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Case Report

Unlocking the mysteries of fulminant hepatitis: exploring diagnoses in multi-organ disease

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ABSTRACT

A male neonate was born to a mother with a history of scant prenatal care and suspected Herpes lesions in the birth canal. The infant presented after birth with severe anemia, thrombocytopenia, and acute liver failure along with multiple organ involvement. He received multiple transfusions and was treated empirically for potential sepsis and viral infection. Differential diagnoses considered included neonatal HSV infection, enterovirus infection, gestational alloimmune liver disease (GALD), hemophagocytic lymphohistiocytosis (HLH), and inborn errors of metabolism. The case underscores the complexity of diagnosing fulminant hepatitis in neonates and emphasizes the necessity of maintaining a broad differential diagnostic approach. This case report highlights the diagnostic challenges and the need for a systematic approach in managing neonates with fulminant hepatitis.

Keywords: Fulminant hepatitis, Neonate, Acute liver failure

INTRODUCTION

Fulminant hepatitis has been extensively studied in the pediatric population. It is a rare disorder that presents with severe liver impairment associated with hepatocellular necrosis and can be accompanied by encephalopathy.[1] Neonates who present with hepatitis have a relatively poor prognosis.[2] Many etiologies have been identified – including infections, toxins, metabolic disorders, infiltrative diseases, autoimmune hepatitis, ischemic or irradiation damage.[1] In neonates, the common causes include gestational alloimmune liver disease (GALD), herpes simplex virus infection, and metabolic disorders.[3] Cases of neonatal fulminant hepatitis have been shown to likely begin in utero.[4] The infant in our case presented with acute liver failure at birth along with worsening pancytopenia, disseminated intravascular hemolysis and acute renal injury, making the differentials broad. Roughly 30%-50% of cases have an indeterminate workup by the time of death or discharge.[3] Authors describe this case with multisystem involvement and elucidate various potential factors to consider when managing such a case.

CASE REPORT

A male neonate, weighing 2096 grams (small for gestational age) and born at outside hospital to a G2P0101 28-year-old mother at 38 weeks gestation, following precipitous vaginal delivery who was subsequently transferred to our Neonatal Intensive Care Unit (NICU). Pregnancy was complicated by scant prenatal care and history of previous preterm birth. All prenatal labs were negative, except unknown GBS status and rubella non-immune. APGARs were 3, 8, and 8 at 1, 5, and 10 minutes respectively. Mother has previous history of active Herpes simplex virus (HSV) infections, for which she was prescribed Valganciclovir one month prior to birth. She was not compliant and was noted to have active draining lesions on the genital tract during delivery. Mother mentioned remote history of rhinorrhea and foot swelling in her third trimester. Baby was

transferred to our NICU due to severe pallor at birth, CBC showing severe anemia with thrombocytopenia (Table 1), and newborn requiring respiratory support for management of meconium aspiration syndrome. Upon presentation to NICU, the patient's temperature is 36.5°C, blood pressure 58/26 mmHg, respiratory rate 84 breaths/min on ventilation, heart rate 153 bpm and was on nasal CPAP (PEEP +7, 100% FiO2. The infant on examination was noted to be pale, alert, crying with good tone, symmetric range of movement and reflexes. Noted to have unremarkable respiratory and cardiac exam.

Hepatomegaly 4 cm below the costal margin and splenomegaly till umbilicus noted on examination. He is anemic, thrombocytopenic, coagulopathic along with acute fulminant hepatitis on presentation. Also had hypokalemia, hypermagnesemia, and was initially oliguric then polyuric (consistent with kidney injury). Initial labs drawn for this baby are mentioned in Table 1. In the first 28 hours, the baby received multiple small aliquots of transfusions of PRBCs and other blood products to stabilize his hematologic condition. Initial LP was not done in view of coagulation abnormalities.

Due to elevated CRP (13.43 mg/dl) on admission, the infant was given ampicillin and gentamicin for suspected sepsis. Also started on empiric acyclovir due to suspected maternal HSV infection. Due to liver failure other TORCH and enterovirus infections were on differentials. Sepsis was ruled out with negative blood cultures (Table 2). HSV PCR and surface culture were negative on DOL 7 was negative. In view of improvement in clinical and laboratory parameters and high suspicion of congenital HSV, acyclovir was continued for total of 21 days. Enterovirus culture was negative. Table 3 shows infectious labs. We had requested the Outside hospital to send Herpes labs on the mother serum and from her lesions but could not get it processed. Due to suspicion of GALD, iron studies were done at 20 HOL (hours of life), which found: Iron 203 ug/dl, UIBC <55.0 ug/dl, Ferritin 696.01 ng/ml. Due to increased ferritin and iron, MRI of abdomen was done to rule out hemochromatosis and labs were also sent for concerns of hemophagocytic lymphohistiocyotsis (HLH), both were negative. Iron studies on discharge were down trending. Blasts were noted on the peripheral smear DOL 2 (1%). This raised concern for leukemia, on further investigation with flow cytometry and slide pathology these cells were more reactive blast cells due to inflammatory or infectious processes. Given the concerns for blasts and initial presentation to the NICU, microarray and chromosomal analysis was sent for Trisomy 21 but was found to be negative.

