Intraplacental choriocarcinoma metastasizing to the maternal lung

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Summary

Background: Although normal pregnancy is the precursor of 25% of cases of maternal choriocarcinoma, intraplacental choriocarcinoma in an otherwise normal placenta associated with viable pregnancy has rarely been reported.

Case: Examination of the placenta after delivery of a pale and small-for-date infant at term revealed intraplacental choriocarcinoma. There was no evidence of metastatic disease in the mother or child, but the mother exhibited postpartum rising levels of beta-HCG. The mother refused chemotherapy and disappeared from follow-up. Nine months later, she presented with metastatic choriocarcinoma of the lung. Eleven courses of the multi-drug EMA CO regimen effected a decrease of beta-HCG to normal and disappearance of lung metastases. To date, 28 months after the end of chemotherapy, the patient is alive and without evidence of gestational trophoblastic disease. Moreover, since then she has given birth to an additional two children.

Conclusions: This case is an example of natural disease progression of intraplacental choriocarcinoma metastasizing to the mother. Furthermore, it supports common knowledge that the multi-drug EMA CO regimen is effective treatment in poor prognosis metastatic choriocarcinoma.

Key words: Placenta; Choriocarcinoma; Trophoblast; Chemotherapy; EMA CO regimen.

Introduction

The prevailing opinion regarding the origin of gestational choriocarcinoma was that choriocarcinoma arises as a sequel to pregnancy, rather than having its origin within the placenta during the course of the pregnancy. It was therefore believed that maternal choriocarcinoma following term pregnancy arises from malignant transformation occurring after delivery in retained trophoblastic tissue such as residual adherent placenta and focal placenta accreta, or retained intravascularly growing trohphoblasts at the placental site [1]. This view has in recent years been challenged by the finding of intraplacental choriocarcinoma, suggesting that maternal choriocarcinoma following pregnancy may originate from malignant transformation of trophoblastic cells occurring within the placenta during the course of the pregnancy [1, 2]. We report a case of intraplacental choriocarcinoma metastasizing to the maternal lung and review the pertinent literature.

Case Report

A 24-year-old Arab Bedouin woman, gravida 4, para 3, who previously had had three spontaneous vaginal deliveries of healthy infants at term, delivered vaginally in November 2001, at 39 weeks' gestation, a pale and small-for-date female infant weighing 2,215 g. Apgar score at 1 and 5 minutes was 9 and 10, respectively. Laboratory tests confirmed neonatal anemia with a hemoglobin concentration of 6.0 g/dl and hematocrit of 24%; however, there was no evidence of hemolysis. The possibility that the neonatal anemia resulted from fetomaternal hemorrhage was entertained, but the Kleihauer-Betke test for the detection of fetal erythrocytes in the maternal blood was negative. Nevertheless, because of the intrauterine growth retardation and neonatal anemia, the placenta was subjected to a through pathological examination.

On gross examination, the placenta weighed 740 g, measured 19 x 16 x 3 cm and had a centrally inserted umbilical cord (length, 12 cm; diameter, 1 cm) containing three blood vessels. The fetal surface was smooth and with some fibrin deposits. On the maternal surface, there was an isolated red to greyish-yellow area measuring 2.5 cm in its largest diameter which was interpreted as a "placental infarct". Sectioning of the placenta revealed solid pale and pinkish tissue. Microscopic examination demonstrated mature placenta compatible with third-trimester gestation. The chronic villi exhibited a moderate degree of vascularization. The isolated area on the maternal surface, which was interpreted on macroscopic examination as a "placental infarct", showed prominent biphasic trophoblastic proliferation (syncytiotrophoblast and cytotrophoblast) with marked cellular atypia, mitotic figures and invasion into the surrounding chorionic villi, but not into the blood vessels (Figure 1). Adjacent to the biphasic trophoblastic proliferation there was an area with tumor necrosis, fibrin deposition and hemorrhage. The trophoblastic cells stained positively for beta-HCG and HPL. These histologic findings were compatible with the diagnosis of intraplacental choriocarcinoma.

