

Case Report

Primary intracranial squamous cell carcinoma with brainstem invasion: a rare case in China with a 41-month follow-up

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Abstract: Primary intracranial squamous cell carcinoma (SCC) is extremely rare and mostly associated with an intracranial epidermoid or dermoid cyst. Here, we present a rare case of primary intracranial SCC with brainstem invasion in a 22-year-old Chinese woman followed up for 41 months. The patient presented in February 2011 with a lesion in the right cerebellopontine area, and was treated by subtotal surgical resection. Histopathology confirmed SCC. Adjuvant radiotherapy (total dose, 50.4 Gy) was given 6 months after surgery, resulting in lesion shrinkage and symptom relief. However, symptom recurrence occurred 13 months after radiotherapy, and imaging revealed invasion into the pons. This was treated by gross total resection, and 12 months later by stereotactic radiosurgery after another recurrence at the same site. The patient died from severe dyspnea and pulmonary infection in June 2014, 41 months after the initial presentation. Surgery with adjuvant radiotherapy is appropriate for primary intracranial SCC, but long-term recurrence is likely.

Keywords: Carcinoma squamous cell carcinoma, malignant primary brain neoplasms, intracranial neoplasms, carcinoma epidermoid

Introduction

Primary intracranial squamous cell carcinomas (SCCs) are rare and mostly associated with malignant transformation of intracranial epidermoid or dermoid cysts [1-8]. These tumors are commonly found in regions of the skull base, such as the cerebellopontine angle (CPA) and jugular foramen [1-8]. Here, we present a case of a 22-year-old woman with primary intracranial SCC in the CPA, who was followed up for 41 months. The patient was treated surgically with subtotal tumor resection, followed 6 months later by adjuvant radiotherapy (total dose, 50.4 Gy). Thirteen months after radiotherapy, the lesion was found to have invaded the pons; this was treated surgically by gross total resection. Tumor recurrence occurred 12 months after this second surgery, and the patient died 10 months later. To the best of our knowledge, this is the first report of this type of primary intracranial SCC in China.

Case presentation

Initial presentation and management

This study was approved ethically by Beijing Tiantan Hospital Affiliated to Capital Medical University. The patient provided informed written consent.

The patient and her next-of-kin provided informed written consent for the publication of this case report. The 22-year-old woman presented to the Department of Neurosurgery, Tiantan Hospital (Beijing, China) in February 2011, with a one-month history of weakness of the left limbs, headache, reduced appetite, recurrent vomiting, cough, dysphagia and weight loss. The patient had apparently been well before this episode. At the time of admission, the patient had a right facial cranial nerve paralysis, dysphagia, decreased sensation to touch in the left half of the body, reduced muscle tone in the left limbs, and a preoperative

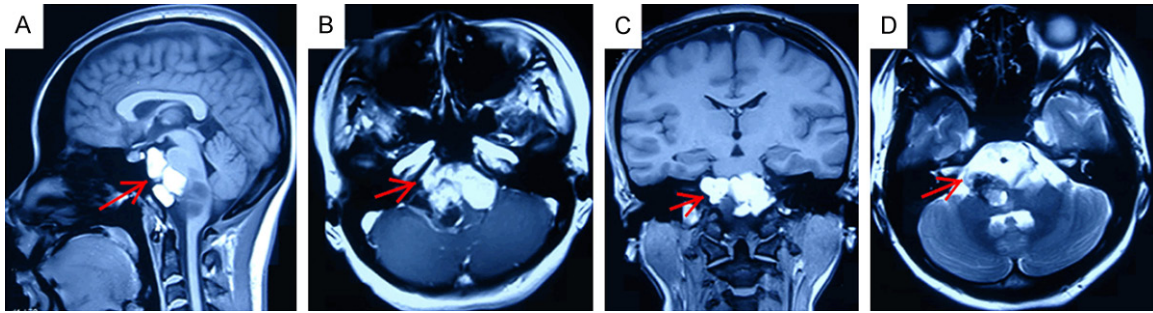


Figure 1. Magnetic resonance imaging (MRI) of the cranium before the first surgical procedure. A, B. A heterogeneous midline mass lesion is present. C. There is enhancement of the wall and an irregular nodule. D. A long T2 intensity lesion is evident in the right and left cerebellopontine angle and prepontine cistern. The brain stem is compressed and there is significant edema.

