

Evidence-based Practice of Oral Pathology and Oral Medicine

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ABSTRACT

Oral pathology is the specialty area of dentistry that deals with the diagnosis and management of oral diseases and more specifically, diseases other than dental caries, periodontal disease, restorative dentistry, and orthodontic therapy. Oral medicine represents the clinical arm of oral pathology and deals with diagnosis and treatment of soft-tissue lesions, whereas oral histopathology is the specialty area that focuses on the microscopic diagnosis of soft- and hard-tissue lesions of the head and neck area. The diagnosis and treatment of oral pathologic conditions is often based on empirical decision-making and many approaches to treatment have not been well-supported by clinicopathologic studies. The need for evidence-based, scientifically documented approaches to both diagnosis and treatment is eminent. Specific diagnostic criteria are lacking for many oral diseases, and therapeutic strategies have not been assessed by the gold standard of placebo-controlled, double-blind trials. Additionally, there are scientific data in the published literature that continue to be ignored by dental practitioners who manage patients with oral pathologic conditions. In this article, specific disease entities that are commonly managed by oral pathologists and oral medicine practitioners will be discussed with recommendations for future scientific studies that can serve as a framework for evidence-based diagnostic and therapeutic approaches.

Oral and maxillofacial pathology is the specialty area of dentistry that is limited to the diagnosis of oral, head, and neck diseases. In addition, many (yet not all) oral pathologists manage and treat diseases of the oral mucosa, whereas jaw diseases are typically managed by oral and maxillofacial surgeons. In Canada, oral medicine is considered to be a separate specialty of dentistry, distinct from oral pathology, whereas in the United States, oral medicine has not attained specialty status. Nevertheless, there are many competent, dentists who practice oral medicine in the United States and have received advanced training in this area of dentistry. Additionally, other specialists also manage oral mucosal diseases, particularly periodontists.

This article will discuss evidence-based practice from two viewpoints: First, the clinicopathologic diagnosis of oral disease, and secondly, the clinical management of soft-tissue diseases of the oral cavity and perioral regions. Histopathologic diagnosis has always been considered an art and a science because many lesions do not have abso-



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CERTAINLY THERE MAY BE MORE THAN ONE OPTION AVAILABLE FOR TREATING ANY GIVEN DISEASE, AND IT IS AXIOMATIC THAT A THERAPEUTIC APPROACH THAT YIELDS A SATISFACTORY OUTCOME FOR ONE PATIENT MAY NOT BE EFFECTIVE FOR YET ANOTHER.

lute diagnostic criteria or the criteria are veiled. In yet other instances, diagnostic criteria are well-defined and substantiated. Oral and maxillofacial pathologists enter into the decision-making process every time a microscopic slide is evaluated; the ultimate diagnosis is based on cell differentiation, basic pathologic processes as seen microscopically and cytologic features of cells within a lesion. Prognostication is based upon published studies that assess lesions with identical or similar microscopic patterns in which follow-up data have disclosed outcomes that are predictable. This is particularly true concerning neoplasms. There remain many oral diseases in which diagnostic criteria are vague or overlapping and numerous publications attest to the fact that inter- and intra-rater reliability indices are low.

With regard to clinical management strategies, be they pharmacologic, surgical or psychotherapeutic, there are many approaches that are evidence-based, backed by reliable outcome data. However, there are many more that are entirely empirical and have no scientifically substantiated validity. Practitioners often select varied therapeutic approaches for the same disease entity without any standardized selection criteria. Certainly there may be more than one option available for treating any given disease, and it is axiomatic that a therapeutic approach that yields a satisfactory outcome for

one patient may not be effective for yet another. Importantly, there are very few data that address such circumstances.

Evidence-based Research in Diagnosis and Treatment of Oral Pathoses

The diseases that are diagnosed microscopically are numerous and protean. Some are quite common; others are so rare that a pathologist may render a diagnosis of such an entity only once or twice in his or her career. The rarities require anecdotal accounts since there are not enough cases to generate a compilation of statistically robust data. These rarities will not be considered here; rather, will concentrate on the more common and clinically significant disease process for which evidence-based criteria may be obtainable. **Table 1** lists the disease entities that are commonly assessed by oral and maxillofacial pathologists with indications as to whether the literature provides evidence-based diagnostic criteria or not. **Table 2** lists the diseases for which therapeutic strategies are based upon scientific data or not. Due to the scope of this communication, only four of these pathologic conditions will be discussed and documented with citations from the literature.

