

# **Metastatic Bronchogenic Carcinoma with Human Chorionic Gonadotropin Production Manifesting as Cerebellar Hemorrhage**

## **—Case Report—**

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### **Abstract**

A 58-year-old male presented with a rare case of brain metastatic bronchogenic carcinoma with human chorionic gonadotropin (hCG) production causing cerebellar hemorrhage with symptoms of nausea, vomiting, and headache. Bronchogenic carcinoma manifesting as gynecomastia had been resected a few months previously. Neurological examination revealed left cerebellar ataxia. Neuroimaging showed multiple cerebellar metastases with cerebellar hemorrhage adjacent to the tentorium. Angiography demonstrated tumor staining fed by the hemispheric branch of the left posterior inferior cerebellar artery. Suboccipital craniectomy was performed. The left cerebellar hematoma was evacuated and the tumor was partially removed to prevent massive intraoperative hemorrhage and avoid brain stem injury. Histological examination showed the resected tumor was large cell carcinoma. hCG was detected in the cerebrospinal fluid and was identified by immunohistochemical staining in tumor cells. The primary lesion of bronchogenic carcinoma showed choriocarcinomatous change because the tumor could produce hCG. The choriocarcinomatous cells with higher metastatic potential formed lesions in the brain, and finally intratumoral hemorrhage occurred producing the rapid development of symptoms.

Key words: bronchogenic carcinoma, cerebellar hemorrhage, human chorionic gonadotropin, metastatic brain tumor

### **Introduction**

Human chorionic gonadotropin (hCG) is a glycoprotein hormone composed of  $\alpha$ - and  $\beta$ -subunits which is normally produced by the trophoblastic tissue of pregnant women and secreted into the blood and urine. Elevated serum levels of immunoreactive hCG or  $\beta$ -subunit of hCG (hCG $\beta$ ) are often found in patients with various nontrophoblastic neoplasms, which are known as ectopic hCG/hCG $\beta$ -producing tumors.<sup>2,4,6-8,16,17</sup> Germ cell tumors and metastatic choriocarcinoma in the brain produce hCG. We report a rare case of a cerebellar tumor which presented as cerebellar hemorrhage and was identified as a metastatic bronchogenic carcinoma producing hCG ectopically.

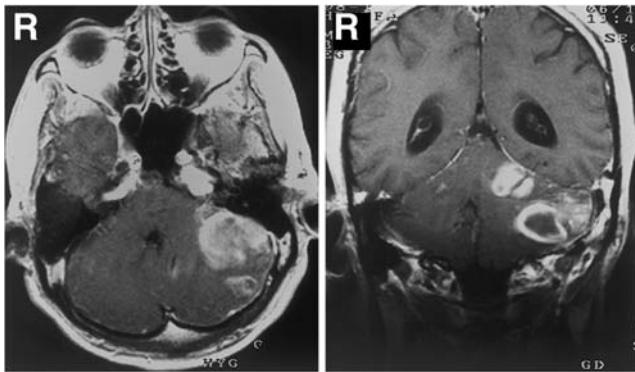
### **Case Report**

A 58-year-old man noted enlargement and pain in the breast and a persistent cough in December 1997 for which he sought medical advice. Radiography of the chest revealed a tumor on the right side thought to be consistent with bronchogenic carcinoma. The upper lobe and part of the lower lobe of the right lung were resected in February 1998. Histological examination revealed large cell carcinoma thought to be the primary tumor. Laboratory studies revealed the serum hCG level was 6.14 ng/ml preoperatively, which decreased to 0.85 ng/ml postoperatively. Metastases had spread to the lymph nodes of the mediastinum, so 50 Gy of local fractionated irradiation was administered.

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**Fig. 1** Computed tomography scan demonstrating a large left cerebellar hemorrhage and a small right cerebellar hemorrhage with deviation of the fourth ventricle to the right.



**Fig. 2** Axial (left) and coronal (right) T<sub>1</sub>-weighted magnetic resonance images obtained after intravenous administration of gadolinium-diethylenetriaminepenta-acetic acid, demonstrating slightly enhanced masses with mixed intensity attached to the tentorium.

tion therapy was given.

