SHORT COMMUNICATION

Double Trisomy 16 and 22 Clinically Mimic Partial Hydatidiform Mole in a Case of Subsequent Pregnancy Loss

Lajos GERGELY[1,2], Miroslav KORBEĽ[2,3], Adam ADAMEC[2,3], Vanda REPISKÁ[1,2], Pavel BABÁL[2,4], Katarína MELIŠOVÁ[1], Petra PRIŠČÁKOVÁ[1,2]

[1]Institute of Medical Biology, Genetics and Clinical Genetics, Faculty of Medicine, Comenius University Bratislava, Bratislava, Slovakia, [2]Centre for Gestational Trophoblastic Disease of Slovak Republic, Bratislava, Slovakia, [3]1st Department of Gynaecology and Obstetrics, Faculty of Medicine, Comenius University Bratislava, Bratislava, Slovakia, [4]Institute of Pathological Anatomy, Faculty of Medicine, Comenius University Bratislava, Bratislava, Slovakia

Received June 7, 2023
Accepted August 27, 2023

Summary

A case of double trisomy 16 and 22 in the second pregnancy loss is presented. DNA analyses (short tandem repeats genotyping) of miscarriage specimen was indicated because of ultrasound suspicion of partial hydatidiform mole. After the partial hydatidiform mole exclusion, further DNA analyses focused on the most common aneuploidies causing pregnancy loss, detected double trisomy 16 and 22 in the product of conception. The couple was referred to clinical genetic consultation and normal parental karyotypes were proved. For further explanatory purposes, archived material from the first pregnancy loss was analyzed and trisomy of chromosome 18 was detected. By comparison of allelic profiles of the mother, father, and both losses, the maternal origin of all aneuploidies was proven what can be attributed to frequent meiosis errors, probably due to advanced maternal age (44 years at the first loss and 45 years at the second loss). In conclusion, aneuploidies can mimic partial hydatidiform mole. Genetic analysis is helpful on the one hand to rule out partial hydatidiform mole and on the other hand to identify aneuploidies and in this way to determine the cause of miscarriage.

Keywords

Partial hydatidiform mole • Double trisomy • Recurrent pregnancy loss • DNA analysis

Corresponding author

L. Gergely, Institute of Medical Biology, Genetics and Clinical Genetics, Faculty of Medicine, Comenius University Bratislava, Sasinkova 4, 811 08 Bratislava, Slovakia. E-mail: lajos.gergely@fmed.uniba.sk

Case Report

Aneuploidies and triploidy (such as partial hydatidiform mole) represent the dominant causes of first-trimester pregnancy losses [1]. Less frequently, more than one aneuploidy can be found in one product of conception. Autosomal double aneuploidy cases are typically characterized by miscarriage in the early weeks of gestation and advanced maternal age appears to be the strongest risk factor [2-3]. On the other hand, mainly because of the low frequency of these cases and because cytogenetic analysis of miscarriage specimens is not routinely performed in all institutions, the amount of published literature on this topic is insufficient to provide a reliable guide for genetic consultation about the prognostic value for further pregnancies.

We present a case of a 45-year-old patient in the 7th week of gestation based on sonography (10th week according to the last menstrual period) with clinically suspected partial hydatidiform mole based on suspicious sonographic appearance – "molar placenta" (Fig.1) combined with serum human chorionic gonadotropin levels 50951 IU/l. No parts of the embryo were detected. In the medical history of the patient there was a cesarean delivery of a healthy boy 4 years ago and an early complete miscarriage in the 8th week of gestation 9 months ago, but the aborted product of conception in the vagina was sent for histopathological examination.

