



# Update from the 5th Edition of the World Health Organization Classification of Head and Neck Tumors: Tumours of the Oral Cavity and Mobile Tongue

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## Abstract

The fifth chapter of the upcoming fifth edition of the 2022 World Health Organization Classification of Tumours of the Head and Neck titled *Tumours of the oral cavity and mobile tongue*, has had some modifications from the 2017 fourth edition. A new section "**Non-neoplastic Lesions**", introduces two new entries: *necrotizing sialometaplasia* and *melanoacanthoma*. The combined Oral potentially malignant disorders and Oral epithelial dysplasia section in the 2015 WHO has now been separated and submucous fibrosis and HPV-associated dysplasia are also discussed in separate sections. Carcinoma cuniculatum and verrucous carcinoma are described in dedicated sections, reflecting that the oral cavity is the most common location in the head and neck for both these entities which have distinct clinical and histologic features from conventional squamous cell carcinoma. This review summarizes the changes in Chapter 5 with special reference to new additions, deletions, and sections that reflect current clinical, histological, and molecular advances.

**Keywords** World Health Organization · Oral cavity · Mobile tongue · Squamous cell · Dysplasia · Proliferative verrucous leukoplakia · Submucous fibrosis · Ectomesenchymal chondromyxoid tumor

## Introduction

Periodic updates of the WHO/IARC Classification of Tumours allow for refinements of tumor classifications and addition of new entities based on evolving molecular findings, immunohistochemical advances and clinical behavior. In the 5th edition of The World Health Organization Classification of Tumours of the Head and Neck, the Chapter 5 titled *Tumours of the oral cavity and mobile tongue*, has had some modifications from the 2017 fourth edition [1].

A Non-neoplastic section is now added to the chapter. Although reactive, necrotizing sialometaplasia has been included as both the clinical and histologic features of this entity can mimic salivary gland tumors and squamous carcinoma. Multifocal epithelial hyperplasia in the past edition was included with the papillomas but in the 5th edition is included in the non-neoplastic section in view of the clinical behavior and spontaneous regression. Another new entry into this section is melanoacanthoma, as the clinical features may be of concern for oral mucosal melanoma.

Tumours of uncertain histogenesis section includes an update on ectomesenchymal chondromyxoid tumor (EMCT) which discusses the recent molecular discovery of a *RREB1::MRTFB* gene fusion in 90% of cases for this entity. Previously covered in this chapter in the 4th edition, soft tissue and neural tumors, oral mucosal melanoma, salivary gland tumors, and hematolymphoid tumors are now presented in chapters dedicated to those tumor categories.

Unlike past editions where oral carcinoma was discussed first, in the current edition the epithelial tumors are organized by tumor behavior and squamous carcinoma is

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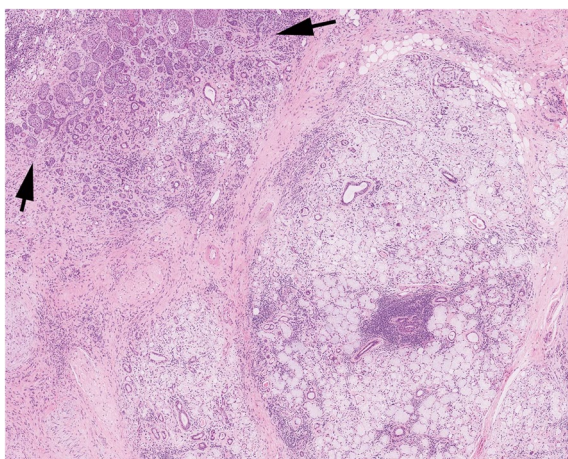
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discussed last. Separate sections have been added on oral potentially malignant disorders, oral epithelial dysplasia, submucous fibrosis, and HPV-associated dysplasia to reflect the advances in our understanding of the clinical, histologic, and molecular findings. Oral epithelial dysplasia grading criteria has been expanded to include several more architectural and cytologic features for the diagnosis of dysplasia with emphasis that architectural features alone may signify dysplasia. Although dysplasia grading remains challenging, the WHO maintains a three-tiered grading system. The section titled Tumours of uncertain histogenesis includes an update on ectomesenchymal myxoid tumor to reflect the molecular findings of a *RREB1::MRTFB* gene fusion in 90% of cases. Soft tissue and neural tumors, oral mucosal melanoma, salivary gland tumors, and hematolymphoid tumors previously covered in this chapter are now presented in chapters dedicated to those tumor categories.

