-1973)	*3**	14	M	Tongue
			14	F	Tongue
			14	M	Lower lip
		*16**	15-19		NS
Thompson et al.[5]	1999 (1966-1999)	20	<20	10 M	Tongue (9 cases)
				10 F	Lip (6 cases)
Soni and Chatterji[19]	1982	1	11	M	L tongue
Son and Kapp[20]	1985	1	10	M	R maxillary alveolus
		1	17	F	R buccal
		1	18	M	R anterior tongue
		1	19	M	L anterior tongue
Earle et al.[9]	1985	1	7	M	R anterior maxillary gingiva
Sacks et al.[21]	1985	1	13	M	Maxillary alveolar mucosa
Usenius et al.[22]	1987	1	14	M	L lateral tongue
Bill et al.[23]	2001	1	14		L mandibular premolar gingiva
Sasaki et al.[3]	2005	1	19	F	NS
O'Regan et al.[24]	2006	2	16-20	M	NS
				F	
Sturgis et al.[25]	2005	2	18	M	Tongue
			16	F	Tongue

M, male; F, female; NS, not specified; L, left; R, right; FOM, floor of mouth.
*These 19 cases were subsequently included in the review by Thompson et al.

a granulomatous process, including a foreign body reaction and less likely, a deep fungal infection or oral manifestation of tuberculosis or Crohn's disease. In cases with intraosseous involvement, the differential diagnosis broadens and may include a central giant cell granuloma and Langerhans cell histiocytosis, among other entities.

Unfortunately, the microscopic diagnosis of OSCC in this young age group is equally challenging. The often bland histologic features of most adolescent OSCCs, particularly those originating from the gingiva, can make distinction from reactive and benign neoplastic processes extremely difficult. Diagnostic pitfalls deserving mention include PEH, as illustrated by our second and fourth cases as well as others[21,23]; keratoacanthoma, as illustrated by our first and third cases and others[21,23,33,34]; and squamous odontogenic tumor.

Pseudoepitheliomatous hyperplasia (PEH). PEH is characterized histologically by elongation of rete ridges and pseudo-invasion of the stroma by squamous epithelium. The epithelial islands often exhibit jagged or irregular outlines with variable keratin pearl formation and mitotic activity.[23] In contrast to OSCC, the pseudo-"invasive" islands of PEH are comprised of cytologically benign cells with a distinct absence of atypical mitotic figures or individual cell keratinization.[23,35,36]

Keratoacanthoma (KA). KA is a controversial entity with purported unique behavioral and microscopic characteristics. Involvement of the oral mucosa, so called solitary intraoral KA, has been documented in isolated case reports.[33,34,37,38] The histologic hallmarks of KA include a central, keratin-filled invagination surrounded by hyperplastic and dyskeratotic squamous epithelium; broad, pushing rete ridges that undermine the adjacent non-neoplastic mucosa, imparting the appearance of acute lateral "lipping"; sheets and islands of epithelium within the stroma; keratin pearl formation; and infrequent mitotic figures.[33,36] Somewhat

Table II. Summary of reported cases adolescent gingival SCC cases

Author	Age/ Gender	Site	Clinical impression	Initial diagnosis	No. of biopsies	Final diagnosis	Treatment	Follow-up
Son and Kapp[20]	10/M	R mx alveolus	NS	NS	NS	SCC, well	"Surgery"	274 mo NED
Earle et al.[9]	6/M	Ant mx gingiva	NS	1	NS	SCC, mod	Hemimx	30 mo NED
Sacks et al.[21]	13/M	L mx gingiva	"abscess"	PEH	1	SCC, well	Partial maxillec Hemimx	24 mo NED
Bill et al.[23]	14/M	L mn gingiva	"inflammatory"	Atypical epithelial proliferation	"multiple"	SCC, well	Excision; Marginal mandibulec	36 mo NED
Present	18/F	Ant Mn gingiva	Atypical epithelial proliferation; traumatic/factitial injury	SOT-like proliferation	2	SCC, well	Hemimn + neck (bilat SOH)	51 mo NED
Present	17/M	L Post mx gingiva	Abscess	PEH	2	SCC, well	Hemimx + neck (L SOH)	At 6 mo, atypical epithelial Proliferation in sinus; 46 mo NED
Present	11/F	R Ant Mx gingiva	NS	SCC, well	1	SCC, well	Hemimx	6 mo NED
Present	11/F	R Mn gingiva	NS	PEH-like	2	SCC, well	Marginal mandibulec	24 mo NED

