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CASE REPORT

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Fatal Postpartum Spontaneous Liver Rupture: Case Report and Literature Review

ABSTRACT: Maternal hepatic rupture is a rare complication of pregnancy that can be fatal to both mother and child. This phenomenon is most often associated with preeclampsia/eclampsia and/or HELLP syndrome, which is defined by a collection of clinical features including hemolysis (H), elevated liver enzymes (EL), and a low platelet count (LP). These disease processes are typically identified and treated during pregnancy, often in the last trimester. The described case is unusual in that the decedent had no known history of preeclampsia/eclampsia or HELLP syndrome during this pregnancy, and she died suddenly several days postpartum of liver rupture with massive intraperitoneal hemorrhage following a routine cesarean section delivery and an uneventful hospital course. Similar cases are infrequent in the literature, which is reviewed in this report.

KEYWORDS: forensic science, pregnancy complication, sudden death, liver rupture, postpartum, thrombophilia

Liver dysfunction has been estimated to complicate as many as 3% of pregnancies (1), and can manifest as a broad spectrum of clinical features that range from mildly elevated plasma liver enzyme levels, to severe functional derangement that can compromise both mother and child. One possible outcome is hepatocellular necrosis, with associated bleeding and hematoma formation both within the parenchyma of the liver and beneath the liver capsule (2–6). While this phenomenon can complicate a preexisting lesion of the liver such as an adenoma, it most often occurs in association with preeclampsia/eclampsia or HELLP syndrome (5). Rupture of the liver is a life threatening emergency, with maternal and fetal mortality estimated as high as 86% and 70%, respectively (3,6,7) in some studies. The obstetric literature appropriately focuses on identification and treatment of these disorders during pregnancy, labor, and delivery. Of concern, however, are observations that both severe hypertension or preeclampsia (8) and HELLP syndrome (9) can manifest for the first time in the postpartum period, and thus also threaten the life of the mother after childbirth.

We present an unusual case of a 25-year-old white woman who experienced a largely uncomplicated pregnancy and cesarean delivery of a healthy, term infant, but died suddenly and unexpectedly 6 days postpartum from liver rupture and massive hemoperitoneum.

Case Report

According to available medical history, this 25-year-old gravida four, para three white woman had a history of three previous cesarean section deliveries. Prenatal care began late at 30.5 weeks gestational age in this most recent pregnancy. Maternal smoking was documented, and Chlamydia, Trichomonas, and bacterial vaginosis were treated with antibiotics. No signs or symptoms of preeclampsia/eclampsia or HELLP syndrome were documented for any previous pregnancies or this current pregnancy. The decedent was admitted for a routine cesarean section and was delivered of a healthy term infant. In the same operation, a repeat bilateral tubal ligation was performed. Vital signs prior to operation showed normal blood pressure (BP, 108/68), pulse, and respiratory rate. Surgery was uneventful and postoperative vital signs were stable. The decedent began eating and ambulating at the hospital, and voiced no specific complaints. She was discharged to home late on the second postpartum day.

The decedent recovered from childbirth without apparent difficulty. On the morning of the sixth postpartum day, she told family members that she was going to lie down and rest. Approximately 40 min later she was discovered lying in bed, cyanotic and apneic, and emergency medical services were summoned. Asystole was identified by first responders, cardiopulmonary resuscitation was initiated, and she was transported to the emergency room. Minimal cardiac function was regained by external pacing. However, the rhythym quickly deteriorated back to asystole and she was declared dead. Transportation and resuscitation time totaled 62 min. Sparse premortem laboratory tests performed during resuscitation demonstrated acidosis (pH 6.72) and low hematocrit (lowest value 18.0%, normal range 35.0–47.0%). No other significant laboratory data were available.

Full autopsy was performed following a 2.5 h postmortem interval. External examination showed a well-developed, well-nourished adult white female weighing an estimated 150 lbs with height 5′6″. Rigor was unfixed in all extremities and jaw, with unfixed livor mortis over the posterior body surfaces. The conjuctiva, lips, and gums were pale. The abdomen was soft with striae across the lower abdominal quadrants. A suprapubic healing incision consistent with recent cesarean delivery was dry, clean, and closed with Steri-Strips™ (3M Corporation, St. Paul, MN). No external evidence of trauma was identified.

