Central nervous system involvement in gestational trophoblastic neoplasia

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Summary

Objective: To evaluate characteristics of patients with central nervous system (CNS) lesions of gestational trophoblastic disease and determine prognostic and therapeutic implications applicable to management.

Methods: Nine patients among 56 cases of malignant gestational trophoblastic neoplasia (GTN) were analyzed prospectively in a single institution between the years 1990 and 1997 with at least two years of follow-up. Brain metastases were documented by physical exam and computed tomography scan or magnetic resonance imaging. In terms of therapy, all of the patients received an etoposide, methotraxate, actinomycin, cyclosphamide and vincristine (EMA-CO) regimen for 5 to 9 courses. To prevent unexpected intracranial hemorrhage, all patients received radiation therapy. No intrathecal chemotherapy was given. Remission was defined as three weekly beta-hCG levels below assay sensitivity (<5 mIU/ml).

Results: The mean age of the patients at diagnosis was 29.6 years. While two of the patients initially presented with symptoms related to cranial involvement, five were diagnosed during routine investigation for metastasis in malignant GTD and the remaining two developed cerebral metastases during the therapy. Besides central nervous system involvement, six had additional lung, two had hepatic and splenic and one had pelvic metastases. Overall survival was 66.6%. Two patients had a fulminant clinical course and were lost one month after initial diagnosis.

Conclusion: Early diagnosis via computed tomography of the head and beta-hCG serum testing along with aggressive, multiagent intervention (EMA-CO) have greatly improved patient prognosis of this once highly fatal condition.

Key words: Brain metastases; Trophoblast; Chemotherapy; Intracranial hemorrhage; Choriocarcinoma.

Introduction

Metastatic gestational trophoblastic neoplasia is a relatively rare disease of the placenta. The reported incidence is approximately between 1/20,000 and 1/50,000 of pregnancies and 1%-3% of hydatiform moles [1]. The incidence of central nervous system (CNS) metastasis from gestational trophoblastic neoplasia is less than 10%. Although more than 90% of patients with metastatic gestational trophoblastic disease survive when appropriate therapy is given, survival rates in patients who develop brain metastases is less than 50% [2]. CNS metastasis is regarded as a poor prognostic sign [2, 3].

Although intensive chemotherapy regimens such as EMA-CO were developed to improve the results of this poor prognostic group of patients, the leading cause of mortality is still sudden unexpected fatal intracerebral haemorrhage or cerebral edema [4].

In this paper, we present our results based on the management of nine patients with CNS metastases from gestational trophoblastic neoplasia treated between 1990-1997 in the Gynecological Oncology Unit, Balcalı Hospital, Adana, Turkey.

Materials and Methods

Nine patients with CNS metastases among 75 cases of metastatic gestational trophoblastic neoplasia were analysed prospectively in a single institution after at least two years of follow-up. In our clinic, all of the patients with rising or plateauing HCG levels after evacuation of a hydatiform mole underwent a metastatic work-up. Brain metastases were documented by physical exam and computed tomography scan or magnetic resonance imaging.

All patients underwent whole brain irradiation (a total dose of 2000-3000 cGy in 8-12 fractions) to prevent unexpected intracranial hemorrhage immediately after the diagnosis. All patients except one received EMA-CO chemotherapy. One patient was treated with MAC chemotherapy. No intracranial chemotherapy was given.

Response to therapy was monitored by plasma hCG measurements at weekly intervals. Patients received three or more courses of EMA-CO after the first normal hCG levels were measured. Complete remission was considered after three consecutive weekly hCG levels were within normal range.

The following data were analysed: age, antecedent pregnancy, duration of disease, metastatic sites, number of chemotherapy courses, length of follow-up and survival.

Results

Seventy-five patients with metastatic gestational trophoblastic neoplasia were treated between the years 1990 and 1997. Nine of these cases (12%) had vaginal metastases. Ages of patients ranged between 18 and 52 and the mean age was 29.6. The antecedent pregnancies were hydatiform mole, term pregnancy and abortion in five, two and two, respectively. The intervals between antecedent pregnancies and the times of beginning of chemotherapy ranged between 2 and 24 months. Pre-

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Table 1. — *Patient characteristics and outcome.*

