"Catch Them before it Becomes Too Late"—Oral Cancer Detection. Report of Two Cases and Review of Diagnostic AIDS in Cancer Detection

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ABSTRACT

Most oral and oropharyngeal squamous cell carcinomas (OOSCCs) are in advanced stages at diagnosis, and treatment does not improve survival rates. Early recognition and diagnosis of OOSCCs might improve patient survival and reduce treatment-related morbidity. The purpose of this article is to create awareness among the general practitioners to recognize the premalignant and early malignant lesions and to review the different diagnostic aids for the detection of cancer.

Key words: Cancer of oropharynx, early diagnosis, precancerous conditions

INTRODUCTION

Cancer of the head and neck including all oral, laryngeal, and pharyngeal sites, is the sixth most common cancer, accounting for about 643,000 new cases annually.[1] Approximately three-quarters of oral and oropharyngeal squamous cell carcinomas (OOSCCs) occur among those living in developing countries. In Southeast Asia, OOSCCs account for 40% of all cancers compared with approximately 4% in the developed countries.[2] Five-year survival of oral cancer varies from 81% for patients with localized disease to 42% for those with regional disease and to 17% if distant metastases are present.[1]

Patients with early lesions have better chances for cure and less treatment associated morbidity, yet despite the easy accessibility of the mouth, most patients present with advanced tumors, when treatment is more difficult, more expensive and less successful compared with earlier interventions.[3] This is largely due to the fact that most advanced lesions are accompanied by extensive invasion and infiltration of important local structures leading to tongue immobility, disturbance of motor or sensory innervation, metastatic spread to lymph nodes that further reduces the chances of survival.[2]

The most logical approach to decreasing morbidity and mortality associated with oral cancer is to increase detection of suspicious oral premalignant lesions and oral malignancies at an early stage. If premalignant or potentially malignant lesions are identified early enough, malignant changes may be prevented

Case Report

altogether or at least the chances of success of the treatment at an early stage is more.[2] Early detection of oral premalignant lesions (OPLs) and early neoplastic changes may be our best and most cost-effective means to improve survival and quality of life for oral cancer patients from all socioeconomic communities.[3]

The purpose of this article is to create awareness among the general practitioners and to emphasize the importance of including comprehensive head and neck examination as a part of the general medical check-up. Here we are presenting case reports of two patients where lesion appeared innocuous but considering the associated risk factors, further investigations were carried out and lesions turned out to be dysplastic. Treatment was advised and thus the morbidity associated with the treatment of oral cancer in late stages was avoided.

CASE REPORTS

Case 1

A 53-year-old male patient reported to the outpatient department (OPD) in the Department of Oral Medicine and Radiology with complaint of pain in the floor of mouth since past 2 months. History revealed that an ulcerative lesion was present since past 6 months at the same site. Patient reported to a private practitioner where medications were prescribed—Antiinflammatory drug, antibiotics, and ointment containing linoleic acid (LA) for topical application. Patient took medication for 5 days but he did not get any relief and then reported to us. On questioning, patient revealed a history of betel quid, tobacco chewing, and bidi smoking (25 bidis/day) since past 25 years. Patient was well-built with normal posture and gait. On extra-oral examination, no significant findings were found. On intra-oral examination, an ill-defined reddish lesion was seen in the floor of mouth that was tender on palpation. [Figure 1] Considering the fact that the nonhealing red lesion is present since past 6 months and that too in the floor of mouth (high risk oval) where the chances for malignant transformation are highest, cytological examination of the scrapings from the lesion was advised. Examination revealed the presence of squamous cells with anisonucleosis, increased nuclear-cytoplasmic ratio, mild nuclear pleomorphism with hyperchromatasia along with nuclear aggregation.

Case 2

A 32-year-old female patient reported with the complaint of ulceration on the left lateral border of the tongue since past 20 days. No history of similar ulceration in the past. Patient was well-built with normal posture and gait. Extra-oral examination did not reveal anything significant. On intra-oral examination, a single ulcer was seen on the left lateral border of the tongue [Figure 2]. It was mildly tender on palpation and the margins were slightly indurated. Margins of the left first and second mandibular molars were sharp and coronoplasty was advised to remove the source of irritation. Following that, a steroid ointment was advised for topical application. On follow-up after 7 days, no significant difference was noticed. Then considering the duration and location of the lesion, biopsy was done to rule out the dysplasia. Histopathological

Figure 1: Ill-defined ulceration in the floor of mouth on left side

Figure 2: Ulcer on the lateral border of tongue

examination showed presence of atypical squqmous cells with nuclear enlargement and hyperchromasia.

