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Paternal uniparental isodisomy of tyrosine hydroxylase locus at chromosome 11p15.4: spectrum of phenotypical presentations simulating hydatidiform moles

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Abstract

Uniparental disomy is an abnormal genetic condition in which both homologous chromosomes or part of the chromosome are inherited from one parent and the other parent's homologous chromosome is lost. We report three cases of gestations with paternal uniparental isodisomy at tyrosine hydroxylase or TH01 locus on chromosome 11p15.4 identified by DNA genotyping. The patients' age ranged from 32 to 35 years and all patients presented with missed abortion during the first trimester. Abnormal chorionic villi were seen in all cases with histomorphological and/or p57 immunohistochemical features simulating either partial or complete mole. While two patients had an uneventful clinical course, one patient presented with clinical complications simulating persistent gestational trophoblastic disease/neoplasia that required multiagent chemotherapy with etoposide, methotrexate, actinomycin D, vincristine, and cyclophosphamide (EMA-CO). In summary, paternal uniparental isodisomy of tyrosine hydroxylase locus at chromosome 11p15.4 may result in an abnormal gestation that simulates a hydatidiform mole both clinically and histologically. The presence of abnormal trophoblastic proliferation combined with loss of p57 expression in villous cytotrophoblast and stromal cells may be associated with an aggressive clinical behavior.

Introduction

Gestations with abnormal villous morphology are frequently encountered in the diagnostic workup for missed abortion or termination of pregnancy with major differential diagnoses including hydatidiform moles and non-molar gestations due to isolated chromosome abnormalities. Accurate classification is critical to ascertain the risk of persistent gestational trophoblastic disease associated with hydatidiform moles and to determine the appropriate

clinical follow-up and treatment options [1–5]. Patients with complete or partial hydatidiform moles are followed up with serial serum beta-human chorionic gonadotropin (hCG) measurements in conjunction with contraception until undetectable levels are achieved. In contrast, spontaneous abortion or termination of non-molar pregnancy does not warrant such molar surveillance program. However, nonmolar chromosomal abnormalities frequently show villous morphology overlapping with molar gestations, most often partial hydatidiform mole. Histological changes characteristically seen in partial mole can be shared with common chromosomal trisomy syndromes and other isolated chromosomal alterations, including uniparental disomy of chromosome 11 [6, 7].

Uniparental disomy is an abnormal genetic condition in which both homologous chromosomes or part of a chromosome are inherited from one parent and the other parent's homologous chromosome is lost. Uniparental disomy develops generally from failure of the two members of a chromosome pair to separate properly into two daughter cells during meiosis in the parent's germline through nondisjunction. Uniparental isodisomy occurs when both chromosome copies are homozygous, as a result of

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duplication of one of the parental chromosomes. Recently, a case of paternal uniparental isodisomy of chromosome 11 combined with multiple trisomies was reported to have abnormal villous histology and loss of p57 expression in villous stromal and cytotrophoblast, therefore simulating a complete mole [6]. Here we report three cases of gestations with uniparental isodisomy at the tyrosine hydroxylase or TH01 locus on chromosome 11p15.4, presenting with a spectrum of morphological changes of chorionic villi and clinical manifestations mimicking a true hydatidiform mole.

Materials and methods

Study case identification

Archived pathology files in the past decade were searched for cases of product of conception that had abnormal villous morphology and DNA genotyping results with the presence of abnormal allelic profiles at the tyrosine hydroxylase locus on chromosome 11p15.4. Nine cases of isolated allelic alterations at tyrosine hydroxylase locus were identified, among which three cases of paternal uniparental isodisomy at the tyrosine hydroxylase locus were eventually identified and presented in the study.

Clinicopathological review

The patients' demographic data, clinical presentations, pre- and post-curettage serum beta-hCG levels, and post-curettage follow-up data were retrieved and reviewed. Available hematoxylin and eosin slides for each case were reviewed by the authors and the following morphological features were systematically assessed: maximum size of chorionic villi, villous shape and contour, presence or absence of two villous populations, trophoblastic pseudo-inclusions, villous hydrops including cistern formation, abnormal trophoblast hyperplasia, presence of nucleated fetal red blood cells (RBCs) and other fetal tissues, villous stromal cellularity, and presence of stromal karyorrhexis.

