

Hyalinizing clear cell carcinoma of tonsil: about a case report and review of the literature

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SUMMARY

Background: Clear cell carcinoma (CCC) is a low-grade malignant tumor that usually appears in the minor salivary glands of the oropharynx and other sites and is a rare feature of salivary gland tumors. **Methods:** We present here the case of a 58-year-old woman with no medical history. She consulted for swelling under the left mandible. On clinical examination, the patient had a swelling of the left tonsil. A biopsy was performed and histological and immunohistochemical results were used to diagnose a Hyalinizing clear cell carcinoma of the left tonsil. Cervical facial CT scan showed a tumor process of the left tonsil compartment with bilateral cervical lymphadenopathies. No other lesions were detected in the systemic evaluation. Surgery was not feasible in this patient and therefore the decision to opt for concurrent chemo-radiotherapy was made. **Results:** The patient was reviewed after 1 month. Clinically, it shows a regression of cervical adenopathies and a decrease in the volume of the tonsillar tumor mass. Skin reactions almost resolved. The patient was doing well.

Conclusion: concurrent chemo-radiotherapy is used in the treatment of locally advanced clear-cell carcinoma of the tonsils that escape surgery with good disease control results.

Key words: hyalinizing clear cell carcinoma, chemo-radiotherapy, tonsil

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INTRODUCTION

Clear Cell Carcinoma (CCC) of the oral cavity is similar to clear cell cancer described in the kidney and other abdominopelvic organs. Hyalinizing clear cell carcinoma (HCCC) is a distinct subtype of CCC of oral cavity. HCCC was first described by Milchgrub in 1994 [1] as a separate entity from Epithelial-Myoepithelial Salivary Gland Carcinoma (EMEC) and is currently classified as clear cell carcinoma, not otherwise specified by the World Health Organization Classification of Tumours [1, 2]. It is histologically distinct based on its round cells with clear cytoplasm arranged in nests or cords with broad bands of hyalinized stroma [1, 2]. Molecular analysis shows the presence of EWSR1-ATF1 gene fusion, distinguishing HCCC from EMEC [3, 4].

This is an exceedingly rare tumor making up <1% of salivary gland tumors, which themselves make up only 3%-5% of head and neck tumors [5]. Clinically, HCCC usually affects adult women at a median age of 60 and is commonly located in the minor salivary gland of the oral cavity with predominance at the base of the tongue and palate [6, 7]. Patients will have a firm non-tender mass usually without any signs of local or distant metastasis [8]. These tumors are known to take an indolent course and wide local excision is the primary treatment with radiotherapy reserved for patients with aggressive features, positive margins or local metastasis [9].

In this article, we describe an unusual case of HCCC presenting as a tonsillar mass and its treatment.

METHODS: CASE REPORT

A 58-year-old woman presented to our hospital with a history of foreign body sensation in the throat for the past two years, with the appearance of swelling under the left mandible gradually increasing in volume over the past 6 months. She denied any significant throat pain, odynophagia, otalgia, dysphagia, dyspnea, dysphonia, weight loss, fevers, chills or fatigue, but she reported a notion of the gurgling to the swallowing. There was no history of smoking or intake of alcohol. Physical examination demonstrated a well-developed and well-nourished woman in no distress. She had a limitation of the mouth opening (Figure 1).

Her oropharynx, hardly examined, had an asymmetric, enlarged, non-obstructive, exophytic left tonsil with erythema



Fig. 1. Images showing a limitation of the mouth opening in the patient

but no exudate. On palpation, the mass was firm, not tender and did not bleed. The tongue movement was normal. The patient had cervical lymphadenopathies palpable on both sides of the neck, the largest was on the left side and measured 2 cm in diameter. Laboratory evaluations including complete blood count, electrolytes and basic metabolic profile were normal. The Computerized Tomography (CT) scan of the neck (axial cuts) with contrast confirmed a left tonsillar mass of 14 cm in greatest dimension with an enhancing irregular rim (Figure 2).

