The Journal of Laryngology and Otology
January 1998, Vol. **112**, pp. 106–109

Pathology in Focus

Metastasizing malignant oncocytoma of the submandibular gland

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Abstract
Malignant oncocytomas are extremely rare tumours of the salivary glands. Fewer than 50 cases have been reported in the world literature so far, 34 of which were located in the parotid gland. Only three of these tumours have been located in the submandibular gland. We report one further case of a malignant oncocytoma of the submandibular gland in a 47-year-old man. Since a definite histological diagnosis of malignant oncocytoma can rarely be made both clinical and histopathological findings are essential in establishing the diagnosis. Treatment consists of wide surgical excision, neck dissection and post-operative radiotherapy. The prognosis with regard to five-year survival is poor because of metastatic disease.

Key words: Submandibular gland neoplasms; Oncocytoma, malignant

Introduction

Benign oncocytomas of the salivary glands are rare (Brandwein and Huvos, 1991; Ellis *et al.*, 1991). Least common are malignant oncocytic carcinomas of the salivary glands. Approximately 50 cases have been reported in the world literature, 34 in the parotid gland and three in the submandibular gland (Table I) (Sikorowa, 1957; Goode and Corio, 1988; Ziegler *et al.*, 1992). Another case is described in this article and the literature is discussed.

Case report

A 47-year-old male was referred in April 1996 with a painless swelling of the left submandibular region first noted one year previously. The patient denied smoking or drinking and had no past medical history. On examination a three cm mass was noted in the left submandibular region. It was mobile and only slightly tender. On ultrasound a 31 × 18 × 17 mm tumour of homogenous structure was seen neighbouring the submandibular gland. The evaluation of the submandibular gland itself was limited to the tumour. Two enlarged lymph nodes were present near the carotid bifurcation and a fine needle aspiration showed nonspecific lymphadenitis.

Intra-operatively the tumour had a smooth surface and could be easily identified bordering the submandibular gland, and was readily removable from the surrounding tissue. The first surgical procedure was limited to the excision of an enlarged lymph node. Microscopy of the lymph node showed moderately differentiated adenocarcinoma.

Subsequent computed tomography (CT) scan of the neck revealed a moderately enlarged left submandibular gland and several ipsilateral enlarged cervical lymph nodes (Figure 1). Complete medical examination, CT scan of the chest and ultrasound of the abdomen were unremarkable and there was no evidence of another tumour secreted elsewhere.

Consequently the left submandibular gland was removed by a modified radical left neck dissection (region I–V) and a supramohyoidal right neck dissection (region I–IV). The post-operative course was uneventful. The final

TABLE I
WORLD LITERATURE DATA OF ALL CASES OF ONCOCYTIC CARCINOMA OF THE SUBMANDIBULAR GLAND

Case	Sex	Age	Tumour extent	Initial therapy	Clinical course	Reference
1	n.a.	n.a.	n.a.	Excision	Three recurrences	Sikorawa, 1957
2	f	60	>4 cm	Excision, radical neck dissection	n.a.	Goode and Corio, 1988
3	f	56	n.a.	Resection and functional neck dissection	NED 3 years	Ziegler *et al.*, 1992 and personal communication
4	m	47	2 × 2 × 1.5 cm	Resection, functional neck dissection, radiotherapy	NED 14 months	Present report

f = female; m = male; n.a. = not available; NED = no evidence of disease.

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Accepted for publication: 23 October 1997.

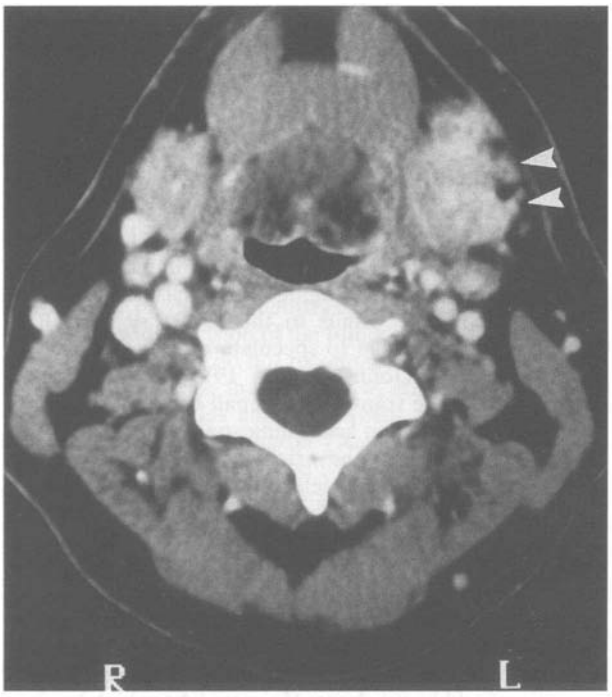

FIG. 1
Computed tomography of the submandibular region, depicting the diffusely enlarged left submandibular gland (➤)

histopathological diagnosis of the surgical specimen was solid, oncocytic carcinoma of the left submandibular gland. No further metastatic deposits were found.

