CASE REPORT

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Expression of somatostatin receptors in arginine vasopressin hormone-secreting olfactory neuroblastoma – report of two cases*

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SUMMARY

***Objective**: Arginine vasopressin hormone-secreting olfactory neuroblastomas are extremely rare, with fewer than twenty cases reported in the literature. Two of these cases, both initially presenting with the syndrome of inappropriate antidiuretic hormone, are presented. The second tumour was successfully identified using somatostatin receptor (octreotide) radiographic scintography.*
***Method**: The pathological specimens from both cases were examined immunohistochemically for somatostatin receptors.*
***Results**: Samples from both cases demonstrated positivity for somatostatin receptors.*
***Conclusions**: This report demonstrates the potential use of somatastatin analogues in the investigation, follow-up and treatment of patients with olfactory neuroblastoma.*

Key words: esthesioneuroblastoma, octreotide, radiographic scintography, syndrome of inappropriate antidiuretic hormone, SIADH

INTRODUCTION

Olfactory neuroblastoma (or esthesioneuroblastoma) (ONB) is thought to arise from the neuroepithelial cells of the olfactory mucosa, which derive from the neural crest. An extensive review [1] identified 945 reported cases and found epidemiologically it represented approximately 3% of intranasal tumours, had an equal sex and racial distribution and could occur at any age from 18 months to 84 years. There were no clear genetic or environmental predisposing factors. It may have a variable histologic pattern which resembles either neuroblastomas or neuroendocrine tumours. Very rarely olfactory neuroblastomas may be associated with ectopic hormone production.

Octreotide scanning is routinely used in the investigation of many neuroendocrine tumours but has only been reported once in association with olfactory neuroblastoma [2]. We describe two patients with arginine vasopressin (AVP) hormone-secreting olfactory neuroblastoma whom initially presented with the syndrome of inappropriate antidiuretic hormone (SIADH). Following the successful identification of the second tumour using octreotide scanning, the pathological specimens from both cases were examined immunohistochemically for somatostatin receptors and the findings are discussed.

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CASE REPORTS

Case 1

A 51 year old caucasian woman was referred to the department of otolaryngology in June 1996 with a lesion in the left nasal cavity that replaced part of the middle turbinate and caused bony displacement of the nasal septum and medial wall of the maxillary sinus. She had a 15 year history of hyponatraemia secondary to the syndrome of inappropriate antidiuretic hormone (SIADH). She was admitted for endoscopic biopsy and this showed an olfactory neuroblastoma.

In 1981 the patient had been admitted to her local hospital with decreased consciousness and generalised oedema and had been diagnosed with hyponatraemia. AVP level was raised despite the hyponatraemia so a diagnosis of SIADH was made. Computed tomography (CT) scans of brain, thorax and abdomen were performed which identified a cerebellar haemangioma as a potential source of ectopic AVP production. Although this was presumed to be the cause it was felt that the morbidity involved in removing this lesion outweighed the risks from SIADH.

Radiological investigation: In 1996 magnetic resonance imaging (MRI) of the brain was performed to see whether any

change in the cerebellar lesion had occurred. This lesion was unchanged but an incidental mass in the left nasal cavity was highlighted (Figure 1). This was 2 cm in diameter and replaced the middle turbinate just posterior to the ostiomeatal complex. There was some mucosal filling of the ethmoid sinuses but the maxillary antrum was clear. There was bony displacement of the septum and medial wall of the antrum and extension to but no invasion of the medio-inferior wall of the orbit. There was heterogenous high signal intensity on T2-weighting, low signal intensity on T1-weighting pre-contrast with a peripheral rim of enhancement following intravenous gadolinium (Figure 1). A post biopsy CT showed no evidence of bony erosion. There was no cervical lymphadenopathy.

