

# Metastatic intracranial large-cell neuroendocrine carcinoma: a study of two cases

Xiaozhen Zhan<sup>1,2</sup>, Weidong Wu<sup>1,2</sup> (Co-first author), Xinmin Wang<sup>1</sup>, Kezhen Wang<sup>1</sup>, Jiyong Leng<sup>1</sup>, Chengzhi Cui<sup>1</sup> (✉), Peiyu Cong<sup>1</sup> (✉)

<sup>1</sup> Department of Neurosurgery, Dalian Municipal Central Hospital, Dalian 116033, China

<sup>2</sup> Dalian Medical University, Dalian 116044, China

## Abstract

**Objective** The occurrence of large-cell neuroendocrine carcinoma (LCNEC), a kind of neuroendocrine tumor (NET), in the cranium is extremely rare. Here we report two such cases and review the literature in order to improve the diagnosis and treatment of intracranial LCNEC.

**Methods** We report two cases of metastatic intracranial LCNEC. In case 1, the patient was diagnosed with lung carcinoma and underwent chemotherapy. Brain metastases were found six months later. The lung and intracranial lesions in case 2 were found at the same time.

**Results** Intracranial multiple-tumor resection was performed in case 1 and the patient died 2 months later. Case 2 patient underwent surgery followed by chemotherapy with etoposide and carboplatin. Six months postoperatively, a recurrence lesion was found in the left cerebellar hemisphere. The patient was treated surgically. At present, a year after the diagnosis, the patient is still alive.

**Conclusion** NETs of the intracranial region are extremely rare, and hence, most of our knowledge is based on lung NETs, and standard treatment strategies for intracranial NETs remain unclear. Our patients had different survival times probably due to different treatments, indicating that effective surgical resection and subsequent multi-agent chemotherapy should be administered to promote long-term survival of intracranial LCNEC patients.

**Key words:** large cell neuroendocrine carcinoma; intracranial; neuroendocrine tumor; prognosis

Received: 11 October 2018  
Revised: 22 November 2018  
Accepted: 10 December 2018

Large-cell neuroendocrine carcinoma (LCNEC) is a kind of neuroendocrine tumor (NET), which is extremely rare in the cranium. NETs are classified as high grade, like small cell carcinoma (SCC) and LCNEC, or low grade, like carcinoid (typical carcinoid and atypical carcinoid). Out of all these, SCC is the most common. LCNEC is extremely difficult to diagnose. Histology and immunohistochemistry (IHC) are considered to be useful for pathological diagnosis. The prognosis of intracranial LCNEC is very poor, and standard treatment remains unclear due to its rarity.

Here we report two patients with intracranial LCNEC in order to improve the diagnosis and treatment of the disease.

## Case 1

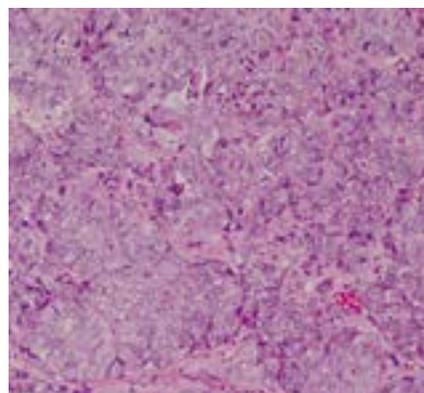
A 57-year-old man was admitted to our hospital with a history for paroxysmal headache and dizziness for half a month, without nausea, emesis, tic of limbs, fever, and chills. Five months before, the patient was diagnosed with lung carcinoma and was administered chemotherapy with gemcitabine and cis-platinum. Physical examination was normal. Laboratory data were within the healthy range, except for sodium (122.3 mmol/L). Cranial computerized tomography (CT) showed multiple intracranial space-occupying lesions. Cranial enhanced magnetic resonance imaging (MRI) also revealed two abnormal circular and enhanced intracranial masses with peritumoral edema; one was approximately 3.9 cm × 3.1 cm in the left

✉ Correspondence to: Chengzhi Cui. Email: cuichengzhi2001@sina.com  
Peiyu Cong. Email: congpeiyu1964@163.com

