CLEAR CELL ODONTOGENIC CARCINOMA OF THE MANDIBLE WITH PERINEURAL INVASION: A REVIEW

Perinöral İnvazyon Gösteren Alt Çene Berrak Hücreli Odontojenik Karsinom: Bir Derleme

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ABSTRACT

Objectives: Clear cell odontogenic carcinoma (CCOC) is a rare aggressive cancer of the oral cavity. Diagnosis is mainly by excluding other pathologic lesions containing clear cells. Perineural invasion may be an important feature in this lesion.

Methods: We performed a literature review. We paid attention to the CCOC and perineural invasion in the search of English language literatures in the Pubmed.

Results: Analysis of previously reported cases of CCOC showed that up to 2014 there were 74 reported CCOC cases in English articles, cited in PubMed. There was only one previous report of perineural invasion. A new case is also presented in this article.

Conclusion: Clear cell odontogenic carcinoma needs a special immunohistochemical protocol and complete workup to reach a correct diagnosis. Perineural invasion should be considered in central lesions of the mandible.

Key words: Clear cell odontogeniccarcinoma, Submentalflap, Mandible, Perineuralinvasion.

ÖZ

Amaç: Berrak hücreli odontojenik karsinom (BHOK), oral kavitede nadir bulunan agresif bir kanserdir. Tanı esas olarak berrak hücreler içeren diğer patolojik lezyonları dışlar. Bu lezyonda perinöral invazyon önemli bir özellik olabilir. Yöntem: Literatür derlemesi yapıldı. Pubmed veri tabanındaki İngilizce makalelerden BHOK ve perinöral invazyon terimleri araştırıldı.

Bulgular: Daha önce rapor edilen BHOK vakalarının analizi, PubMed'de taranan İngilizce makalelerde, 2014 yılına kadar 74 tane BHOK vakası bulunduğunu gösterdi. Perinöral invazyona ilişkin sadece bir önceki rapor vardı. Bu makalede de yeni bir vaka sunulmuştur.

Sonuçlar: BHOK, tanıya ulaşmak için özel bir immünohistokimyasal protokole ve doğru tanıya ulaşmak için eksiksiz bir çalışmaya ihtiyaç duyar. Perinöral invazyon mandibulanın orta lezyonlarında düşünülmelidir.

Anahtar Kelimeler: Berrak hücreli odontojenik karsinom, submental flep, alt çene, perinöral invazyon

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INTRODUCTION

Clear cell odontogenic carcinoma (CCOC) is a rare aggressive carcinoma of the oral cavity.[1] There are no net pathologic criteria to distinguish this carcinoma from the other clear cell carcinomas.[2] Good workup to rule out the metastasis of clear cells to the oral cavity, mainly from the kidney, and an appropriate immunohistochemical plane to reach a correct diagnosis are necessary.[3] Clear cell odontogenic carcinoma was first described by Hansen *et al.*[4] in 1985.

Table 1: Historical look at clear cell odontogenic carcinoma

Year	Authors	Number of patients in review of the literature
1985	Hansen,*et al*[4]	Introduction of the lesion
1996	Muramatsu,*et al*[9]	18
2004	Siriwardena,*et al*[10]	35
2005	Ebert,*et al*[11]	43
2009	werle,*et al*[12]	59
2013	Swain,*et al*[13]	74

CCOC often involves the mandible and most often occurs in female patients.[5] Recurrence and metastasis can occur years after the excision of the primary lesion.[6,7]

Diagnosis is often challenging because there are no pathognomonic histopathologic criteria. In this stage, the pathologist confronts a clear cell neoplasm.[8]

In this article, workup and surgical management are discussed with a case report.

PATIENT & METHODS

Patient

The patient was a 42-year-old female who was referred by her dentist for "loose teeth in the left mandible". On panoramic radiographic examination there was a radiolucent lesion in the mandible with hanging tooth appearance and ill-defined borders; spiked root resorption of mandibular premolar teeth was apparent (Figure 1).

Figure 1a. Intraoral photograph of the lesion;

Figure 1b. Panoramic view of the jaw with hanging tooth (left mandibular premolar and first permanent molar) and ill-defined borders;

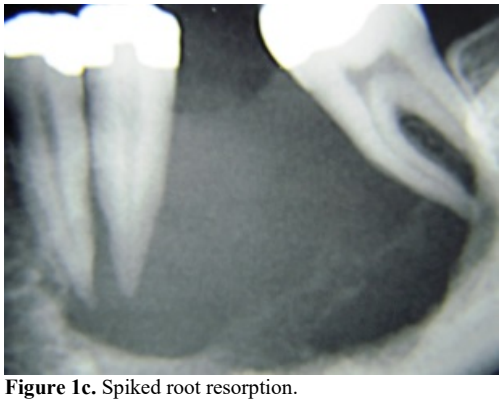


Figure 1c. Spiked root resorption.