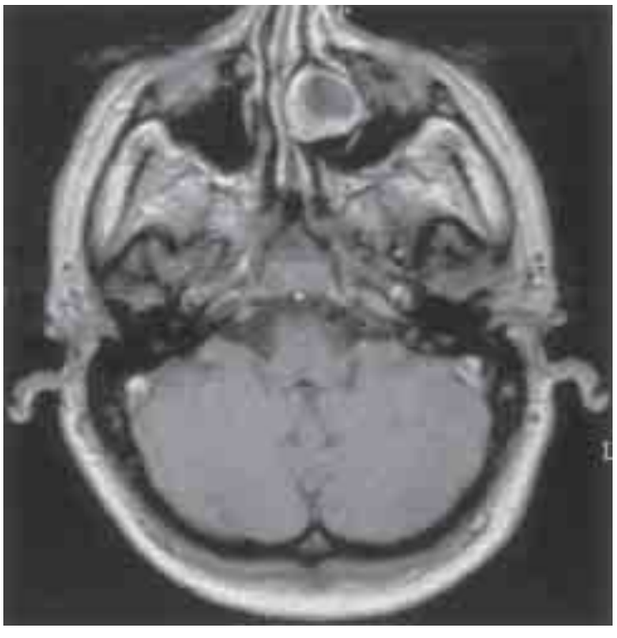

Figure 1. T1-weighted axial MRI of Case 1 showing the unusual feature of peripheral rim enhancement of olfactory neuroblastoma following contrast.

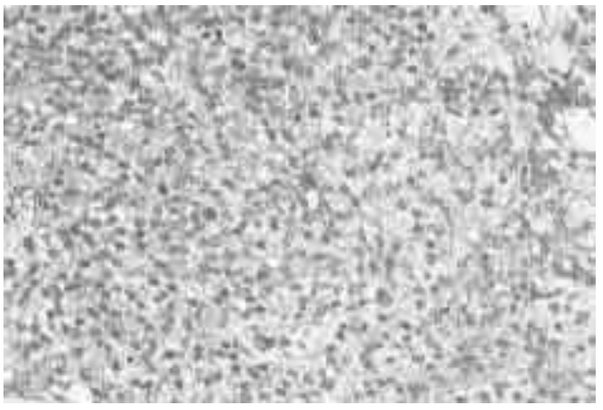

Figure 2. Immunohistochemical staining of lesion from Case 1 for somatostatin receptors (shaded cytoplasm demonstrates positivity).

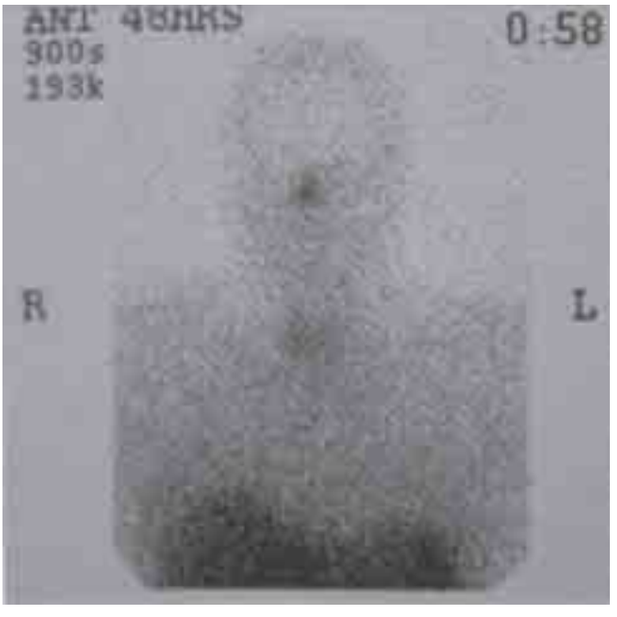

Figure 3. Octreotide scan from Case 2 showing increased uptake in the right sinonasal region.

Surgical Treatment: The patient underwent a craniofacial resection in December 1996. Five months postoperatively the patient underwent a water load test with a 3 litre fluid challenge and had a normal response. There has since been no further evidence of SIADH and no evidence of tumour recurrence (7 year follow-up).

Histology: Both the original biopsies and the main specimen were morphologically identical. The tumour cells were arranged diffusely and in lobules and were small with a moderate quantity of cytoplasm. Cell boundaries were indistinct. The nuclei showed mild pleomorphism with granular chromatin pattern. Nucleoli were present in some cells but were not prominent. In areas the cells formed pseudorosettes. There was focal ganglionic differentiation suggested by larger cells with increased quantity of pink cytoplasm and nuclear clearing. Mitotic figures were rare. There was no evidence of anaplasia, stromal desmoplasia or necrosis. The background was composed of eosinophilic fibrillary material resembling neurophil. Immunohistochemistry showed diffuse positive staining with chromogranin, synaptophysin, neurone specific enolase, S100 protein and AVP. Stains for cytokeratin and neurofilament were negative. The morphology and immunohistochemistry were those of a low grade (Hyams grade 1) olfactory neuroblastoma. Electron microscopy was not performed. Following identification of the second case, the specimens were subsequently examined immunohistochemically for somatostatin receptors and found to be diffusely positive (Streptavidin Biotin Peroxidase (StrepABC) Duet Technique [3]) (Figure 2).

