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Multiple Organ Manifestation in Neonatal Lupus Erythematous (Report of Two Cases)

Lubis A., Widayanti R., Hikmah Z., Endaryanto A., Harsono A., Harianto A., Etika R., Handayani D. K., Sampurna M.

***Abstract*—**Neonatal lupus erythematous (NLE) is a rare disease marked by clinical characteristic and specific maternal autoantibody. Many cutaneous, cardiac, liver, and hematological manifestations could happen with affect of one organ or multiple. In this case, both babies were premature, low birth weight (LBW), small for gestational age (SGA) and born through caesarean section from a systemic lupus erythematous (SLE) mother. In the first case, we found a baby girl with dyspnea and grunting. Chest X ray showed respiratory distress syndrome (RDS) great I and echocardiography showed small atrial septal defect (ASD) and ventricular septal defect (VSD). She also developed anemia, thrombocytopenia, elevated C-reactive protein, hypoalbuminemia, increasing coagulation factors, hyperbilirubinemia, and positive blood culture of *Klebsiella pneumonia*. Anti-Ro/SSA and Anti-nRNP/sm were positive. Intravenous fluid, antibiotic, transfusion of blood, thrombocyte concentrate, and fresh frozen plasma were given. The second baby, male presented with necrotic tissue on the left ear and skin rashes, erythematous macula, athropic scarring, hyperpigmentation on all of his body with various size and facial haemorrhage. He also suffered from thrombocytopenia, mild elevated transaminase enzyme, hyperbilirubinemia, anti-Ro/SSA was positive. Intravenous fluid, methyprednisolone, intravenous immunoglobulin (IVIG), blood, and thrombocyte concentrate transfution were given. Two cases of neonatal lupus erythematous had been presented. Diagnosis based on clinical presentation and maternal auto antibody on neonate. Organ involvement in NLE can occur as single or multiple manifestations.

***Keywords*—**Neonatus lupus erythematous, maternal autoantibody, clinical characteristic.

I. Introduction

NEONATAL lupus erythematous is an uncommon acquired autoimmune disease on fetus with clinical characteristic and maternal autoantibody (anti SSA/Ro with/or anti SSB/La) that cross placental passively [1], [2].

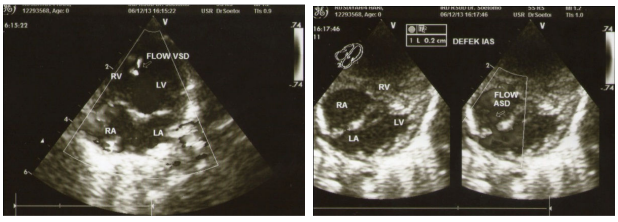
The true incidence of NLE manifestation is not known, most data are collected from case reports or retrospective studies [3]. That is a reason why NLE is not a common disease, but a study stated that it occurs in 1 of 20,000 live births [1], in Dr. Soetomo hospital there were 3 cases from 2012-2013 [4].

Neonatal lupus erythematous can have single or multiple organ manifestation. Most common organ manifestations were cutaneous, cardiac, hematologic, hepatologic. In the recent literature showed that cutaneous manifestation in infant found about 70.6%, cardiac manifestation 64.7%, hepatobiliary manifestation 52.9%, and hematologic 35.3% [5].

Lubis A., Widayanti R., Hikmah Z., Endaryanto A., Harsono A., Harianto A., Etika R., Handayani D. K., and Sampurna M. are with the University of Airlangga, Faculty of Medicine, Departement of Child health, Surabaya, East Java, Indonesia (phone: +6231-5501681; fax: +6231-5501748; e-mail: azwinlubisdr@ gmail.com).

II. Case Report

Both babies were premature, SGA (Ballard score: 35-36 weeks and 33-34 weeks, Lubscencho score: P10 and P10-25) and born through caesarean secion from SLE mother. In the first case, we found a baby girl with birth weight of 1800 g and length of 40 cm. She suffered from dyspnea and grunting. Chest X ray showed RDS 1st grade and echocardiography showed small ASD and VSD. She also suffered from anemia (10.1 g/dL), thrombocytopenia (27,000/µL), elevated C-reactive protein (140.6 mg/L), hypoalbuminemia (2.2 g/dL), increasing coagulation factors (APTT 44.5s (26.6s) and PPT 11.5s (11.8s)), hyperbilirubinemia (total bilirubin 17.25 mg/dL and direct bilirubinemia 0.56 g/dL) and positive blood culture of *Klebsiella pneumonia*. Anti-Ro/SSA and Anti-nRNP/sm were positive. Intravenous fluid, phototherapy, follow up echocardiography for cardiac lesion, antibiotic, transfusion of blood, thrombocyte concentrate, fresh frozen plasma were given.

