Clinical Case Report

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Choriocarcinoma with brain metastasis after term pregnancy

A case report

Liang Song, MD[a,b], Qingli Li, MD[a,b], Rutie Yin, MD[a,b], Danqing Wang, MD[a,b,*]

Abstract

Rationale: Although the incidence of postpartum choriocarcinoma is extremely low, careful postpartum placental examination, histopathological examination in patients with abnormalities, and blood β-human chorionic gonadotropin (HCG) monitoring in high-risk pregnant women are necessary for early diagnosis of postpartum choriocarcinoma and improvement in prognosis.

Patient concerns: A 32-year-old woman presented with the chief complaint of postpartum irregular vaginal bleeding for 45 days and coughing and hemoptysis for 7 days.

Diagnosis: Clinical findings when combined with her medical history and various physical examinations confirmed the diagnosis as postpartum choriocarcinoma with brain metastases (stage IV postpartum choriocarcinoma and a risk score of 16).

Interventions: The patient was administered three courses of multidrug chemotherapy (5-fluorouracil + actinomycin D) with intrathecal methotrexate injection. The 5-fluorouracil + actinomycin D maintenance chemotherapy regimen was continued for 4 cycles; whole brain radiotherapy was also administered.

Outcomes: After the completion of chemotherapy and radiotherapy, the patient underwent regular follow-up examinations; no recurrence was noted for 17 months.

Lessons: Timely diagnosis of postpartum choriocarcinoma can significantly improve its prognosis. A stratified treatment should be administered according to the International Federation of Gynecology and Obstetrics staging and World Health Organization prognostic scoring systems. Blood β-HCG is a sensitive marker for evaluating therapeutic efficacy and follow-up after remission.

Abbreviations: 5-FU = 5-fluorouracil, CT = computed tomography, GTD = gestational trophoblastic disease, GTN = gestational trophoblastic neoplasia, HCG = human chorionic gonadotropin, MTX = methotrexate.

Keywords: brain, choriocarcinoma, metastasis, postpartum, pregnancy

1. Introduction

Gestational trophoblastic disease (GTD) includes formation of a benign hydatidiform mole (partial and complete), invasive and metastatic hydatidiform mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor. The latter 4 types of malignant GTD are also classified as gestational trophoblastic neoplasia (GTN).

Benign hydatidiform moles can transform into malignant hydatidiform moles. The probabilities of this transformation are 15% to 20% and 0.1% to 5% for complete and partial hydatidiform moles, respectively.[1–3] Hydatidiform moles are relatively common in the Asian population, with an incidence of 2 in 1000 pregnancies.[4,5] The incidence of hydatidiform moles in Europe and North America is usually <1 in 1000 pregnancies.[6,7] In recent years, the incidence of hydatidiform moles in Asia seems to be decreasing. This may be due to economic and dietary improvements and decrease in the birth rate. Choriocarcinomas are extremely rare, and it is difficult to differentiate between choriocarcinomas secondary to hydatidiform moles and invasive hydatidiform moles due to the lack of histopathological evidence in clinical settings. Therefore, it is difficult to estimate their incidence accurately. According to some reports, the incidence of choriocarcinomas is around 1 in 40,000 to 9 in 40,000 pregnancies, and its prevalence has been decreasing.[3] The incidence of postpartum choriocarcinoma after term pregnancy is even lower, at around 1 in 160,000 pregnancies.[8] Due to the difficulty of diagnosis, treatment is often delayed, resulting in poor outcomes. However, if choriocarcinomas are diagnosed and treated timely, their remission rate reaches 87.5%.[9]

In this report, we present a rare case of choriocarcinoma with brain metastasis after term pregnancy in a 32-year-old woman at 45 days after the birth of a healthy baby.

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We obtained written consent from the patient for publication of this case report.

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[a] The Department of Obstetrics and Gynecology, West China Second University Hospital of Sichuan University, [b] Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, Chengdu, Sichuan, China.