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Internal examination showed all organs in normal anatomic position. The sternum, anterior, and posterior ribs were intact. The pulmonary arteries were manually explored *in situ* and no obstruction was identified. Sectioning of pulmonary vessels showed no thromboembolus. The heart was unremarkable. The brain (1450 gm) appeared mildly edematous but otherwise was unremarkable. Copious liquid blood (conservative estimate, 2500 mL), was present in the peritoneum. The 1575 g liver showed a glistening, intact capsule over much of the anterosuperior surface. Foci of subcapsular hematoma were noted on the posteroinferior surface of the liver adjacent to a gaping defect which deeply penetrated the liver parenchyma, $9 \times 6 \times 3$ cm (Fig. 1). This lesion, roughly located in the caudate lobe, showed irregular, ragged tears extending into the liver parenchyma. Large venous connections within the defect could be probed to outlet in the inferior vena cava. Extravasated blood had infiltrated into soft tissues surrounding the diaphragmatic crura and the gastroesophageal junction. Sectioning showed no other liver lesions. Splenomegaly (325 gm) was apparent. The uterus showed an intact and closed healing surgical incision consistent with the history of previous procedure. On opening, the uterus demonstrated a roughened, hemorrhagic area on the endometrial surface consistent with placental attachment site. No placental remnants were evident. Both fallopian tube stumps were identified and showed changes of recent surgical manipulation. The remaining organs were unremarkable. Standard postmortem toxicology screen was negative for ethanol or other drugs.

Histologic examination of the liver surrounding the rupture showed subcapsular hematoma and hemorrhage disrupting the liver parenchyma. There were areas of hepatocellular necrosis which were not clearly zonal (Fig. 2). Distant from the defect, the liver parenchyma was well preserved. Focally, sparse small lymphocytes were seen around a few portal tracts. No glycogenated hepatocyte nuclei were evident. No liver neoplasm or other mass lesion was identified. No amniotic fluid embolism was identified in blood vessels in the lung or other tissues. No retained products of conception were identified in the endometrium. Scattered blood vessels with luminal fibrin thrombi were identified in the liver and lungs.

DNA was extracted from formalin-fixed, paraffin-embedded autopsy tissue (spleen) using the DNeasy Tissue Kit (Qiagen, Inc., Valencia, CA) and tested for selected thrombophilia markers including factor V Leiden (FVL) and prothrombin 20210G → A (PT) mutations using Roche LightCycler® assays (Roche Molecular Systems, Inc., Branchburg, NJ), and methylenetetrahydrofolate reductase (*MTHFR*) polymorphisms 677C → T and 1298A → C using a laboratory developed PCR–restriction fragment length polymorphism based assay. Neither FVL or PT mutations were identified in the decedent's sample, while one copy each of the *MTHFR* 677C → T and 1298A → C polymorphisms was present (compound heterozygote, i.e., 677C/677T and 1298A/1298C).

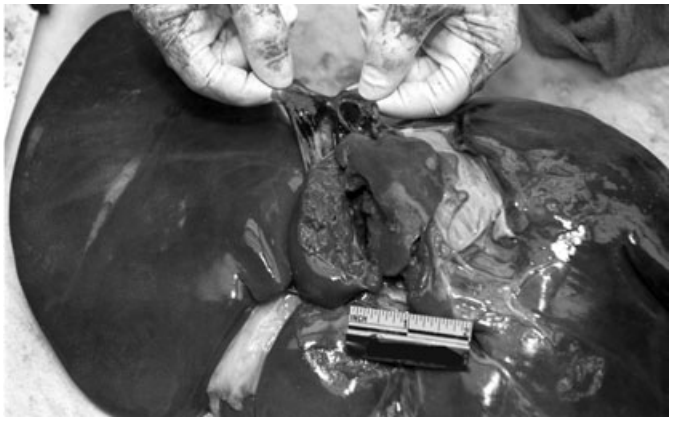

FIG. 1—*Gross image of the undersurface of the liver showing a gaping, ragged defect in the area of the caudate lobe. The soft tissue connections on the posterior liver are extended to show red blood cell infiltration. The black bar under the scale reference has been electronically altered to remove case identification.*