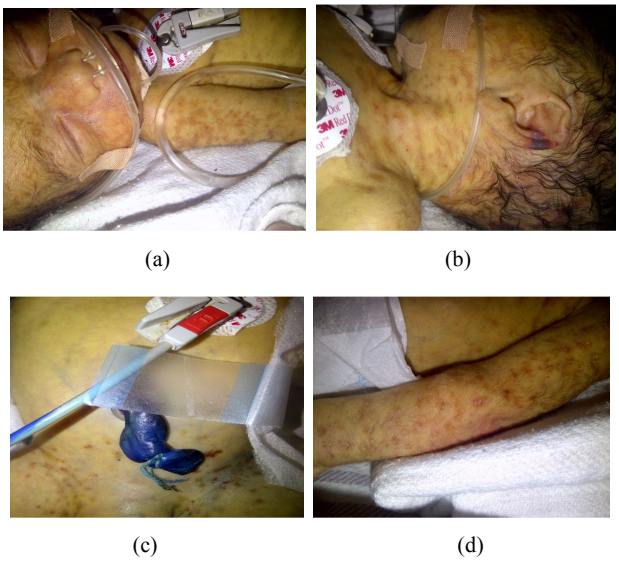


(a) (b)

Fig. 1 Echocardiography of the first baby showed: (a) VSD and (b) small ASD

In the second case, we found a baby boy with birth weight of 1600 g and length of 39 cm. The mother's age was 36 years old. There were necrotic tissues in the left ear and skin rashes, erythematous macula, athropic scarring, hyperpigmentation to all of his body with variant size and facial haemorrhage. He also suffered from persistent thrombocytopenia (24,000/16,000/21,000/19,000 µL), mild elevated transaminase enzyme (ALT 97 U/L and AST 21 U/L), hyperbilirubinemia (total bilirubin 11.62 mg/dL and direct bilirubinemia 2.68 mg/dL); anti-Ro/SSA was strongly positive. Intravenous fluid, antibiotic intravenous injection, methyprednisolone intravenous injection, IVIG, blood, and thrombocyte concentrate transfution were given. Both babies

was improved after having medical therapies and discharged from hospital with good condition.



(a) (b)

(c) (d)

Fig. 2 Erythematous macula (erythematous lesions), hyperpigmentation which developed to round, oval and annular patches on the whole body, with distributed (a) forehead, (b) neck, (c) thoracoabdominal region, and (d) extremities with varying sizes.

III. Discussion

To establish diagnosis of NLE we must find clinical characteristic and maternal auto antibody like Anti SSA/Ro with or Anti SSB/La [6]. There are clinical characteristic of NLE from a few different study shown in Table I [7].

The maternal autoantibodies that passively cross placental from mother to fetus may cause damage to the developing tissues and increase the risk of bearing infants with NLE [6].

Approximately 98% of affected infants have maternal autoantibodies that cross the placenta passively. But only 1-2% of mothers with these autoantibodies have baby with NLE, regardless of whether the mother are symptomatic or not. Systemic lupus erythematosus pregnancy is considered high risk for the fetus or baby because of the SLE disease or medical treatment that given to the mother. There is an increase risk for spontaneous miscarriage, pre eclampsia, intrauterine growth restriction (IUGR), fetal death and pre term delivery [6], [8], [9]. Medical treatment for SLE mother, like steroid during pregnancy that usually as prophylaxis for mother with autoantibodies with anti SSA/Ro, high risk mother with previous child with congenital heart block (CHB), treatment of fetus with complete or incomplete CHB can cause premature rupture of the membrane, IUGR, and precipitation of maternal complication such as gestational diabetes, hypertension, osteoporosis, and avascular bone necrosis [6], [10]. Intrauterine growth restriction by lupus pregnancy can cause LBW defined as < 2500 g at delivery and SGA newborns defined as birth weight less than 10th percentile for gestational age. These outcomes are reported in 10-30% of infants of SLE mother and are considered the most frequent complication of pregnancy in SLE. Risk factors identified for fetal growth restriction and LBW are lupus activity, maternal age over 35 years, low complement and hypertension (Table II) [6], [11]. In our case report, two cases of NLE with different manifestation, first case manifested in cardiac and second case was with cutaneous manifestation with mother's 36 years old. Both babies were premature, LBW, SGA, with positive maternal autoantibodies, and also had hematologic and hepatologic manifestation.