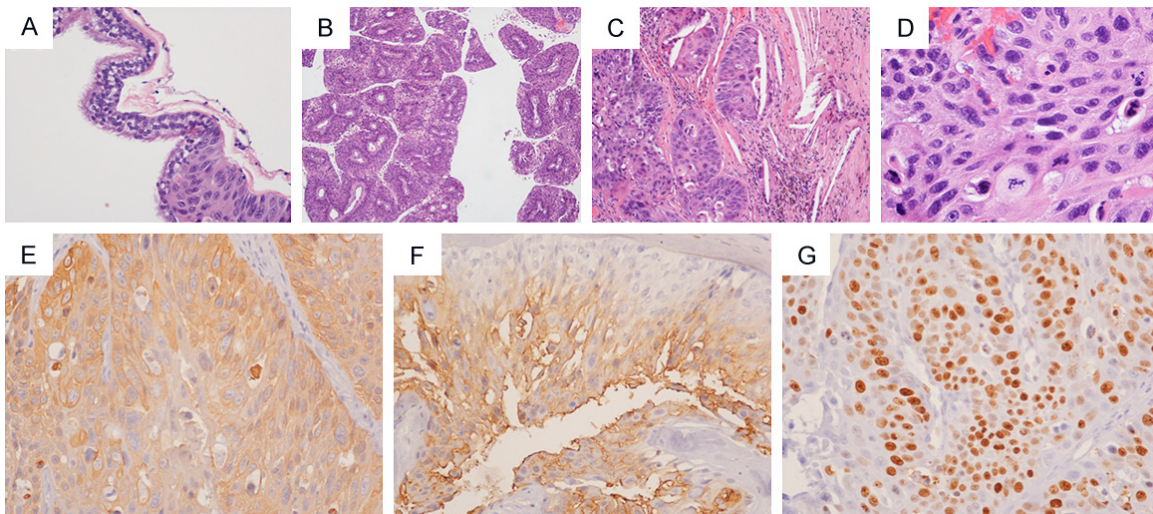


Figure 2. Light microscopy images of resected tumor specimens, demonstrating malignant transformation of the epidermoid cyst to squamous cell carcinoma. A. Portions of a dense, fibrotic cyst wall lined by benign squamous epithelium are shown, in continuity with dysplastic squamous epithelium showing marked hyperplasia (HE, 100 ×). B. The dysplastic squamous epithelium merged with areas of nested schistose infiltrating into interfibrillar substance and the mammillary protuberance (HE, 400 ×). C. There were numerous typical and atypical mitoses, and extensive areas of necrosis. The adjacent stroma showed hemorrhage, hemosiderin deposition and cholesterol clefts (HE, 100 ×). D. Malignant cells, with small-to-large anaplastic nuclei and a variable amount of finely vacuolated cytoplasm, can be seen. Scattered multinucleated tumor giant cells are also present (HE, 100 ×). Immunohistochemical staining showed that the cells of the SCC were: E. Positive for cytokeratin 5/6 (100 ×); F. Focally positive for carcino-embryonic antigen (CEA; 200 ×); G. 60% positive for Ki-67 (200 ×).

Karnofsky performance score of 60. There was no visual impairment or papilledema. Routine hematologic and serum biochemistry investigations revealed no abnormalities.

Magnetic resonance imaging (MRI) of the cranium (Magnetom 3.0 T; Siemens Corp. Gemen) revealed a heterogeneous midline mass lesion of size 5.5 × 5.0 × 4.5 cm, located in the right and left CPA and prepontine cistern (**Figure 1**). Compression of the brainstem and significant edema were evident, but there was no oppres-

sion of the ventricle or hydrocephalus (**Figure 1**). Computed tomography (CT) revealed an absence of calcification. The lesion was diagnosed initially as an epidermoid or dermoid cyst.

Resection of the tumor was carried out by a surgeon with substantial experience of skull base neurosurgery. A right retromastoid approach was used. On gross inspection, the lower part of the lesion was firm in consistency and adhered to the brainstem, while the upper part

