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Two Cases of Dizygotic Twins with Androgenetic Mole and Normal Conceptus

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ABSTRACT

Two cases showing a molar placenta with a fetus/infant were analyzed for karyotype and enzyme polymorphisms and found to be dizygotic twin pregnancies with an androgenetic mole and a normal conceptus. One case resulted in spontaneous abortion at 19 weeks' gestation and was subsequently diagnosed as an invasive mole and required chemotherapy. The other case was a conception following clomiphene plus human menopausal gonadotropin (HMG) therapy and resulted in a normal female infant born at 33 weeks.

It is emphasized that, since dizygotic twins in which one is an androgenetic mole have a high propensity for malignancy, they should be carefully differentiated from partial moles with which they might be confused by analysis of genetic polymorphisms and they should be followed up with care.

Hydatidiform moles with a coexistent fetus/infant, a rare condition of pregnancy, are divisible into two groups: dizygotic twins with a complete mole and normal conceptus, and partial moles originating from one conceptus. Recent studies based on genetic polymorphisms of the mole and its parents[1-3] have revealed that complete moles are androgenetic in origin, mostly originating as a result of fertilization of an empty egg by a haploid sperm followed by duplication of its genome, although a small proportion result from fertilization of an empty egg by two spermatozoa. Therefore, analysis of genetic polymorphisms is considered to be the most reliable method for diagnosis of dizygotic twins consisting of an androgenetic mole and a normal conceptus. Honda et al[4] and Fisher et al[5] analyzed genetic markers of hydatidiform moles with a coexistent fetus and found that they were dizygotic twins. In the present paper we will report two additional cases in which androgenetic moles and normal conceptuses were confirmed by analysis of chromosomes and enzyme polymorphisms.

CASE REPORT

Case 1: The patient was a twenty-five year old woman who had previously given birth to an anencephalic infant. She had continuous painless vaginal bleeding since the 14th week of gestation and was admitted to our department when 19 weeks pregnant. Ultrasonographic examination revealed a normally developed fetus having positive heart beats and an abnormal cystic echo covering the internal os of the cervix. The urinary human chorionic gonadotropin (hCG) level was high at 614,000 IU/liter. On the first day of her admission, painful uterine contractions started and gradually increased accompanyed with dilation of the cervix. Molar tissues and massive blood clots were expelled and, subsequently the membrane ruptured followed by the expulsion of a 225 g male fetus and a placenta. Autopsy of the fetus showed no morphological abnormalities. The placenta, 122 g in weight, was apparently normal and clearly separated

from the molar tissues. The molar tissues, about 50 g in weight, was composed mainly of cysts 5 to 6 mm in size and showed histologically marked trophoblastic hyperplasia and stromal edema without fetal vessels. The patient had prophylactic chemotherapy with methotrexate (15 mg × 2 days) and recurettage of the uterine cavity done five days after the abortion. The urinary hCG levels which had dropped to 1,000 IU/liter in two weeks rose up again to 4,000 IU/liter six weeks after the abortion and the pelvic angiography showed an intra-uterine lesion. Based on these findings, she was diagnosed as having an invasive mole and was treated by two courses of chemotherapy with methotrexate (15 mg × 7 days/ course). Consequently, the urinary hCG levels returned to normal in four weeks and the patient remains well. Chest X-rays were consistently negative for metastasis.

Case 2: The patient was a twenty-six year old woman who had had a previous spontaneous abortion. Her menstrual cycle was irregular, often associated with anovulation which required ovulation induction therapy. She conceived after clomiphene plus human menopausal gonadotropin (HMG) therapy. She developed toxemia with hypertension and albuminuria and was admitted to our department at 29 weeks' gestation. The ultrasonographic examination on admission showed a normally developed fetus, a normal placenta and an abnormal cystic echo suggesting a hydatidiform mole. Laboratory data showed an extremely high urinary hCG level (1,190,000 IU/liter), a normal serum human placental lactogen (hPL) level (6 μg/ml) and a normal urinary estriol level (over 20 mg/day). A chest X-ray was negative for metastasis. The high blood pressure (160/90 mmHg on admission) fell to the normal range through bed rest and periodical ultrasonographic measurement showed normal development of the fetus, but no growth of the cystic placenta. At 33 weeks, uterine contractions started spontaneously leading to regular labor pains and the birth of an infant with an Apgar score of 9, followed by the expulsion of a normal and a molar placenta.

The infant, 1575 g in weight, was an apparently normal female and showed normal physical and mental development at one year of age. The normal placenta, 332 g in weight, was clearly demarcated from the molar tissues which weighed about 2000 g and consisted mainly of large cysts more than 10 mm in size. Histologically, the molar tissues showed marked trophoblastic hyperplasia and stromal cystern formation without fetal vessels. The patient had prophylactic chemotherapy with a combination of methotrexate (15 mg × 7 days) and actinomycin D (0.2 mg × 5 days) after the birth and showed an uneventful puerperal course.

