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Cytomegalovirus as a Seldom Cause of Non-Immune Hydrops Fetalis: Case Report and Review of the Literature

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Abstract

Introduction: Hydrops fetalis (HF) secondary to cytomegalovirus (CMV) is a rare but potentially fatal entity in neonates. This study aimed at providing data for diagnosis, management, and prevention of CMV associated HF in neonates. Herein, a case of non-immune hydrops fetalis (NIHF) associated with CMV infection is described and a review of the literature is presented.
Case Presentation: A female neonate was born at 373/7 weeks of gestational age with clinical findings of HF in Istanbul, Turkey, during year 2015. The infant was admitted to the Neonatal Intensive Care Unit (NICU) due to respiratory distress. The CMV Ig M was positive for both the baby and the mother. Polymerase chain reaction (PCR) demonstrated 6640 copies of CMV in the urine sample. Therefore, CMV infection was considered as the main cause of NIHF and ganciclovir therapy was initiated. As the patient responded well and survived, to the best of our knowledge, this is the first long-term survived case of CMV associated HF.
Conclusions: Congenital CMV infection should be kept in mind as a seldom and life-threatening cause of NIHF. Because serologic tests are not sensitive, antenatal sonographical, postnatal clinical and laboratory findings are crucial for accurate diagnosis and early treatment. All these cautions may be associated with for a better prognosis.

Keywords: Non-Immune Hydrops Fetalis, Congenital Infection, Cytomegalovirus, Neonate

1. Introduction

Hydrops fetalis (HF) has been defined as extracellular accumulation of abnormal fluid in at least 2 different fetal compartments, including soft tissues and serous cavities. It may either be immune or non-immune. Non-immune hydrops fetalis (NIHF) develops in the absence of maternal circulating red cell antibodies and it is responsible for at least 85% of all HF cases (1). Although cardiovascular problems (20%) were reported as the most common reason for NIHF, intrauterine infections (7%) represent a rare cause of NIHF (2). Parvovirus B19 has been defined as the most common infectious agent associated with NIHF. Infectious agents were suggested to cause HF through the effects on bone marrow, myocardium or vascular endothelium (1-3). Cytomegalovirus is the most frequent agent of congenital infections, affecting 0.2% to 2% of all live births (4). Prevalence of congenital CMV infection was reported as 0.64% (2). Although fetal transmission rate is 15% to 50% in the primary infection of mothers, this rate decreases to 0.15% to 1% with recurrent maternal infections (4). While congenital CMV infection is asymptomatic in 90% of cases, rest of the patients becomes apparent with typical symptoms (2). Congenital CMV infection is associated with severe neurodevelopmental morbidity and long-term neurologic injury (1). Congenital CMV infection is a cause of death as it is responsible from 0.3% of all stillbirths and 0.5% of all neonatal deaths (4, 5). Vertical transmission could lead to fetal death or cytomegalic inclusion disease that might be fatal in up to 30% of neonates (6). Although congenital CMV infection is common, HF due to CMV is usually rare (7, 8).

Herein, the study reports a term newborn that presented NIHF due to CMV infection, and survived after ganciclovir therapy. The authors also reviewed the literature about CMV associated NIHF.

2. Case Report

A female neonate was born at 373/7 weeks of gestational age by C-section because of hydrops fetalis to the first pregnancy of 22-year-old mother at Kanuni Sultan Suleyman Training and Research Hospital in Istanbul, Turkey, during year 2015. This is a governmental hospital with a total of 72 incubators in neonatal intensive care unit (NICU) and serves as a referral center for Departments of Perinatology and Neonatology. The patient was prenatally diagnosed as hydrops fetalis with severe ascites and cerebral hyperechogenic lesions were also detected. The pla-

