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Clear cell odontogenic carcinoma: a rare pathology with an innovative resolution

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SUMMARY

Clear cell odontogenic carcinoma (CCOC) is an uncommon condition that has been considered malignant since 2005. The clinical presentation usually involves an asymptomatic swelling, which typically affects the anterior mandible in middle-aged women; it has neither clinical nor radiological defining features. Immunohistochemical analysis usually aids diagnosis, as clear cells are also associated with other clear cell carcinomas and benign tumors. Radical surgery is the gold standard of treatment and usually needs microsurgical reconstruction with bone transference for restoration of facial anatomy and adequate function.

We present the case of a young woman with CCOC whose tumor removal and reconstructive surgery were planned virtually and assisted by intraoperative navigation. The novelty of the reconstructive procedure was the replacement of the fibula cutting guides for intraoperative navigation of the osteotomies. We present a brief review of CCOC and the benefits of using computer-assisted surgery (CAS) in high-complexity cases like this one.

Key words: clear cell odontogenic tumors, virtual planning, intraoperative navigation.

INTRODUCTION

Malignant odontogenic tumors represent 6% of all odontogenic tumors. Clear cell odontogenic carcinoma (CCOC) is an uncommon tumor, which was first described in 1985, but officially recognized as malignant in 2005 (1-4).

CCOC clinical presentation usually involves asymptomatic swelling, located mainly in the anterior mandible. It most frequently affects middle-age females. Radiological findings show a well-defined radiolucent uni or bilocular tumor, with or without bone resorption. Even though clear cells are the most representative histological distinctive attribute, immunohistochemistry is usually needed to make the diagnosis. The gold standard of treatment is surgical removal with oncological margins. Adjuvant therapy is still in discussion (1-7).

We present the case of a young woman with CCOC, not only because of its rare pathology, but also because her surgical treatment was virtually planned and assisted by intraoperative navigation. We have made a brief review of both CCOC and computer assisted surgery (CAS).

CASE REPORT

We present the case of a 28-year-old woman with no relevant background, who was referred to our institution with a 6-month history of a painless swelling located in the right hemi-mandible. Oral examination revealed a non-tender, well-defined tumor and no other relevant findings. The panoramic radiography showed a radiolucent lesion and the computed tomography scan (CT) evidenced a 34×20 mm expansive osteolytic lesion with ill-defined limits (Figure 1). A biopsy was performed confirming CCOC.

The surgical treatment consisted in a segmentary mandibulectomy with lymph node dissection and reconstruction using a microvascular fibula flap. Both procedures were planned virtually and assisted by intraoperative navigation (Figure 2). A CT scan and magnetic resonance imaging (MRI) fusion was performed for virtually planning, in order to outline the tumor margins and define the exact location of the osteotomies for tumor resection. After virtual planning, 3D print models were used to pre-bend the 2.0 mm reconstruction plate, saving intraopera-

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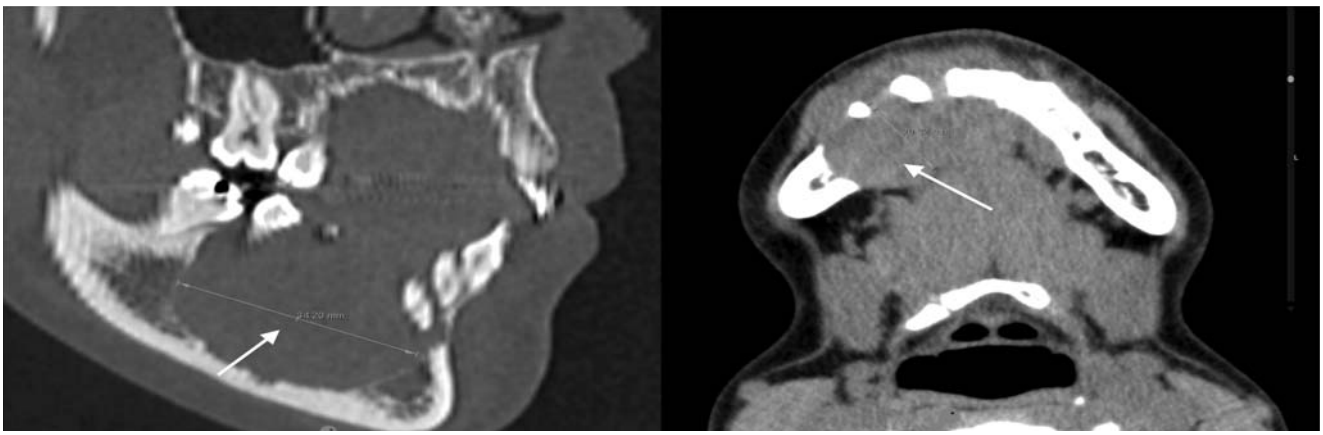

