Syncytio-trophoblast pulmonary embolism: cause of death or incidental finding. Case report and literature review

Mihai Ceausu1*, Silvia Dermengiu1, George Cristian Curca1, Dan Dermengiu1, Lacramioara Luca1

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Abstract: A 37 years old female performed in vitro fertilisation and artificial insemination resulting in a multifetal pregnancy (4 embryos). A fetal reduction was performed at 16 weeks gestational age, by transcervical puncture and potassium chloride injection in the fetal heart. After several hours the state of health of the patient started to decline rapidly with dyspnea, tachypnea and progressive arterial hypotension. The patient died 40 hours after the fetal reduction procedure due to DIC and MOFS. A post-mortem blood culture was evidenced a Citrobacter freundii bacteriemia. The autopsy revealed a suppurrative acute endometritis, multiple foci of leukocyte sticking in visceral vessels, scattered hyaline membranes, marked vascular congestion and alveolar edema in the lungs, micro thrombi of fibrin in sinusoidal capillaries of the liver and renal glomeruli, focal renal tubular necrosis and extensive degenerative changes in kidneys. Syncytio-trophoblast fragments, (IHC positive to hPL and β-HCG) present in the pulmonary capillaries were apparently a collateral histopathological finding. Although the histopathological, histochemical and microbiological data suggested the idea of a disseminated intravascular coagulation in the context of a septic shock syndrome, the presence of multiple syncytio-trophoblast fragments in the pulmonary capillaries cannot be completely dismissed as a incidental finding, having no contribution to the pathologic chain of events leading to the death of the patient.

Key words: fetal reduction, transcervical puncture, DIC, MOFS, Citrobacter freundii bacteriemia, leukocyte sticking, syncytio-trophoblast embolism, septic shock

A 37 years old female performed in vitro fertilisation and artificial insemination resulting in a multifetal pregnancy (4 embryos). A fetal reduction was performed at 16 weeks gestational age, by transcervical puncture and potassium chloride injection in the fetal heart. After several hours the state of health of the patient started to decline rapidly with dyspnea, tachypnea and progressive arterial hypotension. Disseminated vascular coagulation (DIC) and multiple organ failure syndrome (MOFS) developed rapidly and despite energetic medical measures (including an emergency hysterectomy) death occurred 40 hours after the fetal reduction intervention.

The autopsy revealed the overwhelming modifications characteristic for DIC and MOFS. A blood culture identified a single germ bacteriemia with Citrobacter freundii.

*) Corresponding author; MD, PhD, Tel. +4021.332.50.08, Fax: +4021 334 62 60, E-mail: ceausu_mihai@yahoo.com

1) “Mina Minovici” National Institute of Forensic Medicine, sos. Vitan Barzesti, nr. 9, sector 4, Bucharest, Romania
Material and methods

Tissue samples of uterus, lung, myocardium (from the left ventricle), liver, kidney and adrenal glands were taken for histopathology investigation. The selected specimens were formalin-fixed and paraffin-embedded. Sections were cut at 5 microns and stained using the standard H&E and van Gieson. Special stains such as phosphotungstic acid hematoxylin (PTAH) for fibrin and PAS have been carried out.

Immunohistochemistry (IHC) was done for the following antibodies: hPL (human placental lactogenic hormone), β-HCG (beta human chorionic gonadotropin hormone), CD34 and CD117 (see table 1 for details); it was used an indirect bistadial technique with hydro soluble polymerized dextran, according to manufacturer specifications (Dako EnVision Systems).

To ensure the reliability of the experimental study, internal quality control of histopathological techniques was performed as a part of an implemented and certified quality assurance system (ISO 9001/2001).

All slides were examined and photographed on a Zeiss AxioImager A1 microscope. Digital images acquired with Zeiss Axio Vision program have been processed and analyzed with ACDSee Pro Photo Manager 3.0, running under Windows XP Professional.

Table 1 Antibodies used in the case study

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Clone</th>
<th>Dilution</th>
<th>Manufacturer</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-HCG</td>
<td>Polyclonal</td>
<td>1:500</td>
<td>Novocastra</td>
<td>Trophoblast</td>
</tr>
<tr>
<td>hPL</td>
<td>Polyclonal</td>
<td>1:250</td>
<td>Neomarkers</td>
<td>Trophoblast</td>
</tr>
<tr>
<td>CD34</td>
<td>QBEND</td>
<td>1:25</td>
<td>DAKO</td>
<td>Stem cells &amp; vessels</td>
</tr>
<tr>
<td>CD117</td>
<td>Polyclonal</td>
<td>1:400</td>
<td>DAKO</td>
<td>Stem cells</td>
</tr>
</tbody>
</table>

Results

Classic histopathology investigation revealed a suppurative acute endometritis with myometrial hemorrhage in the uterine wall (fig. 1).

A partial thrombosis of medium and small pulmonary vessels, associated to foci of leukocytic thrombi (“sticky thrombi”, “leukocyte sticking”) in lung capillaries and scattered hyaline membranes highlighted by PAS stain (fig. 2), on a background of marked vascular congestion and alveolar edema were identified.