[*] Correspondence: Danqing Wang, Department of Obstetrics and Gynecology, West China Second University Hospital of Sichuan University, No. 20 The third section of South Renmin Road, Chengdu, Sichuan 610041, China (e-mail: danqingwang@163.com).

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2. Case report

2.1. Presenting concerns

A 32-year-old gravida 3 para 3 woman with no disease history was referred to our hospital due to postpartum irregular vaginal bleeding for 45 days and coughing and hemoptysis for 7 days. In June 2016, the patient had successfully delivered a newborn outside the hospital. It was not known whether the placenta was expelled, and the patient had not undergone a medical examination at the hospital. After the childbirth, she continued experiencing small amounts of vaginal bleeding. On postpartum day 5, vaginal bleeding had increased. On postpartum day 12, the patient experienced dizziness and underwent infusion and dilation and curettage; however, her symptoms did not improve. On postpartum day 24, the patient was transferred to a higher center. Because of severe anemia (hemoglobin, 50.0 g/L), 3 blood transfusions and supportive treatment were administered; however, the therapeutic efficacy was poor. On postpartum day 45, the patient was transferred to our hospital.

2.2. Clinical findings

On physical examination, coffee-like secretions could be seen in the vagina, the cervix was smooth, and no bleeding was present in the cervical canal. An enlarged anteverted uterus, similar to that in a 3+ month pregnancy, with soft texture and smooth surface, no tenderness, and no palpable abnormalities in the bilateral appendages, was visible.

Ultrasonography revealed an $8.6 \times 5.7 \times 5.6$ cm heterogeneous mass located in the uterine cavity. The mass and myometrium did not have distinct boundaries. The blood β-human chorionic gonadotropin (HCG) level was 90,153.2 mIU/mL. The lung computed tomography (CT) revealed solid nodular shadows (around 8) in both lungs, with diameters ranging from 0.5 to 2.7 cm (Fig. 1A). It could not be determined whether the placenta was expelled from the patient after childbirth. Ultrasonography suggested a space-occupying lesion in the uterine cavity, and the possibility of placental implantation was considered. The lung CT suggested diffuse nodules in both lungs, and the blood β-HCG level was abnormally elevated. Therefore, postpartum choriocarcinoma could not be excluded. Pelvic magnetic resonance imaging was performed for further identification, which showed a significant enlargement of the corpus uteri ($7.0 \times 9.2 \times 12.6$ cm) (Fig. 2A). A $6.9 \times 4.1 \times 8.7$ cm space-occupying lesion could be seen in the uterine cavity, with irregular invasion of the myometrium, exceeding one-half of the myometrium. A significant invasion of the anterior uterine isthmus and significant thinning of the myometrium surrounding the lesion in the anterior uterine isthmus, with local perimetrium only, were noticed. Postpartum choriocarcinoma was suspected, and chemotherapy was proposed. At this stage, the patient's symptoms of headache and dizziness had exacerbated. Cranial CT revealed a 3.2×4.2 cm high-density mass shadow in the left frontal lobe, and the cerebral midline was slightly shifted to the left (Fig. 3A). The left lateral ventricle was compressed and appeared smaller.

2.3. Diagnostic focus and assessment

The above findings were combined with the patient's medical history and various examinations to confirm a diagnosis of postpartum choriocarcinoma with accompanying brain metastasis (IV: 16). Her risk score was 16; thus, she was an ultrahigh-risk patient.

