Rev Estomatol. 2023; 31(1):e12306. DOI: 10.25100/re.v31i1.12306

NARRATIVE REVIEW

Immunohistochemistry in oral and maxillofacial pathology: The role and rational use of antibodies in the diagnosis of surgical lesions.

Inmunohistoquímica en patología oral y maxilofacial: El rol y uso racional de anticuerpos en el diagnóstico de lesiones quirúrgicas.

Jaime Santiago Guerrero Berrocal [1] | Jairo Alberto Bustillo Rojas [1] | Guillermo Enrique Blanco Ballesteros [2] |

OPEN ACCESS

Institutional Affiliation

[1] Pontificia Universidad Javeriana, School of Dentistry, Department of Buccal System, Division of Pathology and Buccal Surgery, Bogotá, Colombia.
[2] Universidad Estatal de Londrina, School of Dentistry, Department of Oral Medicine and Pediatric Dentistry, Division of Oral and Maxillofacial Radiology, Londrina, Brazil.

Citation:
Guerrero Berrocal J.S., Bustillo Rojas J. A., Blanco Ballesteros G.E. Immunohistochemistry in oral and maxillofacial pathology: The role and rational use of antibodies in the diagnosis of surgical lesions. *Rev Estomatol.* 2023; 31(1):e12306. DOI: 10.25100/re.v31i1.12306

Received: October 24th 2022
Evaluated: December 16th 2022
Accepted: December 25th 2022
Published: February 17th 2023

Correspondence:
Jaime Santiago Guerrero Berrocal. Address: Carrera 7 # 40 – 62, School of Dentistry, Pontificia Universidad Javeriana, Bogotá, Colombia. Email: jsguerrerodds@gmail.com

ABSTRACT

Background: Immunohistochemistry have had a huge impact on oral and maxillofacial pathology diagnosis. As a method it determines distribution and amount of certain cellular molecules via specific antigen-antibody reaction. Whereas in most cases a definitive diagnosis is achieved based on detailed hematoxylin and eosin cytomorphological analysis, along with clinical and radiological features, some challenging and equivocal neoplasms need to be further assessed with immunohistochemistry.
Objective: This article reviews and updates immunohistochemistry technique fundamentals, its role and relevance in the diagnosis of common oral and maxillofacial lesions encountered in daily practice.
Materials and methods: A literature review on the topic was carried out by searching pertinent and available papers on PubMed, ClinicalKey and Scielo platforms with no date restriction, up to 2022.
Conclusion: Immunohistochemistry is an important tool that has been integrated into conventional histopathology and provides diagnostic assistance in the interpretation of common but equivocal neoplasms.

KEYWORDS
Immunohistochemistry; antibodies; oral pathology; odontogenic cysts; odontogenic tumors; salivary gland neoplasms.

RESUMEN

Antecedentes: El uso de la inmunohistoquímica ha tenido un gran impacto en el diagnóstico de patología oral y maxilofacial. Como técnica, determina la distribución y la cantidad de ciertas moléculas celulares a través de una reacción antígeno-anticuerpo específica. Aunque en la mayoría de los casos se logra obtener un diagnóstico definitivo basado en el análisis cito morfológico con hematoxilina y eosina, junto con las características clínicas y radiológicas, algunas neoplasias microscópicamente equívocas deben evaluarse más a fondo con inmunohistoquímica.
Objetivo: Este artículo revisa los fundamentos básicos actuales de la técnica y su relevancia en el diagnóstico de algunas lesiones orales y maxilofaciales frecuentemente tratadas en la práctica clínica diaria.
Materiales y Métodos: Se realizó una búsqueda y revisión de artículos científicos relacionados con el uso immunohistoquímica en patología oral y maxilofacial en PubMed, ClinicalKey y Scielo.
Conclusión: La immunohistoquimica es una herramienta importante que ha sido integrada a la histopatología convencional y brinda asistencia diagnostica en la interpretación de neoplasias comunes pero equívocas.

PALABRAS CLAVE
Immunohistoquímica; anticuerpos; patología bucal; quistes odontogénicos; ameloblastoma; mixoma; carcinoma de células escamosas; neoplasias de las glándulas salivales.

Revista Estomatología

CLINICAL RELEVANCE

Oral and maxillofacial pathology diagnosis consist in integrating fundamental knowledge and specialized skills with experience to match the facts of a particular case to a diagnostic category. As the specialty has moved toward an era of sophistication in diagnosis, immunohistochemistry has found a role and is being used with increasing frequency as a diagnostic tool. Despite this advancement, clinicians should understand that on most occasions oral and maxillofacial pathologies are diagnosed by routine histologic sections examination alone. However, when it is coupled with immunohistochemistry it provides highly sensitive information, which is crucial for patient management.

INTRODUCTION

Oral and maxillofacial pathology (OMP) is a recognized dental specialty which deals with the nature, identification, diagnosis and management of diseases that affects the oral cavity and maxillofacial complex.[1] The procurement and provision of an accurate diagnosis of the pathologic condition is at the core of its practice. To do so, integration and correlation between the clinical history, radiographic appearance of the condition and the macroscopic and microscopic examination of the tissue sample is essential. Thus, all this information needs to be gathered by the oral and maxillofacial pathologist –or general medical pathologist– to achieve a proper diagnosis. The analysis of hematoxylin and eosin (H&E)-stained tissue sections is still the standard in OMP and hence the first step to diagnose any condition from tissue samples before considering any other staining. In most of the cases a definitive diagnosis is reached based on the microscopical features of the cells seen using H & E staining by means of a conventional light microscope. However, there are some cases in which a special protein-based technology like immunohistochemistry (IHC) is useful in the practice of the diagnostic pathologist.[2-4] The clinician –general dentist or specialist– working in the oral and maxillofacial complex should have an understanding of this technology and how it is applied in the day-to-day practice. This article outlines basic technical aspects of IHC and its relevance in the diagnosis of selected oral and maxillofacial lesions.

