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Carcinomas indiferenciados de glándula salival: Nuevos conceptos en la clasificación y el diagnóstico

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Undifferentiated carcinomas of the salivary gland are uncommon malignant epithelial neoplasms that lack histomorphological features of either glandular or epidermoid differentiation and cannot be characterized as any other type of salivary gland carcinoma. They are sometimes difficult to recognize as epithelial neoplasms, based only on light microscopic evaluation.
A broad definition of undifferentiated carcinoma includes three types: neuroendocrine high-grade carcinoma, lymphoepithelial carcinoma and large cell undifferentiated carcinoma.

Neuroendocrine high-grade carcinoma

Neuroendocrine high-grade carcinoma of the salivary glands is a malignant tumor composed of cells undifferentiated by light microscopy, but it shows neuroendocrine differentiation, when immunohistochemical or ultrastructural studies are used. This tumor usually occurs in the fifth through the seventh decades of life (mean age 56 years; range 5 to 86 years), with a higher incidence in men than women (1-4). Over 80 percent of cases arise in the parotid gland (1, 2); in some series, also the submandibular gland is equally involved (3).
This neoplasm shows the same histological characteristics of a small cell carcinoma or large cell neuroendocrine carcinoma of other sites. The neoplastic cells are small, intermediate or large sized with large, hyperchromatic nuclei and scant or moderately large cytoplasm. Frequent mitotic figures and necrosis can be seen. Focal ductal differentiation in some tumors, suggesting salivary gland duct origin has been reported (3).
To perform a proper diagnosis of this entity, cytokeratins and at least one neuroendocrine marker should be expressed (4,5). Most salivary gland small cell carcinomas express CK20 and are negative for CK7, but also some CK20-negative cases have been reported (5,6). Due to these immunohistochemical properties the salivary gland small cell carcinomas have been considered to be closely related biologically to Merkel cell (cutaneous neuroendocrine) carcinoma. Indeed a better prognosis of these tumors in comparison with those of pulmonary or gastrointestinal origin has also been observed (5). To perform the diagnosis of primary small cell carcinomas of salivary glands first of all a metastasis both from pulmonary and intestinal small cell carcinoma and from cutaneous Merkel cell carcinoma must be ruled out. The latter has a special tendency to metastasize to the parotid gland (6).

Lymphoepithelial carcinoma

Lymphoepithelial carcinoma (LEC) is a distinctive large cell undifferentiated carcinoma in which malignant epithelial cells are accompanied by a dense lymphoid inflammatory component. It must be distinguished from undifferentiated carcinoma with an inflammatory response, because it has ethnic, geographical predilections, a frequent association with the Epstein-Barr virus (EBV) infection and different clinico-pathological characteristics (1,2-7,8).

Most of the cases have been reported in Eskimos/Inuits of Greenland, Canada and Alaska, as well as in Asians from southeastern China and Japan. Actually, the Inuit population presents the highest worldwide incidence of malignant salivary gland tumours with the majority represented by LEC (2). However, EBV- associated LEC in non-endemic areas affecting Caucasian population have been described (9,10). Some cases develop from a pre-existent benign lymphoepithelial lesion (myoepithelial sialadenitis), and for this reason salivary gland LEC has been also called "malignant lymphoepithelial lesion". However, even in these cases developed from a benign lymphoepithelial lesion EBV has been detected (9,10).

The patients have a median age of 40 years, with a wide age range (10-86 years). Over 80% of LECs of salivary gland arise in the parotid, and the rest in the submandibular (1,2).

Histologically, the tumour usually have a lobular pattern, at a low magnification, There is a prominent, dense lymphocyte infiltration and malignant epithelial cells are often inconspicuous. Germinal lymphoid centers are often identified. At a higher magnification, irregular-shaped groups of large, polygonal cells are more obvious within the lymphocyte-rich stroma. The malignant epithelial cells are arranged in small nests, cords, trabeculae, syncitial masses or isolated cells, resembling EBV- associated nasopharyngeal LEC. The undifferentiated cells can be polygonal or slightly spindle. The cytoplasm is usually wide and nuclei atypical, vesicular, often with one or more nucleoli. The mitotic index is variable. The lymphoid infiltrate is a mixture of B and T cells, and plasma cells are also present. Sometimes, benign lymphoepithelial lesions are identified.

