Case Report

Hydrops Fetalis Caused by Parvovirus B19 Infection: Case Report and Literature Review

Sukanya Taksaphan MD*, Pilaiwan Kleebkaew MD**,
Rattana Komwilaisak MD**, Pakaphan Kiatchoosakun MD*,
Junya Jirapradittha MD*, Thawalwong Ratanasiri MD**

** Departments of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen*
*** Departments of Obstetrics and Gynecology, Faculty of Medicine, Khon Kaen University, Khon Kaen*

An intrauterine parvovirus B19 infection can result in severe fetal anemia and hydrops fetalis, which can lead to death. A case of fetal hydrops, diagnosed at 31 weeks gestation, is reported. Cordocentesis revealed fetal hemoglobin of 5 g/dL. Due to fetal distress 18 hours later, the baby was delivered by emergency cesarean section and died two days later. Characteristic intra-nuclear inclusions in nucleated red blood cells were found in histopathological examinations of the liver and placenta, which supported the diagnosis of parvovirus B19 infection. Literatures about parvovirus B19 infection, especially intrauterine infection, its effects on the fetus, methods of diagnosis and management, were reviewed.

Keywords: *Parvovirus B19, Intrauterine infection, Anemia, Hydrops fetalis*

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Human parvovirus (B19) was first described in 1975 as parvovirus-like particles found in the serum of healthy blood donors[1]. Six years later, it was confirmed as the cause of transient aplastic crisis in children with sickle-cell anemia[2]. The association between erythema infectiosum (fifth disease) and human parvovirus was identified a few years later[3,4]. Then in 1984, the first cases of intrauterine parvovirus infection, having a poor outcome, were reported when hydropic fetuses were shown to have anti-B19 immunoglobulin M[5,6].

Studies have shown that intrauterine parvovirus B19 infection is related to Non-Immune Hydrops Fetalis (NIHF) and intrauterine fetal death[7-18], but asymptomatic fetal infection has also been reported[18-19]. A meta-analysis revealed that 19.1% of etiology-unknown cases of NIHF were associated with parvovirus B19 infection[9]. The transplacental transmission rate was estimated at between 25 and 51%[18-20].

A 10.2% excess risk of fetal loss occurred in women infected with this virus during pregnancy[9]. The adverse fetal effect was highest when maternal infection occurred in the second trimester of pregnancy[9,18]; however, most fetuses from mothers who acquired the infection before pregnancy appeared unaffected[18-20].

The authors reported a case of NIHF resulting from intrauterine parvovirus infection, confirmed by inclusion bodies in nucleated red blood cells found in the placenta and liver. A comprehensive literature review about this virus, its effects on the fetus, diagnosis and management of intrauterine infection were included.

Correspondence to : Taksaphan S, Departments of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.

Case Report

A 26-year-old woman (gravida 3; para 0) was admitted for evaluation of hydrops fetalis. Her previous two pregnancies ended at 36 weeks' gestation in another hospital from intrauterine hydrops of unknown etiology. This time she had had seven unremarkable antenatal care visits. The ultrasonographic study at 31 weeks' gestation, however, indicated fetal hydrops had developed again.

Her blood type was A, Rh-positive with negative antibody screen. Tests for VDRL and anti HIV were

non-reactive. Her hematocrit was 32%. Cordocentesis revealed a fetal hemoglobin of 5 g/dL, blood type A, Rh-positive with a negative direct antiglobulin test and a normal XY karyotype. A sinusoidal pattern was noted during fetal monitoring. Due to fetal distress 18 hours later, the baby was delivered by emergency cesarean section. The Apgar score was 0 at 1 minute and 1 at 5 minute. Immediate intubation, ventilation and abdominal paracentesis were performed and the baby was transferred to the NICU.

A physical examination revealed a markedly pale 1 800 g male baby with hepatosplenomegaly and generalized edema. The liver was enlarged down to RLQ, 9 cm below the right costal margin. The CBC revealed Hb 2 g/dL, Hct 5%, WBC37 000/mm^3, PMN 53%, L 44%, Mono 3%, NRC 105/100 WBC, platelets 285 000/mm^3. Microcytes, spherocytes and polychromasias were observed in the peripheral blood smear. Hemoglobin electrophoresis was performed on serum samples from the baby and his parents. The results were: mother-EA, father-A2A, baby-F. The MCV were 80.6, 84, 85.1 fL, respectively. The rubella, toxoplasma and CMV titer tests were negative and G6PD level was normal.