TABLE I
Clinical Characteristics of NLE in Different Study [7]

Study, author (country, year)	No. Of cases (F/M ratio)	Congenital heart block (%)	Cutaneous lesion (%)	Hematologic manifestation (%)	Hepatic manifestation (%)	Autoantibody	Maternal status	Mortality rate, %
Liu et al (Taiwan, 2001)	10 (4:1)	5/10 (50)	5/10 (50)	7/10 (70)	6/10 (60)	ANA: 80% (+) Ro: 80% (+) La: 50% (+)	SLE: 8/10 SS: 1/10	20
Buyon et al [7] (US, 1998)	166 (1:1)	128/166 (77)	35/166 (34)	N/A	N/A	N/A	Ro/La (+): 105/142 (73%)	13
Ng et al [15] (Singapore, 1998)	10 (2.3:1)	0/10	10/10 (100)	N/A	2/10 (25)	ANA: 80% (+) Ro: 60% (+) La: 50% (+)	SLE:4/9 SS: 2/9 High ANA: 2/9	0
Kaneko et al [17](Japan, 1992)	60 (1.6:1)	5/60 (8)	43/60 (72)	6/60 (10)	10/60 (17)	ANA: 83% (+) Ro: 76% (+) LA: 61% (+)	ANA: 97% (+) Ro: 78% (+) La: 63% (+)	N/A

Abbreviations: N/A = not available; ANA = antinuclear antibody; SLE = systemic lupus erythematous; SS = sjogren syndrome

TABLE II
NEONATAL OUTCOME IN INFANTS FROM SLE MOTHER AND RISK FACTORS [11]

Neonatal outcome	Frequency risk	Risk factors
Pregnancy loss	10-50%	Active lupus, renal diseases, aPL, prior history of fetal losses
Preterm birth	21-52%	Active lupus, renal diseases, aPL, hypertension, high dose prednisone, anti rheumatic drugs at the onset of pregnancy
IUGR/SGA*	10-30%	Active lupus, maternal age over 35, low complement, hypertension

*Intrauterine growth restriction/small for gestational age

Cardiac manifestation in NLE can cause by disorder in electrical, mechanical, or structural of the fetus/neonate heart (Table III).

TABLE III
SPECTRUM OF CARDIAC MANIFESTATION ASSOCIATED WITH NLE [12]

Electrophysiogical	Myocard/ Functional	Structural
1_Atrioventricular block 2_Atrioventricular block Complete atrioventricular Atrial and vebtricular ectopic beats Atrial flutter Junctional ectopic tachycardia Ventricular tachycardia Sinus node dysfunction Long QTc interval	Myocarditis Cardiomyopathy Endocardiofibroelastosis (diffuse or patchy) Pericarditis/pericardial effusion	AV valve dysplasia, stenosis, regurgitation Semilunar valve dysplasia, stenosis, regurgitation Patent ductus arteriosus Atrial septal defect Ventricular septal defect

Structural cardiac disease has been reported occasionally in association with NLE. Probably it cause by inflammation from maternal antibody specially anti SSA/Ro that cause fibrosis on cardiac tissues and influence the organogenesis, so it can cause some anatomical structural abnormalities in cardiac anatomy. The most common among these are ASD, PDA and VSD. Ventricular septal defect has been reported in association with NLE [6], [12]. From histological the presence of myocardial inflammation has been substantiated by the demonstration of immunoglobulin G, complement, and fibrin deposition on the myocardium, because the fetus is unable to produce this immunoglobulin, the demonstration of IgG deposits on myocardium implicates maternal immunoglobulin as the likely source of the pathology. In vitro experiments have demonstrated that apoptosis of cardiomyocyte leads to expression of Ro and La on the cell surface and that these apoptotic cells can activate production of proinflammatory cytokines, which may lead to scarring. Some data suggest children with NLE are more likely to have TNF α polymorphism which associated with high TNF α production, and TGF β gene polymorphism which is associated with increased TGF β production and therefore may lead to fibrosis [6], [13].

