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CLEAR CELL RENAL CELL CARCINOMA METASTASIC TO THE SUBMAXILLARY GLAND, A RARE EVENT: CASE REPORT AND LITERATURE REVIEW.

Metástasis de carcinoma renal de células claras a la glándula submaxilar, un raro evento. Reporte de un caso y revisión de la literatura.

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Introduction

Clear cell renal cell carcinoma (CCRCC) represents the most common renal epithelial malignant neoplasms, accounting for 65-70 % of all renal carcinomas[1]. Metastases are most frequently hematogenous, to lung, bone, liver, central nervous system (CNS) etc. Lymphatic way to hilar, aortic and cavil lymph nodes is less common[2,3]. Head and neck metastasis represent 8-15% while salivary gland metastasis involvement is rare, accounting for 3-5 %, of the cases, being the submaxillary gland affected in 1%[2,4,5,6].

Keywords. Submaxillary, Clear cell renal cell carcinoma, Clear cell carcinoma metastasis.

Case report

A 73-year-old man presenting with because of asthenia, weight loss, and hard nodule in the site of the right submaxillary gland. He had a medical history of right radical nephrectomy for clear cell renal carcinoma 13 years before. It was a tumor of 4.3 cm, nuclear WHO grade II, with acinar and tubular pattern, without invasion of renal vein, limited to the kidney and with all margins negative for invasive carcinoma.

Two years earlier, the patient was treated with radiotherapy and Cetuximab for a high-grade pharyngeal intraepithelial neoplasia that affected the left tonsillar region, pharynx, and base of the tongue.

In his medical history he had also a poorly differentiated prostate adenocarcinoma, Gleason 8 (3 + 5), 7 years before. It was treated with radiotherapy and hormone therapy.

The patient underwent a right submaxillectomy. Pathological examination revealed a submandibular gland composed of multiple acini and ducts with chronic sialadenitis and a nodule that is composed of a neoplasm replaced by a neoplasm formed by compact nests and sheets of cells with clear cytoplasm and distinct membrane and network of arborizing small, thin-walled vessels. (Figure 1).

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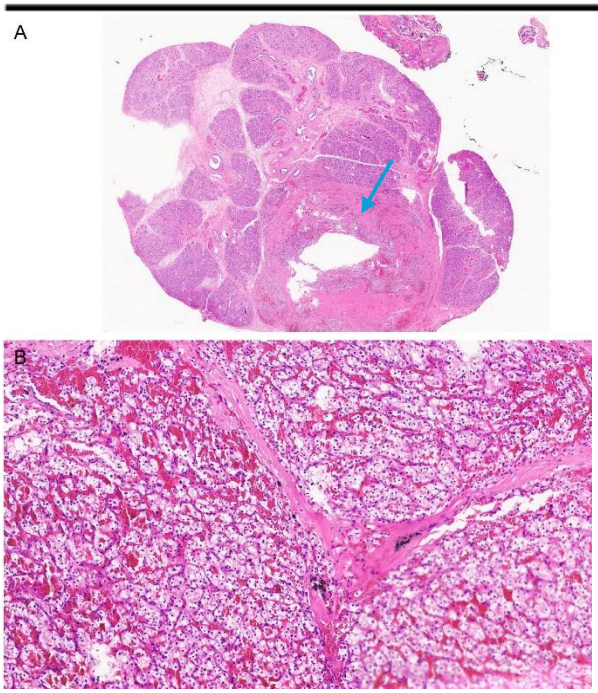

Fig. 1. A. Panoramic view showing multiple seromucinous acini and ducts of the salivary gland replaced by a neoplasm composed of clear cells. (H&E, x2). B. Neoplasm composed of clear cells distributed in nests separated by septa of fibrous connective tissue highly vascularized (nuclear grade WHO 2). (H&E, x10). C. Higher magnification shows low nuclear grade and abundant capillaries interspersed with clear cells (H&E, x20).

