

Choriocarcinoma in a Patient with Human Immunodeficiency Virus:

Case Presentation and Review of the Literature

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Abstract

A 26-year-old woman with choriocarcinoma and acquired immunodeficiency syndrome initially presented with hydatidiform mole and was treated with dilation and curettage. Because of persistent elevation of serum human chorionic gonadotropin, the patient was treated with combination chemotherapy with etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine (EMACO) for high-risk gestational trophoblastic tumor. The patient's initial stage was IIc. The serum human chorionic gonadotropin level returned to normal. Fourteen months later, the gonadotropin level again increased. The patient was treated with uterine curettage followed by vaginal hysterectomy. Despite further chemotherapy (with methotrexate and leucovorin, then oral etoposide), she died following metastasis of the tumor to the brain.

Only four other cases of human immunodeficiency virus (HIV) infection with choriocarcinoma have been reported. There is no evidence to date that gestational trophoblastic disease is more prevalent in patients with acquired immunodeficiency syndrome. HIV infection and other immunodeficiency states, however, can influence the course of treatment and outcome in these patients. The low CD4 count in HIV infection may lead to a poor outcome despite chemotherapy.

Key Words: Choriocarcinoma, acquired immunodeficiency syndrome, HIV.

Introduction

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS) due to human immunodeficiency virus (HIV) infection is frequently associated with lymphoproliferative neoplasms, Kaposi's sarcoma, and some squamous carcinomas (cervical, vaginal, and vulvar). Other cancers are rare in AIDS patients (1). In this latter group are gestational trophoblastic tumors (GTT), which include a spectrum of diseases that arise from placental trophoblastic tissue after abnormal fertilization. Most GTTs result in a hydatidiform "molar" pregnancy characterized by the lack of a fetus, trophoblastic hyperplasia, edematous chorionic villi and a loss of normal villous blood vessels.

A total of four cases of choriocarcinoma in HIV-positive patients have been reported. Three such patients were first described by Ojwang and Otieno in Africa in 1992 (2). One patient received prolonged chemotherapy without remission, the second had a remission only after hysterectomy and chemotherapy, and the third had extensive metastatic disease in spite of low-risk factors (see the World Health Orga-

nization scoring system, Table 1). In 1998, Tangtrakul and Linasmita reported a case of an HIV-infected woman with choriocarcinoma presenting as a nasal mass (3). This patient had complete resolution of her disease following multiagent chemotherapy. No other cases have since been documented in the literature.

Case Report

A 26-year-old African American woman was admitted to the intensive care unit of a community hospital with a history of shortness of breath, and blood-tinged sputum for two to three days. Medical history included AIDS, HIV positive for three years, asthma, pulmonary tuberculosis, and pneumocystis pneumonia. The patient had delivered a normal full-term infant 8 months previously. On physical examination, the patient was afebrile, thin, tachypneic, with small, pea-sized cervical and axillary lymphadenopathy. The lungs revealed diffuse rhonchi and wheezing. The abdomen was soft but tender in the right lower quadrant.

The leukocyte count was $7100/\text{mm}^3$, hemoglobin 11.2 g/dL, hematocrit 32.1%, and platelets $263,000/\text{mm}^3$. Liver function tests and serum electrolytes were normal, and the CD4 count was $173/\text{mm}^3$. The serum β -HCG level was greater than 5 million IU/L (normal = 0–10 IU/L). The serum T_3 and T_4 levels were 190 ng/dL (normal 59–174 ng/dL) and 16 $\mu\text{g}/\text{dL}$ (normal 4.5–12 $\mu\text{g}/\text{dL}$) respectively.

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TABLE 1
World Health Organization Prognostic Scoring System for GTT* (4)

Score Factor	0	1	2	4
Age	<35	>35		
Prior Pregnancy Interval	Hydatidiform Mole <4 months	Abortion 4–6 months	Term 7–12 months	>12 months
Serum -HCG (IU/L)	<1,000	1,000–10,000	10,000–100,000	>100,000
ABO blood group		O or A	B or AB	
Largest Tumor Size	< 3 cm	3–5 cm	> 5 cm	
Metastatic Sites	Lung	Spleen, kidney	GI tract, liver	Brain
# of Metastases		1–3	4–8	> 8
Prior Chemotherapy			1 drug	2 or more drugs

*GTT= Gestational trophoblastic tumors

The ultrasound of the pelvis showed that the uterus was enlarged (5 cm) with endometrial thickening and a small fluid collection. No yolk sac was seen. A chest X-ray revealed extensive bilateral alveolar infiltrates.

