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Original Article

Small cell carcinoma of the brain without apparent extracranial origin in the same intracranial region one year following resection of malignant glioma

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Abstract: Primary small cell carcinoma (SCC) of the brain is rare, and there have been no reports of small cell carcinoma located at the resection site of a glioma without extracranial tumours. Herein, we report a case of brain SCC in the same intracranial region from which a malignant glioma had been surgically resected a year prior. The patient, a 68-year-old male, had headaches as a symptom, and brain CT and MRI revealed a hyperdense region measuring 5.5×5 centimetres. Blood test results showed no significant changes. H&E staining suggested that these tumour cells had the characteristics of small cell lung carcinoma cells. Immunohistochemical staining for the glioma marker S100 was negative, but immunohistochemical staining for the neuroendocrine marker synaptophysin and for the cell adhesion molecule CD56 was strongly positive; meanwhile, staining for thyroid transcription factor-1 (TTF-1), a relatively specific marker of lung and thyroid carcinoma, was positive, and the Ki67 index was 75%. The pathological examination strongly suggested that the tumour was a small cell lung carcinoma, but CT and MRI scans indicated that there were no extracranial tumours. Hence, the tumour could be a primary small cell brain carcinoma. The patient underwent surgical resection again; the excised tumour was a mass of grey and white tissues with fragmentary morphology, and its dimensions were 3.0 cm×1.5 cm×0.8 cm.

Keywords: Small cell carcinoma, glioma, neuroendocrine tumour

Introduction

Small cell carcinoma (SCC) is a highly aggressive neuroendocrine tumour marked by rapid cell growth and proliferation [1]. Histological analysis of SCC shows a high mitotic index. The tumours are composed of small, round to spindle-shaped cells with dense nuclei and have a trabecular growth pattern. In addition, there is often necrosis within the tumour [2]. Small cell carcinoma belongs to the neuroendocrine tumour (NET) family, a heterogeneous group of tumours with neuronal and endocrine differentiation [1, 3]. Immunohistochemical staining of some neuroendocrine markers is generally used to diagnose the origin of these tumours [4-6].

SCC is primarily diagnosed in the lung. In 1930, the first report of extrapulmonary small cell carcinomas (EPSCCs) appeared, and these tumours have now been documented to occur in all organs. Small cell carcinomas of the lung frequently metastasize to the brain, but extracranial small cell carcinomas are generally recognized earlier. Recently, small cell carcinomas (SCCs) originating from extrapulmonary organs have been detected and reported, but cases of primary SCC are relatively rare, with an overall incidence of approximately 0.1%-0.4%. Primary small cell carcinomas of the brain are even rarer [2, 7-11].

Herein, we report a case of brain small cell carcinoma located at the resection site of a prior glioma, and serial CT, MRI and other examinations did not detect any extracranial primary tumour sites. This case is unique, as primary SCC was found at the site of the resected glioma.

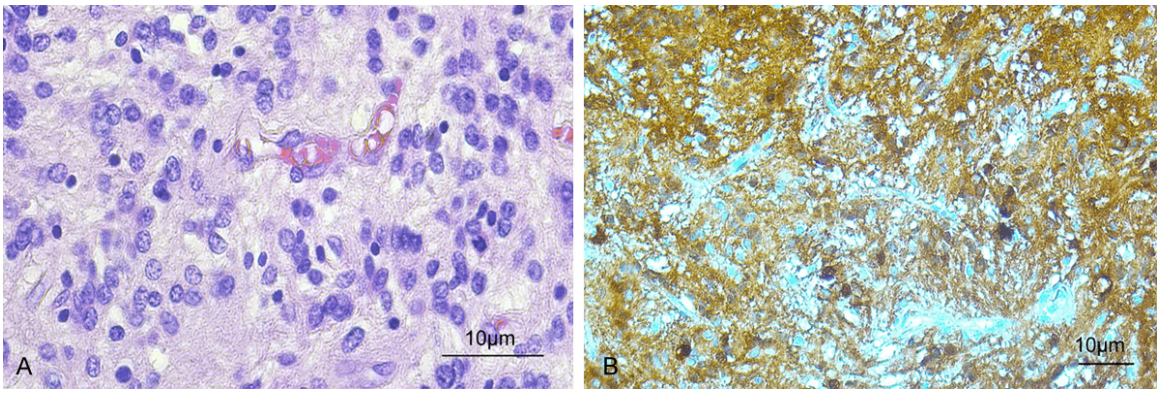

Figure 1. The patient's malignant glioma diagnosis. A. H&E staining (×20); B. Positive staining for the glioma marker S-100 in the tumour cells (×10).