## Non-neoplastic Lesions

A new entry in the 2022 WHO, Non-neoplastic lesions add two new entries. Necrotizing sialometaplasia (NSM) is described, principally to highlight the clinical and histological features of a reactive, self-limiting entity that can mimic squamous cell carcinoma and salivary carcinoma [2–4]. The histologic feature of salivary lobular architecture preservation is emphasized as a desirable diagnostic criterion. Diagnostic challenges can be encountered when lobular preservation is poor or in later stages of NSM when squamous metaplasia of the ducts and acini mimic mucoepidermoid carcinoma (Fig. 1). Pseudoepitheliomatous hyperplasia is another histologic finding in some NSM and may raise the



**Fig. 1** Necrotizing sialometaplasia showing the outline of residual acini with necrosis with preservation of the lobular architecture of the glands and squamous metaplasia of residual ducts (arrows). Courtesy of Dr. K Magliocca

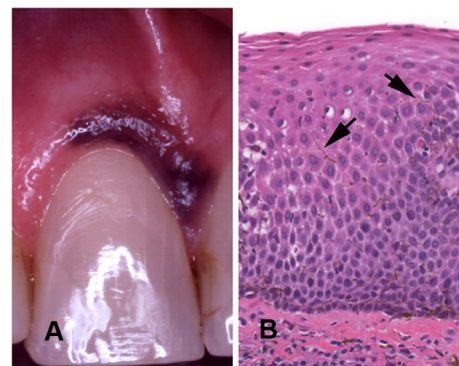
suspicion of squamous cell carcinoma, however the bland cytologic features are helpful criteria [2, 3, 5].

Multifocal epithelial hyperplasia (MFEH) in the 4th edition was grouped with the papilloma section, but it was moved to the Non-neoplastic lesion section for the 5th edition to better reflect the clinical behavior and spontaneous regression of these lesions. When MFEH occurs in children, regression is generally noted at puberty [6]. Low socioeconomic status is also associated with MFEH and with improved living conditions the lesions will regress.

Melanoacanthoma is another new entry in the 2022 WHO, chiefly added due to the alarming clinical presentation of an initially rapidly growing pigmented lesion, raising the concern for oral mucosal melanoma (Fig. 2A). The unique histology of melanoacanthoma is supported by epithelial acanthosis and dendritic melanocytes within the intercellular spaces which can be highlighted by S100 protein, HMB45, or Melan A immunohistochemistry (Fig. 2B) [7–9]. Melanoacanthoma lacks atypia and invasion of melanocytic nests are absent, important features to distinguish from mucosal melanoma.

## Epithelial Tumors

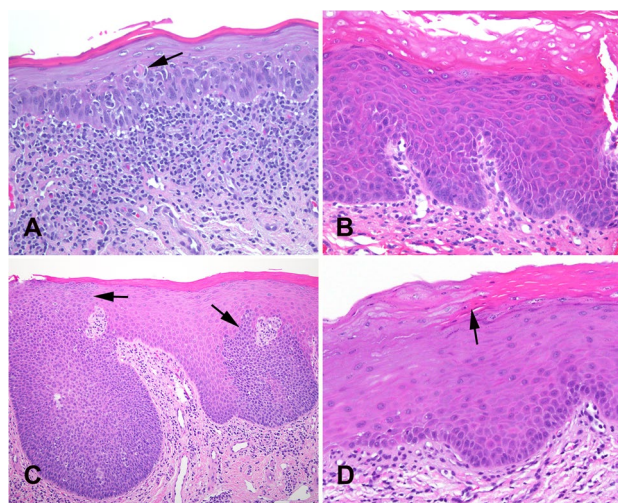
In the 5th edition, the epithelial tumor section is organized by tumor behavior with squamous carcinoma discussed last. Papillomas are presented first and are combined with condyloma acuminatum and verruca vulgaris. As previously stated, MFEH is now discussed under Non-neoplastic lesions.