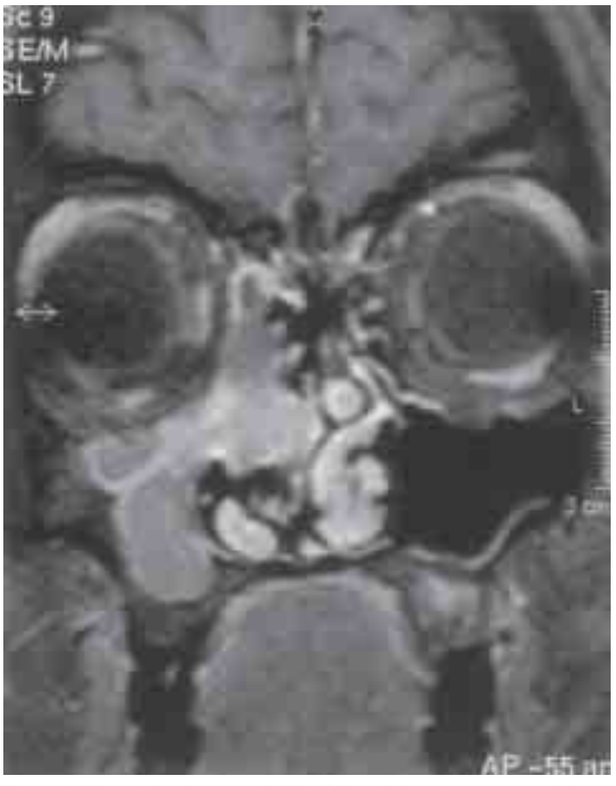

Figure 4. T1-weighted coronal MRI of Case 2 showing some peripheral rim enhancement following contrast and also extension to the cribriform plate.

Case 2

A 42 year old arabic woman was referred to the department of otolaryngology in January 2001 with a lesion in the right maxillary and ethmoid sinuses extending to the nasal cavity and a 7 year history of hyponatraemia secondary to SIADH. She was admitted for endoscopic biopsy and this showed an olfactory neuroblastoma.

Radiological investigation: A somatostatin receptor (octreotide) scan was performed and showed an area of increased uptake in the right maxillary sinus (Figure 3). Magnetic resonance imaging (MRI) showed soft tissue opacification in the right maxillary and anterior ethmoid sinuses extending to but not through the roof of the air cells and through a widened ostium into the nasal cavity with no evident bony destruction (Figure 4). There was high signal intensity on T2-weighting, low signal intensity on T1-weighting pre-contrast with a peripheral rim of enhancement following intravenous gadolinium (Figure 4). A CT scan showed some local resorption of bony treculae within the ethmoid air cells. A repeat MRI following biopsy confirmed no extension through the cribriform plate but showed an enlarged (> 1 cm) right jugulodigastric lymph node with uniform signal intensity.

Surgical Treatment: The patient underwent a craniofacial resection with excision biopsy of the enlarged lymph node (confirmed as reactive only by frozen section) and dural repair with a fascia lata graft in May 2001. The sodium level had returned to normal (135mmol/l) within two days of surgery and there has been no further evidence of SIADH or tumour recurrence (2 year follow-up).

Histology: The tumour was histologically similar to case 1 except that it infiltrated bone and was present within lymphovascular channels. It was composed of cellular nests with a vascular, fibrillary background. Most cells had small, round, hyperchromatic nuclei with eosinophilic cytoplasm and infrequent mitoses. No pseudorosettes were seen. Immunohistochemical features were also similar to case 1, including positive staining to both AVP and somatostatin receptors except there was focal staining of the background fibrillary material with neurofilament protein.