Table 1. Immunohistochemical staining of glioma of the brain

Antigens	Results
CK7	-
TTF-1	+++
CgA	-
S100	-
CD34	-
Ki67	about 75%
CD56	+++
Synaptophysin	+++

+++, 60-100%; ++, 30%-60%; +, 10-30%; -, negative.

Case description

Presentation

In March 2019, a 68-year-old male was admitted to our hospital complaining of headache and once suffered surgical resection of an intracranial tumour because of a malignant glioma (diagnosed as grade II-III; **Figure 1** and **Table 1**) last year. After surgery, the patient underwent whole brain radiotherapy and chemotherapy. The headache was limited to the left temporal region of the brain and presented episodically with no accompanying language disorder or limb weakness. He also had no symptoms of high intracranial pressure.

Investigation

The patient's Glasgow Coma Scale (GCS) score was 15, and there was an old surgical scar measuring approximately 10 cm in the left frontotemporal region of the brain. Brain MR revealed prominent abnormal signals located in the region of the previous glioma resection surgery (**Figure 2**). Further CT-MR investigation verified that changes existed in the post-operative region of the left frontal and temporal lobes. Serum biochemistry and tumour markers showed abnormal results. To diagnose whether the SCC in the brain had metastasized from an unknown primary tumour, multiple organs, including the lung, kidney, liver, pancreas, gall bladder, bladder, and spleen, were investigated by CT-MRI and B-scan ultrasound and demonstrated no extracranial carcinoma.

Diagnosis

The patient underwent a left parietal craniotomy followed by en bloc surgical excision of the larger tumour mass in the left temporal region. The excised tumour mass, which measured 9×6×2 centimetres, was a pile of medium-soft black tissue (**Figure 3A**), in contrast to the first excised glioma tissue, which was a pile of soft white tissue (**Figure 3B**). The histopathological analysis of the medium-soft black tissue showed that the tumour was composed of sheets of pleomorphic round cells with hyperchromatic nuclei, irregular nuclear outlines, and a high mitotic rate, which is consistent with small cell carcinoma (**Figure 4A** and **4B**).

Immunohistochemical staining exhibited negative results for CK7, CEA, CD34 and S100, but the cell adhesion molecule CD56 (**Figure 4D**) and the specific lung and thyroid carcinoma marker TTF1 were strongly positive (**Figure 4C**), and the neuroendocrine marker synaptophysin was also positive (**Figure 4E**), and Ki67 showed strong and diffuse positive staining (approximately 75% positive) (**Table 2**).