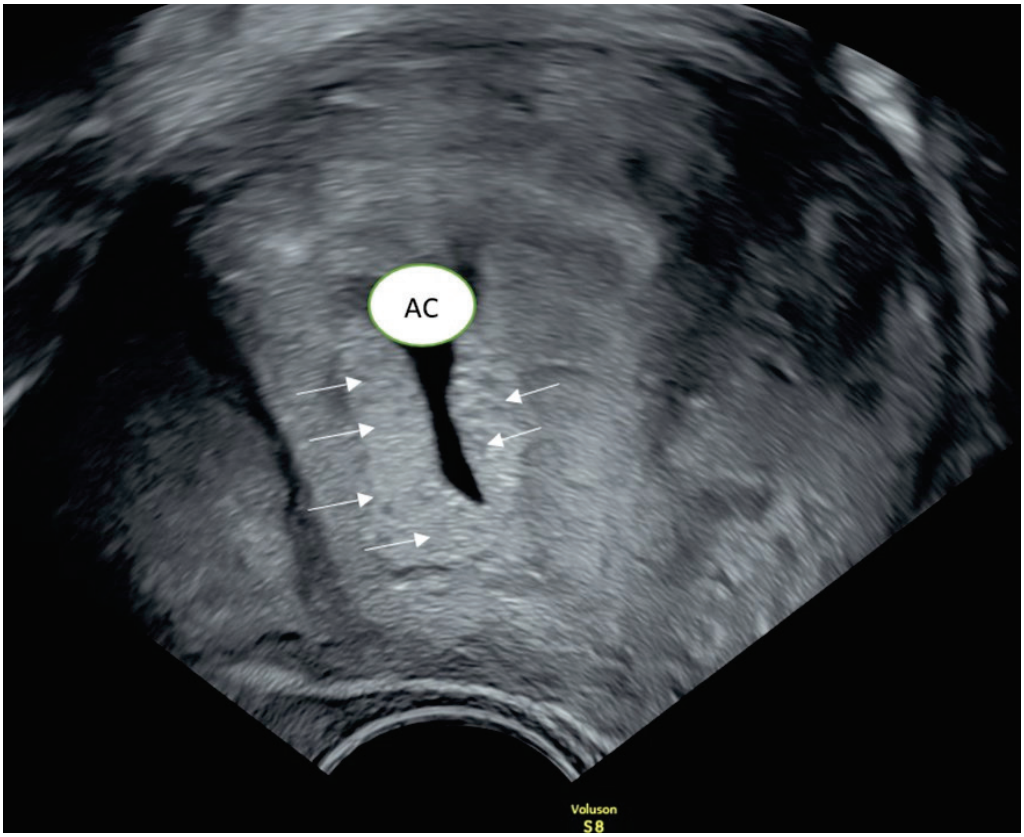

Fig 1. Transvaginal ultrasonographic picture of the second pregnancy loss (Voluson S8 GE, source: Centre for Gestational Trophoblastic Disease of Slovak Republic). AC - irregular amniotic cavity without embryonic structure, white arrows - multiple small cystic spaces inside the placenta ("molar placenta") – „swiss - cheese" appearance

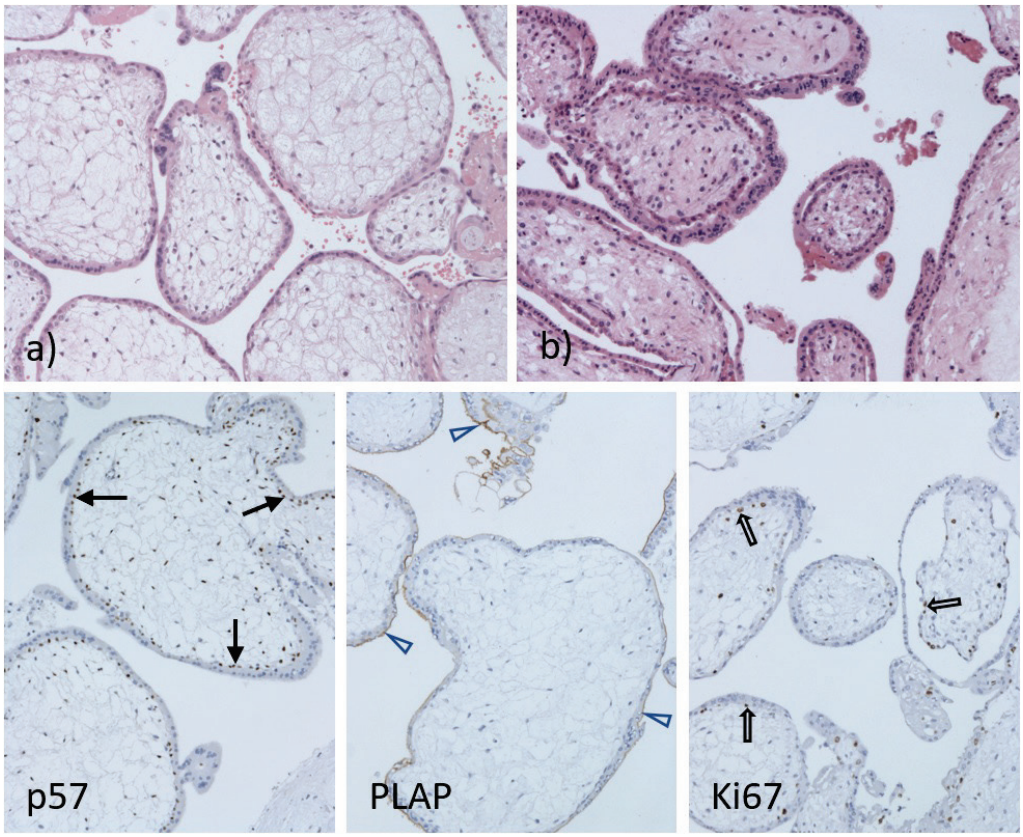

Fig. 2. Histology of the placental tissue obtained from the abortion 1 year ago (**a**) and the recent abortion (**b**). The first was classified as an abortion with hydropic villous degeneration. The placenta of the recent abortion showed more pronounced trophoblast proliferation, p57 nuclear positivity in up to 70 % of the cytotrophoblast cells but only weak incomplete PLAP membrane positivity of the syncytio-trophoblast and low (< 25 %) Ki67 cytotrophoblast proliferation index, excluding the diagnosis of hydatidiform mole. a, b: Hematoxylin and eosin; immune - peroxidase technique, DAB; 200x.

