Oncocytic carcinoma of Submandibular gland-A case report

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Abstract

Oncocytic carcinoma is an extremely rare malignancy of salivary glands accounting for 0.5% of all epithelial salivary gland malignancies and 0.18% of all epithelial salivary gland tumors. In 1894 Hurthle, a German pathologist first described oncocytes in thyroid glands of normal canine. The term 'Oncocyte' was coined by Hamperl in 1931. The oncocytic carcinoma represents 5% of all oncocytic salivary gland neoplasms and less than 1% of all salivary gland tumors. This case report describes a classical case of oncocytic carcinoma in 55 year old male patient.

Keywords: Oncocytic carcinoma, Submandibular gland, Salivary gland neoplasm

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Introduction

Oncocytoma is an extremely rare benign parotid gland tumor which accounts for about 0.4% to 1% of all salivary gland neoplasms[1]. Oncocytoma occurs most commonly in the 6 to 8th decade of life with a mean age of 58 years. There is no sex predilection[2]. The oncocytic carcinoma also occurs in chronic HBV infection[3]. Oncocytic carcinoma is an unusual proliferation of cytomorphologically malignant oncocytes and adenocarcinomatous architecture phenotypes mainly found in glandular tissue[4]. The terms oncocytic carcinoma is synonyms with oncocytic adenocarcinoma, malignant oncocytoma and malignant oxyphilic adenoma.The abnormal morphological features and infiltrative growth differentiates the malignant nature of oncocytic carcinoma from oncocytoma[5]. The oncocytic carcinoma,a high-grade malignant tumor is characterized by necrosis, perineural spread, pleomorphism, intravascular invasion and distant metastasis to the cervical lymph nodes, kidneys, lungs and mediastinum[4]. It represents 5% of all oncocytic salivary gland neoplasm and less than 1% of all salivary gland tumors[6]. In majority of cases, oncocytic carcinoma involve parotid gland followed by submandibular gland and minor salivary glands of the palate. However it can also involve nasal, thoracic cavities, ovary, kidney, thyroid gland, breast and parathyroid[7]. 84% of oncocytic carcinoma occurs in the parotid gland having same predilection for male and female (1:1) and the remainder arises in the submandibular gland. Minor salivary gland sites include the lower lip, palate, pharynx and buccal mucosa[2]. The term "oncocyte" was first used by Hamperl[8] in 1931 to describe cells with abundant, finely granular, eosinophilic cytoplasm. The terms 'oncocytoma' and 'oncocytic carcinoma' are commonly used to designate tumors consisting of oncocytic cells. Hamperl is considered to be the 'Father of Oncocytes'. He designated 'Oncocyte' (from Greek onkosthai - swollen and cytoscell) as a special type of epithelial cell characterized by a larger than the original cell with a mitochondria rich dense cytoplasm containing acidophilic granules[9]. The diagnosis can be confirmed by both light and electron microscopic identification of mitochondrial differentiation[10,11]. On gross examination, oncocytoma are usually 3-4cm in size possess a well-defined capsule and have characteristic light brown mahogany color[3]. Oncocytic metaplasia in the parotid gland is an age-related process. The percentage of the population with focal oncocytosis increases with age until nearly universal in the population over the age of 70 years[12]. Oncocytic cells in salivary glands can be categorized as oncocytic metaplasia, nodular oncocytic hyperplasia and oncocytoma[11]. Brandwein and Huvos[9] defined oncocytoma as a single nodular mass with monotonous appearance and nodular oncocytic hyperplasia as two or more distinct tumor nodules. They are less organized and circumscribed than oncocytoma as per Hartwick and Batsakis[13] Oncocytoma has centrally located nuclei with granular eosinophilic cytoplasm with monomorphic polygonal cells[2,3]. Oncocytomas clinical behavior is generally benign. Complete surgical excision is the treatment of choice[2]. Local recurrence of an oncocytoma is extremely rare but when it occurs it may be due to incomplete excision, multifocality and bilateral nature[2]. There have been rare examples of malignant oncocytic tumors and the criteria for malignancy includes capsular invasion, destructive growth, necrosis, increased pleomorphism, lymphatic or distant metastasis, vascular/neural invasion and mitotic Fig. etc[2,14]. Oncocytic carcinoma is an extremely rare