Fig 1. Cross-sectional image showing a 20 x 34 mm destructive lesion (white arrows) eroding the bone of the right hemimandible

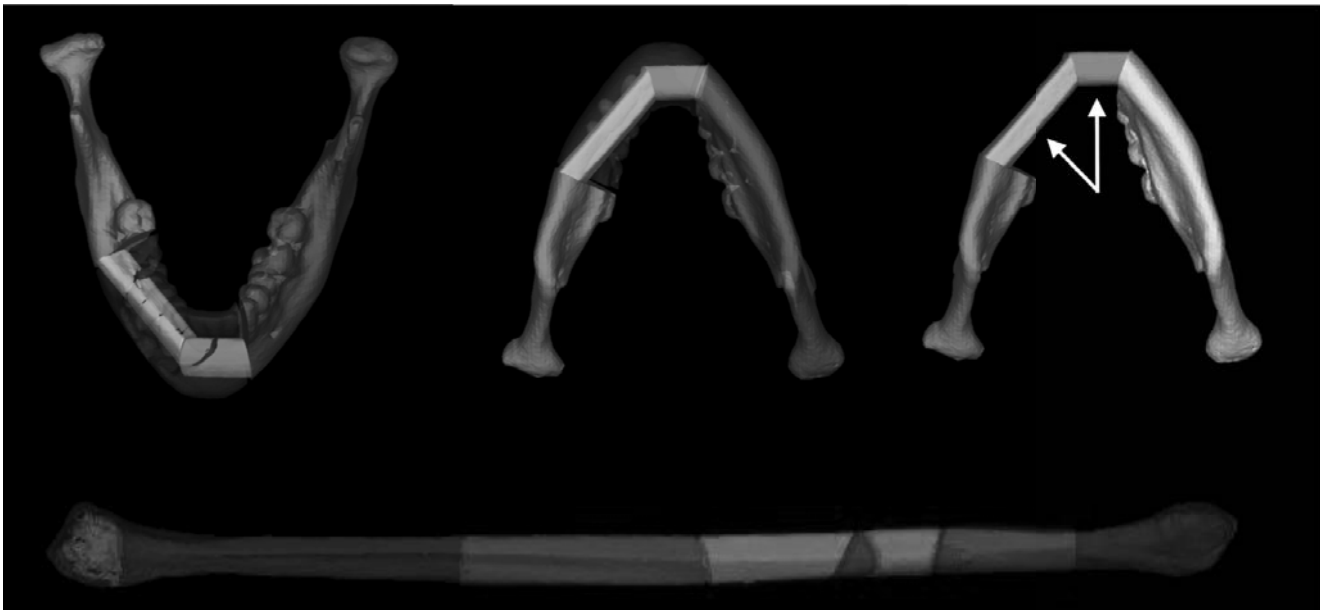

Fig 2. Virtual reconstruction of the mandible and fibula showing the planned osteotomies. Each individual bone fragment is given a color to make the real reconstruction easier and more accurate. The white arrows show the final outcome planned.

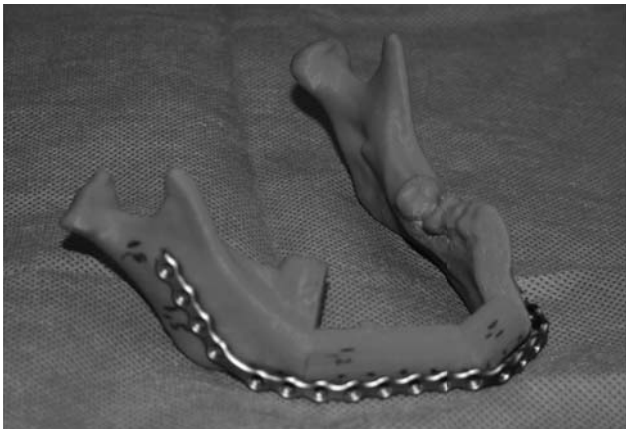

Fig 3. A 3D model was printed to pre-bend the 2.0 mm reconstruction plat

tive time (Figure 3). Once in the operating room, after exposing the tumor, virtual registration was performed and real-time images were displayed on the navigator's screen (Stryker Navigator, Chart II, Freiburg, Germany). These images were overlapped with the ones used for the virtual planning enabling the surgeon to do an accurate en bloc resection. The fibula surface was also registered, in order to navigate the planned osteotomies. For this purpose, the registration pins were installed on the fibula, guiding the osteotomies. This step replaced the classical cutting guides (Figure 4). Intraoperative navigation was also useful to fix correctly the reconstruction plate on the fibula sections (2.0 mm MatrixMANDIBLE Reconstruction Plates, DePuy Synthes, USA) (Figure 5); a postoperative CT scan showed an acceptable minimal difference between the planning and the final outcome (Figure 6).

