Case Report

Early Rebleeding of Multiple Hemorrhagic Metastatic Choriocarcinoma with Intracerebral Hemorrhage

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Abstract

Choriocarcinoma is a rare, highly malignant gestational trophoblastic neoplasia. This tumor is known for its rapid hematogenous spread to multiple organs and good response to chemotherapy. However, cerebral metastases occur frequently, and hemorrhage from cerebral metastases is a common cause of death. Therefore, patients with cerebral metastases require intensive multimodal therapy to achieve remission. Here, we report the case of a 38-year-old woman with multiple hemorrhagic metastases of choriocarcinoma who developed intracerebral hemorrhage, for which she underwent craniotomy and total removal of the hematoma. Five days after surgery, rebleeding of a large intracerebral hemorrhage developed and an emergency reoperation was performed. We suggest that surgeons carefully consider all patient-related data and always pay attention to changes in the neurological state of a patient. Surgeons should also do their best to completely remove the intracerebral choriocarcinoma in the first operation.

Keywords: Choriocarcinoma, metastases, intracerebral hemorrhage, rebleeding

INTRODUCTION

Gestational trophoblastic neoplasia (GTN) is an uncommon complication of pregnancy that includes a spectrum of cellular proliferation ranging from hydatidiform mole (complete and partial), invasive mole, and choriocarcinoma, to placental-site trophoblastic tumor\(^3\). Choriocarcinoma is the most common malignant form of GTN, which can arise from a previous mole or an abnormal
conceptus, and is characterized by sheets of anaplastic cytotrophoblast and syncytiotrophoblast without chorionic villi. In the past, choriocarcinoma was a fatal disease; however, over the past 4 decades there has been a substantial improvement in the survival of patients with choriocarcinoma. Over 90% of patients with choriocarcinoma can be expected to achieve complete or prolonged remission if treated with adequate and appropriate therapy. GTN usually metastasizes as choriocarcinoma because of its propensity for early vascular invasion with widespread dissemination. The most common metastatic sites are the lung (80%), vagina (30%), brain (10%), and liver (10%). Because trophoblastic tumors are perfused by fragile vessels, metastases are often hemorrhagic and fatal. Therefore, in cases where metastases of choriocarcinoma are suspected, more careful and close patient care and proper treatment are needed. Here, we describe the case of a 38-year-old woman with multiple hemorrhagic metastases of choriocarcinoma who developed early rebleeding after removal of an intracranial choriocarcinoma and we review the literature.

