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Acute Liver Failure in Neonatal Lupus Erythematosus

Novel Treatment With Exchange Transfusion, Intravenous Immunoglobulin, and Steroids

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INTRODUCTION

Acute liver failure (ALF) is a rare and potentially life-threatening complication of neonatal lupus erythematosus (NLE), thought to be caused by transplacental passage of maternal IgG antibodies directed against fetal liver antigens (1). ALF in NLE has no standardized treatment protocol reported in the literature. We describe a novel treatment protocol for NLE-associated liver failure in the postnatal period.

CASE DESCRIPTION

The female patient was born at full term to a primigravida mother with no prior miscarriages, who had systemic lupus erythematosus with positive anti-Ro/SSA and anti-La/SSB antibodies. Prenatal labs demonstrated immunity to rubella and varicella and no evidence of hepatitis B, syphilis, or Group B Streptococcus infections. Pregnancy was complicated by a lupus flare in the first trimester requiring 10 mg of oral prednisone daily and 24 hours of stress dose steroids at delivery. The mother's maintenance medications, azathioprine, hydroxychloroquine, and aspirin, were continued during pregnancy.

The patient initially had an uneventful postnatal course and received the routine 1 mg intramuscular vitamin K injection after birth. On day of life (DOL) 5, a screening electrocardiogram and echocardiogram were normal. That day, she was found to have hypoalbuminemia and elevated transaminases (Table 1).

On DOL 13, gastroenterology was consulted for cholestasis, worsening hepatitis, and persistent hypoalbuminemia. Infectious workup was negative for herpes simplex virus, Epstein-Barr virus, cytomegalovirus, and human immunodeficiency virus. Creatine kinase, thyroid studies, cortisol, lactic acid, glucose, and an abdominal ultrasound with Doppler were normal. On DOL 15, rheumatology was consulted for positive anti-Ro antibody (with negative anti-La antibody) and exam findings of erythematous annular lesions with central clearing over the upper eyelids consistent with cutaneous NLE.

On DOL 18, the infant was found to be in ALF with an international normalized ratio (INR) of 2.3, so received an additional 5 mg subcutaneous vitamin K injection. On DOL 19, INR was 2.5 with elevated ferritin and a normal ammonia. To avoid delay in starting potentially life-saving therapy, a liver biopsy was not performed. The patient was transferred to the intensive care unit, and on DOL 20 was treated with double volume exchange transfusion using 500 mL of red blood cells constituted with fresh frozen plasma, followed by 1 g/kg of intravenous (IV) immunoglobulin (IVIG) and 2 mg/kg of IV methylprednisolone. IV methylprednisolone was continued at 2 mg/kg daily, and the patient's INR initially improved to 1.8 then rose to 2.1 on DOL 22 prompting a second dose of 1 g/kg IVIG. After improvement in her bloodwork, wakefulness, and feeding, the patient was transferred to the acute care floor. On DOL 25, IV methylprednisolone was decreased to 1.5 mg/kg daily. The patient was transitioned to oral steroids on DOL 27 and weaned off steroids by 2 months of life (Table 1). She was discharged home on DOL 29 on ursodiol and fat-soluble vitamins.

Transaminases and INR normalized by DOL 29, albumin normalized by DOL 55, cholestasis resolved by DOL 74, and anti-Ro antibodies became undetectable 3 months following treatment. Her cutaneous lesions resolved prior to a 3-month follow-up appointment. A repeat abdominal ultrasound at 2 months old was normal, showing no evidence of portal hypertension. The infant is currently healthy with no clinical concerns.

DISCUSSION

Given a maternal history of systemic lupus erythematosus, positive anti-Ro antibodies in our patient, cutaneous findings of NLE, and the patient's swift recovery with treatment, we suspected that our patient's ALF was secondary to NLE hepatobiliary disease.

Severe NLE may lead to ALF and death. The pathophysiology of ALF in NLE is not fully delineated, although it is thought to be due to maternal antibody-mediated injury (1). This is similar to cardiac manifestations of NLE where the risk of congenital heart block is highest in infants born to mothers with high anti-Ro antibody levels (>50 U/mL) (2–4).