A partial exchange transfusion with packed red blood cells was performed soon after the baby was stabilized in the NICU: this raised the hematocrit to 40%. The infant was placed on a high frequency ventilator because of persistent pulmonary hypertension. Twelve hours later, his blood pressure and hematocrit dropped and the abdominal circumference increased. Abdominal tapping yielded a bloody fluid. The coagulogram was checked and all parameters were prolonged (PT > 60 sec, APTT > 120 sec, INR > 10), and the platelet count had dropped to 50 000/mm^3. Vitamin K was given and multiple doses of PRC, FFP and platelets were transfused but the infant's blood pressure and hematocrit did not stabilize and the baby died on the second day of life.

Histopathology revealed inclusion bodies in the nucleated red blood cells in the placenta and liver, which supported the diagnosis of a parvovirus infection.

Discussion

This is a case of NIHF from severe fetal anemia due to parvovirus B19 infection diagnosed from histopathology after the baby had expired. An important cause of fetal anemia leading to NIHF in Thailand is hemoglobin Bart's disease. In the present case hemoglobin electrophoresis was done and had ruled out this condition. Other causes of anemia such as blood group incompatibility, G6PD deficiency and congenital infection were also ruled out. Unfortunately, the detection of viral DNA or specific antibodies to parvovirus cannot be performed at the presented institution so the diagnosis can only be confirmed by histopathology. In cases of fetal anemia with unexplained cause, the parvovirus B19 infection should be considered among the differential diagnoses.

Literatures review

Parvovirus B19

Parvovirus is a small, non-enveloped, single-stranded DNA virus in the family Parvoviridae (*parvum* is Latin word for small). Parvoviruses replicate in the nuclei of infected cells and require the host cells go through the S phase before replicating[21]. The autonomous parvoviruses propagate in actively dividing cells. Parvovirus B19 is a member of the erythrovirus genus, which propagates best in erythroid progenitor cells[22].

Pathogenesis

Human erythroid progenitor cells are target cells of parvovirus B19 infection[23-25]. The virus binds to globoside, a neutral glycosphingolipid, also known as P antigen (an antigen of the P-system blood group) found on erythrocytes, erythroblasts, megakaryocytes, endothelial cells, placental cells, fetal hepatocytes and myocardial cells[26]. Rare persons, whose erythrocytes lack the P antigen, are not susceptible to parvovirus B19 infection; that is, their marrow erythroid progenitors proliferate normally in the presence of high concentration of viruses[27].

The virus is directly cytotoxic, causing apoptosis of the infected cells[28]. It attacks the erythroid precursors and causes both hemolysis and red cell aplasia. The characteristic is anemia without reticulocytosis that lasts about 7 to 10 days[29]. Recovery of the bone marrow usually occurs within 2 to 3 weeks in immune-competent patients with the disappearance of viremia after the onset of antibody response. IgG antibodies appear necessary to neutralize parvovirus activity. The lack of an effective antibody response in fetuses and immuno-compromised hosts may result in viral tolerance where viral replication is blunted but not eradicated. This may lead to persistent infection that allows the development of infected pronormoblasts through later stages of erythroid maturation[30].

Crook et al[31] have reported bone marrow findings in immuno-compromised patients, unlike the

typical pattern of marked erythroid hypoplasia, found in aplastic crisis of immuno-competent hosts. In such patients, the bone marrow shows normal or increased erythroid precursors with a complete maturational spectrum and abundant intra-nuclear inclusions similar to the finding in infected fetuses.

Epidemiology and clinical manifestation (Table 1)

The parvovirus B19 infection is common in school-aged children and can be epidemic because it is very contagious and may be asymptomatic. About 35% of pregnant women in Spain are already seropositive[20]. Reported seroprevalence ranges between 30 and 60% in adults[32]. The virus is spread by respiratory droplets though transfusion-associated transmission is reported[33].

The most common clinical presentation of a parvovirus B19 infection is erythema infectiosum or fifth disease, characterized by a "slapped cheek" rash on the face and a reticulated rash on the trunk and extremities[34]. After an incubation period of approximately 1 week, the virus produces a febrile illness accompanied by reticulocytopenia that lasts about 7 days and recovers without evidence of anemia in normal persons[29]. In patients with increased red blood cell destruction or shortened half-lives (such as sickle cell disease and hemolytic anemia), infection with this virus can cause an aplastic crisis[35,36]. Chronic anemia can also develop in some immuno-deficient persons owing to the persistence of viral replication in the bone marrow[37,38].

