Ganglioneuroblastic Transformation in Olfactory Neuroblastoma

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Abstract Ganglioneuroblastic transformation in olfactory neuroblastoma (ONB) is an exceptionally rare phenomenon. We document the case of a patient with a poorly differentiated sinonasal malignancy that recurred following treatment with chemoradiotherapy and showed ganglioneuroblastic transformation. Although the index tumour showed neuroendocrine differentiation, it did not have the typical clinico-pathological features associated with ONB. We highlight the diagnostic difficulties in establishing an accurate diagnosis for undifferentiated sinonasal tumours and present evidence that the index tumour was an ONB.

The current report is only the third case of ONB showing complete ganglioneuroblastic transformation.

Keywords Olfactory neuroblastoma · Ganglioneuroblastic transformation · Neuroendocrine carcinoma · Sinonasal undifferentiated carcinoma

Introduction

Olfactory neuroblastoma (ONB) is a rare malignant neuroectodermal neoplasm that arises exclusively in the sensory mucosa of the upper nasal cavity [1]. ONB is composed of primitive neuroblastic cells that have the cytological features of ‘small round blue cells’ (SRBC). There is a wide differential diagnosis for SRBC tumours presenting in the head and neck region: accurate diagnosis requires close clinic-pathological correlation and the use of panels of immunohistochemical markers. Ancillary laboratory methods such as electron microscopy, cytogenetics and molecular biology techniques may be required to secure the diagnosis. The specialised neuroectodermal olfactory cells in the upper nasal cavity that give rise to ONB are also thought to be the progenitors for sinonasal neuroendocrine carcinomas (NC) [1]. In addition, sinonasal undifferentiated carcinoma (SNUC) may also show evidence of neuroendocrine differentiation [2]. Typically, ONB is distinguished from NC and SNUC by its characteristic site, lobular growth pattern, lack of cytokeratin expression, and the presence of S100-positive sustentacular cells (Table 1) [3]. Ganglioneuroblastic transformation is a well-recognized phenomenon in neuroblastomas occurring at other sites [4], such as the adrenal glands, but is rare in ONB and has not been reported in NC or SNUC [5–8].

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Table 1 Morphological and immunohistochemical features distinguishing olfactory neuroblastoma, neuroendocrine carcinoma and sinonasal undifferentiated carcinoma [1, 3, 10]

	Olfactory neuroblastoma	Neuroendocrine carcinoma	Sinonasal undifferentiated carcinoma
Architecture	Lobules Sheets Nests	Sheets Ribbons Nests	Lobules Sheets Nests
Rosettes	Variable	Not present	Not present
Stroma	Vascular	Variable	Variable
Nuclear size	Small	Small	Medium to large
Chromatin	‘Salt and pepper’	‘Salt and pepper’ Nuclear molding	Hyperchromatic
Nucleoli	Inconspicuous	Inconspicuous	Single; prominent
Cytoplasm	Minimal	Minimal	Minimal
Mitotic count	Variable	High	High
Necrosis	Variable	Common	Common
Pan-cytokeratin	Occasionally positive	Positive; punctate	Positive
Simple epithelial keratins (CK7, CK8, CK19)	Negative	Negative	Positive
EMA	Negative	Negative	Occasionally positive
S100	Positive sustentacular cells	Negative	Occasionally positive
CD56	Positive	Positive	Negative
CD57	Variable	Negative	Negative
Synaptophysin	Positive	Variable	Occasionally positive
Chromogranin	Variable	Variable	Occasionally positive
TTF-1	Negative	Variable	Negative
Neuron-specific enolase	Positive	Variable	Variable
GFAP	Variable	Negative	Negative
CD99	Negative	Negative	Occasionally positive

We document the case of a patient with a poorly differentiated sinonasal malignancy that recurred following treatment with chemoradiotherapy and showed evidence of ganglioneuroblastic differentiation. We present evidence that the index tumour was an ONB. This is, to the best of our knowledge, only the third case of ONB showing complete ganglioneuroblastic transformation reported.

Case Report

In 2009 a 60-year-old female patient presented to the ENT department, Newcastle-upon-Tyne Hospitals NHS Foundation Trust, with an area of abnormal mucosa in the posterior roof of the left nasal cavity. The lesion was identified during post-treatment surveillance following a long-standing history of sinonasal malignancy.