P57 immunohistochemistry

Immunohistochemical stain was performed using p57 antibody (Leica, NCL-p57) at 1:100 dilution by the EnVision+ System from DAKO (Carpinteria, CA). Presence of nuclear immunostaining was assessed, and positive staining in chorionic villous stromal cells, cytotrophoblast, and intermediate trophoblast were considered a normal expression pattern. Absence of nuclear staining in villous cytotrophoblast and villous stromal cells were interpreted as abnormal imprinting loss of p57 expression. P57 staining in decidual tissue was used as positive internal control.

Table 1 STR loci analyzed by DNA genotyping (adapted from Promega, Inc)

Locus	Location	Number of alleles
TPOX	2p23-2pter	8
D3S1358	3p	9
FGA	4q28	28
D5S818	5q23.3-32	10
CSF1PI	5q33.3-34	10
D7S820	7q11.21-22	9
D8S1179	8p	12
TH01	11p15.5	10
vWA	12p12-pter	13
D13S317	13q22-q31	9
Penta E	15q	20
D16S539	16q24qter	9
D18S51	18q21.3	22
D21S11	21q11-21q21	26
Penta D	21q	14
Amelogenin	Xp22.1-22.3;Y	2

STR short tandem repeat

Tissue DNA genotyping

Tissue genotyping using PowerPlex® 16 System (Promega Corporation, Madison, WI, USA) was performed by multiplex polymerase chain reaction (PCR) at 15 short tandem repeat (STR) loci according to the manufacturer's instructions. Detailed chromosome locations and allelic information of each STR locus are provided in Table 1. One µl of the PCR product was mixed with 13 µl of Hi-Di and 0.5 µl sizing marker (GeneScan-500LIZ, Applied Biosystems, Inc.), followed by capillary electrophoresis on an ABI3130 platform. Data collection and analysis were performed using the GeneMapper software version 3.7 (Applied Biosystems, Inc., Foster City, CA, USA). PCR products were identified by fluorescent color and expected size range. Normal paired gestational endometrial tissue genotype was comparatively reviewed. The allelic patterns of maternal decidua and chorionic villous tissue were compared. The presence of two copies of paternal allele at a given locus without identifiable maternal allele was interpreted as evidence of paternal uniparental disomy. Paternal uniparental isodisomy was considered if the two copies of the paternal alleles were identical (homozygous) and paternal heterodisomy was considered if the two copies of the paternal alleles were different (heterozygous).

Clinicopathological presentations

The age of the three patients, including two Caucasians and one Asian patient, ranged from 32 to 35 years. All three

Table 2 Clinical presentation of paternal uniparental isodisomy of TH01 locus

Case no.	Patient race and age	Pregnancy history	Gestational age (weeks) at D/C	hCG prior to D/C (mIU/ml)	hCG after D/C (mIU/ml)	Clinical management
1	Asian; 35 years	Unknown	Missed abortion at 9 weeks of gestation	43,667	778 (1 week); 135 (3 weeks), 0 (8 weeks)	hCG monitoring
2	Caucasian; 35 years	G5P3A2	Missed abortion at 12 weeks of gestation	57,867	104 (2 weeks); 36.9 (4 weeks)	hCG monitoring
3	Caucasian; 32 years	G2P0	Missed abortion (? weeks of gestation)	19,055	6566 (1 week); 7018 (2 weeks), 7564 (3 weeks)	hCG monitoring, methotrexate chemotherapy followed by EMA-CO

D/C dilation and curettage, EMA-CO etoposide, methotrexate, actinomycin D, vincristine, and cyclophosphamide, hCG human chorionic gonadotropin

Table 3 Histology, p57 immunostain, and differential diagnosis

| Case #	Chorionic villous morphology								P57 immunostain	Differential diagnosis
	Villous enlargement	Two villous populations	Trophoblastic pseudo-inclusions	Fetal RBC	Villous hydrops	Villous stromal karyorrhexis	Hypercellular villous stroma	Abnormal trophoblast proliferation		
1	Marked	Yes	None	None	Marked	None	No	None	Loss of expression in cytotrophoblast of enlarged hydropic villi and stromal cells in all villi	Partial mole
2	Marked	No	Rare	None	Marked	Present	Present	Mild	Normal expression	Complete Mole
3	None	No	None	None	None	Present	No	Marked	Loss of expression in villous stromal cells and cytotrophoblast	Early partial and complete mole

