

## Case Report

# Glycogen Storage Disease Type IV: A Case With Histopathologic Findings in First-Trimester Placental Tissue

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**Summary:** A 30-yr-old woman presented with 2 consecutive miscarriages within 7 mo. Histopathologic examination of the placental tissue showed intracytoplasmic inclusion vacuoles with a strong reaction in Periodic acid-Schiff staining and a slightly pallor reaction in alcian blue staining. Additional molecular genetic analyses confirmed glycogen storage disease Type IV with the finding of compound heterozygosity for 2 mutations (c.691+2T>C and c.1570C>T, p.R524X) in the *GBE1* gene. We conclude that glycogen storage disease Type IV can cause early miscarriage and that diagnosis can initially be made on histopathologic examination. Genetic analysis is required to confirm the diagnosis and to offer prenatal genetic testing in future pregnancies.

**Key Words:** Glycogen storage disease Type IV—Placenta—Intracytoplasmic inclusion vacuoles—First trimester.

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Glycogen storage disease Type IV (GSD-IV) also known as Andersen disease is a rare autosomal recessive disorder caused by deficient activity of glycogen branching enzyme (GBE) leading to the accumulation of amylopectin-like structures in the affected tissue (1,2). GBE is encoded by the glycogen branching enzyme 1 (*GBE1*) gene located on chromosome 3p14. It is the only gene in which mutations are known to cause GSD-IV. The disease is characterized by a highly variable expressivity both in terms of tissue involvement and the age of onset, and the GSD-IV phenotype ranges from mild to severe (1). Placental tissue involvement was first described in 2008 in 2 pregnancies with fetuses delivered in the third trimester (2). In this case report, we present GSD-IV as a cause of early miscarriage

with fetal loss as early as in the first trimester and with pronounced histologic findings in the placental tissue.

## CASE REPORT

A 30-yr-old otherwise healthy woman presented with 2 consecutive miscarriages in the first trimester within 7 mo. In the first pregnancy, she experienced some bleeding at gestational week 12+3 and in the second a routine ultrasound scan revealed no fetal heartbeat at gestational week 10+1. Surgical removal of the tissue was performed and the tissue was histologically examined.

### Placental Histopathology

The histologic examinations confirmed the presence of 2 first-trimester abortions with sheets of decidua and partly degenerated chorionic villi. The chorionic villi showed an irregular trophoblastic layer, whereas the villous stroma was unremarkable without any vacuolar changes in the stromal or Hofbauer cells. In the intervillous space, big clusters

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of cells with an appearance of signet-ring cells were found either surrounded by trophoblastic cells or adjacent to the chorionic villi (Fig. 1). These “signet-ring”-like cells had a big central intracytoplasmic inclusion vacuole containing a light eosinophilic, homogenic material, which showed a strong reaction in Periodic acid-Schiff staining (Fig. 2), a slightly pallor reaction in alcian blue staining, and partially strong reaction in Periodic acid-Schiff staining treated with amylase. The tissue was stained with a broad panel of immunohistochemical stains, which showed positive staining in the vacuolated cells with CK7, p57, CD10, and HCG (Fig. 3), whereas there was negative staining with CD68, CD45, ER, Muc2, Muc5AC, CDx2, MAMGL, GCDFP, and Ki67, thereby documenting that the cells represented extravillous trophoblastic cells. These unique findings in both missed abortions raised suspicion of GSD-IV, and the tissue was prepared for genetic analysis.

#### Molecular Genetics

DNA was extracted from the placental tissue and molecular genetic testing with sequencing of *GBE1* was performed. This revealed compound heterozygosity for 2 previously described mutations, c.691+2T>C and c.1570C>T, p.R524 × (3,4). Testing of the couple showed biallelic inheritance and the diagnosis GSD-IV was confirmed. The couple was offered prenatal genetic testing in subsequent pregnancies.

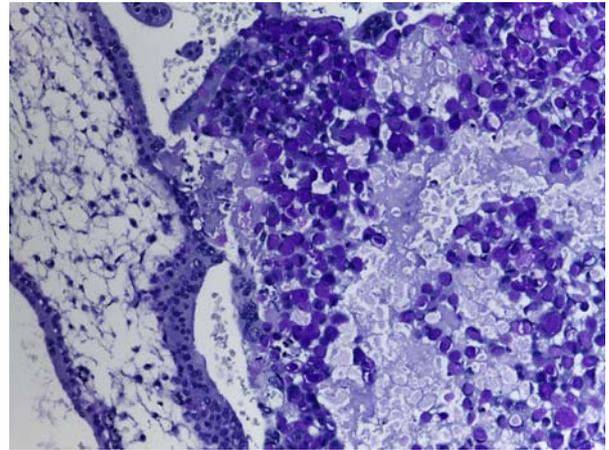


FIG. 2. Periodic acid-Schiff staining (20 × magnification) of the intracytoplasmic vacuoles.