Intraoral examination revealed good oral hygiene, with loose mandibular left premolar teeth. On physical examination, there were no enlarged neck lymph nodes. There were no systemic diseases, with a negative history of cigarette smoking and alcohol intake. There was no alteration in lower lip sensation. Incisional biopsy was performed under local anesthesia.

Histopathologic examination: Mononuclear cells with clear cytoplasm, hypochromic centrally located nucleolus and some cellular atypia were present in hematoxylin and eosin (H&E) staining.

Hyperchoromatic epithelial nest including cluster of cells with abundant clear cytoplasm (Figure 2).

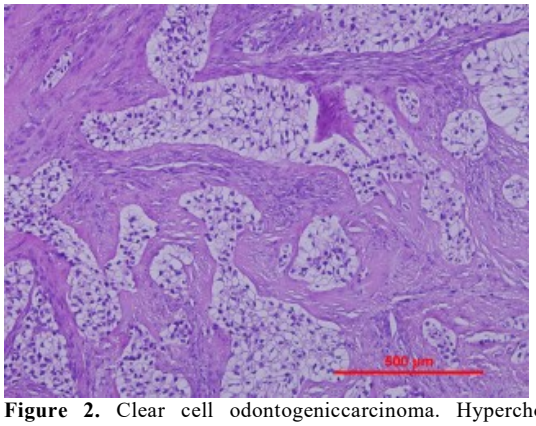


Figure 2. Clear cell odontogeniccarcinoma. Hyperchoro-maticepitjelial nest including cluster of cells with abundant clear cytoplasm.

Clear cells were arranged in nests and cords. Hyalinized connective tissue was separately evident between clear cell nests. The tumoral cells presented a degree of nuclear pleomorphism with perineural invasion. Necrosis was seenin tumor islands and areas of calcification were present. Immunohistochemical analysis revealed that clear cells were positive for CK 7 and none were positive for CD 10, vimentin, and CK 20 (Figure 3).

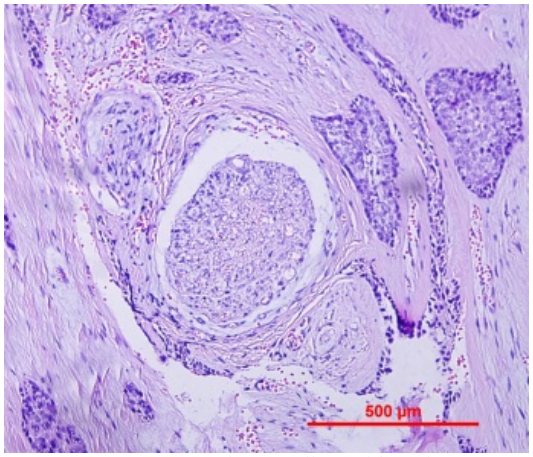


Figure 3a. Mononuclear cells with clear cytoplasm withhypochromiccentrally located nucleus and some cellular atypia with perineural invasion (H&E ×10).

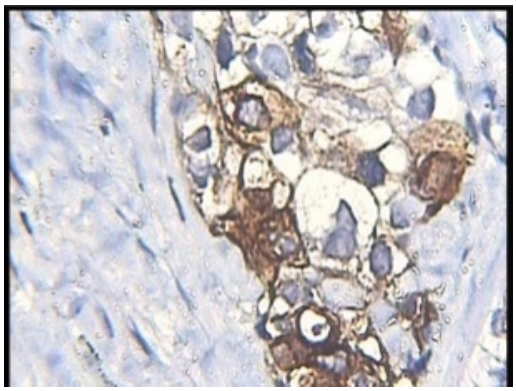


Figure 3b. Immunohistochemical staining for CK7 was positive.

Workup: Abdominal sonography was carried out to evaluate the possibility of metastasis from kidney. Mammography was ordered to rule out any possibility of occult primary breast cancer. Chest x-ray was ordered to evaluate lung metastasis from the intraoral carcinoma and/or detection of primary lung cancer with probable metastasis to the oral cavity. Contrast enhanced neck CT scan was carried out to evaluate neck lymph nodes and also thyroid and parathyroid endocrine glands (Figure 4).

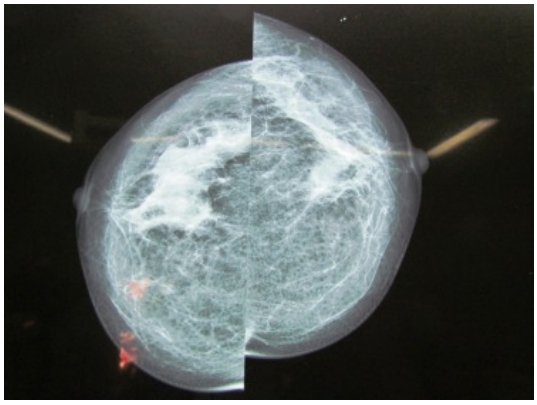


Figure 4. Workup: **a.** Mammography.

