Clinical Update

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8901 Wisconsin Ave
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Vol. 26, No. 10 October 2004

Oral cancer: part II

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Squamous cell carcinoma

Squamous cell carcinoma and its histologic variants account for over 90% of all malignancies of the oral cavity. Early squamous cell carcinoma often presents as a white lesion (leukoplakia), red lesion (erythroplakia), or a combination of both (erythroleukoplakia).[1,2,3,4] However, with time, superficial ulceration of the mucosal surface may develop. As the lesion grows, it may become an exophytic mass with a fungating or papillary surface architecture. Some tumors demonstrate an endophytic growth pattern that is characterized by a depressed, ulcerated surface with a raised, rolled border.[3,4] Pain is not a reliable indicator as to whether a particular lesion may be malignant and interestingly, most oral cancers will be totally asymptomatic or may be associated with only minor discomfort.

The most common site for intraoral carcinoma is the tongue, which accounts for approximately 40% of all cases in the oral cavity proper.[5] These tumors most frequently occur on the posterior lateral border and ventral surfaces of the tongue. The floor of the mouth is the second most common intraoral location. Less common sites include gingiva, buccal mucosa, and hard palate.[3] The lateral tongue and floor of mouth combine to form a horseshoe-shaped region of oral mucosa, which is at greatest risk for cancer development. Two major factors help to explain why this region is at such a high risk. First, any carcinogen may mix with saliva, pool in the floor of the mouth, and constantly bathe these anatomic sites. Second, these regions of the mouth are covered by a thin, nonkeratinized mucosa, which provides less protection from carcinogens.[6]

In addition to the oral cavity proper, squamous cell carcinomas also develop on the lip vermilion and the oropharynx. Vermillion carcinomas show a striking predilection for the lower lip, and usually occur in light-skinned individuals with a long history of solar damage. The lesion usually arises in an actinic cheilosis which is itself a premalignant condition. Actinic cheilosis is characterized by atrophy of the vermilion border which may develop dry, scaly changes. As the condition progresses, ulcerated sites may appear partially healed, only to recur at a later date. The evolving cancer slowly becomes a crusted, nontender, indurated ulcer or mass.[3]

Oropharyngeal carcinomas have a clinical appearance that is similar to cancers found in the oral cavity proper. Such tumors often arise on the lateral soft palate and tonsillar region, but also may originate from the base of the tongue. Unfortunately, such tumors are typically larger and more advanced at the time of discovery than compared to the more anteriorly located cancers of the oral cavity.[1,3] Presenting symptoms often include difficulty in swallowing (dysphagia), pain during swallowing (odynophagia), and pain referred to the ear (otalgia).

Histopathology and tumor grade

Classic microscopic histopathologic alterations observed with squamous cell carcinoma include:

- Enlarged nuclei as well as cell size
- Large and prominent nucleoli
- Increased nucleus-to-cytoplasm ratio
- Hyperchromatic (excessively dark-staining) nuclei
- Dyskeratosis (premature keratinization of cells)
- Increased and / or aberrant mitotic activity

Predicated upon the above mentioned histopathologic features, squamous cell carcinoma can then be histologically graded. Although the grade of tumor does not factor into the staging protocol, it does serve as an important adjunctive aid to the overall biologic behavior of the tumor. In general, tumors that more closely resemble their native tissue are considered to be well-differentiated and tend to have a better long term prognosis. In contrast, tumors with abundant amounts of cellular and nuclear alteration with little or no resemblance to squamous epithelium or those that lack keratin production may be classified as poorly differentiated tumors.[3] These lesions, also termed as anaplastic or high grade, have an increased propensity for regional metastasis and correlate to a poorer prognosis.

A more in depth view of histologic grading and tumor staging will be presented in Clinical Update III.

Histologic variants of squamous cell carcinoma

Verrucous carcinoma

Verrucous carcinoma is defined as a warty variant of squamous cell carcinoma characterized by a predominately exophytic overgrowth and comprises up to 10% of all oral squamous cell carcinomas.[2,3] This slow growing, low-grade tumor is classically observed on the buccal mucosa, mandibular vestibule, and mandibular gingiva presenting as a non-ulcerated, white, exophytic mass with a verruciform or papillary architecture. It is not unusual for this tumor to be clinically present for 2-3 years prior to diagnosis and involve an extensive surface area. Verrucous carcinoma is generally found in older males and has an association with the use of any type of smokeless tobacco. This tumor displays a deceptively benign histologic appearance characterized by wide, elongated and blunted rete ridges that push into the underlying connective tissue as opposed to frank infiltration.[7] The squamous epithelium is extremely well differentiated and the normal histopathologic features associated with epithelial dysplasia are absent, therefore, the histologic diagnosis of this entity can be challenging for the pathologist. Furthermore, superficial biopsies are likely to produce a diagnosis of "benign hyperkeratosis and epithelial hyperplasia." It is imperative that the clinician provide a generous biopsy specimen to include the epithelial-stromal interface for adequate histologic interpretation. Prognosis is excellent after complete surgical removal, and neck dissection is seldom indicated. Verrucous carcinoma is locally aggressive but does not appear to give origin to neck node metastasis and as such, 90% of patients are disease free after 5 years.[2,3]