In the process of ruling out Trisomy 21, a 16p11.2 recurrent deletion was uncovered. Head ultrasound on DOL 2, secondary to severe anemia and thrombocytopenia, revealed a Grade II intraventricular hemorrhage (IVH) with cystic changes. Given transaminitis, direct hyperbilirubinemia, severe anemia and metabolic acidosis, a metabolic workup was performed to rule out metabolic disorders and was negative. Table 1 details the initial and follow-up liver and renal injury labs. Completed 3 weeks of acyclovir and the patient's coagulopathy improved after multiple blood transfusions. Hepatosplenomegaly was still observed on the MRI done prior to infant's discharge. The infant was discharged on DOL 44.

Table 1: Describes laboratory data for the infant during the hospital stay, includes complete blood count, coagulation profile, liver function tests and renal function tests.

	DOL 1	DOL 1	DOL 2	DOL 3	DOL 4	DOL 7	DOL14	DOL32	DOL 40 (Prior to discharge)
Total leukocyte count (k/µl)	20.2	18	16.0	6.0	6.5	8.3	16.0	11.2	9.8
Differential leukocyte count (%)									
Neutrophils (%)	45	66	67	70	53	55	11	24	20
Bands (%)	13	9	2	1	1	0	1	0	2
Lymphocyte (%)	32	3	13	12	30	23	69	59	53
Blasts (%)	0	1	0	0	0	0	0	0	0
Red cell count (mil/ul)	1.51	2.61	2.79	4.90	4.46	3.58	4.13	3.13	4.09
HCT (%)	15.9	22.5	23.3	38.5	35.0	28.0	32.0	24.2	34.1
Hb (g/dl)	5.1	7.5	7.9	13.4	12.3	9.7	10.9	8.2	11.8
Platelets (k/ul)	7	47	47	46	41	29	91	214	211
Prothrombin time (PT) (sec)	42		20	19.3		16.8	14.1		
Partial thromboplastin time (PTT) (sec)	107		51	44.9		75.8	27.6		
International normalized ratio (INR)	4.6		1.74	1.65		1.39	1.10		
Fibrinogen (mg/dl)	126		375	343		213	207		

Continued.

	DOL 1	DOL 1	DOL 2	DOL 3	DOL 4	DOL 7	DOL14	DOL32	DOL 40 (Prior to discharge)
D-dimer (µg/ml FEU)	2.76								
Factor V level (%)	15 (L)					66 (N)			
Factor VII level (%)	10 (L)					50 (N)			
Factor VIII level (%)	145 (N)								
ALT (U/l)	509		319	191	83	46	230	143	84
AST (U/l)	2761		1456	614	220	83	304	184	103
Alkaline phosphatase (U/l)	337		123	103	107	171	419	519	387
Ammonia (umol/l)	105								
Total bilirubin (mg/dl)	9.5		16.2	19.9	19.9	12.6	18.5	9.2	5.6
Direct bilirubin (mg/dl)	5.3		8.7	15.3	15.6	7.4	13.7	5.2	3.2
Creatinine (mg/dl)	1.1		1.4	1.0	0.6	0.3	0.4	0.4	
BUN (mg/dl)	15		17	21	19	13	12	9	
Cholesterol (mg/dl)								149	

Day of life, RBC- Red blood cells, HCT- Hematocrit, Hb- Hemoglobin, ALT- Alanine transaminase, AST- Aspartate aminotransferase, Cr- Creatinine, BUN- Blood urea Nitrogen. L- low range, N- normal range, FEU- fibrinogen equivalent units).

Table 2: Elaborates the maternal infectious laboratory results and infant's work up on infectious etiology.