Radiologically there were also bilateral cervical pathological lymphadenopathies and sub-channels, the largest of which was on the left side and measured 5 cm in diameter (Figure 3).

CT scan of the chest and abdomen did not reveal any metastases (Figure 4).

The tumor has been classified T3N2M0 according to the 8th edition of the AJCC/IUCC. The patient underwent a biopsy was taken under general anesthesia of the left tonsil, which was suggestive of hyalinizing clear cell carcinoma. Since the tumor was locally very advanced and invading the neighborhood structures with multiple large lymphadenopathies, the patient was surgically rejected and the decision was made to start the patient on definitive concurrent chemo-radiotherapy immediately. Radiotherapy was administered via an Intensity-Modulated Radiotherapy (IMRT) technique with fields prescribed to the 100% isodose line in Simultaneous Integrated Boost (SIB), using 6-MV photons, with a total dose of 70Gy in 35 fractions daily in 7 weeks (2 Gy per day) on tumor and lymphadenopathy (Figures 5 and 6).

A dose of 63Gy in 35 daily fractions (1.8Gy per day) in the lymph node areas including lymphadenopathys as well as upstream and downstream node areas (Figure 7).

The dose constraints to organs at risk have been respected, with optimal coverage and satisfactory target volumes. We used cisplatin as a radiosensitizer at 40 mg/m² weekly schedule with standard premedications for antiemesis and hydration. During concomitant chemo-radiotherapy treatment, the patient developed acute toxicity in the form of grade II oral radiomucitis and dysphagia, and grade I neck radiodermatitis, starting from the 3rd week of treatment. For her oral radiomucitis, the patient was put on symptomatic treatment with mouthwash and corticosteroid therapy, and a healing cream was prescribed for the patient for her neck radiodermatitis. The patient tolerated concomitant chemo-radiotherapy very well and completed her

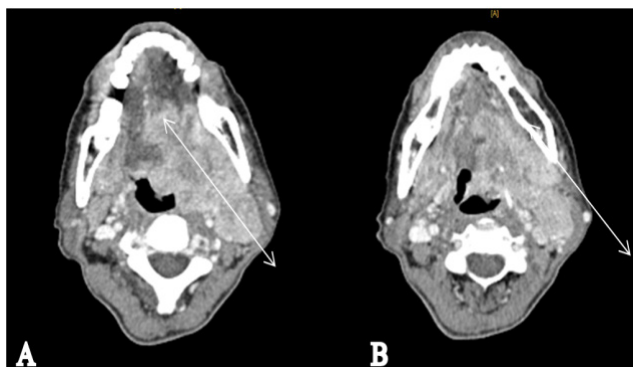


Fig. 2. Axial scan sections showing the tonsillar tumor with irregular rim

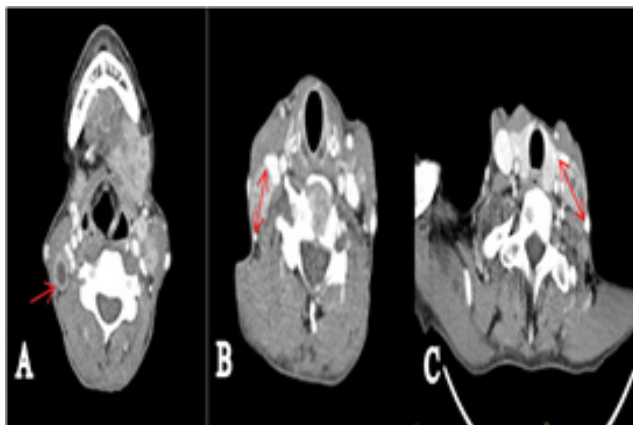


Fig. 3. Axial scan sections showing bilateral cervical pathological lymphadenopathies