RBC red blood cell
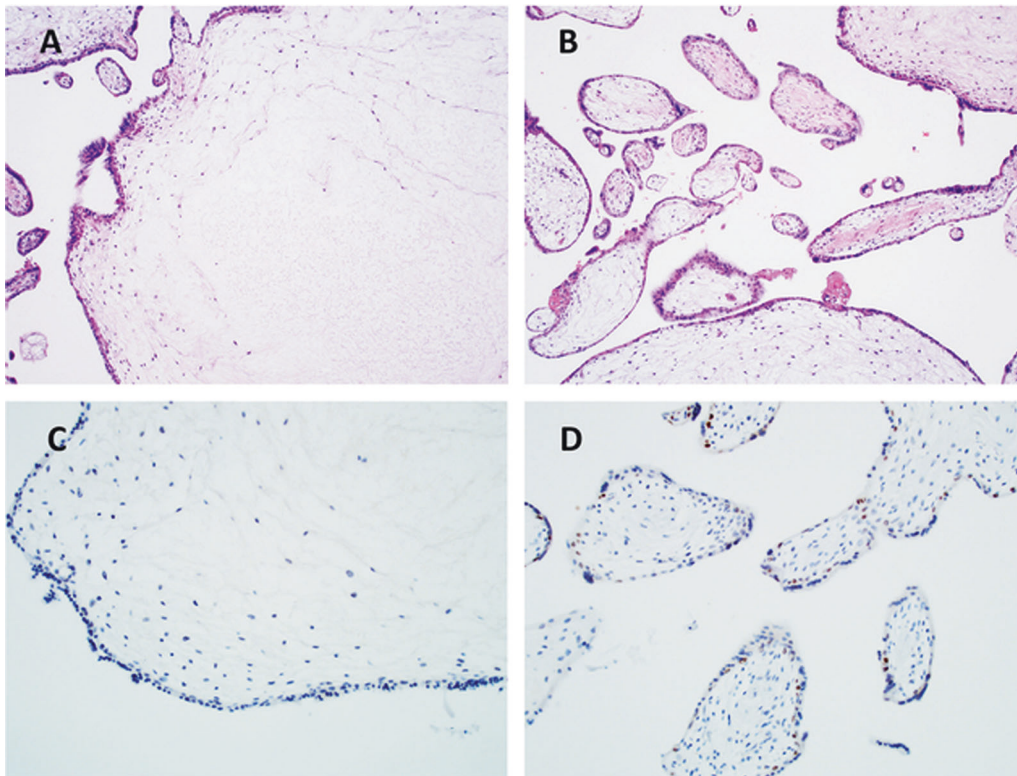
Fig. 1 Histopathological features of case 1. Markedly enlarged hydropic villi with cistern formation (**a**) are admixed with small, non-hydropic villi with mild fibrosis (**b**). P57 immunostaining is absent in the stromal cells of both types of chorionic villi (**c**, **d**) and in the cytotrophoblasts of enlarged, hydropic villi (**c**). However, retained p57 expression is observed in the cytotrophoblasts of small fibrotic villi (**d**)

patients presented with missed abortion during the first trimester of gestation (Table 2). All three cases showed abnormal chorionic villi with histological and p57 immunohistochemical features mimicking either partial or complete mole (Table 3).

Case 1 was a 35-year-old Chinese woman who presented with missed abortion at 9 weeks of gestation with serum beta hCG of 43,667 mIU/ml. The curettage specimen consisted of an aggregate of partially hydropic chorionic villi on gross examination. Microscopically, there were two distinct populations of chorionic villi: markedly enlarged hydropic villi with cistern formation and small, non-hydropic villi with mild fibrosis (Fig. 1a, b). Trophoblastic pseudo-inclusions, abnormal trophoblastic proliferation, and fetal development including nucleated RBCs were not present. There was absence of p57 immunostaining in stromal cells of both types of chorionic villi and in the cytotrophoblasts of the hydropic villi. However, retained p57 expression was observed in the cytotrophoblasts of small fibrotic chorionic villi (Fig. 2c, d). The patient had an uneventful clinical course with tapering off serum beta hCG to zero at 8 weeks after the curettage.