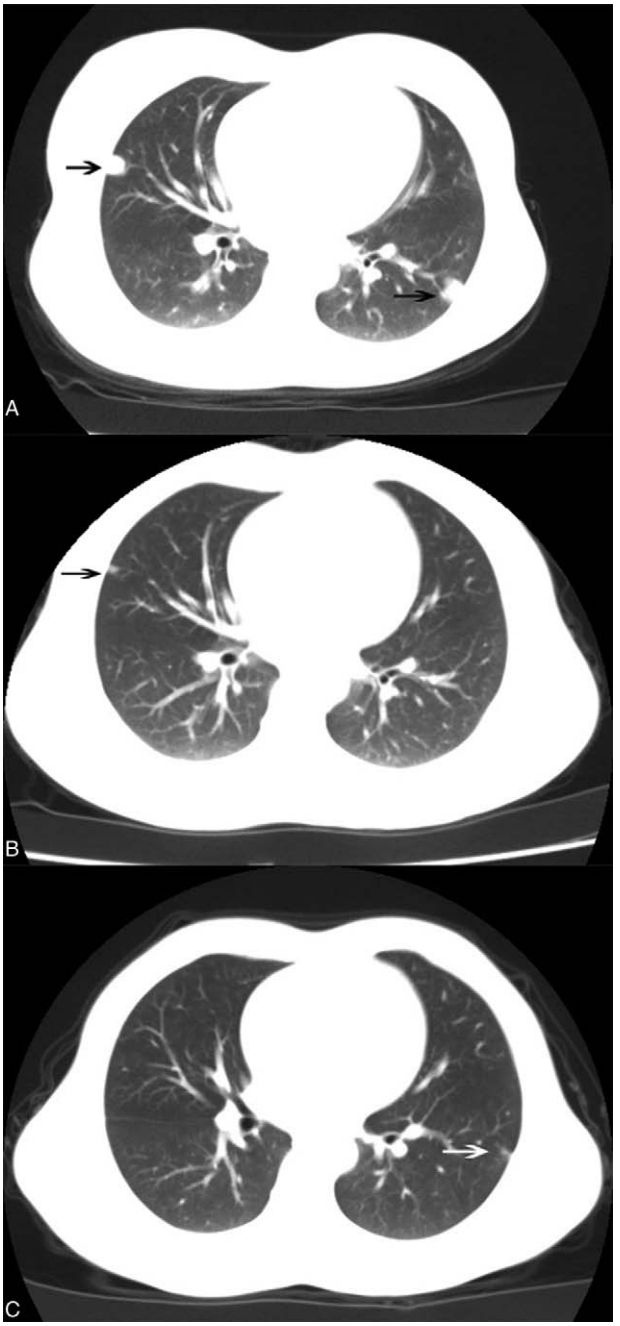

Figure 1. Comparison of pulmonary lesions. (A Lung computed tomography before chemotherapy. (B) Lung computed tomography 2 months after chemotherapy. (C) Lung computed tomography 8 months after chemotherapy.

2.4. Therapeutic focus and assessment

A multidrug chemotherapy regimen consisting of 5-fluorouracil (5-FU) and actinomycin D, along with intrathecal methotrexate (MTX) injection, was used. The patient's general condition was poor, and she was unable to tolerate full-dose chemotherapy. Full-dose chemotherapy would result in intracranial lesion necrosis in large areas. This could easily lead to increased intracranial pressure and induce brain herniation, which might be

