Molecular Distinction of Consecutive Molar Pregnanacies

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BACKGROUND: It may be difficult to differentiate the consecutive occurrence of two independent molar pregnanacies from gestational trophoblastic neoplasia after the initial molar pregnancy, especially when the interval between them is short.

CASE: A 25-year-old woman who had had a complete hydatidiform mole 6 months earlier presented with a 6-week history of secondary amenorrhea. Serum human chorionic gonadotropin had increased to 19,857 micro-international units/mL, with no gestational sac demonstrated. Dilation and curettage was performed. Pathologic examination identified a tiny amount of hydropic villi compatible with complete hydatidiform mole. Analysis of short tandem repeat polymorphisms revealed that the molar tissues were of

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References

different genetic origin. The patient went into remission spontaneously without chemotherapy.

CONCLUSION: Genetic profiling was useful to discriminate a recurrent mole from suspected gestational trophoblastic neoplasia. (Obstet Gynecol 2011;117:492–5)

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Women with complete hydatidiform mole have a 10–30% chance of gestational trophoblastic neoplasia, and human chorionic gonadotropin (hCG) follow-up is indicated after complete hydatidiform mole evacuation.1 To perform this successfully, contraception is necessary because it may be difficult to differentiate a new conception from an early gestational trophoblastic neoplasia. The distinction is especially difficult when the second pregnancy is abnormal, as in the case of early abortion, in which the hCG level is continuously low, endometrial thickening remains minimal, the gestational sac is absent or obscure, and genital bleeding continues. Pathologic examination of evacuated tissues is useful for differential diagnosis as long as tissue samples are identified. If not, then monitoring the hCG level and the clinical course is the only way to make the diagnosis.

Here, a case of recurrent complete molar pregnancies in which two independent molar pregnancies were differentiated based on analysis of short tandem repeat polymorphisms is presented.

CASE

A 25-year-old gravida 3 para 1 woman was referred to our hospital because of a suspected molar pregnancy. Her serum hCG was high (192,108 micro-international units/mL), and ultrasonographic findings were characteristic of molar pregnancy. Dilatation and curettage (D&C) was performed at 8 weeks of pregnancy. Both the macroscopic and microscopic findings were compatible with complete hydatidiform mole. The serial hCG levels decreased to 2.5 micro-international units/mL (the cut-off value is 2.7 micro-international units/mL; DPC Immulyze 2000; Siemens Healthcare Diagnostics, Tokyo, Japan) at 7 weeks after evacuation, and the patient was lost to follow-up thereafter.

She presented again 24 weeks after the first D&C because of a 6-week history of amenorrhea. Her menstrual cycle had been irregular after the D&C, and she had sexual intercourse after her last menstruation, although her husband wore a condom. The serum hCG level was 10,584 micro-international units/mL, but a gestational sac was not clearly identified in utero. One week later, the hCG level was further increased to 19,857 micro-international units/mL, and ultrasonography demonstrated a mixed pattern of 15-mm-thick endometrium without any evidence of a gestational sac. After D&C, a small amount of chorionic tissue was found on stereomicroscopic dissection, which was pathologically diagnosed as complete hydatidiform mole, showing hydropic villi with circumferential trophoblastic hyperplasia. The chest X-ray, chest computed tomography, abdominal computed tomography, and transvaginal ultrasound including color Doppler showed no residual lesions both inside and outside of the uterus.

To exclude the possibility of gestational trophoblastic neoplasia, genotyping of the first and second molar tissues and patient and partner blood with analysis of short tandem repeat polymorphisms (The PowerPlex 16 System, Promega US) was performed as previously described2 (Fig. 1). This study was approved by the Chiba University Hospital Ethics Committee (number 575) and was performed after obtaining written informed consent from the woman and her partner.

The first conceptus had only one allele of paternal origin for each of 14 informative loci with different repeat numbers, suggestive of an androgenetic homozygous mole. The second conceptus was again composed of paternal alleles only but was bi-allelic in six of 14 informative loci, suggestive of an androgenetic heterozygous hydatidiform mole. The allelic profiles were different between both concepti for nine loci (D3S1358, TH01, D18S51, Penta E, D13S317, D7S820, D16S539, VWA, and FGA). Thus, it was concluded that the two concepti were from different zygotes.

The patient went into remission spontaneously without chemotherapy. She has not relapsed more than 1 year later.

COMMENT

A case of repeated hydatidiform moles in which genetic profiling clearly demonstrated that the two came from different zygotes was presented. Without the genetic diagnosis, chemotherapy might have been considered based on the suspicion of low-risk gestational trophoblastic neoplasia. Thus, genetic diagnosis of molar tissues was crucial to eliminate unnecessary chemotherapy and to predict the prognosis.