malignancy in salivary glands accounting for just 0.5% of all epithelial salivary gland malignancies and 0.18% of all epithelial salivary gland tumors[15]. Criteria for the diagnosis of malignancy in salivary oncocytic tumors include local lymph node metastasis, distant metastasis, peri-neural, vascular or lymphatic invasion, frequent mitoses and cellular pleomorphism with extensive invasion and destruction of adjacent structures[16]. This tumor is predominantly composed of round or polyhedral cells arranged in small clusters and occasional solid sheets. Cells have abundant eosinophilic cytoplasm as result of excessive numbers of mitochondria[17]. Oncocytic neoplasms comprise a group of rare tumours of the parotid glands and their incidence represents approximately 1% of parotid neoplasms[17]. Histologically they are classified according to the new World Health Organization classification in three distinct types, namely oncocytosis, oncocytoma and oncocytic carcinoma[18]. Oncocytomas usually occur in the elderly and affect the parotid glands in 80%[5]. Pathologically, oncocytoma is described as a well circumscribed mass composed of layers of oncocytes (small round nucleus, micro-granular, eosinophilic cytoplasm). Oncocytes are large, granular, eosinophilic epithelial cells mainly found in glandular tissue including that of the salivary glands and thyroid. Oncocytomas that originate from oncocytes are very rare neoplasms that account for less than 1% of all salivary gland tumors[19]. Oncocytic carcinomas are even more uncommon, they represent 11% of all oncocytic salivary gland neoplasms[15,20]. The terms oncocytic carcinoma, oncocytic adenocarcinoma, malignant oncocytoma and malignant oxyphilic adenoma are synonymous[21]. Other differential diagnosis includes oncocytic metaplasia, diffuse oncocytosis, nodular oncocytosis and multifocal nodular oncocytic hyperplasia[22]. Distant metastasis is very rare. Only one case of oncocytic carcinoma arising in the submandibular gland with disseminated bone metastases was reported in the literature[23]. Local recurrence was also considered as one of the characteristics of oncocytic carcinoma. According to the WHO histological typing of salivary gland tumors (2005)[24], two criteria are necessary to establish the diagnosis of oncocytic carcinoma. Firstly, the tumor cells must be identified as oncocytes. Secondly, the diagnosis of malignancy should be based not only on cellular and nuclear pleomorphismbut also on local infiltration and metastasis. Oncocytic carcinoma can be differentiated from benign oncocytoma by the presence of a connective tissue capsule in oncocytic carcinoma. Comparatively oncocytic carcinoma usually shows a greater mitotic activity and more nuclear pleomorphism. Goode and Corio[25] reported that tumors smaller than 2 cm in diameter appeared to be associated with a better prognosis. It has been suggested that elected neck dissection be indicated when the tumor size is larger than 2 cm or the histopathologic features suggest the tumor spreads to the cervical lymph nodes. Fine needle aspiration is the procedure of choice for making a diagnosis in the majority of cases. The submandibular gland location of oncocytic carcinoma has been associated with aggressive tumor behavior. Tumor size was also reported to be a prognostic factor[7,26]. For salivary gland oncocytic neoplasms, the index of Ki-67 immunostaining was recommended by Ito et al[29] to distinguish benign from malignant oncocytomas. The most reliable histological criterion for the diagnosis of oncocytic carcinoma was not the cytologic atypia of oncocytes but the invasive growth pattern. c-kit and/or p53 overexpression might be helpful ancillary markers and may represent possible involvement of these genes in oncocytic carcinogenesis.

Case Report

A 55 year old male patient (**Fig. 1**) reported a swelling involving left side of face since 1 year. The swelling was progressively increasing in size causing disfigurement. The patient had no significant dental/medical history. He was well built, intelligent and well oriented to surroundings. He has normal gait and posture. There no sign of pallor, cyanosis. His vitals were within normal limits. On extra-oral examination a firm to hard swelling of 4x4 cm involving left mandibular angle and submandibular region was noted. The skin overlying the swelling was of normal color and texture (**Fig. 2**). There was no associated symptoms except facial disfigurement. There was no intra-oral extension of swelling. Intra-orally patient had partially edentulous maxillary arch while mandibular arch is edentulous (**Fig. 3 and Fig. 4**). There was associated left submandibular lymhadenopathy. The patient was advised for radiographic investigations. The high resolution ultrasound of neck and submanudibular swelling shows an ill-defined heterogenous lesionwith few calcifications with internal vascularity noted in left submandibular gland.Multiple enlarged submandibular lymph nodes noted with largest lymph node having dimension of 9.6x 8 mm.The right submandibular nodes and bilateral parotid nodes are within normal limit. The high resolution ultrasound of neck and submanudibular swelling is suggestive of neoplastic lesion in left submandibular gland with left cervical lymphadenopathy(**Fig. 5, Fig. 6, Fig. 7, Fig. 8**). The CECT of head and neck shows bulky left submandibular gland and heterogeneously enhancing with few hypodense areas with infilteration into adjacent subcutaneous fat plane and mild perilesional fat plane stranding. The lesion measuring 3.0x2.0.x2.5cm is seen abutting ipsilateral mandible, sternocleidomastoid muscle with ill defined interface however no obvious cortical erosion is noted. Multiple rounded to oval soft tissue attenuation lesion suggestive of lymph nodes are seen in level Ia, bilateral Ib, left level II, IV & V. The largest lymph node was 1 to 1.5cm in left level II(**Fig. 9, Fig. 10**). The CECT features were suggestive of neoplastic lesion of left submandibular gland. On the

