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Nongestational Choriocarcinoma in the Postpartum Period: A Case Report

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Purpose: To determine the tissue of origin (gestational versus nongestational) of an extensive metastatic choriocarcinoma in an 18-year-old woman to determine prognosis and treatment.
Methods: DNA microsatellite polymorphisms after polymerase chain reaction (PCR) amplification of the tumor tissue and blood from the patient, husband, and daughter were used to determine the tissue of origin.
Results: Molecular analyses revealed that the tumor shared the genetic features of only the patient. She responded well to multiagent chemotherapy.
Conclusions: Molecular analysis is a useful tool to determine whether a choriocarcinoma occurring in a female patient of childbearing age is gestational or nongestational when clinical findings are not clearly indicative of the primary.
Key Words: Oncology—Choriocarcinoma—Gestational—Nongestational—Germ cell tumor—Molecular analysis—PCR.

Choriocarcinoma is a malignant tumor which can arise from trophoblastic tissue either from a fertilized ovum or a primitive germ cell. The former is termed "gestational choriocarcinoma" and occurs in association with a normal pregnancy or spontaneous abortion (carrying a maternal-paternal genotype), complete hydatidiform mole (carrying a paternal genotype), or a partial mole (carrying a triploid maternal-paternal genotype). In contrast, "nongestational choriocarcinoma" is a malignant germ cell tumor arising from an aberrant meiosis which carries a maternal genotype. The distinction between gestational and nongestational tumors is important because of marked differences in prognosis and treatment (1–5). Although discerning between the two is usually straightforward, the clinical distinction is not as clear in some situations. Recently, DNA analysis has been used to distinguish gestational from nongestational tumors (6–12). We describe an 18-year-old woman with a widely metastatic, presacral choriocarcinoma 8 months postpartum and report the results of genetic analysis used to confirm the origin of her tumor.

CASE REPORT

An 18-year-old G1 P1 A0 woman had urinary incontinence, constipation, and menstrual irregularity 4 months after delivering a full term infant daughter. Pelvic examination suggested the presence of a mass and an ultrasound confirmed a 4×5 cm tumor. Serum beta-human chorionic gonadotropin (β-hCG) was >200,000 units/mL and a laparoscopic exam showed no abnormalities. A dilatation and curettage was also negative. The patient was then transferred to Stanford University Medical Center. Physical exam was remarkable for decreased rectal tone with absence of sensation to light touch and pinprick over the buttocks, posterior thighs, left calf, and areas of her feet including her heels. She also had decreased strength on dorsiflexion of the left ankle, a limp favoring the right leg, and decreased deep tendon reflexes on the left side.

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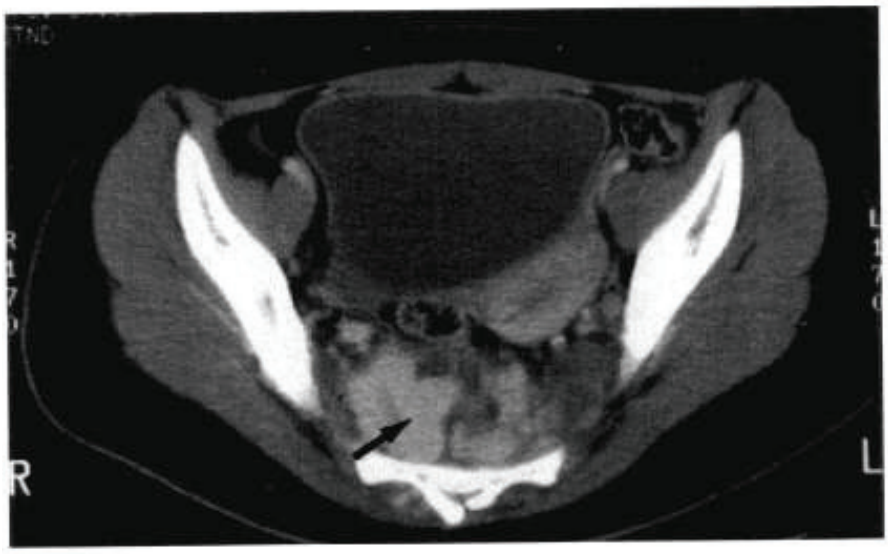

FIG. 1. CT scan of the pelvis at diagnosis. Arrow indicates presacral mass.