M, male; R, right; L, left; Ant, anterior; Mn, mandible; Mx, maxilla; NS, not specified; PEH, pseudoepitheliomatous hyperplasia; SCC, squamous cell carcinoma; mod, moderately; Hemimx, hemimaxillectomy; Hemimn, hemimandibulectomy; Maxillec, maxillectomy; Mandibulec, mandibulectomy; bilat, bilateral; SOH, supraomohyoid neck dissection; mo, months; NED, no evidence of disease.

worrisome features such as individual cell keratinization[33] and mild cytologic atypia[39] may also be seen. In contrast to OSCC, true stromal invasion should not be present. Furthermore, the "classic" clinical course of KAs (i.e., rapid onset followed by regression) is not expected in OSCC. To date, the issue of whether KA warrants separate designation from SCC or if it simply represents a very well differentiated SCC remains debatable.

Squamous odontogenic tumor (SOT). SOT or SOT-like proliferations are composed microscopically of bland squamous epithelial islands with smooth peripheral borders.[40] The islands may occasionally undergo central cystic change and dystrophic calcification. In contrast to OSCC, the constituent cells of SOT do not demonstrate cytologic atypia or increased mitotic activity. Furthermore, true SOTs are predominantly intraosseous lesions.

Last, a rare entity known as carcinoma cuniculatum (CC) also deserves mention as it was a histologic consideration for our first case. CC is considered to be either a variant of a well-differentiated SCC or verrucous carcinoma as it bears clinical and histologic resemblance to both. A slow-growing lesion with a tendency toward deep osseous invasion, CC is characterized architecturally by branching, keratin-filled crypts alternating with prominently keratinized papillary projections.[41] There is broad invasion of the stroma by islands of minimally atypical squamous cells that may exhibit microabscess formation.[41] Most CC originate from the gingival or palatal mucosa although the bulk of the tumor mass may be found within bone.[41]

Because of difficulties in clinical and microscopic interpretation of adolescent OSCC, it has been suggested that lesions exhibiting unusual behavior, such as delayed healing, continued enlargement, and/or osseous destruction, be re-biopsied or excised with adequate margins.[23] A similar approach is recommended for lesions demonstrating histologic ambiguity on initial biopsy.

Etiology

The etiologic basis of OSCC affecting young patients has long been debated. The "classic" environmental risk factors most strongly implicated in OSCC development (e.g., tobacco smoking, alcohol consumption, and betel quid use[30]) are of questionable etiologic significance in this population. Many authors have remarked that these habits are infrequent in younger individuals and that the shorter exposure times may be insufficient to induce carcinogenesis.[3,24,31,42,43] Schantz et al.[44] postulated that tumorigenesis is not only dependent on the type and level of carcinogen exposure but genetic sensitivity of the individual as

Table III. Hereditary conditions associated with adolescent-onset oral squamous cell carcinoma

1. Xeroderma pigmentosum
2. Fanconi anemia
3. Epidermolysis bullosa
4. Juvenile papillomatosis
5. Dyskeratosis congenita

well. Their group found that young adults with SCCs of the upper aerodigestive tract exhibited increased susceptibility to mutagen-induced chromosomal damage.[44] OSCC in this young age group has also been linked to several heritable conditions, including the familial genodermatoses and chromosomal instability syndromes (Table III).[9,23,46-50] Furthermore, systemic factors leading to immunologic deficiencies, such as solid organ transplantation, bone marrow transplant, and long-term immunosuppressive therapy, have been documented in some cases.[45,46,51,52] All 4 patients in our study were healthy and well, with no suggestion of such predisposing factors.

Although the molecular pathogenesis of adolescent OSCC is of interest, the paucity of reported cases has precluded extensive study on this subject. In contrast, OSCC in patients between the ages of 20 and 40 has garnered considerable research attention in recent years. Factors of probable relevance include viral infections and a wide array of genetic markers.