basis of clinical and radiological features a provisional diagnosis of neoplastic laesion was made. The patient was advised for FNAC of left mandibular swelling.FNAC from left submandibular swelling on gross examination shows blood mixed materials. 4 smears are prepared and stained. The microscopic examination shows highly pleomorphic cells disposed in loose clusters forming vague acini as well as lying singly in a necrotic and haemorrahgic background. Individual atypical cells are highly pleomorhic roud to oval to plasmacytoid having high nucleo-cytoplasmic ratio, hyperchromatic nuclei, inconspicuous nuclei and moderate eosinophillic cytoplasm. Occasional binucleated and multinucleated cells are also seen along with few atypical mitosis. The cytomorphology is suggestive of high grade epithelial malignancy. The suggested differential diagnosis by pathologist were Acinic cell adenocarcinoma, oncocytosis, salivary duct carcinoma and epithelial- myoeithelial carcinoma. The patient is further advised for total submandibular gland resection with radical neck dissection till level V(**Fig. 11**). After total submandibular gland resection and radical neck dissection 2 specimens have sent for histopathology reporting. The specimen one (MND) labeled as threaded single soft tissue piece measuring 11x7x2 cm. Outer surface is smooth and congested, cuts firm. Cut surface shows solid white growth occupying almost whole of gland measuring 2.8x3.5 cm. At periphery of gland, thin rim of compressed glandular parenchyma is also identified. Level Ib- 3 lymph nodes identified measuring 2x1.5.1 cm. Sternocleidomastoid-Muscle identified (Three thread) measuring 5x2.5x1cm. Outer surface smooth and cuts firm. The cut surface shows grayish brown muscles. Digastric muscles(four thread). Cuts firm. The cut surface shows grayish brown muscles. The microscopic examination shows highly pleomorphic oncocytes cells disposed in loose clusters forming vague acini as well as lying singly in a necrotic and haemorrahgic background. Individual atypical cells are highly pleomorhic roud to oval to plasmacytoid having high nucleo-cytoplasmic ratio, hyperchromatic nuclei, inconspicuous nuclei and moderate eosinophillic cytoplasm. Occasional binucleated and multinucleated cells are also seen along with few atypical mitosis(**Fig. 12**). On the basis of histopathology a final diagnosis of oncocytic carcinoma submandibular gland is reached. The patient is advised radiotherapy post-operatively. The patient is followed for 1 year post-radiotherapy. There is no recurrence of lesion reported.

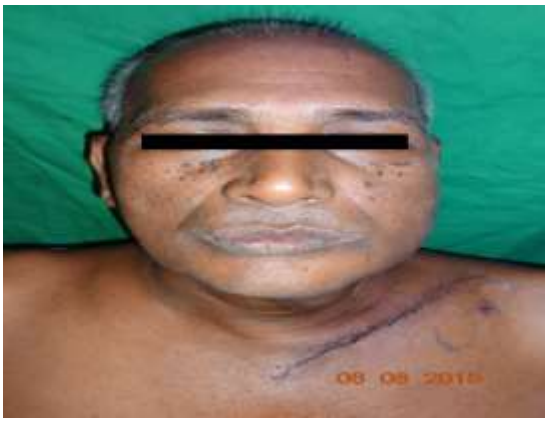


Fig. 1: Profile picture of patient

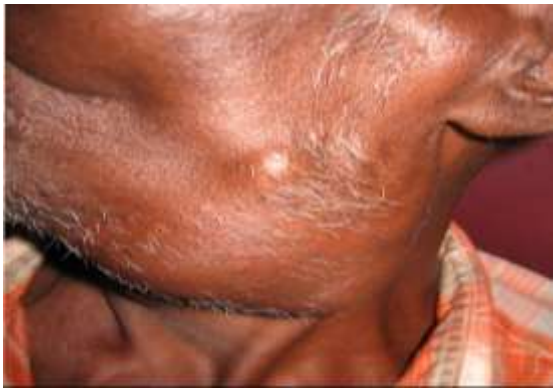


Fig. 2: Showing firm to hard swelling of 4x4 cm involving left mandibular angle and submandibular region