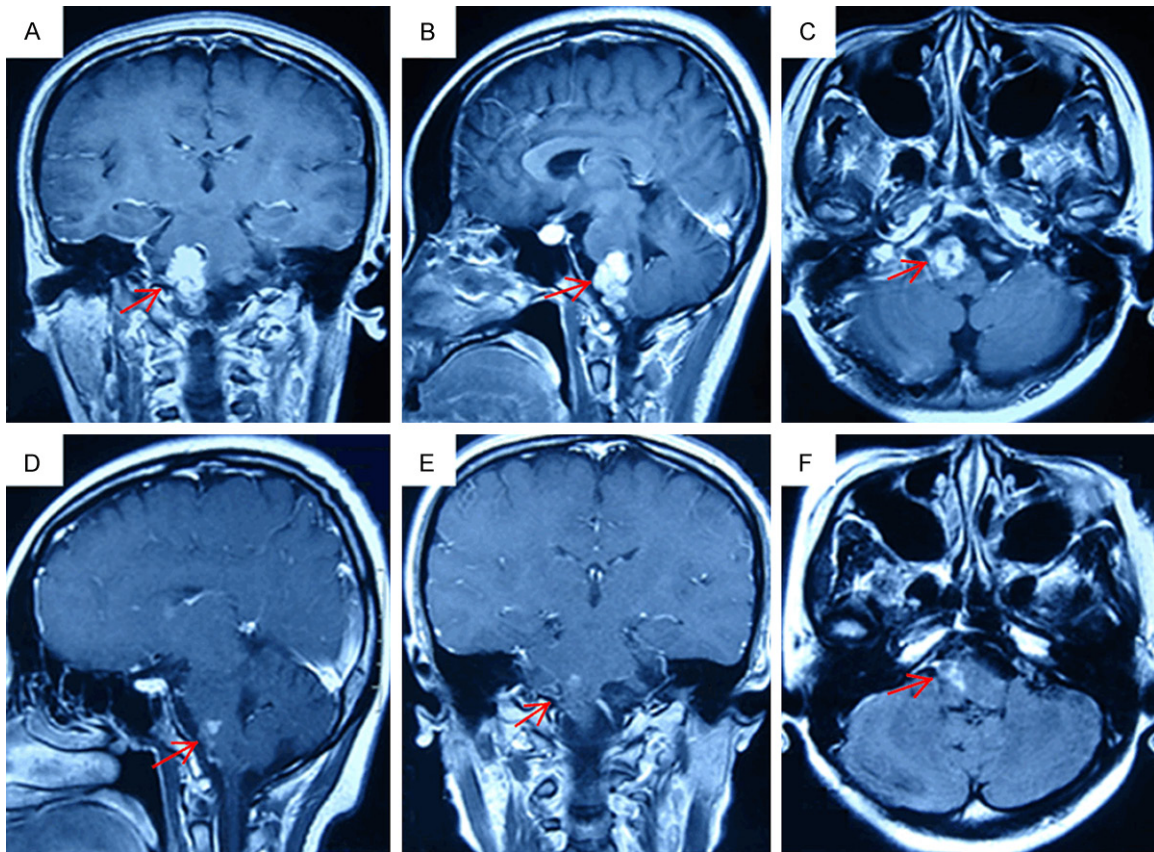


Figure 3. Magnetic resonance imaging (MRI) of the cranium after the first surgical procedure and radiotherapy. A-C. A $2.5 \times 2 \times 2$ cm remnant of tumor remained in the right cerebellopontine angle. D-E. The residual tumor shrank after radiotherapy, but a tumor nodule remained in the brainstem.

consisted of a yellowish caseous material with pearly cyst contents, features suggestive of an epidermoid cyst. Since a solid part of the tumor was adhered to the brainstem, a subtotal resection was carried out to minimize potentially serious damage to the brainstem. Multiple surgical specimens were submitted for histologic evaluation. The residual tumor comprised a $3 \times 2 \times 2$ cm nodule in the right medial brainstem.

Histopathology findings

Pathologic assessment of the excised tumor revealed SCC and an epidermoid cyst with malignant transformation (**Figure 2**). Examination under the light microscope revealed a dense, fibrotic cyst wall lined by benign squamous epithelium in continuity with dysplastic squamous epithelium showing marked hyperplasia (**Figure 2A**). The dysplastic squamous epithelium merged with areas of nested schistose infiltrating into the interfibrillar substance and mammillary protuberance (**Figure 2B**). There were numerous typical and atypical mitoses,

and extensive areas of necrosis. The adjacent stroma showed evidence of hemorrhage, hemosiderin deposition and cholesterol clefts (**Figure 2C**). Malignant cells were also present, with small-to-large anaplastic nuclei and a variable amount of finely vacuolated cytoplasm, as well as multinucleated tumor giant cells (**Figure 2D**).

Immunohistochemical staining techniques revealed that the SCC cells were: positive for cytokeratin 5/6 (**Figure 2E**); negative for P53; focally positive for carcinoembryonic antigen (CEA; **Figure 2F**); negative for neuron-specific enolase (NSE); negative for the epidermal growth factor receptor (EGFR); weakly positive for vascular endothelial growth factor (VEGF); and 60% positive for Ki-67 (**Figure 2G**).

