

CASE REPORT

An unusual presentation of clear cell odontogenic carcinoma in mandibular anterior region

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ABSTRACT

Clear cell odontogenic carcinoma (CCOC) is a rare, potentially aggressive odontogenic epithelial tumor with tendency for recurrence. It was first described as a clinicopathological entity in 1985 and to date only 73 cases has been reported in English literature. A case of CCOC in 64-year-old male patient in mandibular anterior region is presented which when recurred in soft tissue 5 years after wide surgical resection of mandible, revealed a biphasic pattern as against monophasic pattern of primary neoplasm and was unusually associated with primary squamous cell carcinoma, suggestive of hybrid tumor.

Key words: Clear cell odontogenic carcinoma, collision tumor, hybrid tumor, odontogenic epithelial tumor

INTRODUCTION

Clear cell odontogenic carcinoma is a rare odontogenic tumor arising from anterior region of mandible and has predilection for females. It is a potentially aggressive tumor which is capable of frequent recurrences and locoregional and distant metastases.^[1]

Here, we present a case of CCOC in a 64-year-old male patient in mandibular anterior region with a soft tissue recurrence, 5 years after wide surgical resection of mandible and was unusually associated with squamous cell carcinoma.

CASE REPORT

A 64-year-old male patient presented with a diffuse swelling in anterior region of mandible extending towards both right and left parasymphiseal region and extending inferiorly upto lower border of mandible. The lesion was of 1-year duration with rapid increase in size since 3 months [Figure 1a].

Intraoral examination revealed an intrabony swelling in symphyseal and parasymphiseal region of mandible extending from 36 to 46. The lesion was of size 8 × 5 cm with expansion of both buccal and lingual cortical plates

and mobility of 33,34,35,43 and 44. Floor of the mouth was raised but overlying mucosa was intact [Figure 1b]. However, lymph nodes were not palpable. OPG showed an ill-defined radiolucency extending from 36 to 46 [Figure 2].

Clinical diagnosis of malignant neoplasm was done and incisional biopsy was performed at Government Medical College and Hospital and histopathological diagnosis of metastatic carcinoma was given, details of which were not available.

To rule out renal cell carcinoma as a primary neoplasm, USG abdomen was done for kidney but was found to be normal except a small, single cortical cyst in right kidney of size 2 × 2 cm.

However, in view of histopathological diagnosis of malignant neoplasm, wide surgical resection of mandible was done from right angle to left angle of mandible, sparing the rami of both sides. However, it was not followed by radiotherapy.

The resected specimen of mandible was sent to Government Dental college and Hospital, for processing. The gross specimen received was a resected part of mandible from left angle to right angle, of size 9 × 5 × 5 cm comprising 33, 34, 35, 43 and 44 teeth. Both the cortical plates were perforated revealing a soft tissue mass, firm in consistency on lingual side in symphyseal and parasymphiseal region of both right and left side, whereas on buccal side this soft tissue mass was seen extending only on right side.

Microscopic examination revealed the presence of numerous, large irregular lobules of malignant odontogenic epithelial clear cells separated by fibrous septae [Figure 3a]. These

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cells were large, polygonal with abundant clear cytoplasm and eccentrically placed nuclei exhibiting significant cellular and nuclear pleomorphism, hyperchromatism and few mitotic figures; revealing a typical monophasic pattern of CCOC consisting entirely of clear cells [Figure 3b].

The abundant clear cytoplasm of cells was positive for PAS stain [Figure 4a]. This PAS positivity was diastase sensitive indicating intracytoplasmic glycogen content. These cells were immunoreactive for pan cytokeratin [Figure 4b] and negative for S-100 protein [Figure 4c].

In view of all the above findings, histopathological diagnosis of CCOC with monophasic pattern was given.

The resection of mandible was further followed by reconstruction of mandible with incorporation of plate, which subsequently got infected and thereby removed and then the patient was lost for follow-up.

