Original article

Management of intracranial invasive olfactory neuroblastoma

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Background  Olfactory neuroblastoma (ONB) is a rare tumor that often arise from the nasal cavity. The aim of this study was to investigate the clinical characteristics and treatments of intracranial invasive ONB.

Methods  Between July 2001 and August 2005, 5 patients with intracranial invasive ONB were treated in our department. Their clinical features, radiological and pathological characteristics, and surgical treatments were analyzed. Among the 5 patients, 1 received transnasal biopsy, and 4 were operated through the transfrontal or extended bifrontal approaches to reconstruct the skull base. After the operation, all the patients received radiotherapy, and one received chemotherapy. They were followed up for 6 to 45 months.

Results  The ONB was resected totally in the 4 patients. In all the patients, nasal obstruction was alleviated without cerebrospinal fluid leakage. The visual acuity was improved in 3 patients, who had a decreased visual acuity before the operation. Two patients had metastasis into the lumbosacral spinal canal 6 and 8 months after the operation, one of them received a second operation and the other died.

Conclusion  ONB has no specific symptoms. Intracranial ONB should be resected as far as possible, and treated by radiotherapy after the operation.

Olfactory neuroblastoma (ONB, also named esthesioneuroblastoma), a rare neuroepithelial tumor, is prone to invade into the adjacent tissues and disseminate through the vessels and lymphatic system in the last stage. Most intracranial ONBs arise from the nasal cavity. The tumor is divided into 4 classes: class I: neoplasm limited within the nasal cavity; class II: neoplasm involving both the nasal cavity and paranasal sinuses; class III: neoplasm arising from the nasal cavity and invading the paranasal sinuses, fossa floor, orbita, and even the intracranial area; class IV: neoplasm with lymphatic or distal metastasis. Between July 2001 and August 2005, we had treated 5 patients with intracranial ONB; the purpose of this study was to analyze the natural history, treatment and prognosis of the patients.

METHODS

Patients  From July 2001 to August 2005, 5 male patients aged 16 to 56 years (mean 38.8) were treated in Beijing Tiantan Hospital. The interval between occurrence of the symptoms and consultation varied from 3 weeks to 6 months (mean 2.7 months). The patients presented with (in a time sequence) rhinostegnosis (4 patients), rhinorrhagia (3), anosmia (4), headache (3), decreased visual acuity (3), and diplopia (2). Neurological examination showed anosmia in single side in 2 patients and both sides in 2, decreased visual acuity in 3, hemianopsia in both temple sides in 2, disturbance of abducens in 1, facial hypesthesia in 1, primary optic nerve atrophy in 2, and cervical lymphadenectomy in 2.

Managements  Head CT and MRI were carried out in all the patients, demonstrated a mass filled the medioposterior part of the nasal cavity and invaded into the anterior fossa. After being admitted, one patient underwent transnasal biopsy assisted by endoscopy, the other 4 received craniotomy. Among the 4 patients, 2 were operated through a transfrontal approach because the intracranial part of the tumor was larger than the extracranial part. During the operation, the subdural part of the tumor was resected firstly, and then was the epidural part. The other 2 patients were operated through a extended bifrontal approach because the extracranial part of the tumor is bigger. By this approach, the epidural tumor was cut off first and then was the subdural part.

The skull base was reconstructed by using pedicle bone flap with peristium in 1 patient, autogenous muscle with sponge assisted by biogel in 1, inner plate of frontal bone with sponge assisted by biogel in 1, and Codubix (Tricomed, Poland) with the peristium of the frontal flap in 1. Lumbar drainage tube was placed before the operation, and kept 7 to 9 days postoperation except in one patient, whose tube was withdrawn immediately after...
the surgery. All the patients received radiotherapy for 1 to 2.4 months after the operation. Chemotherapy was applied to only one patient. The patients were followed up for 6 to 45 months (mean 31 months).