The infant's anemia was resolved by blood transfusions. Physical examination and whole body computed tomography (CT) scanning of the mother as well as physical and ultrasound examination of the infant did not disclose metastatic disease. The serum beta-HCG level of the infant was < 10 mIU/ml and the mother and baby were discharged home. The mother was instructed to be followed-up with serial serum beta-HCC exam-

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inations and to avoid pregnancy for one year. However, the patient and her husband declined the usage of any contraceptive method. During the next three, five, six and seven postpartum weeks, the patient's serum beta-HCG level increased to 619 mIU/ml, 1,941 mIU/ml, 2,972 mIU/ml and 8,342 mIU/ml, respectively. Despite failure of ultrasound examination to demonstrate a pregnancy, the patient and her husband refused to accept that the rising beta-HCG levels indicated gestational trophoblastic neoplasia rather than a new pregnancy, declined our advice to start single-agent chemotherapy (methotrexate 25 mg on days 1 - 5 of every 12 days) and disappeared from follow-up.

In August 2002, nine months after the delivery and diagnosis of intraplacental choriocarcinoma, the patient presented with the complaint of increasing cough and respiratory distress. Her serum beta-HCG level was 413,220 mIU/ml and chest X-ray demonstrated a huge space-occupying lesion measuring about 10 cm in its largest dimension in the middle of the right lung (Figure 2). Whole body CT scanning did not reveal other lesions. Since more than four months had elapsed from her last pregnancy, the serum beta-HCG level was > 40,000 mIU/ml and her last pregnancy was a term pregnancy, the diagnosis of poor prognosis metastatic choriocarcinoma was made. The patient was offered systemic multi-drug chemotherapy, but she and her husband refused treatment. Even when her respiratory distress exacerbated and serum beta-HCG level increased to 529,000 mIU/ml, the patient still refused chemotherapy and demanded surgical removal of the mass from her lung. Thoracotomy, which was performed in September 2002, revealed an irregular 8-cm mass located at the hilum and infiltrating the upper and middle lobe of the right lung, and a 3-cm mass located in the lower lobe of the right lung. Since complete excision of the masses would necessitate complete resection of the right lung, only open biopsy of the central mass and partial resection of the lower lobe mass were performed. Pathological examination confirmed metastatic choriocarcinoma. The patient made a protracted postoperative recovery but still refused chemotherapy. Only in October 2002, when the dyspnea further increased and the serum beta-HCG level was 671,690 mIU/ml, did the patient eventually agree to receive multi-drug chemotherapy.

The EMA CO five-drug chemotherapy regimen was given as detailed in Table 1. The patient received during a 5-month period, from October 2002 through March 2003, a total of 11 courses of EMA CO. She tolerated chemotherapy well and dose reduction or delay of treatments because of toxicity was not required. The cumulative absolute dose received by the patient for etoposide was 2,200 mg/m^2, actinomycin-D – a total of 11 mg, methotrexate – 3,300 mg/m^2, vincristine – 11 mg/m^2, and cyclophosphamide – 6,600 mg/m^2. During treatment with EMA CO the patient's dyspnea gradually decreased and eventually completely resolved. Chest X-ray at the end of chemotherapy demonstrated a > 50% decrease in the largest dimension of the lung metastases (Figure 3). Serum beta-HCG levels in relation to EMA CO courses are detailed in Table 2.

Table 1. — *EMA CO chemotherapy.*

	EMA
Day 1	Etoposide (VP-16) 100 mg/m^2 in 200 ml NaCl 0.9% by 30-minute intravenous infusion Actinomycin-D (Dactinomycin) 0.5 mg in 150 ml NaCl 0.9% by 5-minute intravenous infusion Methotrexate 100 mg/m^2 in 150 ml NaCl 0.9% by 5-minute intravenous infusion followed by methotrexate 200 mg/m^2 in 1,000 ml dextrose 5% by 12-hour intravenous infusion
Day 2	Etoposide (VP-16) 100 mg/m^2 in 200 ml NaCl 0.9% by 30-minute intravenous infusion Actinomycin-D (Dactinomycin) 0.5 mg in 150 ml NaCl 0.9% by 5-minute intravenous infusion Folinic acid (leucovorin, rescue factor) 15 mg by either intramuscular injection or oral tablets every 12 hours for 4 doses beginning 24 hours after start of methotrexate
	CO
Day 8	Vincristine (oncovin) 1 mg/m^2 in 150 ml NaCl 0.9% by 5-minute intravenous infusion Cyclophosphamide (endoxan, cytoxan) 600 mg/m^2 in 150 ml NaCl 0.9% by 30-minute intravenous infusion