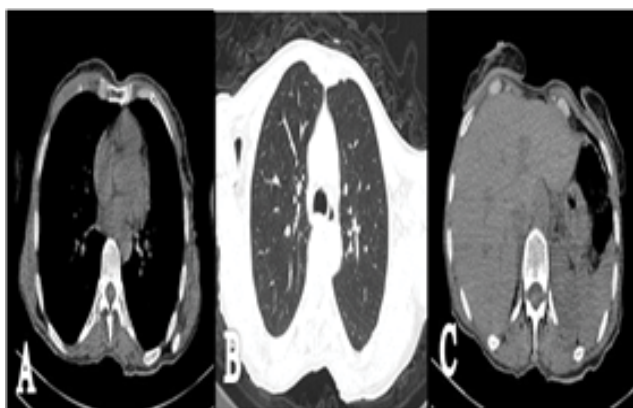


Fig. 4. Axial scan sections of the thoracic and abdominal floors showing the absence of distant metastases

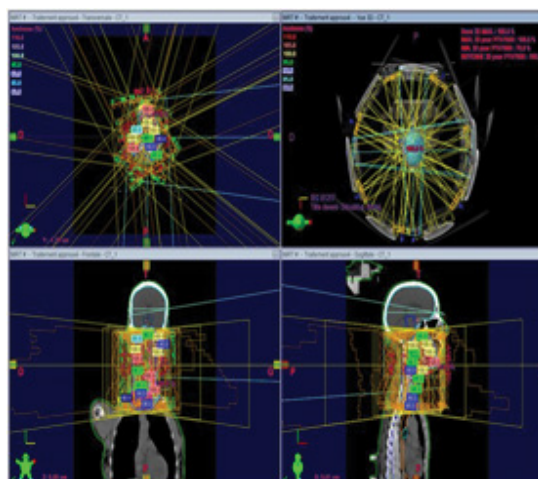


Fig. 5. Disposition of multiple IMRT beams on the three plans (axial, sagittal and coronal)

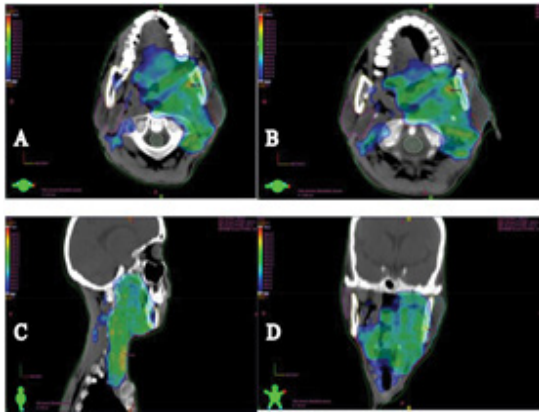


Fig. 6. (A,B): Axial view of the conformity of the prescribed dose to the target volume in blue and the respect of the left parotid (cyan) and the spinal cord (light green); C: sagittal plan; D: coronal plan

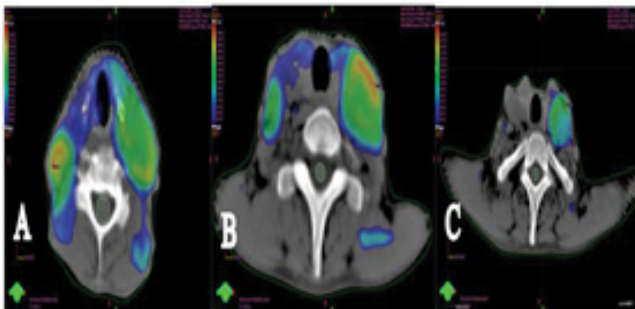


Fig. 7. Axial view of the conformity of the prescribed dose to the target volume in the lymph node areas including lymphadenopathies as well as upstream and downstream node areas in blue

treatment without a period of therapeutic discontinuation. In terms of food, the patient was managed by a feeding jejunostomy.

RESULTS

The patient was reviewed after 1 month. She reports an improvement in clinical signs such as a decrease in trismus and swallowing discomfort. On clinical examination, it shows a regression of cervical adenopathies and a decrease in the volume of the tonsillar tumor mass. Skin reactions are almost resolved. The patient was doing well. ACT scan will be performed after 3 months to check on the treatment response.