However, the patient reported back after 5 years with a diffuse swelling on left side of face since 2 months, associated with intermittent pain. Patient was unable to open the mouth completely because of the strictures formed in the labial and buccal vestibule. However, a soft tissue growth could be observed in lower labial vestibule in 32, 33 region extending onto the labial mucosa near the angle of the mouth on left side. A single, firm-to-hard submandibular lymph node was palpable on left side. OPG has revealed previous post-surgical



Figure 1: Clinical Photograph of recurrence (a) Extraoral swelling (b) intraoral ulcerated growth

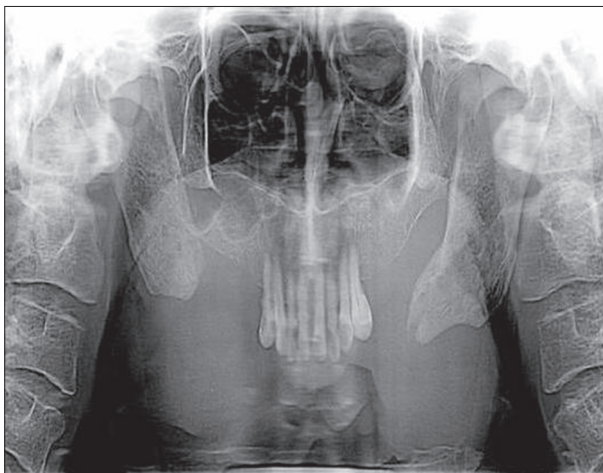


Figure 2: OPG showing absence of mandible from left angle to right angle region of mandible after resection

findings. Provisional diagnosis of squamous cell carcinoma was made.

Incisional biopsy was performed from a soft tissue growth in lower labial vestibule and was sent for processing. A specimen received was a brownish white soft tissue, of size 1 × 0.5 cm and was soft in consistency.

Microscopic examination revealed a highly confusing picture. Superficial part of the lesion consisted of severely dysplastic stratified squamous surface epithelium with infiltration of large sheets of malignant epithelial cells in subjacent connective tissue [Figure 5a and b].

Whereas deepest part of the lesion comprised of numerous small lobules of malignant odontogenic clear cells [Figure 6a and b] and numerous small groups of darkly stained basaloid cells [Figure 6c] scattered in a loose connective tissue stroma, revealing a typical biphasic pattern of CCOC.

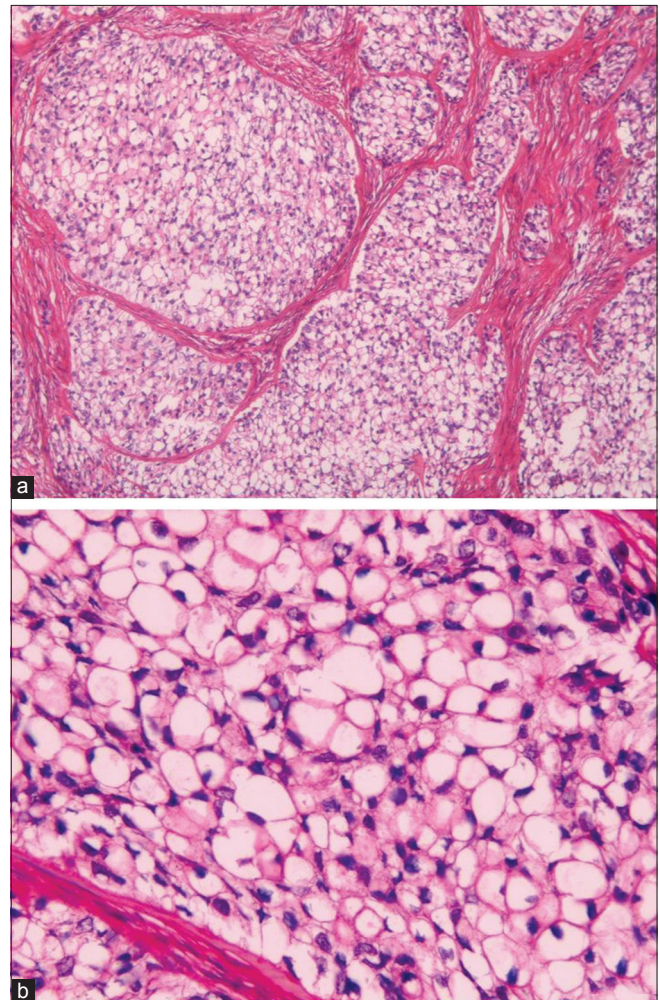


Figure 3: Photomicrograph of primary clear cell odontogenic carcinoma lesion (monophasic pattern) showing (a) large lobules of clear cells separated by fibrous septae (H&E stain, x100) (b) Clear cells with cellular and nuclear pleomorphism, hyperchromatism and few mitotic figures (H&E stain, x400)