**Fig. 2** Melanoacanthoma. **A** Diffuse melanin pigment affecting the attached gingiva of the maxillary central incisor. **B** Acanthotic epithelium with dendritic melanocytes (arrows) within the intercellular spaces

## Oral Potentially Malignant Disorders and Oral Epithelial Dysplasia

Oral potentially malignant disorders (OPMD) and oral epithelial dysplasia (OED) sections have been greatly expanded to reflect advances in clinical, histological, and molecular findings. Oral lichenoid lesions have been added as an OPMD [10, 11]. These are specified as lesions that may resemble oral lichen planus but lack the typical clinical or histopathological appearance. An asterisk next to smokeless tobacco keratosis has been added acknowledging that risk varies with tobacco type. Oral lichen planus is still listed as an OPMD although this was a contentious issue. Many publications have recently refined the histologic and clinical features of oral lichenoid lesions to distinguish them from oral lichen planus, but these were thought to be insufficient to remove lichen planus as an OPMD [12, 13]. Oral graft versus host disease is seen in patients receiving allogeneic stem cell transplants for hematologic malignancies, and progression to cancer has been reported [14]. Although lupus erythematosus remains listed as an OPMD it is uncertain whether the risk is solely to the lip vermilion rather than inside the oral cavity [14]. Familial cancer syndromes in addition to dyskeratosis congenita have expanded to include Fanconi anemia, xeroderma pigmentosum, Li Fraumeni syndrome, Blooms syndrome, ataxia telangiectasia and Cowden syndrome. Deletions from the OPMD table include chronic candidiasis, syphilitic glossitis, and actinic keratosis, the latter being associated with UV exposure.



**Fig. 3** Oral epithelial dysplasia. **A** Moderate dysplasia with a band-like inflammatory infiltrate at the epithelial-stromal interface imparting a lichenoid appearance but with general preservation of a slightly expanded and hyperchromatic basal cell layer. A dyskeratotic cell (arrow) is present in the spinous layer. **B** Mild dysplasia showing primarily an architectural or differentiated pattern of dysplasia with marked orthohyperkeratosis, loss of basal cell polarization, budding of rete, increased hyperchromasia, and mitotic figures confined to basal and parabasal layer. **C** Skip areas of dysplasia (arrows) indicate a clonal pattern which can be present in HPV-associated dysplasia. This case was negative for HPV16 by in situ hybridization. **D** Sharp demarcation from normal parakeratotic epithelium to orthokeratotic epithelium in mild epithelial dysplasia. The small basal cells give rise to cells with eosinophilic cytoplasm without cytologic atypia. This pattern of dysplasia is primarily an architectural pattern

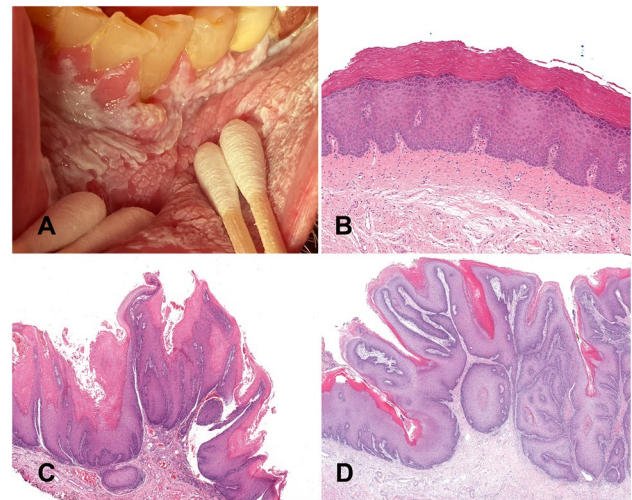
**Table 1** Modifications to the WHO diagnostic criteria for oral epithelial dysplasia