DISCUSSION

The clinical concept of oral mucosal premalignancy is now more than 150 years old. The presence of epithelial dysplasia is generally accepted as one of the most important predictors of malignant development in premalignant lesions. However, epithelial dysplasias will not necessarily develop into cancer, and some may even regress.[4] There is good correlation between higher grades of dysplasia and increasing risk of cancer but less so with the lower grades.[5]

The dentist is most familiar with the normal appearance of the oral mucosa, is best equipped to examine it, and is the individual with greatest opportunity to intercept premalignant oral disease. When an abnormal lesion is found in a patient at risk for oral cancer, when an abnormality fails to respond to removal of a presumed local irritant, or when no local factor is present to account for a lesion, the dentist should not hesitate to perform a biopsy or to promptly refer the patient to a dental specialist for further investigations.[2]

The rate of visual detection of premalignant oral lesions at an early stage has remained problematic because early lesions of oral cancer and precancer are often subtle and rarely demonstrates the clinical characteristics observed in advanced cases: ulceration, induration, pain or associated cervical lymphadenopathy. Besides their clinical subtlety, premalignant lesions are highly heterogenous in their presentation and may mimic a variety of common benign or reactive conditions. Conventional oral examination (COE) may detect lesions such as a red patch, white patch but recent data suggests that some precancerous lesions may be lurking within mucosa that appears clinically normal by clinical examination alone. Therefore while COE may be useful in the discovery of some oral lesions, it does not identify all potentially premalignant lesions, nor does it accurately detect the small proportion of biologically relevant lesions that are likely to progress to cancer.[6] A variety of diagnostic aids and adjunctive techniques are available to potentially assist in the screening of healthy patients for evidence of otherwise occult cancerous change and to assess the biologic potential of clinically abnormal mucosal lesions. Conventional and advanced diagnostic aids in the early detection of oral cancer are listed in the table. But the important fact is to identify the lesions and patients where dysplasia should be suspected and subsequent investigations should be carried out to establish the diagnosis.

Techniques that contribute to the Diagnosis of Oral Cancer in addition to Conventional Oral Examination

i. Toluidine blue
ii. Light-based detection systems
   - Chemiluminescence (Vizilite plus, Microlux/DL)
   - Tissue Fluorescence Imaging (Velscope)
   - Tissue Fluorescence Spectroscopy)
iii. Cytological Techniques
   - Oral Brush Biopsy (Oral CDX)
   - Liquid-Based Cytology
iv. Molecular Analyses
   - Gene Alterations
   - Epigenetic alterations, loss of Hetrozygosity and Microsatellite instability
   - Viral genome studies
   - Proliferation index and AgNOR analysis
   - Immunohistochemical identification of tumor markers
v. Specific Blood Analysis-CEA, SCCAA, IAP, ANXA
vi. Specific Saliva analysis-IGF, MMP-2, MMP-9, TPS, IL-1B, HA3, S100P,SAT, miRNA
vii. Imaging (DPT, CT, CBCT, MRI)
viii. Optical Coherence Tomography

Conventional Intraoral examination is best accomplished with a white light source (halogen). A gloved hand and tongue blade or dental mirror can be used to retract the lips and extend the cheeks for visual examination and palpation. Use gauze wrapped around the tongue to assist with retraction and examination of the lateral borders of the tongue. The first site of spread of oral malignancy is usually to the cervical lymph nodes. Palpation of these nodes must be included as part of every comprehensive head and neck examination. Any lymph node larger than 1 cm should be noted, and the patient should be referred for further evaluation and diagnosis.[2]

Use of Toluidine blue as a diagnostic aid for the detection of oral cancer has been evaluated for decades. It provides information on lesion margins, accelerate the decision to biopsy, guide biopsy

site selection, and treatment of oral potentially malignant and malignant lesions. The sensitivity of staining reported was 72%, specificity 65%, positive predictive value 43.5%, and negative predictive value 88.9%.[7]

In a prospective study, use of Vizilite which is based on the principle of chemiluminescence, as a diagnostic marker for oral cancer reported that sensitivity is 100%, specificity is 14.2%, accuracy is 80.6%.[8] Fluorescence imaging and spectroscopy utilize the potential of tissue autofluorescence for cancer detection. The presence of cellular alterations will change the concentration of fluorophores, which will affect the scattering and absorption of light in the tissue, thus resulting in changes in color that can be observed visually. Both Fluorescence imaging and spectroscopy are excellent at distinguishing between normal and malignant tissue.[6] In a study, Velscope demonstrated a 98% sensitivity and a 100% specificity for discriminating dysplasia and cancers from normal oral mucosa, using histology as the gold standard.[9]

