Variability of clear cell tumour presentation: case reports

Clinical Case

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Abstract

Cancer significantly affects the world's population, and it was estimated in 2018 that Head and Neck Cancer would be the seventh most prevalent.
Clear cells can be the result of different physiological processes and are found in various benign and malignant tumours. Although they are rare in head and neck tumours, they are mostly found in salivary glands. Clear cell tumours of the head and neck, namely Hyalinizing Clear Cell Carcinoma and Odontogenic Clear Cell Carcinoma are malignant tumours, morphologically and genetically similar, with functional, psychological, social and aesthetic impact on these patients. Histopathological and immunohistochemical tests are essential to distinguish clear cells lesions from other differential diagnoses.
This work aims to demonstrate the clinical variability of presentation associated with the immunohistochemical overlap of these two types of clear cell tumours of the head and neck.

Keywords: Head and Neck Cancer, clear cells, immunohistochemical

Introduction

In 2018, head and neck cancer was classified as the seventh most prevalent type of cancer worldwide. In the oral cavity, the majority of these cancers are squamous cell tumors and can affect any area, including the tongue, lips, alveolar crest, buccal mucosa, and floor of the mouth.[1, 2] The prognosis depends on the location, among other factors. The treatment of oral cancer includes surgical resection with reconstruction, radiotherapy, and chemotherapy.[2] Clear cells (CCs) may result from different processes, including cellular organelle degeneration and the accumulation of intracellular substances, most frequently glycogen, but sometimes also mucopolysaccharides, mucins, lipids, or foreign bodies[3] (Figure 1). Although CCs can be observed in all types of benign or

Figure 1
Classification of physiologic clear cells, adapted from Premalatha BR et al.

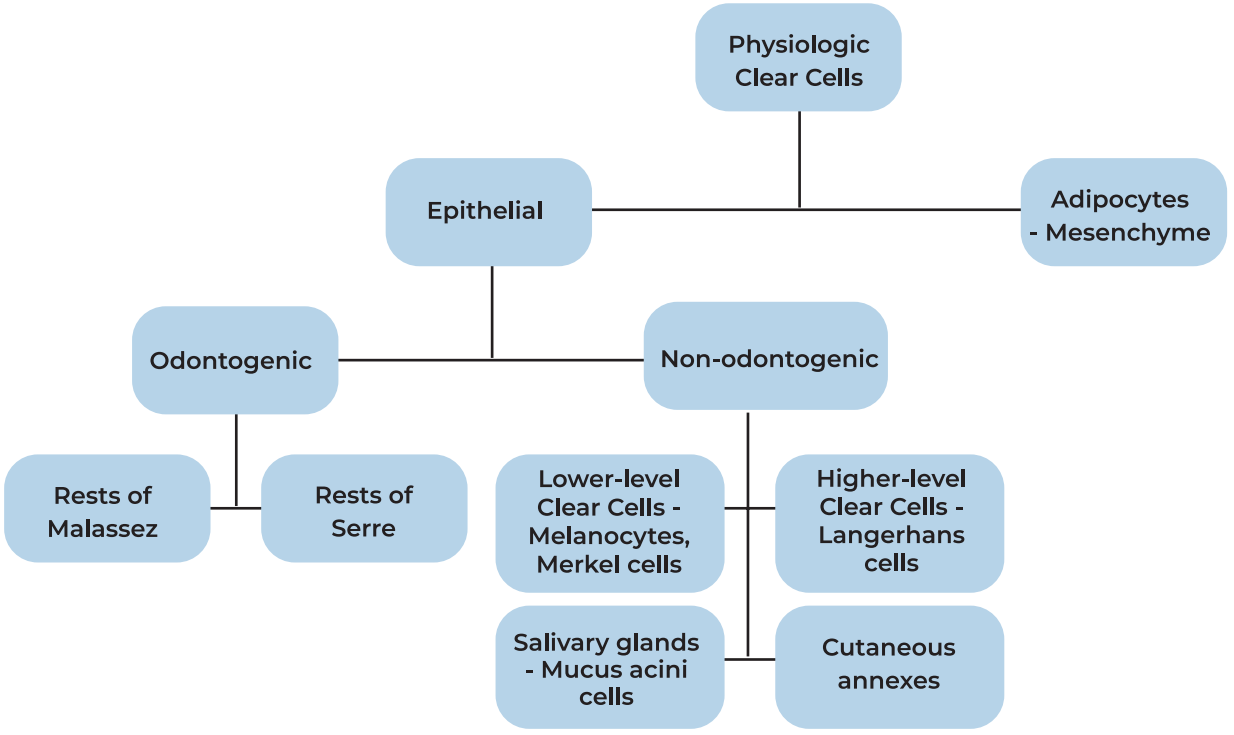


Figure 2
Types of clear cell lesions and tumors, adapted from Premalatha BR et al.