Fig. 3: Intra-oral view showing partially edentulous maxillary arch

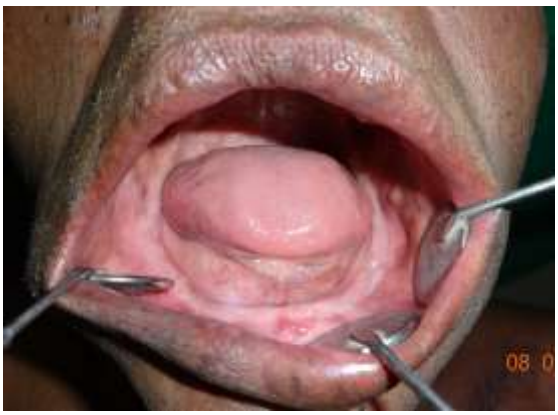
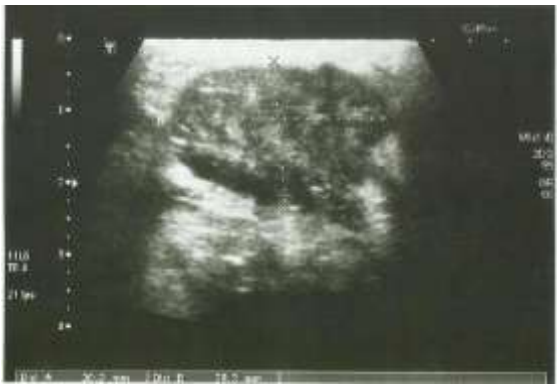


Fig. 4: Intra-oral view showing edentulous mandibular arch and having no extension of swelling



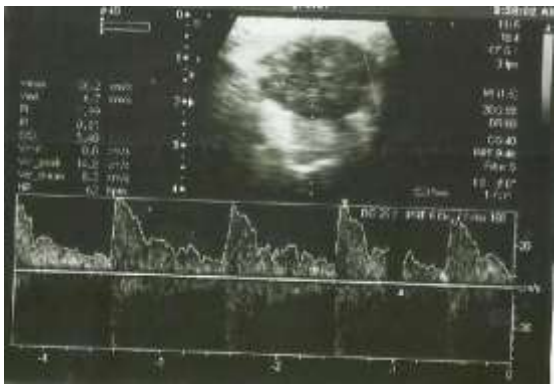
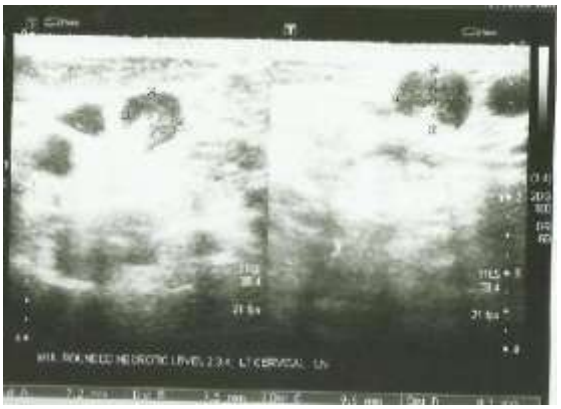


Fig. 5 & 6: HR USG of swelling showing ill-defined heterogenous lesion with few calcifications with internal vascularity noted in left submandibular gland



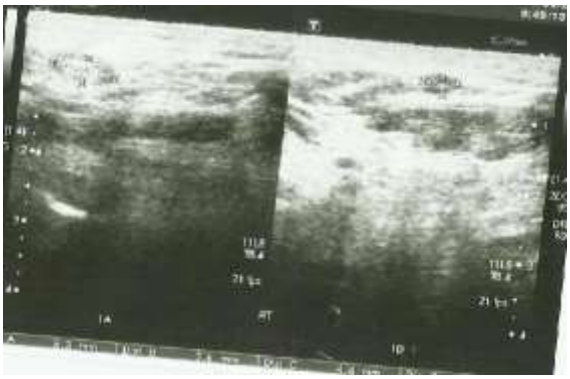


Fig. 7 & 8: HR USG of swelling showing multiple enlarged submandibular lymph nodes noted with largest lymph node having dimension of 9.6x 8 mm