centa seemed to be bigger than normal, hydropic and edematous in macroscopic evaluation. However, as microscopic evaluation of the placenta has not been routinely performed, the authors did not have this data. The infant was 3.100 g in weight, and her 1st and 5th minute Apgar scores were 5 and 7, respectively. The baby was admitted to the neonatal intensive care unit (NICU) due to respiratory distress. The infant was intubated. She required high ventilator settings such as a peak inspiratory pressure of 25 mmHg and a positive end expiratory pressure of 8 mmHg. Her physical examination revealed bad general status, generalized edema, microcephaly with a bulging anterior fontanelle, petechial skin lesions on abdomen, massive hepatosplenomegaly with abdominal distention (Figure 1). The patient was monitorized with Nihon Koden monitor, all clinical variables, including heart rate, blood pressure, and respiratory rate were recorded with a monitor during hospitalization. Laboratory tests revealed leukocytosis, anemia, and thrombocytopenia with a white blood cell count of 15.600/mm^3, hemoglobin of 10g/dL, and platelet count of 49.000/mm^3. The patient required multiple transfusions of erythrocyte suspensions for intractable anemia. Chest X-ray showed cardiomegaly, pleural effusion consistent with hydrops fetalis. Cranial Ultrasonography (US) revealed dilatation of 3rd and lateral ventricles, right grade 1 intraventricular hemorrhage with calcifications at periventricular areas (Figure 2). Cranial Computed Tomography (CT) also showed intracranial calcifications and triventricular hydrocephaly (Figure 3). Minimal pericardial effusion was seen on echocardiography with no other cardiac anomaly. Ascites and hepatosplenomegaly were detected by abdominal US. Therefore, abdominal paracentesis was performed and samples were analyzed for both biochemically and microbiologically. As chromosomal analyses and hemoglobin electrophoresis were found to be normal, alpha thalassemia and structural chromosomal anomalies were excluded. Peripheral blood smear was evaluated as normal with no finding of hemolysis. The patient had severe persistent hypotension that could be controlled with repeated albumin infusions and high dose noradrenalin infusion. The patient was extubated on the 11th postnatal day.

The CMV Ig M was positive for both the baby and the mother. PCR also demonstrated 6640 copies of CMV in the urine sample. The CMV infection was considered as the main cause of NIHF. Therefore, ganciclovir therapy (12 mg/kg/day) was started on the first day of life. Daily paracentesis was continued until no extracellular fluid remained in the abdomen. Both hepatosplenomegaly and ascites disappeared on abdominal US at postnatal day 12. Gancyclovir therapy continued for 6 weeks. The number of viral copies in PCR regressed to 280 at weekly controls. At the 7th week of life, the patient was discharged as breastfed with 5,220 g of weight. Typical corioretinitis was not detected on ocular examination. Her hearing tests were normal. Currently, she is 23 months old with neuromotor retardation and has been followed by the Departments of Pediatric Infectious Disease, Pediatric Neurology and Neonatology.

