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CASE REPORT

Neuroendoscopic surgery for neuroendocrine cancer of the skull base

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Abstract

BACKGROUND: Neuroendocrine cancer is an extremely rare malignant tumor that originates from the nervous and the endocrine systems. This type of cancer can exist in almost any organ, although it is mainly found in the lung and gastrointestinal system according to current clinical reports. It is rarely found in the skull base, including primary and secondary neuroendocrine cancers. Therefore, diagnosis and treatment face a huge challenge.

CASE DESCRIPTION: A 50-year-old female patient was introduced. She was admitted to the hospital due to persistent headaches, accompanied by nausea, vomiting, and decreased vision. Her case was primarily considered as a skull base malignant tumor based on clinical manifestations, imaging, and hormonal examinations. The patient then subsequently underwent neuroendoscopic surgery to remove the skull base tumor and repair cerebrospinal fluid leakage repair. The patient suffered from complications such as ghosting of the right eye after surgery, and she was given vitamin B1 orally. Pathological examination results show that the patient had neuroendocrine cancer (originated from sinus). We followed up the patient 2 months and 6 months after operation. At present, the patient recovered well, had no headache, and her spirit was significantly better than that before operation.

CONCLUSIONS: Cranial neuroendocrine cancer has diverse clinical manifestations. CgA, Syn, Ki-67, CD56, and ACTH are important reference indicators for the diagnosis of neuroendocrine cancer. Neuroendoscopic transsphenoidal approach is a safe and effective surgical method.

INTRODUCTION

Neuroendocrine cancer is a rare malignant tumor, which is commonly found in the digestive and respiratory systems (Nasi *et al.* 2017). Certain neuroendocrine cancers can invade and metastasize. However, they rarely occurred for invasion or metastasis to the saddle area (Siqueira *et al.* 2015). In such case, summarizing the diagnosis and treatment of neuroendocrine cancer of the skull base is greatly important.

This case introduces a neuroendocrine cancer of the skull base that originated from the sinus area. The patient's admission symptoms, related

examinations and treatment procedures are introduced. According to relevant literature, the clinical manifestations, diagnosis, and treatment options of neuroendocrine cancer of the skull base are discussed.

CASE DESCRIPTION

LF, a 50-year-old female, was admitted for treatment on July 28, 2019 for six days due to persistent headache. The pain was leaping pain, accompanied by intermittent nausea, and vomiting. The visual acuity on the right side was weaker than that on the left side, and the visual field was slightly damaged. Hormonal examination revealed abnormal results of ACTH and serum cortisol (Table 1). MRI showed that the sinus sphenoidalis and saddle base were mainly occupied, with signs of malignant tumors. The saddle base, skull base, and slope were affected, and the left top wall of the nasopharyngeal cavity was partially affected. The left top wall of the nasopharynx was partially swollen. In addition, the hypophysis was enlarged and compressed. The possibility of bone-derived tumors and chordomas was considered, and the possibility of pituitary tumors was not eliminated (Figure 1:A1 and A2). After thorough examination, the patient underwent surgical treatment, and prednisone tablets (TID) were continuously administered orally three days before the operation. Neuroendoscopic surgery was performed to remove the skull base tumor and repair cerebrospinal fluid leakage repair. During the surgery, a pedicled mucosal flap was first taken out. Thus, the tumor was invaded into the sinus sphenoidalis, slope, cavernous sinus, soft and rich in blood supply. Under neuroendoscopy, the masses in the slope area and the upper side of the slope were first removed. The masses in the cavernous sinus and the medial wall of the right internal carotid artery were then removed and stuffed with cotton sponge to stop bleeding (Figure 2:E1). Finally, the mass in the lateral wall of the right internal carotid artery was removed (Figure 2:E2). As the bottom bone was damaged substantially, the right thigh fascia was taken for repair of cerebrospinal fluid leakage. Two sets of aspirators were used in the surgery—one for sucking blood from the surgical area to keep the surgical vision clean, and the other one for hemostasis during the surgery. No residual tumor was found in pituitary MRI on the second day after operation (Figure 1:B1 and B2). Symptoms, such as headache, nausea, and vomiting, were alleviated before operation. In addition, complications such as ghosting appeared on the right eye were alleviated via oral administration of vitamin B1. The histopathological examination of the specimen during the surgery showed that the patient had neuroendocrine cancer (originated from sinus) and immunohistochemistry. Film 2: CgA (-), Syn (+), GH(reversible focal Weak +), PRL (-), ACTH (+), TSH (-), GFAP (-), S-100 (-), EMA (-), CD56 (+), TIF-1 (-), Ki-67 (5% +); Film 3: AL1 / 3 (+), LCA (-) (Figure 2:F). After the surgery, ENT physicians and oncologists were jointly consulted. They recommended performing further radiochemotherapy. However, the patient did not accept the recommendation and was discharged on the 13th day after surgery. The right eye ghost was not alleviated when discharged.