RESULTS

Imaging findings
On CT or MR images, the tumor presented with a homogeneous mass with clear margin. The both cribriform plates, corpus sphenoidalis and lesser wings of the sphenoid bone were destructed. Contrast enhancement in CT scan showed that the mass was enhanced inhomogeneously. Axial MRI found a tumor isointense on the T_1-weighted images and hyperintense on the T_2-weighted images. Gadolinium enhancement was observed in all the cases. (Fig. 1) Fat saturated images showed tumors invasion into the ethmoid and sphenoidal sinuses. In 3 patients, the extracranial part of the tumor was larger than the intracranial part.

Surgical findings
During the operations, the olfactory nerve was identified definitely in 2 patients and highly suspected in the other 2. Prunusus soft tumors with rich blood supply were detected, some of them had a cyst inside with yellow fluid. The tumors passed by the dural and cribiform plates and invaded into the nasal cavity. The intracranial tumors had clear margin without adhesion to the surrounding brain tissues, even though the posterior clinoid process was invaded. Under a microscope, the intracranial part of the tumor was totally removed and the part within the nasal cavity was subtotally removed without cerebral spinal fluid (CSF) leakage in the 4 patients. In all the patients, nasal obstruction was alleviated; visual acuity and visual field were improved, but olfactory sensation remained after the operation.

Six or eight months after the operation, MRI showed no recurrent tumor in 3 patients and tumor metastasis to the vertebral canal in the other 2 (Fig. 2). One of the recurrent patients was re-operated 20 days after the metastatic tumor was diagnosed. During the second operation, we found a soft tumor located at the cauda equine and filum terminale with normal blood supply. The other recurrent patient refused a second operation and died in 8 months.

Histological diagnosis
Under a microscope, we observed small round or fusiform neuroepithelial cells arranged in a pseudorosette pattern with fibrillar intracellular background and marked microvascularity; and nearly homogeneous cells with few cytoplasms. The nuclei were round, orbicular-ovate, or fusiform in shape, and the nucleolus was poor stained with karyokinesis inside. The intercellular acidophilic fibers made the cells lobulated in Homer-Wright or Flexner rosette patterns. Immunohistochemical staining showed neuron specific enolase (NSE) and CD99 positive and SYN and CEA negative in most of the cells, EMA positive in scattered cells, and CK negative in all the cells. (Fig. 3)

DISCUSSION

ONB accounts for 3% to 5% of neoplasms in the nasal cavity and 16.7% of the malignant tumors in the anterior fossa.\(^1\) Nearly 1000 cases of ONB have been reported around the world.\(^4\) However, no convincing conclusions on
the treatments of the tumor, especially for those invaded into the crania, have been drawn. The purpose of this study was to summarize the natural history, treatments and prognosis of this tumor, based on our experiences on 5 cases.

Epidemiology
ONB has a bimodal age distribution between 20—30 years and 60—70 years. Men are more liable than women to develop such a tumor. In this study, all the patients were male aged from 16 to 56 years. Compared with the older patients, the 2 patients aged between 20 and 30, whose tumors arose from the nasal vestibule, presented the symptoms earlier, and the tumor seldom spread intracranially. While the other 3 patients, whose tumors arose from the medioposterior part of the nasal cavity or fila olfactoria, had no specific symptoms in an early stage except a “stuffy nose”, which is neglectable. In our patients, the olfactory nerve was destroyed in 2, in whom the intracranial part of the tumor was larger than the extracranial part. It needs a further investigation on whether these tumors originated from the fila olfactoria or the nasal cavity.

Clinical features
Because about 70% of the patients with ONB present with signs of the tumors in late stages, the consultation is often delayed, providing an chance for the tumors to invade into the paranasal sinuses, fossa, orbita, and pharynx, etc. It may also metastasize to the cervical lymph nodes, bones or lungs through the lymphatic system or vessels.

The staging system of ONB, which based on the extension of the tumor, has been widely accepted; however, some researchers suggested that the system cannot present the correlation between the stage and prognosis of the tumor, and preferred of TNM staging system, with which we agree. In our patients, most of them had nasal obstruction and anosmia, which are the symptoms in the last stages. The tumors had metastasized to the cervical lymph nodes in 2 patients, and to the vertebral canal in 2. The canal metastasis, we think, is caused by surgical intervention, since the tumor had no envelope and could spread through the CSF circulation.