There have been many publications that have detailed the histopathologic criteria for head and neck tumors, defining so-called classic criteria and histologic variations that

may be encountered for a given diagnostic category. Tumors with similar histologic patterns have been grouped as case studies and long-term follow-up analyses have compared and contrasted therapeutic approaches, usually surgical, sometimes radiation therapy. Kaplan survival curves yield reliable data that compare and contrast various treatment modalities for any given tumor in a specific anatomical location. From **Table 1** it is evident that most head and neck neoplasms have been assessed in this fashion and treatment outcomes can be predicted. This data appears in a variety of publications that have been documented in the literature over the past 30 years, providing surgeons, radiotherapists, and chemotherapists with appropriate therapeutic protocols. Arguing against the evidence-base is the fact that diagnostic inter-rater and intra-rater reliability correlation analyses among pathologists, at least for some tumors, is not always robust.¹⁻⁴ In this context, the advent of immunohistochemical, IHC, marker studies has improved reliability for diagnostic accuracy for many tumors with equivocal microscopic patterns.

Another factor that bodes ill for diagnostic accuracy and reliability in pathology is nosologic designation.⁵⁻⁷ Many neoplasms have been reclassified based on new IHC findings or molecular pathobiological gene expression data, and these new classifications may

Table 1**Commonly Encountered Oral Diseases of the Oral Cavity and Jaws***Assessment of evidence-based diagnostic criteria from published data*

Disease entity	Evidence-based criteria
Salivary gland tumors	Yes
Connective tissue tumors	Yes
Epithelial tumors, benign	Yes
Epithelial tumors, malignant	Partial
Fibro-osseous lesions of the jaws	Partial
Odontogenic tumors	Yes
Odontogenic cysts	Yes
Epithelial dysplasia	No
Lichen planus/lichenoid reactions	No
Neuralgia-inducing cavitation osteonecrosis	No
Atypical facial neuralgia	No
Vesiculo-bullous and immunopathologic diseases	Partial
Infectious diseases (specific)	Yes
Reactive proliferations	Yes
Sarcomas	Partial
Metabolic diseases of genetic origin	Yes

be confusing to clinicians who have for years relied upon previously established classification schemata. A case in point is the neoplasm malignant fibrous histiocytoma. Many pathologists have recently presented research findings that deny the presence of such an entity. Many reports have detailed the features of this tumor, along with treatment outcomes, and now clinicians are told that such a tumor is nonexistent. So problems continue to surface, but for the most part, diagnosis and treatment of the vast majority of neoplasms is evidence-based.

In this communication, four diseases have been selected in which diagnostic and therapeutic criteria have been forwarded; however, sound scientific data fail to support a com-

monly accepted criterion standard. Again, referring to **Table 1**, the author would like to address oral epithelial dysplasia, lichen planus, atypical neuralgia and neuralgia-inducing cavitation necrosis of the jaws. These four entities are commonly reported in the dental and medical literature and diagnostic criteria have been established for many years. Nevertheless, there are significant pitfalls with these criteria with resultant obfuscatory features that affect sound treatment plan decision-making.

Oral Epithelial Dysplasia

Dysplasia is a histopathologic change that putatively identifies cytologic changes that are predictive for progression to carcinoma. The estab-

lished criteria for dysplasia of the oral mucosa were derived from cytopathologic changes as identified in cervical epithelial dysplasias, also referred to as cervical intraepithelial neoplasia. In the cervix, dysplasias have been graded as low, moderate, and severe. These are all preinvasive lesions with mild dysplasias showing atypical cytologic change in the lower strata of the epithelium, moderate dysplasia involving lower- and mid-spinous level atypia, severe dysplasia involving most layers of the epithelium, and carcinoma in situ affecting all layers with atypical cytologic features. These same criteria have been applied to oral dysplasias (oral intraepithelial neoplasia); however, there are conflicting data indicating that low-grade dysplasias carry a lower risk for progression to invasive squamous cancer than do high-grade lesions. In some studies, dysplastic leukoplakias have been shown to carry a higher risk for progression to invasive cancer than lesions without dysplasia.⁸ There are additional data that indicate oral dysplasias have a high risk for progression to carcinoma, however, not all dysplastic lesions follow such a course.^{9,10} Intuitively, pathologists have assumed that escalating degrees of dysplastic severity in an oral lesion portend a worse prognosis and a higher risk for cancer progression. Such a notion has recently been challenged in studies that indicate the degree of dysplasia severity does not serve as a predictor for carcinomatous transformation. Indeed, even non-dysplastic oral keratotic white lesions have been shown to undergo progression to carcinoma.^{11,12}

