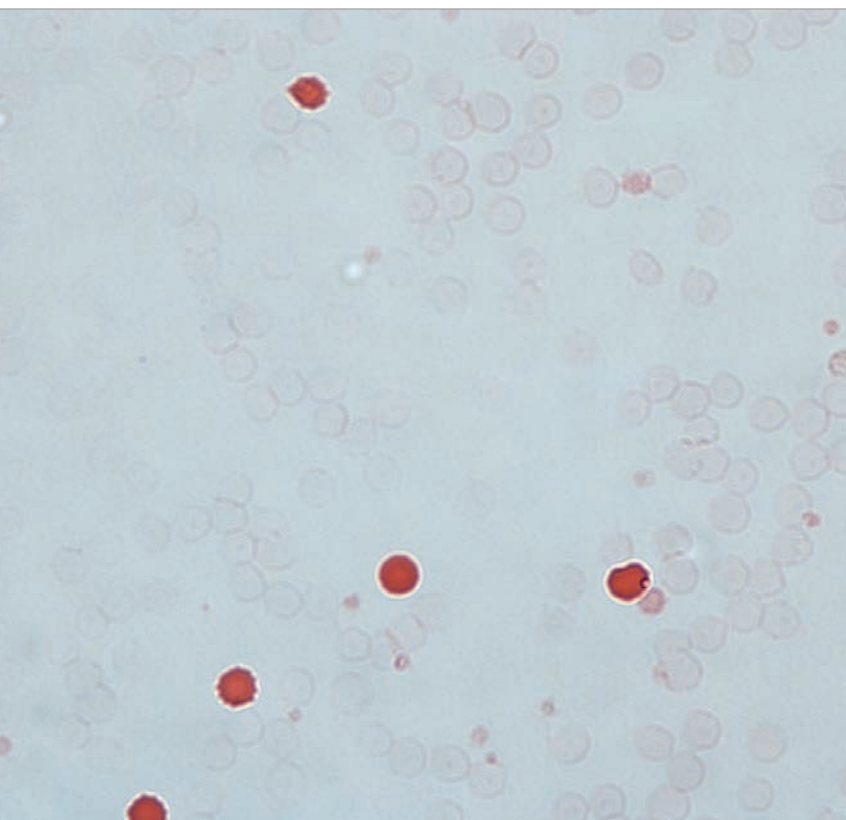


Massive fetomaternal  
hemorrhage secondary to a  
non-metastatic intraplacental  
choriocarcinoma

March 2015





Intraplacental choriocarcinoma (IC) is a rare but the most aggressive form of gestational trophoblastic disease (GTD), seldom diagnosed at the time of delivery. We describe a case of neonatal asphyxia associated with a massive feto-maternal hemorrhage (FMH). The histological examination of the placenta led to the unexpected diagnosis of IC. Since the pregnancy was complicated by four additional events, we reviewed the literature and raise new questions about potential physiopathological mechanisms related to IC development.

## CASE REPORT

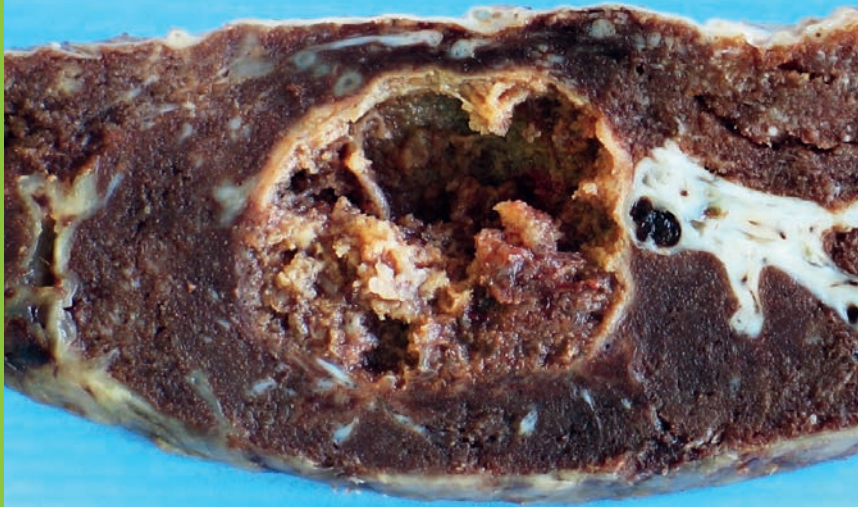
This 3450 g full term baby boy was born by normal vaginal delivery to a 34-year-old Greek G2/P1, O negative mother. Maternal past medical history was remarkable for well-controlled hypothyroidism and a previous miscarriage. First trimester ultrasound at 12 weeks of gestation had shown increased nuchal translucency (NT) of 6.4 mm. Chorionic villous sampling (CVS) revealed a normal karyotype (46, XY). Fetal follow-up ultrasound examinations throughout pregnancy were unremarkable.