Imaging features
The ONB should be differentiated from other malignant tumors in anterior skull base. CT and MRI is helpful to identify the margin and spread approaches of the tumor. On CT scan, the tumor usually present with a heterogeneous mass, sometimes with focal necrosis or calcification. The paranasal sinuses and anterior skull base are often destroyed, while the clivus is intact. On a T1-weighted MRI image, the ONB shows isointense, while in a T2-weighted image, it shows hyperintense, which is significantly different from the mucosal fluid. The tumor can be heterogeneously enhanced with Gadolinium injection. The signals are homogeneous with patching hyperintense or punctiform hypointense when necrosis or calcification occurs. Extensive cerebral edema may appear when the tumor invades into the sellar area. In all of our patients, CT showed broken cribriform plates, through which the tumor invaded into the crania.

Pathology
In an ONB, microscopically, the neuroepithelial cells arrange in the classic pseudorosette pattern with fibrillar intracellular background and marked microvascularity. The cells are round or fusiform cells in shape with few cytoplasm. Homer-Wright or Flexner like substances scatter within the tumor. Recently, immunohistochemical methods allows further confirmation of ONB to differentiate it from small cells malignant tumors, such as lymphoma, anaplastic carcinoma, etc.

Treatments
To our experience, operation is the first choice for intracranial ONB. Some surgeons advocated tumor
resection through the combined cranial-facial approach, which involves the nasal cavity, ethmoid sinuses, orbital and maxillary sinuses if being invaded, bringing about huge damages and great psychic depressions to the patients. We think the optimum operation for ONB is a total removal of the intracranial part of the tumor, which can lead to a better life quality and less complications.

The transfrontal approach was chosen for the tumors with larger intracranial part than the extracranial part. Because the exposure of skull base is limited by this approach, the subdural part of the tumor was resected first and then was the extradural part. It is notable that earlier dural open increases the opportunity of tumor spreading through CSF. For the ONB with bigger extradural part, the extended bifrontal approach should be selected, since this approach can better expose the skull base, making the total removal of the tumor easier, especially for the extradural tumors, such as those invaded the nasal cavity, parasinal sinuses, orbita, sphenoid bone, and even the clivus. In addition, attention should be paid to the subdural tumors located at the anterior skull base, supra-sella and posterior clinoid process. Some authors consider that palliative treatment is of benefit to the patients with local recurrence. However, we suggest a second operation combined with postoperative radiotherapy, which achieved a good result in one of our recurrent patients.

Reconstruction of the anterior cranial fossa is also a critical step in the operation. Following principle of using the multi-layer tissues, we succeeded in reconstruction of the skull in the 4 cases by using variable methods without postoperative CSF leakage. At present, the materials for reconstruction of the skull comprise autogenic fascia, muscles and polymers. It is notable that polymers had good rigidity and histocompatibility, and do no show shadows on CT and MR images.

It has been reported that radiotherapy followed by chemotherapy result in good outcomes for patients with ONB. The 5-year survival rate was 48% after surgical interventions, while it could reach 65% in the patients treated by surgery combined with postoperative radiotherapy. Jannis and colleagues put forward that preoperative radiotherapy would improve the results of surgical resection; but Ferlito proposed that the extent of the resection is the most important factor effecting prognosis. In our opinion, tumors with intracranial invasion should be treated by postoperative radiotherapy routinely, especially for those who had positive cervical lymph nodes, which always signify a poor prognosis. The role of chemotherapy is needed to be further evaluated.

**Prognosis**

Our patients have been followed up for a mean of 31 months. To our experiences, the prognostic factors in the management of ONB include the grade of cytodifferentiation and locally aggressive behaviors. Thus, we suggest that the patients should be followed up at 3, 6 and 12 months after operation, then with an interval of 1 year for 5 years.

**REFERENCES**