Immunohistochemistry essentials

One of the most incredible advances made during the last four decades in the practice of diagnostic pathology is the development and continuing refinement of immunostaining; the identification of defined proteins or antigens with specific antibodies in routinely prepared tissue sections.[5] This technique is especially helpful when a definitive diagnosis cannot be reached on the sole basis of findings in H&E sections, i.e. in cases of difficult or equivocal neoplasms, either because they look identical or exhibit variable and overlapping histological patterns or are poorly differentiated.[6,7] In any case, the pathologist is solely responsible to determine, select and request the specific protein marker or markers (antibodies) to be used for the immunohistochemical testing to confirm the diagnosis (Table 1).

Table 1. Commonly used antibodies for OMP diagnosis in our practice.

Antibody	Pathologies
Cytokeratins (CKs)	Carcinoma, AOT, CEOT, Ameloblastoma, ameloblastic carcinoma
S100	Salivary gland tumors, plemorphic adenoma, polymorphus low-grade adenocarcinoma, hyperplastic dental follicle
Actin (∝SMA)	Salivary gland tumors, adenoid cystic carcinoma, mixoma
Calretinin	Ameloblastoma
Ki-67	Carcinoma, ameloblastoma, ameloblastic carcinoma
Vimentin	Mixoma
Calponin	Salivary gland tumors, adenoid cystic carcinoma, mixoma
GFAP	Salivary gland tumors, mucoepidermoid carcinoma, adenoid cystic carcinoma, pleomorphic adenoma

The selection of the antibody or cocktail of antibodies is based on clinical history, morphological features, the basis of their tumor specificity and the likelihood that they will react with the tumor that is being analyzed[2]. e.g. it would be reasonable to use a cell proliferation marker like Ki-67 in the identification of a potential malignant odontogenic tumor; on the contrary, it would not be justified or logical the use of a specific neural marker like S100 to identify neoplastic odontogenic epithelium in a odontogenic keratocyst. Many tumors display a complex distribution of antigens, hence it is advisable to use a cocktail of antibodies in problem cases to reduce the chance of misinterpretation of results on single immunostains.

The proper manipulation and preparation of a tissue for immunohistochemical analysis to arrive at a conclusive diagnosis depends on critical steps taken by the clinician and the histotechnician. From the clinician's standpoint, more than proper surgical technique is required to facilitate the diagnosis of an oral biopsy specimen. To obtain the best possible outcome from the sent tissue is important that the clinician takes adequate care to immerse the specimen in the appropriate fixative. Fixation has a significant influence on immunostaining –as well as on conventional H & E and other special stains– since many antigens and epitopes can be altered during the process. Surgical specimens should be immediately fixed in 10% neutral buffered formalin to arrest autolysis and preserve tissue and cellular morphology.[2,8] Immersing the tissue sample in an improper "fixation" medium –still a recurrent practice in our milieu– such as tap water, distilled water, 0.9% normal saline solution or alcohol compromises immunoreactivity and the outcome of the immunohistochemical staining. From the histotechnician standpoint, once the sample has been received, following a consistent and standardized protocol –manual or automated– is critical to process and to prepare the tissue sections. This action includes paraffin embedding and sectioning, antigen retrieval to unmask the antigen epitopes that have been masked by formalin fixation so that the antibodies are able to bind; protein blocking to reduce unwanted background staining, i.e. non-specific binding sites; application of primary antibody –either polyclonal or monoclonal–, application of secondary antibody, which is usually tagged with one enzyme –peroxidase or alkaline phosphatase– and that will bind to the primary one; addition of chromogen substrate –diaminobenzidine for brown or aminoethylcarbazole for red– and finally, counterstaining –usually blue–, which provides a contrast to the chromogen and helps the pathologist to visualize the underlying tissue structure (Figure 1).[2] The use of appropriate positive and negative controls is strongly recommended to validate the results. A positive control provides evidence that the right antibody has been applied to the appropriate slide. A negative control demonstrates that the reaction visualized is due to the interaction of the antigen's epitope and the antibody.[9,10] The pathologist should interpret their results as an integral part of the IHC analysis and report.

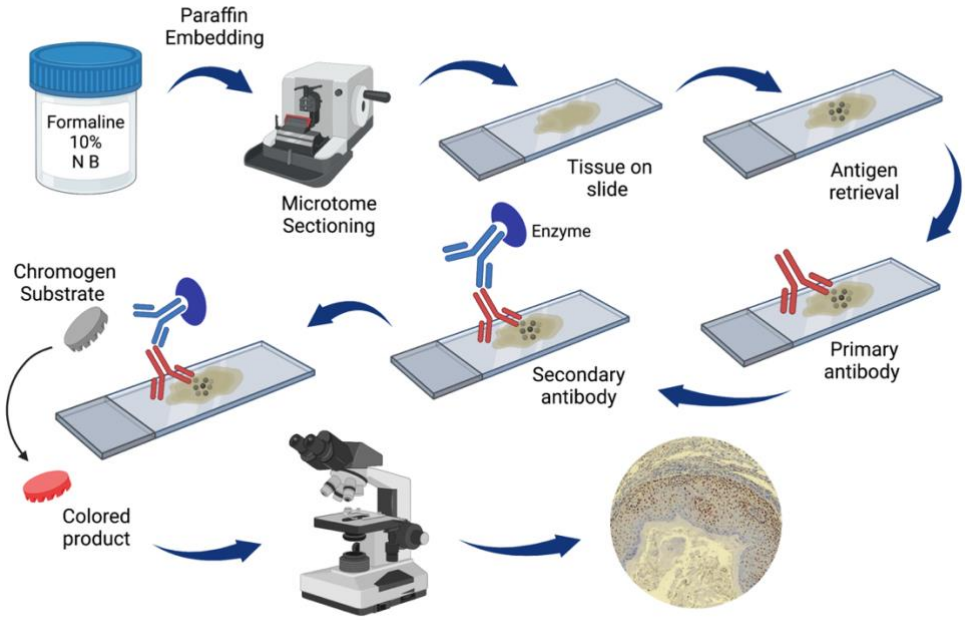

Figure 1. Illustration of indirect immunohistochemistry technique. Created with Biorender.com.