CASE PRESENTATION

A 38-year-old woman was admitted to the emergency room with a 1-day history of hemoptysis. Laboratory evaluation revealed hemoglobin 8.7 g/dL and β-hCG 21,732 mIU/mL. Three months before coming to our hospital, the patient underwent ultrasonography (US) at another obstetrics and gynecology (OB/GYN) hospital due to a positive pregnancy test result; US revealed no gestational sac. She received advice on testing of plasma β-hCG; however, she believed that the pregnancy test kit had just malfunctioned, and rejected any additional examination. Vaginal bleeding occurred 1 month later, and she mistook the vaginal bleeding for the return of her normal menstrual cycle. She complained of nausea and myalgia. A pregnancy test was positive and her blood plasma β-hCG was 22,531 mIU/mL. She underwent dilatation and curettage, but the conceptus tissue did not come out nearly. She was transferred to another university hospital and underwent chest and abdominal computed tomography (CT) and cranial magnetic resonance imaging (MRI) at an outpatient clinic. Chest and abdominal CT revealed a heterogeneously enhancing mass measuring 7.5 cm in the right upper chest and another measuring 3.1 cm in the right kidney. Cranial MRI revealed 2 small tumors with enhancement on the left frontal lobe. However, because the patient could not be hospitalized for treatment, she did not receive inpatient care, but instead simply underwent a radiological test at an outpatient care clinic. Moreover, as Chuseok (Korean Thanksgiving Day) occurred during that time, the appointment date for the outpatient care center was delayed; thus, she was unable to confirm the results from the radiological test. While she was waiting for the follow-up appointment, she had to visit the emergency room of our hospital due to sudden hemoptysis. Chest and abdominal CT at admission to our hospital revealed a slight increase in the size of the heterogeneously enhancing mass within the hemorrhagic component in the right upper lobe compared with the previously performed CT with right hemothorax. An increase in the size of the hemorrhagic mass in the right kidney was also observed. She underwent emergency closed chest tube insertion followed by right upper lobectomy and mass removal. She was transferred to the OB/GYN department for chemotherapy, and then next day she complained of right hemiparesis (grade IV). Cranial CT revealed a hyperdense intracerebral hemorrhage on the left frontal lobe with a small strong enhancing mass within the hemorrhage. Preoperative CT angiography revealed no abnormal vascular finding except hypoplasia of right
vertebral artery (Figure 3B). Emergency craniotomy and removal of mass and hematoma was performed. The hematoma and tumor mass were completely removed under a microscope. Postoperative CT revealed complete removal of the hematoma (Figure 3C). Histopathological examination of the pulmonary resection specimen revealed a choriocarcinoma composed of an admixture of syncytiotrophoblast, cytotrophoblast, and intermediate trophoblast with prominent hemorrhage, and the tumor cells were immunoreactive for β-hCG and pancytokeratin. These tumor cells were also present in brain tissue and intermixed with abundant red blood cells (Figure 4A-D). On postoperative day 5, the patient complained of dysarthria and right hemiparesis (grade III). Cranial CT revealed large rebleeding in the previous operation site of the left frontal lobe that had significantly increased in size compared with previously performed preoperative CT (Figure 5A). Craniotomy and hematoma evacuation were immediately performed. In the second cranial surgery, there were no specific microscopic findings besides the large hematoma. However, histopathological examination of the hematoma revealed that tumor cells were mixed with the hematoma. CT performed on postoperative day 10 revealed complete removal of the hematoma (Figure 5B). The postoperative course was uneventful, and her symptoms gradually improved postoperatively. After 3 weeks, she was transferred to a OB/GYN and then received five course of chemotherapy using EMA-CO (etoposide, methotrexate, actinomycin D/vincristine, and cyclophosphamide) regimen. She continued to improve, and her hematological parameter (including β-hCG) was normalized. Whole brain radiotherapy was not performed because the follow up brain MRI obtained 6 months and 1 year after operation showed no evidence of tumor recurrence or metastases. She is doing well 1 year postoperatively.

![Figure 1: (A, B) Contrast chest and abdominal computed tomography (CT) from another hospital before admission showing a heterogeneously enhancing mass on the right upper lobe and right kidney (asterisk). (C) Gadolinium-enhanced cranial magnetic resonance imaging (MRI) from another hospital before admission showing 2 small tumors with enhancement on the left frontal lobe (arrows).](image-url)
Figure 2: (A) Contrast chest CT at admission showing a heterogeneously hyperdense hemorrhagic mass with peripheral halo on the right upper lobe (asterisk) with right hemothorax. (B) Contrast abdominal CT at admission showing a slight increase in the size of the heterogeneously enhancing mass within the hemorrhagic component compared with the previously performed CT.

Figure 3: (A) Preoperative cranial CT showing hyperdense intracerebral hemorrhage on the left frontal lobe. The small strong enhancing mass within the hemorrhage was noted. (B) Preoperative CT angiography showing no abnormal vascular finding except hypoplasia of right vertebral artery. (C) Postoperative CT showing complete removal of the hematoma.
Figure 4: Histopathological examination of the pulmonary resection specimen showing choriocarcinoma composed of an admixture of syncytiotrophoblast, cytotrophoblast, and intermediate trophoblast with prominent hemorrhage (A); (H&E, 200×) The tumor cells were immunoreactive for β-hCG (B) and pancytokeratin (C) (200×). These tumor cells were also present in brain tissue intermixed with abundant red blood cells (D) (H&E, 100×).