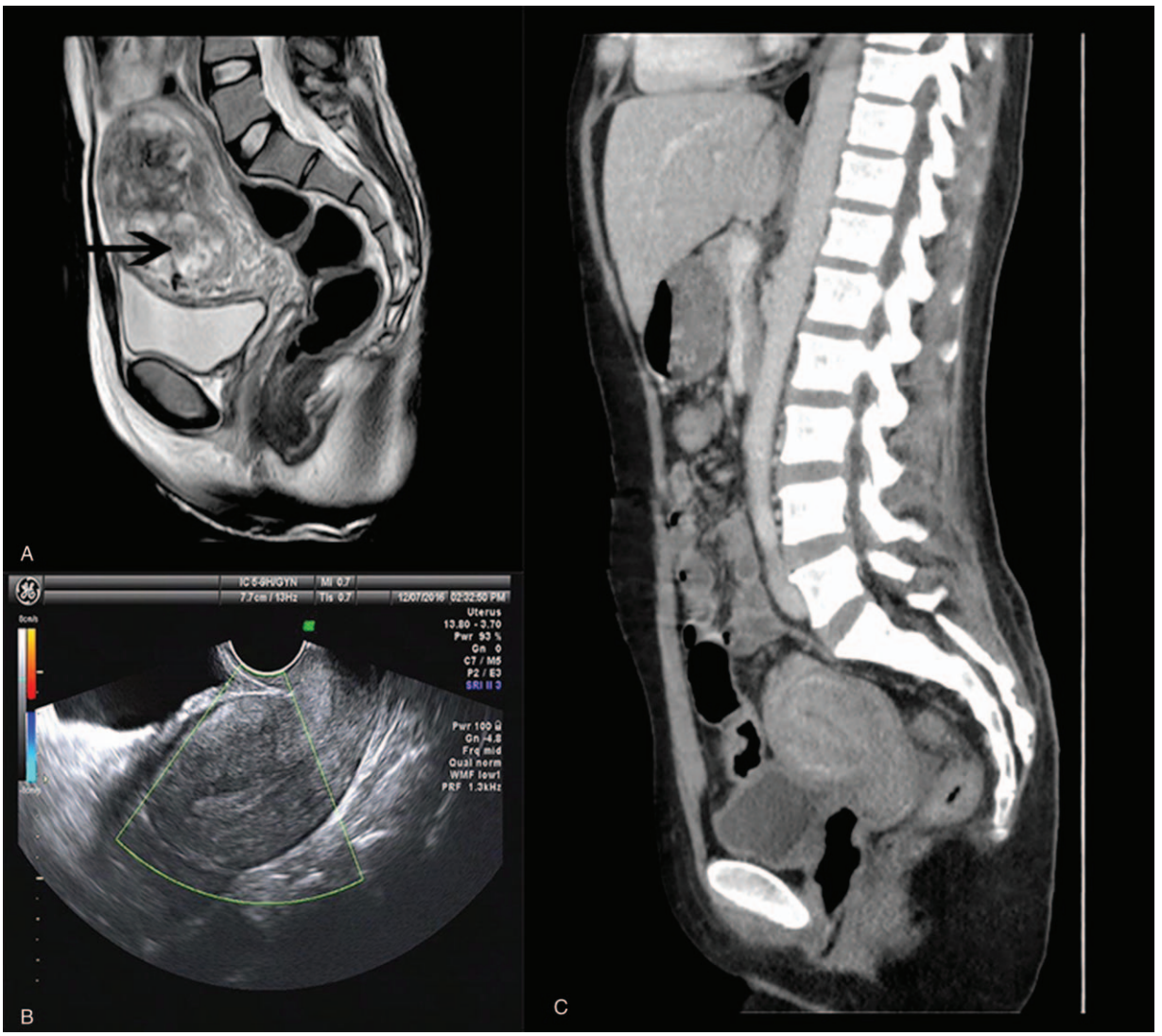

Figure 2. Comparison of uterine lesions. (A) Pelvic magnetic resonance imaging before chemotherapy. (B) Ultrasonography of the uterus after 3 cycles of chemotherapy. (C) Pelvic computed tomography after 3 cycles of chemotherapy.

fatal for the patient. To avoid this, the chemotherapy dose was reduced; this could be restored to normal dosage after the patient's condition improved. In August 2016, the patient was started on a chemotherapy regimen of 5-FU (20 mg/kg/day) and actinomycin D (4 μg/kg/day) for 8 days. During chemotherapy, intermittent intrathecal MTX (15 mg) was administered twice. After 1 cycle of chemotherapy, vaginal bleeding was reduced, and headache was alleviated. However, the patient still experienced I-II° nausea and vomiting and II° granulocytopenia. After 3 cycles of chemotherapy, the patient's β-HCG level decreased to <2 mIU/mL. After the administration of 4 intrathecal MTX injections, the β-HCG level in the cerebrospinal fluid was 8 mIU/mL. Follow-up ultrasonography revealed that the size of the uterus was 4.0 × 5.4 × 5.3 cm, and no abnormal space-occupying lesion was found in the uterine cavity (Fig. 2B). Follow-up CT revealed no clear abnormal enhancing lesions in the uterine cavity (Fig. 2C). Several small nodules (around 6) could be seen in both lungs, with the largest nodule having a diameter of 1.8 cm. Compared with the findings of the CT scan performed before chemotherapy, the space-occupying lesion in the uterine cavity had disappeared, and the number and volume of nodules in both lungs had reduced. Considering that the patient had stage IV postpartum choriocarcinoma and a risk score of 16, which indicates an ultra-high risk, and the intracranial lesions were large, 5-FU and actinomycin D maintenance chemotherapy was continued for 4 cycles. In addition, whole brain radiotherapy was administered. Subsequently, the patient attended a regular follow-up.