The patient complained of vertigo and subsequent mild headache in April 1998. On admission, the patient complained of nausea and vomiting. His vertigo worsened gradually, so the patient was admitted to our hospital in June 1998.

Neurological examination found left cerebellar ataxia. Computed tomography revealed high- and low-density areas in the left cerebellar hemisphere to

middle cerebellar peduncle and right middle cerebellar peduncle adjacent to the tentorium (Fig. 1). The lesion appeared as high signal intensity with irregular low signal intensity on T<sub>1</sub>- and T<sub>2</sub>-weighted magnetic resonance imaging with slight enhancement around the lesion after administration of gadolinium (Fig. 2). Left vertebral angiography demonstrated tumor staining fed by the hemispheric branch of the left posterior inferior cerebellar artery.

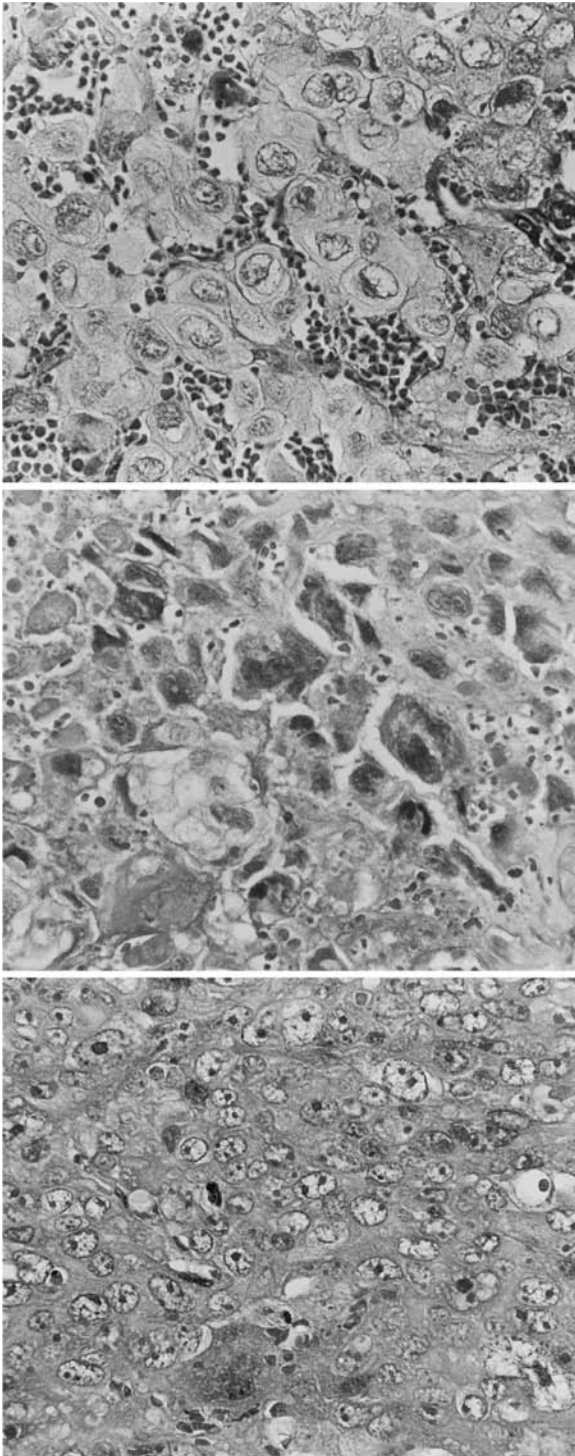
A midline suboccipital craniectomy was performed. The tense dura was opened, revealing subarachnoid hemorrhage on the posterior lateral surface of the left cerebellar hemisphere. The subarachnoid hemorrhage was removed by suction to reveal a reddish-brown, soft tumor. The tumor was removed by Cavitron ultrasonic surgical aspirator in spite of considerable bleeding from the tumor. An associated large hematoma was aspirated. The anterior superior portion of the tumor was strongly adherent to the tentorium. The residual tumor was removed piece by piece using tumor forceps. The medial portion of the tumor that had infiltrated the brain stem could not safely be removed.