Figure 5: (A) Cranial CT obtained 5 days after the first cranial operation showing a significant increase in the size of the hemorrhage on the left frontal lobe compared with the previously performed preoperative CT. (B) CT performed on postoperative day 10 showing complete removal of the hematoma.
DISCUSSION

Gestational choriocarcinoma may follow any type of pregnancy; 50% of choriocarcinomas are preceded by hydatidiform mole, 25% by abortion, 23% by normal pregnancy, and 3% by ectopic pregnancy\(^4,5\). Over the past 4 decades, there has been a substantial improvement in the survival of patients with choriocarcinoma\(^4,5,7,8\). The vast majority of patients with low-risk and non-metastatic disease can now be cured if treated appropriately with cytotoxic chemotherapy\(^4,5\). However, the presence of brain metastases usually indicates a poorer prognosis, and is used as a predictor of poorer outcome in both World Health Organization (WHO) and International Federation of Gynecology and Obstetrics (FIGO) staging systems for GTN\(^3-5,7\). Cerebral metastases have been reported in 3–28% of patients with choriocarcinoma\(^1,8,9\). However, in a pathological study of patients who died of choriocarcinoma, Kobayashi et al found that the incidence rate of cerebral metastasis increased significantly (by 66.7%)\(^6\). Cerebral metastases may present prior to treatment, while on treatment, or as a relapse in the central nervous system (CNS) after a complete or partial remission. The low response rate of this brain metastasis to therapy can be attributed to adverse prognostic factors such as diagnostic delay, decreased chemosensitivity due to the blood brain barrier, and fatal intracerebral hemorrhage\(^8\).

In the past, the mortality rate for GTN with CNS metastases using single agent chemotherapy with methotrexate (MTX) was very high. However, in 1989, Rustin et al reported complete remission in 69% of patients using combination chemotherapy with MTX/EMA-CO\(^2\). A combination of systemic and intrathecal chemotherapy or systemic chemotherapy and whole brain radiotherapy may be utilized. Whole-brain irradiation, which has the dual advantage of being both tumorcidal and hemostatic, can be given simultaneously with initiation of chemotherapy\(^4,5\). Yordan et al reported a retrospective study of patients with GTN with CNS involvement\(^10\). In the chemotherapy and radiation group, 50% survived and none of the deaths were caused by CNS involvement. In the chemotherapy alone group, 24% survived and 58% of deaths were due to CNS involvement. In the no treatment group (in which most patients died before treatment began), there were no survivors and 74% of deaths were due to CNS involvement.