Metastatic work-up showed a large presacral mass (Fig. 1) with liver and lung metastases, several metastatic brain lesions, and a negative bone scan. Computed tomography (CT)-guided fine needle aspiration biopsy of the presacral mass was consistent with choriocarcinoma (Fig. 2) but was not of sufficient volume to perform genetic analysis. Examination of cerebrospinal fluid showed no malignant cells but a β-hCG level of 7472 units/mL. Because the presacral location of the tumor was more typical of a nongestational germ cell tumor, the patient was treated on Pediatric Oncology Group Study #9049 for high risk malignant germ cell tumors.

The patient received five cycles of therapy with cisplatin (20 mg/m^2 ×5 days), etoposide (100 mg/m^2 ×5 days), and bleomycin (15 mg/m^2 ×5 days) (PEB). After the first cycle, she underwent a repeat CT-guided aspiration biopsy on which to perform genetic analysis. After 4 cycles of PEB, the patient had a significantly improved neurologic status but decreased rectal tone and no perianal sensation. The serum β-hCG had decreased to 6 units/mL and cerebrospinal fluid β-hCG levels had decreased to <2 units/mL, but CT showed minimal decrease in the size of the primary tumor. Additionally, metastatic work-up showed resolution of lung metastases and >50% decrease in size of brain metastases which were thought not to contain residual tumor given the normal level of cerebrospinal fluid β-hCG. After the fifth cycle, in accordance with the protocol, the patient underwent an exploratory laparotomy to attempt tumor resection of the residual mass. In the operating room, the presacral mass was found to be firmly attached to the sacrum and unresectable without a sacrectomy. A biopsy showed necrotic, atypical cells but no viable tumor. Chemotherapy was stopped electively on the assumption that there was no viable tumor because she had a biochemical complete response. Sixteen months after completion of therapy, the patient is clinically well without disease progression and improving neurologic status.

METHODS

Genetic Analysis

High molecular weight DNA from the tumor and blood samples from the patient, her husband, and her daughter were isolated with an IsoQuick extraction kit according to the manufacturer's instructions (Microprobe Corporation, Garden Grove, CA). Oligonucleotide primers used for amplification of the microsatellite loci were obtained from Research Genetics (Huntsville, AL): D3S1300, D8S1824, D8S264, D8S1781, and D8S1788. These microsatellite loci were analyzed with a polymerase chain reaction (PCR)-based assay (13). PCR was performed in 25-μL reaction volumes consisting of the following: 50 mM KCl, 10 mM Tris (pH 9.0), 1.5 mM $MgCl_2$, 0.01% Triton X-100, 100 μM of each deoxynucleotide triphosphate, 40 nM unlabeled primer, 0.5 units Taq-polymerase, and 100 to 200 ng of genomic DNA. One primer was end labeled with [γ-^{32}P] adenosine triphosphate by T4-polynucleotide kinase. DNA denaturing was at 95°C for 1 minute, annealing at 55 to 60°C for 1 minute, strand elongation at 72°C for 1 minute, and final elongation at 72°C for 10 minutes. The PCR products were diluted 1:1 with loading buffer (95% deionized formamide, 20 mM EDTA, 0.025% xylene cynol, and 0.025% bromophenol blue). The diluted 4-μL samples were heat denatured and electrophoresed on 7% polyacrylamide gels containing 5.6 M urea and 32% formamide for 3 hours at 55°C. The gels were exposed to X-ray film at -80°C.

RESULTS

The comparison of the allelic variations obtained by PCR analysis are shown in Table 1 and Figure 3. Of 6 loci tested, 4 were informative. At all of these loci, the tumor genotype was identical to that of the patient. The first two loci in Table 1 indicate complete absence of the paternal