Table 1. Clinical entities of parvovirus B19 infection

Host	Manifestation
Children	Erythema Infectiosum
Adults	Arthralgia, Arthritis
Chronic hemolytic anemia	Aplastic crisis
Immuno-compromised	Chronic anemia
Pregnant women	Spontaneous abortion
	NIHF
	Fetal death
	Congenital anemia

In adults, particularly middle-aged women, arthralagia or arthritis may develop and can mimic rheumatoid arthritis[39-41]. The result of a test for rheumatoid factor may be positive[22]. Pathogenesis is assumed to be the deposition of immune complexes.

Parvovirus B19 infection in pregnancy

Fetal parvovirus B19 infection can completely resolve without sequelae, but it *can* cause spontaneous abortion or hydrops-fetalis, which can result in fetal death or stillbirth[42]. Prospective studies have shown that although the transplacental transmission rate is rather high (25-51%), most women with B19 infection in pregnancy had a satisfactory outcome[5,18-20,43]. The

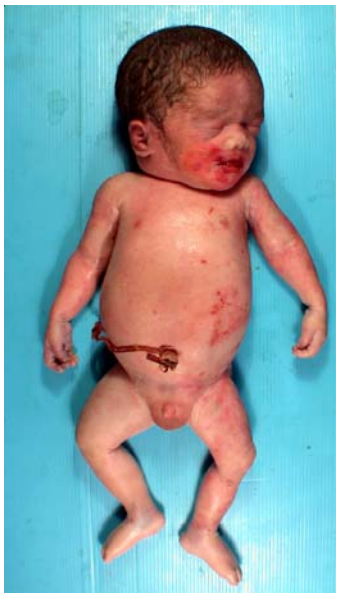

Fig. 1 Pale hydropic baby

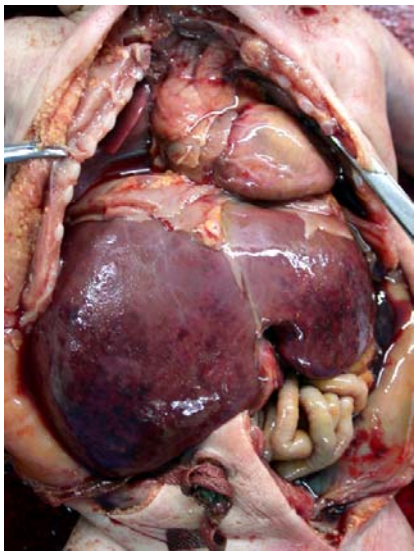

Fig. 2 Internal organs showing marked hepatomegaly and carediomegaly

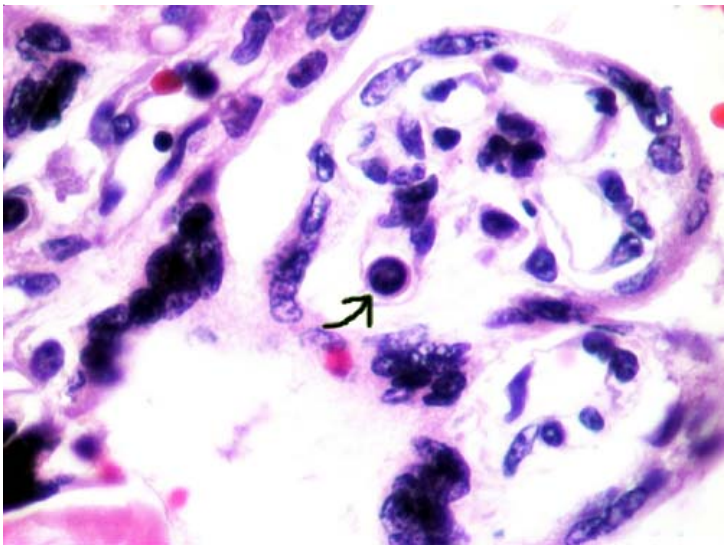

Fig. 3 Section of the placenta with inclusion body in nucleated red blood cell of chorionic villi

high rate of fetal loss was confined to the first 20 weeks of gestation and was about 10%[15]. Although many infants had serological evidence of intrauterine infection, they were asymptomatic at birth. No congenital anomalies or severe neuro-developmental problems were found in these studies. However, a few cases describing anomalies in the eyes and nervous system of infants possibly related to B19 infection[44-46]. Nevertheless there is no supporting evidence of any correlation between maternal parvovirus B19 infection and an increased risk of birth defects[15,18,47,48].