To minimize the chance of intracerebral hemorrhage, solitary cerebral metastases can also be surgically excised before chemotherapy. Only in selected cases is consideration given to a neurosurgical procedure; indeed, the use of craniotomy for the treatment of these cerebral metastases is uncommon. Xiang et al treated 61 patients with cerebral metastases over a 14-year period with combination chemotherapy, and only 4 of the patients required craniotomy\(^9\). Rustin et al carried out a craniotomy in 3 of 25 patients with choriocarcinoma metastases, and in the series by Bakri et al, 3 of 23 patients with cerebral metastases underwent craniotomy\(^1,7\). Hemorrhage from cerebral metastases is a common cause of death in patients with GTN. The most common reason for performing a craniotomy in a patient with choriocarcinoma was evacuation of intracranial hematoma\(^3,5\). In a pathological study on patients who died of choriocarcinoma, Kobayashi et al found that most cerebral metastases were hemorrhagic, and were intratumoral, peritumoral, or subarachnoid\(^6\). Choriocarcinoma cerebral metastases have also been associated with embolic vascular occlusion, subdural hematoma, arterial aneurysm, and spinal epidural hematoma\(^3\). The neoplastic cells form emboli that are trapped in the cerebral...
circulation and metastasis develops. These metastases have a predilection for invasion of the vessel wall, and this can result in a hemorrhage within the tumor mass, or the development of a fusiform cerebral aneurysm that may rupture, resulting in an intracerebral or subarachnoid hemorrhage\(^{(2,4,6,8)}\). Most patients with cerebral metastases present with symptoms such as vomiting, seizures, headache, hemiparesis, slurred speech, or visual disturbances. These neurologic symptoms usually result from increased intracranial pressure or intracerebral bleeding\(^{(3)}\). The tumor volume may be so small that the patient appears to have a spontaneous hemorrhage without any obvious tumor mass on CT or at surgery, but histological examination of the clot will show choriocarcinoma cell invasion of the vessel wall and aneurysm formation\(^{(8)}\). Therefore, all patients with persistent GTN should undergo a careful metastatic workup, including the following: (1) chest radiography or CT, (2) US or CT of the abdomen and pelvis, and (3) CT or MRI of the head. When the pelvic examination and chest radiographic findings are negative, metastatic involvement of other sites is uncommon\(^{(3)}\). Liver US and CT or MRI will disclose most hepatic metastases in a patient with abnormal liver function tests. CT or MRI of the head can facilitate the early diagnosis of asymptomatic cerebral lesions. Chest CT may detect micrometastases not visible on chest radiography. Chest CT demonstrates pulmonary micrometastases in approximately 40% of patients with presumed non-metastatic disease\(^{(3)}\). In patients with choriocarcinoma or metastatic disease, hCG levels can be measured in the cerebrospinal fluid (CSF) to exclude cerebral involvement if the CT scans of the brain are normal. In the presence of cerebral metastases, the plasma-to-CSF hCG ratio tends to be less than 60:1\(^{(3)}\). Primary surgery for choriocarcinoma metastases followed by chemotherapy with or without radiotherapy has been advocated, particularly if there is any evidence of increased intracranial pressure. The reasoning for this is that surgical removal of the tumor lessens the likelihood of hemorrhage or tumor necrosis and the resulting increase in mass that can occur when the patient is undergoing chemotherapy for the primary disease. Surgery can also reduce the tumor load for the chemotherapy\(^{(8)}\).

Two possible pathogeneses have been postulated for the development of rebleeding: (1) hemorrhage from remnant tumor that was incompletely removed at the first operation, (2) increased bleeding tendency, which can develop during chemotherapy. In the present case, we suspected rebleeding from incomplete removal of tumor for the following reasons. The time to development of rebleeding was short (5 days) and she had not received chemotherapy yet. Moreover, there was no laboratory evidence of coagulopathy. A comparative retrograde analysis of the MRI, which was performed at another hospital before the operation and the CT, which was performed after the first operation, showed 2 masses on the MRI. A distal mass, which did not appear clearly on CT, was found to be imperfectly resected during the first surgery; thus, this was thought to be the cause for the recurrence of bleeding.

Although the role of the surgical treatment may be small, its importance is very high because surgery has a close relationship with the life of the patient. Patients with stage IV disease are at the greatest risk of developing rapidly progressive and hemorrhagic tumors despite intensive multimodal therapy. Preferably, they should be referred to centers with special expertise in the management of GTN\(^{(3)}\). However, in the case of our patient, the examination was performed at the outpatient clinic despite multiple metastases to the lungs, kidney, and brain. Unfortunately, because of the holiday, confirmation of the radiological
examination results was delayed. In addition, the complication, rebleeding that occurred only 5 days after surgery, was caused by incomplete tumor resection during the first intracranial surgery.

When CNS metastases of choriocarcinoma are suspected, early and intensive treatment can help achieve a better prognosis and avoid a fatal outcome. Surgeons should also do their best to remove intracerebral choriocarcinoma as completely as possible at the first operation.

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