Viral infections. Human papillomavirus (HPV) appears to be of controversial significance in OSCC affecting persons under the age of 40 years. Koch et al.[53] stated that HPV of the oral mucosa was exceptionally rare in preadolescent children prior to sexual activity. Similarly, El-Mofty and Lu[54] found 0/15 (0%) OSCCs in patients under 40 were positive for HPV-16 by polymerase chain reaction (PCR).

Genetic markers. Lingen et al.[28] explored *p53 expression* in SCCs of patients 40 and under with no identifiable risk factors. This group found that 17/21 (81%) of the tumors studied overexpressed p53 via immunohistochemistry (IHC). This percentage was reportedly equal to or higher than p53 expression in SCCs of older patients with traditional risk factors.[55] Tremblay et al.[56] confirmed significantly lower expression level of *GSTP1* and the Fanconi's anemia gene, *FANCA*, in OSCCs samples of their younger cohort compared to their older cohort. Zheng et al.[57] concluded that *cyclin D1 gene polymorphism* is associated with early-onset head and neck SCCs, especially in young individuals without smoking or drinking histories. Last, Wang et al.[58] found tongue cancers in their younger demographic to have higher frequencies of *microsatellite instability*, the variable shortening or lengthening of short tandem repeats attributable to DNA repair defects.[58]

These studies highlight possible differences in the molecular and genetic mechanisms driving oral carcinogenesis in younger patients compared to the older population. Whether OSCC in the younger population represents an entity distinct from its adult counterpart remains unresolved at this time.

Clinical management and prognosis

Undoubtedly, treating adolescent patients with OSCC can pose challenges as well. In this very young population, special consideration must be given to optimizing esthetics, prosthetic reconstruction and modification, psychological implications, and follow-up. In most cases, a comprehensive medical/dental team will be required for proper management. In the very limited number of cases published, treatment has consisted predominantly of wide surgical excision with or without neck dissection. Some of these patients have also undergone adjuvant radiation therapy and/or chemotherapy.[5,20,25] Gingival OSCC cases have been managed with a hemimaxillectomy or segmental/marginal resection, with the neck being addressed if deemed necessary. Fortunately, most reported patients have had long disease-free intervals with no recurrence.[20,21,23]

Interestingly, conflicting data exist regarding the prognosis of young patients with OSCC. Some authors contend that OSCCs affecting patients younger than 40 pursue a more aggressive course with early metastasis[15,17] and poorer survival outcomes.[17,20,59] In contrast, other groups have found either comparable or improved 5-year survival rates when compared with older patients with OSCC.[1,31,60-65] Goldstein and Irish[66] and Friedlander et al.[67] found that younger individuals with OSCC exhibited higher locoregional recurrence, although this did not portend to a poorer survival outcome. Myers et al.[68] correlated decreased survival with presence of perineural invasion, lymphovascular invasion, and surgical margins of less than 5 mm. Meticulous long-term follow-up appears warranted in all cases, including thorough evaluation for second primaries and cervical metastasis.[6,59]

In summary, we present 4 cases of gingival OSCC occurring in otherwise healthy adolescents. Moreover, we have reviewed common difficulties encountered in the clinical and microscopic interpretation of such cases. It is encouraging that significant strides have been achieved in understanding the molecular pathoetiology of OSCC in the younger population. However, it is also clear that little is known about OSCC in the adolescent patient. Ultimately, continued study of this unique patient population may help in establishing diagnostic parameters and management guidelines.