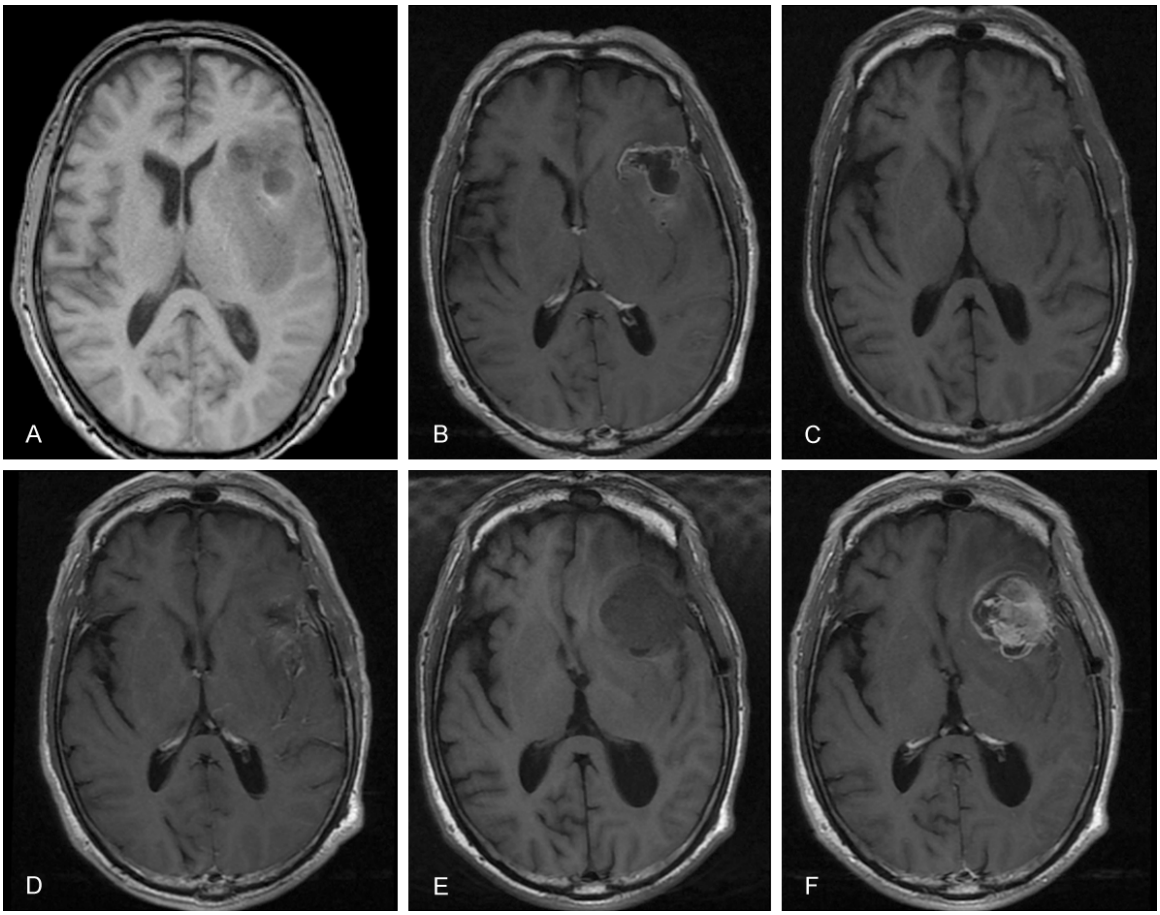

Figure 2. Abnormal signal in the region of the old scar from the patient's prior glioma resection. A. MR T1 presentation of glioma in the intracranial region of the brain (3*1.54*5.0*0.8 cm). B. MR+C presentation of giloma in the intracranial region of the brain (3*1.54*5.0*0.8 cm). C. MR T1 presentation of giloma four months after surgery. D. MR+C presentation of giloma four months after surgery. E. MR T1 presentation of a new tumour located in the site of glioma resection (9*6*2 cm). F. MR+C presentation of a new tumour located in the site of glioma resection (9*6*2 cm).

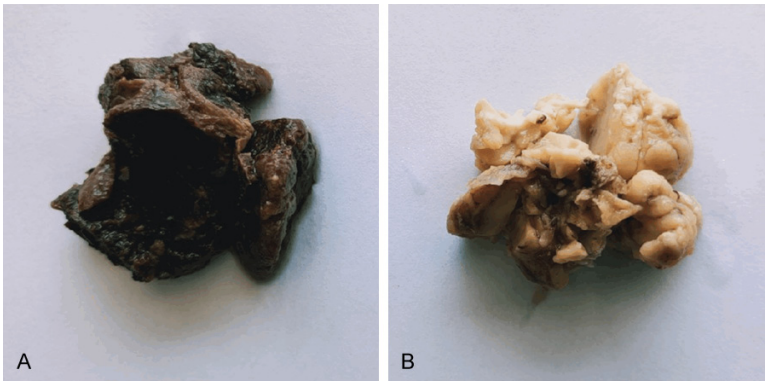

Figure 3. The patient's tumour specimens of surgical resection. A. The small cell carcinoma specimen; B. The glioma specimen.

The immunochemical profiling described above was suggestive of lung primary small cell carcinoma; however, extrapulmonary sites including the renal tract and neck had no abnormalities. The pathological tests were externally reviewed and validated by another pathologist from another hospital.

