Large Cell Neuroendocrine Carcinoma in the Sinonasal Cavity with Large Intracranial Extension Treated with Endonasal Endoscopic and Transcranial Combined Surgery: A Case Report

Yurie RA1, Hiroshi NISHIOKA,2,3 and Takayuki HARA1,3

1Department of Neurosurgery, Toranomon Hospital, Tokyo, Japan
2Department of Hypothalamic and Pituitary Surgery, Toranomon Hospital, Tokyo, Japan
3Okinaka Memorial Institute for Medical Research, Tokyo, Japan

Abstract

Large cell neuroendocrine carcinoma (LCNEC) is a rare malignant tumor that typically arises in the lungs. It is especially rare in the sinonasal cavity, and treatment has not been established. In this study, we present the case of a 56-year-old woman with a large sinonasal LCNEC that extended into her brain. We performed endonasal endoscopic and transcranial combined surgery followed by chemoradiation therapy. The combined surgery enabled us to approach and remove the extensive tumor from two different directions at one time less invasively. We have achieved good tumor control for 18 months so far.

Keywords: large cell neuroendocrine carcinoma, endonasal endoscopic and transcranial combined surgery, minimally invasive, anterior skull base

Introduction

Large cell neuroendocrine carcinoma (LCNEC) is a rare malignant tumor, which was first proposed in 1991 by Travis et al. as a classification of pulmonary neuroendocrine tumors.1 Since then, LCNEC from other origins has been reported.2,3 Among them, LCNEC in the sinonasal cavity is especially rare, and no consensus has been reached regarding its treatment. In this study, we present a case of a large sinonasal LCNEC with intracranial extension. We performed radical surgical resection followed by chemoradiation therapy and have succeeded in controlling the tumor for 18 months so far. As far as we know, this is the first report to resect a large sinonasal LCNEC that extended into the brain with a combination of endonasal endoscopic and transcranial approaches, and to achieve good tumor control. In this report, we discuss the treatment of sinonasal LCNEC based on previous reports.

Case Report

The patient is a 56-year-old woman who consulted our institute because of progressive exophthalmos, chemosis in her left eye, double vision, severe headache, and nausea. She also suffered from anosmia and tasting disturbance 1 month before consultation. Brain CT demonstrated a large mass in her left nasal cavity that had expanded into the left frontal lobe, and hence, she was admitted to our institute. Enhanced MRI showed a cystic tumor in her frontal lobe with perifocal edema, with a maximum diameter of 55 mm. MRI also showed a solid mass in her nasal cavity compressing her left eye (Figs. 1A–C). Tumor biopsy was performed from the nose under local anesthesia, and the pathological diagnosis was a small round cell tumor with neuroendocrine differentiation. Because of the rapid progression of her symptoms including increased intracranial pressure and the pathological malignancy of the tumor, we tried to resect the tumor in one session with a combination of
endonasal endoscopic and transcranial approaches. Prior to surgery, angiography (Fig. 1D) and vascular embolization were performed to control hemorrhage. Two days before the surgery, under general anesthesia, left ethmoidal arteries were embolized with N-butyl-2-cyanoacrylate, and left sphenopalatine artery, infraorbital artery, and lateral nasal artery were embolized with Embosphere microspheres and free/detachable coils.

**Surgery**

The patient was placed in the supine position. Under general anesthesia, an endoscope was introduced through her left nasal cavity. The tumor had invaded the nasal mucosa of the left middle turbinate and expanded into sphenoid sinus and maxillary sinus through each ostium. The nasal septum and the right nasal cavity were intact. The tumor in the left nasal cavity was removed in a piecemeal fashion using an ultrasonic aspirator (SONOPET; Stryker, Tokyo, Japan). The tumor was solid and hemorrhagic. The transcranial surgeon performed a left frontal craniotomy, and the large intracranial cystic tumor, whose base adhered to the left frontal lobe, was removed en bloc to avoid dissemination.

The tumor had expanded into the intradural space from the left cribiform plate, and therefore, the frontal base bone was drilled out from the frontal sinus to the sphenoid sinus. The tumor, which tightly adhered to the left periorbital area and extended into the left maxillary/frontal/sphenoid/ethmoid sinuses with mucosal invasion, was dissected by a combination of endonasal endoscopic and transcranial approaches. To avoid intracranial
Fig. 2 Postoperative images. (A and B) Enhanced iMSDE MRI showing that the high-intensity tumor had been radically removed and that compression of the left eye was relieved.

Fig. 3 Pathological findings. (A) Hematoxylin and eosin staining showing large cells with variably coarse chromatin and prominent nucleoli. (B) Immunohistochemical imaging showing that tumor cells were positive for synaptophysin.