DISCUSSION

In this article, we present a rare HCCC involving the tonsil. To the best of our knowledge, the location of hyalinizing subtype of the CCC of the tonsil, chemoradiotherapy, and treatment effects with prognosis have been reported in cases reported in the literature.

Hyalinizing Clear Cell Carcinoma (HCCC) is a distinct clinico-pathological entity. Microscopically, it is composed exclusively of a monomorphic population of undifferentiated cells with optically clear cytoplasm [10]. It is a rare entity accounting for less than 1% of all salivary gland tumors [11]. They arise from the minor salivary glands within the oral cavity and are commonly located in the palate, lips and buccal mucosa [1, 12]. The base of tongue [13], hypopharynx [14], larynx [14], nasal cavity [15] and jawbones [16] are the other rare documented sites of tumor occurrence. As the presentation, in this case, HCCC most commonly affects adult women between the fifth and seventh decades of life [1, 17]. A painless, slowly growing mass

in the oral cavity that occasionally ulcerates with adjunct trauma is the most common presentation. Other presenting symptoms include foreign body sensation, dysphonia, dysphagia, bleeding, and obstruction, whereas pain as a presenting symptom is unusual [8]. Our case report identifies a representative patient, a female in her fifties, in an unusual location. Based on available literature, HCCC generally seems to behave as a low-grade malignancy with tendency to recur locally after resection [5, 8, 18]. Isolated cases of aggressive forms have, however, been reported with early distant metastasis or multiple recurrences [6]. The World Health Organization has not included HCCC as a separate entity in its classification of salivary gland neoplasms [19]. Prior to its description by Milchgrub et al. [1], a few cases of the same tumor had been reported in the literature under various synonyms, such as clear cell carcinoma, glycogen-rich clear cell adenocarcinoma, and glycogen-rich clear cell carcinoma. At present, it has the status of a distinct clinico-pathological entity, with the behavior of a low-grade neoplasm with a low propensity towards recurrence, nodal and distant metastasis [10, 13]. A few cases of the tumor metastasizing to the regional lymph nodes [1] and two cases with metastasis to the lungs [12, 14], have also been reported in the literature. Although increased mitosis was found in these cases [1], it is not a reliable feature in predicting tumor behavior, as this feature was also seen in tumors with no metastasis.

Histologically, the tumor has infiltrative borders, with the neoplastic clear cells arranged in thick trabeculae, nests, cords or solid sheets with a hyalinizing stroma [1, 17]. Eosinophilic cells may also be a component of the tumor [16]. The clear cells have distinct cell borders with uniform small nuclei, which may show mild nuclear pleomorphism. The special stain, PAS with and without diastase, shows variable amounts of PAS-positive diastase-sensitive material, representing glycogen, in the cytoplasm of the tumor cells [1, 17]. Tumor cells do not contain mucin. Immunohistochemistry shows expression of epithelial markers especially cytokeratins, and negativity for vimentin, S-100 and SMA [1, 17]. Differential diagnosis of HCCC on histopathology includes mucoepidermoid carcinoma, acinic cell carcinoma, clear cell oncocytoma, epithelial myoepithelial carcinoma, malignant myoepithelioma, sebaceous carcinoma, odontogenic tumors and metastatic renal cell carcinoma, all of which show a significant proportion of clear cells [1, 17, 20]. The use of special stains and immunohistochemistry, along with careful histological examination of the tumor, for identifying the typical features found in each of these neoplasms, help in arriving at a correct diagnosis [1, 13, 16, 17]. The clear cells of mucoepidermoid carcinoma contain cytoplasmic mucin highlighted by mucicarmine stain. In sebaceous carcinoma, the presence of cytoplasmic lipid which is lost in routine histological processing accounts for the optically clear cytoplasm and is demonstrated by fat stain on frozen tissue. The clear cells in a clear cell oncocytoma contain glycogen, while the oncocytic cells contain abundant mitochondria, which stain with phosphotungstic acid hematoxylin. The tumor cells in acinic cell carcinoma contain zymogen granules, which are PAS-positive and diastase resistant. Neoplastic myoepithelial cells in epithelial/myoepithelial carcinoma and malignant myoepithelioma express S-100 protein and SMA, which are not expressed by HCCC. The odontogenic tumors show a

biphasic growth pattern with expression of cytokeratin and S-100 protein [16]. Neoplastic cells in renal cell carcinoma co-express cytokeratin and vimentin, whereas neoplastic cells in HCCC are negative for vimentin. Radiological imaging studies are also helpful in ruling out the possibility of metastatic renal cell carcinoma.

