CASE REPORT

Primary Neuroendocrine (Merkel Cell) Carcinoma of the Anterior Skull Base

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ABSTRACT—A case of a primary neuroendocrine (Merkel cell) carcinoma arising in the anterior skull base involving the dura, both frontal lobes, and the paranasal sinuses is presented. The tumor was completely removed by an enlarged bifrontal transbasal approach. The neuropathological, immunohistological, and electron microscopical investigation revealed all characteristics of a Merkel cell carcinoma, normally presenting as a skin carcinoma of the head and neck. The history, treatment, neuropathology, and possible explanation for this rare manifestation are discussed.

Merkel cell (neuroendocrine) carcinoma was first described in 1972 by Toker under the name of trabecular carcinoma of the skin. It has become a well defined entity with distinct pathological and immunohistochemical profile.¹⁻³ According to the appearance of its cell of origin, the primary site is the skin, mainly on the head and neck.⁴ We report a case of primary neuroendocrine carcinoma presenting as an anterior skull base tumor, invading the brain and paranasal sinuses.

CASE REPORT

A 47-year-old male presented with a 3-month history of right-sided headache and bloody nasal discharge. He was referred under the diagnosis of frontal sinusitis to the ENT Clinic of our hospital. Physical examination revealed right-side exophthalmos, anosmia, and a slight right-sided oculomotor nerve palsy. CT and MRI scans of the head showed the presence of a 6x5x4 cm contrast enhancing mass of the anterior skull base with destruction of the bone and extension into both frontal lobes, both orbits, frontal sinus and the upper nasal cavity (Fig. 1). Carotid angiography revealed bilateral cranial displacement of the pericallosal and frontopolar arteries, and rich vascularization of tumor by

sphenopalatal branches of the external carotid arteries on both sides. Ultrasound examination of the body and bone scintigraphy were normal. A transnasal biopsy from a blue coloured mass in the right middle nasal duct revealed the diagnosis of a small cell neuroendocrine tumor. Radical resection of the tumor was carried out through an enlarged bifrontal transbasal approach combined with right radical neck dissection. The intraoperative findings are shown in Figure 2. A soft tumor with well defined borders was found (Fig. 2A). The tumor spread through the anterior skull base with infiltrated dura as well as both frontal lobes. The tumor had destroyed the anterior skull base, and had invaded all paranasal sinuses, the cavum nasi, and the hard palate. Using an enlarged transbasal approach, the tumor was removed totally in an combined procedure together with the ENT surgeon (Fig. 2B). Reconstruction of the anterior skull base was performed using an autologous bone graft from the tabula interna, fixed by direct sutures at the surrounding normal bone structures (Fig. 2C), demonstrated in a 6 week postoperative MRI scan (Figs. 3A/B).

Light microscopic examination of routine hematoxylin-eosin (H+E) stained sections revealed a small round cell tumor. Morphological, immunohistochemical and ultrastructural investigations were performed. The tumor showed the distinct pattern of a Merkel cell carcinoma.

Figure 1. Preoperative MRI scans in coronar (A) and sagittal (B) plane. (Figure continued on the next page.)

Figure 2. Intraoperative view via a transbasal approach. The tumor is dissected from both frontal lobes (A). After total removal, the view through the anterior skull base into the nasal cavity and the opened paranasal sinuses (B). Reconstruction of the bony defect using an autologous tabula interna bone graft (C)

Figure 3. Postoperative MRI scans in coronar (A) and sagittal (B) plane, demonstrating the tumor totally removed.

noma of compact epithelium-like sheets of tissue composed by small round cells, traversed by thin fibrovascular septa (Figs. 4A, B), lacking rosettes/pseudorosettes and neurofibrillary stroma as normally present in olfactory neuroblastomas. Tumor cells with round

nuclei with delicate granular chromatin and one or several nucleoli showed a relatively well defined, eosinophilic, and sparse cytoplasm lacking PAS positivity (Fig. 4B). Numerous mitotic nuclei and necrotic foci were present. Immunohistochemistry demonstrated an

Figure 4. Compact epithelium-like sheets of tumor tissue composed by small round cells. Hematoxylin-eosin (H+E) stain, $\times 160$. Densely packed tumor cells with delicate nuclear chromatin and prominent nucleoli. H+E-stain, $\times 630$.