The patient's past medical history was notable for squamous cell carcinoma (SCC) of the right maxillary antrum that was treated with external beam radiotherapy in 1995. The carcinoma recurred 1 year later and was treated

by salvage surgery (right partial maxillectomy with orbital exenteration) and brachytherapy.

The patient had a long (11 years) disease-free interval. In 2007, however, she presented with a new polypoid lesion in the left nasal cavity. Imaging (CT and MRI) revealed an extensive tumour involving the left nasal cavity, paranasal sinuses, and anterior skull base. A biopsy of the lesion demonstrated a poorly differentiated malignant neoplasm. The tumour had a lobular architecture and was composed of small to medium sized basaloid cells (Fig. 1a, b). The nuclei were pleomorphic with a coarse chromatin pattern and small distinct nucleoli. There were 6 mitoses per 10 high power ($\times 400$) fields; Ki67 demonstrated a high proliferation fraction of at least 70%. There was no squamous differentiation or keratinisation; no glandular structures were identified. The investing stroma was fibrotic and contained a chronic inflammatory cell infiltrate. Immunohistochemistry showed strong cytoplasmic expression for a pan-cytokeratin marker (AE1/AE3; Fig. 1c); however, specific cytokeratin (CK) markers (CK5/6, CK7 and CK20) were negative. Markers for

Fig. 1 Photomicrographs of the index tumour diagnosed in 2007. **a, b** A poorly differentiated neoplasm with a lobular architecture composed of small round blue cells (H&E); **c** pan-cytokeratin (AE1/AE3); **d** CD56; **e** synaptophysin; **f** chromogranin

neuroendocrine differentiation (CD56, synaptophysin, chromogranin, microtubule associated protein-2; MAP-2) were all strongly positive (Fig. 1d–f); calcitonin and TTF1 were negative. The neural markers NeuN, neurofilament and GFAP were also negative. The malignant cells did not stain with S100 and there were no sustentacular cell networks. Following exclusion of metastasis by clinical examination and imaging, the differential diagnosis at that time was considered to lie between NC and SNUC. The previous history of sinonasal SCC treated with multimodal therapy raised the possibility of a radiation-induced second primary tumour. The tumour was treated with chemotherapy (carboplatin/fluorouracil) and intensity-modulated radiation therapy (IMRT). There was an excellent response to chemoradiotherapy, with significant tumour shrinkage on imaging (CT and MRI).

After a clinically disease-free period of 2 years, an erythematous area was identified in the posterior roof of the left nasal cavity (2009). An incisional biopsy demonstrated ulcerated and inflamed mucosa covered by squamous

epithelium. The stroma was fibrotic and sclerosed and contained nests and interconnecting strands of neural tissue that filled the lamina propria, submucosa and abutted the native bone of the sinonasal complex. The islands and nests varied in size but were characterised by neuronal cells that contained neuropil (Fig. 2a, b). The neuronal cells ranged in appearance from a population of undifferentiated neurocytic cells to a smaller population of ganglionic cells. No glial elements were identified. The neuronal cells expressed CD56, synaptophysin, chromogranin, MAP-2, NeuN, and neurofilament protein (Fig. 2c, d). Synaptophysin showed a synaptic pattern of staining that highlighted the neuropil component. The latter was also decorated by neurofilament protein, which demonstrated a dense meshwork of neuritic processes within islands and nests of the tumour cells (Fig. 2d). Chromogranin highlighted the ganglion cells. Only occasional isolated cells were pan-cytokeratin positive; the majority were negative. S100 did not stain the tumour cells and there were no sustentacular cells. Ki67 showed a very low (<5%) proliferative fraction,

Fig. 2 Photomicrographs of the recurrent tumour diagnosed in 2009. **a, b** A moderately cellular neoplasm with a lobular architecture. There are small round cells and ganglion cells (H&E); **c** NeuN; **d** Neurofilament; **e, f** electron microscopy showing nuclear invaginations (**e** magnification $\times 6,000$) and dense core granules within a cytoplasmic process (f magnification $\times 12,000$)