| Architectural features   | Cytological features                  |
|--|---------------------------------------|
| Irregular epithelial stratification  | Abnormal variation in nuclear size    |
| Loss of polarity of basal cells  | Abnormal variation in nuclear shape   |
| Drop-shaped rete ridges  | Abnormal variation in cell size       |
| Increased number of mitotic figures (moved to cytological features)                  | Abnormal variation in cell shape      |
| Abnormally superficial mitotic figures (now: mitoses high in epithelium)             | Increased N:C ratio                   |
| Premature keratinization in single cells (now: generalized premature keratinization) | Atypical mitotic figures              |
| Keratin pearls within rete ridges  | Increased number and size of nucleoli |
| Loss of epithelial cell cohesion   | Hyperchromasia                        |
| 2022   | Additions                             |
| Altered keratin pattern for oral sub-site  | Single cell keratinization            |
| Verrucous or papillary architecture  | Apoptotic mitoses                     |
| Extension of changes along minor gland ducts   | Increased nuclear size                |
| Sharply defined margin to changes  |                                       |
| Multiple different patterns of dysplasia   |                                       |
| Multifocal or skip lesions   |                                       |
| Expanded proliferative compartment   |                                       |
| Basal cell clustering/nesting  |                                       |

Grading of OED is a contentious issue and reaching a consensus difficult as different regions of the world apply different grading criteria. This edition expands the architectural and cytological features of OED (Table 1; Fig. 3A–D) [15–18]. A distinction between generalized premature keratinization and single cell keratinization was made. Single cell keratinization was moved to cytological features. Generalized premature keratinization refers to cells in the lower spinous layer with prominent eosinophilic cytoplasm (Fig. 3B). A three-tiered OED grading system is maintained, although it is acknowledged that defining dysplasia by thirds oversimplifies the complexity of OED [15]. There are instances when OED may be limited to the basal third and yet may qualify as severe dysplasia due to a number of cytological and architectural features. Like the last edition, a binary grading system was mentioned but this system continues to lack validation against malignant transformation [19, 20]. A lichenoid host response in OED is discussed, which is an important addition to the 2022 edition, due to the confusion this may cause with oral lichen planus. It is emphasized that the presence of any cytological or architectural features of dysplasia in the presence of a lymphohistiocytic band-like infiltrate precludes a diagnosis of oral lichen planus [12, 15]. With absent or minimal cytological features of dysplasia, OED grading is challenging. This is particularly true in papillary and verrucous lesions which is discussed in more detail below. The term carcinoma in situ in the oral cavity is not recommended and is considered synonymous with severe dysplasia.

### Proliferative Verrucous Leukoplakia

The section on proliferative verrucous leukoplakia (PVL) has been expanded to reflect the several studies that have been published since the 2017 edition. The early lesions of PVL demonstrate many of the newly added architectural features of OED including premature keratinization, sharp lateral margins, skip keratoses, and increased keratin (Table 1; Fig. 4A, B). In the presence of a band-like lymphohistiocytic infiltrate the early lesions of PVL can be misdiagnosed as oral lichen planus [12, 15, 17, 21]. Unlike lichen planus, intact basal cells at the epithelial-stroma interface and/or dysplasia is seen in PVL. Corrugated hyperortho- or parakeratotic lesions with a verrucous-papillary architecture in the absence of or with minimal cytologic atypia are typical in early PVL. This specific architectural feature is not commonly present in other oral lesions and this verrucous morphology without cytologic atypia should be considered mild dysplasia [17, 18, 21]. With disease progression, PVL can have both an exophytic or endophytic growth pattern showing a verrucous, nodular, or bulky architecture with variable dysplasia (Fig. 4C, D) [21].



