Case Report

Term Delivery Choriocarcinoma Patient with Brain and Lung Metastases Successfully Treated by Etoposide, Methotrexate, Actomyacin D, Cyclophosphamide and Vincristine (EMA-CO) Chemotherapy

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It is well known that antecedent term delivery and metastasis to sites other than the lungs and vagina are high risk factors for patients with gestational trophoblastic neoplasia. Here we report on a patient with choriocarcinoma who presented with brain and lung metastases after term delivery and was treated by EMA-CO chemotherapy. A 31-year-old woman delivered a healthy infant at term. Frequent episodes of hemoptysis occurred beginning 3 weeks after the delivery. On admission to our hospital, she had lesions in the uterus, lungs and brain as well as motor aphasia and hemiplagia. The pretreatment β-hCG level was 21,000 ng/ml and the WHO score was 16 (high-risk group). The EMA-CO regimen was administrated as first-line chemotherapy and the patient achieved complete remission after 7 courses. Treatment was terminated after 11 courses and maintained with etoposide (25 mg/day) for 6 months. The patient has remained in complete remission for more than 16 years without other adjuvant therapies. We believe that EMA-CO can currently be considered the regimen of first choice for most high-risk patients with gestational trophoblastic neoplasia in view of its effectiveness and excellent tolerability.

Key words: choriocarcinoma, term delivery, EMA-CO chemotherapy, metastasis

Recently, gestational trophoblastic neoplasia has become the most curable of gynecological malignancies for several reasons. DiSaia and Cresman [1] summarized these reasons as follows: 1) a sensitive marker is produced by the tumor i.e., human chorionic gonadotropin (hCG), and the amount of hormone produced is directly related to the number of viable tumor cells; 2) this tumor is extremely sensitive to various chemotherapy agents; 3) risk factors for recurrence are known, allowing treatment to be individualized; and 4) the aggressive use of multiple treatment modalities, such as single- and multiple-agent chemotherapy regimens, radiation, and surgery.

Nevertheless, the failure rate among “high-risk” patients is still too high despite the use of aggressive multi-drug regimens [2-4]. These patients usually have
multiple metastases (including brain and liver), high hCG levels, and term delivery.

Here, we report a case of choriocarcinoma presenting after term delivery with more than 16 years of survival in complete remission. The patient initially had lung and brain metastases with motor aphasia and hemiplegia, and was treated by etoposide, methotrexate, actomycin D, cyclophosphamide and vincristine (EMA-CO) regimen.

Case Report

A 31-year-old woman (gravida 3, para 2) who had no history of chorionic disease delivered a 3,265 g male infant on August 8, 1988. The placenta was macroscopically normal. The patient continued to have daily slight vaginal bleeding after delivery and frequently episodes of hemoptysis which began at the end of August. A physician detected coin lesions in both lungs by radiographic examination. She had generalized convulsions on September 30. A computed tomographic (CT) scan of the brain revealed a lesion in the left frontal lobe; motor aphasia subsequently developed. Further examination revealed that the urinary hCG level was over 300,000 IU/l and the serum hCG level was 497,000 IU/l. The patient was referred to the Okayama University Hospital for further examination and treatment.

On admission, physical examination revealed right hemiplegia, motor aphasia, and genital bleeding, and the uterus was the size of a 10-week pregnancy. The pretreatment serum hCG level was 866,000 IU/l, the serum \( \beta \)-hCG level was 21,000 IU/l, and the urinary hCG level was 512,000 IU/l. Ultrasonographic examination detected an intrauterine mass of 6 cm in diameter (Fig. 1). A chest X-ray (Fig. 2A) and thoracic CT scan detected scattered metastatic lesions in the bilateral lungs, and the brain CT examination revealed a large metastasis in the left frontal lobe (Fig. 2B). According to the modification of Bagshawe’s scoring system by the World Health Organization (WHO) the patient scored 16, placing her in the high risk group \((\geq 8)\) and the FIGO stage was IVa. Therefore, the EMA-CO regimen of Bagshawe (Table 1) \([5]\) was used as first-line chemotherapy for this patient.

With the first course of treatment, the patient suffered nausea, vomiting, and myelosupression. However, few
Table 1  EMA-CO Regimen

<table>
<thead>
<tr>
<th>Course 1 (EMA)</th>
<th>Day 1</th>
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<tbody>
<tr>
<td>Etoposide: 100 mg/m², i.v. infusion in 200 ml of saline over 30 min</td>
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</tr>
<tr>
<td>Actinomycin D: 0.5 mg, i.v. push</td>
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</tr>
<tr>
<td>Methotrexate: 100 mg/m², i.v. push followed by a 200 mg/m², i.v. infusion over 12 h</td>
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<table>
<thead>
<tr>
<th>Day 2</th>
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</thead>
<tbody>
<tr>
<td>Etoposide: 100 mg/m², i.v. infusion in 200 ml of saline over 30 min</td>
</tr>
<tr>
<td>Actinomycin D: 0.5 mg, i.v. push</td>
</tr>
<tr>
<td>Folic acid: 15 mg, i.m. or orally every 12 h for 4 days beginning 24 h after start</td>
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<table>
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<tr>
<th>Course 2 (CO)</th>
<th>Day 8</th>
</tr>
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<tr>
<td>Vincristine: 1.0 mg/m², i.v. push</td>
<td></td>
</tr>
<tr>
<td>Cytoxan: 600 mg/m², i.v. in saline</td>
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</table>