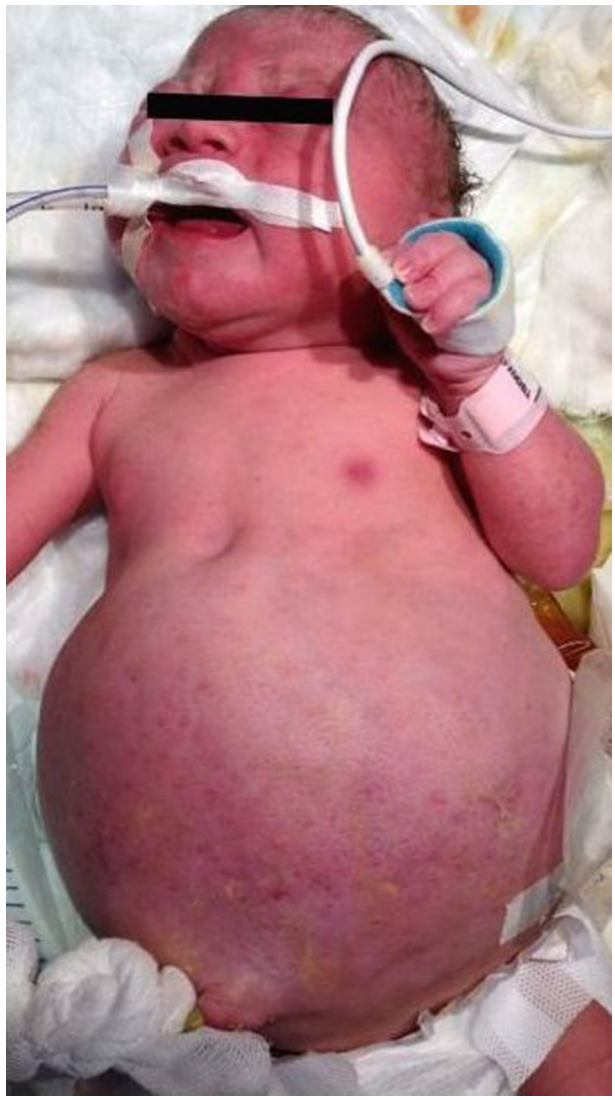

Figure 1. The Infant Had Generalized Edema, Microcephaly, Petechial Skin Lesions, and Abdominal Distention with Hepatosplenomegaly in Her First Physical Exam.

3. Discussion

The excessive fluid accumulation within the fetal extravascular compartments and body cavities has been defined as hydrops fetalis. Although the incidence of Rh

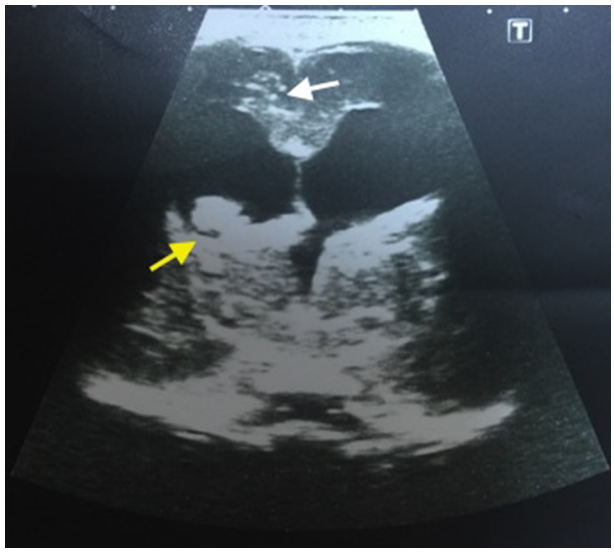

Figure 2. Cranial US revealed dilatation of 3rd and lateral ventricles, right grade 1 intraventricular hemorrhage (yellow arrow) and calcifications at periventricular areas(white arrow).

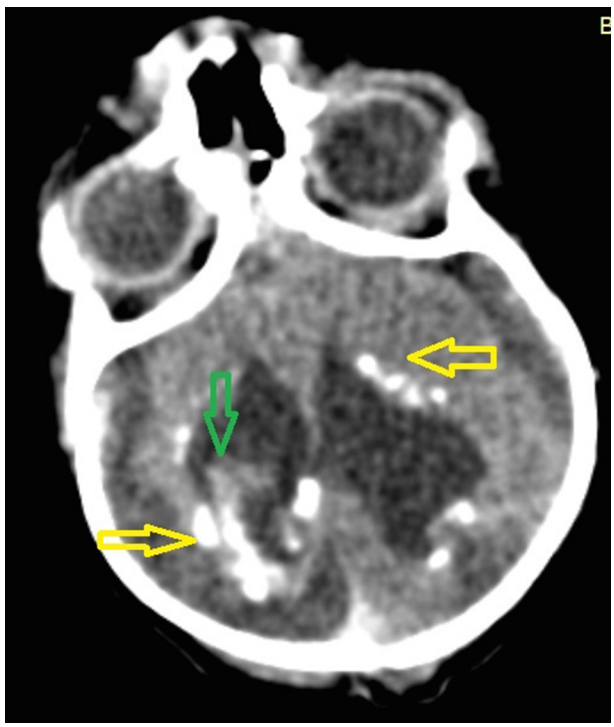

Figure 3. Cranial CT Demonstrated Dilatation of 3rd and Lateral Ventricles, Right Grade 1 Intraventricular Hemorrhage (Green Arrow) and Calcifications at Periventricular Areas (yellow Arrows).

hemolytic disease declined in the past 4 decades, NIHF remains the main cause in these cases. According to a recent review, infections were reported to cause NIHF with 7% frequency (3).