Histological examination of the resected specimen revealed that much of the tumor was necrotic. Surviving portions appeared to be undifferentiated large cell carcinoma of the same morphology as the original lung tumor, and was regarded as metastatic (Fig. 3). However, re-examination of the original tumor revealed scattered syncytiotrophoblastic-like giant cells. Similar cells were gathered around the vessels in the cerebellar tumor. Immunohistochemical study showed that antibody against hCG stained the cytoplasm of these cells (Fig. 4). This finding was consistent with the high level of hCG in the cerebrospinal fluid (37.5 ng/ml), collected during the operation.

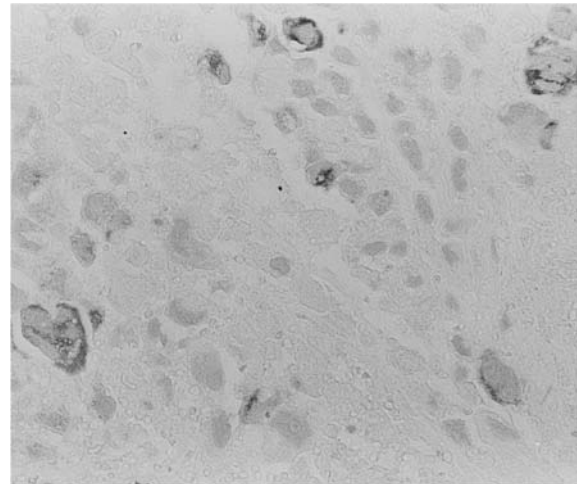
Postoperatively, his cerebellar signs and symptoms were improved. Whole brain irradiation was planned as adjuvant treatment, but was not performed because the patient suffered ileus of unknown etiology. The patient died in July 1998 of progressive cachexia. Autopsy was not permitted.

## Discussion

Brain tumor is an important cause of spontaneous, nontraumatic, intracranial hemorrhage not due to cerebral aneurysm, vascular malformation, or hypertensive cerebrovascular disease.<sup>10,11,13,14,18</sup> Hypertension and coagulopathy are thought to be risk factors of intratumoral hemorrhage in some cases, but the etiologies of intratumoral hemorrhage are often considered to be endothelial proliferation



**Fig. 3** Photomicrographs of the metastatic tumor showing cerebellar tumor tissue composed of undifferentiated large cells with abundant vessels (upper) and syncytiotrophoblastic-like giant cells (middle). Photomicrograph of the primary lesion demonstrating syncytiotrophoblastic-like giant cells scattered among undifferentiated large cells (lower). HE stains,  $\times 400$ .



**Fig. 4** Photomicrograph showing immunohistochemical staining for human chorionic gonadotropin in the cytoplasm of the syncytiotrophoblastic-like giant cells. Nuclei are stained by hematoxylin.  $\times 400$ .

with vascular obliteration, vessel compression, and/or distortion due to rapid tumor growth, vessel necrosis, invasion of vessel walls by the tumor, and/or increased venous pressure associated with increased intracranial pressure.<sup>9-15,19</sup> The histological features of tumors that bleed microscopically or macroscopically include tumor necrosis as well as the vascular changes of vessel-wall hyalinization, degeneration or necrosis of vessel walls, thrombosis, and the presence of many thin-walled fragile vessels and ruptured vessels. Hemorrhage from tumors is also believed to be influenced by treatment, disturbance of venous drainage, or rapid tumor necrosis. Hemorrhage from a brain tumor was confirmed clinically, surgically, or at autopsy in 94 of 1861 cases (5.1%) treated during the past 18 years.<sup>18</sup> Hemorrhage was seen in 49 of 311 pituitary adenomas (15.8%) and in 45 of 1550 other brain tumors (2.9%).<sup>18</sup> The rates of hemorrhage from primary and metastatic brain tumors were both 2.9%. Among primary brain tumors, malignant glioma, oligodendroglioma, and germ cell tumors have the highest risk of hemorrhage.<sup>10,18</sup> Among metastatic brain tumors, choriocarcinoma, malignant melanoma, bronchogenic carcinoma, and renal cell carcinoma frequently develop significant hemorrhage.<sup>10,11,13,14,18</sup> Both primary and metastatic choriocarcinomas very frequently show hemorrhage. Such hemorrhage is considered to be due to the inherent propensity of trophoblasts to specifically invade and destroy vessel walls.<sup>14,18</sup> In our case, the primary lesion in the lung was considered to ex-