Odontogenic clear cell lesions
- **Odontogenic cysts**
  - Gingival cyst of adult
  - Lateral periodontal cyst
  - Clear cell calcifying odontogenic cyst
- **Odontogenic tumors**
  - Clear cell odontogenic carcinoma
  - Ghost cell odontogenic tumor
  - Clear cell calcifying epithelial odontogenic tumor

Clear cell salivary gland tumors
- Clear cell myoepithelioma
- Cleal cell oncocytoma
- Clear cell mucoepidermoid carcinoma
- Myoepithelial-epithelial carcinoma
- Clear cell hyalinizing carcinoma

Clear cell metastatic tumors of the:
- Kidney
- Liver
- Thyroid
- Prostate
- Colon

Clear cell keratinocytic tumors
- Clear cell variant of squamous cell carcinoma
- Clear cell variant of basal cell carcinoma

Clear cell melanocytic tumors
- Balloon cell nevus
- Balloon cell melanoma

Clear cell osseous and cartilaginous tumors
- Clear cell chondrosarcoma
- Clear cell osteosarcoma

Adipocytic tumors
- Lipoma
- Liposarcoma

Clear cell tumors of cutaneous annexes

Trichilemmoma
- Clear cell acanthoma
- Sebaceous adenoma
- Sebaceous carcinoma
- Syringoma
- Eccrine spiradenoma
- Clear cell hydradenoma

Other clear cell conditions
- Storage diseases – Hurler Syndrome
- Koilocytes
- Alveolar soft-part sarcoma
- Paraganglioma

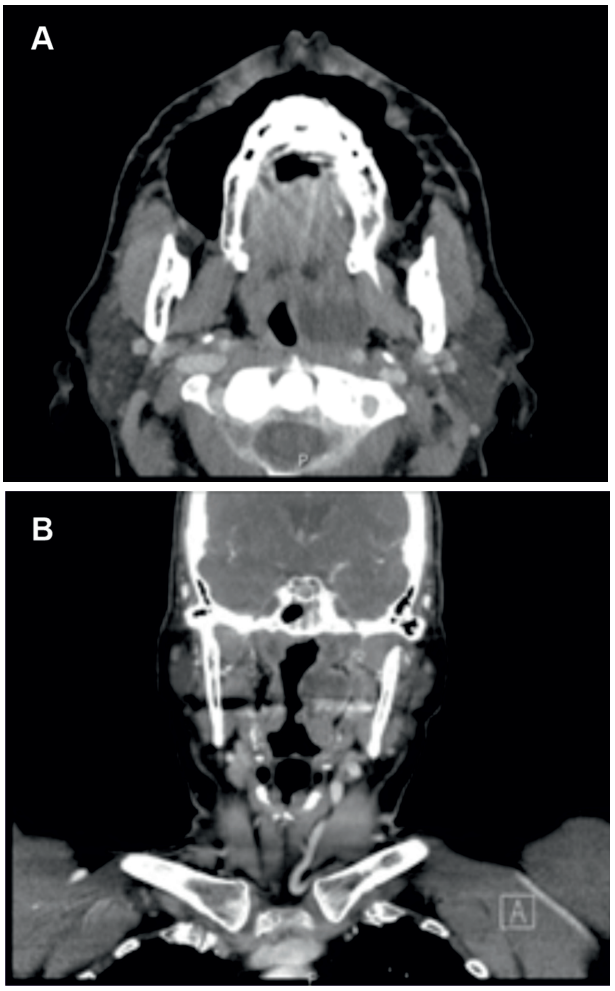
malignant tumors of epithelial, mesenchymal melanocytic, and hematopoietic origin, they are rarely detected in the head and neck area.[4] In the head and neck area, CCs are found mainly in salivary gland tumors, but they can also be observed in squamous cell tumors or tumors with an odontogenic epithelial origin, metastatic or primary carcinoma, malignant or benign melanocytic lesions, or malignant or benign mesenchymal tumor[3,4] (Figure 2).
The aim of the present study was to demonstrate the variability of the clinical presentation associated with the immunohistochemical overlap between two types of CC head and neck tumors.