Primary small cell carcinoma of the brain without extracranial involvement was diagnosed in the region of the previous malignant glioma resection.

Treatment

Brain SCC is clinically treated by surgery in combination with brain radiotherapy and chemotherapy [12, 13]. The patient was treated with a

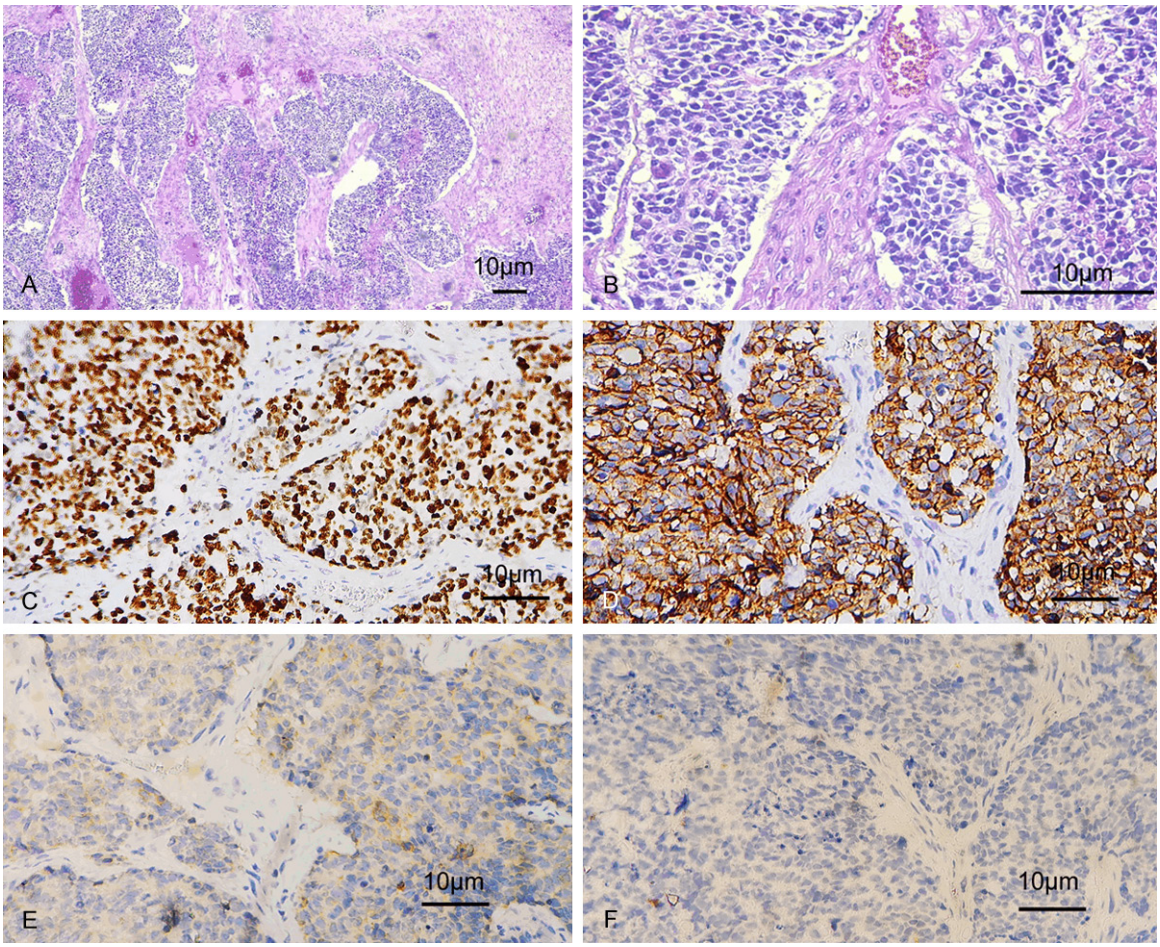

Figure 4. The patient's small cell carcinoma diagnosis. A. H&E staining (×4); B. H&E staining (×20); C. Positive staining for TTF1 (×10); D. Positive staining for the neuroendocrine marker CD56 (×10). E. Positive staining for the neuroendocrine marker synaptophysin (×10). F. Negative staining for the glioma marker S-100 (×10).