Congenital CMV is the most common congenital infection complicating up to 2% of all pregnancies throughout the world. It is one of the leading causes of hearing loss and neurological deficits during infancy and childhood (9). Congenital CMV infection may also result intrauterine fetal death, HF, cytomegalic inclusion disease, and pneumonia (10). Although parvovirus B19 infections are the most common cause of hydrops fetalis, CMV may also be responsible from hydrops fetalis. To the best of our knowledge, only 14 cases were found to have a similar clinical manifestation of CMV associated NIHF, yet the current case was unique due to having a long-term survival with conventional therapy (5, 7, 11-20). Table 1 shows all clinical variables of cases in the literature.

The pathogenesis of NIHF due to perinatal CMV infection was suggested to be mostly multifactorial. Fetal bone marrow, myocardium and vascular endothelium represent the main target organ systems for intrauterine infections. Fetal congestive heart failure, anemia, sepsis leading to anoxia, endothelial cell damage, and increased capillary permeability may constitute the possible mechanisms of perinatal infections associated with NIHF (1). The inotrope resistant hypotension in the current case may be explained with increased capillary permeability secondary to endovascular cell injury and sepsis. However, it is usually difficult to elucidate these mechanisms during the postnatal period.

Congenital CMV infections may develop either in females with primary infection during pregnancy or in women with reactivation of a latent infection or reinfection with a heterologous strain of the virus (4). The case was thought to be caused by primary infection of the mother because her mother was negative for CMV Ig G. Presentation of congenital CMV infection is reported to be life-threatening in offspring of liver transplant recipients (18). Thus, maternal immune status may also have an important role in fetal CMV infection's severity.

Approximately 30% to 50% of pregnant females are seronegative at the early stages of pregnancy and 1% will develop primary infection during pregnancy (6, 21). However, maternal antibody status does not prevent congenital CMV infections, it seems to provide protection from the more severe sequelae of congenital CMV, such as cytomegalic inclusion disease (6). Therefore, as serological tests do not have adequate sensitivity and specifity for the diagnosis of congenital CMV infection, the current standard for the diagnosis is CMV culture from the urine or saliva, by rapid viral detection in culture by immunohistochemistry. Recently, saliva or urine quantitative real-time polymerase

Table 1. All Clinical Variables Of Cases In The Literature

	GW	BW	APGAR	MI	m-IgM	n-IgM	MV	n-PCR	Comorbidity	Treatment	Final Outcome
Sampath et al. (11)	29	695	1/1	-	-	+	+	N/A	Oligohydramnios	Ganciclovir	Exitus
Tongsong et al. (14)	20	450	-	N/A	N/A	+	-	-	Hyperechogenic bowel	-	Termination
Moxley K et al. (15)	37	2246	9/9	-	-	+	-	+	Hyperechogenic bowel	CMV hyperIg	Discharged
Jackups et al. (5)	28	N/A	N/A	N/A	N/A	N/A	-	N/A	IUGR	N/A	Exitus
Lujan-Zilbermann et al. (13)	32	2618	1/6	N/A	N/A	N/A	+	N/A	-	N/A	Exitus
Sato Aet al. (16)	29	1219	1/5	-	-	+	+	N/A	-	In utero CMV hyperIg	Exitus
Salmaso et al. (19)	23	-	-	+	+		-	+	-	-	Termination
Ortiz et al. (12)	23	-	-	N/A	-	+	-	+	IUGR, microcephaly Cerebellar hemorrhage	-	Termination
Syridou et al. (20)	N/A	N/A	N/A	N/A	N/A	N/A	-	+	-	-	Intrauterine fetal deaths (Two cases)
Takci et al. (17)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ko et al. (10)	24	640	N/A	-	N/A	N/A	-	N/A	-	-	Exitus
Laifer et al. (18)**Case 1**	23	587	N/A	+	+	-	-	N/A	-	Maternal Ganciclovir	Exitus
Laifer SA et al. (18) **Case 2**	23	630	N/A	+	+	+	-	N/A	Olygohydramnios	Maternal Ganciclovir	Exitus
Beksac et al. (7)	24	N/A	N/A	+	+	N/A	-	N/A	-	-	Termination