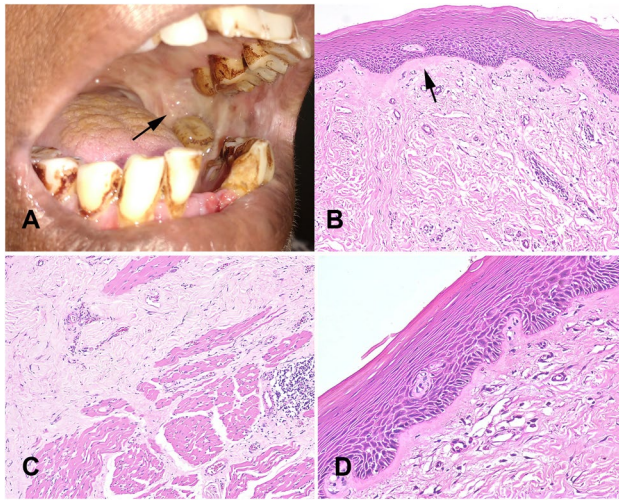
**Fig. 4** Proliferative verrucous leukoplakia. **A** An advanced case with a large area of leukoplakia involving the labial mucosa, mandibular vestibule and attached gingiva. **B** Early lesion exhibiting subtle histology with orthokeratosis, prominent granular layer, and no cytologic atypia. **C** A late stage of PVL showing acanthosis and a well-developed papillary architecture with a lichenoid immune response. **D** Bulky hyperkeratotic exophytic and endophytic growth pattern covered by parakeratin with an undulating surface and surface crypts filled with parakeratin

### Submucous Fibrosis

Oral submucous fibrosis (OSF) is a chronic, insidious disease characterized by progressive submucosal fibrosis of the oral cavity and the oropharynx with a risk of transformation to squamous cell carcinoma. OSF is added to the WHO classification for the first time allocating a separate section. It was listed in the group of Oral potential malignant disorders in the previous editions.

OSF is mostly prevalent among people in South Asia and among the Pacific Islanders. Cases are also reported in a few Southeast Asian countries and among migrants from the Indian subcontinent to Europe, USA and South and East Africa. The worldwide prevalence of OSF has been reported as 4.96% with a 95% CI=2.28–8.62 [22, 23]. Areca nut is the main etiological factor for OSF [23]. The clinical features vary according to the stage of the disease. Early cases present with burning sensation to spicy food. With the progression of the disease patients develop depapillation of the tongue, blanching, and leathery mucosa (Fig. 5A). Fibrous bands in the buccal mucosae, lip, or palate leads to progressive limitation of mouth opening [24].

Microscopically, initial lesions show mildly hyperplastic epithelium and subsequently progresses to marked atrophy with loss of rete ridges. The corium shows minimal changes at early stage including slightly increased vascularity, inflammatory infiltrate, and increased fibrillar collagen. With the progression of the disease, collagen becomes



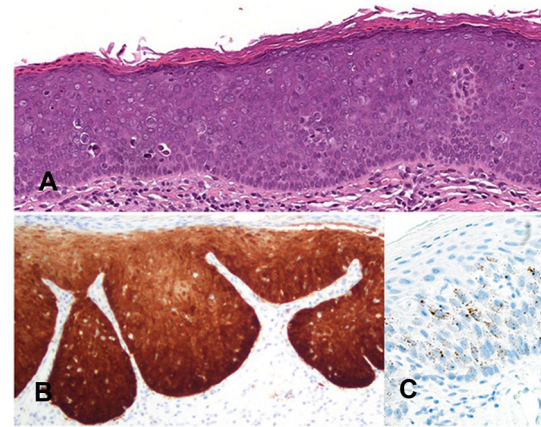
**Fig. 5** Submucous fibrosis **A**. Leathery mucosa, blanching and trismus (arrow). Teeth show betel quid staining. **B** Atrophic epithelium and dense fibrosis of the corium with juxta-epithelial hyalinization (arrow). **C** Progressive replacement of muscle by fibrous tissue. **D** Epithelial dysplasia starts to appear with budding rete morphology in the atrophic epithelium