Table 2. Small cell carcinomas of the brain reported in the literature

Antigens	Results
CD34	+++
S-100	+++
Vimentin	+
Ki67	about 5%
P53	-
SMA	-
CK	-
EMA	-

CK, cytokeratin; TTF-1, thyroid transcription factor-1; Syn, synaptophysin.

second surgery, but he experienced symptom aggravation and herniation after surgery, and he was in a state of lethargy. The patient's relatives called for the withdrawal of treatment and removed him from our hospital. The patient died a few days later.

Discussion

SCC is a poorly differentiated neuroendocrine tumour typically of pulmonary origin, and has a high mitotic index, displaying neuroendocrine markers [1, 6, 14]. SCLC (small cell lung carcinoma) is believed to be derived from neuroendocrine cells (NECs) or neuroendocrine progenitors (NEPs) in the lung [3, 9, 15]. Extrapulmonary small cell carcinoma (EPSCC) is defined as biopsy-proven small cell carcinoma in a non-pulmonary primary site [16]. In the present study, the patient's brain tumour showed typical histological features of SCC; immunohistochemical staining for neuroendocrine antigens (CD56 and synaptophysin) revealed strong positivity, and no extracranial tumours were

Table 3. Immunohistochemical staining of small cell carcinoma of the brain

References	Age/Sex	Treatment	Year	Description
[23]	43/Female	Radiotherapy	2017	Primary SCC
[23]	75/Male	Radiation/cisplatin-based chemotherapy	2010	Primary SCC
[21]	56/Male	Radiotherapy/chemotherapy	2009	Primary SCC
[21]	71/Female	Radiotherapy/chemotherapy	2009	Primary SCC
[20]	59/Female	Chemotherapy	2008	Primary SCC

+++, 60-100%; ++, 30%-60%; +, 10-30%; -, negative.

observed on serial CT, MRI or other examinations. These examinations showed that the small cell carcinoma in the patient's brain was a primary brain tumour.

TTF-1, a relatively specific marker of lung and thyroid carcinoma, is expressed in 70-90% of SCLC cases but can also be positive in 44-80% of extrapulmonary small cell carcinomas and therefore is not useful in determining the primary site of SCLCs [17]. In the present case, TTF-1 was strongly positive, and we hypothesized that these SCC cells could have originated from carcinogenesis in the lung tissues, entered the brain, reached the site of the surgical scar, and proliferated and grown with blood circulation. Of course, they could also have originated from carcinogenesis in the tissues surrounding the former glioma site.

Extrapulmonary SCC is a rare neoplasm [6, 9, 10, 18, 19], and extrapulmonary SCC in the brain is especially rare; we performed a literature search from 1983 to 2020 in PubMed using the keywords "neuroendocrine carcinoma", "small cell" and "brain", and we found only 5 cases (**Table 3**) [20-23]. The case that we report in the present article is unique in that a primary SCC of the brain was located in the site of an old surgical scar from glioma resection; we believe that this case report offers some new findings for the study of extrapulmonary SCC origin.

Acknowledgements

We are grateful to the patient in our case study. The case report was performed in accordance with appropriate ethical standards.

The authors certify they have obtained the informed consent of the patient. The patient allowed his clinical information to be reported in the journal.

Disclosure of conflict of interest

None.

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References

[1] Karachaliou N, Pilotto S, Lazzari C, Bria E, de Marinis F and Rosell R. Cellular and molecular biology of small cell lung cancer: an overview. Transl Lung Cancer Res 2016; 5: 2-15.

[2] Lobins R and Floyd J. Small cell carcinoma of unknown primary. Semin Oncol 2007; 34: 39-42.

[3] Kloppel G. Neuroendocrine neoplasms: dichotomy, origin and classifications. Visc Med 2017; 33: 324-330.

[4] Oronsky B, Ma PC, Morgensztern D and Carter CA. Nothing but NET: a review of neuroendocrine tumors and carcinomas. Neoplasia 2017; 19: 991-1002.