Evacuation of the uterine cavity was carried out. One part of the chorionic villi was collected in a physiological solution for DNA analysis and the rest of the gained material was fixed in formalin and sent for histopathological and immunohistochemical examination. The peripheral blood sample of the patient was also collected for DNA analysis. Histopathological and immunohistochemical examination revealed only regressively hydropically changed residues of pregnancy with a positivity of p57 in the cytotrophoblast (excluding complete hydatidiform mole) (Fig. 2b). DNA from the peripheral blood of the patient and unfixed chorionic villi of a product of conception was isolated using *DNeasy Blood & Tissue Kit* (Qiagen) and short tandem repeats (STR) genotyping with quantitative fluorescence polymerase chain reaction (QF-PCR) technique was performed using kit *GenePrint® 10 System* (Promega). Monogynic monoandric diploidic (biparental) genome composition of the product of conception was detected, excluding the diagnosis of partial hydatidiform mole (triploid genome).

The DNA was further examined with QF-PCR technique using kit *Devyser Extend v2* (Devyser) to detect aneuploidies of chromosomes 13, 15, 16, 18, 21, 22, X and Y as possible causes of miscarriage. This kit also works on the principle of STR genotyping. The analysis revealed gonosomal complement XX, the physiological number of chromosomes 13, 15, 18, 21, and trisomy of chromosomes 16 and 22 (Fig. 3a). Due to the unusual finding of double trisomy in the product of conception and the medical history of previous pregnancy loss, the patient and her 48-year-old partner were referred to clinical genetic consultation. Peripheral blood samples from both were collected for karyotyping, revealing normal karyotypes of the patient and the partner.

Archived paraffine blocks from the first abortion of the patient (Fig. 2a) were searched, chorionic villi were microdissected and DNA was isolated using the *QIAamp DNA FFPE Tissue Kit* (Qiagen). The isolated DNA was analysed for aneuploidies in the same way. Gonosomal complement XY, a physiological number of chromosomes 13, 15, 16, 21, 22, and trisomy of chromosome 18 was proved (Fig.3b).

In order to determine whether the found aneuploidies (which are the definite cause of the pregnancy losses) are the result of abnormal oogenesis or spermatogenesis, DNA was also isolated from the peripheral blood of the partner, then both the DNA of the patient and the partner were examined using the kit *Devyser Extend v2* (Devyser). STR alleles of the patient, the partner, and both products of conception were compared, and the maternal origin of the extra chromosome 18 in the first loss and maternal origin of the extra chromosomes 16 and 22 in the second loss were established (Fig. 3). The maternal origin of the aneuploidies in combination with normal parental karyotypes points out abnormal oogenesis potentially attributable to advanced maternal age.

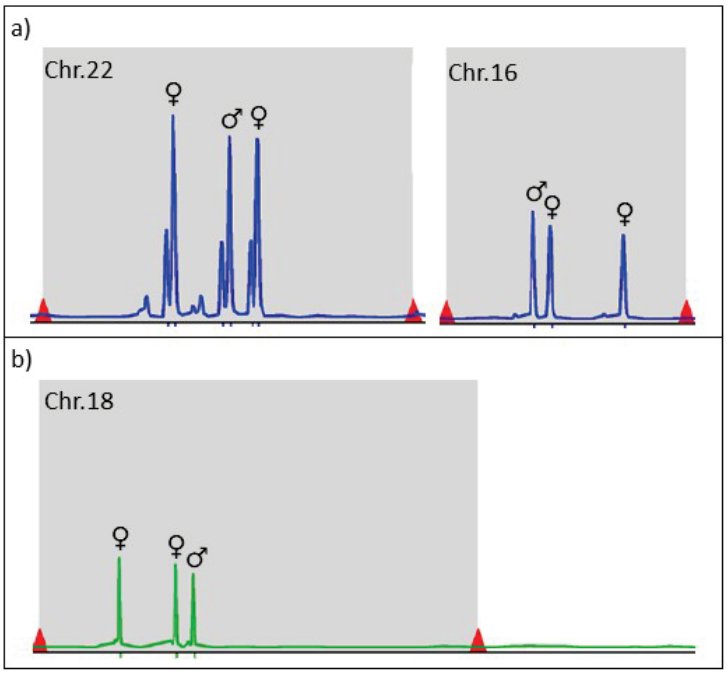

Fig. 3. Parts of QF-PCR electrophoretograms for the first (**b**) and the second (**a**) pregnancy loss. a) Double trisomy of chromosomes 16 (Chr.16) and 22 (Chr.22) of maternal origin. b) Trisomy of chromosome 18 (Chr.18) of maternal origin. The maternal (♀) or paternal (♂) origin of alleles was determined by comparing with electrophoretograms of the patient and her partner.