Postoperative course
The patient did not show any newly developed neurological deficits, and her headache and nausea disappeared soon after surgery. Postoperative MRI showed gross total resection of the tumor (Fig. 2). The final pathological diagnosis was LCNEC (Fig. 3), and she received adjuvant chemoradiation therapy with reference to small cell lung carcinoma (SCLC): four cycles of cisplatin ($80 \text{ mg/m}^2$/day 1) and etoposide ($100 \text{ mg/m}^2$/days 1–3) together with 40 Gy/20 fractions local radiation therapy to cover the tumor margin and boost stereotactic radiotherapy (Cyberknife: margin dose 25 Gy/5 fractions) to the tumor origin (anterior skull base). During the follow-up period of 18 months, the patient has not shown any local recurrence or metastasis as confirmed with positron emission CT, and her performance status has remained good (Karnofsky performance scale: 90).

Discussion
LCNEC was introduced as a new distinct category of lung cancer by Travis et al. in 1991. LCNEC is histologically characterized by large cells with abundant cytoplasm, necrotic areas, a high mitotic
rate, and neuroendocrine features. Since then, LCNEC has been reported in other origins including the gastrointestinal tract\(^2\) and genital organs.\(^3\) Sinonasal LCNEC is especially rare. In 2012, Kao et al. showed that patients with head and neck LCNEC are older, more commonly have advanced stage disease with a poorer prognosis, and more commonly have tumors that overexpress p53. These authors insisted that LCNECs should be separated from other carcinoids.\(^4\) According to this proposal, in the 2017 World Health Organization classification of head and neck tumors, LCNEC was defined as a poorly differentiated NEC. Thus, sinonasal LCNEC is a relatively new concept, and its treatment strategy has not been developed. Even lung LCNEC does not have any evidence-based treatments. Surgery followed by chemoradiation therapy is often conducted for lung LCNEC based on the regimen for SCLC.\(^5\) Hence, here we performed surgery and adjuvant chemoradiation therapy with the SCLC regimen.

To plan the surgery, we referred to treatment for malignant tumors in the anterior skull base. Esthesioneuroblastoma, for example, is treated with radical resection of the tumor and postoperative radiotherapy.\(^6\) In such cases, the craniofacial approach, which was first described in 1963, is chosen to expose the tumor.\(^7\) The approach enables removal of the tumor en bloc with a safe tumor margin, whereas internal decompression is not recommended to prevent dissemination of malignant cells. A previous study showed that negative margins were achieved in a higher percentage of cases with en bloc resection than with piecemeal resections, and recurrence-free survival was superior with en bloc resection.\(^8\) Therefore, one-piece removal with the craniofacial approach has been considered the gold standard for anterior skull base malignant tumors.\(^9\)

However, the craniofacial approach requires a large facial skin incision, which may lead to morbidities such as osteomyelitis, wound infection, facial anesthesia, and diplopia, and postoperative cosmetic results are not satisfactory and involve a longer recovery time.\(^10\) The endoscopic endonasal approach, which can help overcome these problems, was initially limited to benign disease in the nasal cavity and has been developed and started to be adopted for malignant tumors that extend into the anterior skull base with piecemeal resection as first reported by Yuen et al. in 1997.\(^11\) This method has been criticized because it ignores the common principal that malignant tumors should be resected en bloc.\(^12\) However, some recent reports showed that less invasive methods with endoscopic endonasal tumor removal result in the same tumor control rate as conventional craniofacial resection with better cosmetic results.\(^13,14\) To select the appropriate approach in each case, Naunheim et al. proposed an algorithm of approaches for malignant tumors in the anterior skull base. He suggested the following four approaches depending on the tumor location and extent: endoscopic, endoscopic and craniotomy, transfacial, and transfacial and craniotomy.\(^15\)

Based on these previous studies, we adopted the endoscopic endonasal approach instead of the craniofacial approach, combined with the transcranial approach. In our institute, the combined endoscopic and transcranial approaches have often been adopted to resect adenomas, and we have expertise in the combined approach.\(^16\) Here we succeeded in radical resection of the large LCNEC without cutting the patient’s face. After postoperative chemoradiation therapy, no local recurrence or metastasis have been detected in the 18-month follow-up. Our case supports the efficacy of piece-meal resection of a malignant tumor with a less invasive approach.

Including our case, 12 sinonasal LCNECs have been reported (Table 1).\(^4,15–20\) Eight cases were resected surgically. The endoscopic approach was used in two cases (Lahma et al.\(^18\)) and our case), and the combined endoscopic and transcranial approaches were used only in our case according to our review of published papers. In four cases, the tumor extended into the intracranial fossa. Our case is the only report of resection of a tumor with intracranial extension and achievement of good tumor control.