The diagnosis of hydatidiform mole was suspected. The patient was treated with dilation and curettage of her molar pregnancy. Histopathology revealed hydatidiform mole with features suggesting partial mole. The abnormal chest X-ray was interpreted as metastatic choriocarcinoma or AIDS-related pneumonia (e.g., pneumocystis pneumonia, pulmonary tuberculosis, pneumonia with cytomegalic virus). Bronchoscopy revealed an infectious cause (streptococcus). Since the patient was allergic to penicillin, the pulmonary infiltrates were treated with erythromycin, and trimethoprim and sulfamethoxazole.

Using the World Health Organization (WHO) (Table 1) prognostic scoring system for GTT, we found that our patient had a score greater than 7 based on the -HCG level (5 million IU/L), tumor size (larger than 5 cm) in the uterus, ABO blood type group, and time interval (more than 4 months previously) since the antecedent pregnancy, and a full-term delivery 8 months previously.

Due to persistent elevation of serum -HCG, and the high-risk prognostic score, one cycle of combination chemotherapy consisting of etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine was administered along with GCSF (granulocyte colony-stimulating factor) and erythropoietin. The -HCG was initially greater than five million IU/L but decreased to normal within 4 weeks and remained normal after chemotherapy. No detectable residual disease was seen on ultrasound.

Fourteen months after the -HCG levels had returned to normal, the serum -HCG again increased (14.6 IU/L). The ultrasound of the pelvis showed no gestational sac, but the uterus was enlarged (6.5×4.5×4.3 cm) and a small amount of free fluid was detected in the cul-de-sac. The -HCG progressively increased (to 387 IU/L), and despite uterine curettage, it remained elevated (59 IU/L). The patient subsequently underwent vaginal hysterectomy.

Histopathological exam of the uterus revealed several areas of choriocarcinoma. The patient was not compliant with her medications, and refused to have the full initial chemotherapy regimen with EMACO, since it made her quite sick. She received etoposide and cisplatin but had prolonged myelosuppression despite GCSF. These drugs were replaced by methotrexate and leucovorin, from which she experienced nausea and vomiting. Three months later, etoposide was again started; the patient complained of headache and was readmitted. Work-up revealed metastatic disease to the brain. Shortly thereafter, the patient died with respiratory distress following herniation of the brain.

Discussion

Gestational trophoblastic disease consists of a group of diseases (Table 2) which include complete and partial molar pregnancy, placental site trophoblastic tumor, and gestational choriocarcinoma; these have variable tendencies for local invasion and metastasis. Although persistent gestational trophoblastic tumor (GTT) most commonly follows a molar pregnancy, it may occur after any type of gestation (4). Most molar pregnancies spontaneously resolve after uterine evacuation. However, malignant trans-

TABLE 2
Characteristics of Complete and Partial Moles

Features	Partial Mole	Complete Mole
Karyotype	69XXY (90%)	46XX (90%)
Genetic parentage	Biparental	Paternal
Villous edema	focal	diffuse
Trophoblastic hyperplasia	focal	diffuse
Embryonic tissue	present	none
Persistent -HCG	0.05%	20%

formation may occur in 10–20% of molar pregnancies. The common metastatic sites of GTT are the lungs (80%); vagina (30%); pelvis (20%); liver (10%); brain (10%); and bowel, kidney, and spleen (5% each). Persistent GTT is one human cancer that may respond very favorably to treatment even in the presence of widespread metastasis but may require more aggressive chemotherapy as well as surgery and/or radiation.

In 1976, Bagshawe described a scoring system intended to define the prognosis of patients with GTT (5). Most of the prognostic factors relate to tumor burden (HCG serum level, size and number of metastases), sites of metastasis, duration of disease, and degree of prior chemotherapy exposure and resistance. The World Health Organization (WHO) later published a modified prognostic scoring system in table form (Table 1) that reliably predicts the probability of resistance to chemotherapy (6). This scoring system included age, antecedent pregnancy, -HCG level, size of the tumor, number and site of metastases, and prior chemotherapy. Several factors were associated with poor prognosis. One of these is the size of the tumor (mass greater than 5 cm) and a very high serum -HCG level. Patients who exhibit metastases to the brain, liver, and intestines have a poorer prognosis than those who have metastases to other sites. Other factors which increase risk include persistent disease 4 months beyond the antecedent pregnancy, older than 39 years of age, maternal/paternal blood type, and failure to respond to a previous course of chemotherapy. The total score for a patient is obtained by adding the individual scores for each factor. A total score of 4 or less corresponds to low-risk disease, while a score of 5–7 is of intermediate risk. When the score is 8 or greater, the patient is considered to be at high risk and requires intensive combination chemotherapy to achieve remission. A patient is considered high risk when a combination of high-risk factors and high score is present.