Tab. 1. Hormonal evalution

Hormone (unit)	Result		Reference
	Before operation	Post operation	
TSH (mIU / L)	1.12	0.84	0.27-1.20
T4 (nmol/ L)	119.3	129.1	66-181
IGF-1 (ng / mL)	185	135	94– 266
ACTH (pg / mL)	80.17	33.71	≤ 46
Cor (AM 8:00 nmol/ L)	555.3	352.6	133-537
Cor (PM 16:00 nmol/ L)	379.8	347.2	99-345
Cor (PM 24:00 nmol/ L)	366.8	106.0	0-166
LH (IU/L)	32.74	19.26	7.7-58.5
FSH (IU/L)	45.56	40.85	25.8-134.8
PRL (mIU / L)	358.28	179.99	102-496
PROG (nmol/L)	0.35	0.7	0.1-2.5
TESTO (nmol/L)	1.58	1.96	< 2.9
E2 (pmol/L)	76.63	86.32	< 505
OD vision	0.8	0.8	≥ 1.0
OS vision	1.2	1.2	≥ 1.0
GH (ng/Ml)	0.241	0.356	0.16-9.88

We followed up the patients 2 months (Figure 1:C1 and C2) and 6 months (Figure 1:D1 and D2) after operation, and no tumor residue and recurrence were found on MRI. With the continuous oral administration of vitamin B1, the complications of the right eye ghost disappeared three months post-surgery. At present, the patient recovered well, had no headache, and her spirit was significantly better than that before operation

DISCUSSION

Neuroendocrine cancer is a rare malignant tumor that originated in diffuse neuroendocrine system, and it is commonly found in the digestive and respiratory systems (Nasi *et al.* 2017). However, this type of cancer can also be found in almost every organ of the human body. Neuroendocrine cancer can be divided into primary and secondary neuroendocrine cancer, with the latter being mostly derived from the lungs (Moshkin *et al.* 2012). Primary intracranial neuroendocrine carcinoma is extremely rare, and it is common in brain metastases of neuroendocrine carcinoma in other organs. The pathology of this case is highly differentiated neuroendocrine carcinoma, which originates from the sinuses and is not a common metastatic sourced system and organ.

According to the 2017 version of "Head and Neck Tumor Classification" from WHO, neuroendocrine tumors are classified into highly differentiated, moderately/slightly differentiated, and poorly differentiated tumor. The prognosis of different types of neuroendocrine tumors varies. The five-year specific survival rates are as follows: 100%, 52.8%, 19.3%, and 15.3% (Perez-Ordoñez, 2018). No systematic diagnosis and treatment is available currently.

The clinical manifestations of neuroendocrine cancer of the skull base are diverse. These symptoms, such as decreased vision, visual field defect, blindness, hydrorrhea cerebrospinalis, polyuria or diabetes insipidus, can vary according to invasion organs. Patients mainly suffer from persistent headache, accompanied by nausea, vomiting, and other symptoms.

Neuroendocrine cancer is difficult to confirm via direct diagnosed through imaging, but it is mainly diagnosed via immunohistochemistry. Neuroendocrine cancers with different origins vary in terms of growth or metastasis methods. Neuroendocrine cancers originated from the uterus, ovary, breast, and kidney are commonly found in lymph node metastasis, whereas nasal and nasopharyngeal neuroendocrine cancers mostly invade surrounding bone and soft tissues (Wang Yingying *et al.* 2017) . Consistent with the CT and MRI images of this case, this type of cancer is mainly characterized by malignant tumors. The iconography manifestation of neuroendocrine cancer at the primary site is a larger tumor, with more necrotic lesions but less calcification, and it easily invades surrounding structures (Qu Jiao *et al.* 2019). The secondary neuroendocrine cancer is difficult to distinguish from the primary tumor in this area. A nuclear medicine examination with high specificity and sensitivity poses an important role in its diagnosis (Ren Qingyu *et al.* 2017). However, the final diagnosis requires immunohistochemistry through pathology. The immunohistochemistry of this case comprises the following: Film 2: CgA (-), Syn (+), GH reversible focal Weak +), PRL (-), ACTH (+), TSH (-), GFAP (-), S-100 (-), EMA (-), CD56 (+), TIF-1 (-), Ki-67 (5% +); Film 3: AL1 / 3 (+), LCA (-). Therefore,