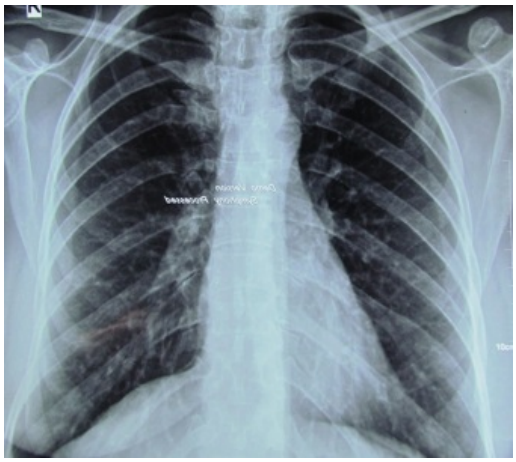
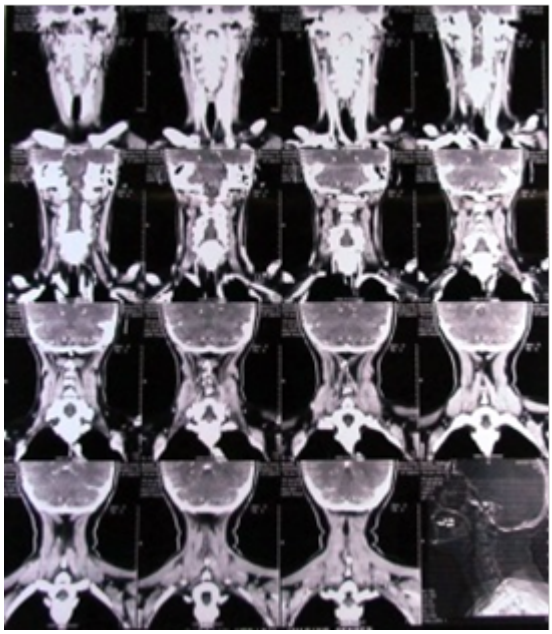


Figure 4b. Chestx-ray;c,contrast-enhanced CT scan of the neck



Surgical management

A decision was made in consultation with Oncology Department to carry out mandibulectomy with continuity defect and 1.5-cm safe margins. Realignment of the resected bone was carried out with titanium reconstruction plate and replacement of resected soft tissues with orthograde submental flap and neck management with supraomohyoid neck dissection (SOHND) during the operation. Patel modification of submental flap with subplatysmal dissection in non-pedicled side and inclusion of anterior belly of digastric and myelohyoid muscles was considered for soft tissue reconstruction (Figure 5).

Figure 5a. Resected lesion with 2-cm safe margins and sacrifice of the inferior alveolar nerve;the buccal cortical plate is destroyed

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Figure 5b. Reconstruction plate in place and orthograde submental flap

Figure 5c. Flap covered the reconstruction plate and replaced the resected mucosa (4 weeks after operation)

The lesion was centrally located in the mandible in posterior region. Potentialof perineural invasion around the inferior neurovascular bundle was probable; therefore, safe margins for this nerve were also considered in surgical treatment planning.

The surgical specimen was subjected to detailed histopathological examination. The surgical margins were negative and perineural invasion was present. The patient underwent a course of radiotherapy, and has remained asymptomatic in the first-year follow-up.

Methods: We performed a literature review. We paid attention to the CCOC and perineural invasion in the search of English language literatures in the Pubmed.

RESULTS

Analysis of previously reported cases of CCOC revealed that Up to 2014 there were 74 reported CCOC cases in English articles cited in PubMed.[4,9-13] There was only one previous report of perineural invasion.[14] The present case is the second report.

DISCUSSION

Three microscopic patterns have been described for clear cell odontogenic carcinoma. The biphasic pattern consists of epithelial cells admixed with eosinophilic polygonal epithelial cells. The second pattern that is similar to the case reported in this article is monophasic, characterized by clear cells that are arranged in nests or cords. The third pattern has a resemblance to ameloblastoma: cells with a clear cytoplasm in peripheral islands demonstrate palisading.[15]

Clear cell variants of odontogenic tumors (Pindborg tumor and ameloblastoma), salivary gland origin (acinin cell carcinoma, mucoepidermoid carcinoma, Epithelial-myoepithelial carcinoma, Myoepithelial carcinoma, Myoepithelioma and oncocytoma), vascular derived (Perivascular endothelial cell tumor) and metastatic carcinoma to the jaws (renal, adrenal, parathyroid, thyroid and breast adenocarcinoma) should be considered in histopathologic differential diagnosis of CCOC.[16-27]