Case 2 was a 32-year-old Caucasian woman presenting with missed abortion and a serum beta hCG of 57,867 mIU/ml. The curettage specimen consisted of a loose aggregate of predominately membranous to papilliferous soft tissue with half of the villi showing marked cystic hydropic changes. Fetal parts were not seen grossly or microscopically. The chorionic villi showed marked stromal edema with frequent cistern formation and abnormal villous trophoblast proliferation (Fig. 2a–c). Occasional trophoblastic pseudo-inclusions were also present. The villous stroma was hypercellular with the presence of karyorrhexis and contained occasional fetal blood vessels although nucleated RBCs were not seen. P57 immunostain showed retained expression in villous cytotrophoblast and stromal cells (Fig. 2d). Despite the retained p57 expression, the histological changes were suggestive of a very early complete mole. The patient had an uneventful post-curettage follow-up with serum beta hCG levels of 104 and 37 mIU/ml at 2 and 4 weeks, respectively.

Case 3 was a 32-year-old Caucasian G2P0 female who presented with ultrasound findings of an intrauterine gestational sac and yolk sac without a definitive fetal pole. No cardiac activity was identified along with a second smaller cystic area within the decidual reaction. Three weeks later, she reported light vaginal bleeding. Ultrasound reidentified the intrauterine gestational sac with a yolk sac but no fetal pole was seen and the second cystic focus persisted and increased in size. Findings were
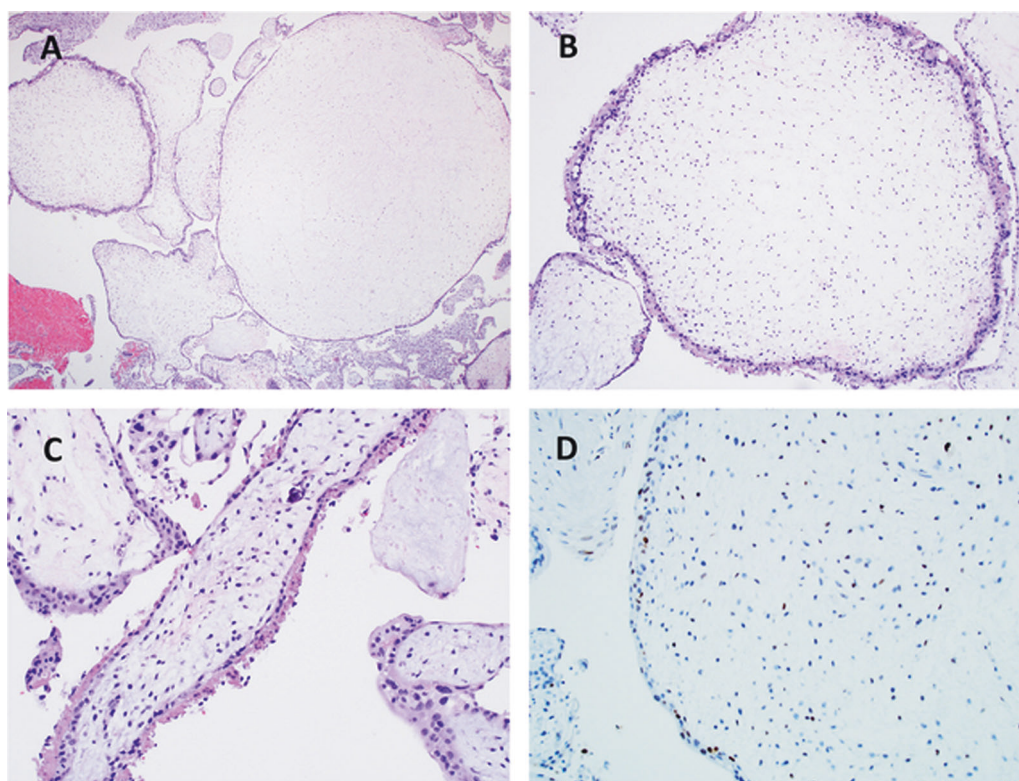
Fig. 2 Histopathological features of case 2. Marked hydropic changes with frequent cistern formation (**a**), abnormal circumferential trophoblast hyperplasia (**b**), and hypercellular villous stroma with karyorrhexis (**c**). P57 immunostain shows retained expression in both cytotrophoblast and villous stromal cells (**d**)