REFERENCES

1. Carniol PJ, Fried MP. Head and neck carcinoma in patients under 40 years of age. Ann Otol Rhinol Laryngol 1982;91:152-5.
2. Tan KH. Oral cancer in Australia. Aust Dent J 1969;14(1):50-6.
3. Sasaki T, Moles DR, Imai Y, Speight PM. Clinico-pathological features of squamous cell carcinoma of the oral cavity in patients <40 years of age. J Oral Pathol Med 2005;34(3):129-33.
4. Krolls SO, Hoffman S. Squamous cell carcinoma of the oral soft tissues: a statistical analysis of 14,253 cases by age, sex, and race of patients. J Am Dent Assoc 1976;92(3):571-4.
5. Thompson L, Castle J, Heffner DK. Oral squamous cell carcinoma in pediatric patients: a clinicopathologic study of 20 cases [abstract]. Oral Surg Oral Med Oral Pathol 1999;88:204.
6. McGregor GI, Davis N, Robins RE. Squamous cell carcinoma of the tongue and lower oral cavity in patients under 40 years of age. Am J Surg 1983;146:88-92.
7. Turner H, Snitzer J. Carcinoma of the tongue in a child. Report of a case and review of the literature. Oral Surg Oral Med Oral Pathol 1974;37(5):663-7.
8. Martin-Granizo R, Rodriguez-Campo F, Naval L, Diaz Gonzalez FJ. Squamous cell carcinoma of the oral cavity in patients younger than 40 years. Otolaryngol Head Neck Surg 1997;117(3 Pt 1):268-75.
9. Earle AS, Park CH, Vlastou C. Oral squamous cell carcinoma in children. Ann Plast Surg 1988;20(2):148-52.
10. Frank LW, Enfield CD, Miller AJ. Carcinoma of the tongue in a newborn child: report of a case. Am J Cancer 1936;26:775-7.
11. Saleeby GW. Cancer of the tongue in young subjects with report of a case. Am J Cancer 1940;38:257-62.
12. New GB, Hertz CS. Malignant disease of the face, mouth, pharynx and larynx in the first three decades of life. Surg Gynecol Obstet 1940;70:163.
13. Merrifield FW, Dalitsch WW, Steiner MM. Epidermoid carcinoma of the tongue and floor of mouth in infancy and childhood: report of case and review of the literature. Am J Dis Child 1955;89:281.
14. Frazell EL, Lucas JC Jr. Cancer of the tongue. Report of the management of 1,554 patients. Cancer 1962;15:1085-99.
15. Venables CW, Craft IL. Carcinoma of the tongue in early adult life. Br J Cancer 1967;21:645-50.
16. Pichler AG, Williams JR, Moore JA. Carcinoma of the tongue in childhood and adolescence. Report of a case and review of the literature. Arch Otolaryngol 1972;95(2):178-9.
17. Byers RM. Squamous cell carcinoma of the oral tongue in patients less than thirty years of age. Am J Surg 1975;130:475-8.
18. Patel DD, Dave RI. Carcinoma of the anterior tongue in adolescence. Cancer 1976;37:917-21.
19. Soni NK, Chatterji P. Carcinoma of the tongue in a young child of eleven years. Indian Pediatr 1982;19:187-9.
20. Son YH, Kapp DS. Oral cavity and oropharyngeal cancer in a younger population. Review of the literature and experience at Yale. Cancer 1985;55:441-4.
21. Sacks HG, Holly R, Blum B, Joy ED. Case 58: maxillary alveolar mass in a 13-year-old boy. J Oral Maxillofac Surg 1985;43:958-63.
22. Usenius T, Karja J, Collan Y. Squamous cell carcinoma of the tongue in children. Cancer 1987;60(2):236-9.
23. Bill TJ, Reddy VR, Ries KL, Gampper TJ, Hoard MA. Adolescent gingival squamous cell carcinoma. Oral Surg Oral Med Oral Path Oral Radiol Endod 2001;91(6):682-5.
24. O'Regan EM, Timon C, Sheils O, Codd M, O'Leary JJ, Toner M. Squamous cell carcinoma of the head and neck in young Irish adults. Br J Oral Maxillofac Surg 2006;44(3):203-6.
25. Sturgis EM, Moore BA, Glisson BS, Kies MS, Shin DM, Byers RM. Neoadjuvant chemotherapy for squamous cell carcinoma of the oral tongue in young adults: a case series. Head Neck 2005;27(9):748-56.