To detect EBV infection in LEC, the most sensitive method is in situ hybridization for EBV-encoded RNA1 (EBER), as transcripts of EBERs are abundant in latent EBV infected cells. However, the immunohistochemical reaction for EBV latent membrane protein (LMP1) is less consistent (11).

About 40% of patients have metastases to cervical lymph nodes, and 20% develop distant metastases. However, when treated with surgery, cervical lymph node dissection and radiotherapy the five-year survival rate is 75-86% (1,2) . Those tumour developed from lymphoepithelial lesion have a better prognosis.

Large cell undifferentiated carcinoma

Large cell undifferentiated carcinoma (LUC) of salivary gland is histologically similar to undifferentiated carcinomas that can arise in other organs and tissues.

The vast majority of LUC of the salivary gland occur in the parotid gland, but rarely in the submandibular gland (1,2).

This neoplasm affects elderly patients (peak incidence in the seventh and eighth decades), with a slightly higher frequency in men than in women. The tumour present a rapid growth, infiltrates surrounding tissues and metastases to cervical lymph nodes are frequently detected at diagnosis (7,8).

Histologically it is composed of large epithelial cells measuring 30 □m or more, with abundant cytoplasm and atypical, sometimes markedly pleomorphic nuclei which can have prominent nucleoli. Some smaller cells can be seen between the large ones.

Keratinization, glandular structures, myopepithelial differentiation are absent. The cells form sheets, nests or trabecular cords, with variable amounts of stroma. Inflammatory response predominantly by lymphocytes or plasma cells can be seen.
Radical surgery, neck dissection and postoperative radiation therapy seem to be the best therapeutic option. Some cases have shown good response to additional chemotherapy. However, this tumour type usually behaves aggressively in spite of treatment.
Undifferentiated carcinoma can also be the dedifferentiated component of other common salivary gland tumors, such as acinic cell carcinoma or adenoid-cystic carcinoma.
A balanced chromosomal translocation, t(15,19), resulting in the *BRD4-NUT* oncogene has been detected in recent years in carcinomas affecting midline anatomic structures of the head and neck. Rare undifferentiated or poorly differentiated carcinomas in parotid or submandibular glands with *NUT*- rearrangement have been reported. These tumours characteristically affect younger patients and the tumours are very aggressive, with resistance to chemo or radiotherapy (12, 13).

Differential diagnosis

To perform the diagnosis of primary undifferentiated carcinomas, first of all a metastasis from an undifferentiated carcinoma, originating in upper respiratory tract, lung, nasopharynx or skin must be ruled out. Moreover, the differential diagnosis includes other primary salivary gland tumors, such as basal cell adenocarcinoma, adenoid-cystic carcinoma with solid pattern and myoepithelial carcinoma. Salivary gland infiltration from a non-Hodgkin lymphoma and metastases of a malignant melanoma or a basaloid squamous cell carcinoma have also to be considered in the differential diagnosis.

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APLICACIÓN PRÁCTICA DE LA INMUNOHISTOQUÍMICA EN LOS TUMORES DE GLÁNDULAS SALIVARES

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El diagnóstico de los tumores de glándulas salivares se basan fundamentalmente en la hematoxilina-eosina. Siendo los estudio inmunohistoquímicos de ayuda escasa, en general.

Las aplicaciones más útiles de la inmnohistoquímica son:

1) ESTABLECIMIENTO DE LA DIFERENCIACIÓN CELULAR:

La presencia en un tumor de diferenciación ductal únicamente o ductal y mioepitelial permite separar los tumores salivares en dos amplios grupos, facilitando el diagnóstico en casos problemáticos.

1.a) DIFERENCIACIÓN DUCTAL-ACINAR:

Ductal: EMA, CEA

Acinar: LIsocima, A-1-AT, A-1-AQT, alfa-amilasa, DOG-1 (más reciente)

1.b) **Mioepitelial:** Calponina, actina músculo liso especifica, son muy específicos y sensibles.

Otros: Actina músculo específico (HHF-35), S-100, Vicentina, p63, Queratina 14, PFGA, Cadena pesada de la miosina muscular lisa, CD10, maspina, H-Caldesmón.

Más recientes: Podoplasmina (D2-40), WT1

1.c) **Oncocitos:** Ac.antimitocondrial

Células sebáceas: Adipofilina, EMA (patrón en burbujas).

2) DIAGNÓSTICO DIFERENCIAL DE TUMORES DE ASPECTO SIMILAR:

De utilidad puntual.