GENETIC ANALYSES

Chromosome preparations were made by tissue culture from the molar tissues and by peripheral blood lymphocyte cultures from the parents and the fetus/infant. Slides were stained with Giemsa and ten cells examined from each specimen. Enzyme polymorphisms of phosphoglucomutase 1 (PGM1), phosphoglucomutase 3 (PGM3) and esterase D (ESD) were analyzed by horizontal starch-gel electrophoresis[12,22] using extracts of the molar tissues and red cell

Table 1. Mode of inheritence of enzyme polymorphisms

Case No.		Karyotype	Enzyme polymorphisms PGM1	PGM3	ESD
1	Mother	46,XX	2–1		2–2
	Father	46,XY	1–1		2–1
	Fetus	46,XY	2–1		2–2
	Mole	46,XX	1–1		1–1
2	Mother	46,XX	1–1	1–1	1–1
	Father	46,XY	2–1	2–2	2–1
	Infant	46,XX	2–1	2–1	2–1
	Mole	46,XX	1–1	2–2	1–1

[ ] Neither of maternal markers transmitted to the mole, indicating its androgenetic origin. [ ] Both paternal and maternal (or at least maternal) markers transmitted to the fetus/infant, indicating normal diploid conceptus.

hemolysates from the parents and the fetus/infant.

The results of analyses of the karyotypes and enzyme polymorphisms are shown in Table 1. The molar tissues were 46,XX in both cases while the fetus (case 1) was 46,XY and the infant (case 2) was 46,XX. In case 1, the ESD of the molar tissues was 1-1, a duplication of the single 1 allele of the father, while the PGM1 of the fetus was 2-1 proving a maternal contribution and supporting it's being a normal diploid conceptus. Therefore, case 1 appeared to be dizygotic twins of an androgenetic mole and a normal male conceptus. In case 2, the PGM3 of the molar tissues was 2-2, both alleles being paternal, while the infant was 2-1, showing a contribution from both parents. Therefore, case 2 appeared to be dizygotic twins with an androgenetic mole and a normal female conceptus.

DISCUSSION

Hydatidiform moles are classified on the basis of morphological and cytogenetic characteristics into two categories: complete and partial moles[24,26]. Partial moles have some normal villi and some that are macroscopically swollen, and an embryo/fetus is usually present. Most partial moles are triploid although a few have been reported to be diploid. Dizygotic twins with a complete mole and a normal conceptus are differentially diagnosed from partial moles by morphological findings: clear demarcation of molar tissues from a normal placenta and marked trophoblastic hyperplasia of molar villi with the absence of fetal vessels. However, an accurate morphologic diagnosis of dizygotic twins is not

Table 2. Summary of reports on the twins with complete mole and normal conceptus

Report	Maternal age	Weeks of gestation	Toxemia	Fetus/Infant		Subsequent malignancy
				Sex	Weight (g)	
Acosta-Sison[1]	36	(4M)				Choriocarcinoma
	19	(3M)	+			Died of blood loss
		(8M)			1500	Choriocarcinoma
Logan[17]		18				
	24	19	+			—
Taylor[25]	28	32		M	1800	—
Goddard[8]	28	33	—	M	1475	—
	27	14	+			—
Sitaratna et al[21]	30	36	—	F	1800	
Beischer[3]	26	36		M	2550	
					2950	
Sherif[20]	38	20	+	M	316	—
Chamberlain[5]	24	(5M)	+	M		—
Hobday et al[9]	25	38	—	M	2780	—
Kirk[15]	19	16	+	M		Invasive mole
Hohe et al[10]	32	36	+	M	1975	Choriocarcinoma
Fukuda et al[7]	31	38	+	F	1500	—
Ladehoff et al[16]	26	32	+	M	1680	—
Akamatsu et al[2]	28	26	+	F	860	—
Suzuki et al[23]	31	32	—	F*	1435	—
Sauerbrei et al[19]	31	20	+	F*		—
	23	22	+	M*	440	—
				M*	370	
Honda et al**[11]	27	14	—	M*		—
Block et al[4]	24	36	—	M	1850	—
	36	35	+	M	2020	Choriocarcinoma
Fisher et al**[6]	27	15		M*		
Present study**	25	19	—	M*	225	Invasive mole
	26	33	+	F*	1575	—

*Chromosomal sex was determined.
**Twins were confirmed by analyses of genetic polymorphisms.

always easy, particularly in cases which are at an early stage of gestation and seriously damaged during the abortion process, or in cases in which inadequate tissues are submitted for histopathologic examination. Sex chromatin and chromosome analyses are useful for detection of the twins, but limited to unlike-sexed twins. Therefore, the use of genetic markers such as chromosomal heteromorphisms, histocompatibility leukocyte antigen (HLA) specificities and enzyme polymorphisms is preferable, not only for the diagnosis of the twins, but also for the detection of the genetic origin of the moles.

Our investigation of the literature on hydatidiform moles with a coexistent fetus/infant has revealed twenty-six reported cases[1-11,15-17,19-21,23,25] that are considered on morphological criteria to be dizygotic twins and data on these twenty-six cases are shown in Table 2. In two instances, one reported by Honda et al[11] and one by Fisher et al[6], the presence of dizygotic twins with an androgenetic mole and a normal conceptus was confirmed by analyses of chromosome heteromorphisms and HLA specificities. Clinical findings in the twin moles are quite similar to those in singleton complete moles in terms of marked elevation of urinary hCG level, development of toxemia and a high propensity for malignancy. One of the two cases presented here was subsequently diagnosed as an invasive mole and required chemotherapy and of the twenty-six cases listed in Table 2, four developed into choriocarcinoma[1,4,10] and one into an invasive mole[15], re-emphasizing the critical need for careful diagnosis and follow up of dizygotic twin molar pregnancies.

It is noteworthy that one of our cases and two of the cases in the literature reported by Sauerbrei et al[19] and by Honda et al[11], were conceptions following clomiphene or clomiphene plus HMG therapy. As an essential cause of an androgenetic mole is inactivation of an egg pronucleus, it is possible that induction therapy tends to cause multiple ovulations often associated with such an abnormal egg.

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