thought to be consistent with fetal demise with no clear etiology for the second focus. At that time, beta hCG was 113,742 mIU/ml and misoprostol was given. One week later, there was no longer a gestational sac present on ultrasound, but there were possible retained products. The patient opted for expectant management. Beta hCG initially declined to 3902 but subsequently rose to 19,055 mIU/ml within 3 weeks. Dilation and curettage was then performed. On gross examination, the curettage specimen consisted of an aggregate of fibro-membranous tissue and no hydropic changes were seen. Microscopically, the chorionic villi showed abnormal villous surface irregularities and mild fibrotic changes, although significant villous size increase was not seen (Fig. 3a). Marked abnormal villous trophoblastic proliferation was present (Fig. 3b, c). Prominent stromal karyorrhexis was observed in the majority of the villi. No fetal development including nucleated RBCs were seen. P57 immunostain showed loss of nuclear staining in both villous cytotrophoblast and stromal cells (Fig. 3d). Despite an initial decline, the serum hCG level rose following the curettage (Table 2). Chest X-ray was negative. The patient was started on single-agent methotrexate; however, the elevated hCG level persisted on methotrexate. She was then switched to single-agent actinomycin D,

which also failed to have an impact on the serum hCG level. Re-staging imaging at this time showed 3 small lung nodules and a 2 × 2.9 cm uterine mass. Head imaging was negative. The patient was ultimately transitioned to multiagent chemotherapy consisting of etoposide, methotrexate, actinomycin D, vincristine, and cyclophosphamide (EMA-CO), with resolution to normal hCG after 1 cycle. She received three additional cycles of consolidation EMA-CO and remained in remission.

DNA genotyping results

DNA genotyping was informative at all STR loci for interpretation in each case. All three cases revealed the presence of two identical, distinct paternal allelic copies at tyrosine hydroxylase locus in chorionic villi without the paired maternal alleles in the corresponding maternal gestational endometrium, consistent with paternal uniparental isodisomy (Fig. 4). In case 2, in addition to uniparental isodisomy at the tyrosine hydroxylase locus, three allelic copies at the D16S538 locus were also found consistent with the presence of trisomy 16 (data not shown). Otherwise, a balanced biparental genetic profile was seen at all other STR loci in all three cases (Fig. 4).
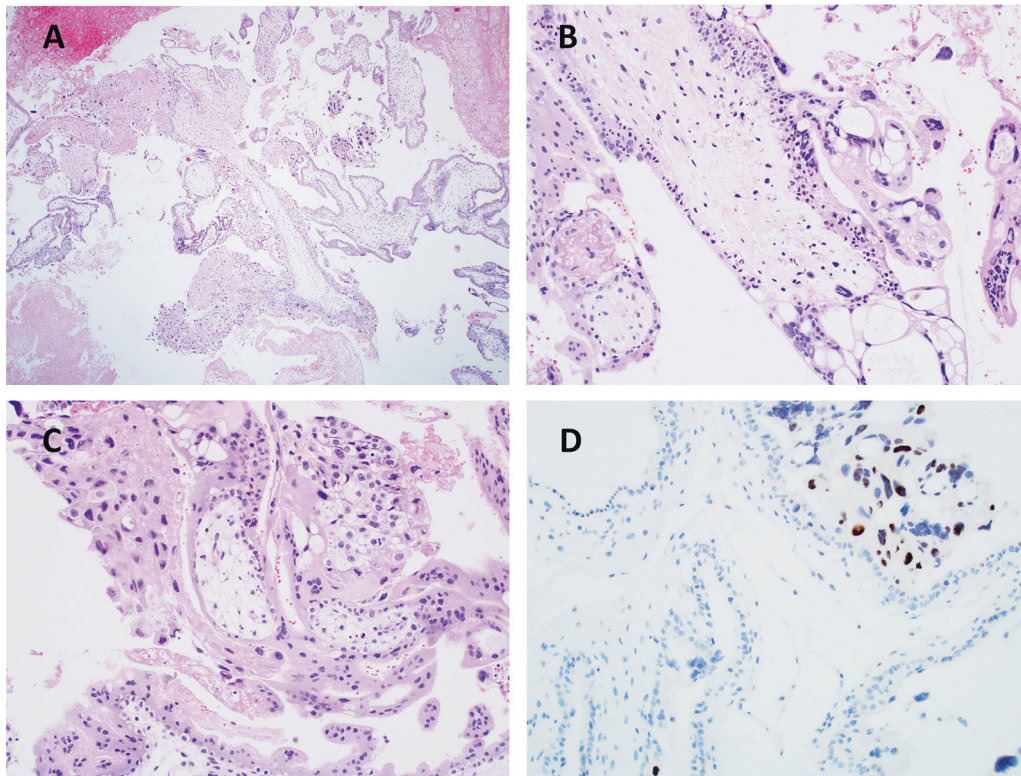
Fig. 3 Histopathological features of case 3. Normal-sized chorionic villi with surface irregularities and mild fibrotic changes (hematoxylin and eosin (H&E); **a**, **b**) and abnormal villous trophoblastic proliferation with marked atypical trophoblastic cells (H&E; **b**, **c**). P57 immunostain shows absent nuclear staining in both villous cytotrophoblast and stromal cells (**d**)