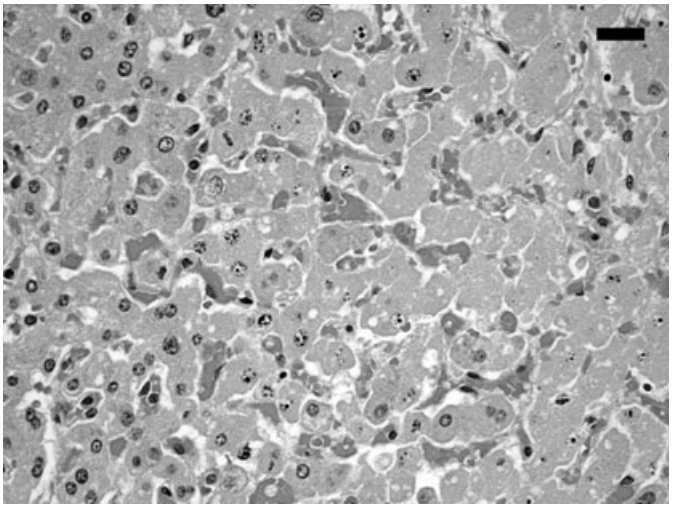

FIG. 2—*Photomicrograph of the liver adjacent to the rupture. A focus of necrotic hepatocytes (right side of image) shows blurring of cytoplasmic borders and loss of nuclear features, and there is a surrounding zone of damaged hepatocytes that contain pyknotic, degenerating nuclei. The remaining sinusoids in this area appear blood filled, and there is some red blood cell extravasation. On the left hand and lower aspect of the micrograph, the hepatocytes are better preserved with good nuclear detail (Hematoxylin and eosin, 400×; Bar = 20 μm.).*

Discussion

In the initial assessment of this case, several possibilities were considered as a potential cause of death. Massive pulmonary thromboembolism was favored by the attending clinical staff, but was quickly ruled out by lack of supporting anatomic findings at autopsy. When the intraperitoneal blood and liver defect were identified, the possibility of trauma, either sustained during delivery, at home after discharge from the hospital, or during resuscitation, was considered. Substantial liver injury that had occurred during an uncomplicated cesarean delivery was felt unlikely, especially in light of an unremarkable 5-day postoperative period in this case. This issue has been previously considered by Irvine (10) for another case of ruptured hepatic hematoma associated with pregnancy, who concluded that the liver is well protected by an intact rib cage during a typical cesarean operation, making iatrogenic liver injury doubtful. No history of injury or foul play was discovered in an investigation by the coroner and local police, and there were no features identified at autopsy in the soft tissue or skeleton suggestive for trauma in this case. With regard to possible resuscitation-related injury, the initial physical assessment by first reponders identified no heartbeat or respiratory effort, so the process(es) that resulted in the death of this individual had already begun before resuscitation was initiated. Since the only significant pathology identified was liver rupture and hemoperitoneum, it was concluded that this event had apparently occurred spontaneously and was clearly the cause of death.

On review of the literature, an association between spontaneous liver rupture and pregnancy was identified, typically in cases complicated by preeclampsia/eclampsia or HELLP syndrome (5,9). Gestational hypertension, a cardinal feature of preeclampsia/eclampsia, is variably defined as systolic BP of at least 140 mmHg and/or a diastolic BP of at least 90 mmHg on at least two occasions and at least 6 h apart after the 20th week of gestation, in a woman known to be normotensive both before pregnancy and earlier in pregnancy (8). A diagnosis of preeclampsia additionally requires proteinuria (≥300 mg/24 h), while eclampsia is present when convulsions manifest. HELLP syndrome, a term first coined by Weinstein in 1982 (11), refers to a constellation of features including hemolysis (H), elevated liver enzyme plasma levels (EL), and a low platelet count (LP) that can affect 4–20% of pregnancies complicated by preeclampsia/eclampsia (5,9). Significant liver dysfunction with hematoma formation occurs in a fraction of these cases, with hepatic rupture estimated to occur in only one in 45,000–225,000 overall deliveries (7).

Such complications typically are identified during pregnancy; however, in this case, the decedent expired 6 days postpartum. Interestingly, Sibai (8) documented that severe hypertension or preeclampsia may develop for the first time in the postpartum period. Matthys et al. (12) reviewed records of 3988 preeclampsia/eclampsia patients and identified 229 cases that were diagnosed in the postpartum period. One hundred and fifty-one (66%) of these patients were readmitted to the hospital at an average of 6.8 days (range 1–24 days) after delivery with a diagnosis of preeclampsia and/or hypertension. Likewise, the clinical and laboratory findings of HELLP syndrome may first manifest in the postpartum period in as many as 30% of cases, with the time of onset varying from a few hours to 7 days (9). The time course of this current case is consistent with this literature.

