Case Report

Olfactory neuroblastoma with epithelial and endocrine differentiation transformed into ganglioneuroma after chemoradiotherapy

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We report a 56-year-old man in whom an olfactory neuroblastoma with epithelial and endocrine differentiation transformed into a mature ganglioneuroma after chemoradiotherapy. The tumor arising from the sphenoidal and maxillary sinuses showed rapid growth into the frontal lobe and metastasis to the cervical lymph nodes. The patient showed signs of a syndrome of inappropriate secretion of antidiuretic hormone (SIADH). A radical craniofacial resection of the primary tumor was performed after 16 Gy of local irradiation and systemic chemotherapy. Three months after the operation, the patient died of mediastinal metastasis. The biopsy before chemoradiotherapy showed a neuroblastoma with Homer–Wright rosettes, fibrillary matrix, Flexner–Wintersteiner rosettes and antidiuretic hormone production. After chemo- radiotherapy, the histology changed to that of a ganglioneuroma consisting of large ganglion cells and Schwann cells without immature neuroblastoma components. Although transformation to ganglioneuroma in an adrenal neuroblastoma is common, an olfactory neuroblastoma showing ganglioneuronal maturation after chemoradiotherapy has not been reported. The pluripotent progenitor cells of the olfactory neurons may be the origin and their existence explains why various neoplasms with neuronal and epithelial differentiation arise from the olfactory mucosa.

Key words: antidiuretic hormone, apoptosis, esthesioneuroepithelioma, ganglioneuroma, olfactory neuroblastoma, stem cell, transformation

An olfactory neuroblastoma (ONB) originating from olfactory neuroectoderm is a rare immature tumor showing neuroblasto- mal, paraganglial and epithelial characteristics.1 We report a case of ONB that showed neuronal differentiation with Homer–Wright rosettes and fibrillary background, epithelial differentiation with Flexner–Wintersteiner rosettes and endocrine features with antidiuretic hormone (ADH) production before treatment, and presented mature transformation to ganglioneuroma after chemoradiotherapy. Although ONB with various histological subtypes is known, no case of ganglioneural maturation without original immature components has been reported.

CLINICAL SUMMARY

A 56-year-old man was admitted with symptoms of recurrent epistaxis and nasal obstruction over 3 months and occasional headaches in the right frontal region. Computed tomography (CT) and magnetic resonance imaging (MRI) (Fig. 1) revealed a large tumor occupying the right ethmoidal sinus with extension to the right sphenoidal sinus and both maxillary sinuses, and reaching the anterior cranial fossa and orbital medial wall that had bony erosion. A biopsy of the tumor was performed and histological diagnosis of ONB was established. After admission, he exhibited consciousness disturbance due to a syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and hyponatremia. After an initial dose of 16 Gy external irradiation to the frontal lesion, radiotherapy was interrupted because of cervical lymph node metastasis. The patient was treated with five courses of systemic chemotherapy (carboplatin and etoposide). After the tumor had decreased in size, it was surgically removed by radical craniofacial resection followed by γ-knife irradiation of the intracranial residual tumor. However, mediastinal metastasis was found and the patient died of aspiration pneumonia 3 months after the operation. An autopsy was not performed.

PATHOLOGICAL FINDINGS

The first biopsy specimen, 10 × 5 × 5 mm in size, was taken from the nasal cavity. The tumor was highly cellular with
lobular growth patterns of cells with oval or elongated, mostly hyperchromatic nuclei (Fig. 2). The nests of closely packed cells were intermingled with Homer–Wright rosettes (Fig. 3) and Flexner–Wintersteiner rosettes with ductal structures (Fig. 4). No external basement membrane of the rosettes was seen. Intercellular fibrillar background was found focally. Mitotic figures and necroses were frequent and vascular invasion was seen at the tumor margin. No ganglion cells were found in the biopsy specimen. The histological grade according to the Hyams grading system was grade 3 (Table 1).

Immunohistochemical studies (Table 2) showed positive reactions for cytokeratin (CK) (Fig. 5a) and epithelial membrane antigen (EMA) in packed cells forming two types of...
These cells also showed positive reactions for chromogranin A and ADH (Fig. 5b). A faint positive reaction for neuron-specific enolase (NSE) was present on the fibrillary structures. Sustentacular cells at the periphery of the cell nests were focally positive for S-100 protein (S-100). CD99 (MIC2) immunostaining was negative and the Ki-67 (MIB-1) staining index of the tumor cells was 35.4%.