Fig. 3 MRI images (fat suppressed, post contrast) of the recurrent tumour diagnosed in 2009 (**a, b**). There is intracranial spread of tumour into the inter-hemispheric fissure through the cribriform plate (coronal scan, arrows and sagittal scan, arrowheads)

with 1 mitosis identified in 10 high power ($\times 400$) fields. Electron microscopy revealed nuclei with convoluted membranes forming invaginations and pockets (Fig. 2e), plus

numerous dense core granules distributed throughout the tumour cells' slender cytoplasmic processes (Fig. 2f). The features were considered to represent ganglioneuroblastic

transformation within an ONB. The diagnosis was based on the location of the tissue in the roof of the nose, the histopathological appearance, the immunohistochemical profile, and ultrastructural features. The diagnosis was supported by subsequent imaging (MRI) showing intracranial extension of lesional tissue through the cribriform plate and into the inter-hemispheric fissure (Fig. 3). Despite residual disease and the radiological evidence of progression, the patient has remained asymptomatic for 18 months.

Discussion

Whilst neuroblastomas at other sites are known to have the ability to differentiate into ganglion cells [4], ganglioneuroblastic transformation in ONB is an exceptionally rare phenomenon: to date, only 6 cases have been reported [5–8]. In 4 cases, ganglioneuroblastic differentiation was a focal change in an otherwise typical ONB [7, 8]. In the other 2 cases, complete ganglioneuroblastic transformation was noted [5, 6]. Both reports involved middle-aged male patients with ONB, which, following treatment with external beam radiotherapy, showed ganglioneuroblastic transformation. The histopathological features of the initial biopsies allowed the diagnosis of ONB to be readily established: both revealed malignant neoplasms comprising islands of SRBCs with occasional Homer Wright rosettes and networks of S100-positive sustentacular cells. The histopathological features of the recurrent tumours were similar to those of the present case, with large, irregular islands of ganglion cells embedded in a densely collagenous stroma. The ganglionic cells, highlighted by neurofilament and NSE, ranged from immature cells with scanty cytoplasm to mature ganglion cells with prominent nucleoli, amphophilic cytoplasm and Nissl granules. Despite the shared morphology of these 2 recurrent tumours, the patients had very different outcomes: one remained asymptomatic following incomplete salvage surgery, with no disease progression for a further 3 years [5]; the other underwent incomplete resection following chemotherapy, but developed a mediastinal metastasis and died as a result of aspiration pneumonia at 3 months after the operation [6].

Considering the present case, the diagnosis of ganglioneuroblastic transformation in an ONB raises the possibility of either a new primary lesion (third metachronous sinonasal tumour following SCC 1995 and NC/SNUC 2007) or recurrence of the index tumour diagnosed in 2007 (NC/SNUC). Whilst the diagnosis of a third metachronous sinonasal primary tumour cannot be entirely excluded, the relatively short interval (2 years) between tumours in the same location makes recurrence most likely. This suggests that the index tumour was neither a NC nor a SNUC, but an

ONB. To some extent, the 2 neoplasms (index and recurrence) had common architectural and cytological features: lobular configuration with a sub-population of SRBCs. The lobular configuration of the index tumour favours a diagnosis of ONB over NC, which is classically arranged in sheets, ribbons and nests. According to Hyams' grading system for ONB [1], the index tumour would be classified as histologic grade IV (high grade), and in this respect would be similar to the case described by Miura et al. [6]. Both tumours showed neuroendocrine differentiation by immunohistochemical studies [4, 9], however, electron microscopy of the index tumour did not demonstrate the ultrastructural features detected in the recurrence. Interestingly, the index tumour showed extensive cytokeratin expression and the recurrence was cytokeratin negative. Whilst there are documented cases of ONB with cytokeratin staining [10, 11], extensive cytokeratin expression has not been described. Although neither tumour showed evidence of sustentacular cells, it is generally accepted that these cells are usually absent in high grade ONB [12].

In conclusion, this case highlights the diagnostic difficulties in assigning an accurate diagnosis when poorly differentiated sinonasal lesions show neuroendocrine differentiation and the problems in separating three uncommon sinonasal malignancies: NC, SNUC and ONB. We present evidence for complete ganglioneuroblastic transformation in an ONB, which is only the third reported in the literature.

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