Discussion

We present three cases of paternal uniparental isodisomy at the tyrosine hydroxylase locus on chromosome 11p15.4 with pathological and clinical manifestations simulating molar gestation at various histological and biological levels. The histological findings are remarkably variable among the three cases. The chorionic villi in case #1 demonstrated significant villous enlargement and hydrops with frequent cistern formation and presence of two villous populations, characteristically seen in partial hydatidiform moles. Inconsistent with a partial mole, however, there was a loss of p57 expression in the stromal cells of all chorionic villi and in cytotrophoblasts of the enlarged hydropic villi, while normal p57 expression was observed in the cytotrophoblasts of the smaller fibrotic villi. The overall histological features of case #2 overlap with those of an early complete mole, including abnormal villous configuration, diffuse villous hydrops, abnormal trophoblastic hyperplasia, hypercellular villous stroma with frequent karyorrhexis, and absence of fetal RBCs. Paradoxically, p57 immunostain showed normal expression in this case. Case #3 is remarkable for its marked atypical villous trophoblastic proliferation without other histological features of either partial or complete mole. However, abnormal loss of p57 expression was observed in both the cytotrophoblast and villous stromal cells.

In all three cases in our study, an abnormal tyrosine hydroxylase locus on chromosome 11p15.4 was observed with two identical copies of paternal alleles without the corresponding maternal allele, consistent with uniparental disomy of chromosome 11. Although in many cases uniparental disomy is without any pathological and clinical consequences, some uniparental disomies can result in abnormality of the affected gestations or individuals through disruption of parent-of-origin gene expression regulation [8]. Only five chromosomes have been shown to have a definite phenotypic effect due to uniparental inheritance of imprinted regions: maternally derived chromosomes 7, 14, and 15; and paternally derived chromosomes 6, 11, 14, and 15 [9]. It should be pointed out that only one locus was analyzed on chromosome 11 in our study, thus whether the tyrosine hydroxylase locus isodisomy in our cases represents partial or entire chromosome 11 isodisomy requires further investigation. Nevertheless, the abnormal loss of p57 expression in two of the three cases is in line with at least regional paternal isodisomy of chromosome 11, particularly the chromosome 11p15 region.

The mammalian placenta is enriched with the expression of imprinted genes, many of which are related to cellular