[5] Rindi G, Klimstra DS, Abedi-Ardekani B, Asa SL, Bosman FT, Brambilla E, Busam KJ, de Krijger RR, Dietel M, El-Naggar AK, Fernandez-Cuesta L, Kloppel G, McCluggage WG, Moch H, Ohgaki H, Rakha EA, Reed NS, Rous BA, Sasano H, Scarpa A, Scoazec JY, Travis WD, Tallini G, Trouillas J, van Krieken JH and Cree IA. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. Mod Pathol 2018; 31: 1770-1786.

[6] Chu C, Hu CY, Batra R and Lin AY. Small cell carcinoma of the kidney: a case report and analysis of data from the surveillance, epide-

miology, and end results registry. J Med Case Rep 2019; 13: 71.
[7] Howard S, O'Regan K, Jagannathan J, Krajewski K, Giardino A and Ramaiya N. Extrapulmonary small cell carcinoma: a pictorial review. AJR Am J Roentgenol 2011; 197: W392-398.
[8] Laprovitera N, Riefolo M, Ambrosini E, Klec C, Pichler M and Ferracin M. Cancer of unknown primary: challenges and progress in clinical management. Cancers (Basel) 2021; 13: 451.
[9] Mirza IA and Shahab N. Small cell cancer of the pleura, kidney, and thymus. Semin Oncol 2007; 34: 67-69.
[10] Chen ZZ, Huang W and Wei ZQ. Small-cell neuroendocrine carcinoma of the rectum - a rare tumor type with poor prognosis: a case report and review of literature. World J Clin Cases 2020; 8: 6095-6102.
[11] Hashmi AA, Ali J, Khan K, Ahmed O, Rehman AU, Irfan M, Haroon S and Asif MG. Clinicopathological spectrum of primary and metastatic neuroendocrine neoplasms. Cureus 2020; 12: e11764.
[12] Koinis F, Kotsakis A and Georgoulias V. Small cell lung cancer (SCLC): no treatment advances in recent years. Transl Lung Cancer Res 2016; 5: 39-50.
[13] Kiesewetter B and Raderer M. How I treat neuroendocrine tumours. ESMO Open 2020; 5: e000811.
[14] Wang D, Rong Y, Wu W and Jin D. Primary small cell carcinoma of the pancreas: rare type of pancreatic cancer and review of the literatures. World J Surg Oncol 2012; 10: 32.
[15] Bennett BM, Wells JR, Panter C, Yuan Y and Penrod JR. The humanistic burden of small cell lung cancer (SCLC): a systematic review of health-related quality of life (HRQoL) literature. Front Pharmacol 2017; 8: 339.
[16] Shahab N. Extrapulmonary small cell carcinoma of the bladder. Semin Oncol 2007; 34: 15-21.
[17] Boutrid H, Kassem M, Tozbikian G, Morgan E, White J, Shah M, Vandeusen J, Sardesai S, Williams N, Stover DG, Lustberg M, Wesolowski R, Pudavalli V, Williams TM, Konda B, Fortier S, Carbone D, Ramaswamy B and Cherian MA. TTF-1 positive primary small cell carcinoma of the breast: a case report and review of the literature. Front Endocrinol (Lausanne) 2020; 11: 228.
[18] Vrouvas J and Ash DV. Extrapulmonary small cell cancer. Clin Oncol (R Coll Radiol) 1995; 7: 377-81.
[19] Kepil N, Akinci O, Batur S and Zengin AK. A rare tumor of the gallbladder: small cell neuroendocrine carcinoma. North Clin Istanb 2020; 7: 624-627.
[20] Hueser CN, Nguyen NC, Osman M, Havlioglu N and Patel AJ. 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.
[21] Chionh F, Azad A and Lee C. Small cell carcinoma of unknown primary presenting with disease confined to the central nervous system. Acta Oncol 2009; 48: 317-318.
[22] Terada T. Small cell carcinoma of the brain without extracranial involvement by serial CT, MRI and PET. Int J Clin Exp Pathol 2010; 3: 323-327.
[23] Noonan C and James M. A case of isolated small cell carcinoma of the brain. Acta Oncol 2017; 56: 1133-1135.