The final biopsy confirmed the diagnosis. It revealed sheets and islands of large clear cells, separated by a delicate fibrous connective tissue stroma of polygonal cells, with clear cytoplasm and minimal nuclear pleomorphism. Occasional islands showed peripheral palisading and desmoplastic stroma, which stained positive for periodic acid-Schiff. The immu-

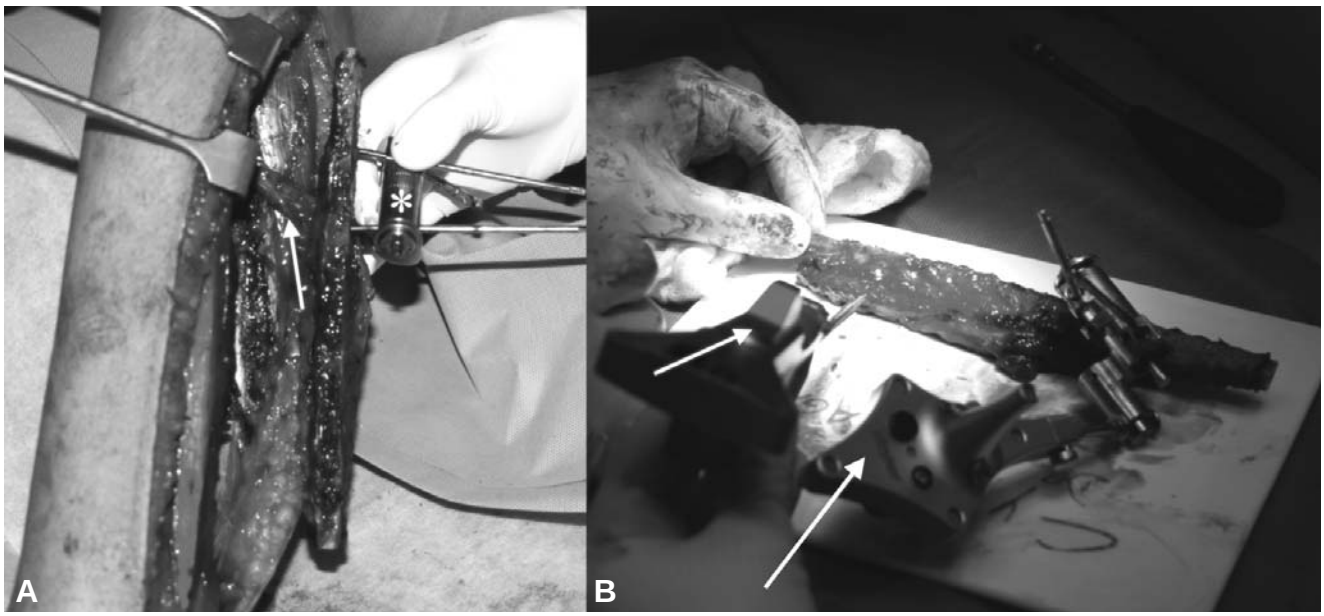

Fig 4. Intraoperative navigation. A – the white arrow shows the pedicle; the white asterisk shows the registration pin installed in the bone. B – the cutting guides for the osteotomies were replaced by intraoperative navigation; the short arrow shows the infrarred registration device.The large arrow shows the registration pin.

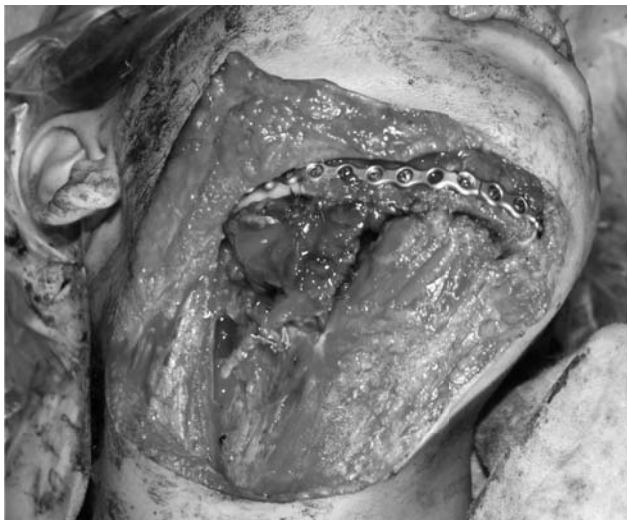

Fig 5. Final position of the fibula fixed with a 2.0 reconstructive-preformed plate (2.0 mm MatrixMANDIBLE Reconstruction Plates, DePuy Synthes, USA)

nohistochemistry was positive for pancytokeratins (CK AE1AE3) and negative for S-100, EMA and vimentin. No metastatic nodes were noted.