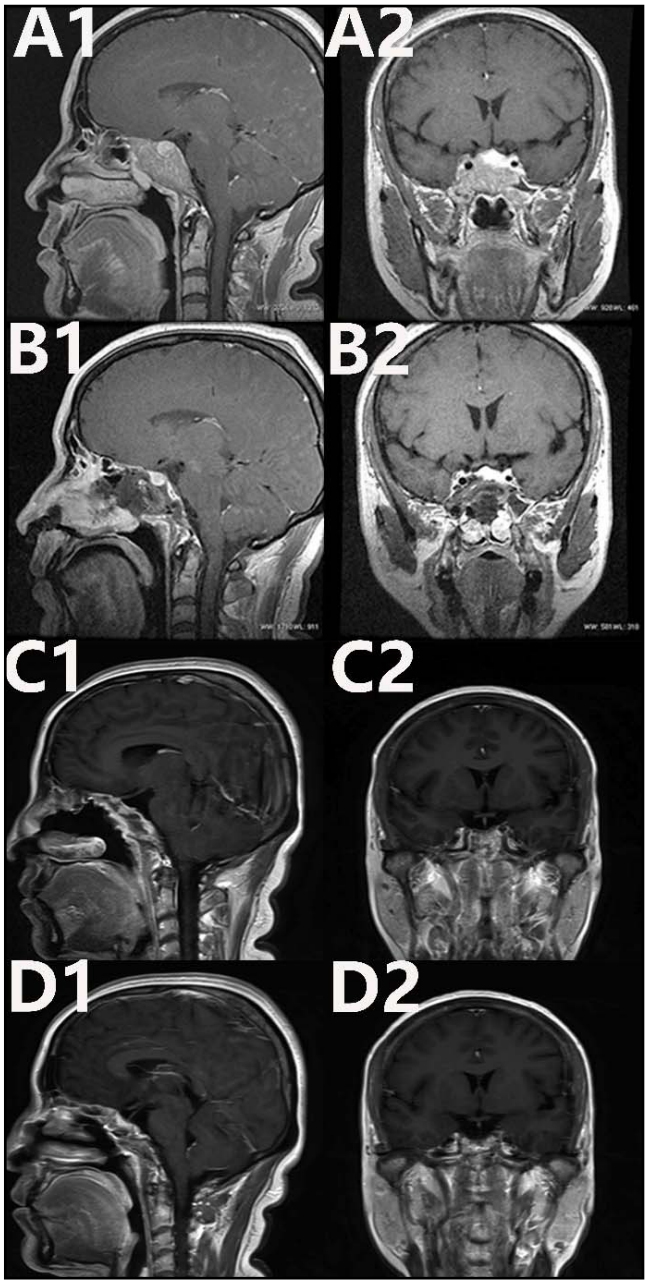

Fig. 1. Preoperative magnetic resonance imaging of the pituitary gland (A1 and A2). Magnetic resonance imaging of the pituitary gland the day after the operation (B1 and B2).Magnetic resonance imaging of the pituitary gland was performed at the second month after surgery(C1 and C2).Magnetic resonance imaging of the pituitary gland at six months after surgery (D1 and D2).

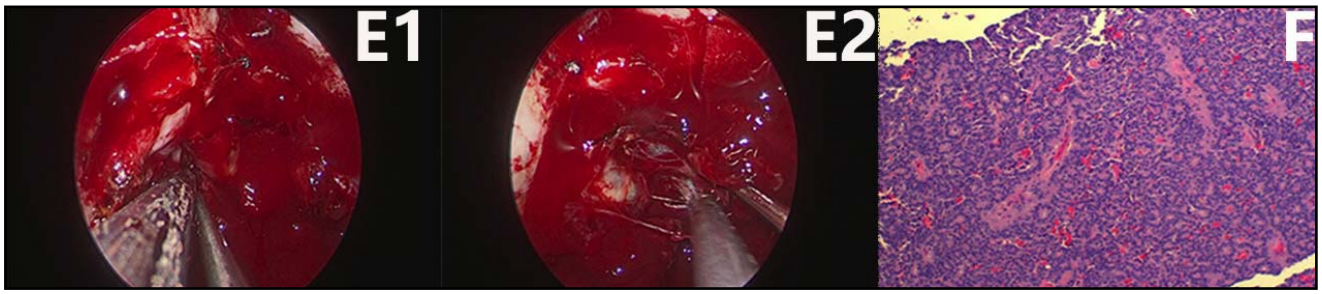

Fig. 2. Resection of the medial wall mass of the right internal carotid artery(E1). Resection of the mass on the lateral wall of the right internal carotid artery(E2). Immunohistochemistry: CgA (-), Syn (+), GH(reversible focal Weak +), PRL (-), ACTH (+), TSH (-), GFAP (-), S-100 (-), EMA (-), CD56 (+), TIF-1 (-), Ki-67 (5% +)(F).