homogeneous, starting superficially with juxta-epithelial hyalinization (Fig. 5B) [25–27]. Advanced cases show loss of vascularity with dense fibrosis extending to underlying muscle and complete replacement of muscle by fibrous tissue (Fig. 5C). Epithelial dysplasia starts to appear with progression of the disease with characteristic budding rete morphology in severely atrophic epithelium (Fig. 5D). This feature is unique to OSF. Prevalence of epithelial dysplasia varies across different studies. [28, 29]

Significant number of oral cancers in South Asia arise in the background of OSF. The malignant transformation rate is approximately 4.2% (CI 2.7–5.6%). It has been reported that cases with oral epithelial dysplasia have a higher potential for malignant transformation compared to cases without dysplasia [30]. Mechanisms of malignant transformation have been described in many studies including both genetic and epigenetic pathways. There are no established molecular predictive markers. LOH in genes within the 13 q14-q33, hypoxia, and ROS may have some predictive value for transformation [30, 31].

### HPV-Associated Dysplasia

Since the last edition there has been greater characterization of HPV-associated dysplasia (HPVOED) and due to its distinction from conventional OEDs has been classified as a separate entity. HPVOED has a strong male predilection (M:F=6:1), with a wide age range of presentation, showing a peak in the 6th decade [32–35]. The ventral/lateral tongue



**Fig. 6** HPV-associated dysplasia. **A** Epithelium with a brightly eosinophilic keratin surface and basaloid morphology showing marked architectural and cytological changes of dysplasia with karyorrhectic and apoptotic cells. **B** Full thickness diffuse and intense cytoplasmic and nuclear immunoreactivity for p16. **C** RNA in situ hybridization for high-risk HPV shows punctate dot-like nuclear and cytoplasmic staining

and floor of mouth are the most common sites, although the buccal mucosa, palate, labial mucosa, and gingiva are affected [32, 34, 36]. Presenting generally as a flat and well-demarcated white to red patch indistinguishable from other oral leukoplakias. The etiology is high risk HPV subtypes, usually HPV 16, but the pathogenesis is unclear but presumed to be comparable to HPV associated cervical dysplasia [32, 34, 36]. The histologic features of HPVOED are distinct from conventional OED. A brightly eosinophilic layer of keratin (usually parakeratin) is usually present overlying epithelial cells with a basaloid morphology with a high nuclear to cytoplasmic ratio (Fig. 6A). Koilocytes may be seen in the superficial epithelium [32, 33, 36, 37]. Karyorrhectic cells exhibiting coarse chromatin that resemble cells in mitosis (mitosoid bodies), with a peri-cellular halo are characteristic for HPVOED. Apoptotic cells with dense eosinophilic cytoplasm are also associated with HPVOED. Although HPVOED shows strong and diffuse p16 immunoreactivity, confirmation with high-risk HPV by DNA or RNA in situ hybridization is still recommended as there is insufficient validation to recommend p16 as a surrogate marker (Fig. 6B, C). Invasive squamous cell carcinoma occurs in 5% to 15% of cases [34]. No grading criteria for HPVOED has been established and it is recommended to currently grade similar to conventional OED pending further studies.

## Squamous Cell Carcinoma

The 2022 WHO section on oral squamous cell carcinoma (OSCC) has been updated to reflect current epidemiology, pathogenesis, and histological prognostic factors. The listed subtypes of OSCC are unchanged but both carcinoma cuniculatum and verrucous carcinoma are described in dedicated sections, reflecting that the oral cavity is the most common location in the head and neck for both these entities which have distinct clinical and histologic features from conventional squamous cell carcinoma.