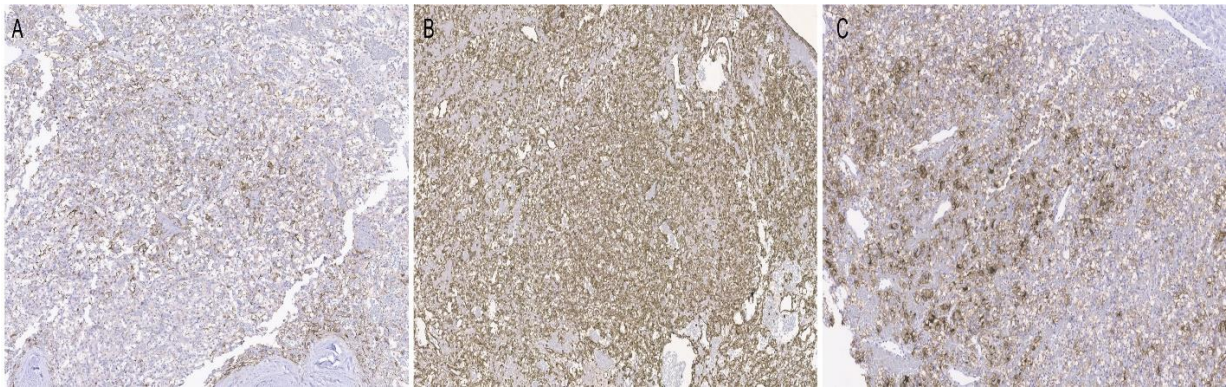

Fig. 2. Immunohistochemistry (IHC). A. Membranous positivity for EMA; B. Diffuse cytoplasmic and membranous positivity for Vimentin; C. Membranous positivity for RCC.

Discussion

Clear cell tumors of Head and Neck are rare and can be benign or malignant neoplasms of epithelial, mesenchymal, melanocytic, or hematopoietic nature[7]. Clear cell change can be explained to different factors including artifactual changes with defects in cellular preservation and hydropic degeneration of organelles, or due to the accumulation of glycogen, mucopolysaccharides, lipid, mucin, or phagocytized foreign body material in the cytoplasm of tumor cells[7,8].

Clear cell neoplasms, always represent a challenge for pathologists, because of the lack

of classical cytological atypia in malignant clear cell variants[8,9]. Clear cell carcinomas of the head and neck are generally low-grade, stage I-II neoplasms, and metastases are rare. They originate mainly in the oral cavity, followed by the salivary glands and the oropharynx[9].

Salivary gland tumors can be intraosseous[8]. They can be derived from ectopic salivary tissue or may arise from neoplastic transformation of the mucous cells found in the lining of dentigerous cysts or from embryonic remnants of submandibular glands found within the mandible or from bony entrapment of mucous cells of the retromolar pad during embryogenesis or theoretically, they may also arise from salivary tissue present in lingual cortical defect of the mandible[8,9].

Salivary gland tumors that show clear cell change, constitute a diverse group of benign and malignant neoplasms of epithelial / odontogenic or myoepithelial nature, with different clinicopathological characteristics. The main entities to have in consideration in the differential diagnosis are CCRCC, Hyalinizing clear cell carcinomas, clear cell odontogenic carcinoma, clear cell variant of calcifying epithelial odontogenic tumor, ghost cell odontogenic carcinoma, clear cell epithelial myoepithelial carcinomas, clear cell myoepithelial carcinoma, clear cell mucoepidermoid carcinoma, acinic cell carcinoma, clear cell oncocytomas[8,9].

Clear cell carcinoma is rare malignant epithelial neoplasm that affects more commonly minor salivary glands[8,9]. It is a low-grade tumor that affects adults with a mean age of 58 years and clinically presents as a salivary gland swelling[8,9]. Histologically the neoplasm is composed of a monomorphic population of clear cells, without features of other specific neoplastic entities[8,9,10].