The Oncological Board Committee discussed the case and recommended adjuvant treatment with radiotherapy (IMRT) receiving 60 Gy.

The patient has not presented recurrences or distant metastases after a 21-month follow-up. She had 20 sessions of hyperbaric chamber treatment with the aim of beginning dental rehabilitation.

DISCUSSION

CCOC is a rare intraosseous tumor that represents a diagnostic challenge for physicians due to its uncharacteristic features. It occurs more frequently in the mandible than in the maxilla (60-75 and 25-40%, respectively) (1) with a mean diameter of 4 cm. Patients complain of a painless slow growing tumor, associated with tooth mobility in one third of them (1, 4, 6). Other symptoms are bleeding, pain, paresthesias and non-healing ulcerations (4). It usually affects middle-aged women, with a mean age of 50-60 years. The female:male ratio is 1:1.8-2 (1, 3). In our case, the patient was younger, but her history was similar to the previous reported cases. Kalsi *et al.* (7) reported only 8 cases with younger age in literature.

Loyola *et al.*'s (4) review found no radiological features either Panoramic radiographs show a radiolucent cystic tumor, with well-defined margins as in our case. CT scans or MRI are helpful to evaluate the inferior dental nerve invasion, soft tissue involvement and bone erosion. Positron emission tomography/TC (PET/TC) has not shown to be useful as a diagnostic tool (1, 3, 4). These uncharacteristic clinical and radiographic presentations might delay diagnosis and treatment (1, 5-7).

Histopathology is not characteristic either as clear cells appear in other neoplasms. They result from accumulation of water, glycogen, mucopolysaccharides and mucin; thus, they stain positive for Periodic Acid-Schiff (4). However, these types of cells also appear in other clear-cell carcinomas and benign odontogenic lesions (4). CCOC has three rather well-defined cellular patterns: the monophasic pattern that comprises only clear cells; the biphasic (most frequent) with two types of cells that combines clear cells, with clear cytoplasm and basaloid cells, with

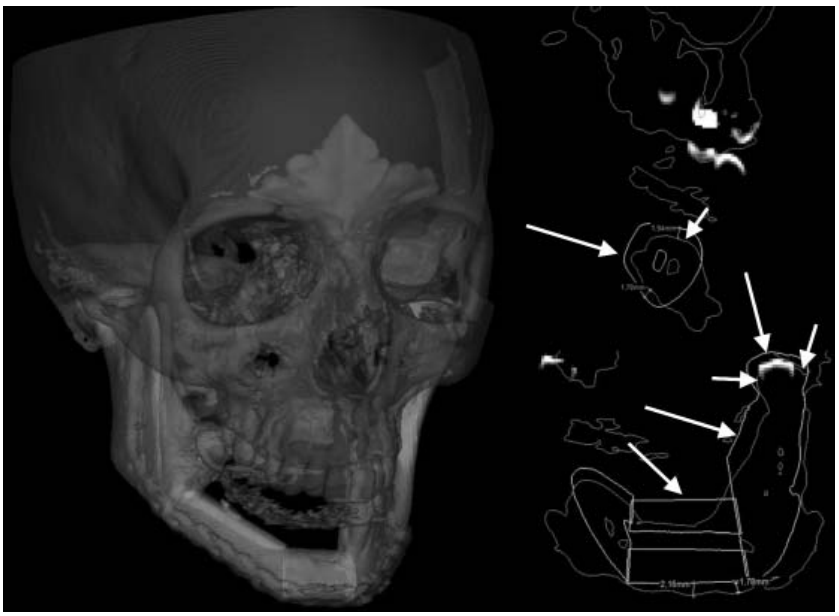

Fig 6. Preoperative planning (orange – short arrows) and post-operative (white – large arrows) images overlapped. The distance errors between them are presented as color-coded images on the right, with the error values indicated in mm for each segment. A corresponding value between 1-2 mm is accepted.

darker eosinophilic cytoplasm; and the ameloblastoid pattern that consists of central columnar clear cells and and ameloblastic differentiation at the periphery of the tumor (1, 3-5). Perineural or vascular emboli might be present (1).