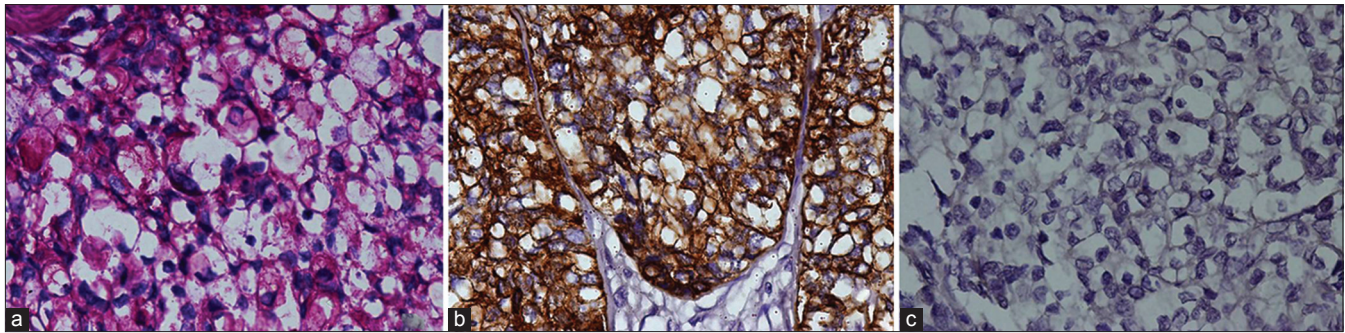


Figure 4: Photomicrograph of primary lesion shows (a) PAS-positive clear cells (PAS stain, x400) (b) Cytokeratin 19 positive clear cells (IHC stain, x400) (c) S-100 negative clear cells (IHC stain, x400)

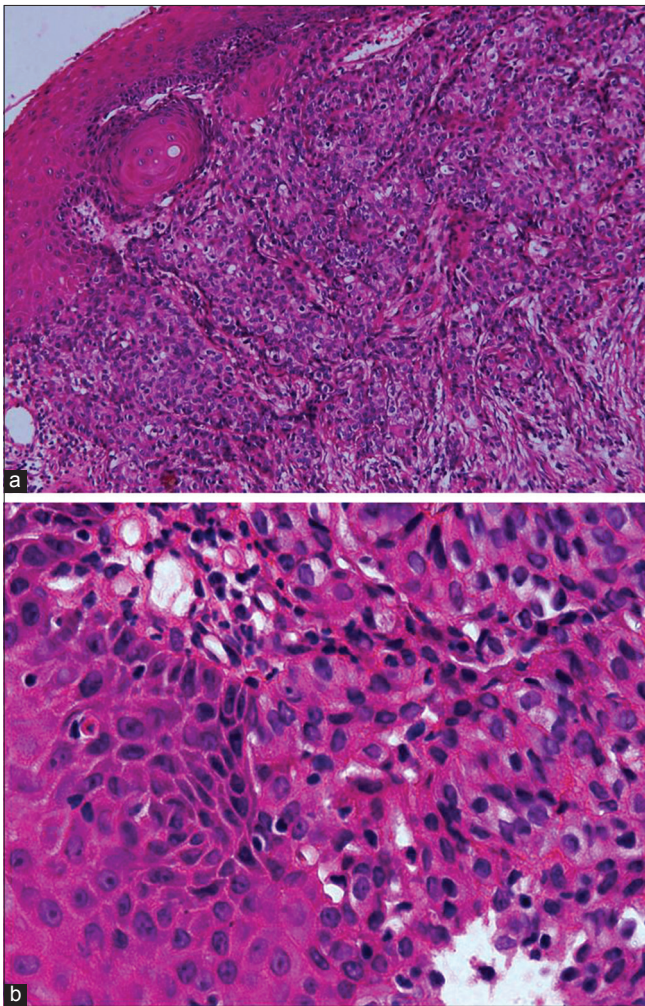


Figure 5: Photomicrograph of recurrent lesion (biphasic pattern) - H & E-stained section of superficial part of the lesion shows (a) Sheets of malignant epithelial cells infiltrating into subadjacent connective tissue (x100) (b) Malignant epithelial cells infiltrating into subadjacent connective tissue (x400)

Intermediate part of the lesion showed somewhat mixed picture with few areas of clear cells and basaloid cells intermixed with few malignant epithelial cells.