The EMA CO regimen is given in cycles of 14 days. Day 15 is Day 1 of the next cycle. Every 14-day cycle is accepted as one course.

Table 2. — *Serum beta-HGC levels in relation to EMA CO courses.*

EMA CO courses	Serum beta-HCG level (mIU/ml)
Before chemotherapy	671,690
After course no. 1	19,129
After course no. 2	687
After course no. 3	200
After course no. 4	80
After course no. 5	53
After course no. 6	28
After course no. 7	20
After course no. 8	< 10
After course no. 9	< 10
After course no. 10	< 10
After course no. 11	< 10

Following chemotherapy, the patient failed to attend regular follow-up visits and ignored our advice to practice contraception for at least one year. Soon, she presented with rising levels of serum beta-HCG, but this time she had a normal intrauterine pregnancy. She delivered vaginally in January 2004 a healthy female infant at term weighing 2,605 g. Chest X-ray at that time demonstrated complete disappearance of lung metastases (Figure 4). Before long, she again became pregnant and delivered vaginally in June 2005 a healthy male infant at term weighing 2,945 g. To date, the patient is alive and well and without evidence of gestational trophoblastic disease.

Discussion

Choriocarcinoma is preceded by hydatidiform mole in 50% of cases, abortion or ectopic pregnancy in 25% of cases and normal pregnancy in 25% of cases. Although normal pregnancy is the precursor of 25% of cases of maternal choriocarcinoma, the detection of intraplacental choriocarcinoma in an otherwise normal placenta associated with viable pregnancy has rarely been reported [1, 3]. Possible reasons for that are: 1) The placentas after normal birth are discarded in most institutions without being microscopically examined; 2) Most maternal choriocarcinomas following an otherwise normal pregnancy are not diagnosed until such an interval after delivery has passed that the placenta is no longer available for microscopic examination; 3) Even in those cases in which the placentas are microscopically examined, the sectioning of the placenta at approximately 1- to 2-cm intervals, as recommended by the College of American Pathologists [4], is likely to miss neoplastic areas less than 1 cm in diameter; 4) The recommendation of the College of American Pathologists [4] that "isolated or very occa-