At 35 1/7 weeks of gestation, the pregnancy was complicated with intrahepatic cholestasis of pregnancy (ICP), with total bile acids reaching a maximum level of 162.7  $\mu\text{mol/l}$  at 36 6/7 weeks of gestation. Cholestyramine was started for 4 days, and then switched to ursodeoxycholic acid (UDCA) for a total of 10 days. Induction of labor for ICP was necessary at 38 6/7 weeks of gestation. Labor was extremely fast, lasting only 2 hours. The newborn was extracted by vacuum secondary to late and deep decelerations without sinusoidal pattern. At birth, the infant was in secondary apnea requiring immediate ventilation and intubation. Apgar scores were 2, 2, and 5 at 1, 5, and 10 minutes, respectively. Umbilical cord blood gas showed severe metabolic acidosis with an arterial pH of 6.89, a venous pH of 6.93, and a lactate of 14.3 mmol/l. Complete blood count revealed acute anemia with a hemoglobin (Hb) concentration of 94 g/l, and

erythroblasts 4/100 leukocytes; a Kleihauer-Betke test was positive (45/1000), but there was no hemolysis.

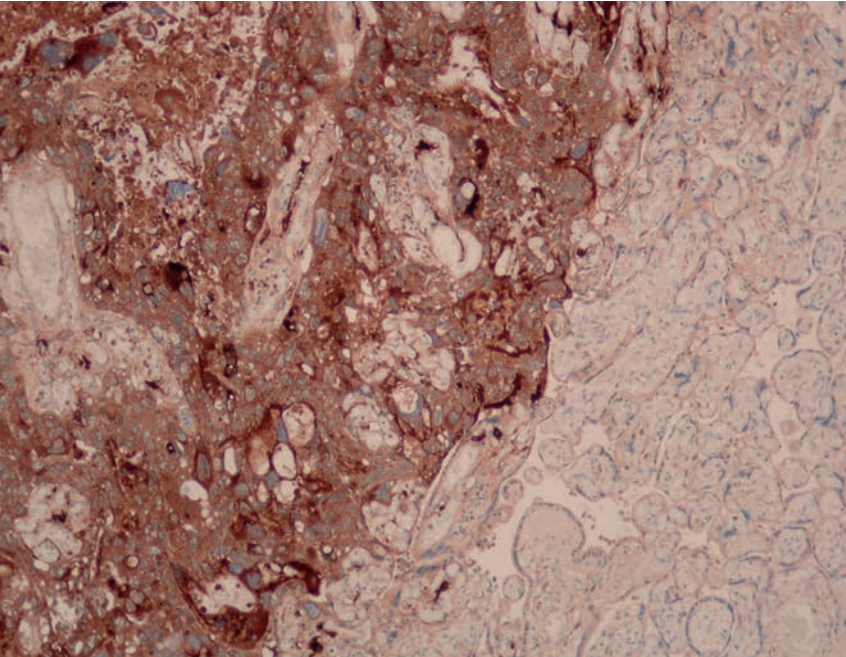
The newborn was transferred in stable condition to a level III neonatal intensive care unit, where he received a single packed red blood cell transfusion. Neonatal hypothermia protocol was implemented for perinatal asphyxia. By day of life 7, both neurological examination and cerebral magnetic resonance imaging of the infant were normal. On day of life 8, pathological examination of the placenta revealed intraplacental choriocarcinoma (IC) (Fig. 1, 2).

The infant's initial serum levels of alpha-fetoprotein (AFP) and  $\beta$ -human chorionic gonadotropin ( $\beta$ -HCG) were within the norm with 14 874 kU/l and 0.21 U/l, respectively (Fig. 3). In addition, a total body scan performed in search for metastasis was unremarkable. The infant was referred to pediatric oncology for outpatient follow-up and monitoring of serum  $\beta$ -HCG and AFP levels. The mother was also investigated to rule out disseminated disease. Full body scan revealed no metastatic lesions. Serial blood analysis showed rapid normalization of maternal  $\beta$ -HCG levels, dropping from 182 U/l to < 4U/l within 20 days. Kleihauer-Betke test decreased from 45/1000 at the day of delivery to < 5/1000 one month later (Fig. 4).