It was also noted focal renal tubular necrosis and extensive degenerative changes in kidneys, accompanied by hemorrhage in both adrenal glands. PTAH stain showed microthrombi of fibrin in sinusoidal capillaries of the liver and in glomerular capillaries of the kidney (fig. 3). The heart showed incipient arteriosclerosis of the coronaries and hypoxic lesions of the myocardic fibers.

The aforementioned histopathological and histochemical data have suggested the idea of a disseminated intravascular coagulation in the context of a septic shock syndrome.

Collateral histopathological findings were some multinucleated syncitial masses in small pulmonary vessels (fig. 4), which were IHC positive to hPL and β-HCG (fig. 5, 6) and a diagnosis of lung amniotic embolism with fragments of syncytiotrophoblast was established.

Differential diagnosis was made with megakaryocytes, but they proved to be completely negative to CD117 and CD34 at IHC investigation (fig. 7). CD34 was positive in small pulmonary vessels (positive intern control), but with no relevance in this case. Although the megakaryocyte possesses a single nucleus, it is lobulated, which gives the appearance of a cell with several nuclei; thus it could be mistaken with other multinucleated cells.
Fig. 1 Acute endometritis with large amount of inflammatory exudate with numerous leukocytes and fibrin (left), and extensive myometrial hemorrhage (right), HE, 10x

Fig. 2 Hyaline membranes lining alveolar walls (black thin arrows), PAS stain, 20x (left) and “sticky” leukocyte thrombi in small pulmonary vessels (blue thick arrows), HE, 10x (right)
Fig. 3 Micro-thrombi of fibrin in sinusoidal capillaries of the liver (left) and in renal glomerulus (right), PTAH, 20x, 40x

Fig. 4 Multinucleated syncytial masses in pulmonary capillaries (arrows), HE, 20x
Fig. 5  Strong positive reaction to hPL of the syncyto-trophoblast fragments in the pulmonary capillaries, IHC, 40x

Fig. 6  Strong positive reaction to β-HCG of the syncyto-trophoblast fragments in the pulmonary capillaries, IHC, 40x
Septic shock is a vascular collapse triggered by either the lipo-polysaccharides (endotoxins) of Gram negative bacteria or by super-antigens of Gram positive bacteria such as streptococcus or staphylococcus; it is a complication of septicemia, sometimes secondary to trauma or surgery and carries a high risk of mortality (up to 50%). Also it complicates with disseminated intravascular coagulation (DIC) in half of cases. [1, 2, 3]

A review of literature reveal that, although relatively rare, (0.7% of all septic disseminations) the mortality generated by Citrobacter septicemia is higher than by Escherichia Coli (48% and respectively 33%) [4], due to the newly aquired resistence to a wide range of antibiotics [5]. The majority of generalised infections with Citrobacter (86%) are triggered by surgical or invasive diagnostic procedures [4, 6].

In this case several lines of evidence support the existence of a septic shock:
- the existence of a septic focus (endometritis)
- post-mortem blood culture positive for single germ *Citrobacter*, (a monomorphic flora plead against the possibility of a post-mortem contamination) [7].
- leukocyte sticking (present in lungs, heart, liver, kidneys) – a landmark of sepsys [2, 3, 8]

Amniotic fluid embolism is a severe but fortunately uncommon complication of labor and the immediate post-partum period (1:50,000 deliveries). It has a mortality rate of 30% and can complicate with eclampsia and pulmonary embolism, half of patients developing DIC, owing to release of thrombogenic substances from amniotic fluid [9]. In recent years it has been suggested that amniotic fluid embolism is an anaphylactoid
reaction to fetal antigens and an elevated serum tryptase level is increasingly being used to support the diagnosis [10].

Amniotic fluid embolism with trophoblast has been previously reported in patients with difficult labor, after therapeutic abortion [11], or in cases with hydatidiform mole [12, 18] and hysterectomy for invasive complete mole [13]. A fatal case with simultaneous presence of syncytiotrophoblast and megakaryocytes in the pulmonary microvasculature, by means of a panel of specific monoclonal antibodies was also reported in the literature [14].

Although in theory an amniotic emboli can be considered a „reasonable” and „sufficient” cause of DIC, in this case there are some elements that make this less certain:
- the microscopic investigation of the lungs do not support the existence of a massive amniotic embolisation
- the gestational age is uncharacteristic for amniotic embolia (in single pregnancies at 16 weeks, the placental weight is approximately 16 grams compared to 470 grams at delivery and the quantity of amniotic fluid 175 ml compared to 600-800 ml at term) [15, 16, 17, 18]
- recent research support the view that small pulmonary embolisation can represent to a certain extent a „physiological” occurrence in normal pregnancies [19], and do not necessarily represent a deadly accident even in pathologic pregnancies [13].

On the other hand, the presence of multiple syncytio-trophoblast fragments in the pulmonary capillaries cannot be completely dismissed as a incidental finding, having no contribution to the pathologic chain of events leading to the death of the patient.

In our view, the aforementioned elements suggest that the death was determined by the cumulative effects of toxic shock and syncytio-trophoblast embolisation (triggered by the fetal reduction procedure performed on a pre-existent endometritis) with subsequent DIC and MOFS.

References