Parvovirus B19 and NIHF

Nearly 20% of NIHF cases are related to parvovirus B19 infection. The virus replicates in erythroid progenitor cells causing severe anemia in children in whom erythrocyte turnover is rapid. The fetus can be severely affected by this virus due to the shorter survival of red blood cells and the increase red blood cell production response to a rapid mid trimester expanding blood volume[9,42]. The development of acute, profound anemia resulting in high-output cardiac failure is the main proposed mechanism responsible for hydrops fetalis in fetuses infected with parvovirus[42]. However, several cases of NIHF, from parvovirus B19, were reported even in the presence of mild fetal anemia[49]. Another proposed mechanism is fetal heart failure secondary to viral myocarditis. This idea is supported by the presence of viral particles[50,51] and inflammatory changes in the myocardium[52] of infected fetuses.

Yaegashi et al [9] performed a meta-analysis of 165 reported cases of NIHF from intrauterine parvovirus B19 infection and discovered that 82% of the cases were diagnosed in the second trimester. The mean gestational age at diagnosis was 22.8 $\pm$ 5.1 weeks. The mean interval between the onset of maternal infection and the diagnosis of NIHF was 6.2 $\pm$ 3.7 weeks, so the estimated critical period of maternal infection leading to NIHF is about 11-22 weeks, which coincides with the hepatic period of hematopoiesis in the fetus. They had previously reported that erythroid lineage cells, derived from the fetal liver during active hematopoiesis, are targets of parvovirus B19 in vitro[25], which suggests that this virus may have an affinity for erythroid lineage cells at the hepatic stage of hemato-poiesis.

NIHF secondary to parvovirus B19 infection may spontaneously resolve with or without intrauterine transfusion[1,53-56]. Rodis et al [56] reported that approximately one-third of the cases of parvovirus-induced NIHF resolved spontaneously, 30% ended in death without intrauterine transfusion and 29% resolved after intrauterine transfusion. Among hydropic fetuses who were transfused 83.5% survived. If a fetus survives hydrops there are generally no long-term sequelae though chronic anemia persisting to early infancy and childhood has been reported[57,58].

Hematological findings

Anemia with reticulocytopenia is the most important hematologic finding in parvovirus B19 infections. Associated changes in other blood lineages,

with varying degrees of neutropenia, thrombocytopenia or pancytopenia are often found. In most cases, these changes are transient and not clinically significant except in patients with an underlying hemolytic disorder or immuno-compromised and fetus.

In an experimental parvovirus infection in human volunteers, Anderson et al [59] observed intense viremia about one week after intranasal inoculation of human parvovirus. Hematological studies demonstrated reticulocytopenia with an associated drop in hemoglobin concentration and platelet count, neutropenia and lymphopenia occurred during the second week after inoculation. No reticulocytes could be found between day 8 and 10 but were found again between day 17 and 26. Hemoglobin levels fell consistently during the week after the disappearance of reticulocytes and returned to pre-inoculation concentrations about 3 weeks later. Neutropenia were followed by compensatory elevated counts one week later. Although the platelet counts remained within normal range, a downward trend was noted between days 5 and 13.

Cessation of red blood cell production due to a parvovirus B19 infection can cause transient aplastic crisis in patients with increased erythropoiesis. This has been described in a wide range of patients with underlying hemolytic disorders, including thalassemia, hereditary spherocytosis, autoimmune hemolytic anemia and red cell enzymopathies[60]. Hematological changes in such patients include severe anemia associated with reticulocytopenia. The bone marrow activity almost always resumes after 7 to 10 days, and is followed by an increase in reticulocytes[61].

Forestier et al [62] reported the hematologic parameters in thirteen cases of NIHF caused by parvovirus B19 infection. All of the cases were severely anemic with mean hemoglobin values of 4.5 g/dL. The reticulocyte count ranged between 1.3 and 5 percent and the erythroblast count between 0.16 and 11 x 10^9 per liter. In one case, the reticulocyte count was very high (49.6%) and was associated with an increase in erythroblasts. Both findings are unusual in a parvovirus B19 infection. Thrombocytopenia was a frequent finding (11/13 cases) in Forestier series but white blood cells were within normal range according to gestational age in all but one case. Six of the 13 fetuses died. The hemoglobin level was not significantly related to the outcome of the fetuses.