Interestingly, the LCNECs in Campos’s and Zhao’s reports achieved complete remission with chemoradiation therapy without surgical resection, although the tumor sizes were relatively large.\(^19,20\) However, the LCNECs in both cases did not extend into the intracranial fossa. Sensitivity to chemoradiation therapy may be different according to tumor size, extent, complications, and molecular findings. Therefore, we do not know whether chemoradiation therapy without surgery is sufficient to achieve complete remission for sinonasal LCNEC with intracranial extension like our case. We also note that complete remission during the relatively short follow-up periods in Campos’s and Zhao’s papers does not always mean a good longer-term prognosis. To investigate better treatments for LCNECs, we need more cases with longer follow-up. We also need to consider other strategies. For example, recent studies showed that lung LCNEC has a quite specific pattern of programmed cell-death-protein-1-ligand-1 (PD-L1) expression, which is associated with prognosis.\(^21,22\) Thus, immunotherapy may be a new strategy to manage LCNEC in the near future, although only a case report\(^23\) and a small cohort
Table 1: Sinonasal LCNEC in previous reports and our case

| Author, year | Age/sex | Symptoms | Location, size (mm) | Treatments | Follow-up period (months), postoperative course |
|--------------|---------|----------|---------------------|------------|-----------------------------------------------|
| Mendis and Malik, 2008 | 73/male | Right nasal obstruction, discharge, epistaxis | Right nasal cavity, frontal sinus, bilateral ethmoid/maxillary sinuses | S+R | 20, NED |
| Kao et al., 2012 | 39/male | ND | Sinonasal tract-nasal cavity | S+R | 45, NED |
| | 42/male | ND | Sinonasal tract-ethmoid sinus | S+C+R | 26, DWD |
| | 80/male | ND | Sinonasal tract-nasal cavity | S+C+R | 53, DWD |
| Gudlavalleti et al., 2016 | 81/male | Headache, right eye ptosis, restricted extraocular movements | Right nasal cavity, orbit, maxilla, cribiform plate, intracranial fossa | C+R | ND |
| Thompson et al., 2016 | 58/male | ND | Sinonasal cavity, intracranial fossa | S+C+R | 12, DWD |
| | 66/male | ND | Sinonasal cavity, neck metastasis | C+R | 18, DWD |
| | 70/female | ND | Sinonasal cavity, intracranial fossa | S+C+R | 9, AWD |
| Lahma et al., 2018 | 70/male | Nasal obstruction, epistaxis | Nasal cavity, 40 × 28 × 35 | S+C+R | 6, NED |
| Campos et al., 2018 | 68/female | Right ocular pruritus, edema, wasting, proptosis, ocular pain, and secretion | Right orbit, maxillary/ethmoid/sphenoid sinuses | C+R | 36, NED |
| Zhao et al., 2019 | 40/male | Nasal obstruction, olfactory anesthesia | Left nasal cavity, bilateral maxillary/ethmoid/frontal/sphenoid sinuses, 70 × 52 | C+R | 10, NED |
| Our case | 56/female | Exophthalmos, left chemosis, double vision, headache, nausea, anosmia, tasting disturbance | Left nasal cavity, maxillary/ethmoid/sphenoid/frontal sinuses, frontal lobe, 83 × 51 × 34 | S+C+R | 18, NED |

AWD: alive with disease, C: chemotherapy, DWD: dead with disease, LCNEC: large cell neuroendocrine carcinoma, ND: not described, NED: no evidence of disease (alive), R: radiation therapy, S: surgery.
study\textsuperscript{24} have been reported in lung. We need more studies from various standpoints to address sinonasal LCNEC.

**Conclusion**

A large sinonasal LCNEC that extended into the intracranial fossa was successfully controlled by radical surgical resection with an endoscopic endonasal and transcranial combined approach followed by chemoradiation therapy.

**Conflicts of Interest Disclosure**

The authors declare that they have no conflict of interest.

**References**

1. Travis WD, Linnoila RI, Tsokos MG, et al.: Neuroendocrine tumors of the lung with proposed criteria for large-cell neuroendocrine carcinoma. An ultrastructural, immunohistochemical, and flow cytometric study of 35 cases. *Am J Surg Pathol* 15: 529–553, 1991

2. Jiang SX, Mikami T, Umezawa A, Saegusa M, Kameya T, Okayasu I: Gastric large cell neuroendocrine carcinomas: a distinct clinicopathologic entity. *Am J Surg Pathol* 30: 945–953, 2006

3. Gilks CB, Young RH, Gersell DJ, Clement PB: Large cell neuroendocrine [corrected] carcinoma of the uterine cervix: a clinicopathologic study of 12 cases. *Am J Surg Pathol* 21: 905–914, 1997

4. Kao HL, Chang WC, Li WY, Chia-Heng Li A, Fan-Yau Li A: Head and neck large cell neuroendocrine carcinoma should be separated from atypical carcinoid on the basis of different clinical features, overall survival, and pathogenesis. *Am J Surg Pathol* 36: 185–192, 2012