It has been shown that short tandem repeat analysis using a commercial kit such as the PowerPlex 16 system is useful to diagnose gestational trophoblastic diseases, including hydatidiform mole.2,3 Such kits were originally developed for individual discrimination in forensic medicine,4 but they are also applicable for precise genetic analysis of gestational trophoblastic disease. It is possible to differentiate two types of complete hydatidiform mole: homozygous “monospermic” complete hydatidiform mole and heterozygous “dispermic” complete hydatidiform mole. Homozygous complete hydatidiform mole is mono-allelic of paternal origin for all alleles, whereas heterozygous complete hydatidiform mole can be bi-allelic of paternal origin, as long as the paternal alleles are different.

In addition to the genetic diagnosis of hydatidiform mole, we have reported another application of...
genetic profiling, namely discrimination of two consecutive moles. We believe this is the first time that genetic profiling has been used, based on computerized searches of MEDLINE via PubMed performed through October 24, 2010 using a search query, \[(\text{[repeat]} \text{ OR} \text{ [recurrent]}) \text{ AND} (\text{[hydatidiform]} \text{ OR} \text{[gestational trophoblastic]})\].

The diagnostic power of short tandem repeat polymorphism analysis is theoretically high for discerning two different zygotes with moles developing. If the two moles are both homozygous, then the probability that truly different zygotes (moles) are misjudged as the same one is less than \(\frac{1}{2^n}\), where \(n\) is the number of heterologous and independent loci in the paternal genome, that is, the number of heterologous chromosomes (Fig. 2A). It has been shown that \(n\) is usually eight or more, so the chance of such a mistaken judgment is virtually negligible.\(^2\)\(^5\) In the case that the two moles are heterozygous, the probability that truly different zygotes (moles) are misjudged as the same zygote is calculated as follows. Two heterozygous moles can be differentiated only when an allelic combination is different between two moles. There are four allelic combinations for every locus with different repeat number alleles: \(P_1P_1\), \(P_1P_2\), \(P_2P_1\), and \(P_2P_2\), where \(P_1\) and \(P_2\) mean the different alleles of informative loci. There are 16 combinations for one locus, and the distinction of moles was impossible for six of the 16 combinations (Fig. 2B). Therefore, the probability to misjudge a truly different heterozygous mole as the same one is \(\frac{3}{8^n}\), where \(n\) is again the number of informative loci in the paternal genome; this probability is lower than that given for discerning homozygous moles, namely less
than $(1/2)^n$. In the case of a homozygous mole and a heterozygous mole, the probability of misjudgment is given simply by $(1/4)^n$ (Fig. 2C). The combination of alleles is given by $(P_1P_1, P_2P_2) \times (P_1P_1, P_2P_2, P_3P_3, P_4P_4)$ for homozygous and heterozygous moles, respectively, and their distinction is impossible in one-quarter of cases. Again, the possibility of misjudgment is quite low. Collectively, distinction of the origins of two moles in one person by short tandem repeat analysis is highly reliable, as for the diagnosis of trophoblastic disease.

The accuracy of the polymerase chain reaction-based DNA analysis depends on the purity of the DNA sample. This is especially true if a tiny amount of possibly mixed tissues is used. In the present case, stereomicroscopic dissection was performed to identify chorionic tissues and eliminate possible contamination with maternal cells. In conclusion, DNA analysis appears to be useful for the differential diagnosis of consecutive moles separated by a short time interval.

REFERENCES


Fig. 2. Combinations of allelic patterns indistinguishable from a truly different mole on an informative locus. A. Homozygous–homozygous allelic pattern. B. Heterozygous–heterozygous pattern. C. Homozygous–heterozygous pattern. $P_1$ and $P_2$, two paternal alleles with different repeat numbers; open circle, distinguishable; X, indistinguishable.


Progesterone Autoimmune Dermatitis With Positive Autologous Serum Skin Test Result

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BACKGROUND: Progesterone autoimmune dermatitis is a rare disease attributable to hypersensitivity to endogenous progesterone and characterized by cyclic dermatologic manifestations at the end of the luteal phase that disappear some days after menses.

CASE: A 35-year-old woman experienced cyclic premenstrual urticaria and angioedema occurring from 4 days before to 5 days after menses. The diagnosis of progesterone autoimmune dermatitis was made by a progesterone-positive skin test. Autologous serum skin test, using sera from estrogenic and luteal phases, also elicited a positive response. The patient became pregnant with near-clearance of the urticaria.

CONCLUSION: Skin tests with progesterone and autologous serum, which are easy to perform, convenient, and...