**Fig. 1**

*Macroscopic view of a random cut through the placenta: presence of a yellow-gray nodule with both hemorrhagic and cystic areas measuring 3.2 × 3.2 × 2.8 cm.*



**Fig. 2**

*Microscopic view through the border of the hemorrhagic-cystic lesion: note very high MIB+ proliferation index of the choriocarcinoma.*

Given the absence of metastasis and the normalization of tumor markers in both the child and the mother, no chemotherapy treatment was initiated. 27 months later, both mother and child are doing well, with no signs or symptoms of malignant disease. Of note, the infant's AFP serum levels remained above the norm for his age for over 2 years (23 kU/l, versus a norm of 6.5 kU/l above 12 months of age), normalizing only thereafter (Fig. 3).

The placenta weighed 640 g and its overall macroscopic examination was unremarkable. On thin sliced macroscopic examination a central hemorrhagic and cystic nodule measuring  $3.2 \times 3.2 \times 2.8$  cm was noted (Fig. 1). Histologically, this lesion showed a well defined border, and was composed of chorial villousities surrounded by two components of atypical trophoblastic cells, which infiltrated the intervillous spaces: the cytotrophoblast with small mononucleated cells and the syncytiotrophoblast containing large pleomorphic polynucleated cells. The lesion included necrotic and hemorrhagic areas. On immunohistochemistry, all trophoblastic cells were highly positive for  $\beta$ -HCG markers, and the syncytiotrophoblast component was positive for the proliferation marker MIB-1, a monoclonal antibody MIB-1 assessing the high proliferating activity of the tumor (Fig. 2).



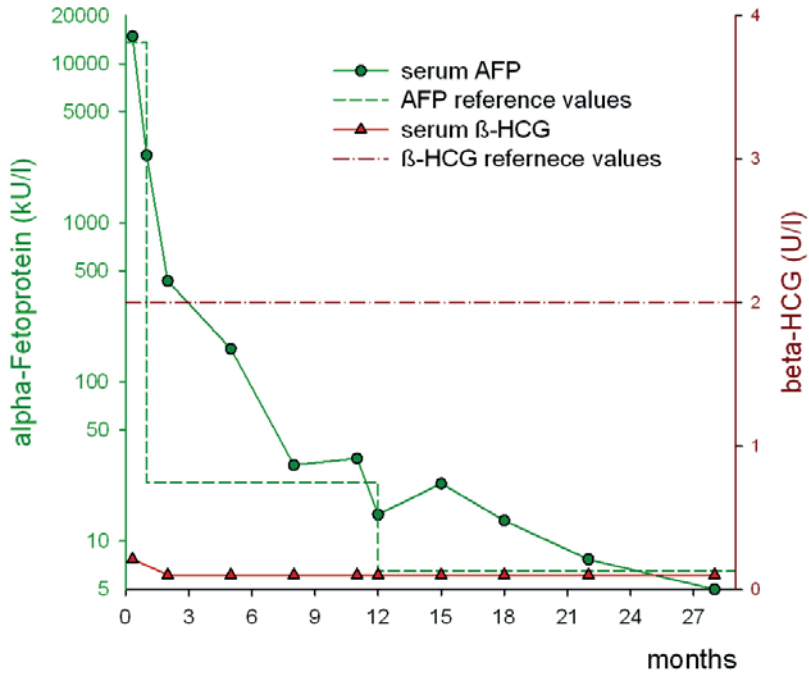


Fig. 3

*Postpartum evolution of the child's serum AFP and  $\beta$ -HCG levels.*

## DISCUSSION

Intraplacental choriocarcinoma (IC) is an extremely rare subtype but a highly malignant variant of gestational trophoblastic disease (GTD) derived from the placenta (villous trophoblast), and belongs to the pregnancy-related disorders. Besides IC, GTD includes partial hydatiform mole, complete hydatiform mole, invasive mole and placental site trophoblastic tumor. The physiopathology of IC is related to a failure of the regulatory mechanisms, which control the invasion abilities of healthy trophoblast. This leads to the development of a highly invasive, metastatic and vascularized gestational trophoblastic tissue (1).