abundant expression of cytokeratin (CK) by most tumor cells (Fig. 5A) and, to a lesser extent, epithelial membrane antigen (EMA). Mesenchymal markers vimentin and desmin were not expressed by the tumor cells, ruling out a sarcomatous tumor. There was moderate den-

sity of perivascular common leucocyte antigen (CLA) positive leukocytes, but no evidence of a lymphoma. Immunoreactivity for both chromogranin A (Fig. 5B) and synaptophysin (SYN) was found in focal distribution; however, neurone specific enolase (NSE) was not

Figure 5. Cytoplasmic labeling of most tumor cells by monoclonal anti-cytokeratins antibody. Immunocytochemical avidin biotin technique, $\times 250$. Focal expression of Chromogranin A. Immunocytochemical peroxidase anti-peroxidase technique with polyclonal anti-chromogranin A antiserum, $\times 250$.

expressed. Electron microscopy was performed and revealed the presence of dense core neurosecretory granules. These findings confirmed the diagnosis of neuroendocrine carcinoma.

The postoperative course was uneventful. After wound healing, the patient received radiation therapy (56Gy). Adjuvant chemotherapy cycles consisting of 50 mg Cisplatin and 190 mg Etoposid each, were started.

DISCUSSION

Since the first description of Merkel Cell carcinoma as a sweat gland carcinoma by Toker in 1972 and the identification of neurosecretory granules by electron microscopy²⁵ confirming the neuroendocrine origin of the tumor, this neoplasm has been characterized in detail^{1,4,15,20,21,23,26,27}. The nearly exclusive appearance as primary skin tumor most common in the head and neck region (54%) followed by the lower limbs (27%) and the arms and trunk (19%)¹² is due to the distribution of the postulated cell of origin, the cutaneous Merkel cell^{1,4,5,20,22,26}.

Although Merkel cells are also described to be present in the oral mucosa⁶ and the palate²⁹, only a few reports of Merkel cell carcinomas locations other than the skin have been published in recent years^{9,14,17,30}. Based on our current knowledge, the Merkel cell carcinoma is believed to derive from an in-transit Merkel cell or precursor cell^{2,7,8,18,13} from the neural crest^{5,29} migrating to the skin during development, similar to melanocytes¹⁰.

The rare anterior skull base location of the tumor in our patient together with the previously described appearance in the calvarial convexity,³⁰ and oral, and nasal mucosa,^{9,14,17} might reflect a disorder of embryonal migration with retention of Merkel cell precursors along their pathway. Considering Merkel cell precursor cells as the origin of neuroendocrine carcinomas^{2,7,8,18} in unexpected locations, like in our patient, might explain why evidence for the existence of Merkel cells in the mucosa of ethmoid cells or frontobasal dura mater is still lacking.

In view of the malignant behaviour of this tumor with a high recurrence rate and metastatic dissemination (three year survival rate is approximately 62% for treated pure skin tumors¹²), wide resection analogous to that for malignant melanoma and prophylactic regional lymph node dissection is recommended¹⁶. However, a review of 234 cases showed that adjuvant radiotherapy or adjuvant node dissection reduced the local recurrence rate from 39% to 26%¹⁹. Regional lymph node involvement occurs in more than 50%^{11,12,32}. Distant metastases are fatal regardless of therapy¹¹. Chemotherapy seems to offer at least palliative benefit to patients with advanced, unresectable, recurrent, or metastatic disease^{3,31}. Due to the wide expan-

sion of the tumor in our patient with involved cervical lymph nodes on both sides, surgery, as well as, radiation and chemotherapy were performed. We removed the skull base tumor en bloc via an enlarged bifrontal transbasal approach in combination with a left supra-omohyoid and right radical neck dissection. Local radiotherapy to the tumor site was given with a dose of 56 Gy. Three-day cycles of chemotherapy, consisting of 50mg Cisplatin and 190mg Etoposid per day, were administered. Despite our aggressive therapeutical approach our patient died 12 months after the operation from progressive, systemic disease.

In conclusion, the rare location of a neuroendocrine (Merkel Cell) carcinoma in the anterior skull base as described here, confirms the theory of the origin of non-skin Merkel cell carcinomas from migration remnants of Merkel cell precursors. Moreover, the limited survival of 12 month in our patient despite of aggressive therapy highlights the still very poor prognosis of this rare neoplasm.

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