Depending on the location of the mass, CT scan and possibly Magnetic Resonance Imaging (MRI) along with a chest X-ray seem to be an appropriately extensive workup, with MRI reserved for nasopharyngeal or base of tongue tumors for further characterization. Biopsy with or without molecular testing is a key portion of the work up to ascertain the diagnosis.

Clinical differential diagnosis of the lesion at the tonsil would include epithelial malignancies, granulomatous conditions, and cysts. Patini R et al. reported one case of diffuse large B-cell lymphoma of the submental region in the early stage [21], which represents the third most common group of malignant lesions in the oral cavity and maxillofacial region, after squamous cell carcinoma and salivary gland neoplasm [22, 23]. Pippi R et al. reported in 2016 one case of the central odontogenic fibroma [24] and in 2017 one case of fibro lipoma of the oral cavity [25]. Coviello V et al. reported one case of a surgical hair cyst occurring 12 years after the maxillary advancement osteotomy initially classified as Le Fort I [26]. Facciolo MT et al. reported one case of oral multisystem Langerhans cell histiocytosis [27].

HCCC tend to have an indolent behavior and relatively low risk for distant metastasis, which makes a careful observation and follow-up an important factor to decide on the treatment plan [8, 28].

As these tumors are rare, there is no standard treatment protocol. There is controversy as to the appropriate surgical margins, the role of radiotherapy and the management of the neck. Even with the paucity of data, surgical excision does seem to be the consensus treatment for these tumors. Wide local excision with 1 to 2 cm safety margin is usually considered adequate and curative in most cases [6]. Despite the widely held view that local excision is the treatment of choice; the available data suggest that a careful assessment of regional lymph

nodes is necessary when managing patients with HCCC [8]. Traditionally, a neck dissection has not been proposed as part of the management for salivary gland malignancies; however, the results of the current review suggest that there is a role for neck dissection in the management of HCCC. Albergotti et al. showed that when neck dissection was performed for clinically N0 disease, there was no regional metastasis found [9].

For patients with locally aggressive features, close margins, unresectable primary tumors or local metastasis, as in our case, radiotherapy appears to be a reasonable primary of adjunctive treatment [29]. Even with dual-modality therapy, however, some of these patients still recurred. Close observation of HCCC patients even a decade after initial presentation still seems necessary [9].

Postoperative radiotherapy is reserved for large tumors (>3 cm) and for positive surgical margins.

Because of the rarity of tonsillar HCCC tumor and the lack of treatment protocol consensus, we extrapolated the Squamous Cell Carcinoma (SCC) head and neck cancer protocols for our patient's treatment [30-35]. The decision was discussed in multidisciplinary tumor board. We used low dose weekly cisplatin therapy with radiation, which has been reported for SCC of head and neck, as most patients are not able to tolerate a high-dose regimen of cisplatin every 3 weeks [35-37]. Excellent clinically outcomes were achieved in our patient.

CONCLUSION

In summary, HCCC of the tonsil is a rare presentation of a rare tumor. It behaves as other HCCCs of the oral cavity and tends to have an indolent course with a risk of local recurrence. It responds well to wide local resection with careful assessment of regional lymph nodes, followed by a strict follow-up. Very locally advanced tumor, not a candidate for surgical resection, was treated effectively by concurrent chemoradiotherapy. Management of tonsillar HCCC remains challenging; therefore, definitive prospective studies comparing oncological and functional outcomes, costs, and quality of life are warranted.

DECLARATIONS

The authors state that they have no conflict of interest.

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