2.5. Follow-up and outcomes

Two months after chemotherapy, the patient's blood β-HCG level was <2 mIU/mL. Ultrasonography showed that the size of the uterus was 3.2 × 4.9 × 4.1 cm, and there was no space-occupying lesion in the uterus. CT scanning showed patchy low-density shadows and a small nodular shadow of size 0.8 × 0.7 cm in the left frontal lobe (Fig. 3B). Compared with the findings of the CT scan before chemotherapy, the size of the left frontal lobe lesion had significantly reduced. Several small nodular shadows (approximately 6) could be seen in the right lung, with the largest lesion

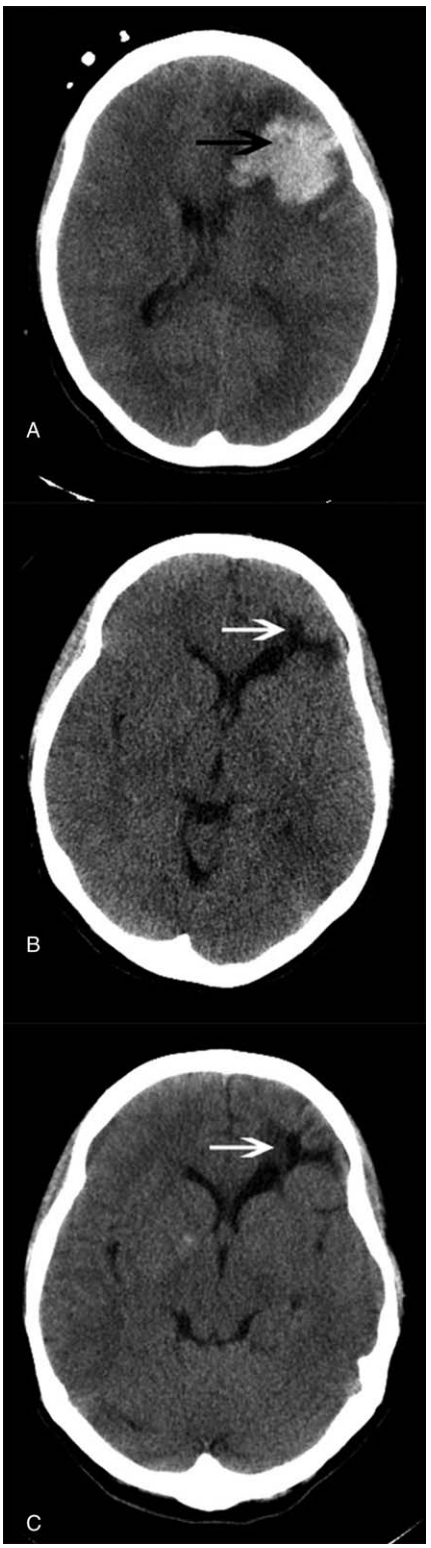

Figure 3. Comparison of cranial lesions. (A) Cranial computed tomography before chemotherapy. (B) Cranial computed tomography 2 months after chemotherapy. (C) Cranial computed tomography 8 months after chemotherapy.

having a size of 1.3×0.8 cm (Fig. 1B). Nodules in both lungs were significantly smaller than those after 3 cycles of chemotherapy.