Como ejemplos: Carcinoma de células claras: Metástasis de carcinoma renal de células claras y melanoma (CD10, RCC, MelanA)

Mioepitelioma vs carcinoma mioepitelial (más o menos del 10% de Ki-67)

3) CARCINOMA INDIFERENCIADO SALIVAR VS LINFOMA:

Como en otros lugares: positividad para queratinas y negatividad para CD45 en carcinoma y a la inversa en linfomas. A veces hay diferenciación neuroendocrina (CD56, Sinaptofisina, Cromogranina). En casos de carcinoma linfoepitelial presencia de virus de Epstein Barr (EBER mediante hibridación “in situ”).

4) DIAGNÓSTICO DE TUMORES ESPECÍFICOS DE GLÁNDULA SALIVAR:

Estos datos han de tomarse con precaución ya que faltan estudio amplios sobre todos los tipos tumorales.

- Adenoma pleomorfo: Presencia de PLAG1.
- Carcinoma adenoide quístico: Myb, CD117 (poco específico).
- Carcinoma de ductos salivares: GCDFP-15, receptor de andrógenos, CerbB-2 (HER2/neu).

5) EVALUACIÓN DE MALIGNIDAD Y FACTORES PRONÓSTICOS:

- Ki67 (MIB-1), con puntos de corte en 5% o en 10% según los tumores. Hay datos discordantes.
- PCNA.
- p53
- HER2/neu.

Ahora mismo se han publicado gran número de estudios con diversos factores pronósticos, algunos con posible utilidad terapeútica (EGFR, otra,) pero todavía se necesita mayor experiencia y casuística para valorar su utilidad real en la práctica.

En cuanto al virus HPV su prevalencia es escasa en estos tumores.

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PSEUDOTUMOR INFLAMATORIO DE ORBITA. NUEVOS CONCEPTOS

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El seudotumor inflamatorio de órbita (STIO), también conocido como inflamación idiopática de la órbita, es una entidad relativamente frecuente y bien conocida desde el punto de vista clínico, que fue descrita por el oftalmólogo alemán Birch-Hirschfeld en 1905.

Clásicamente se define como un proceso no tumoral, de etiología desconocida, que afecta primariamente la órbita, en el que no se puede encontrar ninguna causa sistémica o local. Es la causa más frecuente de masa orbitaria dolorosa en el adulto y la tercera enfermedad orbitaria en frecuencia, después de la orbitopatía tiroidea y los procesos linfoproliferativos, supone aproximadamente el 10% de todas masas orbitarias.

PTIO es un diagnóstico de exclusión, basado en una combinación de datos clínicos, radiológicos y en algunos casos histológicos. El proceso puede estar confinado en una sola estructura orbitaria, pero frecuentemente afecta diferentes estructuras así como la grasa orbitaria. La edad media de los pacientes está en la quinta década pero PTIO puede darse a cualquier edad. Se suele presentar de forma aguda, pero también hay formas crónicas. La mayoría de los casos tienen una respuesta muy favorable a los corticoides y no precisan biopsia, ésta se utiliza cuando no se logra dicha respuesta y en los casos en que se plantea diagnóstico diferencial con otras masas orbitarias.

Histológicamente se trata de un proceso inflamatorio con infiltrado compuesto por linfocitos pequeños, histiocitos, escasos eosinófilos y abundantes células plasmáticas entremezclados con grados variables de fibrosis.

En años recientes se ha ido reconociendo la denominada “enfermedad relacionada con IgG4”. Descrita primero en el páncreas (pancreatitis autoinmune), se trata de un proceso inflamatorio con una base inmunitaria, que se encuentra implicado en numerosas enfermedades que afectan virtualmente cualquier órgano. Las glándulas salivales, vía biliar, tiroides, pulmón, retroperitoneo, vías urinarias, riñón, son algunas de las localizaciones mejor conocidas. Recientes publicaciones han demostrado que un número considerable de STIO se asocia a la enfermedad relacionada con IgG4.

Los mecanismos patogénicos responsables de las anomalías inmunológicas que ocurren en esta enfermedad permanecen sin aclarar. Los anticuerpos IgG4 son moléculas dinámicas con funciones inmunológicas muy complejas.

El diagnóstico de la enfermedad se basa en la demostración de una elevación importante de la IgG4 en el suero (>135mg/dl) de los enfermos, o bien de un porcentaje elevado de células plasmáticas en los tejidos afectados (>40% de células plasmáticas positivas para IgG4). La enfermedad relacionada con IgG4 responde en general bien al tratamiento con corticoides aunque algunos pacientes se hacen resistentes y necesitan terapias alternativas como metotrexato. Se han descrito algunos casos de respuestas muy favorables con rituximab en casos de afectación ocular.