Abbreviations: BW; birth weight (in grams); GW; gestational week; MI; maternal infection; m-IgM, maternal immune globulin M; MV, mechanical ventilation; n-PCR; neonatal polymerase chain reaction.

chain reaction assay was found as a highly sensitive and specific technique, as the gold standard culture for CMV diagnosis (22, 23).

Because serological tests cannot be used as diagnostic parameters alone, sonographical findings may provide valuable data for diagnosis. Sonographical signs of intrauterine CMV infection were reported as cerebral calcifications, cerebellar hemorrhage, hyperechogenic bowel, fetal hydrops, pericardial effusion, cardiomegaly, placentomegaly, and oligohydramnios (22). In this manner, these findings in a NIHF case should alert practitioners for the possibility of CMV infection. This requires prompt investigation of amniotic fluid, even if maternal serology does not support recent maternal seroconversion (24). For this case, cerebral hyperechogenic lesions and hydrops fetalis were detected on prenatal US, and maternal CMV Ig M was found to be positive but Ig G was negative. The use of brain magnetic resonance imaging to reveal early fetal neurological involvement of CMV infection, proved to be distinctly useful in identifying the findings not disclosed by routine US (19).

Fetal infection may lead to microvascular pressure changes and disturbance of blood flow to the organs, according to the fluid leak from endothelial distances and basal membrane. Typical CMV inclusions could be seen in epithelial cells and in endothelial cells of kidney, lung, and liver (10). In a study including 2 CMV-associated NIHF, villitis was found to be greatly associated with PCR-positive placental tissues, although placental hydrops may be one of the reasons obscuring its presence in some cases (20). Although there is a high mortality rate for CMV associated NIFH, there are only 2 patients of survival including the current case in the literature. Therefore, prompt diagnosis and early initiation of treatment is important for a good prognosis. Treatment of CMV infection includes three approved antivirals, including gancyclovir, foscarnet, and cydofovire (4). Recommended therapy for CMV infection is 6 weeks of treatment with gancyclovir and it is known to be effective in decreasing viruria and the risk of hearing impairment (24). In accordance, gancyclovir therapy was started from the first day of life and continued for 6 weeks, and viral copy number decreased substantially during the follow-up in the current case. No adverse effect due to gancyclovir therapy was observed. She had no hearing loss at the time of discharge and also during the follow-up period. Currently, she is 23 months old and her neurodevelopmental tests are in accordance with 12 months.

Resolution of hydrops secondary to congenital CMV could rarely be evident by the administration of maternal and fetal hyperimmune globulin (16, 17). The CMV hyperimmune globulin might also be promising for prevention of fetal infection.

The strength of this case could be suggested as the early diagnosis and treatment of CMV infection in a newborn with NIHF and the long-term survival of the infant. Therefore, the authors suggest that viral perinatal infections should be considered as a rare cause of NIHF in neonates. The weak point of this study could be that microscopic evaluation of the placenta at birth was not performed.

In conclusion, though it is a seldom cause of nonimmune hydrops fetalis, congenital CMV infection should be kept in mind in all cases. Because serologic tests are not sensitive, antenatal sonographical, postnatal clinical, and

laboratory findings are crucial for accurate diagnosis and early treatment.

Footnote

Conflict of Interest: We had no conflict of interest.

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