Diagnostic applications

Odontogenic Keratocyst (OKC)

Although not the most common odontogenic cyst, it is one of the most important to be recognized by the pathologist. However, currently the role of immunohistochemistry to assist in the diagnosis of OKC is of little value. This lesion possesses a combination of distinctive, almost pathognomonic histologic features –epithelial lined lumen 6 to 10 cells thick lacking rete pegs, palisaded and hyperchromatic basal cell layer and parakeratin in a corrugated alignment– that are never found in any other cyst and make the diagnosis based on H & E staining quite straightforward.[11-13]

Adenomatoid Odontogenic Tumor (AOT)

AOT is a relatively uncommon benign epithelial tumor that shows duct like structures lined by cuboidal cells and is surrounded by a well-defined capsule. Mainly, there are few diagnostic difficulties posed by AOT and up until today IHC does not seem to be useful. In some cases, the overlap between OAT and Calcifying Epithelial Odontogenic Tumor (CEOT) can raise diagnostic difficulties, yet an odontogenic ameloblast-associated protein (ODAM), expressed in CEOT but not in AOT may represent a potential useful biomarker. Similar diagnostic challenge presents in differentiating AOT from Adenoid Ameloblastoma with Dentinoid (AAD) but no immunohistochemical marker to distinguish these entities have been reported.[11,14,15]

CEOT

Also known as Pindborg tumor, represents a true but slowly growing painless tumor. The diagnosis based on histologic features is not difficult. A characteristic finding in many CEOTs is the presence of an amorphous acellular amyloid, which may be calcified and highlighted by congo red or Thioflavin-T fluorescence. If the CEOT is composed of a high proportion of clear cells the diagnosis can be challenging since it may be confused with a salivary gland tumor or a clear cell odontogenic carcinoma (CCOC). Yet, lack of patent cellular atypia, the presence of Congo-red positive and the absence of PAS-positive staining can rule out malignancy. In such a case these stains are more likely to be of help than markers such as Ki-67, S-100 and actins in its evaluation.[13-16]

Ameloblastoma, Conventional (AMC)

AMC is one of the most common epithelial odontogenic tumors and not difficult to be recognized histologically. It encompasses a number of variants and is typically composed of epithelial islands simulating the stellate reticulum with peripheral basaloid cells with reverse nuclear polarity. Although immunohistochemistry is not usually employed to assist in its diagnosis, some markers may be helpful in doubtful situations to confirm or to exclude entities that share similar histological characteristics. Expression of cytokeratin (CK) patterns have been reported in both AM and unicystic ameloblastoma (UA). CK 13 and Calretinin are expressed in stellate reticulum-like cells, whereas CK14 and CK19 in peripheral cells and in all cells respectively. Likewise, CD56 is expressed in the peripheral cells of the tumor islands in all types of AM.[11,17,18]

Ameloblastic Carcinoma (AC)

AC is the malignant counterpart of ameloblastoma and is characterized by ameloblastic epithelium that displays malignant cytopathologic features. Namely, stellate reticulum-like tissue with peripheral columnar cells with reverse nuclear polarity combined with areas undergoing high-grade transformation, such as cellular pleomorphism, increased mitotic activity, increased nuclear and cytoplasmic ratio, hyperchromatism, perineural and vascular invasion (Figure 2A). When the cytologic atypia in AC is obvious it is not difficult to differentiate it from AMC on routine H & E examination. However, AC can prove microscopic overlap with AMC and make a case challenging when the cytologic atypia and loss of ameloblastic differentiation is intermediate. In this regard, some studies support the expression of CK18 as a distinctive feature of AC compared with AMC. Moreover, the expression of SOX2, a new immunohistochemical marker and a significant Ki-67 proliferation index can support the diagnosis of AC[19-21] (Figures 2 B and C).

Odontogenic Myxoma (OM)

OM is a benign odontogenic but potentially destructive tumor characterized by stellate and spindle-shaped mesenchymal fibroblasts dispersed in an abundant myxoid extracellular matrix (Figure 3A). OM may present some histopathologic diagnostic dilemmas due to morphological overlap with a number of myxoid lesions from which it should be differentiated, especially when the origin of the lesion is out of tooth-bearing areas of the jaws. However, like with any other odontogenic lesion histological, clinical and radiographic correlation is critical to ensure proper diagnosis. There is agreement in the literature about expression of vimentin within the stellate and spindle-shaped cells (Figure 3B). It has also been found that a subpopulation of these cells express actins in some OM. Some authors have also reported positivity for CK14, CK19