Eight months after chemotherapy, the patient's blood β-HCG level was <2 mIU/mL, and CT scanning (Fig. 3C) showed patchy low-density shadows and a small nodular shadow of size 0.9×0.7 cm in the left frontal lobe. No significant changes were observed in comparison with the CT scan findings at 2 months after chemotherapy. Several small nodular shadows (approximately 6) could be seen in the right lung (Fig. 1C). Nodules in both lungs were significantly smaller than those at 2 months after chemotherapy.

At the time of writing this report, the patient had discontinued chemotherapy for 17 months, and her blood β-HCG level was <2 mIU/mL. Moreover, no tumor recurrence or adverse events had been observed.

3. Discussion

Choriocarcinoma is a highly malignant epithelial tumor, which can develop from any gestational trophoblastic tissue resulting from a hydatidiform mole, miscarriage, and ectopic pregnancy, but it is rarely seen after a normal, full-term pregnancy.[10,11] Routine β-HCG monitoring is usually not recommended after a normal and full-term pregnancy. Postpartum choriocarcinoma is usually diagnosed based on symptoms due to metastatic lesions, such as abnormal vaginal bleeding; abdominal, pulmonary, and cerebral hemorrhage; coughing; hemoptysis; and hemiplegia.[3] Our patient was diagnosed based on the symptoms due to lung and brain metastases, thereby resulting in timely treatment.

It is difficult to detect choriocarcinomas during pregnancy without a histopathological examination of the placenta. Postpartum choriocarcinomas are extremely rare, and obstetricians do not usually conduct routine histopathological examinations of the placenta after childbirth, which may delay the diagnosis of postpartum choriocarcinoma. During postpartum placental examinations, if white nodular tissues accompanied with infarction in the surrounding regions are found, the physician should suspect the possibility of choriocarcinoma.[12] After normal childbirth, if the β-HCG level does not decrease within 1 month and the retained placenta is expelled so that there is no residual tissue in the uterine cavity, the possibility of choriocarcinoma should be considered.[13,14]

Delayed diagnosis of postpartum choriocarcinoma may increase the risk of metastasis and monochemotherapy resistance, thus affecting its prognosis.[15] The high-risk factors for poor prognosis of postpartum choriocarcinoma after term pregnancy accompanied with metastasis are a lesion > 5.0 cm in size, a β-HCG level > 30,000 IU/mL before treatment, changes in maternal immune responses, and delayed diagnosis (> 6 months).[16,17] The patient described in this report had an intrauterine lesion that was 8.0 cm in size, accompanied with brain metastasis, and a β-HCG level of 90,153.2 mIU/mL. Although she was an ultrahigh-risk patient, due to timely diagnosis and treatment using a multidrug chemotherapy regimen, a good prognosis was obtained.

The mainstay treatment for GTN is chemotherapy, and the appropriate regimen is determined via staging and grading. Low-risk patients (stages I, II, and III and a risk score ≤ 6) are treated with MTX or actinomycin D monochemotherapy. After the β-HCG levels have returned to normal, consolidation chemotherapy is continued for 2 to 3 cycles to decrease the risk of recurrence. Complete response rates are close to 100%.[2,3] Multidrug combined chemotherapy regimens are used to treat high-risk patients (stages II, III, and IV with a risk score > 6). The most common regimen is etoposide, MTX/leucovorin, and actinomycin D, followed a week later by cyclophosphamide and vincristine (Oncovin) (EMA-CO); the complete response rate is 85%, and the 5-year overall survival rate is 75% to 90%.[17] Patients with comorbid liver and/or brain metastases have poorer prognosis.[18–20] High-risk patients should undergo 4 cycles of consolidation chemotherapy. Ultrahigh-risk