These clear cells were diastase-labile PAS positive [Figure 7a and b] and were mucicarmine negative

[Figure 7c]. All the cells were intensely positive for cytokeratin 19 [Figure 8a and b] and were negative for S-100 protein [Figure 8c] excluding the possibility of salivary gland neoplasm. Malignant squamous epithelial cells present in the superficial part of the neoplasm were negative for calretinin [Figure 8d] excluding the possibility of odontogenic origin.

Therefore, the case was diagnosed histopathologically as recurrence of CCOC in soft tissue with typical biphasic pattern as against monophasic pattern seen in the primary neoplasm with an unusual association of primary squamous cell carcinoma.

Since, the patient was old, debilitated and reluctant to undergo any further therapy; he was kept on symptomatic treatment and regular follow-up. But he did not report for follow-up and died of the disease almost after 1 year of recurrence.

DISCUSSION

Hansen *et al.* and later Waldren in 1985 reported a locally aggressive odontogenic neoplasm and named it as clear cell odontogenic tumor.^[1] Although originally it was thought to be benign and classified as a CCOT by WHO in 1992: On the basis of their aggressive behavior, predilection for local recurrence, evidence of distant metastasis, histologically distinct malignant features and tumor related deaths, these tumors were considered as malignant and subsequently classified as clear cell odontogenic carcinoma by WHO in 2005.^[1] To date 73 cases has been reported in English literature.^[2]

Odontogenic neoplasms composed predominantly of clear cells are quite unusual and pose a diagnostic challenge. CCOC is one of them and therefore should also be considered in differential diagnosis.

The classic clinical presentation of CCOC is painful anterior mandibular swelling in elderly women, loosening of adjacent teeth and ill defined irregular radiolucency with resorption of roots.^[1]

Histopathologically CCOC may show one or more of the architectural patterns, biphasic, monophasic and

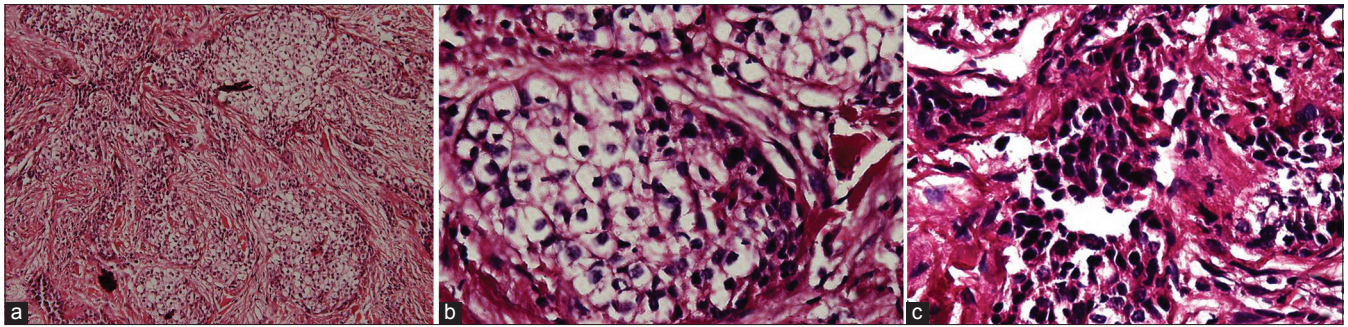


Figure 6: Photomicrograph of recurrent lesion (biphasic pattern) - H&E-stained section of deeper part of the lesion shows (a) Small lobules of clear cells (x100) (b) high power-view of small lobules of clear cells (x400) (c) Small groups of basaloid cells (x400)