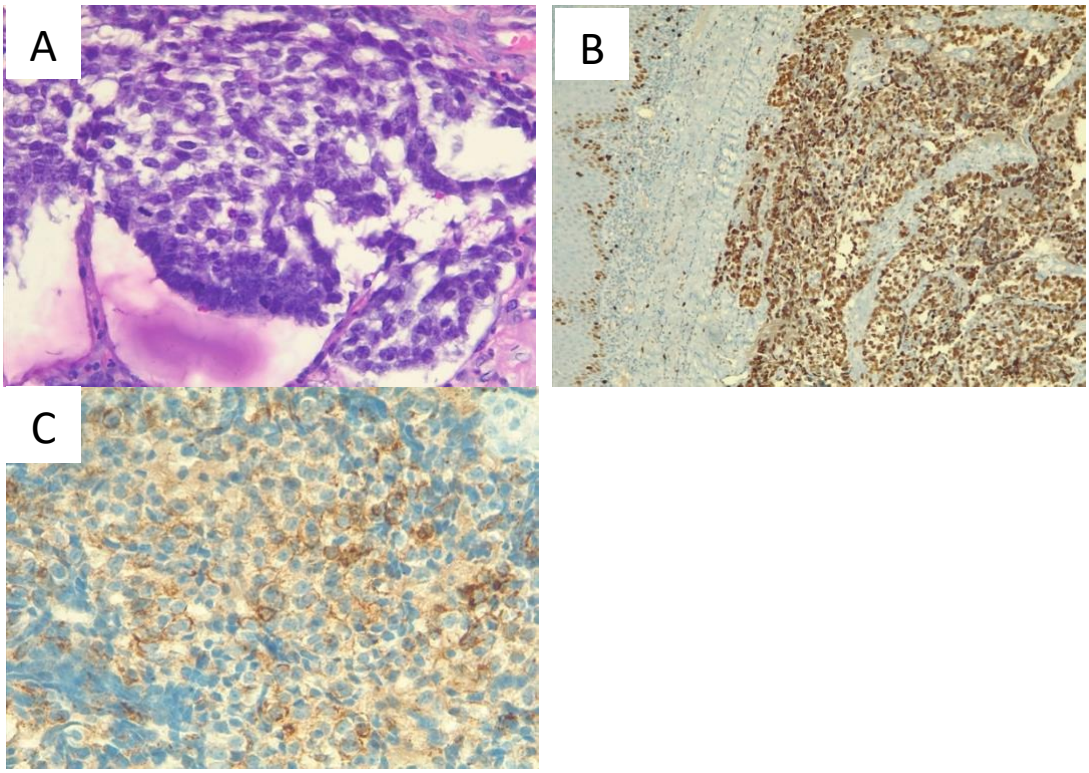

Figure 2. A) Ameloblastic carcinoma, stellate reticulum–like structure with palisaded peripheral columnar cells. Tumor cells exhibit hyperchromatism and polymorphism (H&E). B) significant expression of Ki-67, showing important proliferation activity. C) IHC positive reactivity for CAM 5.2.

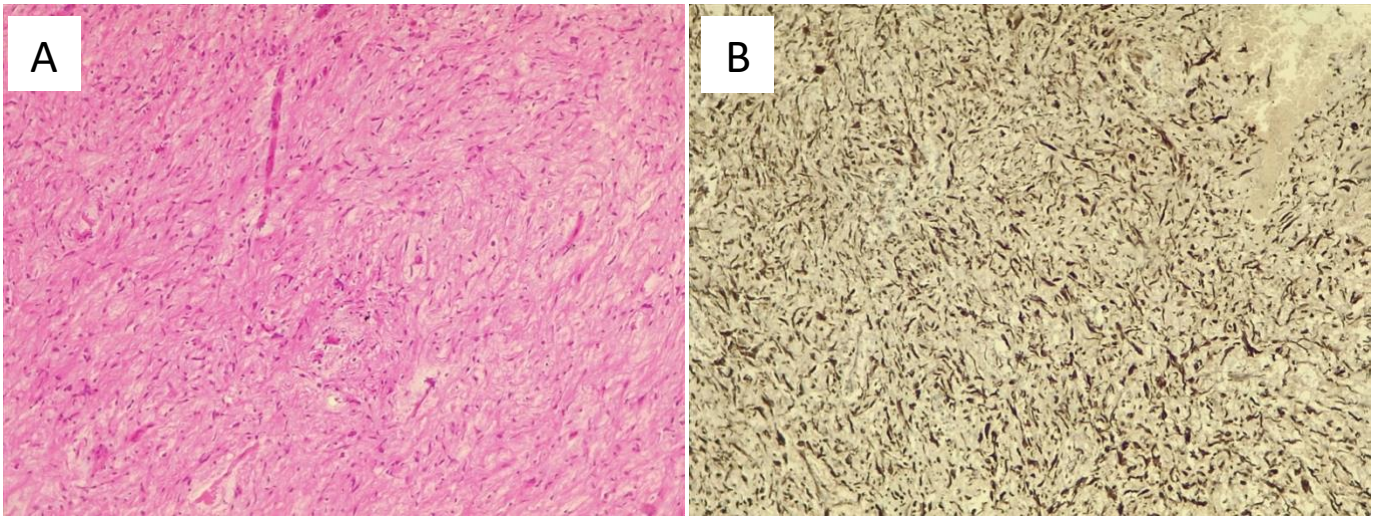

Figure 3. A) Odontogenic myxofibroma showing stellate and spindle-shaped mesenchymal cells (H&E). B) positive staining for vimentin.

and S-100 protein, yet in contrast to vimentin these findings are not reproducible enough to be of diagnostic value. The role of proliferative markers such as Bcl-2 and Ki-67 has also been studied and has been found to be insignificant. A very common misdiagnosis is to interpret a Hyperplastic Dental Follicle (HDF) as OM. Although a HDF should not be a difficult diagnosis –since it exhibits a myxoid stroma with reduced enamel epithelium–, in this regard it has been suggested that the expression of S-100 may indicate a HDF rather than a OM.[11,22-25]

Squamous Cell Carcinoma (SCC)

An epithelial malignancy arising from the squamous epithelium of the oral mucosa, characterized by sheet and cords of dysplastic epithelial cells with pleomorphic nuclei, a high nuclear to cytoplasmic ratio and some mitotic figures. These features increase with tumor grade and although the diagnosis can usually be made with routine H & E staining, in case of a poorly differentiated carcinoma IHC may be necessary to confirm an epithelial lineage (Figure 4A). Because SCC produce both high and low molecular weight Cytokeratins (CKs), it is practical to use antikeratin antibodies for this purpose. AE1/AE3 (a commercially available pan-specific cocktail of antibodies for human keratins) and CKs 5/6 are useful markers (Figures 4B and C). Other diagnostic tumor markers including p63, p40 and Ki67 are also valuable in the evaluation of undifferentiated SCC [26-30] (Figure 4D).