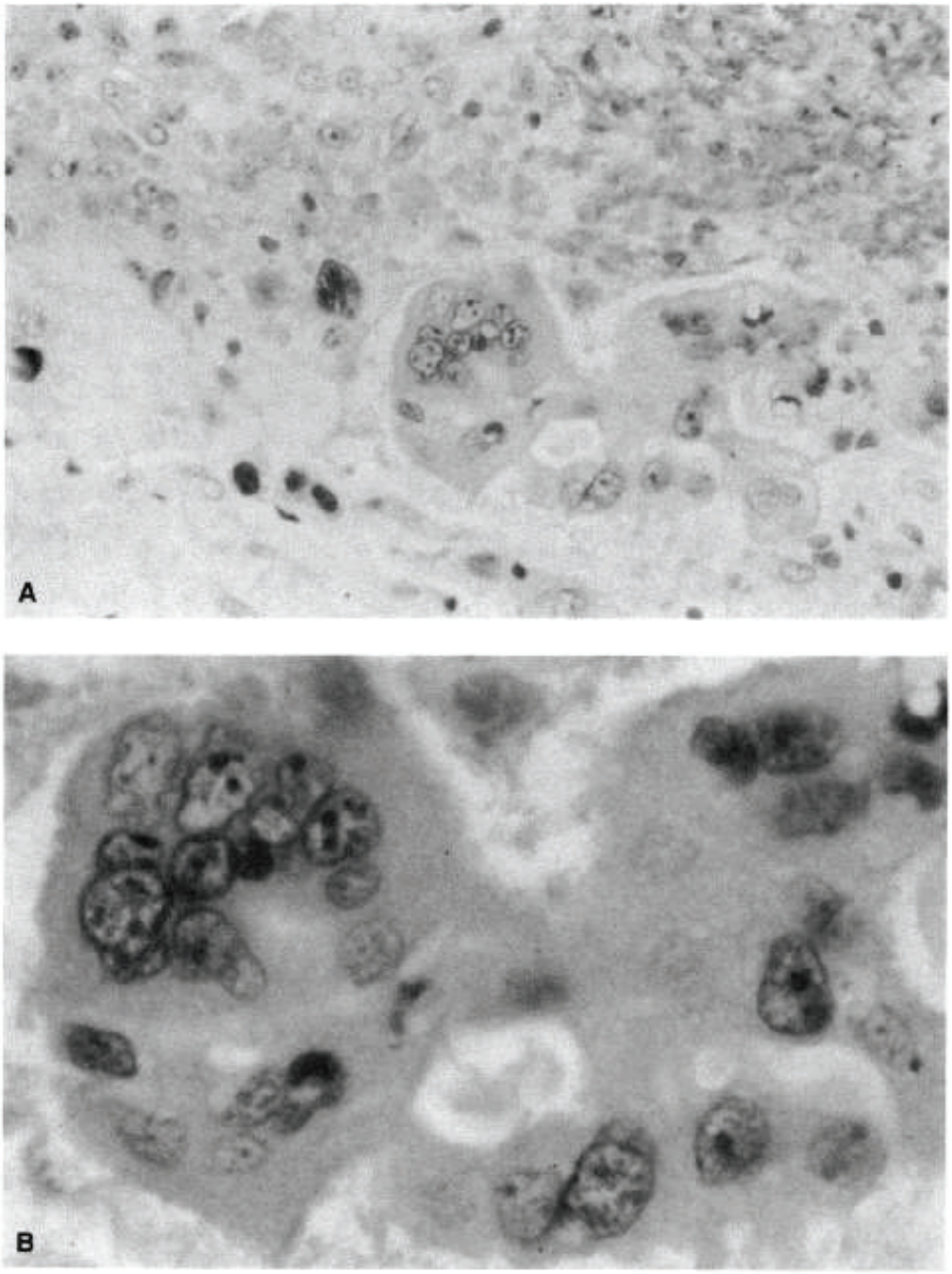

FIG. 2. Cytopathology from first needle biopsy showing syncytiotrophoblast (**A:** ×200 and **B:** ×400).

alleles. Additional analysis was not possible due to the minute quantity of tumor available for analysis. As expected, biparental origin was observed in the daughter and her genotype did not match the tumor, which is consistent with a nongestational origin of the tumor.

DISCUSSION

Determination of the gestational or nongestational origin of a choriocarcinoma impacts the clinical course, therapy, and prognosis of the patient. In general, patients with metastatic gestational choriocarcinoma are treated successfully with chemotherapy along with radiotherapy administered to metastatic brain lesions (1). Our patient's clinical presentation was not typical of either gestational or nongestational choriocarcinoma and the antecedent pregnancy raised the possibility of an unusual presentation of a gestational tumor.

Molecular DNA analysis to elucidate the cell of origin in choriocarcinoma has recently been reported (6–12). The results of the DNA analysis in this patient showed that the tumor collected from the second CT-guided biopsy of the presacral mass shared genetic features with the patient's peripheral blood but not with that of her husband or daugh-

TABLE 1. *Polymorphisms identified in the tumor and the patient's family*

Locus symbol	Daughter	Husband	Tumor	Patient
D3S1300	AB	BC	AD	AD
D8S1824	BC	AB	CD	CD
D8S264	BC	AC	BC	BC
D8S1781	AC	CC	AB	AB
D8S1788	AA	AB	AB	AB

ter. Therefore, the tumor arose from the patient's own cells and not from her previous gestation, in which case the pattern would have been identical with her daughter's. There are several issues that complicate the interpretation of these results. First, the highly vascular nature of the tumor could have resulted in the contamination of the specimen by the patient's blood; however, if the tumor were of antecedent gestational origin, one would expect to see representative markers from both the patient and the paternal elements in her daughter even in the presence of contamination. Second, the biopsy was performed after one cycle of chemotherapy, which might have decreased the yield of DNA from the specimen. Even with these limitations, we think that the results obtained are an accurate representation of the tumor cells.