En el hospital Ramón y Cajal se registraron 176 casos de patología orbitaria quirúrgica en los últimos 10 años. Doce de estos casos correspondían a PTIO y en 6 de ellos se pudo demostrar por IHQ una proporción elevada de células plasmáticas IgG4 en el tejido, lo que los vincula con la mencionada enfermedad.

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Lesiones Precursoras del Carcinoma Escamoso de Cabeza y Cuello

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In 1995, the seminal book “Epithelial Hyperplastic Lesions of the Larynx”, by Kambic, and Gale (1) made known the Ljubljana Classification (LC). Ever since then, the LC has progressively gained in acceptance, being recognized in 2005 by the WHO (2) and presented as the most reliable standard for grading precursors of HNSCC (3, 4). The histopathological features of the LC have been well documented (5, 6) and are categorized as follows: Simple hyperplasia (SH), basal – parabasal cell hyperplasia (BPCH), atypical hyperplasia (AH) and carcinoma in situ (CIS).

Simple Hyperplasia

SH shows one single layer of basal cells and an increased number of the layers of keratinocytes.

Basal-parabasal Cell Hyperplasia

BPCH is characterized by piling-up of benign basal cells at the parabasal and higher layers.

Atypical Hyperplasia

AH “true risky epithelium” shows significant nuclear atypia of keratinocytes at different layers. CIS is characterized by marked cytological atypia in the practical full thickness of the squamous epithelium. At the molecular level, the studies performed by the Ljubljana group early in this decade (7, 8), demonstrated that the index of reactivation of the catalytic subunit of telomerase hTERT, followed a pattern of progression that matched the LC grading system. Statistical analysis revealed significant differences at the level of AH as compared with BPCH. The group has recently completed its studies over 1200 patients, covering a period of 25 years, proving that 9.5% of patients with

AH progressed to SCC, while only 1.1% of the patients with SH/BPCH did, strongly justifying the predictive value of the LC (9).

Carcinoma in situ

The term carcinoma in situ (CIS) is reserved for lesions showing the features of carcinoma without invasion. In CIS, as in AH, the lesion may show a spinous cell type or a basal cell type.

From the diagnostic point of view, the key innovative contribution of the LC is the recognition of the histopathological features of BPCH and its clear cut separation from atypical hyperplasia. The precise identification of BPCH is of uppermost relevance to avoid over-diagnosis and potential unnecessary treatment of patients with precursor lesions. The main problem when comparing the dysplasia and the squamous intraepithelial neoplasia (SIN) systems with the LC grading, is the lack of recognition by the former two of BPCH, as proposed by the WHO in 2005 (2). BPCH is a benign lesion that neither biologically nor histologically matches with the concepts of mild dysplasia or SIN1 (2), since mild dysplasia and SIN1 represent the lower grade of a premalignant lesion. Already in 1995, the nuclear accumulation of p53 in low-grade dysplasia lesions was reported within a range similar to other frankly benign lesions; in contrast, high-grade dysplasia, which equates atypical hyperplasia, presented a significantly higher p53 nuclear accumulation, which was quite similar to that of SCC (10). Mitochondrial DNA content increase, used as a measure of progression in HNSCC, showed at the step of mild dysplasia a ratio similar to that of normal mucosa; it was minimally increased in moderate dysplasia and it was twice as high in severe dysplasia (11). Luckily enough, good agreement exists on the most advanced steps of both grading systems; as AH or “risky epithelium” of the LC, bears analogy to moderate and severe dysplasia, as well as CIS has similar significance in both systems.

It is our view that the controversy of the last years between the advocates of the LC and those in favour of the dysplasia system may be quite soon a matter of the past. The LC will prove its better predictive value for grading lesions developing in heavy cigarette smokers and alcohol drinkers, as postulated in 1999 by Hellquist et al (5). At the same time, the dysplasia and SIN systems, whose criteria for grading head and neck precursors of HNSCC follow steps similar to those used by the WHO in 2003 for the uterine cervix (12), will keep its indisputable value for grading intraepithelial precursor lesions related to the recently identified epidemic of HNSCC associated with high-risk HPV infections (13). The progress made, over the last years, on the molecular biology of HNSCC are supportive of this view (14).

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