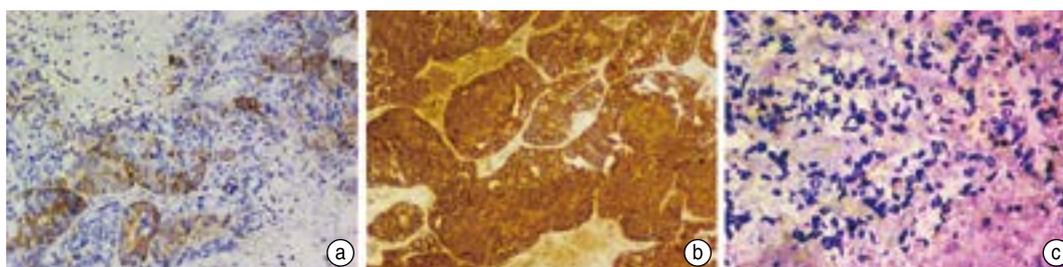




**Fig. 4** CT showed a lesion in the left cerebellar region



**Fig. 5** Pathological examination showed poorly differentiated neuroendocrine carcinoma



**Fig. 6** IHC stains were utilized with tumor cells positive for Syn (a), CK (b), CD56 (c)

Histomorphology and IHC were confirmed intracranial LCNEC. At present, a year after the diagnosis, the patient is still alive.

## Discussion

NET is a kind of heterogeneous carcinoma<sup>[1]</sup> with the very low incidence of about 5.25 cases per 100,000<sup>[2]</sup>. It is mainly observed in the lungs, the thyroid, the jejunum, the ileum, and the pancreas<sup>[2]</sup>, while intracranial NET is rarely reported. It was first described in 2005 by Peng *et al*<sup>[3]</sup>. To our knowledge, only two relevant studies on intracranial LCNEC, a kind of NET, have been reported until now<sup>[4-5]</sup>.

NETs of the cranium are exceedingly rare, and consequently, most of the knowledge is based on lung NETs. In the 2015 WHO classification, lung NETs were classified as high grade, small cell carcinoma (SCC) and LCNEC, or low grade, carcinoid (typical carcinoid and atypical carcinoid). Out of all these, SCC is the most common<sup>[6]</sup>. NET tumor cell originated from neuroendocrine cells and peptidergic neurons ubiquitous in the neuroendocrine system. Travis *et al*<sup>[7]</sup> first reported lungs LCNEC and proposed that LCNEC have large and polygonal cells with a low nucleo-to-cytoplasmic ratio, coarse nuclear chromatin, and frequent nucleoli but shows more necrosis and a higher mitotic rate (>10/10

HPFs). Cytologically, LCNEC tumor cells are larger than those of SCC and have distinct instead of molded cell borders<sup>[8]</sup>. Typical carcinoids have nests of round cells and a low mitotic rate. Like LCNEC, atypical carcinoids have vesicular nuclei, prominent nucleoli, and pleomorphism and necrosis but a low mitosis rate<sup>[9]</sup>.

It is extremely difficult to diagnose LCNEC before surgery. Travis *et al*<sup>[6]</sup> reported that LCNEC can only be diagnosed in a surgically resected tumor, and it should not be applied to cytology or small biopsy specimen. To confirm the neuroendocrine features, tumor cells require IHC to document neuroendocrine marker expression. Ki-67, synaptophysin, chromogranin, neuron-specific enolase, and CD56 are the most sensitive and specific<sup>[10]</sup>. Recently, a novel IHC marker, TTF-1, has been considered to be a useful marker for LCNEC<sup>[6]</sup>. Among the pulmonary tumors, TTF-1 was reported to have high positive rates in atypical carcinoid tumors (100%), SCCs (83%–100%) and LCNECs (25%–75%)<sup>[5]</sup>.

In our patients, case 1 presented with paroxysmal headache and dizziness, and was diagnosed using histology and immunohistochemistry. Pathology of the tumor showed that large cells with hyperchromatic nuclei and nucleoli, focal necrosis, and high mitotic rate, all of which aided in distinguishing it from a SCC and carcinoid. IHC analysis revealed the neoplastic cells were positive for CD56, Ki-67 (> 80%), CK7, and CK.

Histomorphology and IHC of this patient were confirmed LCNEC. Case 2 presented with headache and nausea. IHC analysis showed Syn, CD56, CK7, CK, and a pathological diagnosis of metastatic intracranial LCNEC was made. It is extremely difficult to diagnose LCNEC. In order to improve the diagnosis of intracranial LCNEC, additional IHC staining of synaptophysin, chromogranin, neuron-specific enolase, CD56, and Ki-67 should be performed.