#### DISCUSSION

GSD-IV is characterized by a marked clinical heterogeneity and since the introduction of the disease by Andersen in 1952, different subtypes of GSD-IV have been identified with different tissue involvement (1) such as the classic Andersen disease with terminal liver failure developing during childhood and a fatal neonatal neuromuscular form with involvement of the central nervous system, liver, skeletal, and cardiac muscle.

The number of described cases with death *in utero* or during the neonatal period is limited (5), and to our knowledge the finding of characteristic histopathologic changes in placenta has only been described in 5 cases including our case with 2 consecutive miscarriages (2,6). Konstantinidou et al. (2) described

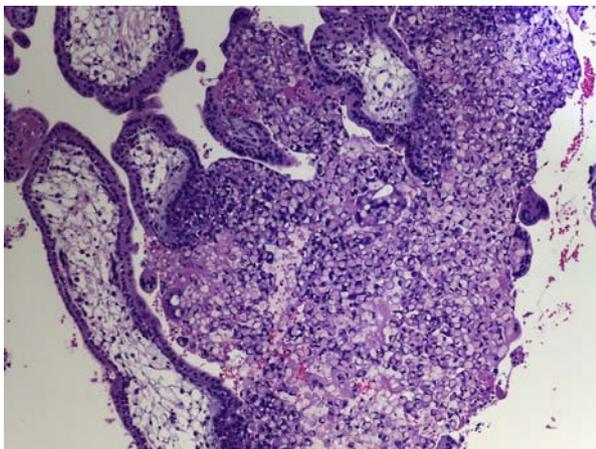


FIG. 1. Hematoxylin and eosin staining (10 × magnification) of cells with intracytoplasmic vacuoles in the intervillous space.

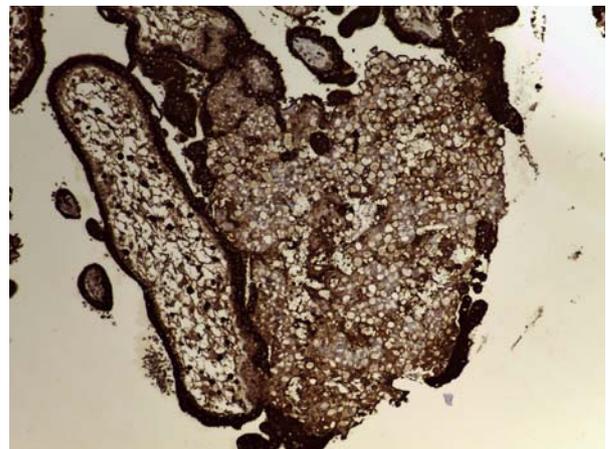


FIG. 3. HCG staining (10 × magnification) of the extravillous trophoblastic cells with intracytoplasmic vacuoles.

2 third-trimester cases (in 2 families at 25th and 35th week of gestation, respectively) with fatal perinatal GSD-IV and findings of polyglucosan inclusions in the placental tissue and a first-trimester miscarriage at gestational week 8 with placental inclusions was recently reported by Dainese et al. (only abstract available) (6). In contrast, L'herminé-Coulomb et al. (7) found no histopathologic changes in placental tissue from 2 consecutive GSD-IV pregnancies, both at gestational week 24, indicating that a normal placental histology does not necessarily exclude GSD-IV. Cox et al. (8) found extensive muscular and epidermal inclusions in fetuses as early as the 12th week of gestation, but no information about the placental tissue was reported. The extent of placental involvement most probably depends on the specific gene mutation, the combination of the mutations, or other yet unidentified modifying factors.

In the cases reported here and by Dainese et al. (6), inclusion vacuoles were found in cells from placental tissue as early as in the 8th, 10th, and 12th weeks of gestation indicating that the changes can be found much earlier than previously thought (2). Early placental involvement was in our case associated with the combination of 2 mutations one of which has been described to cause a nonlethal neonatal neuromuscular variant (3) and the other the classic hepatic variant (4), but other factors may have contributed to the early presentation. GSD-IV was probably the sole cause of the repeated miscarriages in our case and without the histopathologic findings in the placental tissue the patient might never have known why she kept having miscarriages. After yet another first-trimester miscarriage caused by GSD-IV our patient finally gave birth to a healthy child who

was found to be heterozygous for the c.1570C>T mutation.

GSD-IV, and especially the fatal neuromuscular subtype, is a very rare disease and may be underdiagnosed. Therefore, our and Dainese and colleague's findings of placental involvement as early as in the first-trimester underlines the importance of histologic examination of placental tissue in cases with repeated miscarriages and to suspect GSD-IV when discovering vacuolated cells in the tissue.

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