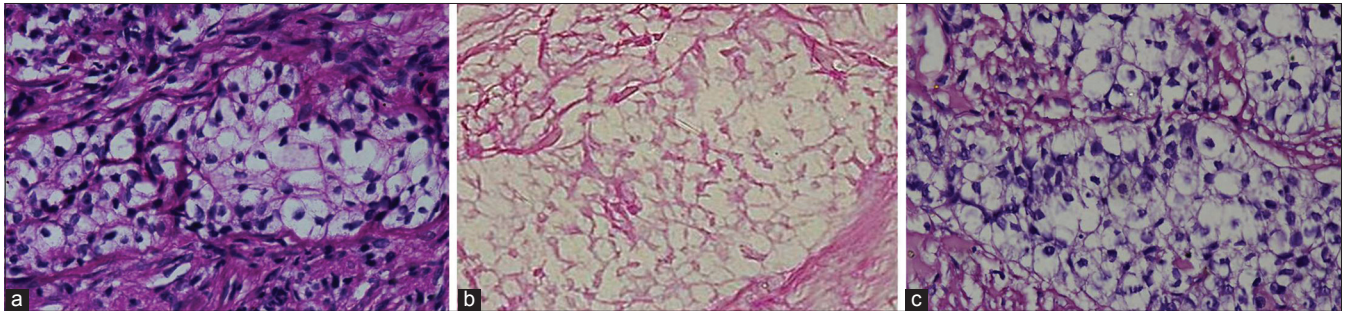


Figure 7: Photomicrograph of recurrent lesion with Special stains (a) PAS-positive clear cells (PAS stain, x400) (b) Diastase labile clear cells (diastase enzyme reaction, x400) (c) Mucicarmine-negative clear cells (Mucicarmine stain, x400)