Laboratory data	
Maternal infectious etiology workup	
HIV	Negative
Hepatitis B	Negative
Syphilis	Negative
HSV 1 IgG titers	3.9
HSV 2 IgG titers	>8
Infant infectious etiology workup	
Infant IgM levels (DOL 5)	324 mg/dl
Infant IgG levels (DOL 5)	814 mg/dl
TORCH (CMV and Toxoplasmosis)	Not Detected
Blood culture (DOL 1)	Negative for 5 days
CRP (DOL 1)	13.43 mg/dl
CRP (DOL 8)	1.43 mg/dl
Enterovirus PCR	Negative
Infant herpes simplex virus specific infectious workup	
HSV PCR surface	Not detected
HSV PCR blood (DOL 1)	Not detected
HSV IgM (DOL 1)	TNP
HSV type 1 IgG (DOL 37)	15.20 IV (Elevated)
HSV type 2 IgG (DOL 37)	0.93 IV (Equivocal)
HSV IgM 1 and/or 2 (DOL 37)	0.66 IV (Not detected)

IgM-Immunoglobulin M, IgG-Immunoglobulin G, CMV-Cytomegalovirus, DOL-Day of life, CRP-C Reactive Protein, PCR-Polymerase chain reaction, IV- Index Value, TNP–Test not performed).

DISCUSSION

The lack of clear etiology for the infant's condition prompted evaluation of exhaustive differentials–ranging from infectious etiology to metabolic disorders. In the light of suspected maternal Herpes infection and inconsistent history of maternal treatment, neonatal Herpes infection was high on the differentials. The elevated initial IgM levels in the infant (IgM 324) along with lower HSV IgM level following acyclovir treatment, suggest that the infant's symptoms were likely associated with congenital HSV. Neonatal HSV disease occurs in roughly 1500 infants a year in the United States and

disseminated disease typically presents around day 10-12 of life.[5] Disseminated disease affects 20% of neonatal HSV cases and affects multiple organ systems.[6]

Affected infants can present with a short prodrome followed by rapid respiratory and hepatic failure, along with disseminated intravascular coagulation (DIC).[5,7] While most infected neonates (85%) get infected in the peripartum period.[8] Studies have shown that prenatal maternal antiviral prophylaxis is not fully protective as it does not completely suppress asymptomatic genital shedding.[6,9] Enterovirus and parvovirus infection as a probability on the differential given mother's risk factors. Enteroviruses cause mild disease in adults but can be an etiology of fulminant hepatitis in the neonatal population. These mothers have respiratory or gastrointestinal symptoms.[10] Treatment is typically supportive, however high-dose immunoglobulin has also been shown to be effective in neonates with severe diseases.[10,11]

The severity of the liver injury, as evidenced by our infant's transaminitis and direct hyperbilirubinemia and coagulation abnormalities, allowed inclusion of gestational alloimmune liver disease (GALD) into the differential. The diagnosis was also supported by increased ferritin and iron levels. GALD, formerly known as neonatal hemochromatosis, is caused by maternal antibodies that attack fetal hepatocytes, initiating a fetal immune response that leads to liver damage. While incidence is four per every 100,000 births, it is the most common cause of neonatal liver failure and a leading indication of liver transplants in infants.[12,13] Patients will have progressive iron deposition in the liver, pancreas, heart, and thyroid during their fetal period. At birth, they will present with fulminant hepatic failure–including hypoalbuminemia, hypoglycemia, coagulopathy, low fibrinogen, thrombocytopenia.

Usually diagnosis is confirmed by MRI, which did not show any extrahepatic siderosis which is seen in cases of GALD.[12] Our patient had hepatosplenomegaly, which is also uncommon in neonatal GALD. Another diagnosis considered is hemophagocytic lymphohistiocytosis (HLH), which results from excessive immune activation and tissue damage in various organs. Affected patients present with fever, hepatosplenomegaly, abnormal liver-function tests, high serum ferritin, elevated triglycerides, hypofibrinogenemia, and cytopenias.[14] HLH can be either familial or sporadic, and typically occurs following an immunologic trigger such as infection, malignancy, or autoimmune disorder.[14,15] Our patient did not meet the complete criteria for HLH.

Several metabolic disorders can present as neonatal fulminant hepatitis–including galactosemia, type 1 tyrosinemia and hereditary fructose intolerance.[16] These can occur in the neonatal period and present with jaundice, hypoglycemia, and progress to acute liver failure.[10] The timing of these metabolic disorders does not align with this case. Galactosemia typically presents after a few days of life, tyrosinemia presents after a few months and hereditary fructose intolerance presents once solid foods are introduced.[10] Infant in our case had negative newborn screen sent at birth and 48 HOL. His metabolic workup was also negative.

During this workup, a 16p11.2 recurrent deletion was found. The 16p11.2 recurrent deletion could account for the neonate to be SGA. This incidental finding of genetic involvement would less likely be the reason for infant's initial presentation, as the neonate would be more likely to show symptoms later in life – such as motor speech disorder, psychiatric conditions, recurrent seizures and neurodevelopment delay.[17,18]

Although a conclusive diagnosis was not reached, the infant was medically cleared for discharge on DOL 44 and has been growing and developing adequately under multidisciplinary care.

CONCLUSION

This case highlights the importance of keeping of a broad differential in a complicated neonate who presents with fulminant hepatitis.

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