this case is diagnosed as a highly differentiated neuroendocrine cancer. Syn is considered the most sensitive marker, and CgA is the most specific indicator (Kim *et al.* 2016). Ki-67 index is a marker of cell proliferation and may be related to NEC pathological level (Kim *et al.* 2016; Perez-Ordoñez, 2018). Higher index leads to lower level, higher degree of malignancy, and worse prognosis (Qiu Mengjun. 2018). According to Qiu *et al.* in neuroendocrine cancers, the positive rates of Syn, CgA, and CD56 were 91.74%, 78.69%, and 85.94% respectively (Qiu Mengjun. 2018). In this case, Syn and Ki-67 indicators were positive. Among the selectivity indicators, CD56 was also positive. Positive ACTH also supported the tumor as a source of neuroendocrine. However, for certain patients with neuroendocrine cancer, CgA may be negative. Therefore, we believe that CgA, Syn, Ki-67, CD56, and ACTH are important reference indicators for the diagnosis of neuroendocrine cancer.

Treatment options for neuroendocrine cancer of skull base are not unified. Liu *et al.* provided a case of primary neuroendocrine cancer in the saddle area (Liu *et al.* 2016). Surgical resection of the lesion was chosen during the treatment of patients. Nasi *et al.* found that surgical treatment, postoperative adjuvant radiotherapy, and chemotherapy can be effectively and safely administered to a patient with pituitary primary neuroendocrine cancer (Nasi *et al.* 2017). The literature of metastatic neuroendocrine cancer of skull base showed that six cases were treated with surgery (including one with radiation therapy after surgery), two with chemotherapy, two with radiation therapy, and one without treatment (Goglia *et al.* 2008). Moshkin *et al.* chose the surgery treatment for carcinoid metastases (Moshkin *et al.* 2012). Atallah-Yunes indicated that treatment options such as palliative radiotherapy and chemotherapy can be administered patients with metastatic small cell lung cancer (Atallah-Yunes *et al.* 2019). Small-cell neuroendocrine cancer of the head and neck should then be treated by combining radiation therapy with chemotherapy, and surgery was a salvage (Li Zhengjiang *et al.* 2008). For medium/highly differentiated neuroendocrine cancer, surgical resection was the main treatment (Mills, 2002). The current case is a highly differentiated neuroendocrine cancer (carcinoid). The mass was removed under neuroendoscopy, combined with postoperative review by MRI and other imaging findings and clinical manifestations. The surgical resection was satisfactory with good recovery. The neuroendoscope is of a lateral perspective. After reaching the surgical area, it can obtain a panoramic field of vision, as featured by a wide range of surgical fields. In the deeper surgical area, the close-range illumination of the neuroendoscope can obtain a clear and bright surgical field, which is conducive to the total resection of the masses. Neuroendoscopy itself is slender and of small surgical trauma. Thorough hemostasis, small side effects, and fast postoperative recovery when passing through natural cavities like nasal cavity can shorten the length of hospitalization. Certainly, neuroendoscopy requires the surgery to be performed in a limited space, and the intraoperative monitor image lacks the sense of traditional stereoscopic vision as a two-dimensional image. Hence, the surgeon must acquire a high level of endoscopic operation, and proficient anatomical structure knowledge. The patient in the current case was suffering from complications, such as ghosting of the right eye after surgery. She was given vitamin B1 orally.

Half a year follow-up showed that the symptoms of headache and ghosting in the right eye (complications) had disappeared. MRI showed that there was no residual and recurrence of the tumor, and no radiotherapy and chemotherapy were performed. Although the symptoms of the patient have disappeared, due to the short follow-up time of this case, it is not possible to evaluate whether postoperative patients with neuroendocrine carcinoma of the skull base benefit from radiotherapy or chemotherapy. Therefore, with the support of neuroendoscopic technical personnel, tumor removal under neuroendoscopy is a safe and effective surgical method for patients with cranial neuroendocrine cancer.

CONCLUSIONS

Cranial neuroendocrine cancer has diverse clinical manifestations. CgA, Syn, Ki-67, CD56, and ACTH are important reference indicators for the diagnosis

of neuroendocrine cancer. Neuroendoscopic transsphenoidal approach is a safe and effective surgical method.

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