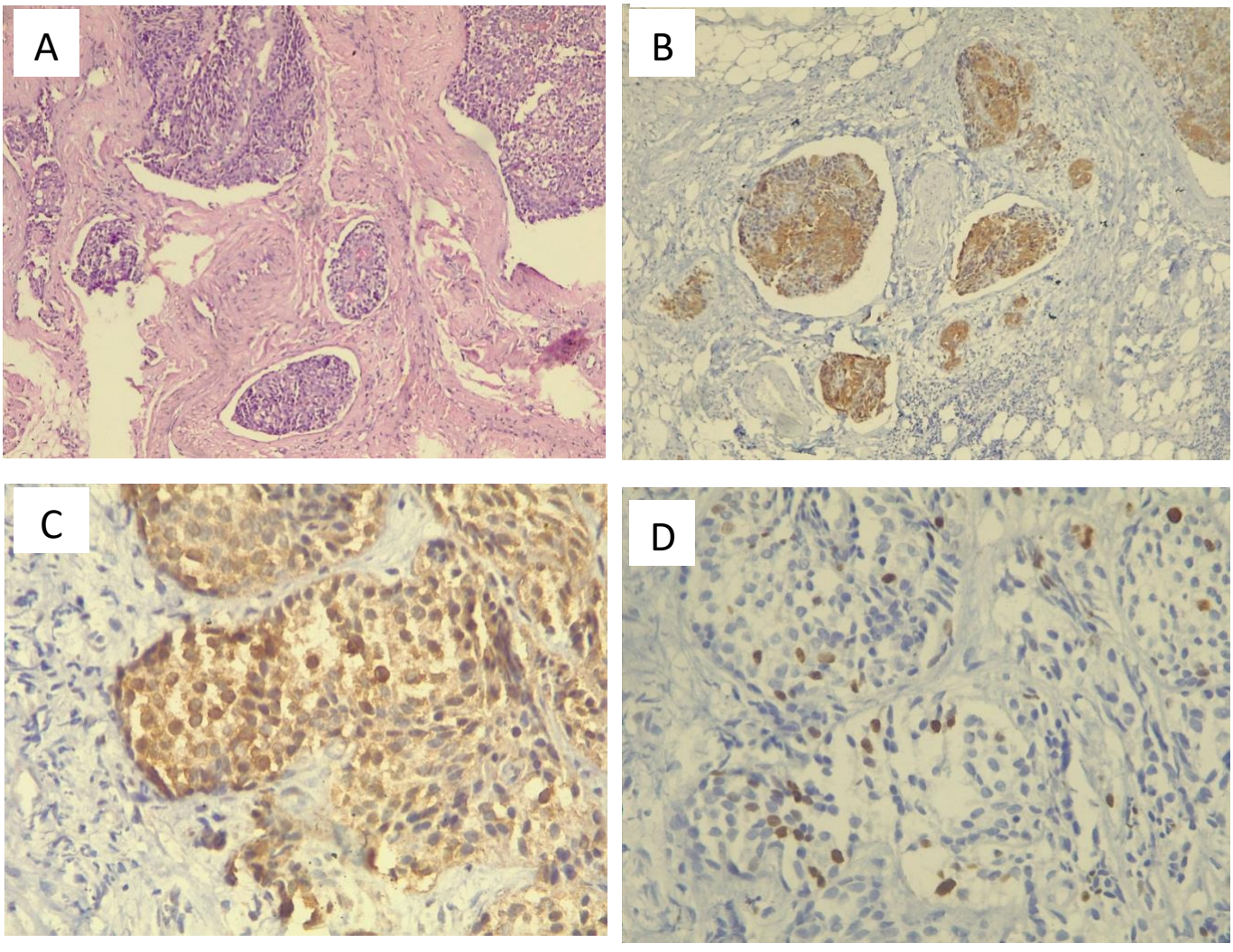

Figure 4. A) Poorly differentiated squamous cell carcinoma exhibiting lymphovascular invasion of tumoral cells (H&E). B) and C) diffuse expression of cytokeratins in malignant squamous cells. D) diffuse and scattered expression of Ki-67.

Revista Estomatología

Salivary Gland Tumors (SGT)

SGT is one of the most complex group of tumors encountered in the practice of OMP due to their extraordinary histologic diversity and capacity to resemble tumors of different origins. Because of these attributes and their tendency to overlap, the diagnosis of SGT is often challenging for the pathologist, particularly on small biopsy specimens. Nevertheless, the use of H&E-stained tissue sections is still the standard for routine SGT diagnosis and IHC plays a supplemental role in some problematic cases by differentiating between luminal (acinar and ductal) and abluminal (myoepithelial and basal) cells (Figure 5A). Markers that stain the epithelial component include low-molecular-weight CKs (e.g. CK7, CK19, CAM 5.2), epithelial membrane antigen (EMA), carcinoembryonic antigen (CAE) and IMP3 –an oncofetal protein (Figures 5 B and C). Also, c-Kit (CD117) frequently highlights luminal cells of various types of SGT. IMP3 has shown high efficacy in the diagnosis of mucoepidermoid carcinoma (MEC) and in differentiating it from PA.