DISCUSSION

Despite the first description in the literature over seventy years ago, there remains relatively little about ONB that is accepted as fact. This is partly because it is evident that the term olfactory neuroblastoma appears to comprise a group of tumours with some similar histopathological characteristics, most notably the ultrastructural identification of neuronal processes and granules [4], but also marked heterogenous differentiation. Mindful of this, several studies have attempted to propose histologic subclassifications into neuroblastoma and neuroendocrine subtypes, but no consistently significant relationship with prognosis has been found [4-7].

In addition to the structural similarity to neuroendocrine carcinoma noted by many authors, over the last three decades it has been increasingly recognized that there is an association of ONB with neuroendocrine function. Several hormones have been identified within these tumour cells including dopamine, epinephrine and norepinepherine, calcitonin, melanin, adrenocorticotrophic hormone and, most commonly, AVP. Although well-recognised, these hormone-secreting tumours are still extremely rare, with less than twenty cases having been reported.

Another feature of ONB that resembles neuroendocrine carcinoma was the finding of a positive octreotide scan in one of our cases, indicating the presence of somatostatin receptors. Octreotide scans are widely used to image tumours of neuroendocrine origin and also successfully images up to 90% of neuroblastomas [8]. Octreotide scan positivity has been reported on one previous occasion in a non-functional ONB, so is not isolated to hormone-secreting tumours, but no correlation with laboratory-detected somatostatin receptors was made in that report [2]. Our cases are the first to have documented immunohistochemical evidence of somatatstatin receptors within the tumour. The fact that this was demonstrated in both tumours suggests that, in keeping with other tumours of

neuroendocrine origin, this may well be a common finding and octreotide scanning should be considered part of the routine investigation and follow up of this tumour. Clearly further studies substantiating the relationship between ONB and somatostatin receptors are also needed.

Radiological investigation of ONB should also include both CT scanning, which optimally demonstrates bony erosion, and MR, which helps to delineate the tumour from surrounding soft tissue structures and secretions [9-12]. The radiological features of ONB are varied, in keeping with its pathological heterogeneity and diverse prognosis. They may have both an expansile tendency, characterized by bowing of sinus walls, and a destructive tendency, manifested as tumour replacement of contiguous areas. It is likely that the latter represents the more aggressive tumour but this has not been qualified as yet. The MR appearance is usually that of hypointense T1-weighted and isointense or hyperintense T2-weighted images when compared to grey matter. Gadolinium contrast enhancement is always present, in keeping with a highly vascular tumour, but may be homogenous or heterogenous. Some authors have found this a useful way of differentiating tumour from the peripheral rim enhancement of obstructed sinonasal secretions [10,12]. It is especially interesting therefore that both our cases demonstrated only a peripheral rim enhancement (Figures 1 and 4), which has not been reported for ONB in the literature previously. It is likely this represents an indolent form of ONB and should be borne in mind when assessing these tumours radiologically.

Most authors agree that ONB is potentially curable with surgery and that this should include a craniofacial resection to try and obtain tumour-free surgical margins, as this often extends to the cribriform plate [13,14]. Several papers have shown that ONB is at least partially sensitive to both radiotherapy and chemotherapy and the discussion surrounds when to treat with these modalities [14-16]. It is generally agreed that for metastatic disease chemotherapy is useful and for stage C disease or recurrence radiotherapy is used. It is unclear if they should be used in combination or whether they have a role in early stages of disease.

It is also possible, given the findings from this paper, that somatostatin analogues may have a role in the treatment of ONB. A recent review of the antineoplastic effects of these agents highlighted their very successful use in the symptomatic control of many hormone-secreting neuroendocrine tumours [17]. Although some claims have also been made regarding their antiproliferative effects, the review concluded that these were limited at best and most studies had been performed in a non-randomised manner. However at present this field is in its infancy and may yet prove to have some substance. Other studies have also commented on the possibility of treating these tumours with radio-labelled somatostatin analogues [2] but again this area needs further research.

CONCLUSIONS

ONB may be positive for somatastatin receptors, in keeping with many other neuroendocrine tumours.

Octreotide scanning has been shown to successfully delineate ONB. Its use should be considered in the preoperative investigation of this tumour and, when positive, the postoperative follow-up. It should also be considered in the investigation of SIADH of unknown cause. Somatastatin analogues may also prove useful in the treatment of ONB.

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