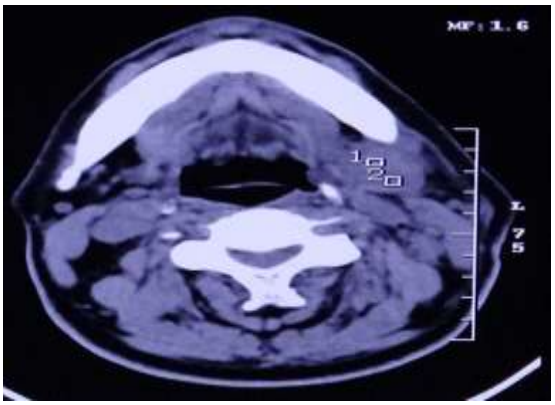


Fig. 9: CECT of lesion showing bulky left submandibular gland and heterogeneously enhancing with few hypodense areas with infilteration into adjacent subcutaneous fat plane and mild perilesional fat plane stranding

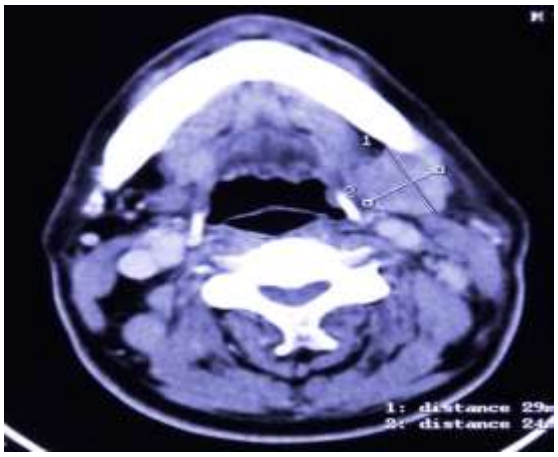


Fig. 10: CECT of lesion measuring 3.0x2.0.x2.5cm is seen abutting ipsilateral mandible, sternocleidomastoid muscle with ill-defined interface however no obvious cortical erosion is noted

Fig. 11: Photograph of patient showing scar mark of total submandibular gland resection with radical neck dissection till level V

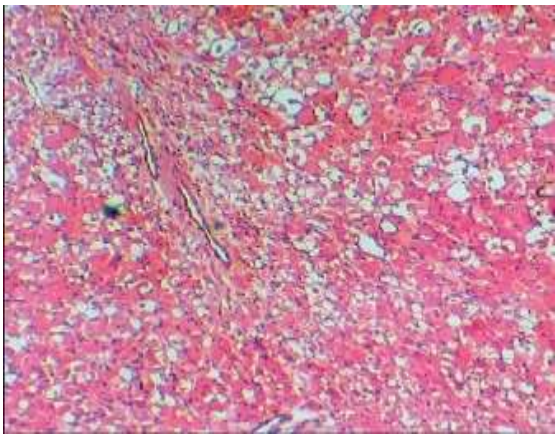


Fig. 12: Histopathological micrograph showing highly pleomorphic oncocytes cells disposed in loose clusters forming vague acini as well as lying singly in a necrotic and haemorrahgic background. Individual atypical cells are highly pleomorhic roud to oval to plasmacytoid having high nucleo-cytoplasmic ratio, hyperchromatic nuclei, inconspicuous nuclei and moderate eosinophillic cytoplasm. Occasional binucleated and multinucleated cells are also seen along with few atypical mitosis