c-Kit (CD117) in conjunction with smooth muscle actin (αSMA), Ki-67 and calponin has shown to be valuable markers in distinguishing adenoid cystic carcinoma (ACC) from polymorphous low-grade adenocarcinoma (PLGA). On the other hand, abluminal cells show positive staining with high-molecular-weight CKs, CD10, vimentin, p63, calponin, anti-muscle-specific actin (HHF35), αSMA, S100, Glial Fibrillar Acidic Protein (GFAP) and maspin.[24].p63 has been found to be statistically significant in diagnosing MEC and ACC (Figure 5 D). HHF35 is expressed to a greater degree in ACC than in PLGA. Conversely, S-100 is typically expressed to a greater degree in PLGA than in ACC. GFAP is of some help in separating pleomorphic adenoma (PA) from ACC and basal cell adenoma (BCA). Other important markers that have been identified for PA with IMH include PLAG1 and HMAG2, a couple of chromosomal translocations whose overexpression can help to differentiate it from ACC and carcinoma ex pleomorphic adenoma (Ca ex-PA), with high specificity.[2,31-35]

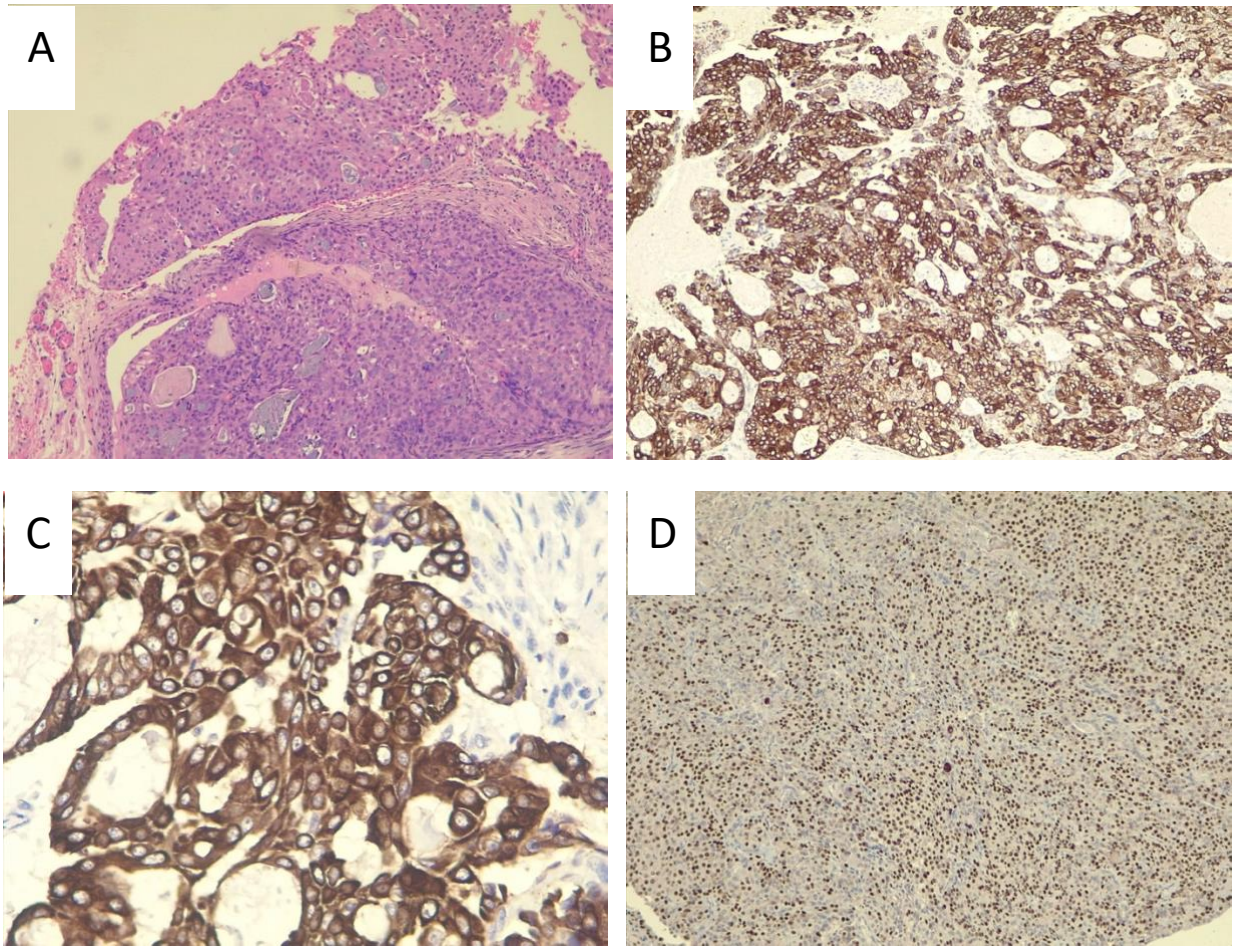

Figure 5. A) Cystic low-grade mucoepidermoid carcinoma (H&E). B) showing AE1/AE3 diffuse immunoreactivity. C) positive immunostaining of CK7. D) p63.

CONCLUSION

IMH has added a new dimension in the practice of OMP by improving the pathologist' capability of rendering an accurate diagnosis. Notwithstanding, it is critical to point out that the use of antibodies as diagnostic markers is limited to identifying some challenging neoplasms with overlapping patterns. The vast majority of oral and maxillofacial osseous and soft tissue lesions can be straightforwardly diagnosed by analyzing distinctive cytomorphological features on H & E stained slides. Clinical and radiological correlation is of paramount importance because it precludes the opportunity of providing a diagnosis founded on histologic findings alone, a practice that is not recommended. This histologic, clinical and radiological correlation entails both direct communication with the responsible clinician and possession of fundamental dentistry knowledge – especially in oral and maxillofacial radiology– and if it is not implemented the pathologist will not be able to arrive at a precise and complete diagnosis whose final report will be issued with no more than "please see microscopic description" or "findings compatible with odontogenic cyst/tumor; please correlate with the clinical and radiological features". With such equivocal information at hand, the clinician will not be able to set a proper treatment plan, which can result in either the provision of unnecessary radical surgery, thus generating avoidable esthetic and functional consequences in the patient, or conversely, the provision of under treatment, leading to persistence, recurrence or malignant transformation of the lesion.