26. Friedman M, Rubenfeld S. Malignant neoplasms of the upper respiratory tract in the young. Am J Cancer 1934;22:786.
27. Williams IG. Cancer in childhood. Br J Radiol 1946;19:182-97.
28. Lingen MW, Chang KW, McMurray SJ, Solt DB, Kies MS, Mittal BB, et al. Overexpression of p53 in squamous cell carcinoma of the tongue in young patients with no known risk factors is not associated with mutations in exons 5-9. Head Neck 2000;22(4):328-35.
29. O'Regan EM, Toner ME, Smyth PC, Finn SP, Timon C, Cahill S, et al. Distinct array comparative genomic hybridization profiles in oral squamous cell carcinoma occurring in young patients. Head Neck 2006;28(4):330-8.
30. Iamaroon A, Pattanaporn K, Pongsiriwet S, Wanachantararak S, Prapayasatok S, Jittidecharaks S, et al. Analysis of 587 cases of oral squamous cell carcinoma in northern Thailand with a focus on young people. Int J Oral Maxillofac Surg 2004;33(1):84-8.
31. Hyam DM, Conway RC, Sathiyaseelan Y, Gebski V, Morgan GJ, Walker DM, et al. Tongue cancer: do patients younger than 40 do worse? Aust Dent J 2003;48(1):50-4.
32. Mathew Iype E, Pandey M, Mathew A, Thomas G, Sebastian P, Krishnan Nair M. Squamous cell carcinoma of the tongue among young Indian adults. Neoplasia 2001;3(4):273-7.
33. Janette A, Pecaro B, Lonergan M, Lingen MW. Solitary intraoral keratoacanthoma: report of a case. J Oral Maxillofac Surg 1996;54(8):1026-30.
34. Svirsky JA, Freedman PD, Lumerman H. Solitary intraoral keratoacanthoma. Oral Surg Oral Med Oral Pathol 1977;43(1):116-22.
35. Calhoun KH, Wagner RF Jr, Kumar D, Hokanson JA. Pseudoepitheliomatous hyperplasia mistaken for cancer after delayed reconstruction. South Med J 1995;88(4):454-7.
36. Bouquot JE, Nikai H. Lesions of the oral cavity. In: Gnepp DR, editor. Diagnostic surgical pathology of the head and neck. Philadelphia, PA: Saunders; 2001. p. 206.
37. Scofield HH, Werning JT, Shukes RC. Solitary intraoral keratoacanthoma. Oral Surg Oral Med Oral Pathol 1974;37(6):889-98.
38. Zegarelli DJ. Solitary intraoral keratoacanthoma. Oral Surg Oral Med Oral Pathol 1975;40(6):785-8.
39. McNulty JR, Sommers SC. Keratoacanthoma as a surgical pathologic entity. Surg Gynecol Obstet 1957;104(6):663-8.
40. Sciubba JJ, Fantasia JE, Kahn KB. Benign odontogenic tumors. In: Sciubba JJ, Fantasia JE, Kahn KB, editors. Atlas of tumor pathology: tumors and cysts of the jaws, third series, fascicle 29. Maryland: AFIP. p. 95-7.
41. Allon D, Kaplan I, Manor R, Calderon S. Carcinoma cuniculatum of the jaw: a rare variant of oral carcinoma. Oral Surg Oral Med Oral Path Oral Radiol Endod 2002;94(5):601-8.
42. Schantz SP, Lui FJ. An immunologic profile of young adults with head and neck cancer. Cancer 1989;64:1232-7.
43. Llewellyn CD, Linklater K, Bell J, Johnson NW, Warnakulasuriya S. An analysis of risk factors for oral cancer in young people: a case-control study. Oral Oncol 2004;40:304-13.
44. Schantz SP, Hsu TC, Ainslie N, Moser RP. Young adults with head and neck cancer express increased susceptibility to mutagen-induced chromosome damage. JAMA 1989;262:3313-5.
45. Socie G, Henry-Amar M, Cosset JM, Devergie A, Girinsky T, Gluckman E. Increased incidence of solid malignant tumors after bone marrow transplantation for severe aplastic anemia. Blood 1991;78:277-9.
46. Millen FJ, Rainey MG, Hows JM, Burton PA, Irvine GH, Swirsky D. Oral squamous cell carcinoma after allogeneic bone marrow transplantation for Fanconi anaemia. Br J Haematol 1997;99(2):410-4.