Hyalinizing clear cell carcinomas affects mostly the minor salivary glands of palate, tongue, buccal mucosa[11]. Rare locations include jaw bones, subglottic larynx, nasopharynx, and tonsillar region. Commonly occurs in adults, median age 6th decade[11]. Histologically has a relatively monotonous appearance and is composed of nests and cords of clear cells with distinct cell borders and oval nuclei. There´s a minority population of cells that can have eosinophilic cytoplasm[11]. The stroma that surrounds the neoplasm is typically hyalinized[11]. Immunohistochemically the neoplasm shows positivity for keratin AE1/AE3, CK7, EMA, High molecular weight cytokeratin, P63 and negativity for S100, SMA, MSA, Calponin[11]. This neoplasm harbors a recurrent and consistent EWSR1-ATF1 fusion, that link this tumor to “clear cell odontogenic carcinoma”[8,11].

Clear cell odontogenic carcinoma is a neoplasm that occurs mostly in the 5-6 decades, with a female preponderance[10,12]. Affects most commonly the mandibular bone with frequent perforation and infiltration of soft tissue[10,12]. Clinically the patient has swelling and pain of the jaw, loosening or mobility of teeth and can also have paresthesia[10]. Microscopically the neoplasm could show three different patterns: biphasic, monophasic, and ameloblastomatous[10].

Biphasic pattern is the most common and is composed of sheets and islands of large clear cells and a second component of basaloid cells with eosinophilic cytoplasm and peripheral palisading They are separated by fibrous connective tissue stroma[10]. The monophasic variant is composed entirely of clear cells[10]. The ameloblastomatous pattern is the less common and resembles ameloblastomas that occasionally include palisading, peripheral clear cells[10]. The Immunohistochemical staining shows positivity for cytokeratin AE1/AE2, EMA y negativity for S100, SOX10, HMB45, SMA[10].

Clear cell variant of calcifying epithelial odontogenic tumor is a rare benign odontogenic neoplasm, that clinically presents as a slow growing asymptomatic swelling or tumor, locally destructive, of the mandible[12]. Microscopically is characterized by sheets and nests of polyhedral epithelial cells with eosinophilic or less common clear cytoplasm[12]. The cells have variable nuclear pleomorphism, but rare mitosis[12]. There's also characteristic stromal amyloid deposition and calcifications[12]. Immunohistochemically the neoplasm shows expression of cytokeratin AE1/AE3, CK 5/6, P63, CK19, Beta catenin, CD138. S100, MSA, Desmin, are negative[12].

Ghost cell odontogenic carcinoma is a rare malignant neoplasm, more common in males that thought to arise from calcifying odontogenic cysts[13]. Clinically presents as a painful, hard swelling of mandible. Microscopically it is composed of ameloblastomatous areas with hyperchromatic palisaded nuclei, stellate reticulum like areas[13]. There are polygonal epithelial cells with eosinophilic cytoplasm that have lost their nuclei (ghosts' cells), There´s also atypia, necrosis, mitosis, and infiltrative growth[13]. A few cases report a component of clear cells[13]. Immunohistochemically the neoplasm is positive for cytokeratin AE1/AE3, P63, P53. Ki67 proliferative index is high[13].

Epithelial Myoepithelial carcinoma is a very rare neoplasm that comprises only 2% of all salivary gland carcinomas[14]. Is primarily a tumor of older adults, with a peak incidence in the sixth - seventh decades of life[14]. Occurs mostly in the major salivary glands, being the parotid, the most frequent; however, it occasionally occurs in the minor salivary glands[14]. It´s present´s as a unilateral, slow growing painless tumor[14]. In aggressive cases it can produce facial nerve paralysis or regional lymphadenopathy[14]. It is a well delimitated neoplasm, partially encapsulated. Histologically, the neoplasm has a combination of an inner layer of duct epithelial cells with eosinophilic cytoplasm and an outer layer of clear myoepithelial cells, that often predominate[14]. Rare variants include epithelial cells with oncocytic or apocrine changes[14]. It can display different patterns as cords, nests, sheets, trabeculae sometimes with stromal basement membrane -like hyalinized matrix in between them[14]. It can also have cystic or papillary areas[14]. High grade transformation occurs in 20% of cases and it characterizes of sheets or solid nests of atypical cells with frequent mitosis and necrosis[14]. It can locally recur (25 –30 of cases), because of incomplete resection[14]. Immunohistochemical evaluation shows positivity for cytokeratin AE1/AE3, EMA, DOG 1 (apical) in the epithelial cells,

P63, SMA, Calponin, DOG 1 (membranous) are positive in the myoepithelial cells, S100, can be positive in both components, PAX8, HER2, GATA3 are negative[8,14].