Diagnosis

Since maternal infection may be asymptomatic, a case of intrauterine parvovirus B19 infection is suspected when NIHF occurs with fetal anemia but no family history of a-thalassemia. Evidence of a parvovirus B19 infection should then be looked for.

This virus can not grow well in routine culture. The diagnosis of intrauterine parvovirus B19 infection can be made by: 1) finding virus-specific IgM antibodies; 2) detecting parvovirus DNA in serum or tissues; or, 3) pathological diagnosis based on histological finding of characteristic eosinophilic intranuclear inclusions and marginated chromatin in erythroid precursors or visualization of the viral particles by electron microscopy.

The measurement of B19 IgM antibodies in a fetus or newborn is not reliable because of immaturity of the fetal immune system. A positive test for B19 IgM antibodies at delivery is helpful in diagnosis of an intrauterine infection but a negative test does not rule it out. Many reports have shown that fetuses with a congenital B19 infection (based on detection of viral DNA by PCR) demonstrated a negative B19 IgM in cord blood[5,14,19,63]. Some authors have suggested that persistent B19 IgG antibodies at 1 year of age is a useful marker of an intrauterine infection[18,64]. Maternal IgM antibodies may also be negative since the IgM response generally lasts only 2-4 months and would have already disappeared by the time fetal hydrops presents[52,63].

Viral DNA can be detected in amniotic fluid, blood, urine, saliva, tissues and placenta by polymerase chain reaction (PCR), dot blot hybridization or *in situ* hybridization[8,19,65-68]. PCR for DNA detection might be the best indicator of infection[66]. Some infants had a negative serum PCR at delivery but the test was positive on the urine or saliva[19]. Tests that directly identify viral particles or genome, however, will be positive only in the viremic stage,[42] so a negative PCR test at delivery does not definitively exclude intrauterine infection.

Pathological features of the placenta and fetal tissues may be very helpful in establishing a diagnosis of intrauterine parvovirus B19 infection, especially when viral-specific IgM or DNA detection is not available.

Using light microscopy, the characteristic eosinophilic intranuclear inclusions with peripheral condensation of chromatin along the nuclear membrane can be seen in erythroid precursor cells[7,52,69,70]. These inclusions are typical of parvovirus. These cells (also called lantern cells) can be detected in the liver, spleen, bone marrow, lung, heart, kidney, pancreas, adrenal, thymus, brain and placenta of the hydropic fetus[7,52]. They are most frequently seen in the liver, which is the major site of erythropoiesis in the second trimester. But in more mature fetuses, greater numbers of these

cells are seen in the bone marrow than the liver, consistent with the changing pattern of erythropoiesis with increasing gestational age[52]. The intranuclear inclusions are rarely reported in patients after the fetal period[31].

Roger et al [71] reviewed autopsy records from 673 fetal and neonatal autopsies. They identified 5 cases of parvovirus associated NIHF in which characteristic erythroid nuclear inclusions were found. These inclusions were resistant to degenerative tissue change. The most reliable tissue for histologic diagnosis was the liver followed by the heart and lung. Only 2 of 5 placentas had diagnostic inclusions and they concluded that examination of the placenta alone was insufficient for ruling out a congenital parvovirus infection. Nerlich et al[72] described infected erythroblasts with intranuclear inclusions found in the smear preparation of cord blood from B-19-DNA positive hydropic fetuses.

Definitive evidence of fetal infection can be documented by electron microscopy. The virus particles, measuring approximately 20 nm in diameter, can be observed within the nuclei of erythropoietic cells. The parvovirus virions are usually randomly distributed[73]. No such particles were seen in similar tissue from neonates or fetuses with erythroblastosis fetalis due to alpha-thalassemia, materno-fetal Rh incompatibility or an erythrocyte membrane protein defect[74].

Mark et al [75] suggested that histology is as sensitive as PCR in detecting parvovirus B19 in fetal autopsy tissues from cases of hydrops fetalis and could be used reliably to diagnose parvovirus infection. They would reserve PCR for cases without inclusions and with a strong suspicion of parvovirus infection, or for fluids in which histological analysis is not available.