Clinical Case Presentation

Clinical Case 1

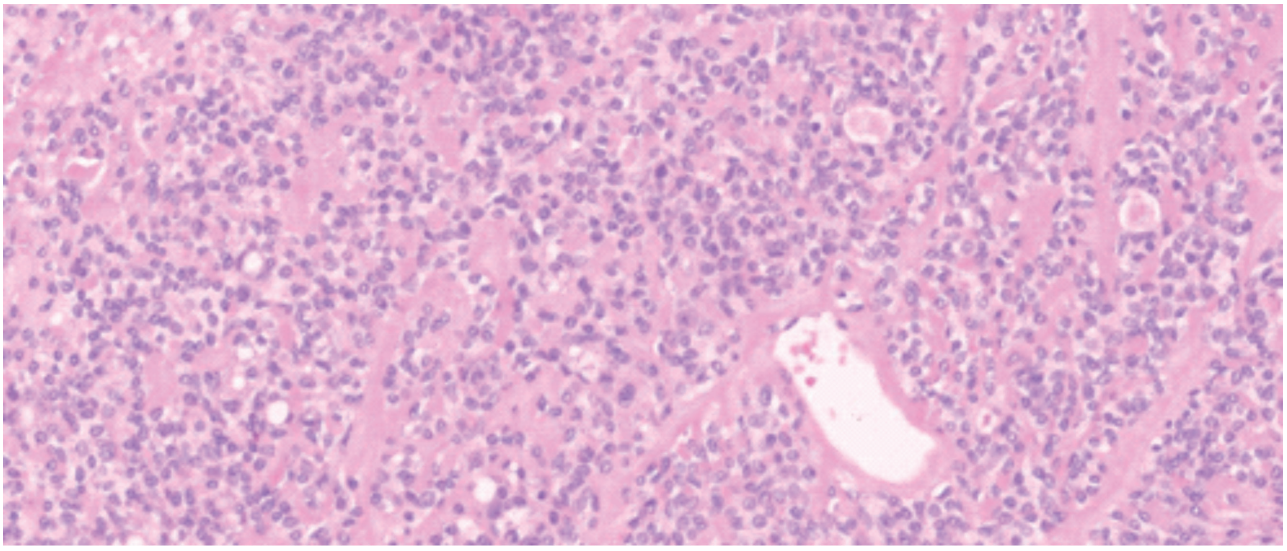
The patient was a 74-year-old Caucasian woman with dyslipidemia, arterial hypertension (AHT), and depressive syndrome, which were pharmacologically controlled. She had a history of a transient ischemic attack (TIA) in 2019 without any sequalae. To investigate vertiginous syndrome, she underwent computed tomography (CT) of the head, which revealed a soft palate mass; therefore, she was referred for a Head and Neck Surgery consultation. On observation, the patient had a submucosal left-sided soft palate mass with a major diameter of ca. 3 cm. Incisional biopsy of the lesion was compatible with clear cell hyalinizing carcinoma (CCHC). Maxillofacial CT (MF-CT) was performed to characterize the lesion, which revealed an expansive lesion that was well demarcated and located on the left side of the soft palate. It measured 32 × 27 mm at the widest cranial-caudal and transverse axes, respectively, extending from the lower margin of the external orifice of the Eustachian tube to the upper pole of the amygdala. The lesion decreased the caliber of the oropharyngeal aerial column and partially obliterated the parapharyngeal fat pad, without signs of invasion of the masticator space, bone invasion, or perineural dissemination (Image 1), and without any cervical ganglia with pathological dimensions or characteristics.

Image 1
Maxillofacial-computed tomography (MF-CT) shows a left-side expansive lesion in the soft palate and palatal amygdala with compression of the airway. A – axial view; B – coronal view



A positron emission tomography (PET) scan was also performed, which highlighted the presence of other suspicious hypermetabolic alterations. Under general anesthesia and with orotracheal intubation, the patient underwent excision of the left-sided soft palate lesion and ipsilateral amygdalectomy. The anatomopathological analysis of the surgical specimen confirmed the diagnosis of CCHC, without lymphovascular or perineural invasion, which was associated with inflammatory and restorative alterations compatible with the previous biopsy findings, as well as a mutation of the *EWSR* (22q12) gene and pT2 pathological stage (Image 2). Focally, the lesion coincided with one of the surgical margins.