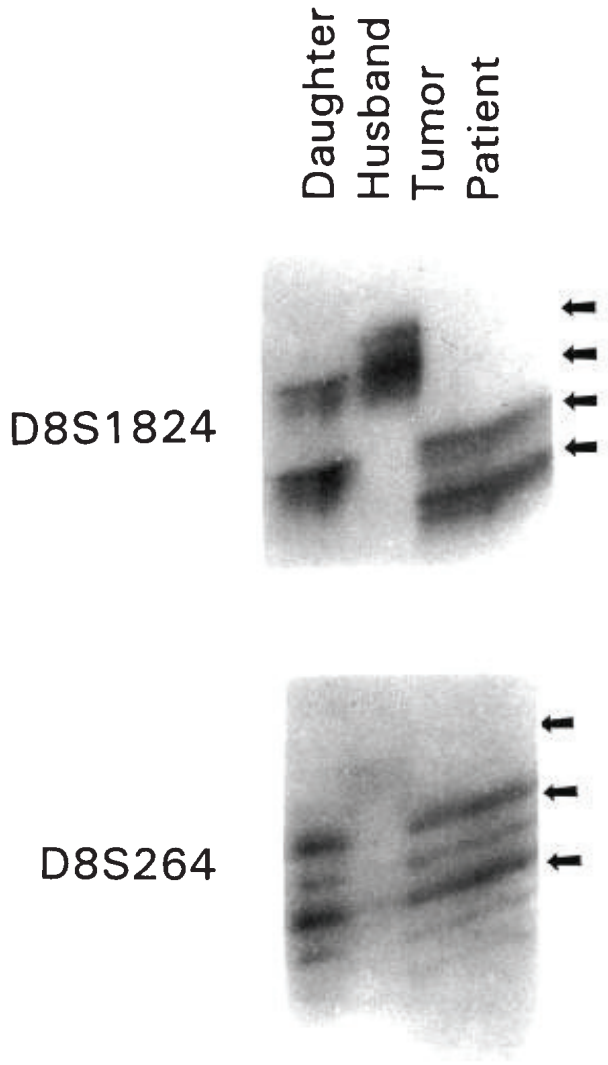

FIG. 3. DNA polymorphisms identified in the tumor and blood from the patient, her husband, and her daughter. The arrows indicate the allelic fragments observed as described in Table 1. D8S1824 data demonstrate the absence of both alleles from the husband in the tumor. D8S264 results indicate that one of the husband's alleles is absent in the tumor. The second allele is noninformative and shared with the patient, the tumor as well as the daughter. The bands in the second lane are very faint due to loading differences.

To our knowledge, genetic analysis to determine the tissue of origin has been reported in 19 patients with choriocarcinoma; tumors in 4 of the 19 had a nongestational origin (including the patient described in this paper) (9,10). These reports indicate that the causal pregnancy in gestational choriocarcinoma can be an antecedent pregnancy or an earlier molar or nonmolar aborted gestation. Furthermore, molecular analysis has also documented placental site trophoblastic tumor arising from an unrecognized pregnancy years earlier (9).

Prognosis and treatment for gestational and nongestational choriocarcinoma differ significantly. The cumulative survival rate according to life-table analysis for widely metastatic gestational choriocarcinoma is 79% (5). Data for widely metastatic nongestational disease are not as available because these tumors are rare and the results of treatment are included with other types of germ cell tumors. However, in one study, patients with extragonadal germ cell tumors had a projected survival of 40% (4). The treatment of choice for patients with high risk gestational choriocarcinoma with brain metastases includes weekly doses of methotrexate, etoposide, and dactinomycin alternating with vincristine and cyclophosphamide, with central nervous system irradiation. Conversely, the treatment of choice for metastatic nongestational tumors is PEB without brain irradiation. In addition, because the acute and long-term complications of therapy are also different, it is essential to determine the tissue of origin to minimize toxicity for patients with gestational tumors and maximize the cure rate for patients with nongestational tumors.

The data presented here confirm our clinical impression that the patient had a nongestational choriocarcinoma. Although we are unaware of any report in the literature linking pregnancy to nongestational germ cell tumor, maternal

hormonal exposure has been associated with elevated risks of both ovarian and testicular germ cell tumors in subsequent progeny (14,15). It could be speculated that the chronic hormonal stimulation provided by this patient's pregnancy may have facilitated the development of a germ cell tumor.

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