OSCC is the 16th most common cancer worldwide accounting for more than 377,000 per year with males accounting for 70% of cases [38]. There is marked variation in incidence throughout the world with the highest estimated incidence in Melanesia and South-Central Asia [39]. The incidence of tongue cancer in persons <45 years-of age has increased worldwide, although the etiology is unclear [40]. The etiology of OSCC is primarily tobacco consumption although areca nut use is the primary carcinogen in some geographic regions [41, 42]. To date, high risk HPV while important for oropharyngeal SCC, has not been shown to be a significant etiologic factor in OSCC [43]. Most OSCC arise from pre-existing OED, however malignant transformation of OED remains poorly understood. OSCC has high mutational load and gross chromosomal changes [15, 17, 44]. Somatic mutations in several genes in OSCC have been identified including NOTCH1, KMT2D, CASP8, AJUBA, NSD1, HLA-A, and TGFBR2. With increasing chromosomal instability, the development of OSCC becomes more likely.

Most OSCC are well-differentiated, conventional keratinizing type. Tumor grade alone does not correlate well with prognosis. Adverse histological prognostic factors in OSCC include depth of invasion > 5 mm, tumor budding, perineural invasion, lymphovascular invasion, bone invasion, worst pattern of invasion 5, and stroma-tumor ratio > 50% in a deeply invasive tumor [45–50]. Positive lymph nodes, particularly those lymph nodes with extracapsular extension are also considered adverse prognostic factors.

## Verrucous Carcinoma

In past edition verrucous carcinoma (VC) was covered in the Hypopharynx, larynx, trachea, and parapharyngeal space chapter. As the presentation of VC differs in the oral cavity, and accounts for 50–75% of all VC cases in the head and neck, a section devoted to VC was added to Chapter 5 in the new edition. The buccal mucosa, gingiva, and tongue are the most frequent oral cavity sites, presenting as a slow growing exophytic tumor that can erode and destroy bone if left untreated. VC accounts for 2–16% of all OSCC and shows a male predominance presenting in the 6th decade or

later [51]. The characteristic histologic features of VC are unchanged and will not be described. VC is associated with a much better prognosis than conventional SCC with an overall 5-year survival rate of 77–86% [51, 52]. In 20% of cases VC may be a precursor to conventional OSCC. The presence of focal dysplasia in VC or invasion  $\leq 2$  mm in depth do not adversely affect outcome and should be treated as VC [53].

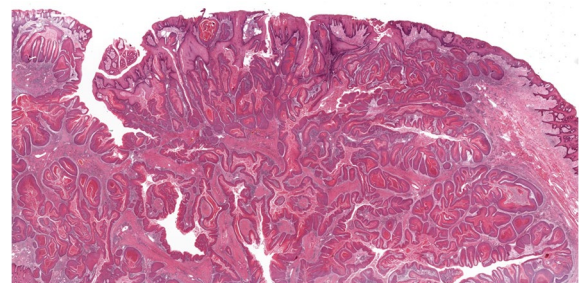
## Carcinoma Cuniculatum

Carcinoma cuniculatum (CC), a rare well-differentiated locally destructive SCC with a unique burrowing invasive pattern, now has a dedicated section in Chapter 5. CC is a non-metastasizing SCC, and most are located on the gingiva-alveolar mandible followed by the maxilla and rarely in other oral cavity sites [54]. CC has no gender predilection and most common in the 7th to 8th decades [55]. The histology of CC is characteristic, with a primarily endophytic growth pattern, but a minor exophytic component may be seen [56, 57]. The tumor consists of burrowing interconnecting keratin-filled crypts of well-differentiated SCC with no more than mild cytologic atypia (Fig. 7). Keratin microabscesses and intraepithelial and stromal neutrophils are typically present. Bone sequestrum are indicative of bone invasion [58]. Treatment of CC is complete excision and local recurrence is uncommon.

## Tumors of Uncertain Histogenesis

This section includes congenital granular cell epulis, granular cell tumor (GCT), ectomesenchymal chondromyxoid tumor (EMCT), and melanotic neuroectodermal tumor of infancy (MNTI).