Image 2
Histological characteristics: proliferation of tumor cells with a clear cytoplasm, organized in cords and nests, and surrounded by hyalinizing stroma (H&E, 100X)



Approximately six weeks after the surgery, the patient remained asymptomatic, without clinical signs of tumor persistence. Because the residual lesion was adjacent to the carotid artery, margin increase was not considered feasible without significant mutilation; therefore, surgical reintervention was not indicated or performed, and clinical surveillance was adopted.

Clinical case 2

The patient was a 63-year-old Caucasian man with a history of pharmacologically-controlled AHT and dyslipidemia. He was referred to our institution because of the history of a mentonian nodule, which progressed over a 3-month period, and exhibited imaging features of an expansive lesion in the mentonian area without invasion of the inferior alveolar nerve. On observation, the patient had a hard nodule located in the inferior incisive area, without any palpable cervical lymphadenopathy.

An incisional biopsy suggested diagnoses of intraosseous carcinoma or metastasis. A PET scan revealed a mandibular lesion at the mentonian level with a metabolic pattern that was suggestive of malignancy, along with left-sided latero-cervical ganglia (at level II) with low uptake. MF-CT showed a lytic lesion located in the alveolar crest of the mandibular symphyseal and parasymphyseal region, with involvement of the dental roots, erosion of the lingual cortical plate of the alveolar crest from 3.4 to 4.3 over an approximate span of 20 mm, as well as erosions of the vestibular cortical plate from 3.3 to 4.3, which were associated with a slight component of the

Image 3
Axial view of axillofacial-computed tomography (MF-CT) shows an osteolytic lesion from 3.4 to 4.3, with erosion of the lingual and vestibular cortical plate

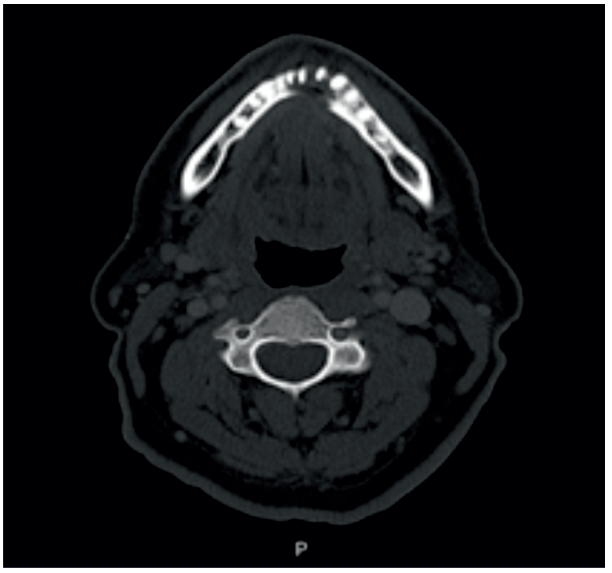
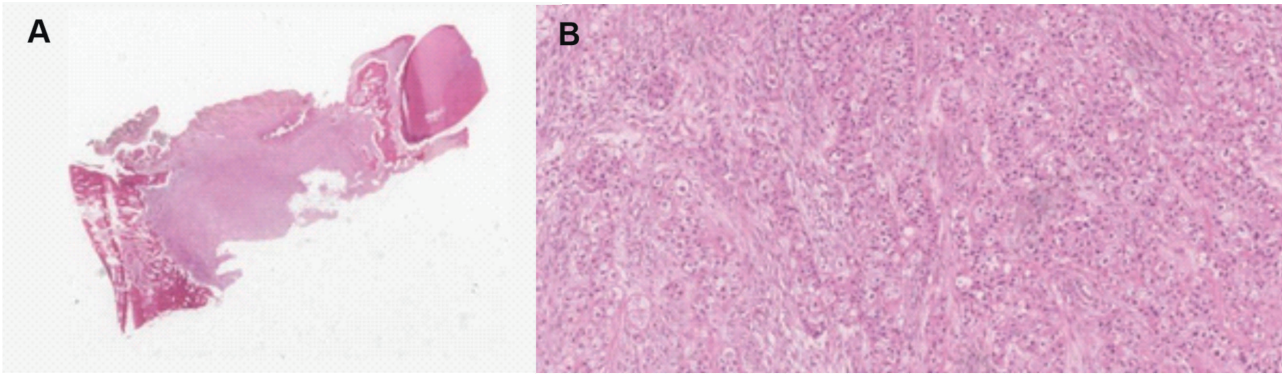