The estimated incidence of IC is 1/50'000-160'000 live births varying with ethnic origin (2). The true incidence of IC is difficult to estimate. Asymptomatic cases probably lead to an underestimation of its prevalence. On the other hand, secondary to reporting bias (only known and severe cases are published), the prevalence of severe obstetrical complications associated with IC is probably overestimated (3). In a review, Smith et al. highlighted that 50% of choriocarcinomas are preceded by a hydatidiform mole, 25% by an abortion, 3% by ectopic pregnancy, and the other 22% by a full-term pregnancy (4). Known risk factors for choriocarcinoma include multiparity, maternal age (<15 years or >45 years) and a history of hydatidiform mole in previous pregnancies (2,5).

IC is often discovered secondary to perinatal complications or after delivery due to clinical manifestations of metastatic disease in the mother (commonly) or in the newborn (rarely) (2,6,7). When diagnosed after delivery at term, up to 60% of mothers will have widespread disease (3). The main complications of IC include severe FMH, retroplacental hemorrhage, placental abruption and fetal hydrops, which often lead to fetal distress, anemia, intrauterine growth restriction or intrauterine fetal death (8–10). However, most of the time, IC is asymptomatic and discovered incidentally when the pathologist carefully examines the placenta. In more than 90% of the reported cases of IC, the tumor lesion is not visible macroscopically (3).

In our case, pathological examination of the placenta was performed because of massive FMH and led to a diagnosis of IC. The Kleihauer-Betke test turned negative after a few weeks (Fig. 4), confirming FMH and making an undiagnosed hemoglobinopathy highly unlikely. The estimated fetal blood loss calculated from the Kleihauer-Betke test result was 225 ml.

First described in 1962 by Benson et al. (7), FMH is the only one known early sign of IC reported in the literature (8, 11). FMH occurred in 38 % of 40 cases with IC (11). A systematic examination of the placenta should therefore be performed in each case of unexplained FMH.

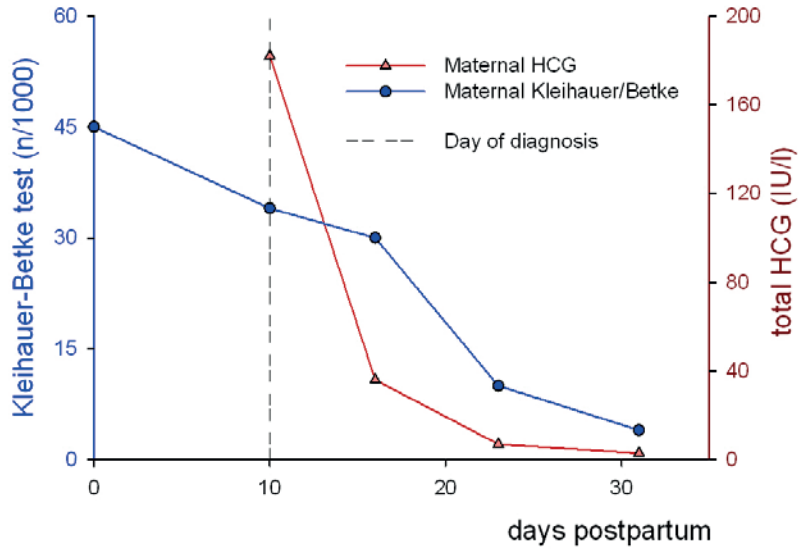


Fig. 4

*Postpartum evolution of maternal serum total  $\beta$ -HCG levels and Kleihauer-Betke test.*

As soon as the diagnosis of IC is confirmed, serial  $\beta$ -HCG and AFP serum levels in both mother and infant should be performed because early identification of this tumor might be life saving. Elevated AFP levels at birth up to 14 000 kU/l are considered physiologic. The isolated delay in normalization of AFP levels in our patient after the first year of age remained non-alarming since the other tumor markers were undetectable and abdominal ultrasounds showed no signs of metastasis. This may be due to a persistent production of fetal hepatic AFP, an isoform that differs from the AFP secreted by germinal tumors or hepatoblastomas (12). Unfortunately, laboratory tests are unable to distinguish the two isoforms (12). Nevertheless, the absence of  $\beta$ -HCG excluded the development of choriocarcinoma in the child, which was also confirmed by the normalization of AFP levels after 24 months of age.

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