In the resected specimen after chemoradiotherapy, a resid-ual tumor infiltrating the paranasal sinus is composed of large ganglion-like cells with round nuclei and Schwann-like elongated cells (Fig. 6). Some cells with pyknotic nuclei were surrounded by numerous lymphocytes (Fig. 7).

Table 2  Antibodies used in this study

| Antigen          | Source                        | Dilution |
|------------------|-------------------------------|----------|
| Cytokeratin (AE1/AE 3 clone) | Biomeva, Foster City, CA, USA | Pre-diluted |
| EMA              | DAKO, Kyoto, Japan            | 1:100    |
| Chromogranin A   | DAKO                          | 1:100    |
| ADH              | Chemicon, Temecula, CA, USA   | 1:1000   |
| NSE              | Novocastra, Newcastle Upon Tyne, UK | 1:100   |
| S-100            | DAKO                          | 1:500    |
| Ki-67 (MIB-1)    | Immunotech, Marseilles, France | 1:50    |
| Synaptophysin    | DAKO                          | 1:20     |
| Neurofilament protein | DAKO                        | 1:100    |
| CD99 (MIC2)      | Signet, Dedham, MA, USA       | 1:100    |
| CD3              | DAKO                          | 1:100    |
| CD20             | DAKO                          | Pre-diluted |

ADH, antidiuretic hormone; EMA, epithelial membrane antigen; NSE, neuron-specific enolase.

Figure 5  The tumor cells forming rosettes are positive for (a) cytokeratin and (b) antidiuretic hormone.

Figure 6  In the resected specimen following chemoradiotherapy, residual tumor infiltrating the paranasal sinus is composed of large ganglion-like cells with round nuclei and Schwann-like elongated cells.

Figure 7  Lymphocytes are focally infiltrated around tumor cells. Some ganglion-like cells with round nuclei show pyknotic nuclei.
neurofilament protein and NSE, while Schwann-like elongated cells were positive for S-100. Focal weak reactivity for CK was found on small round cells near ganglion-like cells (Fig. 8). Most infiltrating lymphocytes were positive for CD3 (Fig. 9). CD20 positive cells were rarely seen. The MIB-1 staining index of the residual tumor cells was less than 1%.

DISCUSSION

Our case showed various histological features, including neuroblastoma with Homer–Wright rosettes, fibrillary matrix, Flexner–Wintersteiner rosettes, ADH production and ganglioneural differentiation after chemoradiotherapy. This histological diversity could be a manifestation of the multipotential nature of olfactory mucosal progenitor cells. Tumors arising from this region of the olfactory mucosa constitute a diverse group of neoplasms such as ganglioneuroblastoma, paraganglioma, esthesioneuroblastoma, olfactory neuroepithelioma, neuroendocrine carcinoma and sinonasal undifferentiated carcinoma. These tumors exhibit a wide range of neuronal and epithelial differentiation. We think these tumors originate from the mitotically active progenitor cells lying on the basal layer of the olfactory epithelium. In adults, basal cells supply epithelial sustentacular cells. Although continuous renewal of olfactory receptor neurons is known in other mammals, it is not known whether olfactory neuronal cells can regenerate in humans.

Neuroblastoma arising from the adrenal medulla and sympathetic ganglia in infants has been known to mature to ganglioneuroblastoma or ganglioneuroma and then spontaneously regress. ONB differs from neuroblastomas of the adrenal and sympathetic nervous system in its occurrence in older patients, distinctive angiomatoid stroma, occasional olfactory rosette formation and extreme rarity of spontaneous regression and transformation to ganglion neuroblastoma or ganglioneuroma.