This regimen consists of 2 courses: 1) course 1 is given on days 1 and 2, 2) course 2 is given on day 8. These courses can usually be given on day 1 and 2, 8, 15 and 16, 22 etc., and the intervals should not be extended without course.

side effects were noted after the first course and the tumors rapidly became smaller. Approximately 4 months after commencing chemotherapy, the patient achieved complete remission, as determined by 3 negative weekly β-hCG assays. At this time, she had received 7 courses of EMA-CO chemotherapy. Five consolidation courses were performed after complete remission and treatment was terminated after a total 11 courses (6 months after presentation). The chest X-ray and brain CT scan obtained after 10 courses are shown in Fig. 3. After 11 courses of EMA-CO chemotherapy, the patient was maintained with etoposide (25 mg/day) for 6 months. The patient has now been in complete remission for more than 16 years.

**Discussion**

Choriocarcinoma is one of the most rapidly invasive and widely metastasizing malignancies, and its incidence is 1 per 150,000–160,000 normal pregnancies. The prognosis for patients with metastatic choriocarcinoma following term gestation is generally poor [3]. The more extensive spread of disease and the decreased responsiveness to chemotherapy following term gestation are postulated to be due to a change in the host immune response and/or a delayed diagnosis. Although vaginal bleeding is the most common presenting symptom of this carcinoma, it can occur at any time during pregnancy and the puerperium for a variety of reasons. Thus, the disease is generally widely disseminated at the time of diagnosis, and there is with a large tumor volume and a markedly elevated hCG titer.

There are several factors that adversely influence the response to treatment in patients with metastatic choriocarcinoma. Lurain et al. [3] proposed the following 6
prognostic factors from a literature review: 1) a
clinicopathological diagnosis of choriocarcinoma; 2) more
than 4 months from the antecedent pregnancy to treat-
ment; 3) a pretreatment hCG titer > 100,000 IU/L; 4)
metastasis to sites other than the lungs and vagina; 5)
antecedent term gestation; and 6) previous failed therapy.
It has also been reported that patients with metastatic
high-risk gestational trophoblastic disease following term
pregnancy have a 50.0% remission rate (11/22) compared
to a 75.0% remission rate (18/24) for women with
metastatic choriocarcinoma following other types of preg-
nancy [3].

The number of high-risk factors present had a very
significant effect on the response to treatment. If there
were only 1 or 2 of the high-risk factors outlined above,
the survival rate was 74%, in contrast to only 27% for
patients with 3 or 4 factors [3]. The patient in this case
had 3 high-risk factors and thus presented a very high-risk
case, but she has survived for more than 16 years in
complete remission.

Several multi-drug chemotherapy schedules have been
reported, including MAC (methotrexate, actinomycin D,
and cyclophosphamide), CHAMOCA, and EMA-CO
[5]. The cure rate achieved with the MAC regimen was
reported to be 51% for primary treatment and 30% for
secondary treatment [3]. The CHAMOCA regimen was
reported to produce complete clinical remission in patients
who were resistant to MAC therapy, but it is a highly
toxic protocol. Bolis et al. [6] reported that the overall
response rate of EMA-CO was 86% with 81% of
subjects surviving a median observation time of 32
months, while the survival rate of high-risk patients was
88% with 76% having no evidence of disease. In addi-
tion, they reported that the remission rate for second-line
treatment by the EMA-CO regimen was 64%, which is
higher than the rates achieved using other regimens such
as MAC or CHAMOCA.

The toxicity of EMA-CO regimen is acceptable and
less than that of the CHAMOCA or MAC regimens.
Our patient was treated with only EMA-CO therapy and
maintenance etoposide. Etoposide shows promise not
only as first-line therapy, but also in treating patients who
have become resistant to conventional therapy [1].
Recently, it was reported that taxanes have also been
effective with relapsed high-risk trophoblastic disease [7,
8].

In gestational trophoblastic disease, it is necessary to
continue treatment even after a negative hCG titer is
achieved. As is well known, a minimum of 10⁴ viable
tumor cells are necessary to produce a detectable β-hCG
titer, so most authors advocate at least three consolida-
tion courses. Moreover, relapse sometimes occurs after
several years of complete remission. The likelihood of
relapse depends on individual risk factors; however, the
overall relapse rate for EMA-CO therapy was reported to
be 11% by Newland et al. [4] and 19.0% by Bolis et al.
[6].

Accordingly, adjuvant therapy is given to most high-
risk patients. Cerebral metastasis may be treated simulta-
neously with whole-brain irradiation of 30 to 40 Gy, while
hysterectomy and thoracotomy are used for the excision of
resistant tumor foci [1, 3].

It is well known that secondary chemotherapy yields
poor results in patients with gestational trophoblastic
disease [3], so it is very important to choose the most
effective regimen for treating high risk metastatic chori-
carcinoma from the start. We believe that currently the
EMA-CO regimen should be considered the first-line for
most high-risk patients with gestational trophoblastic
disease in view of the good response rate it has achieved
and its excellent tolerability.

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