47. Harper JI, Copeman PW. Carcinoma of the tongue in a boy with xeroderma pigmentosum. Clin Exp Dermatol 1981;6(6):601-4.
48. Yagi K, Ali A el-G, Abbas K el-D, Prabhu SR. Carcinoma of the tongue in a patient with xeroderma pigmentosum. Int J Oral Surg 1981;10(1):73-6.
49. Kaplan MJ, Sabio H, Wanebo HJ, Cantrell RW. Squamous cell carcinoma in the immunosuppressed patient: Fanconi's anemia. Laryngoscope 1985;95(7 Pt 1):771-5.
50. Anil S, Beena VT, Raji MA, Remiani P, Ankathil R, Vijayakumar T. Oral squamous cell carcinoma in a case of dyskeratosis congenita. Ann Dent 1994;53(1):15-8.
51. Lancaster L Jr, Fournet LF. Carcinoma of the tongue in a child: report of case. J Oral Surg 1969;27(4):269-70.
52. Lee YW, Gisser SD. Squamous cell carcinoma of the tongue in a nine year renal transplant survivor: a case report with a discussion of the risk of development of epithelial carcinomas in renal transplant survivors. Cancer 1978;41(1):1-6.
53. Koch WM, Hansen SV, Nielsen NM, Palefsky J, Melbye M. HPV detection in children prior to sexual debut. Int J Cancer 1997;73:621-4.
54. El-Mofty SK, Lu DW. Prevalence of human papillomavirus type 16 DNA in squamous cell carcinoma of the palatine tonsil, and not the oral cavity, in young patients: a distinct clinicopathologic and molecular disease entity. Am J Surg Pathol 2003;27(11): 1463-70.
55. Field JK. Oncogenes and tumour-suppressor genes in squamous cell carcinoma of the head and neck. Eur J Cancer B Oral Oncol 1992;28B(1):67-76.
56. Tremblay S, Pintor Dos Reis P, Bradley G, Galloni NN, Perez-Ordonez B, Freeman J, et al. Young patients with oral squamous cell carcinoma: study of the involvement of GSTP1 and deregulation of the Fanconi anemia genes. Arch Otolaryngol Head Neck Surg 2006;132(9):958-66.
57. Zheng Y, Shen H, Sturgis EM, Wang LE, Eicher SA, Strom SS, et al. Cyclin D1 polymorphism and risk for squamous cell carcinoma of the head and neck: a case-control study. Carcinogenesis 2001;22(8):1195-9.
58. Wang Y, Irish J, MacMillan C, Brown D, Xuan Y, Boyington C, et al. High frequency of microstatellite instability in young patients with head-and-neck squamous-cell carcinoma: lack of involvement of the mismatch repair genes hMLH1 and hMSH2. Int J Cancer 2001;93(3):353-60.
59. Amsterdam JT, Strawitz JG. Squamous cell carcinoma of the oral cavity in young adults. J Surg Oncol 1982;19:65-8.
60. Pitman KT, Johnson JT, Wagner RL, Myers EN. Cancer of the tongue in patients less than forty. Head Neck 2000;22(3): 297-302.
61. Verschuur HP, Irish JC, O'Sullivan B, Goh C, Gullane PJ, Pintilie M. A matched control study of treatment outcome in young patients with squamous cell carcinoma of the head and neck. Laryngoscope 1999;109:249-58.
62. Veness MJ, Morgan GJ, Sathiyaseelan Y, Gebski V. Anterior tongue cancer: age is not a predictor of outcome and should not alter treatment. ANZ J Surg 2003;73:899-904.
63. Vermund H, Brennhovd IO, Harvei S, Kaalhus O, Poppe E, Wiley AL Jr. Carcinoma of the tongue in Norway and Wisconsin. I. Incidence and prognosis related to sex and age. Acta Radiol Oncol 1982;21(3):155-68.
64. Schantz SP, Yu GP. Head and neck cancer incidence trends in young Americans, 1973-1997, with a special analysis for tongue cancer. Arch Otolaryngol Head Neck Surg 2002;128:268-74.
65. Annertz K, Anderson H, Biorklund A, Moller T, Kantola S, Mork J, et al. Incidence and survival of squamous cell carcinoma of the tongue in Scandinavia, with special reference to young adults. Int J Cancer 2002;101(1):95-9.
66. Goldstein DP, Irish JC. Head and neck squamous cell carcinoma in the young patient. Curr Opin Otolaryngol Head Neck Surg 2005;13(4):207-11.
67. Friedlander PL, Schantz SP, Shaha AR, Yu G, Shah JP. Squamous cell carcinoma of the tongue in young patients: a matched pair analysis. Head Neck 1998;20:363-8.
68. Myers JN, Elkins T, Roberts D, Byers RM. Squamous cell carcinoma of the tongue in young adults: increasing incidence and factors that predict treatment outcomes. Otolaryngol Head Neck Surg 2000;122(1):44-51.