Standard treatment strategies for intracranial NETs remain unclear due to the rarity of this neoplasm<sup>[11–12]</sup>. High-grade tumors are frequently regarded as a systemic disease<sup>[13]</sup>. Cao *et al.*<sup>[14]</sup> demonstrated that complete surgical treatment is warranted for symptomatic mass effect. Postoperative adjuvant chemotherapy and radiotherapy might be effective to high-grade intracranial NECs. However, Francisco *et al.*<sup>[15]</sup> reported that chemotherapy is the mainstay of therapy, and surgery or radiotherapy should be considered. Van der Laan *et al.*<sup>[16]</sup> reported that LCNEC, a kind of malignant cancer with poor prognosis, has a 5-year survival rate of 14.4%. Prognosis is very poor once LCNEC metastasize to the brain and most patients survive for less than 6 months<sup>[10]</sup>. Cao *et al.*<sup>[14]</sup> reported that postoperative chemotherapy (YH-16 combined with temozolomide) is effective against intracranial LCNEC. The treatment of intracranial LCNEC is less reported. In our patients, case 1 underwent a complete surgery and died two months later, and case 2 underwent surgery followed by chemotherapy with etoposide and carboplatin and is still alive. There is a difference in the survival time between the two cases, which may be due to the different treatments given. This shows that effective surgical resection and subsequent multi-agent chemotherapy should be performed to promote long-term survival of intracranial LCNEC patients.

In conclusion, intracranial LCNEC is an extremely rare malignant cancer. There have been only a few reports of the disease in the literature. Here, we report a patient with intracranial LCNEC to improve the diagnosis and treatment of the disease.

### Acknowledgments

The authors thank all the patients and their families for participating in this research.

### Conflicts of interest

The authors declare no potential conflicts of interest.

### References

- Hu HK, Ke NW, Li A, *et al.* Clinical characteristics and prognostic factors of gastroenteropancreatic neuroendocrine tumors: a single center experience in China. *Hepatogastroenterology*, 2015, 62: 178–183.
- Liu W, Chen W, He X, *et al.* Cholecystectomy with gallbladder bed cauterization might be sufficient for T1bN0M0 neuroendocrine carcinoma of gallbladders: Cases report and literature review. *Medicine (Baltimore)*, 2017, 96: 8778.
- Peng L, Cheng JP, Huang LJ. Intracranial neuroendocrine carcinoma: report of one case. *Di Yi Jun Yi Da Xue Xue Bao (Chinese)*, 2005, 25: 597–598.
- Terada T. Pulmonary large cell neuroendocrine carcinoma diagnosed in a brain metastasis. *Int J Clin Exp Pathol*, 2012, 5: 159–162.
- Tsugu A, Yoshiyama M, Matsumae M. Brain metastasis from large cell neuroendocrine carcinoma of the urinary bladder. *Surg Neurol Int*, 2011, 2: 84.
- Travis WD, Brambilla E, Nicholson AG, *et al.* The 2015 World Health Organization Classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. *J Thorac Oncol*, 2015, 10: 1243–1260.
- Travis WD, Linnoila I, 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*, 1991, 15: 529–553.
- Kusafuka K, Abe M, Iida Y, *et al.* Mucosal large cell neuroendocrine carcinoma of the head and neck regions in Japanese patients: a distinct clinicopathological entity. *J Clin Pathol*, 2012, 65: 704–709.
- Dunn A, Broadfoot BG, Hunt J, *et al.* Metastatic laryngeal large cell neuroendocrine carcinoma: A rare case of presentation and extreme tumor burden. *J Cutan Pathol*, 2018, 45: 229–233.
- Leader M, Collins M, Patel J, *et al.* Antineuron specific enolase staining reactions in sarcomas and carcinomas: its lack of neuroendocrine specificity. *J Clin Pathol*, 1986, 39: 1186–1192.
- Zhang S, Cai Q, Fan L, *et al.* Primary intracranial small cell carcinoma: a case report and review of the literature. *Onkologie*, 2013, 36: 428–431.
- Hueser CN, Nguyen NC, Osman M, *et al.* Extrapulmonary small cell carcinoma: involvement of the brain without evidence of extracranial malignancy by serial PET/CT scans. *World J Surg Oncol*, 2008, 6: 102.
- Chen SB, Yang JS, Yang WP, *et al.* Treatment and prognosis of limited disease primary small cell carcinoma of esophagus. *Dis Esophagus*, 2011, 24: 114–119.
- Cao J, Xu W, Du Z, *et al.* Pathologic progression, possible origin, and management of multiple primary intracranial neuroendocrine carcinomas. *World Neurosurg*, 2017, 106: 1054.
- Tustumi F, Takeda FR, Uema RH, *et al.* Primary neuroendocrine neoplasm of the esophagus – Report of 14 cases from a single institute and review of the literature. *Arq Gastroenterol*, 2017, 54: 4–10.
- van der Laan TP, Plaat BE, van der Laan BF, *et al.* Clinical recommendations on the treatment of neuroendocrine carcinoma of the larynx: A meta-analysis of 436 reported cases. *Head Neck*, 2015, 37: 707–715.

DOI 10.1007/s10330-018-0306-6

Cite this article as: Zhan XZ, Wu WD, Wang XM, *et al.* Metastatic intracranial large-cell neuroendocrine carcinoma: a study of two cases. *Oncol Transl Med*, 2018, 4: 255–258.