Post-operative radiotherapy was applied and the patient has been free of tumour for over 14 months.

Histopathological examination

Microscopy of an enlarged cervical node showed lymphoid and highly vascularized fibrous tissue infiltrated by large neoplastic cells partly showing some glandular formation (Figure 2). PAS-staining was weakly positive. Immunohistochemistry was positive for cytokeratin (KL1) but negative for calcitonin. B-cell-antigen (CD20) was positive in the lymphoid follicles. The proliferation marker Ki-S5 was present in the proliferation zones. The tumour cells were positive for prostate specific antigen and for negative thyroglobulin. These findings were interpreted as a metastasis of an adenocarcinoma; possibly originating from a primary adenocarcinoma of the prostate.

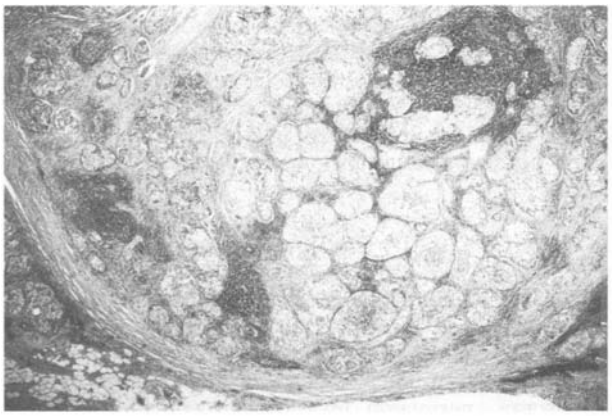

FIG. 2
Metastasis of the oncocytic carcinoma in a cervical lymph note. (H & E; × 28).

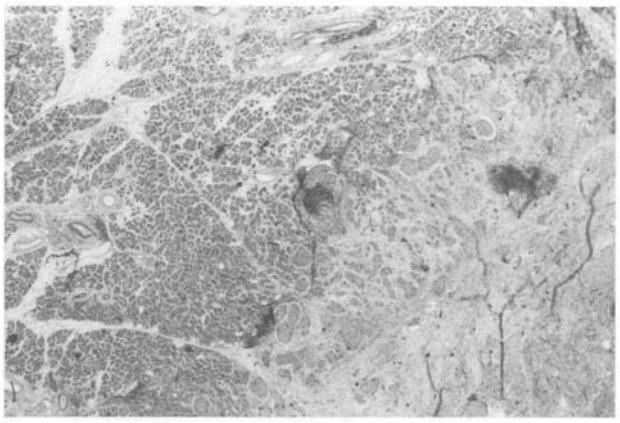

FIG. 3
Infiltration of intact submandibular gland tissue (left side) by the oncocytic carcinoma (right side). (H & E; × 28).

Left submandibular gland, right and left neck dissection specimen

The left submandibular gland contained a 20 × 20 × 14 mm large tumour formed by large epithelial cells with pleomorphic, partially foamy nuclei and mostly small but prominent nucleoli (Figures 3, 4 and 5). The cytoplasm was tensely eosinophilic and filled with fine and bright granules. The tumour nests were framed by fibrous tissue. Isolated lymphocytic infiltrates were noted and there were tumour cell groups present in the fatty tissue surrounding the submandibular gland. Additional histochemical stains were positive for PTAH and CEA. Two neighbouring lymph nodes were negative. Histopathology revealed no tumour in the right and left neck area.

The final histopathological diagnosis was oncocytic carcinoma of the left submandibular gland. The TNM classification (UJCC, 1987) was pT_1 N_1 M_0.

Discussion

Epidemiology

Oncocytomas of the salivary glands are rare benign

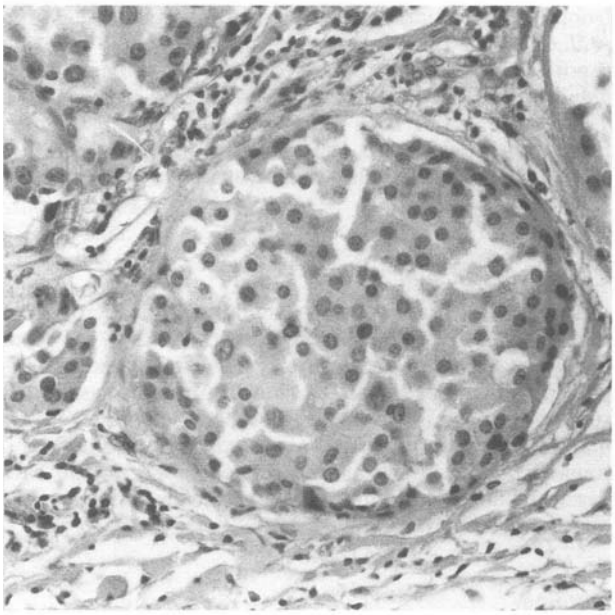

FIG. 4
Nodules of an oncocytic carcinoma, in the centre more regular tumour cells with uniform nuclei. (H & E; × 280).