In this case, precise genetic diagnosis (STR genotyping) of suspected partial hydatidiform mole helped to definitely differentiate between a partial hydatidiform mole and hydropic abortion. Follow-up because of potential malignant transformation is indicated only for patients with proven partial mole, which eliminates unnecessary traumatization of other patients [4]. Genetic analysis of products of conception represents a helpful tool in the investigation of causes of recurrent pregnancy loss and enables to define the cause of losses in a plenty of cases which were according to standard recurrent pregnancy loss workup (parental karyotyping, hematological, endocrinological, sonographic etc. examinations) labelled as idiopathic [5]. In the presented case, analyses based on the QF-PCR technique were used for their practicality and reliability. This technique eliminates the risk of culture failure or maternal cell contamination frequently experienced with conventional karyotyping, further, it makes it possible to analyze DNA isolated from unviable or even formalin fixed paraffin embedded tissue samples [4,6-8].

Conclusion

In the presented case of two subsequent pregnancy losses, the cause of both losses was determined using the QF-PCR technique, further, the maternal origin of all detected aneuploidies was proved which points out abnormalities in meiosis during oogenesis possibly attributable to advanced maternal age. In similar cases with unusual cytogenetic findings in products of conception (double trisomy 16 and 22), especially in the context of recurrent pregnancy loss, clinical genetic consultation is highly recommended to appropriately answer the questions of parents and to provide reliable medical information for their decisions according to further reproduction.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

The study was funded by the Ministry of Education, Science, Research and Sport of the Slovak Republic through grant VEGA 1/0559/22. We would like to express our gratitude to our laboratory technicians, Dagmar Nováková, Brigita Jašková, and Alena Hollá, for their invaluable assistance and cooperation.

References

1. Malova J, Bohmer D, Luha J, Pastorakova A, Cierna Z, Braxatorisova T. Single umbilical artery and reproduction losses in Slovak population: relation to karyotype and fetal anomalies. Bratisl Lek Listy 2018; 19:330-334. https://doi.org/10.4149/BLL_2018_062
2. Diego-Alvarez D, Ramos-Corrales C, Garcia-Hoyos M, Bustamante-Aragones A, Cantalapiedra D, Diaz-Recasens J, Vallespin-Garcia E, Ayuso C, Lorda-Sanchez I. Double trisomy in spontaneous miscarriages: cytogenetic and molecular approach. Hum Reprod 2006;21:958-966. https://doi.org/10.1093/humrep/dei406
3. Subramaniyam S, Pulijaal VR, Mathew S. Double and multiple chromosomal aneuploidies in spontaneous abortions: A single institutional experience. J Hum Reprod Sci 2014;7:262-268. https://doi.org/10.4103/0974-1208.147494
4. Gergely L, Petrovic R, Feketova Z, Klimova D, Danihel L, Mosna K, Mrazova H, Korbel M, Repiska V, Priscakova P. Partial hydatidiform moles with unclear histopathological profile - importance of genetic diagnostics. Ceska Gynekol 2021;86:381-386. https://doi.org/10.48095/cccg2021381
5. Papas RS, Kutteh WH. A new algorithm for the evaluation of recurrent pregnancy loss redefining unexplained miscarriage: review of current guidelines. Curr Opin Obstet Gynecol 2020;32:371-379. https://doi.org/10.1097/GCO.0000000000000647
6. McClelland LS, Allen SK, Larkins SA, Hamilton SJ, Marton T, Cox PM, Hargitai B, Johnston EH, Morgan C, Hardy G. Implementation and experience of an alternative QF-PCR and MLPA diagnostic strategy to detect chromosomal abnormalities in fetal and neonatal pathology samples. Pediatr Dev Pathol 2011;14:460-468. https://doi.org/10.2350/11-01-0971-OA.1

7. Zou G, Zhang J, Li XW, He L, He G, Duan T. Quantitative fluorescent polymerase chain reaction to detect chromosomal anomalies in spontaneous abortion. Int J Gynaecol Obstet 2008;103:237-240. https://doi.org/10.1016/j.ijgo.2008.07.014
8. Russo R, Sessa AM, Fumo R, Gaeta S. Chromosomal anomalies in early spontaneous abortions: interphase FISH analysis on 855 FFPE first trimester abortions. Prenat Diagn 2016;36:186-191. https://doi.org/10.1002/pd.4768