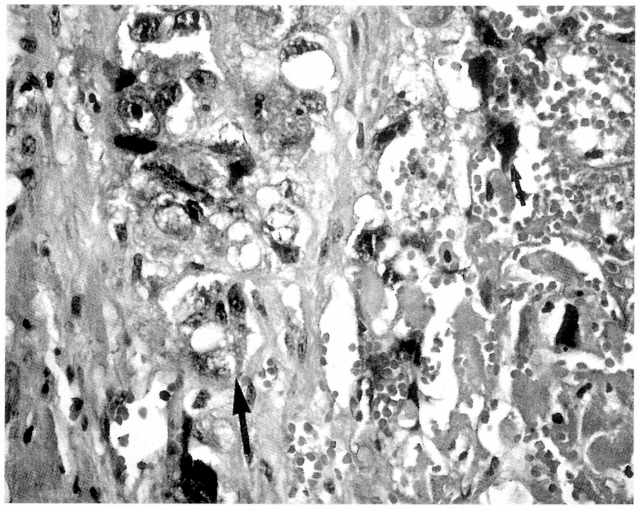

Fig. 1

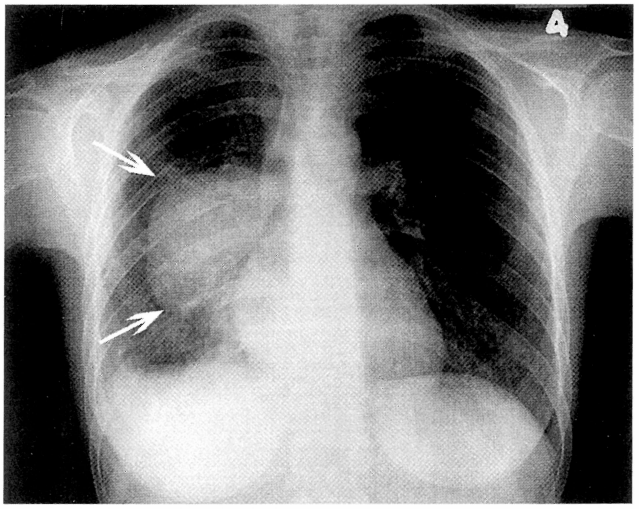

Fig. 2

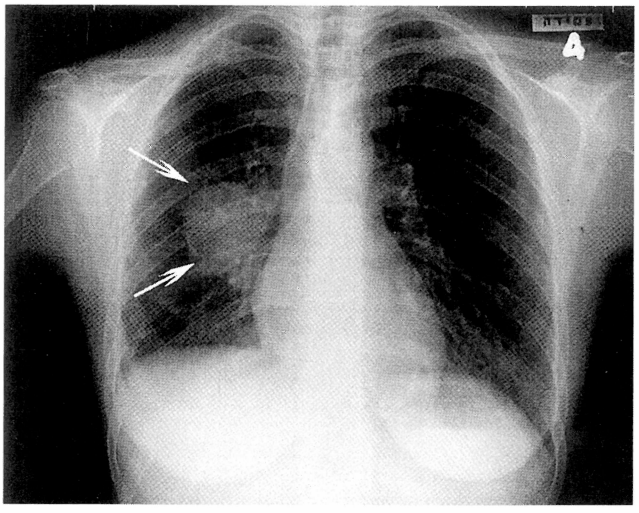

Fig. 3

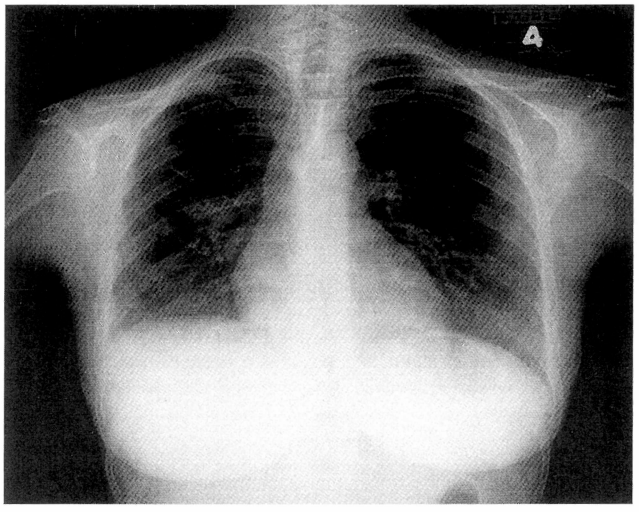

Fig. 4

Figure 1. — Intraplacental choriocarcinoma. The tumor is composed of prominent biphasic trophoblastic proliferation: syncytiotrophoblastic (large arrow) and cytotrophoblastic proliferation with cellular atypia and mitotic figures (small arrow) (hematoxylin-eosin x 400).

Figure 2. — Lung metastases of intraplacental choriocarcinoma. Chest X-ray at the beginning of chemotherapy with the EMA CO regimen showing lung metastases measuring about 10 cm in the largest dimension in the middle of the right lung.

Figure 3. — Lung metastases of intraplacental choriocarcinoma. Chest X-ray at the end of chemotherapy with the EMA CO regimen showing a > 50% decrease in the largest dimension of the lung metastases in the right lung.