Discussion

Oncocytes are epithelial cells which appear as cells with abundant granular eosinophilic cytoplasm, a central pyknotic nucleus and ultrastructurally are crammed with numerous mitochondria of various sizes. Oncocytes are seen in various organs like salivary glands, thyroid, parathyroid, pituitary, nasal cavities, sinuses, ocular caruncle, lacrimal glands, buccal mucosa, eustachian tube, larynx, esophagus and organs like liver, pancreas, and kidney[30]. In 1894, the German pathologist Hurthle first described these granular cells in normal canine thyroid glands while the term 'Oncocyte' was coined by Hamperl in 1931[31]. This tumor represents 5% of all oncocytic salivary gland neoplasms and less than 1% of all salivary gland tumors[32]. Oncocytic carcinoma is an extremely rare malignancy in salivary glands accounting for just 0.5% of all epithelial salivary gland malignancies and 0.18% of all epithelial salivary gland tumors[33]. By electron microscopy Tandler et al[34] revealed that the oncocytes contained unusually large number of mitochondria. Oncocytic cells are thought of as metaplastic cells formed in response to adverse changes with the normal cells losing their original specialization[31]. Oncocytic neoplasms rarely develop in the salivary glands and oncocytic carcinoma also called oncocytic adenocarcinoma, malignant oncocytoma, and malignant oxyphilic adenoma is rarer[35]. The differential diagnosis between oncocytoma and oncocytic carcinoma may be difficult because a benign appearing oncocytic tumor without malignant cellular morphology can recur or metastasize[36]. Oncocytic carcinomas are malignant oncocytic neoplasms which may have general malignant features such as cellular atypia, pleomorphism, large irregular nuclei, invasive growth, and perineural invasion[37]. The occurrence of this tumor is equal in both the sexes and occurs mainly between 50-60 years of age[38]. World health organization classification of salivary gland neoplasms recognizes three oncocytic entities: Oncocytosis, oncocytoma and oncocytic carcinoma[31]. Oncocytosis is considered a hyperplastic change which may present with generalized enlargement of salivary gland. Oncocytosis has further been categorized as diffuse hyperplastic oncocytosis and multifocal nodular oncocytic hyperplasia[39]. Oncocytomas are more common than oncocytic carcinomas[31]. Diffuse hyperplastic oncocytosis can only be diagnosed on histopathology by finding an unencapsulated lesion with the entire gland replaced by oncocytic cells while in oncocytomas we usually get a well-circumscribed encapsulated lesion comprising of an apparent organoid pattern and thin capillary network, with features of compression to adjacent tissue[31]. Criteria for the diagnosis of malignancy in salivary oncocytic

tumors include: local lymph node metastasis, distant metastasis, peri-neural, vascular or lymphatic invasion, frequent mitoses and cellular pleomorphism with extensive invasion and destruction of adjacent structure[40]. Oncocytic differentiation of neoplastic cells was demonstrated by immunohistochemical positivity for mithochondrial antigen[41], keratin, alpha-1-antichymotrypsin[42]. On ultrastructural analysis numerous mitochondria seemed to fill the cytoplasm. FNAC has increasingly been used as a primary screening tool for salivary gland lesions with high levels of sensitivity and specificity. However as salivary glands are notorious for having overlapping morphological features diagnosis by cytology alone often becomes difficult[31]. The differential diagnosis of this tumor includes other tumors of salivary glands with granular eosinophilic cytoplasm i.e., oncocytoma, acinic cell carcinoma and salivary duct carcinoma. Oncocytoma can be differentiated by the presence of a well differentiated connective tissue capsule. Moreover compared to oncocytoma, oncocytic carcinoma shows greater nuclear pleomorphism and mitotic activity. Acinic cell carcinoma can be differentiated from oncocytic carcinoma by the presence of amphophilic or basophilic granules in the cytoplasm of tumor cells and their predominant microcystic and papillary growth pattern. Salivary duct carcinoma, in contrast forms duct like spaces with papillary and cribriform growth pattern and also shows necrosis[43]. The prognosis of oncocytic carcinoma in salivary gland is not well known because of its rarity. Goode and Corio have reported that tumors smaller than 2 cm in diameter appeared to have a better prognosis than those that were larger[44]. A number of studies have reported multiple recurrences of this tumor and regional or distant metastases[40]. The cervical lymph nodes may be affected as with other malignant tumors of the parotid gland but prophylactic neck dissection must be considered individually in the absence of consensus in the literature. Nakada et al. published a review of 28 cases of oncocytic carcinoma of the parotid gland. They concluded that distant metastasis appeared to be the most important prognostic feature of oncocytic carcinoma local lymph node metastasis was not necessarily a critical factor in the overall prognosis[45]. Distant metastasis sites include the lung, liver, kidney, mediastinum, thyroid gland and bone. The prognosis of oncocytic carcinomas is not well known because of their low incidence. Patients with malignant oncocytoma appear to have good short-term survival but poor long-term survival[46]. The average survival period has been estimated at 3.8 years with metastasizing tumors[47].

Conclusion

Oncocytic carcinomas of salivary gland origin are high-grade tumors with local recurrences regional or distant metastases diagnosis of which are based on a combination of clinical and histopathological features. Immuno-histochemistry for mitochondria is considered helpful for the adjuvant diagnosis. Complete surgical excision is the treatment of choice while the role of radiotherapy or chemotherapy is still controversial and careful long-term follow-up is necessary.

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