Myoepithelial carcinoma is a rare carcinoma that is composed exclusively of tumor cells with myoepithelial differentiation and that shows an invasive behavior[15]. Affects a wide range of age from 14 to 77 years with and average age of 57 years[15]. The parotid gland is the most common site of involvement, followed by minor salivary glands and submaxillary gland[15]. May arise de novo or in Pleomorphic adenomas[15]. Clinically it present´s as painful multinodular mass. Microscopically the tumor shows reticular, trabecular, or solid patterns[15]. Morphologically the neoplasm is heterogeneous displaying a multinodular architecture, with hypercellular peripheral areas and hypocellular myxoid or necrotic centers[15]. Myoepithelial cells can display several cytological types that varies from epithelioid, hyaline, clear, spindle, or mixed cell types[15]. The stroma can be of hyalinized, myxoid or mixochondroid type[15]. Immunohistochemically the neoplasm classically presents reactivity for cytokeratins (AE1/AE3, CAM 5.2) and myoepithelial markers, which includes vimentin, calponin, S100, p63, glial fibrillary acidic protein, SMA[15]. There is also positivity for SOX10, p40[15]. An infiltrative growth pattern and a Ki-67 mitotic index more than 10%, are indicative of myoepithelial carcinoma[15].

Mucoepidermoid carcinoma is the most common primary carcinoma of major and minor salivary glands; It represents 10-15% of all salivary tumors[16]. Occurs in adults, median age of 49 years and in children, median age of 13 years[16]. Clinically presents as a slow growing painless swelling or mass[16]. Microscopically the neoplasm can be solid or cystic[16]. It´s composed of three cell types in varying proportion: mucous cells, epidermoid (squamoid) cells and undifferentiated small cells (intermediate cells), that can vary in proportion[16]. This characteristic explains the heterogeneous aspect of the neoplasm, with solid nest or cords of epidermoid cells mixed with mucous or intermediate cells[16]. Pools of luminal or extracellular mucin can be observed[16]. The stroma can be hyalinized. Perineural or lymphovascular invasion may be observed[16]. The presence of necrosis, increased mitosis or nuclear pleomorphism, indicates high grade tumor[16]. There are many histologic variants: clear cell (glycogen accumulation), oncocytic, spindle cell, sclerosing, warthin like, ciliated, mucoacinar[16]. Immunohistochemically the neoplasm is positive for cytokeratin AE1/AE3, CK 5/6, p63, p40, MUC1, MUC2, MUC 4, MUC5 AC and negative for S100, calponin, SMA, GFAP, GATA 3[16].

Acinic cell carcinoma is a low - intermediate grade malignant epithelial neoplasm, that represents 6-8 % of all salivary gland neoplasms[17]. Affects commonly the parotid gland and has a wide age range of distribution from children to older adults (median 53 years)[17]. Clinically its presents as a slow growing mass, the tumor can be of infiltrative type or well delimitated[17]. Histologically the neoplasm can display different growth patterns including serous acinar, solid/tubular,

papillary-cystic, microcystic, follicular non-specific glandular, vacuolated, and clear cell patterns[17]. Clear cells are found in approximately 6% of acinic cell carcinomas[17]. But only in 1% of cases constitute the predominant population of tumor cells[17]. Most commonly they are accompanied by serous tumor acini that surrounds them[17]. Mitosis, necrosis and significant nuclear pleomorphism are usually absent. Immunohistochemically the neoplasm shows positivity for pancytokeratins, CEA, EMA, DOG 1, SOX 10 y negativity for Calponin, p63, SMA[17].