To explain the spontaneous regression of adrenal neuroblastoma in children, three hypotheses have been advanced: the immunological theory, the delayed apoptosis theory and the maturation theory. In the immunological theory, the tumor cells are attacked by the infant’s immune system or by transplacentally acquired maternal immune cells and maternal antibody while in the delayed apoptosis theory, the developmental time-switch for apoptosis is delayed in tumors. In the maturation theory, immature neuroblastic components disappear and ganglion cells increase in number and accompany rich Schwannian stroma. Spontaneous maturation of neuroblastic tumors has been a well-known phenomenon since early last century. Cushing and Wolbach reported a case of a child with a sympathetic neuroblastoma that was biopsied in infancy and resected 10 years later, at which time the tumor was a ganglioneuroma. The ganglioneuroma is a neuroblastoma at the final stage of maturation, and all ganglioneuromas were once neuroblastomas at an earlier time in their development.

Our ONB case showed maturation to ganglioneuroma at the primary site after chemoradiotherapy. CD3-positive lymphocytic infiltration around the remaining immature epithelial components of cytokeratin-positive cells suggests that the process of neuroblastic regression was associated with the cytotoxic effects of lymphocytes. T lymphocytes had probably induced the immature neuroblastic cells to undergo apoptosis.

Neuroblastomas consist of two main cell populations: neuroblastic/ganglionic cells and Schwann cells. Recent genetic analysis indicates that the Schwann cells in neuroblastic tumors are likely to be reactive in nature and are recruited
from the surrounding non-neoplastic tissues by the tumor cells. This suggests that neoplastic neuroblasts produce Schwann cell mitogens and chemotactic factors that are important for the recruitment of Schwann cells.

Kadish and associates have proposed a system that defines the disease stages as follows: stage A, disease confined to the nasal cavity; stage B, disease confined to the nasal cavity and paranasal sinuses; and stage C, local or distant spread beyond the nasal cavity or paranasal sinuses. The disease incidence is 30% for stage A, 42% for stage B and 28% for stage C. Our case showed stage B at the first presentation but rapidly progressed to stage C and finally showed distant metastasis to the mediastinum. Although ganglioneuroma generally shows good prognoses, this case presented lymph node and mediastinal metastasis. After treatment, the primary site had no immature components and no mitotic activity, with a low MIB-1 staining index. The immature components had probably metastasized before treatment because vascular invasion had already been found in the biopsy specimen. Only the primary sites of the nasal and paranasal cavity were irradiated, not the metastatic sites. Mature transformation occurred only in the primary site. A few cases of ONB showed ganglionic differentiation and two cases showed abundant ganglion cells after irradiation.

Because the biopsy specimen was limited in amount, it is possible that ganglion cells were a component of the tumor from the beginning and that only mature components remained in the irradiated primary site.

Hyams et al. proposed a grading system based on histological findings (Table 1). According to this system, this case correlated to a histological grade of 3 before therapy and showed no characteristics of ONB after chemoradiotherapy. Examination of the limited data presented in 1983 by Hyams (assessing 46 tumors from the Armed Forces Institute of Pathology registry) showed a correlation between tumor grade and prognosis. With a mean follow up of 5 years, none of the six patients with grade 1 tumors died of the disease, while three of the 25 (12%) with grade 2 tumors, six of the 11 (55%) with grade 3 tumors and all four patients with grade 4 tumors died of the disease. A recent report supports the predictive value of this histological grading system. Of the six patients with Hyams grade 1 or 2 tumors, four remained disease free for more than 2 years compared with only four of 15 patients with Hyams grade 3 or 4 tumors.

Some tumor recurrences are rapid and lethal whereas others are slow and progressive, with patients surviving for many years. Fifty to 70% of patients develop local recurrence, and 20 to 30% eventually develop distant metastasis. A recent study from the University of Iowa reported that the 5- and 10-year survival rates for ONB were 56 and 42%, respectively.

Hirose et al. have reported that longer survival rates are related to a higher incidence of S-100 protein-positive cells and a low MIB-1 staining index (<10%). Our case exhibited few S-100 protein-positive cells and a high MIB-1 staining index (35.4%) at the initial biopsy and followed an unfavorable course. Out of the five reported cases of ONB associated with SIADH, all cases had Homer–Wright rosettes, three were accompanied by hypertension and only one showed true rosette-forming duct-like spaces.

In conclusion, this case of ONB is an extremely rare case showing epithelial and endocrine differentiation. These features may depend upon the progenitor or basal stem cells of the olfactory neurons. Pluripotent cells may have been the origin in our case, and their existence explains why various neoplasms with neural and epithelial differentiation arise from the olfactory mucosa.

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