patients (high-risk subgroup with a risk score ≥ 12 or patients with comorbid liver, brain, or widespread metastasis) show poor responses to the first-line combination chemotherapy.[21] Ultra-high-risk patients with a comorbid serious disease may develop severe myelosuppression when standard chemotherapy is administered. This may result in bleeding, sepsis, or even multiorgan failure, which could be avoided by using a low-dose regimen with a reduced frequency protocol for 1 to 3 chemotherapy cycles. After the patient's condition has stabilized, a routine chemotherapy dose can be administered.[22] When the EMA-CO regimen is administered to patients with brain metastasis, increasing the dose of MTX to 1.0 g/m^2 can aid in penetration of the blood brain barrier by the drug.[17] While using CO, 12.5 mg of MTX can be administered through intrathecal injections. At certain centers, the practice of simultaneous administration of whole brain radiotherapy (total dose, 3000 cGy) or stereotactic radiotherapy and chemotherapy is followed. However, it is still debatable whether radiotherapy is more effective than intrathecal MTX injection.[19,23] It has been reported that the cure rate for GTN with brain metastasis is 50% to 80%. This is determined by the symptoms and quantity, size, and location of brain metastasis in patients.[20,24–27] According to our center's data on previous cases of GTN with brain metastasis, increasing the MTX dose to 1.0 g/m^2 results in unbearable side effects in patients. Patients who are administered low-dose 5-FU and actinomycin D chemotherapy with intermittent intrathecal MTX (15 mg) injection (2–3 times per cycle) until β-HCG is absent in the cerebrospinal fluid, with or without radiotherapy based on the efficacy of chemotherapy, have a remission rate of 75% (6/8). These patients experience less side effects and can tolerate chemotherapy. However, the total number of cases for this treatment regimen is small, and there is no comparative study using the EMA-CO regimen, so more case data are needed to prove its effectiveness. The patient in this report received this chemotherapy and showed a good prognosis, with no relapse at the 17-month follow-up.

An accurate diagnosis of postpartum choriocarcinoma at an early stage can significantly improve its prognosis. Although the incidence of postpartum choriocarcinoma is extremely low, a regular monitoring is necessary. Careful postpartum placental examination, histopathological examination in patients with abnormalities, and blood β-HCG monitoring in high-risk pregnant women can aid in the early diagnosis of postpartum choriocarcinoma and improvement in the prognosis. A stratified treatment should be administered according to the International Federation of Gynecology and Obstetrics staging and the World Health Organization prognostic scoring systems. Furthermore, blood β-HCG is a sensitive marker for evaluating therapeutic efficacy and follow-up after remission of postpartum choriocarcinoma.

Author contributions

Investigation: Qingli Li, Rutie Yin, Danqing Wang.
Resources: Qingli Li, Rutie Yin, Danqing Wang.
Supervision: Qingli Li, Rutie Yin, Danqing Wang.
Writing – original draft: Liang Song.
Writing – review & editing: Liang Song, Danqing Wang.