In the new 2022 WHO edition the pathogenesis of GCT has been updated to reflect the molecular findings associated with the LEOPARD, Noonan syndrome and PTEN hamartoma tumor syndrome which present with multiple GCT [59,



**Fig. 7** Carcinoma cuniculatum showing the characteristic infiltrative labyrinthine network of keratin-filled crypts. Courtesy of Dr. Amrita Jay

60]. PTPN11 and PTEN mutations are not associated with sporadic GCT [61]. Overexpression of transcription factor E3 (TFE3) is observed in skin and subcutaneous lesions, but not in oral GCTs [62]. ATP6AP1, ATP6AP2 and ATP6V1A, mutations, components of the vacuolar APTase (V-ATPase) complex have been reported in GCT affecting different tissue types [63]. The histogenesis of GCT is still uncertain but a Schwann cell origin is favored. The oral cavity accounts for 70% of GCTs in the head and neck with the tongue being the most common location. The microscopic features are unchanged from the prior edition.

The 2017 WHO introduced EMCT with about 60 cases reported at that time. To date fewer than 100 cases have been reported and the anterior dorsal tongue remains the predominant site of occurrence [64, 65]. Rare occurrences include the palate and mandible. EMCT occurs over a wide age range (7 to 78 years-of age) but is most common in young adults. No gender predilection is seen. The histogenesis of EMCT is unknown but an uncommitted ectomesenchymal progenitor cell is favored. Recent molecular studies show that about 90% of EMCT have *RREB1::MKL2* fusions while a minority of EMCT have other molecular drivers, including *EWSR1* [66]. This *RREB1::MKL2* fusion is not specific to EMCT which has been reported in biphenotypic sinonasal sarcoma, mediastinal mesenchymal neoplasms, and oropharyngeal sarcoma [67]. The histology of EMCT shows diverse morphology of sheets, cords and/or reticular arrangement of spindle-stellate to polygonal cells. The intervening stroma varies including myxoid, hyaline or collagenous features. Most tumors are diffusely GFAP positive. Other immunostains show variable patchy or weak expression in EMCT including S100, actin, desmin, smooth muscle actin, myogenin CD56, CD57, keratin, and EMA [64–66].

MNTI in the 2017 WHO edition was in Chapter 8, *Odontogenic and maxillofacial bone tumours*. MNTI is not an exclusive tumor of bone, also presenting in the brain, neck, the testis, and epididymis, among other locations. Therefore, MNTI is now in Chapter 5 under Tumours of uncertain histogenesis. The pathogenesis of MNTI is still unknown but germline mutations in *CDKN2A* and *BRAF* p.V600E mutations are reported [68, 69]. Of note is that MNTI shares DNA methylation profile with high grade medulloblastoma (MB G3) but does not share in its clinical behavior [70]. MNTI, although rapidly growing and locally destructive has low grade behavior, although about 2% of MNTI behave in a malignant fashion with metastases [71].

## Other Changes

The previous edition included various neoplasms in this chapter that are now included elsewhere. Rhabdomyoma, lymphangioma, hemangioma, neural tumors and Kaposi

sarcoma are now in the *Soft Tissue Tumour* chapter. Oral mucosal melanoma now appears in the *Melanocytic Tumour* chapter. Salivary gland lesions are now included in the *Salivary gland* chapter and CD30-positive T-cell lymphoproliferative disorder, plasmablastic lymphoma, Langerhans cell histiocytosis, and extramedullary myeloid sarcoma are in the *Haematolymphoid proliferations and neoplasia* chapter.

## Conclusion

Pathology is a dynamic and rapidly evolving field and the fifth chapter of the upcoming fifth edition of the 2022 World Health Organization Classification of Tumours of the Head and Neck titled *Tumours of the oral cavity and mobile tongue* reflects this. With future discoveries, further WHO blue book updates, modifications, and reclassifications will be required. Stay tuned!

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## Declarations

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**Ethical Approval** This article does not contain any studies with human participants or animals performed by any of the authors.

**Consent to Participate** Not Applicable.

**Consent for Publication** Not Applicable.

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