The location of a liver rupture associated with pregnancy is typically the right hepatic lobe (6,7,9,13), although the left lobe and rarely, the caudate lobe have been involved (6,13). In some reported cases, the liver parenchyma shows multiple, patchy areas of hemorrhage (6,14), a finding not present in this case. The distribution of this lesion within the liver is not understood. Several histologic features are characteristically seen in the liver from patients with preeclampsia/eclampsia, and include deposition of fibrin along the hepatic sinusoids, and occasionally in portal tract vessels. In some cases, patchy necrosis of hepatocytes is present, along with periportal and portal tract hemorrhage (3,4). Liver findings in HELLP syndrome can range from nonspecific portal and periportal inflammation with glycogenated nuclei, to a picture similar to that seen in preeclampsia with periportal necrosis and fibrin deposition (4). Well-demarcated zones of periportal hemorrhage and hepatocellular necrosis have been identified in rare reports of fatal HELLP syndrome (15,16). However, such changes are not always present (3,4). In this case, patchy hepatocellular necrosis was present in the area of the liver rupture, along with hemorrhage, which did not clearly show zonality. There were scattered foci of periportal lymphocytic inflammation. These features are not specific, but do suggest the possibility of preeclampsia/eclampsia or HELLP syndrome in this current case.

While it is interesting to speculate that postpartum preeclampsia/eclampsia and/or HELLP syndrome played a direct, causative role in the death of this woman, it must also be noted that spontaneous liver hematoma and/or rupture have also been reported in association with normal pregnancy and delivery. Xavier et al. (13) reported such a case at 36 weeks gestation, with development of a spontaneous liver hematoma in an otherwise unremarkable pregnancy. Schwartz et al. (17) identified 10 cases of pregnancy-associated liver rupture or hematoma that were not clearly associated with preeclampsia or the HELLP syndrome. Matsuda et al. (18), Abdi et al. (19), and Irvine (10) each reported cases of hepatic hematoma with rupture or intra-abdominal bleeding that followed apparently normal pregnancies and occurred in the first 1–24 h after delivery. Shaw et al. (20) reported a similar case of spontaneous liver rupture following a normal pregnancy and delivery which was detected on the third postpartum day. However, the signs and symptoms of preeclampsia/eclampsia or the HELLP syndrome can be subtle or atypical in presentation (21), and thus may be under-recognized. Also, Guntupalli and Steingrub note in a recent review (5) that HELLP syndrome may not be simply a variant of preeclampsia, but instead a unique entity unto itself that is not well understood. These observations may account for the lack of correlating clinical manifestations in some of these case reports, or in the current case.

A number of groups have suggested that inherited thrombophilia may be associated with preeclampsia/eclampsia and other complications of pregnancy, although data on this issue are conflicting (22). This literature was the stimulus for our interest in assessing for thrombophilia markers in this case. In postmortem testing using decedent DNA, FVL and PT mutations were both absent. While these mutations are associated with venous thromboembolism (22,23) and some obstetric complications such as placental abruption or intrauterine growth retardation (24), a recent large study of 5000 patients found no association of FVL or PT mutations with preeclampsia (24). *MTHFR* polymorphisms, which have a much weaker association with thrombophilia risk than either FVL or PT (22,23), were present in the heterozygous state in the decedent (677CT/1298AC). *MTHFR* functions in the conversion of homocysteine to methionine, but inherent sequence polymorphisms can slow the pathway, resulting in hyperhomocysteinemia. Mild to moderate elevations in plasma homocysteine levels are explained only in part by *MTHFR* polymorphisms, but alone may result in an increased risk of severe preeclamptic toxemia that may persist postpartum (25–27). Nagy et al. (28) identified the MTHFR 677CT mutation in about 75% of a small subset of patients with both HELLP syndrome and eclampsia, and the *MTHFR* 677TT homozygous state in about 25% of 63 HELLP syndrome patients, suggesting a possible relationship between *MTHFR* polymorphisms and these disorders. While various studies suggest that compound heterozygosity (*MTHFR* 677CT/1298AC genotype) may also confer an increased thrombotic risk in other settings (29), overall the significance of the *MTHFR* results in this case remains uncertain.

In conclusion, the major finding at autopsy in this case was a 9 cm ragged defect in the liver with massive hemoperitoneum, in an atraumatic 25-year-old postpartum woman. Mild hepatosplenomegaly and brain edema were also present. The liver showed areas of hepatocellular necrosis and hemorrhage surrounding the defect. The rapid deterioration from apparent health to being *in extremis* in less than an hour supports the interpretation that a catastrophic, spontaneous rupture of the liver with resultant intraperitoneal hemorrhage was the cause of death for this individual. Additionally, this case also highlights an unexpectedly late, rare, and deadly complication of pregnancy, and thus is of interest to all practitioners of forensic pathology.

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