https://doi.org/10.1017/S0022215100140034 Published online by Cambridge University Press

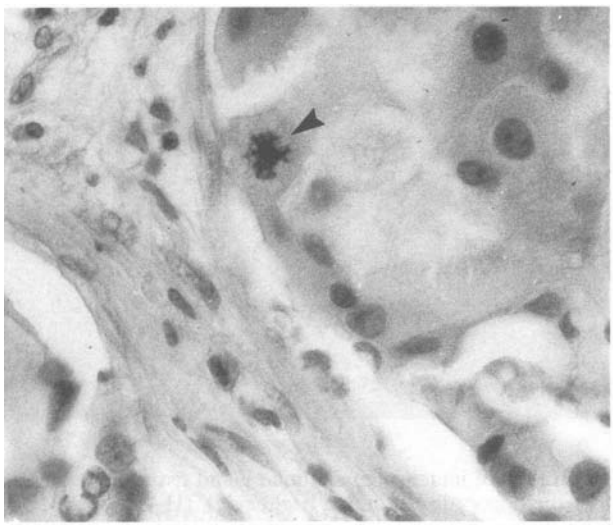

FIG. 5

Oncocytic carcinoma with variable shape and size of the tumour cells, large nuclei and prominent nucleoli. In the centre an atypical mitosis (➤) (H & E; × 560).

tumours. They are estimated to amount to less than one per cent of all salivary gland tumours and most commonly occur in the parotid gland (Ellis *et al.*, 1991). Oncocytomas are also found in other organs such as the kidneys, the adrenal, thyroid and pituitary glands (Chang and Harawi, 1992). The submandibular gland or minor salivary glands are very seldom affected (Brandwein and Huvos, 1991). The occurrence of malignant oncocytomas is even rarer (Bauer and Bauer, 1953; Johns *et al.*, 1973). Of all epithelial salivary gland tumours they only account for 0.005 per cent (Goode and Corio, 1988). To date, 34 cases of oncocytotic carcinoma of the parotid gland have been reported in the world literature. The first report dates back to 1953 (Bauer and Bauer, 1953). As oncocytomas are mostly found in patients between the ages of 60 and 70 (Johns *et al.*, 1973) their malignant variant most commonly occurs in the seventh decade (Ellis *et al.*, 1991). In 34 cases of malignant oncocytoma of the parotid gland reported in the world literature the age of the affected patients ranged from 30 to 91 years with a mean of 58 years (Sugimoto *et al.*, 1993). To our knowledge there has been only one report on a malignant oncocytoma of the submandibular gland in the English literature (Goode and Corio, 1988). Two further cases have been described in the German literature (Ziegler *et al.*, 1992) and in the Polish literature (Sikorowa, 1957). The clinical data available on these cases is listed in Table I.

Clinical presentation

The clinical presentation of malignant oncocytomas of the major salivary glands is similar to that of other malignant tumours of these organs. Sometimes patients present with a long history of a slowly growing mass with a sudden increase in size which has been attributed to the malignant transformation of a pre-existing benign oncocytoma (Ellis *et al.*, 1991). This did not apply to the case described here. Our patient first noted a swelling one year prior to presentation.

Histology

The term 'oncocyte' goes back to Hamperl (Hamperl, 1931) who described the presence of large and apparently swollen epithelial cells with a densely filled eosinophilic and granular cytoplasm found among the ductal and acinar cells of the salivary glands. Derived from the Greek word for to swell or to increase in size (*ονκοζτηαι*) he introduced the descriptive term oncocyte. The oncocytic cells are characterized by abundant, fine, brightly eosinophilic cytoplasmatic granules (Hamed *et al.*, 1994). They have round and uniform nuclei which contain one or more small nucleoli (Hamed *et al.*, 1994) and are pyknotic (Johns *et al.*, 1973). The cells, thus, have a low nuclear-cytoplasmic ratio (Hamed *et al.*, 1994). Oncocytes are a common feature in the salivary glands of the aging individuals and are found anywhere from the acinus to the excretory duct. It is, therefore, only possible to speculate on the origin of the oncocytotic cell (Johns *et al.*, 1977). However, the observation of the transition of small basophilic cuboidal lining cells into swollen acidophilic granular cells has been taken as evidence for the origin of the oncocytes to be from the multipotential cells of the intercalated ducts (Bauer and Bauer, 1953; Chu and Strawitz, 1978).