Fig. 4 Paternal uniparental isodisomy at the tyrosine hydroxylase locus by short tandem repeat genotyping. Representative five short tandem repeat loci are shown from each of the three cases. All three cases demonstrate the presence of two identical, distinct paternal allelic copies at the tyrosine hydroxylase locus (second locus from left, arrow heads) in chorionic villi (V) without a matching maternal allele, comparing with the allelic pattern in their corresponding gestational endometrium (E)
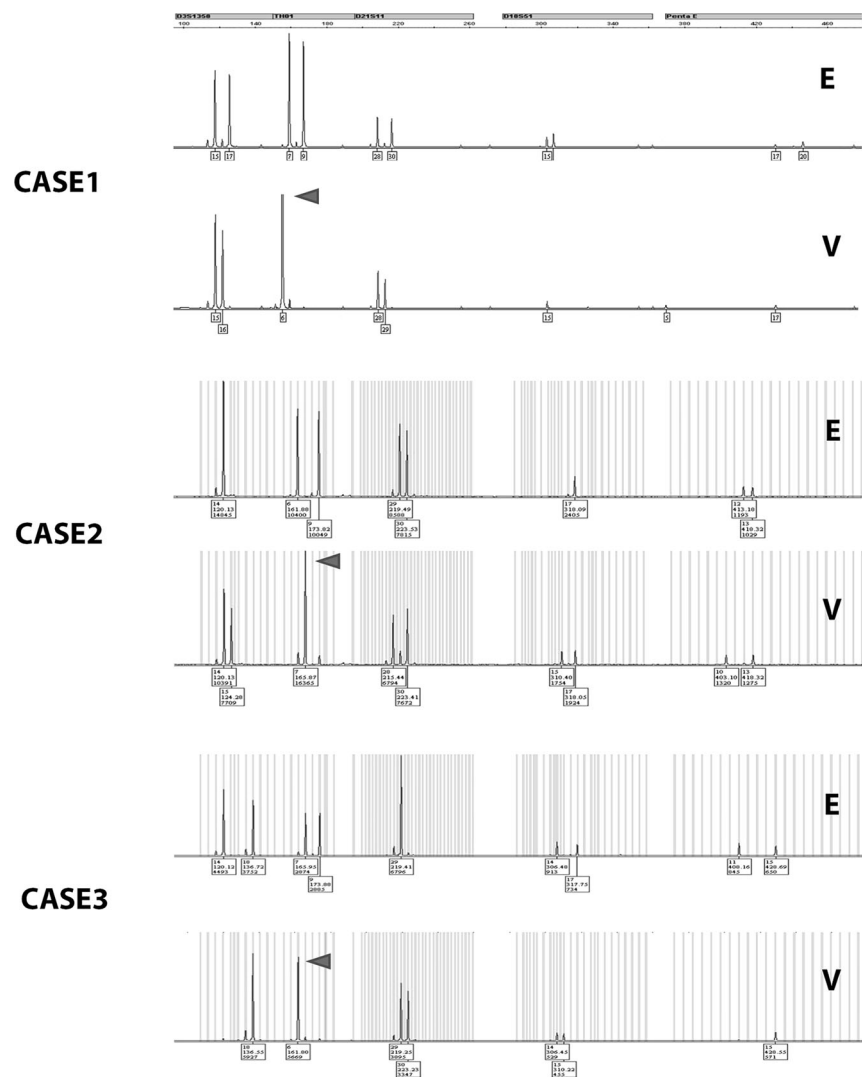
proliferation and growth [10, 11] and are imprinted only in the placenta. Moreover, almost all imprinted genes known to be specific to the placenta are paternally imprinted and are functionally expressed only from the maternal alleles [12–14]. Absence of the maternal genome together with abnormal paternal imprinting gene expression are considered key molecular bases for the development of hydatidiform moles [15, 16]. Chromosome 11p15.5 region contains a large number of paternally imprinted genes that are important for human placental development and function. The Kcnq1 imprinting control center on chromosome 11 is critical for imprinting control of many such genes through RNA coating and epigenetic modification [14]. It should be noted that the tyrosine hydroxylase locus at chromosome 11p15.4 is close to this major imprinting region at 11p15.5, within which the Kcqu1 imprinting control center and a large number of paternally imprinted genes including p57 are located. Beckwith–Wiedemann syndrome is a disorder characterized by accelerated growth

with organomegaly, increased risk of tumor development, and abnormal placenta in the form of placental mesenchymal dysplasia or "pseudo-partial mole" [17]. The genetic basis of the disorder is the abnormal imprinted gene regulation on chromosome 11 leading to disrupted imprinting gene expression. It is worth noting that an estimated 25% of Beckwith–Wiedemann syndrome cases are associated with uniparental isodisomy of chromosome 11 resulting in an imbalanced paternal and maternal imprinting gene expression [17]. It can be speculated that paternal uniparental disomy of either regional or the entire chromosome 11 may lead to an altered imprinting gene regulation, sufficient for the development of molar-like conditions.