As above mentioned, clear cells are hallmark but not pathognomonic, hence, differential diagnoses include other clear cell tumors such as kidney, thyroid, prostate and colon carcinoma metastasis, calcifying odontogenic carcinoma or Pindborg's tumor, atypical odontogenic tumors, adenocarcinoma, ameloblastoma, mucosal melanoma, myoepitelioma, pleomorphic adenoma and acinic cells carcinoma (1-5). Immunochemistry generally defines the diagnosis staining positive for pancytokeratins, among them, CK8, CK13, CK14, CK18, CK19, CK20 and AE1/AE2 and for epithelial membrane antigen (EMA). It is usually negative for protein S-100, HMB-45, desmin, SMA, CD31, CD45 and GFAP. Many reports describe low levels of p53 and ki-67 (under 88%)(4).

The hypothesized relation between ameloblastoma, CCOC and ameloblastic carcinoma is worth noting. In general terms, ameloblastic carcinoma (AMECA) or CCOC could be phenotypic variants of the same lesion that arise from a malignant transformation within an ameloblastoma (1, 4).

Radical resection with oncological margins remains as the gold standard of treatment (1-7). This particular case was planned virtually and intraoperatively navigated due to its complexity. To summarize, the primary endpoint of virtual planning is achieving more predictable and precise postoperative results, as surgeries can be performed virtually multiple times. It also delivers precision in terms of tumor size, margin resection and implants location (8-11). In this case, VP determined tumor extension, and subsequently the precise placement of the mandible osteotomies. It also located the fibula sections and their final position. INV is generally used as a positioning system that provides real-time guidance by identifying the anatomy (8, 11). In our case, a 3D model of the "new" mandible was printed after planning, to facilitate prebending of the titanium plate with the aim of saving intraoperative time. The novelty of our procedure was the replacement of the classical cutting guides for fibula osteotomies with intraoperative navigation. The registration pins were installed on the bone, guiding the osteotomies and the plate final positioning. Afterwards, the bone and soft tissue flap was transferred with microsurgery. A post-operative CT scan was used to compare virtual and post-operative results. According to Levine *et al.* (9), excellent accuracy is achieved within 1 to 5 mm. Some other authors like Azarmehr *et al.* (11), suggest a maximum difference of 2 mm between the virtually planned surgical procedure and the actual outcome. In our case, the posoperative outcome had a minimal difference of less than 2 mm. In summary, both virtual planning and intraoperative navigation prevent inaccurate surgical procedures and guarantee the success of the entire procedure (8-11).

The incidence of recurrence and distant metastases is about 41% and 31-34%, respectively. Most of them appear in lungs and bones (3, 4, 6, 7). As previously mentioned, radical surgery is the gold standard of treatment. As a result, conservative procedures, such as enucleation or marginal resection, are totally contraindicated. Inadequate resection with positive or close margins is one of the most important factors for recurrent or metastatic disease. Free margins achievement is recommended in these cases to increase long-term survival. In Loyola *et al.*'s (4) review, the univariate survival analysis identify size, ameloblastic pattern, regional and distant metastases, and local recurrence as prognostic factors. Lymph node dissection should be performed if node invasion is confirmed. The general recommendation is to perform at least Level I dissection, which is the most frequently affected (4). In our case, even though the patient was clinically N0, we performed

a supraomohyoid dissection. Adjuvant radiotherapy might benefit patients with perineural or vascular invasion, cortical erosion or inadequate margins but there is still not enough data to support this indication (4, 5, 7). Loyola *et al*. (4) found there is no evidence of long-term control of the disease with chemo and radiotherapy. In Said *et al*.'s (1) revision, 21.6% of patients received radiotherapy but long-term results are still needed to define the validity of the treatment. Furthermore, neither fraction nor doses was entirely described (1). As other oncological diseases, long-term follow-up is suggested.

CONCLUSION

CCOC is an unusual type of tumor with difficult characterization. The final diagnosis is usually reached by IHQ. Surgery with safety margins continues to be the recommended treatment, while adjuvant treatment has not demonstrated to prolong survival yet.

Nowadays, CCOC is considered as an aggressive tumor due to the high frequency of recurrences and metastases. As a result, both follow-up and treatment should be directed to prevent and rapidly identify them.

On the other hand, in this particular case, virtual planning and intraoperative navigation have resulted in an invaluable tool bringing accuracy into the operating room and leading to excellent post-operative results.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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