Management

Pregnant women with clinical evidence of erythema infectiosum or an incidental finding of NIHF on a routine ultrasound examination should undergo serologic testing. Those who are positive for B19 IgM antibodies have been infected and their fetuses may be at risk of intrauterine infection. Termination of pregnancy is not recommended since the infection is not related to an increased rate of congenital malformation[18,42,56,76].

Weekly fetal ultrasonographic examination for evidence of hydrops should be performed for at least 6 to 8 weeks. If hydrops develops, cordocentesis should be considered, especially when there is any sign of worsening hydrops or fetal distress. This would be very useful for both diagnosis and treatment especially if the cause of hydrops is unknown. Fetal infection can be documented by positive specific IgM antibodies or PCR of the cord blood. Intrauterine blood transfusion can be considered in severely anemic fetuses (hemoglobin < 8 gm/dL)[11,42,43,56,76]. Although some preferred conservative management, recent data shows a benefit of transfusion therapy over conservative management[11,76].

The volume of blood to be transfused should be calculated in order to bring the fetal hemoglobin to the third percentile for gestational age thereby minimizing the stress on the fetal heart which may be compromised by B19 myocarditis[77]. Some authors have suggested that the maternal serum alpha fetoprotein level should be monitored because an elevated value is correlated with adverse outcomes in fetuses[78,79]. This elevated level probably arises from damaged fetal liver cells or infected placenta cells; however, a normal value has been described in spite of severe fetal infection[80].

Prognosis

Adverse prognostic parameters are maternal infection (or seroconversion) early in gestation, early gestational age at detection of NIHF, the number and results of fetal blood samples and prolonged duration from intrauterine transfusion to resolution of hydrops[76].

Approximately 63% of cases resolve either spontaneously or after intrauterine transfusion[56]. Resolution usually occurs within 6 weeks in the majority of cases either with or without transfusion with a subsequent normal perinatal outcome[56,76]. However, congenital anemia requiring postnatal transfusion persisting to early infancy and childhood has been reported in surviving infants[57,58].

Long term neuro-developmental outcome of children following intrauterine parvovirus B19 infection is good. There is no significant neuro-developmental delay[15,81,82].

Conclusion

Intrauterine parvovirus B19 infection is a common cause of NIHF associated with fetal anemia. Diagnosis can be made by identification of B19 specific IgM antibodies or DNA in the fetus or by histologic findings of characteristic intranuclear inclusions in erythroid precursor cells. Weekly ultrasonographic examination for signs of worsening hydrops and intrauterine blood transfusion in a severely anemic fetus are the treatment options. There is no apparent increase

in the frequency of neuro-developmental delay among surviving infants.

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ภาวะทารกบวมน้ำจากการติดเชื้อ parvovirus B19: รายงานผู้ป่วยและทบทวนวรรณกรรม

สุกัญญา ทักษพันธุ์, พิไลวรรณ กลีบแก้ว, รัตนา คำวิไลศักดิ์, ผกาพรรณ เกียรติชูสกุล, จรรยา จิระประดิษฐา, ถวัลย์วงศ์ รัตนศิริ

การติดเชื้อ parvovirus B19 ตั้งแต่ในครรภ์มารดา จะทำให้ทารกซีดมาก จนเกิดภาวะบวมน้ำตามมา ทารกบางรายอาจเสียชีวิตในครรภ์มารดา ได้รายงานผู้ป่วยที่มีภาวะบวมน้ำซึ่งได้รับการวินิจฉัยเมื่ออายุครรภ์ 31 สัปดาห์ จากการเจาะเส้นเลือดสายสะดือพบว่าฮีโมโกลบิน 5 กรัม/ดล. ทารกคลอดโดยการผ่าตัดเนื่องจาก fetal distress 18 ชั่วโมงต่อมา และเสียชีวิตเมื่ออายุ 2 วัน การตรวจทางพยาธิวิทยาพบ intranuclear inclusions ในเม็ดเลือดแดงตัวอ่อนที่ตับและรกซึ่งช่วยในการวินิจฉัยการติดเชื้อ parvovirus B19

คณะผู้รายงานได้ทำการทบทวนวรรณกรรมที่เกี่ยวข้องกับการติดเชื้อ parvovirus B19 โดยเฉพาะการติดเชื้อในครรภ์มารดาและผลต่อทารก ตลอดจนการวินิจฉัยและการรักษา