DECLARATION OF CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

FINANCIAL FUNDING

Authors declare that this study was autofinanced.

REFERENCES

1. Jones K, Jordan RC. Patterns of second-opinion diagnosis in oral and maxillofacial pathology. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010 Jun;109(6):865-9. doi: 10.1016/j.tripleo.2009.12.023.
2. Jordan RC, Daniels TE, Greenspan JS, Regezi JA. Advanced diagnostic methods in oral and maxillofacial pathology. Part II: immunohistochemical and immunofluorescent methods. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2002 Jan;93(1):56-74. doi: 10.1067/moe.2002.119567.
3. Bilodeau E, Alawi F, Costello BJ, Prasad JL. Molecular diagnostics for head and neck pathology. Oral Maxillofac Surg Clin North Am. 2010 Feb;22(1):183-94. doi: 10.1016/j.coms.2009.10.006.
4. Jaffer S, Bleiweiss IJ. Beyond hematoxylin and eosin--the role of immunohistochemistry in surgical pathology. Cancer Invest. 2004;22(3):445-65. doi: 10.1081/cnv-200034896.
5. Miettinen M. Immunohistochemistry in oral pathology: An Adjunct Tool in Tumor Typing. Oral and Maxillofacial Surgery Clinics of North America, Volume 6, Issue 3,1994,Pages 391-400. /doi.org/10.1016/S1042-3699(20)30761-5.
6. Ajura AJ, Sumairi I, Lau SH. The use of immunohistochemistry in an oral pathology laboratory. Malays J Pathol. 2007 Dec;29(2):101-5. PMID: 19108402.
7. Araújo ALD, Fonsêca JM, do Amaral-Silva GK, de Lima Morais TM, Mariz BALA, Fonseca FP, Lopes MA, Vargas PA, Santos-Silva AR, de Almeida OP. The Role of Immunohistochemistry for Primary Oral Diagnosis in a Brazilian Oral Pathology Service. Appl Immunohistochem Mol Morphol. 2021 Nov-Dec 01;29(10):781-790. doi: 10.1097/PAI.0000000000000960.
8. Jain N. Essentials Before Sending Biopsy Specimens: A Surgeon's Prespective and Pathologists Concern. J Maxillofac Oral Surg. 2011 Dec;10(4):361-4. doi: 10.1007/s12663-011-0234-9.
9. Torlakovic EE, Nielsen S, Francis G, Garratt J, Gilks B, Goldsmith JD, Hornick JL, Hyjek E, Ibrahim M, Miller K, Petcu E, Swanson PE, Zhou X, Taylor CR, Vyberg M. Standardization of positive controls in diagnostic immunohistochemistry: recommendations from the International Ad Hoc Expert Committee. Appl Immunohistochem Mol Morphol. 2015 Jan;23(1):1-18. doi: 10.1097/PAI.0000000000000163.
10. Hewitt SM, Baskin DG, Frevert CW, Stahl WL, Rosa-Molinar E. Controls for immunohistochemistry: the Histochemical Society's standards of practice for validation of immunohistochemical assays. J Histochem Cytochem. 2014 Oct;62(10):693-7. doi: 10.1369/0022155414545224. Epub 2014 Jul 14. PMID: 25023613; PMCID: PMC4212362.
11. Hunter KD, Speight PM. The diagnostic usefulness of immunohistochemistry for odontogenic lesions. Head Neck Pathol. 2014 Dec;8(4):392-9. doi: 10.1007/s12105-014-0582-0. Epub 2014 Nov 20. PMID: 25409846; PMCID: PMC4245415.
12. Robinson RA. Diagnosing the most common odontogenic cystic and osseous lesions of the jaws for the practicing pathologist. Mod Pathol. 2017 Jan;30(s1):S96-S103. doi: 10.1038/modpathol.2016.191. PMID: 28060370.
13. Bilodeau EA, Collins BM. Odontogenic Cysts and Neoplasms. Surg Pathol Clin. 2017 Mar;10(1):177-222. doi: 10.1016/j.path.2016.10.006. Epub 2016 Dec 29. PMID: 28153133.
14. Crivelini MM, Felipini RC, Miyahara GI, de Sousa SC. Expression of odontogenic ameloblast-associated protein, amelotin, ameloblastin, and amelogenin in odontogenic tumors: immunohistochemical analysis and pathogenetic considerations. J Oral Pathol Med. 2012 Mar;41(3):272-80. doi: 10.1111/j.1600-0714.2011.01079.x. Epub 2011 Sep 21. PMID: 21936873.
15. Rai HK, Pai SM, Dayakar A, Supriya H. Adenoid ameloblastoma with dentinoid: A rare hybrid variant. J Oral Maxillofac Pathol. 2017 May-Aug;21(2):319. doi: 10.4103/jomfp.JOMFP_53_15. PMID: 28932051; PMCID: PMC5596692.
16. Chen CY, Wu CW, Wang WC, Lin LM, Chen YK. Clear-cell variant of calcifying epithelial odontogenic tumor (Pindborg tumor) in the mandible. Int J Oral Sci. 2013 Jun;5(2):115-9. doi: 10.1038/ijos.2013.29. Epub 2013 May 24. PMID: 23703711; PMCID: PMC3707072.
17. Martínez-Martínez M, Mosqueda-Taylor A, Carlos-Bregni R, Pires FR, Delgado-Azanero W, Neves-Silva R, Aldape-Barrios B, Paes-de Almeida O. Comparative histological and immunohistochemical study of ameloblastomas and ameloblastic carcinomas. Med Oral Patol Oral Cir Bucal. 2017 May 1;22(3):e324-e332. doi: 10.4317/medoral.21901. PMID: 28390135; PMCID: PMC5432081.
18. Evangelou Z, Zarachi A, Dumollard JM, Peoc'h M, Komnos I, Kastanioudakis I, Karpathiou G. Maxillary Ameloblastoma: A

19. Yoon HJ, Hong SP, Lee JI, Lee SS, Hong SD. Ameloblastic carcinoma: an analysis of 6 cases with review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009 Dec;108(6):904-13. doi: 10.1016/j.tripleo.2009.06.045. Epub 2009 Oct 2. PMID: 19800270.