Recent studies have explored the use of biomarkers that target protein and gene expression within oral leuko- and erythroplakias; such markers include cyclins and other cell cycle proteins, growth factor receptors and signal transduction enzymes. The two

most important markers identified so far are ploidy analysis (i.e., DNA content assessment of biopsy material) and computerized image analysis.¹³⁻¹⁷ Abnormal DNA content, aneuploidy, has been found to be an important predictor of progression to cancer from leukoplakias while, as previously mentioned, microscopic assessment of degree of dysplasia does not. The second predictor is a compilation of nuclear morphologic parameters that are evaluated by computer image analysis yielding an index pattern that predicts progression to cancer. A clinical biomarker, the vital dye toluidine blue, has been shown in one study to predict a poor prognosis when the dye is retained in the tissues after painting the lesion.¹⁸ Further confirmatory studies are needed to substantiate these new findings, and in the future, surely other biomarkers will be identified that may prove to be of prognostic value.

What about the treatment of dysplasia? Certainly if dysplasias as a group carry a risk of progression to cancer in nearly 40 percent of cases evaluated with a mean follow-up period of five years, then wide excision should prove to be an effective approach to removal of atypical cells, abrogating progression to invasive carcinomas. Disappointingly, this has not been born out in the literature. In fact, there are studies that indicate that the progression of a precancerous lesion into cancer is the same whether a dysplastic lesion has been excised (treated) or simply subjected to a incisional biopsy without further intervention (untreated).¹² So one could reasonably take the position there is no reason to remove dysplasias since some of them will progress to cancer whether they are treated or not. Therefore, additional research is required to answer this perplexing and enigmatic outcome. Were the excised specimens assessed for

Table 2

Commonly Encountered Oral Soft-Tissue Diseases of the Oral Cavity

Assessment of evidence-based clinical therapeutic criteria from published studies

Disease entity	Evidence-based criteria
Herpes virus types I and II	Yes
Candidiasis	Yes
Leukoplakia	Partial
Oral dysplasia	No
Lichen planus	Partial
Mucous membrane pemphigoid	Yes
Pemphigus vulgaris	Yes
Allergic stomatitis	Yes
Aphthous stomatitis	No
Burning mouth syndrome	No
Atypical facial neuralgia	No
Dysgeusia	No
Proliferative verrucous leukoplakia	No
Focal epithelial hyperplasia	Yes
Connective tissue hyperplasias/reactive proliferations	Yes
Benign connective tissue neoplasms	Partial
Geographic tongue	No
Erythema migrans	No
Median rhomboid glossitis	No
Metabolic diseases	Yes

margins? Could the margins appear to be cytologically normal as assessed by the pathologist, yet still harbor genetic lesions that are not yet identifiable by current technological assays? Are there topical chemotherapeutic drugs that could be applied to tissues outside the diameter of lesional excisions that could reverse the early molecular events of neoplasia? Until these questions are addressed and analyzed, evidence-based approaches to treatment will remain lacking.

Oral Lichen Planus

Lichen planus is a common dermatologic disease that affects approximately one in 200 people.¹⁹ It is found worldwide affecting almost every ethnic group. Interestingly, when lichen planus evolves on the skin, the lesions persist for less than one year and ultimately resolve. In oral mucosa, most patients take their lichen planus to the grave. The microscopic criteria for this disease of unknown etiology are well-established and immunological studies con-

firm that the lesions are a T lymphocyte mediated response to antigens (planted antigens, contact antigens, autoantigens) in the overlying epithelium.²⁰ It has also been documented that lichen planus lesions of both skin and oral mucosa may be caused by a variety of systemically administered medications, although the vast majority of cases are idiopathic (or the clinician has been unable to identify an antigenic source).