Cytological study of oral cells is a nonaggressive technique that is well accepted by the patient, and is therefore an attractive option for the early diagnosis of oral cancer,[10] including epithelial atypia and squamous cell carcinoma with a 90% sensitivity and a 3% specificity.[11] Molecular methods of disease diagnosis has gained importance as changes occur at the molecular level before they are seen under the microscope and before clinical changes occur. The analysis of molecular alterations is objective and tries to identify specific genetic anomalies.[10]

Immunological and biochemical alterations in the serum have been sought to help in the early diagnosis of oral cancer while serum tumor markers for OSCC have shown only moderate degrees of sensitivity for diagnosis. The diagnostic capacity of salivary analysis is based on the permanent and intimate contact between the saliva and the mucosa where the cancer evolves. Patients with OSCC have a global alteration of salivary composition.[12]

Imaging studies are frequently used to supplement the clinical evaluation and staging of the primary tumor and regional lymph nodes. Computed tomography (CT) is technique of choice to evaluate bone invasion by the tumor while magnetic resonance imaging (MRI) is more informative when evaluating the extent of soft tissue invasion, neurovascular bundle infiltration and cervical lymph node involvement. cone-beam computed tomography (CBCT) provides an alternative to CT with advantage of lower cost and lower radiation dose than CT and useful in the preoperative staging of oral cancer and in the planning of surgical resection.[12] Optical Coherence Tomography is based on low-coherence interferometry using broadband light to provide cross-sectional high-resolution subsurface tissue images. This permits *in vivo*, noninvasive imaging of the macroscopic characteristics of epithelium and subepithelial structures.[13] These adjunctive techniques can be used to increase our ability to differentiate between benign abnormalities and dysplastic/malignant changes as well as identify areas of dysplasia/early OSCC that are not visible to naked eye.

Prevention of cancer is crucial but, since it involves lifestyle decisions, can be difficult to achieve. Often it is lifestyle factors that are the most important in predisposing to cancer, such as use of tobacco, betel, alcohol or sometimes environmental and genetic factors may also play a role to varying degrees.[14] Tobacco and alcohol are considered as the main risk factors for cancer of the upper aero-digestive tract. Nondrinking smokers have two to four times the risk of developing carcinoma as abstrainers of alcohol and tobacco. Heavy drinking smokers have a risk 6–15 times greater than abstrainers. The cancer risk for alcohol is more dose related as compared for cigarettes. The data indicated that for someone who smokes and drinks, doubling the alcohol consumption leads to much greater risk of oral cancer than doubling cigarette consumption.[15] Other risk factors, for example, Syphilis, Vitamin deficiency, chronic irritation from dentures, sharp teeth, hot or spicy foods are of little relevance. The floor of mouth, ventrolateral tongue and soft palate complex (soft palate proper, lingual aspect of retromolar trigone, and anterior tonsillar pillars) are regarded as high risk sites comprising the high risk oval. Tissues at high risk sites have a thin epithelium relatively devoid of keratin and a submucosa that contains fat and glands. Unprotected by keratin or specialized structures, high risk oval may be more subject the local effect of carcinogens.

In our first patient, considering the presence of risk factors such as use of tobacco, reddish lesion

in high risk oval, patient was advised cytological examination and dysplastic changes were seen. In our second patient, considering the duration of ulcer and its unresponsiveness to removal of local irritants, further investigation was advised and it turned out to be dysplastic. We consider that in both the cases by carrying out the investigations at appropriate time, we diagnosed the presence of dysplasia at an early stage and probably saved our patients from being turned into an overt malignancy where treatment is difficult, more expensive, and less successful compared with earlier interventions.

CONCLUSION

The oral cavity and oropharynx are important areas that should be carefully inspected and palpated, particularly in tobacco and alcohol users, to evaluate for oral and oropharyngeal cancer. A red or white patch or a change in color, texture, size, contour, mobility, or function of intraoral, perioral, or extraoral tissue should arouse suspicion of the presence of malignant or premalignant lesions in these regions. Comprehensive head and neck examinations should be part of all medical and dental examinations. Primary care physicians are well suited to providing head and neck examinations and to screening for the presence of suspicious lesions. Referral for biopsy and further diagnosis might be indicated, depending on the experience of examining physicians.[3]

It must be realized that the "dentist" who detects, diagnoses, and causes a premalignant lesion to be effectively treated has essentially prevented his or her patient from developing oral cancer and has likely contributed significantly to saving that patient's life.

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