Spindle cell carcinoma

Spindle cell carcinoma, also called pseudosarcoma, sarcomatoid squamous cell carcinoma, "collision" tumor, or sarcomatoid

carcinoma, is a biphasic tumor composed of squamous cell carcinoma cells and pleomorphic spindle shaped cells.[1,2,3] Unlike conventional squamous cell carcinoma, spindle cell carcinoma classically presents as a pedunculated, polypoid lesion that could initially be interpreted as a reactive lesion.[2,8] There appears to be no sex predilection with this tumor. The larynx, esophagus, and oral cavity (primarily lower lip, posterior lateral tongue, and alveolar ridges) are frequent sites of occurrence.[2,3,8] More than one third of all mucosal lesions develop as recurrences after radiotherapy for a more differentiated squamous cell carcinoma, a phenomenon known as dedifferentiation.[3] Pain and paresthesia are prominent features. The tumor has a rapid growth rate, has a tendency to metastasize early, and is typically diagnosed in a late stage (stage III-IV).[1,2,3] This tumor is characterized by a dysplastic surface mucosa with an invasive pleomorphic spindle cell component that, by light microscopy, may not be readily distinguished from a connective tissue sarcoma. Although once considered to be a true "collision" tumor, immunohistochemical and ultrastructural analysis studies support the concept that the spindle cell component is of epithelial origin with the ability to differentiate along mesenchymal tissue lines.[1,2,8] The association with a dysplastic surface epithelium also helps to support this assertion. Spindle cell carcinoma is a high-grade tumor and despite aggressive management, approximately 50% of patients die within 2 years of diagnosis.[2]

Basaloid squamous cell carcinoma

Basaloid squamous carcinoma is a rare but aggressive, high-grade variant of squamous cell carcinoma with a predilection for the hypopharynx, piriform sinus and base of tongue.[2,3,8] As the name suggests, the histopathologic features exhibit a biphasic cellular pattern of basaloid and squamous cell components in an intimate relationship. This deeply invasive tumor commonly demonstrates comedonecrosis and intercellular deposits of mucohyaline material.[2,8] Among the most common complaints at patient presentation include: neck mass, dysphagia, hoarseness, weight loss, otalgia, sore throat, cough and hemoptysis. This tumor has a high prevalence in the older population, a male predominance, and presentation at a high stage (stage III-IV).[2,3,8] Radical surgery with adjunctive radiation and chemotherapy is included in the initial management. Rapidly fatal, basaloid squamous carcinoma is associated with a high mortality rate within the first year of diagnosis.

Nasopharyngeal carcinoma

Nasopharyngeal carcinoma refers to a group of malignancies that arise from the lining epithelium of the lymphoid tissue rich nasopharynx.[3] Although relatively rare in the U.S., the rate approximates 55 cases per 100,000 in southern Chinese males.[3] Among this population who migrate to the U.S., the rate is intermediate, which seems to suggest an environmental causative agent. Suspected etiologies include viral (Epstein-Barr), genetic, and salt fish that contain potentially carcinogenic N-nitrosamines.[2,3,8] Nasopharyngeal carcinoma is notoriously difficult to diagnose in its early stages due to the anatomy of the nasopharynx and non-specific symptoms (headache, otalgia, nasal obstruction). The first sign of disease for most patients is an enlarged cervical neck mass, which represents metastatic tumor. In addition, an alarming 5-10% of patients also have distant metastases at the time of diagnosis.[3] The World Health Organization recognizes three histologic subtypes: Type I Keratinizing, Type II Non-keratinizing, and Type III Undifferentiated. Due to the anatomic inaccessibility of the nasopharynx and the usual advanced stage of disease at diagnosis, radiation therapy, usually combined with chemotherapy, is the treatment of choice. Prognosis depends on stage of disease and histologic subtype. Ironically, the keratinizing (well-differentiated) subtype is generally radioresistant while the undifferentiated subtype is more radioresponsive and is, therefore, associated with a higher 5-year survival rate.[2,3,8]

Clinical Update Part III will examine a more in depth view of histologic grading, AJCC staging overview, and treatment modalities.

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