Image 4
Histological characteristics of clear cell odontogenic carcinoma (CCOC). A - Infiltration of neoplastic cells into the bone trabeculae (H&E, 40X); B – Cells arranged in trabeculae and nests, with nuclear pleomorphism and a clear cytoplasm (H&E, 100X)



soft parts, with uptake in the region adjacent to the lingual border (Image 3). There was no involvement of the floor of the mouth, tongue muscles or ventral surface; there was no compromise of the mentonian spaces and inferior alveolar canals or signs of perineural dissemination along the V3. No latero-cervical or retropharyngeal lymphadenopathy was documented.

Under general anesthesia and nasotracheal intubation, the patient underwent a lip split with marginal mandibulectomy from 35 to 45, with sacrifice of the bilateral inferior alveolar nerves and left-side cervicotomy, as well as left-side cervical lymphadenectomy (levels I–III and IV) with sacrifice of the facial vessels and anterior jugular vein.

The anatomopathological examination of the surgical specimen yielded the diagnosis of low-grade infiltrating clear cell odontogenic carcinoma (CCOC), without lymphovascular or perineural invasion and with negative margins. The left-sided latero-cervical lymph nodes (levels I–III and IV) did not show metastasis (Image 4).

At the 6-month post-operative follow-up, no clinical or imaging signs of local recurrence were observed.

Discussion

Clear cell tumors account for about 1%–2% of all head and neck tumors. In the oral cavity, these tumors are derived from the odontogenic/non-odontogenic epithelium or mesenchyme, or can be metastatic, and have been diagnosed in various anatomical areas.

The diagnosis of CC head and neck carcinoma can be challenging, with a considerably broad differential diagnosis.[5]

CCs are frequently observed within a great variety of primary cancers of the salivary glands, including pleomorphic adenoma (PA), myoepithelial carcinoma (MC), oncocytoma, mucoepidermoid carcinoma (MEC), acinar cell carcinoma, epithelial-myoepithelial carcinoma (EMC), and adenoid cystic carcinoma (ACC).[6,7]

In the majority of the cases, CCs are a minor cellular component of these neoplasms. However, in some tumors, CCs are the major cellular component, which complicates the diagnosis. CCs are generally the main diagnostic factor in two salivary gland cancers, i.e., EMC and CCHC.[3,7]

In the present study, we described two clinical cases of CCHC of the palate and mandibular CCOC.

CCHC was well described as a unique entity for the first time in 1994 by Milchgrub et al. It is diagnosed most commonly between the fifth and sixth decades of life, with a slight predominance in women. Its clinical presentation varies according to the location of the primary tumor. In the majority of the cases, it manifests as a painless submucosal mass, although it can also present with hemorrhage, ulceration, and dysphagia.[6-8]

The most common site of occurrence of CCHC, reported in 283 cases, is the palate (23.1%), followed by the tongue (21.0%) and nasal cavity (10.5%). The size of the mass at clinical presentation was found to be 2.49 cm on an average in a study including 197 patients (77.6%).[6,9]

In the case reported here, the lesion presented as a painless mass in the soft palate. Because CCHC exhibits squamous characteristics on immunohistochemistry, the most probable differential diagnoses are squamous cell carcinoma and MEC. Although CCHC does not demonstrate myoepithelial differentiation upon staining for actins and calponin, myoepithelial tumors, such as MEC, are also included in the differential diagnoses. Various tumors with an odontogenic origin can present with cellular alterations. In particular, two of these tumors overlap with CCHC: CCOC and clear cell calcifying epithelial odontogenic tumor (CEOT), which is also known as Pindborg tumor. These odontogenic neoplasias may be mistaken for mucous CCHC, which exhibits bone invasion in approximately 17% of the cases. Finally, metastatic renal cell carcinoma (RCC) is always included in the differential diagnosis of CCHC in all studies related to the differential diagnosis of CC salivary tumors. However, its similarity with CCHC is negligible and RCC never expresses p63.[10]

Bilodeau et al. examined the *EWSR1* gene translocation in CCOC and CCHC, as these two types of tumor have been shown to exhibit extensive morphological and immunohistochemical overlap. The most recent evidence suggests that CCHC may be the bone homolog of CCOC.[10-12]