Table 2: Clear cell neoplasms in oral cavity

Tumor origin	Clear cell variant	Reference
Odontogenic	Pindborg tumor	16
	Ameloblastoma	17
Salivary gland	Acinic cell carcinoma	18
	Mucoepidermoid carcinoma Epithelial- myoepithelial carcinoma Myoepithelial carcinoma	19
	Myoepithelioma	20
	Oncocytoma	21
Vascular	Perivascular epithelial cell tumor	22
metastatic	Renal	23
	Adrenal	24
	Parathyroid	25
	Thyroid	26
	Breast adenocarcinoma	27

On immunoprofile evaluations, clear eosinophilic cells shows positive reactivity for cytokeratins 8, 13, 14, 18, and 19 and epithelial membrane antigen, but a negative reaction to vimentin, S-100 protein, desmin, smooth muscle actin, HMB-45, alpha (1)-chymotrypsin, CD45, CD31, and glial fibrillary acidic protein.[11]

But in the present case, Immuno stains for cytokeratin 7 showed strong positivity, and none were positive for CD 10, vimentin, and CK 20.

Submental flap was introduced by Martin in 1993.[28] After that many modifications of this flap have been presented.[29-31] The presented case; submental flap was a suitable option for soft tissue reconstruction. It has appropriate hairless skin paddle (in females) for coverage of reconstruction plate and replacement of resected mucosa. It is not bulky so the need for flap revision and plate exposure is not a concern. Bridging the mandibulectomy segment in the lateral region of the mandible by reconstruction plate without bone grafting in malignant lesion is asimple and acceptable method.[32]

The resultant skin scar is the same length as necessaryfor placement of reconstruction plate even if the flap is not in the plane. Removal of excess submental chin by this flap also has esthetic beneficial effects. Skin flap incision allows concomitant access to the neck for SOHND.

Perineural invasion (PNI) is one of the established prognostic factors for adenoid cystic carcinoma (ACC) and squamous cell carcinoma (SCC).[33]

PNI is tropism of tumor cells for nerve bundles in surrounding tissues. It is a form of metastatic tumor spread that leads to more local recurrence, increasing the probability of neck lymph node metastasis. PNI has a negative effect on surveillance rate.[34,35] The concept of PNI has beena known entity for more than 150 years but its clinical significance has been noticed from

three decades ago.[36] There are two famous definitions for PNI; at the first is Batsaki definition in 1985:"Tumor cell invasion in, around and through the nerve" and Liebig *et al*'s definition in 2009: "The finding of tumor cells within any of the three layers of the nerve sheath."[37,38]

Accepted pathologic mechanism for neural extension is secretion of certain growth factors by cancer cells and the presence of receptors in nerve sheath.[39] Neurotropic malignancies are melanoma, polymorphous low grade adenocarcinoma of salivary glands (PLGA), adenoid cystic carcinoma, prostate and pancreatic cancers.[40]

When the cancer has central position in the mandible and in close proximity to the inferior alveolar nerve, then involvement of this nerve should be considered by the surgeon. Ina study by Ariji *et al.*[41,42] on 5 patients with central SCC of the mandible, there were perineural invasions in 4/5 of patients, which is much higher than PNI in mucosal SCC (27%).

Extension of carcinoma via this route (PNI) to the CNS is possible. In the presence of PNI related to the inferior alveolar nerve, involvement of the mandibular branch of trigeminal nerve and extension to the cranium through the oval foramen should be considered.[43] MRI that shows nerve enlargement and CT scan that shows enlargement and/or destruction of oval foramen are useful aids.[44, 45]

Anatomical location (proximity to the inferior alveolar nerve) is related to increased incidence of PNI; therefore, intraoperative control with nerve biopsy and frozen section is necessary in such situations.[46]

Lip sensation alteration, such as numbness (paresthesia, tingling, formication and pain) is a warning sign for the potential involvement of the inferior alveolar nerve in central mandibular lesions, located in bone between the mental and mandibular foramina.[47,48] However, it should be considered that perineural invasion is a process with slow progression and it is possible that despite extensive PNI, there is no sign of lip numbness (like the case presented here). Review of literature for PNI and CCOC revealed just only a histopathologically proven PNI.[32] The importance of PNI in the case presented and the effect on treatment planindicate the need for more radiographic investigation of the nerve canal, an increase in the extent of surgery, incorporation of radiotherapy to the protocol and the need for more attention to neck dissection.

CONCLUSION

Clear cell odontogenic carcinoma needs a special immunohistochemical protocol and complete workup to reach a correct diagnosis. Combination of titanium reconstruction plate and orthograde submental flap is a good choice for reconstruction of the lateral mandibular segment and provision of soft tissue coverage after wide surgical resection. Perineural invasion should be considered in central lesions of the mandible.

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