Dental restorative materials have been documented to be a cause of lichen planus-like lesions (lichenoid) in the oral mucosa, particularly, old corroding amalgams. These lichenoid white patches have been referred to as "contact lesions" and in most, allergy skin testing has documented delayed hypersensitivity responses to mercury although other metals have been implicated less often. Removal of the old filling material results in eventual resolution of the lesions.^{21,22}

Diagnostic criteria for oral lichen planus can be blurred by more recently described pathologic processes that manifest overlapping microscopic features. Cinnamon is allergenic for some subjects, and will induce red, white, and ulcerative lesions that can mimic oral erosive lichen planus although evidence-based studies have, in fact, shown that cinnamon reactions exhibit lichenoid features, yet also contain perivascular lymphoid aggregates in the submucosal connective tissues. Poignant questioning and antigenic dietary elimination will often confirm the diagnosis.²³

Leukoplakias may also present with a histopathologic lichenoid reaction and when cytologic atypia is seen, such lesions may be referred to as lichenoid dysplasias.²⁴ Are these instances of lichen planus that are undergoing carcinomatous transformation? Or, are they precancerous leukoplakias that manifest a delayed hypersensitivity reaction to neoantigens

expressed during molecular events that lead to dysplasia? Malignant transformation among patients with lichen planus has been reported to be about 1 percent, certainly far higher than that in the general population.²⁵⁻²⁷ So, there is no clear-cut criteria to separate these two entities, if in fact they are separate.

Lastly, lichenoid lesions are commonly seen among patients who do not exhibit the classical stria of Wickham. They may be seen in isolated as well as multifocal lesions and microscopically exhibit a chronic interface lymphocytic mucositis, essentially identical to that of lichen planus. So, it is evident that a variety of lesions share microscopic and clinical features identical to, or at the least, consistent with, lichen planus. Reliable diagnostic criteria are of utmost significance, since therapy is predicated upon an accurate diagnosis. There is still much to be learned about these T cell mucositis, and as with dysplasias, biomarkers will probably play an increasingly important adjunct to diagnostic refinement.

Evidence-based studies on treatment for lichen planus have been well-documented in the literature, corticosteroids being most effective.²⁸⁻³¹ Even so, there are many patients that respond poorly or not at all to both topical and systemic steroids. Perhaps these response disparities can be attributed to the lack of aforementioned confusion over diagnostic criteria for this disease. There are publications that attest to the effectiveness of tacrolimus and cyclosporine topical or mouth rinse preparations in oral lichen planus.³²⁻³⁹ Combination multiagent therapy has not been evaluated in controlled trials.

Atypical Facial Neuralgia and Neuralgia-inducing Cavitation Osteonecrosis

Facial pain diagnosis has been an ongoing enigma. The criteria employed

for specific or typical neuralgias is well-supported by evidence-based studies.⁴⁰ Of course, facial pains are commonly subsumed under the organic pathogenetic categorization of infection/inflammation to include: dentoalveolar abscesses, periodontal abscesses, and osteomyelitis. Sialogenic, neuromuscular, TMJ arthralgic, and vasoactive pain syndromes of the head and neck also possess a discrete pattern of features that allow for a definitive diagnosis when specific clinical, imaging and microscopic characteristics are uncovered. The literature is replete with documentation of diagnostic criteria and therapeutic interventions. When none of these diagnostic criteria are evident in the facial pain patient, then by exclusion, the term "atypical facial neuralgia" is applicable.⁴¹⁻⁴⁴ In essence, patients who fall into this group represent a population of facial pain patients for which there is no pathophysiologic basis for their pain. Psychosomatic mechanisms have been touted as etiologically relevant, and some credence is provided by studies that have indicated successful response to treatment with psychotropic drugs, particularly antidepressants.

Notably, antidepressant serotonin reuptake drugs may have pain attenuating properties unrelated to psychological effects.⁴⁵ There is no extant theory that justifies a psychogenic causation, and for now, it can be assumed that a psychopathologic mechanism for atypical facial pain is merely a hypothesis.

Ratner and colleagues first implicated an organic lesional origin for atypical pain in a series of publications that proposed the pain symptoms could be attributed to gnathic intraosseous cavitations.^{46,47} He hypothesized that atypical jaw pains were due to necrotic foci in the jawbones and that surgical intervention could be curative. Furthermore,

such lesions were not evident on dental radiographs and could only be detected by injection of local anesthesia in the region of pain symptoms. If the administration of local anesthetic alleviated the pain, surgery in the area would uncover a vacant marrow space (bone hole), and curettage would relieve the pain symptoms.