P57 is a gene product of paternally imprinted gene *CDKN1C* on chromosome 11p15.5, a cyclin-dependent kinase inhibitor [18] that has biological functions as a tumor suppressor and its expression has been reported in various human malignancies [19]. Loss of its expression is associated with trophoblastic hypertrophy and placentomegaly

in mice [20] and abnormal trophoblastic proliferation in human molar gestations [18, 21, 22]. In the human placenta, the gene is paternally imprinted and the maternal allele is responsible for the nuclear expression of the protein in villous cytotrophoblasts and stromal cells [22]. In gestational tissue, loss of chorionic villous p57 expression may occur in the following settings: diandric complete mole, paternal uniparental disomy of chromosome 11, and a mutation of the maternal allele of p57 gene in a non-molar gestation. Complete hydatidiform moles characteristically demonstrate loss of p57 expression in villous cytotrophoblast and stromal cells as a result of their paternal-only genome. However, aberrant p57 expression with abnormal villous morphology has been documented in diploid and biparental gestations including familial biparental complete mole and Beckwith–Wiedemann syndrome [23]. Loss of p57 expression and abnormal villous morphology resulting from paternal uniparental isodisomy may be erroneously interpreted as a complete mole without molecular genetic studies [24]. Loss of maternal chromosome 11 material may explain the abnormal p57 expression in our cases #1 and #3 and may be responsible for the abnormal villous morphology and atypical trophoblastic proliferation in case #3. Recently, a case of paternal uniparental isodisomy of chromosome 11 combined with multiple trisomies was reported to have abnormal villous morphology and loss of p57 expression in villous stroma and cytotrophoblast, therefore simulating a complete mole [6]. Such abnormal loss of maternal chromosome 11 may explain the abnormal expression of p57 and is likely responsible for the abnormal villous morphology and atypical trophoblastic proliferation observed in our cases. However, the reason for the retained p57 expression in cytotrophoblasts of the small fibrotic villi in case #1 and the normal p57 expression in case #2 is largely unclear but relaxation of imprinting may be a possible explanation. Another possible explanation is the presence of mosaicism in the placental tissue in case #1. However, all three specimens were obtained by curettage procedure, therefore the molecular data represent the genetic profile of mixtures of chorionic villi from different areas of the placenta. The fact that the allelic patterns in all three cases are distinct at tyrosine hydroxylase locus without the presence of maternal allele makes mosaicism a less likely event.

While the post-curettage clinical course was uneventful in two patients (cases #1 and #2) with normalization of serum beta hCG within 4–8 weeks, the third patient (case #3) presented with clinical complications simulating persistent gestational trophoblastic disease/neoplasia. Despite an initial decline from pre-curettage 19,055 to 6566 mIU/ml in the first week, beta hCG rose to 7018 (2 weeks) and 7564 mIU/ml in the third week. After failing a single-agent chemotherapy and with further development of a

uterine mass and possible lung lesions, the patient ultimately received multiagent chemotherapy consisting of EMA-CO leading to normalization of serum beta hCG and a long-term remission. While the risk of developing post-curettage gestational trophoblastic disease is 8.9–20% following a complete mole and 0.2–4% after a partial mole [1–5], non-molar gestations generally have a minimal risk of persistent gestational trophoblastic disease. It can be speculated that, in case #3, paternal uniparental isodisomy of chromosome 11 may have disrupted the imprinting regulation in such a significant way that was sufficient to promote abnormal trophoblastic proliferation and biological behavior simulating a true hydatidiform mole with possible malignant transformation into bona fide trophoblastic neoplasia. While the current classification of complete hydatidiform mole is defined at the genetic level by its androgenetic-only genome [25], in-depth molecular investigations (array comparative genomic hybridization and/or next-generation sequencing) are needed to fully characterize the genetic abnormalities of the involved chromosome 11 loci or entire chromosome 11 to ascertain if indeed gestations with uniparental isodisomy at tyrosine hydroxylase locus can fully recapitulate a complete mole and therefore can be classified as a variant of hydatidiform mole for patient management.

In conclusion, paternal uniparental isodisomy at the tyrosine hydroxylase locus results in abnormal gestations that may mimic hydatidiform moles morphologically and clinically. The degree to which it simulates a hydatidiform mole may depend on the extent of altered expression of paternally imprinted genes on chromosome 11p15. Patients after a missed abortion with paternal uniparental disomy at the tyrosine hydroxylase locus, particularly those with significant atypical trophoblastic proliferation and abnormal p57 expression, should be followed clinically by serum hCG monitoring. Future studies of additional cases combined with in-depth molecular investigations are essential to elucidate the pathogenesis of paternal uniparental disomy of chromosome 11 in the development of hydatidiform mole-like conditions.

Compliance with ethical standards

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