While GTT can be cured with chemotherapy, 10–25% of patients with metastatic disease die of this cancer. Choriocarcinoma is a malignancy which has an excellent prognosis, with 93% of patients without metastatic disease achieving remission using single agent chemotherapy and 87% of patients with metastatic disease achieving remission using combination chemotherapy. The administration of combination chemotherapy with the selective use of surgical and radiation therapy in high-risk patients has resulted in dramatic improvements in survival. Remission rates, even for patients with higher scores, approach 90% in some series (7–9). Nonetheless, some patients are resistant to current combination chemotherapy despite intensive treatment.

DuBeshter and Berkowitz reviewed the records of 51 patients with metastatic gestational trophoblastic tumor (11). The clinical characteristics and therapy of patients who died were compared to those of patients who attained remission, to identify parameters associated with treatment failure. The presence of liver, brain, or intestinal metastases and the failure of prior chemotherapy were found to portend a poor prognosis. They did not find, as had the WHO, that markedly elevated -HCG levels, time interval longer than 4 months from the antecedent pregnancy to treatment, and post-term choriocarcinoma were independently associated with treatment failure. The mean prognostic score and the mean number of high-risk factors for patients who died were 13 and 3, as compared to 7 and 2, respectively, for patients who achieved remission. Intensive chemotherapy regimens need to be administered to patients with liver, brain, or intestinal metastases, failed prior chemotherapy, or a high prognostic score. Remission rates of patients receiving triple therapy with methotrexate, actinomycin-D, and cyclophosphamide (MAC) are poor, resulting in only 50% complete responses. However, a remission rate of 83% is possible in patients whose disease includes high-risk factors and elevated scores, using a combination regimen which includes etoposide, methotrexate, actinomycin-D, cyclophosphamide, and vincristine (10–12).

In AIDS patients, the HIV infection selectively attacks T-derived lymphocytes of the helper/inducer subtype, causing qualitative and quantitative deficiencies in both cellular and humoral immunity (13). There is global immune depression. Trophoblastic tissue, which is an allograft, exhibits transplantation antigens and invades maternal tissue to form the maternal surface of the placenta. It is not rejected by

the maternal immune response at this site. While trophoblastic emboli are shed into the maternal serum during normal pregnancy, they are effectively destroyed by the mother's immune response and do not result in any neoplastic process. Theoretically, it is possible that in AIDS patients, a failure of an immune response to destroy these tumor cells leads to metastatic lesions, thus predisposing such patients to the development of choriocarcinoma. When chemotherapy is given, there is an initial reduction of tumor mass. Further reduction in tumor mass is enhanced by the effect of a normal immune system. This forms the basis for the use of immunotherapy combined with chemotherapy (14). There is reason to believe that suppression of cell mediated immunity by HIV infection can significantly hamper effectors of tumor immunity (2, 13). It has been recommended that HIV infection be included in the list of WHO prognostic factors for choriocarcinoma (2). In patients with AIDS, the effectiveness of the immune system is suboptimal; thus response to chemotherapy can be expected to be poor (2). The benefits/risks of further immunosuppression with chemotherapy versus malignancy progression must be carefully weighed in these patients and may require that dosage be lowered and used in conjunction with administration of GCSF if neutropenia is present.

In three of the four cases reported in the literature of HIV infection with choriocarcinoma, as described by Ojwang et al. (2), one had a prolonged course of chemotherapy without remission; a second responded only after hysterectomy combined with chemotherapy; and the third had extensive metastases with tumor in unusual sites despite low-risk factors. Since all three patients were lost to follow-up after initial treatment, no long-term information is available. Because the clinical manifestations of the three cases were aggressive, HIV infection was proposed to be a poor prognostic risk factor for GTT. CD4 counts in these patients were not reported. The fourth case, of an HIV-positive woman with choriocarcinoma, was reported by Tangtrakul et al. (3) and presented with a nasal mass and a normal CD4 count. The normal CD4 count may explain why the patient tolerated the multiagent chemotherapy and achieved a complete remission. In our patient, the CD4 count was low.

As the AIDS epidemic continues to spread, we may see an increased incidence of GTT. We need to have a better understanding of the interaction between HIV and GTT. The key to any poor response to chemotherapy may be the ex-

tent to which the CD4 count is suppressed. In the parallel situation of AIDS-related lymphoma, chemotherapy also is not well tolerated and these patients have a poor outcome when their CD4 count is below 200/mm³.

HIV-positive patients with choriocarcinoma present challenges in diagnoses. Metastatic lesions in the lung or brain must be differentiated from disease due to infectious etiologies. With regard to our patient, the role played by HIV is uncertain. Her noncompliance with treatment might itself have led to a poor outcome.

Conclusion

More data are needed to determine the appropriate management of choriocarcinoma in the HIV-positive patient. With only a few published cases in the literature, it is difficult to draw any definitive conclusions. To date, there is no evidence that gestational trophoblastic tumor is more prevalent in AIDS patients.

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