References

[1] Hancock BW, Nazir K, Everard JE. Persistent gestational trophoblastic neoplasia after partial hydatidiform mole incidence and outcome. J Reprod Med 2006;51:764–6.
[2] Seckl MJ, Sebire NJ, Berkowitz RS. Gestational trophoblastic disease. Lancet 2010;376:717–29.
[3] Lurain JR. Gestational trophoblastic disease I: epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole. Am J Obstet Gynecol 2010;203:531–9.
[4] Martin BH, Kim JH. Changes in gestational trophoblastic tumors over four decades. A Korean experience. J Reprod Med 1998;43:60–8.
[5] Steigrad SJ. Epidemiology of gestational trophoblastic diseases. Best Pract Res Clin Obstet Gynaecol 2003;17:837–47.
[6] Loukovaara M, Pukkala E, Lehtovirta P, et al. Epidemiology of hydatidiform mole in Finland, 1975 to 2001. Eur J Gynaecol Oncol 2005;26:207–8.
[7] Lybol C, Thomas CM, Bulten J, et al. Increase in the incidence of gestational trophoblastic disease in The Netherlands. Gynecol Oncol 2011;121:334–8.
[8] Ganapathi KA, Paczos T, George MD, et al. Incidental finding of placental choriocarcinoma after an uncomplicated term pregnancy: a case report with review of the literature. Int J Gynecol Pathol 2010;29:476–8.
[9] Ghaemmaghami F, Karimi Zarchi M. Early onset of metastatic gestational trophoblastic disease after full-term pregnancy. Int J Biomed Sci 2008;4:74–7.
[10] Seckl MJ, Fisher RA, Salerno G, et al. Choriocarcinoma and partial hydatidiform moles. Lancet 2000;356:36–9.
[11] Berkowitz RS, Goldstein DP. Chorionic tumors. N Engl J Med 1996;335:1740–8.
[12] Soper JT, Mutch DG, Schink JC. American College of Obstetricians and Gynecologists. Diagnosis and treatment of gestational trophoblastic disease: ACOG Practice Bulletin No. 53. Gynecol Oncol 2004; 93:575–85.
[13] Berkowitz RS, Goldstein OP. Berek IS, Hacker NF. Gestational trophoblastic neoplasia. Practical Gynecologic Oncology 4th ed. Lippincott Williams & Wilkins, Philadelphia, PA:2005;603–25.
[14] Miller JMJr, Surwith EA, Hammond CB. Choriocarcinoma following term pregnancy. Obstet Gynecol 1979;53:207–12.
[15] Lage JM. Gompel C, Silverberg SG. The placenta. Pathology in Obstetrics and Gynecology 4th ed.Lippincott Williams & Wilkins, Philadelphia, PA:1994;448.
[16] Niemann I, Petersen LK, Hansen ES, et al. Predictors of low risk of persistent trophoblastic disease in molar pregnancies. Obstet Gynecol 2006;107:1006–11.
[17] FIGO Oncology CommitteeFIGO CANCER REPORT 2015: update on the diagnosis and management of gestational trophoblastic disease. Int J Gynaecol Obstet 2015;131:s123–6.
[18] Ahamed E, Short D, North B, et al. Survival of women with gestational trophoblastic neoplasia and liver metastases: is it improving? J Reprod Med 2012;57:262–9.
[19] Neubauer NL, Latif N, Kalakota K, et al. Brain metastasis in gestational trophoblastic neoplasia: an update. J Reprod Med 2012;57:288–92.
[20] Newlands ES, Holden L, Seckl MJ, et al. Management of brain metastases in patients with high-risk gestational trophoblastic tumors. J Reprod Med 2002;47:465–71.
[21] Crawford RA, Newlands E, Rustin GJ, et al. Gestational trophoblastic disease with liver metastases: the Charing Cross experience. Br J Obstet Gynaecol 1997;104:105–9.
[22] Alifrangis C, Agarwal R, Short D, et al. EMA/CO for high-risk gestational trophoblastic neoplasia: good outcomes with induction low-dose etoposide-cisplatin and genetic analysis. J Clin Oncol 2013;31:280–6.
[23] Piura E, Piura B. Brain metastases from gestational trophoblastic neoplasia: review of pertinent literature. Eur J Gynaecol Oncol 2014;35:359–67.
[24] Evans ACJr, Soper JT, Clarke-Pearson DL, et al. Gestational trophoblastic disease metastatic to the central nervous system. Gynecol Oncol 1995;59:226–30.
[25] Small WJr, Lurain JR, Shetty RM, et al. Gestational trophoblastic disease metastatic tothe brain. Radiology 1996;200:277–80.
[26] Rustin GJ, Newlands ES, Begent RH, et al. Weekly alternating etoposide, methotrexate and actinomycin D/vincristine and cyclophosphamide chemotherapy for treatment of CNS metastases of choriocarcinoma. J Clin Oncol 1989;7:900–4.
[27] Bakri Y, Berkowitz RS, Goldstein DP, et al. Brain metastases in gestational trophoblastic tumor. J Reprod Med 1994;39:179–84.