Different criteria have to be met in order to diagnose an oncocytoma (Tandler *et al.*, 1970). The cells have to occur in a mature organ as was the case in our patient. A high oxidative activity must be proven for the individual cells by histochemical staining. The cells must have a very high number of mitochondria with varying degrees of pleomorphism and bizarre shapes. In cases where high levels of oxidative activity can be shown by histochemical staining of the mitochondria-rich oncocytes with PTAH, the diagnosis of oncocytoma is sufficiently proven and does not necessarily require ultrastructural studies (Johns *et al.*, 1973). Ultrastructurally, the cytoplasm of oncocytoma cells is filled with masses of mitochondria. This has been attributed to a mitochondrial enzyme deficiency (Johns *et al.*, 1973).

The distinction between benign oncocytoma and malignant oncocytic carcinoma depends largely on the clinical presentation since the malignant oncocytoma lacks well-defined histological and even ultrastructural differences from its benign variant (Johns *et al.*, 1977). However, histological criteria which speak for the presence of a malignant oncocytic carcinoma are atypical oncocytic cells with increased mitotic activity, local infiltrative growth with perineural (33 per cent of the cases) or vascular spread (15 per cent of the cases), soft tissue infiltration – as in the case reported here – and the absence of a capsule (Goode and Corio, 1988; Seifert, 1996). The nuclei are often large and excentric (Brandwein and Huvos, 1991; Ellis *et al.*, 1991). In malignant oncocytic carcinoma the oncocytic cells express solid and glandular formations. Necrosis is found in 20 per cent of the cases (Seifert, 1996). Clinically, recurrences and metastasis indicate malignancy (Johns *et al.*, 1977; Seifert, 1996). Immunohistochemical staining of oncocytic carcinoma cells is positive for glandular markers such as α-1 antitrypsin, α-1 antichymotrypsin, lactoferrin, and CEA (Sugimoto *et al.*, 1993). Since S100 and actin are usually negative myoepithelial cells are most likely not involved in this tumour (Seifert, 1996).

Diagnosis

Since a definite histological diagnosis of malignant oncocytoma can rarely be made (Batsakis, 1974; Johns *et al.*, 1977) both clinical and histopathological criteria have to be considered. These criteria include local lymph node metastases, perineural invasion, intravascular invasion, lymphatic invasion, frequent mitosis, cellular pleomorphism and distant metastasis (Goode and Corio, 1988). In the present case the diagnosis of malignancy was based on the

https://doi.org/10.1017/S0022215100140034 Published online by Cambridge University Press

histological pattern of the tumour, the metastases to a lymph node and the infiltration of the surrounding fatty tissue by neoplastic cells.

Therapy

Due to the low incidence of this particular malignancy uniform guidelines have not been established. Recommendations in the literature mostly apply for onocytic carcinomas of the parotid gland. Once oncocytic carcinoma is diagnosed the pre-operative work-up has to rule out locoregional or distant metastasis. The primary therapy should be a wide excision of the tumour (Chu and Strawitz, 1978). Some authors do not recommend prophylactic neck dissection but advise the removal of clinically detectable regional lymph nodes and subsequent neck dissection if they show deposits of tumour (Harker, 1977). However, others suggest that at least the local regional lymph nodes should be removed in all cases with clinical evidence of malignancy in the salivary gland (Johns *et al.*, 1977). Given the high rate of metastasis a prophylactical neck dissection is, in our opinion, indicated. Post-operative radiotherapy has been advocated (Chu and Strawitz, 1978).

Prognosis

The data available from the few cases reported in the literature suggest that metastases, mostly to local lymph nodes, occur in 50–60 per cent of the cases (Brandwein and Huvos, 1991; Ellis *et al.*, 1991) and 20–40 per cent of these cases take a lethal course. The interval between metastases and death ranges from one to nine years. Recurrences occurred in 25–52 per cent of the cases (Brandwein and Huvos, 1991; Sugimoto *et al*, 1993). In general, the five-year survival is poor (Goode and Corio, 1988; Seifert, 1996).

Conclusion

We report the fourth case of a malignant oncocytoma of the submandibular gland. Diagnosis was established by histopathological findings, including histochemistry and immunocytochemistry. The patient was treated by surgery and post-operative radiotherapy and has been free of recurrence for over 14 months. However, literature data indicate that the prognosis with regard to five-year survival is poor because of metastatic disease.

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