No	Age	Pregnancy	Antecedent pregnancy	Site of CNS metastases	Other metastases	CNS symptoms	Follow-up (months)	Interval antecedent pregnancy and treatment (months)	Cranio-tomy	No. of courses	Results
1	32	9	Term	Parietal	Lung, liver, spleen, vagina	Headache nausea vomiting	48	24	No	5	Alive
2	38	1	Mole	Temporal	No	Headache	26	4	No	11	Alive
3	28	2	Mole	Multifocal	Lung, liver, spleen	Nausea headache	74 (4)	13	No	19 (4)	Died (cerebral odema)
4	26	4	Mole	Parietal	Lung	–	30	3	No	6	Alive
5	19	2	Mole	Frontal	Lung	–	35	4	No	8	Alive
6	20	5	Term pregnancy	Multifocal	Lung	Severe headache nausea	29	2	No	1	Died (intracranial hemorrhage)
7	33	2	Mole	Multifocal	Lung	–	56	6	No	7	Alive
8	18	1	Abortion	Multifocal	?	Increased intracranial pressure	1	5	No	1	Died (intracranial hemorrhage)
9	52	3	Abortion	Frontal	No	Hemiparesia	25	18	Yes	6	Alive

treatment serum hCG levels ranged between 12,000-240,000 mIU/ml. Three of the patients were asymptomatic. Severe headache associated with nausea and vomiting was the most common symptom. Table 1 shows patient characteristics and outcome.

The sites of involvement were the parietal lobe in two, temporal lobe in one, frontal lobe in two and multifocal in four patients. Three of four patients with multifocal lesions were lost to follow-up.

Five patients underwent routine metastatic works-up because of rising or plateauing hCG levels during follow-up after evacuation of a hydatiform mole. Patients 6 and 9 presented initially with symptoms related to cranial involvement. Patient 9 presented initially with hemiparesis and underwent craniotomy because of a solitary lesion detected by CT. Her last pregnancy was aborted 18 months before. The histologic diagnosis was choriocarcinoma. Patient 3 presented initially with a metastatic lesion of the mandibula. This interesting case had a hydatiform mole 16 months before admission and she got pregnant within four months after evacuation of the hydatiform mole. She delivered three months before her second admission. She was treated with MAC chemotherapy. She was in complete remission for about four years. Then she had headache and nausea. CT scanning detected multiple brain metastases and her plasma hCG level was 12,000 mIU/ml. She received an additional 4 cycles of EMA-CO chemotherapy. hCG levels diminished, but she died four months later due to cerebral herniation.

Two patients had a fulminant clinical course and were lost in the month of initial diagnosis. The remaining six patients have been off treatment for periods ranging from 25 to 48 months. The median follow-up for survivors was 36.6 months (range 1-56 months) and overall survival was 66.6%.

Discussion

Although recent developments in chemotherapy have resulted in an improved prognosis for most patients with gestational trophoblastic neoplasia, the same improvement was not seen in the patients with brain metastases [5]. There are still some arguments about intrathecal chemotherapy and whole brain irradiation. In 1983, Athanassiou *et al.* showed that more than 50% of patients with brain metastases were cured without radiotherapy. Overall survival rate in 1999 is still similar to Athanassiou's study [2]. We believe that whole brain irradiation can prevent sudden death due to intracranial hemorrhage. We also believe that systemic chemotherapy with radiotherapy is a highly effective regimen for brain metastases and intrathechal chemotherapy is unnecessary. Our overall survival rate (66.6%) supports this concept.

Brain metastases of gestational trophoblastic neoplasia have been known to cause sudden death due to intracranial hemorrhage, edema and associated herniation before the completion of chemotherapy. In our patients, the most common cause of death was the CNS disease itself, either by gradually increasing intracranial pressure (2 cases) or by intracranial hemorrhage (one case).

All of the patients who died had multifocal lesions. As a result multifocal lesions in the brain must be considered as a fatal prognostic sign.

Patient 3 was a very interesting case [6]. After she had remained free of the disease for four years, gestational trophoblastic neoplasia recurred as multifocal brain metastases. hCG levels were not too high. Consequently patients with poor prognostic gestational trophoblastic neoplasia must be followed for a longer period.

The use of surgery plays a minor role in the treatment of brain metastases. Excision of a solitary lesion resistant to chemotherapy might be useful. In our cases, craniotomy was performed on one patient for diagnosis.

One patient who developed brain metastases after prior chemotherapy died. If two patients who died just after the diagnosis were excluded from the study all of our patients treated with whole brain irradiation and primary EMA-CO chemotherapy would be in complete remission. Although some authors suggest that the use of intrathecal chemotherapy with systemic chemotherapy has resulted in improved control compared with CT alone, we think that intrathecal chemotherapy does not have an important place in the treatment of brain metastases [2, 7]. Early diagnosis via computed tomography of the head and beta-hCG serum testing with aggressive, multiagent intervention and whole brain irradiation can improve patient prognosis of this once highly fatal condition.

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