Figure 4. — Chest X-ray 10 months after the end of chemotherapy with the EMA CO regimen showing complete disappearance of lung metastases.

sional small infarcts or thormbi, which have been clearly identified and described grossly, need not to be sectioned" can result in missing of visible lesions that might be choriocarcinoma. Nevertheless, since the occurrence of intraplacental choriocarcinoma is very rare, routine microscopic examination of all placentas after normal birth is superfluous, non-economic and not advised. Rather than microscopic examination of all placentas, we would recommend serial serum beta-HCG examinations in the mother after birth. It is more cost effective and easier than placental microscopic examination. Serum beta-HCG levels drop after delivery and rising levels should trigger a work-up for gestational trophoblastic neoplasia. In this patient, even if the placenta had been discarded after delivery without microscopic examination, we would still have been able to make the diagnosis of gestational trophoblastic neoplasia because of the postpartum rising maternal serum beta-HCG levels.

Up to date, less than 15 cases of intraplacental choriocarcinoma without evidence of metastatic disease in the mother or child during pregnancy, at the time of delivery, and at follow-up after birth have been reported in the English literature. The indications for microscopic examination of the placenta were fetal-maternal hemorrhage in five cases (leading to fetal hydrops and intrauterine fetal death in one) [5-8], failure to progress and variable decelerations with meconium-stained amniotic fluid in two cases [1], stillbirth in two cases [2, 9], intrauterine growth

retardation in one case [3], "routine" examination of a third-trimester placenta in three cases [2, 10, 11] and not known in one case [1]. It has been suggested that if there is no evidence of metastasis or postpartum rising levels of beta-HCG, an expectant management is recommended rather than prophylactic chemotherapy [5].

In most reported cases, however, intraplacental choriocarcinoma is associated with metastatic disease in the mother and child [7, 9, 12-17]. Intraplacental choriocarcinoma with metastases may present during pregnancy or at the time of delivery; but more commonly, the diagnosis is made several months after delivery. Evidence of maternal metastatic disease during pregnancy or at the time of delivery has been the most frequent indication for intense microscopic examination of the placenta for a primary tumor site. In this patient, however, there was no evidence of metastatic disease in the mother or child at the time of delivery, and the indications for microscopic examination of the placenta were intrauterine growth retardation and neonatal anemia. The median interval between birth and the diagnosis of maternal choriocarcinoma has been shown to be five months [12], with the most common presenting symptom being vaginal bleeding due to metastases to the maternal uterus and vagina [7, 9, 13, 14], although many women also present with symptoms of extrauterine metastatic disease such as metastases to the lung [7, 15, 16], brain [7, 16], breast [7, 16], and fetal organs [7, 13-15, 17]. In this patient, although during pregnancy and at the time of delivery, there was no evidence of metastatic disease in the mother or child, the rising levels of maternal serum beta-HCG shortly after birth indicated progressive maternal gestational trophoblastic disease. At this point, when less than four months had elapsed from the last pregnancy, her serum beta-HCG level was < 40,000 mIU/ml, there was no metastasis to the brain or liver and the patient had had no prior chemotherapy, the maternal disease was assigned a good prognosis and consequently single-agent chemotherapy with methotrexate was offered. Unfortunately, the patient declined chemotherapy and by that allowed natural progression of the maternal disease towards poor prognosis metastatic choriocarcinoma of the lung. Even then, the patient still refused chemotherapy and agreed just to have a thoracotomy. Only after further time elapsed, during which the serum beta-HCG level and the dyspnea further increased, the patient eventually agreed to received chemotherapy. Fortunately, her metastatic lung disease responded to the multi-drug EMA CO regimen with resolve of the dyspnea, return of the serum beta-HCG level to normal levels and complete disappearance of the lung metastases. This allowed the patient to return to a normal life and to give birth to an additional two children.

Conclusion

This case is an example of natural disease progression of untreated intraplacental choriocarcinoma metastasizing to the mother and progressing towards poor prognosis metastatic choriocarcinoma of the lung. Fortunately, when finally the patient agreed to receive chemotherapy, her metastatic lung disease responded to the multi-drug EMA CO regimen. This is an agreement with common kwnoledge that the multi-drug EMA CO regimen is effective in poor prognosis metastatic choriocarcinoma.

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