In general, CCHC is characterized by nests or cords of polygonal or round cells with a clear or light-pink cytoplasm. Immunohistochemically, CCHC can generally be differentiated with confidence from other etiologies based on the positive expression of high-molecular-weight cytokeratins and p63, positivity for periodic acid-Schiff (PAS) staining, and sensitivity to diastasis. The absence of staining for the S-100 protein, smooth muscle actin, glial fibrillary acidic protein, and vimentin are also characteristics of this type of tumor.[9]

Patients with CCHC have a good prognosis after adequate tumor resection with clear surgical margins.[10] Although the CCHC lesion that was resected in the clinical case presented here coincided with one of the surgical margins, a potential surgical re-intervention would have posed a greater risk to the patient; therefore, we opted for strict clinical surveillance. Locoregional disease is not common. In the presence of lymphadenopathy, cervical lymph node dissection is recommended.[9]

CCOC, which was known previously as clear cell odontogenic tumor or clear cell ameloblastoma, is a rare maxillary bone tumor.[13]

This tumor was described for the first time in 1985 by Hansen et al.[14] and was classified as a benign odontogenic tumor. However, because of its capacity for malignancy, its aggressive behavior with a tendency to recur, and its propensity for local-lymph-node and distant metastasis, it has been classified as a malignant tumor.[15]

The majority of the cases occur in the fifth and sixth decades of life, predominantly in women. The jaw is more frequently affected compared with the maxilla. The clinical characteristics vary between an asymptomatic presentation and nonspecific pain, increased tooth mobility, or tooth luxation and cortical destruction.[16,17,19] Radiologically, they present with poorly defined radiolucencies, radicular resorption, and at times, soft tissue invasion. Approximately 84% of CCOCs exhibit the *EWSR1-ATF1* gene translocation. Locoregional metastasis occurs in 20%–25% of the cases.[17]

The diagnosis of this tumor is complex. It is a rare tumor with limited clinical data, which has led to it being underdiagnosed. Molecular biology and histopathological anatomy contribute significantly to an accurate diagnosis.[18]

The main histopathological characteristic is the presence of islets of cells with a clear or eosinophilic cytoplasm, well-defined borders, and centrally positioned nuclei. However,

CCOC is not the only lesion that exhibits CCs; therefore, it should be considered in the differential diagnosis of maxillary neoplasias with CCs.[19]

In the present case, the patient did not experience any pain, which probably contributed to the progression of the lesion before diagnosis. Radiologically, the lesion was unilocular, with irregular and poorly defined margins, indicating bone destruction. The diagnosis was compatible with CCOC. Because of the rarity of the lesion, no therapeutic protocols have been established, with mandibulectomy accompanied by cervical lymph node dissection the most recommended treatment. In the case reported here, anterior marginal mandibulectomy and selective cervical lymph node dissection were performed.

In the literature, the overall recurrence rate after jaw resection is 29.8%, with 17% cases of recurrence exhibiting distant metastases. For these tumors, long-term follow-up is recommended to monitor the occurrence of metastases.[19]

Clear cell tumors have been poorly studied, mainly because of their rarity. Only case reports, case series, and reviews of these case series have been published. CCHC is a rare malignant neoplasia of the head and neck region that is locally aggressive and occurs more frequently in women in the oral cavity, minor salivary glands, and oropharynx. The outcomes of surgical treatment are generally favorable.[20] Here, we reported two cases of clear cell carcinoma of the oral cavity with morphological and immunohistochemical overlap and expression of the *EWSR1* gene.

In the two reported cases, the follow-up period is still not sufficient to allow a discussion of the long-term prognosis and survival of these patients. However, the surgical resection of the lesions was performed without any complications, and no recurrences have been documented to date.

Conclusion

Although rare, clear cell tumors of the head and neck, namely CCHC and CCOC, are malignant tumors that are morphologically and genetically similar, and have a functional, psychological, social, and esthetic impact on the patients. Histopathological and immunohistochemical examinations are crucial to distinguish these CC lesions from other differential diagnoses. The most adequate treatment for these tumors, which are mainly composed of CCs, is surgical resection with safety margins, because of the high potential for recurrence. In all such cases, long-term follow-up is always necessary.

Conflicts of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

Data Confidentiality

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

Protection of humans and animals

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the 2013 Helsinki Declaration of the World Medical Association.

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Availability of scientific data

There are no datasets available, publicly related to this work.

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