Hepatic complications are less commonly reported than cardiac manifestations of NLE due to lower incidence or under detection (5, 6). Three manifestations of hepatobiliary sequelae of NLE have been observed: transient conjugated hyperbilirubinemia, transient elevation of transaminases, and liver failure (7). In patients with NLE

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The parents of the patient in this case report are aware of the intent to publish and give their consent.

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TABLE 1. Laboratory values before and after intervention

Laboratory test	Normal reference range	DOL 1	5	13	15	18	19	20	21	22	26	29	55	74	111	168
Total bilirubin	< 1.0 mg/dL	6.4	15.4	16.8	—	—	14.8	6.8	6.1	4.8	3.6	3.2	1.7	0.9	0.4	0.2
Direct bilirubin	< 0.40 mg/dL	—	—	7.1	7.09	—	6.92	—	2.82	2.62	1.78	1.4	0.56	0.23	< 0.20	< 0.20
Alkaline phosphatase	122–469 U/L	—	518	632	—	—	877	259	330	476	672	660	409	332	360	402
GGT	< 40 U/L	—	—	—	—	—	37	—	18	—	54	—	281	152	55	25
AST	< 30 U/L	—	350	593	—	—	459	109	164	222	82	66	42	33	62	66
ALT	< 30 U/L	—	92	113	—	—	69	23	30	36	28	28	21	16	16	34
INR	≤1.1	—	—	—	—	2.3	2.5	1.8	2	2.1	1.5	1.2	—	1	1	1
Albumin	3.8–5.4 g/dL	—	2.7	2.8	—	—	2.5	1.9	1.8	1.7	2.1	2.5	3.9	3.9	4.3	4.6
Platelets	150–400 K/uL	154	—	—	131	—	184	82	96	106	—	—	157	—	551	—
Anti-Ro antibody	<20 U/mL	—	—	—	100	—	—	—	82	—	—	—	—	33	< 20	—
Intervention																
Double exchange transfusion								DOL 20								
IVIG									DOL 20: 1 g/kg	DOL 22: 1 g/kg						
Steroids									DOL 20–24: 2 mg/kg IV Methylprednisolone daily	DOL 25–26: 1.5 mg/kg IV Methylprednisolone daily	DOL 27—2 months of life: oral steroid taper					

Dashes indicate in the lab section means that that the laboratory study was not drawn on that day.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; DOL = day of life; GGT = gamma-glutamyl transferase; INR = international normalized ratio; IV= intravenous; IVIG = intravenous immunoglobulin.

who have severe hepatic sequelae, the risk of mortality is high. Lee et al (6), utilizing a national NLE registry, reported on 19 patients with hepatobiliary disease, of which 6 died due to severe liver disease in utero or shortly after birth. For 1 mother of an infant that died at 7 weeks of age due to ALF, her next child developed a coagulopathy on DOL 2 and died on DOL 6. The timing of ALF in our patient is unclear, as INR was not checked until DOL 18. However, given death reported in neonates with NLE and ALF as early as DOL 6, we advocate for screening labs including alanine aminotransferase, total and direct bilirubin, INR, albumin, and anti-Ro antibodies on DOL 1 in all neonates born to mothers who have anti-Ro antibody autoimmune disease to allow early treatment if needed and decrease morbidity and mortality in this population.

There are no standard guidelines reported in the literature for treating ALF in NLE. A triple therapy protocol with plasmapheresis, IVIG, and steroids for mothers with anti-Ro/La-related congenital atrioventricular block and postnatal IVIG only in their neonates has been described (3, 8). In ALF, due to gestational alloimmune liver disease (GALD), treatment protocols employ IVIG and exchange transfusion (2, 9). As the mechanism for NLE is thought to be immune-mediated similar to GALD, we applied therapy previously established for GALD to minimize antibody-mediated injury.

In the absence of standard management guidelines of ALF in NLE, we describe a novel treatment protocol utilizing exchange transfusion, IVIG, and steroids to halt ongoing antibody-mediated injury by removing, binding, and neutralizing circulating maternal antibodies. This treatment strategy led to the full recovery of liver function in an infant who is now 1 year old without any clinical sequalae. Although further data are needed to generalize these results, this novel treatment protocol has the potential to successfully treat ALF in NLE, a complication that may otherwise lead to mortality in newborns.

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