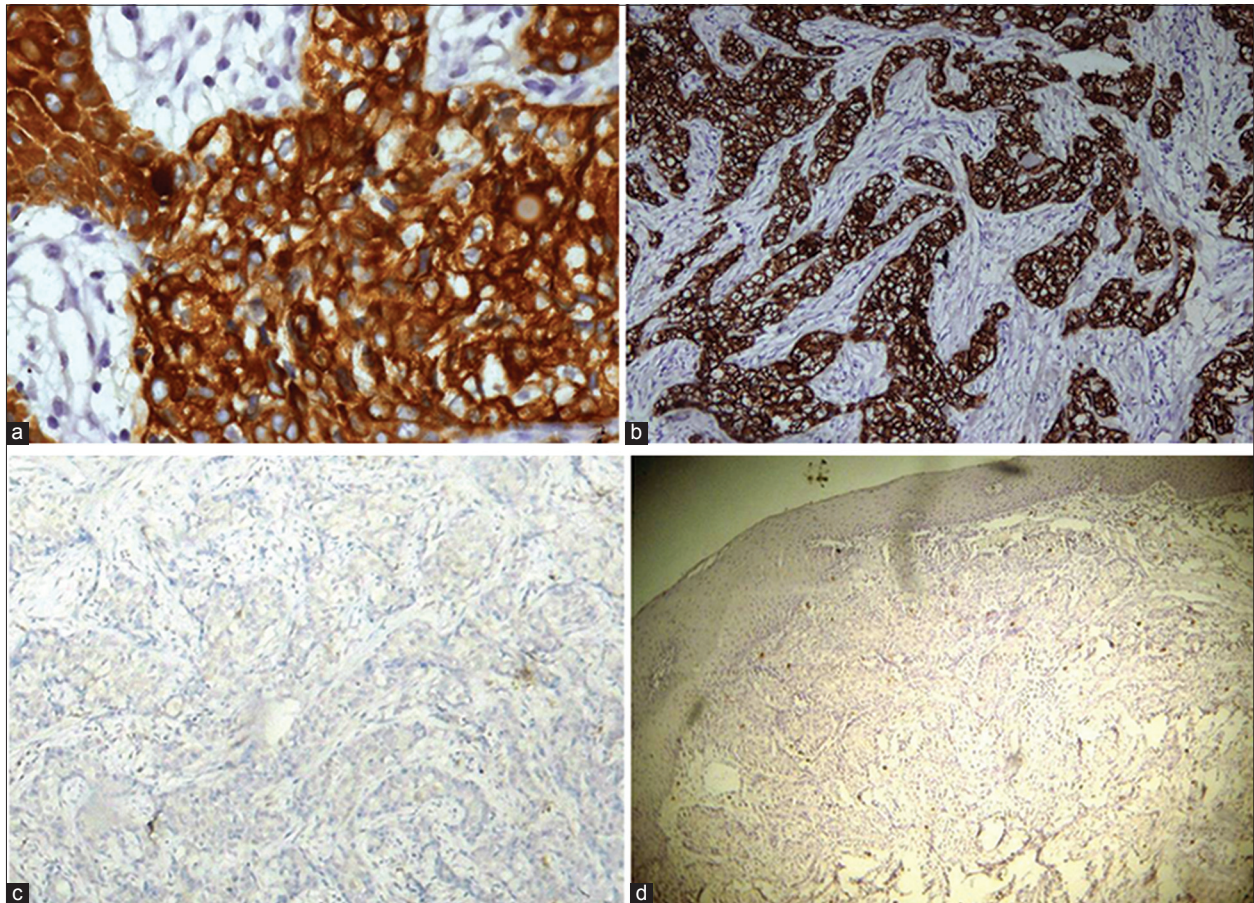


Figure 8: Immunohistochemistry of the recurrent lesion (a) Cytokeratin 19 positive malignant epithelial cells (IHC stain, x400) (b) Cytokeratin 19 positive cells in intermediate part (IHC stain, x100), (c) S-100 protein negative cells in intermediate part (IHC stain, x100) (d) Calretinin-negative malignant epithelial cells (IHC stain, x40)

ameloblastomatous. The most common biphasic pattern consists of both clear cells and basaloid cells in a fibrous stroma. The monophasic pattern composed entirely of clear cells whereas ameloblastomatous pattern resembles the growth pattern of ameloblastoma with peripheral palisading and reversal of polarity.^[1]

Mitotic figure is not a reliable factor for detecting malignancy in odontogenic tumors so the diagnosis of malignancy is done considering significant cyto-nuclear atypia.^[3]

The differential diagnosis includes intraosseous MEC; metastatic renal cell carcinoma; clear cell variant of CEOT; clear cell differentiation in ameloblastoma, squamous cell carcinoma and amelanotic melanoma.

This case of CCOC had primarily involved anterior mandible in 64-year-old male, which comprised entirely of clear cells revealing typical monophasic pattern. These clear cells showed significant cellular and nuclear pleomorphism with hyperchromatic nuclei and few mitotic figures.

In the primary lesion, metastatic carcinoma was ruled out by ultrasound. Various special stains like PAS, mucicarmine and immunostaining (S-100 protein) was done to rule out other clear cell neoplasms.

Wide surgical resection of mandible was done for primary lesion of CCOC but was not followed by radiotherapy, since no obvious soft tissue involvement was seen during surgery along with absence of lymph node involvement.

It is known that 43% of cases recur even after wide surgical resection whereas overall rate of recurrence is 55%. Of course this figure is quite low compared to much higher recurrence rate of 80% after curettage.^[4] So the treatment should be aimed at achieving wide surgical resection with tumor-free margins, loco-regional control by lymph node resection and adjuvant radiation in cases with extensive soft tissue invasion. And long-term follow-up is necessary to look for loco-regional recurrence and distant metastasis to lungs and bone even after appropriate therapy.

In this case, the lesion recurred after 5 years of wide surgical resection of mandible indicating its potential aggressiveness or possibly since both cortical plates were perforated, some soft tissue involvement might have been present.

But the interesting part was that this recurrence in soft tissue was with an unusual presentation. The recurrence was in the form of soft tissue growth in lower labial vestibule on left side. Since there was diffuse swelling of left side of face, we tried to locate for the growth in buccal vestibule on the same side but could not do so, as the patient was unable to open the mouth because of strictures formed on that side after surgery. So, the incisional biopsy was done from lower left labial vestibule.

We received a small soft tissue specimen of size 1 × 0.5 cm. The histopathology of this recurrent lesion posed a great diagnostic challenge to us. Firstly, this lesion has shown typical biphasic pattern of CCOC comprising several small lobules of odontogenic clear cell and small groups of darkly stained basaloid cells in a loose connective tissue stroma instead of monophasic pattern, entirely of clear cells of primary lesion. Secondly, still more interesting finding was the infiltration of malignant epithelial cells in the superficial most part of the lesion just beneath the dysplastic stratified squamous surface epithelium breaking the basement membrane, suggestive of squamous cell carcinoma.

Although, these features were obviously of CCOC indicative of recurrence, presence of these malignant epithelial cells posed a problem in final diagnosis.

So to rule out clear cell differentiation in SCC, adenosquamous carcinoma and salivary gland neoplasms, special staining and immunohistochemistry was done.