5. Hiroshima K, Mino-Kenudson M: Update on large cell neuroendocrine carcinoma. *Transl Lung Cancer Res* 6: 530–539, 2017

6. Diaz EM, Johnigan RH, Pero C, et al.: Olfactory neuroblastoma: the 22-year experience at one comprehensive cancer center. *Head Neck* 27: 138–149, 2005

7. Ketcham AS, Wilkins RH, Van Buren JM, Smith RR: A combined intracranial facial approach to the paranasal sinuses. *Am J Surg* 106: 698–703, 1963

8. König M, Osnes T, Jebsen P, Meling TR: Craniofacial resection of malignant tumors of the anterior skull base: a case series and a systematic review. *Acta Neurochir (Wien)* 160: 2339–2348, 2018

9. Howard DJ, Lund VJ, Wei WI: Craniofacial resection for tumors of the nasal cavity and paranasal sinuses: a 25-year experience. *Head Neck* 28: 867–873, 2006

10. Albonette-Felicio T, Rangel GG, Martínez-Pérez R, Hardey DA, Carrau RL, Prevedello DM: Surgical management of anterior skull-base malignancies (endoscopic vs. craniofacial resection). *J Neurooncol* 150: 429–436, 2020

11. Yuen AP, Fung CF, Hung KN: Endoscopic cranionasal resection of anterior skull base tumor. *Am J Otalaryngol* 18: 431–433, 1997

12. Krischek B, Carvalho FG, Godoy BL, Kiehl R, Zadeh G, Gentili F: From craniofacial resection to endonasal endoscopic removal of malignant tumors of the anterior skull base. *World Neurosurg* 82: S59–65, 2014

13. Naunheim MR, Goyal N, Dedmon MM, et al.: An algorithm for surgical approach to the anterior skull base. *J Neurol Surg B Skull Base* 77: 364–370, 2016

14. Nishioka H, Hara T, Usui M, Fukuhara N, Yamada S: Simultaneous combined supra-infrasellar approach for giant/large multilobulated pituitary adenomas. *World Neurosurg* 77: 533–539, 2012

15. Mendis D, Malik N: Sinonasal neuroendocrine carcinoma: a case report. *Ear Nose Throat J* 87: 280–282, 2008

16. Gudavalleti A, Dean R, Liu Y, Dhamoon AS: Diagnosis and treatment of a rare sinonasal neuroendocrine tumour: adding to the evidence. *BMJ Case Rep* 2016: bcr2016217319, 2016

17. Thompson ED, Stelow EB, Mills SE, Westra WH, Bishop JA: Large cell neuroendocrine carcinoma of the head and neck: a clinicopathologic series of 10 cases with an emphasis on HPV Status. *Am J Surg Pathol* 40: 471–478, 2016

18. Lahma J, Heijouji R, Gicquel P, Essakalli L: Large cell neuroendocrine carcinoma of the nasal cavity: an extremely rare and new distinct entity. *Pan Afr Med J* 30: 188, 2018

19. Campos HG, Altemani AM, Altemani J, Soares DF, Reis F: Poorly differentiated large-cell neuroendocrine carcinoma of the paranasal sinuses. *Radiol Bras* 51: 269, 2018

20. Zhao Q, Wei J, Zhang C, et al.: Large-cell neuroendocrine carcinoma of nasal cavity and paranasal sinuses after successful curative therapy: a case report and literature review. *Onco Targets Ther* 12: 2975–2980, 2019

21. Guleria P, Kumar S, Malik PS, Jain D: PD-L1 expression in small cell and large cell neuroendocrine carcinomas of lung: an immunohistochemical study with review of literature. *Pathol Oncol Res* 26: 2363–2370, 2020

22. Arpin D, Charpentier M-C, Bernardi M, et al.: PD-L1 expression patterns in large-cell neuroendocrine
carcinoma of the lung: potential implications for use of immunotherapy in these patients: the GFPC 03-2017 “EPNEC” study. Ther Adv Med Oncol 12: 1758835920937972, 2020

23) Zhang X, Sun Y, Miao Y, Xu S: Immune checkpoint inhibitor therapy achieved complete response for drug-sensitive EGFR/ALK mutation-negative metastatic pulmonary large-cell neuroendocrine carcinoma with high tumor mutation burden: a case report. Onco Targets Ther 13: 8245–8250, 2020

24) Sherman S, Rotem O, Shochat T, Zer A, Moore A, Dudnik E: Efficacy of immune check-point inhibitors (ICPi) in large cell neuroendocrine tumors of lung (LCNEC). Lung Cancer 143: 40–46, 2020

Corresponding author: Takayuki Hara, MD, PhD
Department of Neurosurgery, Toranomon Hospital, 2-2-2 Toranomon, Minato-ku, Tokyo 105-8470, Japan.
e-mail: thara@toranomon.gr.jp