20. Yoon HJ, Jo BC, Shin WJ, Cho YA, Lee JI, Hong SP, Hong SD. Comparative immunohistochemical study of ameloblastoma and ameloblastic carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011 Dec;112(6):767-76. doi: 10.1016/j.tripleo.2011.06.036. Epub 2011 Oct 19. PMID: 22014999.

21. Lei Y, Jaradat JM, Owosho A, Adebiyi KE, Lybrand KS, Neville BW, Müller S, Bilodeau EA. Evaluation of SOX2 as a potential marker for ameloblastic carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol. 2014 May;117(5):608-616.e1. doi: 10.1016/j.oooo.2014.01.017. Epub 2014 Jan 20. PMID: 24603057.

22. Kim J, Ellis GL. Dental follicular tissue: misinterpretation as odontogenic tumors. J Oral Maxillofac Surg. 1993 Jul;51(7):762-7; discussion 767-8. doi: 10.1016/s0278-2391(10)80417-3. PMID: 8509916.

23. Takahashi H, Fujita S, Okabe H. Immunohistochemical investigation in odontogenic myxoma. J Oral Pathol Med. 1991 Mar;20(3):114-9. doi: 10.1111/j.1600-0714.1991.tb00903.x. PMID: 2037972.

24. Lombardi T, Lock C, Samson J, Odell EW. S100, alpha-smooth muscle actin and cytokeratin 19 immunohistochemistry in odontogenic and soft tissue myxomas. J Clin Pathol. 1995 Aug;48(8):759-62. doi: 10.1136/jcp.48.8.759. PMID: 7560205; PMCID: PMC502805.

25. Martínez-Mata G, Mosqueda-Taylor A, Carlos-Bregni R, de Almeida OP, Contreras-Vidaurre E, Vargas PA, Cano-Valdéz AM, Domínguez-Malagón H. Odontogenic myxoma: clinico-pathological, immunohistochemical and ultrastructural findings of a multicentric series. Oral Oncol. 2008 Jun;44(6):601-7. doi: 10.1016/j.oraloncology.2007.08.009. Epub 2007 Nov 8. PMID: 17996487.

26. Morgan PR, Shirlaw PJ, Johnson NW, Leigh IM, Lane EB. Potential applications of anti-keratin antibodies in oral diagnosis. J Oral Pathol. 1987 Apr;16(4):212-22. doi: 10.1111/j.1600-0714.1987.tb02068.x. PMID: 2442335.

27. Chu PG, Weiss LM. Keratin expression in human tissues and neoplasms. Histopathology. 2002 May;40(5):403-39. doi: 10.1046/j.1365-2559.2002.01387.x. PMID: 12010363.

28. Karantza V. Keratins in health and cancer: more than mere epithelial cell markers. Oncogene. 2011 Jan 13;30(2):127-38. doi: 10.1038/onc.2010.456. Epub 2010 Oct 4. PMID: 20890307; PMCID: PMC3155291.

29. Bishop JA, Montgomery EA, Westra WH. Use of p40 and p63 immunohistochemistry and human papillomavirus testing as ancillary tools for the recognition of head and neck sarcomatoid carcinoma and its distinction from benign and malignant mesenchymal processes. Am J Surg Pathol. 2014 Feb;38(2):257-64. doi: 10.1097/PAS.0000000000000119. PMID: 24418859; PMCID: PMC4313886.

30. Li LT, Jiang G, Chen Q, Zheng JN. Ki67 is a promising molecular target in the diagnosis of cancer (review). Mol Med Rep. 2015 Mar;11(3):1566-72. doi: 10.3892/mmr.2014.2914. Epub 2014 Nov 10. PMID: 25384676.

31. Turk AT, Wenig BM. Pitfalls in the biopsy diagnosis of intraoral minor salivary gland neoplasms: diagnostic considerations and recommended approach. Adv Anat Pathol. 2014 Jan;21(1):1-11. doi: 10.1097/PAP.0000000000000000. PMID: 24316905.

32. Iyer J, Hariharan A, Cao UMN, Mai CTT, Wang A, Khayambashi P, Nguyen BH, Safi L, Tran SD. An Overview on the Histogenesis and Morphogenesis of Salivary Gland Neoplasms and Evolving Diagnostic Approaches. Cancers (Basel). 2021 Aug 3;13(15):3910. doi: 10.3390/cancers13153910. PMID: 34359811; PMCID: PMC8345412.

33. Ibrahim TR, Ahmed MM, Hegazy AA. Diagnostic Utility of Immunohistochemical Expressions of IMP3 Versus DOG1 and p63 in Salivary Gland Tumors. Turk Patoloji Derg. 2020;36(3):227-236. English. doi: 10.5146/tjpath.2020.01496. PMID: 32692399.

34. Cheuk W, Chan JK. Advances in salivary gland pathology. Histopathology. 2007 Jul;51(1):1-20. doi: 10.1111/j.1365-2559.2007.02719.x. Epub 2007 May 31. PMID: 17539914.

35. Chitturi RT, Veeravarmal V, Nirmal RM, Reddy BV. Myoepithelial Cells (MEC) of the Salivary Glands in Health and Tumours. J Clin Diagn Res. 2015 Mar;9(3):ZE14-8. doi: 10.7860/JCDR/2015/11372.5707. Epub 2015 Mar 1. PMID: 25954719; PMCID: PMC4413169.