Postoperative course

The patient was reviewed every 6 months by means of MRI and physical examinations, including neurologic examination of the limbs, and assessments of the cough reflex, swallow-

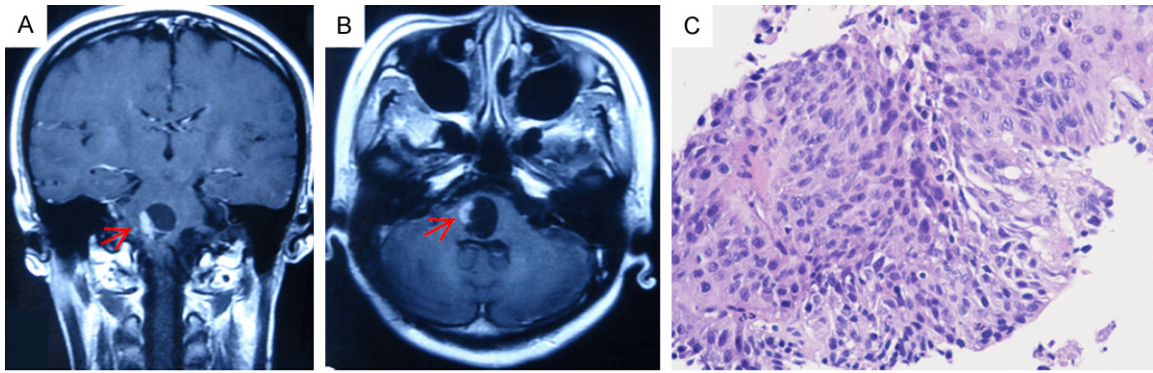


Figure 4. Magnetic resonance imaging (MRI) of the cranium before the second surgical procedure, and histology of the tumor that was subsequently resected. A, B. The tumor nodule had enlarged and invaded the pons. A cyst had formed and was causing a mass effect. C. Histology of the resected tumor revealed a squamous cell carcinoma similar to that seen in the original presentation.

ing reflex and facial sensation. Postoperatively, there were improvements in symptoms associated with high intracranial pressure, such as headache and vomiting, but not in limb weakness, cough or dysphagia. Positron emission tomography (PET) revealed normal uptake and no signs of tumor in any other regions of the body, including the nasopharynx, oropharynx, visualized sinuses, orbits, chest, abdomen, pelvis, and cutaneous and subcutaneous tissues. Systemic X-ray and ultrasound scanning excluded the possibility that the tumor was a cerebral metastasis from a primary focus located elsewhere in the body. Post-operative MRI demonstrated residual tumor, of size $3 \times 2 \times 2$ cm, in the right CPA (**Figure 3A-C**).

Six months after surgery (August 2011), the patient received intensity-modulated radiation therapy applied to the tumor remnant (total dose, 50.4 Gy: 28 applications of 1.8 Gy each; total course were 38 days). No chemotherapy was administered. Subsequent to the radiotherapy, there was resolution of the symptoms of left limb weakness, right facial cranial nerve paralysis and dysphagia. A follow-up MRI on January 2012 showed shrinkage of the residual tumor in the brainstem to a volume $< 0.5 \text{ cm}^3$ (**Figure 3D-F**). As the patient was symptom free, no further treatment was given, but follow-up was continued every 6 months.

Second presentation and management

Thirteen months after radiotherapy (September 2012), the patient presented at our department with a one-week history of headaches and weakness of the left limbs. MRI showed a solid and cystic mass in the right pons with an enhanced tubercle. However, there was no evi-

dence of recurrence at the original site of the tumor, namely the CPA and prepontine cistern (**Figure 4A, 4B**).

A gross total resection of the tumor was undertaken, using a far-lateral approach. During the operation, cicatrix-like tissue was found in the right CPA, and was presumed to be the remnant of the first operation. A relatively soft tumor nodule was identified in the brainstem, with no distinct boundary between it and the adjacent brain tissue. A stoma was made into the pons, and the tumor nodule removed. Intraoperative bleeding was not considered excessive.

Pathologic examination of the tumor revealed a similar SCC to that identified following the first surgical resection. Under the light microscope, irregular atypical cells and keratinization were seen, together with atypical mitoses and extensive areas of necrosis. On immunohistochemical staining, the cells of the SCC were positive for cytokeratin 5/6, weakly positive for VEGF, and 70% positive for Ki-67.

After the operation, the patient showed progressive improvements in the symptoms and signs of left limb weakness, paresis of the sixth cranial nerve and dysphagia. The patient was discharged after two weeks and subsequently followed-up every 3 months.