Since clear cells were mucicarmine negative and S-100 protein negative, the possibility of salivary gland neoplasm was excluded. These clear cells were positive for diastase digestive PAS stain indicating the presence of intracytoplasmic glycogen, consistent with CCOC. All the lesional cells were also intensely positive for cytokeratin. So, to separate out SCC from recurrent CCOC, calretinin tumor marker was applied where superficially placed malignant squamous epithelial cells were negative indicating their non-odontogenic nature; however, deeper part of the section was washed out during staining and another section could not be obtained as the tissue was exhausted.

So the final diagnosis of recurrence of CCOC in soft tissue with a biphasic pattern as against monophasic pattern of primary neoplasm along with unusual association of it with primary squamous cell carcinoma was made.

The loco-regional recurrence of neoplasm following treatment arises from microscopic cells of original neoplasm that have escaped therapeutic intervention and later become clinically visible at original site.^[5]

Whereas, second primary neoplasm which is known to occur commonly in SCC of head and neck is an abnormal growth of tissue that follows a previous or index neoplasm but not the metastatic one, should have at least 2 cm of normal mucosa between primary and second primary neoplasm. Also the second primary neoplasm should occur within 6 months (synchronous type with same histological pattern) or appear after 6 months but within 5 years (metachronous type with different histological pattern) after appearance of primary neoplasm or index tumor. But in all cases they arise from an independent oncogenic event.^[6] As well, the development of second primary neoplasm may or may not be

related to treatment for the previous neoplasm since genetic risk or predisposing factor may actually be the cause.

This lesion seems to be the secondary (recurrent) neoplasm since the lesion appeared well after 5 years of duration. Probably the microscopic cells of original neoplasm might have escaped radical surgical resection, since the lesion has perforated the cortical plates as was evident during grossing of the specimen.

But then it is also said that varying degrees of uncertainty can persist with a minority of cases remaining unresolved.^[7]

Although no evidences of second primary neoplasm of CCOC are available in the literature, it is essential to distinguish between two from treatment and prognostic point of view. These two are polygenic traits, determined by multiple low penetrance loci.

It is also essential to distinguish second primary neoplasm and recurrent neoplasm, the reason being, although the lymph node metastasis on initial presentation is infrequent, nodal involvement markedly increases in those with recurrent diseases (33%) as was seen in the present case where recurrent lesion was associated with lymph node involvement but unfortunately this could not be evaluated further.

Another interesting feature of this lesion was simultaneous presence of primary SCC and recurrent CCOC. Simultaneous existence of two entirely different, distinct neoplasms as a single lesion at a single site is called as a hybrid tumor, whereas two neoplasms that arise at independent topographic site and invade each other are called as collision tumor.^[8]

It is a matter of debate whether this neoplasm should be considered as a hybrid tumor or collision tumor.

But since the incisional biopsy was done from a single site comprising two different, distinct neoplasms, superficially present primary SCC and deeply present recurrent CCOC as a single lesion, goes in favor of hybrid tumor.

As diagnostic and therapeutic approach continue to improve the ability to accurately predict recurrence and second primary neoplasm in early stage of malignancy, this would facilitate intensive surveillance or targeted intervention for high risk patterns and therapy and will reduce the mortality and morbidity.

Various recent diagnostic aids for the prediction of recurrence are genetically analyzed using p53 and K-ras genotyping.^[9]

The patients who have p53 alterations in their primary tumor and/or in resected margins are deemed to have a high risk for recurrence and thus need more aggressive adjuvant therapy.^[10]

Unfortunately such recent predictive aids for recurrence were not carried out for the primary lesion which has led to recurrence and ultimately the patient succumbed to death within 1 year of recurrence.

Thus the simultaneous occurrence of primary SCC and secondary or recurrent CCOC in soft tissue with different histopathological pattern than its primary lesion seems to be quite unusual and possibly first of its kind in the literature appeared so far.

CONCLUSIONS

An unusual case of CCOC in anterior part of mandible in 64-year-old male patient is presented with no obvious soft tissue involvement. The lesion recurred in soft tissue after 5 years in spite of wide surgical resection of mandible indicating its potential aggressiveness and high recurrence rate. This recurrent soft tissue lesion revealed a different microscopic pattern than its primary lesion along with unusual association of squamous cell carcinoma, possibly suggestive of hybrid tumor. It is learnt from this case that it is always safe to advise diagnostic aids for the prediction of recurrence, so that radiotherapy can be given after surgery to avoid recurrence.^[9]

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