This theory was further promulgated by Bouquot and colleagues who applied the appellation “neuralgia-inducing cavitation osteonecrosis” or NICO.⁴⁸⁻⁵⁰ They proceeded to corroborate Ratner’s hypothesis and also proposed that a subset of patients with NICO suffered from an underlying thrombocyte disorder.⁵¹ Additionally, histopathologic criteria for the diagnosis of NICO have been published by Bouquot et al. in which bone necrosis and accompanying microscopic changes touted to be diagnostic for NICO have been detailed.

There are others who vehemently oppose the concept of NICO.^{52,53} Surgical interventions have been reported to be ineffective and the entire conceptual framework of pathogenesis has been questioned. Herein lies an important precept in the assessment of the scientific literature. Published results from a single center, without corroboration from other clinics or laboratories should not be taken as evidence-based documentation until other centers are able to substantiate or support the findings. In the histopathologic assessment of NICO, it is noteworthy that normal edentulous jaw sites among patients without pain symptoms have never been included as a control group.

Summary

An overview of various oral pathologic entities has been reviewed with regard to extant evidence-based clinical and histopathologic criteria for diagno-

sis and decision-making for therapeutic interventional strategies. A broad spectrum of oral diseases has been evaluated in the literature (not cited here due to the restricted scope of this communication), some empirically, others using scientific methods with control groups. Many yield evidence-based criteria for accurate reliable diagnosis and yet, others show documented support for sound therapeutic strategies. Those that do not have a robust scientific basis require further sturdy, using the principals of the scientific method.

Four oral pathology/oral medicine diagnoses have been singled out for more detailed assessment since they represent either common diseases or diseases with controversial diagnostic and therapeutic criteria. Oral epithelial dysplasia is a histopathologic entity that has always been considered precancerous and is typically detected on biopsies of leukoplakias and erythroplakias. The diagnostic criteria appear to be evidence-based when distinguishing dysplasia from benign keratosis; however, gradations of dysplasia among pathologists are not reliable: neither intra- nor inter-relater reliability correlation coefficients are robustly significant. Emerging evidence teaches that molecular biomarkers are more reliable than histopathologic grading of dysplasias concerning prediction for progression from a precancerous lesion to invasive carcinoma.

Lichen planus is a common oral disease with both clinical and histopathologic criteria for diagnosis. Studies have disclosed that these criteria are not always applicable and hence, a diagnosis of “lichenoid reaction” is rendered when diagnostic criteria are not classically present. The term “chronic interface mucositis” is often applied by pathologists when the clinician does

not provide a history of classic clinical findings such as stria of Wickham. Is lichen planus a disease unto itself, or is it merely a T cell mediated hypersensitivity reaction to a plethora of as of yet unidentifiable antigens or auto-antigens? Clinically, lichen planus, as well as lichenoid reactions, respond to topical anti-inflammatory agents, yet treatment outcomes can be quite varied among a cohort of affected patients.

Facial pain syndromes include a miasma of clearly defined entities with precise diagnostic criteria in contrast to another group who suffer from vague, poorly understood symptomatology. Atypical facial pain is a “wastebasket” term for jaw pains that do not conform to a specific or classic form of facial pain such TMJ arthritis, TMJ internal derangement, stress-induced myalgia, trigeminal neuralgia, or cluster headache. The pathophysiology is poorly understood and the diagnostic criterion is one of disease entity exclusion. Many atypical facial neuralgias have been subsumed under the diagnosis of neuralgia-inducing cavitation osteonecrosis, an entity not accepted by many experts in the field. Clearly, evidence-based diagnostic criteria and therapeutic interventions require focused attention where idiopathic facial pain is concerned. Patients suffer considerably from this category of facial pain syndromes and for most, no relief has been forthcoming.

Erratum: During the writing of this manuscript, the veracity of data provided by Sudbo et al. has been called to question by the Norwegian government and by the journals in which his data was published.^{12,15-17} This offers another lesson in diligence when assessing the literature for evidence-based information and reemphasizes the necessity for evaluating data from the findings of more than one author or institution. CDA

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