Long-term outcome

Tumor relapse at the same site in the brainstem was discovered 12 months after the second operation (September 2013) and was accompanied by symptoms of bulbar palsy,

such as dyspnea, dysphagia and choking. Stereotactic radiosurgery was used as a treatment modality, but the tumor was not controlled, resulting in a gradual worsening of the patient's condition. The patient died in July 2014, due to severe dyspnea and pulmonary infection. The total survival time was 41 months from the initial presentation at our department.

Conclusions

To the best of our knowledge, this is the first report of primary intracranial SCC, without a previous history of epidermoid or dermoid cyst, in a patient in China. Primary intracranial SCC is extremely rare. The mechanisms underlying the malignant transformation of an epidermoid cyst are unknown, but chronic inflammation, due to repeated cyst wall rupture and/or subtotal resection, resulting in mesenchymal metaplasia has been suggested as a possibility [9, 10]. When malignant transformation does occur, the course is more aggressive than that of a benign epidermoid cyst [11, 12].

Garcia *et al.* and Hamlat *et al.* have proposed a set of criteria that need to be met for a lesion to be classified as primary intracranial SCC: the tumor is restricted to the intracranial intradural compartment; there is no invasion of or extension beyond the dura or cranial bones, or through cranial orifices; there is no communication with the middle ear, air sinuses or sella turcica; there is no evidence of a nasopharyngeal tumor; benign squamous epithelium is present within the tumor mass; and there is no evidence of a tumor elsewhere [1, 5].

In the present case, the patient presented with only a short (1-month) history of symptoms, and there was neither any history of previous surgery nor any evidence indicative of a preceding benign intracranial cyst. A thorough workup, including multiple PET-CT scans, revealed no evidence of a primary tumor at an alternative location. Furthermore, histopathologic examination of the resected tumor specimen showed features of a SCC. Therefore, the present case met the criteria for a primary SCC, as proposed by Garcia *et al.* and Hamlat *et al.* [1, 5].

The treatment of choice for primary intracranial SCCs is gross total resection followed by radiotherapy, which is especially useful in cases where complete resection is not possible [13-

15]. The effectiveness of chemotherapy has yet to be definitely established. If there is intimate involvement of the brainstem, an attempt to completely remove an adherent lesion can result in unacceptable morbidity. Of 27 patients described in the literature, four were reported to have died in the immediate postoperative period following aggressive surgical resection [3, 16-18]. Thus, the desire to achieve gross total surgical resection must be tempered by the natural history of this tumor.

As surgery alone is not curative and frequently limited by the necessity for subtotal resection, adjuvant therapy has often been used in an effort to control the disease process. The survival time with combined adjuvant therapy is longer than that with surgery alone [2, 19, 20], and this is dependent on the sensitivity of the SCC to radiotherapy and/or chemotherapy.

Radiosurgery has been used widely to control malignant epidermoid tumors, and the benefits have been well documented [6, 21, 22]. Patients who receive surgical treatment alone for intracranial SCCs tend not to survive for more than 3 months. In contrast, the survival time for patients who receive postoperative radiotherapy is 21.5 ± 17.4 months [3, 18, 19, 23-25]. Indeed, Nishio *et al.* reported a disease-free survival of > 2.5 years in one patient with primary intracranial SCC after local irradiation [19], while Link *et al.* reported the successful control of an intracranial SCC for 27 months following stereotactic radiosurgery and external-beam radiotherapy [11].

In the case we present here, only subtotal resection of the tumor was possible during the first surgery due to tight adherence of the lesion to the brainstem. The patient received postoperative intensity-modulated radiotherapy to the resection bed, and this led to shrinkage of the tumor remnant and a progression-free period of 13 months. However, subsequent invasion of the tumor into the pons resulted in a recurrence of symptoms. We believe that the mass effect of the cyst was the cause of symptom recurrence. During the second surgery, gross total resection of the tumor was achieved with minimal disturbance to the brainstem. As a result, the condition was controlled for 12 months, at which point the next relapse occurred. The stereotactic radiosurgery that

was used to treat this further relapse was not as effective as the first adjuvant radiotherapy.

In summary, we report a case of primary intracranial SCC with a follow-up of nearly 3.5 years. The case was characterized by initial shrinkage of the tumor remnant and subsequent invasion into the brainstem after subtotal resection and adjuvant radiotherapy. Since intracranial SCC involves important brain structures, including the brainstem and/or cranial nerves, complete removal of the tumor is essentially impossible; therefore, gross total or subtotal resection coupled with adjuvant therapy is likely to be the optimal management strategy. Radiotherapy may be useful for short-term control of intracranial SCCs, but the effects are not well maintained long-term. In the present case, stereotactic radiosurgery was of little benefit.

Disclosure of conflict of interest

None.

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