Oncocytoma, is a rare benign neoplasm that constitute approximately 1% of all salivary gland tumors. Affects a patient in the 6th-7th decade of age[18]. Sometimes there´s a previous history of radiation therapy or radiation exposure[18]. It is a well delimitated tan-red, brown, neoplasm[18]. Histologically it can be composed of clear cells (because of intracytoplasmic glycogen o fixation artifact) or most often of polyhedral cells with eosinophilic granular cytoplasm and small dark nuclei[18]. It is a benign neoplasm and immunohistochemically show positivity for PTAH, CK5/6, CK 8/18, EMA and is negative for myoepithelial markers[18].

Metastatic clear cell neoplasms should always be taken into account due to their therapeutic implications. Most of metastasis are from lesions of head and neck and consist of melanomas in 45% and squamous cell carcinomas of the skin in 37%[8,9]. A small percentage proceed from distant sites such as lung, breast, kidney, gastrointestinal tract, prostate[8,9].

Renal cell carcinoma is the third most frequent neoplasms, that metastasize to head and neck region following lung and breast carcinomas[8]. The most common locations for metastasis of clear cell renal carcinoma in the head and neck are the nasal cavity and paranasal sinus, throat, oropharynx, temporal bone, thyroid, and parotid gland[5,8]. A possible explanation for head and neck metastasis is that de neoplasm disseminates through Batson´s plexus, that is an extensive anastomosis between the valvular vertebral and epidural venous system, being the sinonasal region the main site affected[19]. Another theory is that tumor metastasis bypasses the inferior cave, lung filtration system and cardiovascular system with concurrent lung and brain metastasis[19]. Other authors postulate a lymphatic route, in which tumor emboly reach regional lymphatics, then flow to thoracic duct and affect head and neck region, trough retrograde flow from intercostal, mediastinal, or supraclavicular lymph vessels[19]. Major salivary gland metastasis a rare, being the parotid gland, the most frequent gland affected, submaxillary gland metastasis, are even more rare[8,9,19].

It is well known the unpredictable behavior of CCRCC. Approximately 25% of patients have distant metastases at the time of the diagnosis, while 20% to 50% of patients experience metastasis many years after the initial surgical treatment[4].

Histologically CCRCC metastasis, present´s as a multinodular tumor with rich vascular network and stromal hemorrhage with hemosiderophages[1,3,20,21]. Histologically, they are composed of tubules and nests, of clear cells with distinct cell membranes and small

round or oval nuclei, chromatin can be homogeneous or vesicular[20,21]. The nucleoli vary from small and inconspicuous to large and prominent[20,21]. Mitotic figures are, in general, absent. Immunohistochemical stains show positivity in the tumor cell´s for CD10, Vimentin (Vim), EMA, PAX8, RCC marker and negativity for S100, P63[20,21].

Clear cell squamous cell carcinomas, it's a neoplasm that microscopically show sheets of predominant clear cells with intercellular bridges and individual keratinization indicating squamous differentiation[22]. The cells are round to polygonal with clear cytoplasm and nuclear hyperchromatic and atypia[22].

Prostate carcinoma sometimes exhibits clear cell morphology[23]. But can be differentiated from renal cell clear carcinomas in that the confluent nests of clear cell´s, lack prominent vascularity and inflammatory cell´s, stain positive for broad-spectrum cytokeratin and PSAP, and do not co-express Vim[23].

We believe that this case is interesting due to the rare occurrence of renal clear cell carcinoma metastatic involvement of the submaxillary gland in a patient with a medical history of oral squamous neoplasia and a poorly differentiated prostate adenocarcinoma. Two of the main potential origins, that need to be taken in consideration in salivary gland metastatic disease. In the present case, the immunohistochemistry study show that the neoplastic cells were positive for EMA, Pan cytokeratin, CD10, RCC,Vimentin and were negative for S100, Calponin, PSA (Figure 2). Histologically the neoplasm lacks intercellular bridges, or any sign of keratinization and the nuclear grade was WHO 2. Faced with these findings and considering the previous medical history, the diagnosis was of metastasis of clear cell carcinoma, probably renal (Figure 1).

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