hibit choriocarcinomatous change because the tumor produced hCG. Apparently the tumor had metastasized to the cerebellum, then intratumoral hemorrhage produced the rapid evolution of symptoms.

Ectopic hCG production in carcinomas had been considered rare, but newer immunohistochemical methods have shown that some carcinomas can unexpectedly produce hCG.<sup>2,4,6-8,16,17</sup> hCG production in cases of bronchogenic carcinoma that also gave rise to gynecomastia is rarely reported.<sup>5,21</sup> However, 12% of patients with lung cancer had elevated levels of immunoreactive hCG/hCG $\beta$ , but the increase in immunoreactive hCG/hCG $\beta$  in the serum was mainly attributable to free hCG $\beta$ , not to intact hCG composed of  $\alpha$ - and  $\beta$ -subunits.<sup>21</sup> In our case, both intact hCG and free hCG $\beta$  were examined in the serum using the same methods, finding that the main hCG $\beta$ -related molecule was intact hCG but not free hCG $\beta$ . The biological activity of hCG is displayed through the  $\alpha$ - and  $\beta$ -subunits and is consistent with the clinical finding of tumor-associated gynecomastia in our patient. However, most patients do not show gynecomastia even when the serum level of immunoreactive hCG/hCG $\beta$  is highly elevated. This is understandable given that immunoreactive hCG/hCG $\beta$  in the serum exclusively represents free hCG $\beta$ , which does not show binding activity with the gonadotropin receptor.

Ectopic production of intact hCG or free hCG $\beta$  mainly occurs in the large cell carcinoma and adenocarcinoma types of bronchogenic carcinoma.<sup>1,3,7,20</sup> Previous immunohistochemical studies on hCG/hCG $\beta$ -producing bronchogenic carcinomas demonstrated that localization of immunoreactive hCG/hCG $\beta$  was usually associated with syncytiotrophoblastic giant cells scattered among the non-trophoblastic carcinoma cells. This finding may indicate that the non-trophoblastic carcinoma retrodifferentiated to choriocarcinoma. In our case, localization of immunoreactive hCG/hCG $\beta$  was recognized in the syncytiotrophoblastic-like giant cells scattered among the undifferentiated large cell carcinoma cells in the primary lesion of the lung. Syncytiotrophoblastic-like giant cells were observed near the hemorrhagic and necrotic areas of the metastatic lesion. The choriocarcinomatous cells with higher metastatic potential formed the lesion in the brain. Ectopic hCG-producing carcinoma has a very poor prognosis.<sup>4,6,16</sup> The hCG-producing cells are preferentially localized to the deep, most invasive, and highly proliferating tumor areas.<sup>4</sup> There is a significant correlation with high-grade and advanced-stage ectopic hCG-producing transitional carcinoma of the bladder. A patient with maxillary

squamous cell carcinoma ectopically producing hCG $\beta$  developed diffuse pulmonary metastases, liver and splenic metastases, as well as brain metastasis in spite of chemotherapy and died of distant disease less than one year after the initial treatment.<sup>16</sup> Therefore, hCG-producing carcinoma can be expected to metastasize and progress rapidly. Our patient died 6 months after the initial diagnosis of bronchogenic carcinoma.

Brain tumors manifesting as cerebral hemorrhage have a poor outcome. Survival time might be prolonged if the brain metastasis can be identified before cerebellar hemorrhage occurs. Our patient suffered cerebellar symptoms of headache and vertigo before the cerebellar hemorrhage, so we suggest that careful neurological examination is necessary in patients with ectopic hCG-producing carcinomas to prevent the serious complication of intratumoral hemorrhage in brain metastases.

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