In our case, from echocardiography examination, the first baby had a small ASD and VSD, and planned for echocardiography for next 3 months.

Rash is present in 15-25% cases of NLE. Histopatology examination from cutaneous NLE showed IgG, IgM and complement are deposited at the dermoepidermal junction [6]. Cutaneous manifestation in NLE was characterized as erythematous patches (91.7%), sub acute cutaneous erythema (50%), ptechiae (41.7%), persistent cutis marmorata (16.7%) and discoid lesions (8.3%) [14]. This manifestation was associated with a particular maternal autoantibody, anti Ro (anti-SSA). Subacute cutaneous lupus erythematous (SCLE) appears as annular, erythematous and scaly lesions, although dyspigmentation may occur. The cutaneous lesions of neonatal lupus occur most often on the face and scalp, but may occur in any area of the skin. The face, scalp and periocular distributions (eye mask/racoon like appearance) are characteristic of NLE. Scarring, follicular plugging and dermal atrophy are unlikely NLE. Dermal athropy has been observed but it is very rare. Skin lesions may be absent at birth and develop after several weeks, with resolution occuring at 6-9 months as the mother's autoantibody disappear from the baby's circulation. There is no specific treatment for the baby, but the baby must be avoided from the sun exposure because it can cause exacerbation of cutaneous lesions [6], [14], [15].

In our case, second baby had erythematous macula, athropic scarring, hyperpigmentation, which developed as round, oval, and annular patches on the whole body, distributed on the forehead, neck, and thoracoabdominal region, genetalia, upper and lower extremity with various size. There was improvement on skin lesions and disappeared after a few months.

Thrombocytopenia is the most common hematologic manifestation in NLE; it may occur in about 10-20% cases and in some cases can be severe. Netropenia, anemia, and panscytopenia also have been reported [16]. Antibodies SSA/Ro and SSB/La are associated with cytopenias in NLE. Netropenia, anemia, and pancytopenia can occur separately or together and getting worse a few days after birth, but these manifestations can resolve after maternal autoantibody dissappear from the baby. Immunosupresion of the bone marrow by maternal autoantibodies is the probability cause of these manifestation, but somehow peripheral destruction of blood components can also occur because autoantibodies and anti Ro antibodies have been demonstrated to bind to neuthrophils [6], [17], [18]. Corticosteroid intravenous is needed for patient with persistent or severe hematological and also renal diseases its effects by reducing the production of anti-platelet antibodies and by decreasing clearance of opsonized platelets, steroids also increase vascular stability in immune trombositopenia purpura (ITP) [6], [19]. Thrombocytopenia in autoimmune disease has been shown to resolve under treatment of IVIG. Mechanism of action IVIG are neutralization of autontibodies by antiidiotypic antibodies and proinflamatory cytokines by anticytokine antibodies (IL1, TNFα, IFNα, IFNɣ, IL6); enhancement of autoantibody clearance through FcRn blockade; inhibition of Fas mediated cell death by Fas blocking antibodies, complement uptake on target tissues and attenuation of complement mediated tissue

damage; Fc receptor blockade of the retikuloendosytem; modulation of dendritic cell maturation and function, macrophage activation and B cell activity through upregulation of the inhibitory FcɣRIIB receptor [20].

In our case, both babies had thrombocytopenia, but only second baby received steroid injection and IVIG because there was persistent thrombocytopenia and facial bleeding.

Hepatobiliary disease is a relatively common finding in NLE, can occur in addition to cardiac or cutaneous manifestation in NLE [6], [16]. In a review from the research Registry for Neonatal Lupus, USA, about 10% of children in the registry had hepatobiliary disease, almost all of them with other signs of neonatal lupus [16]. Histological features of neonatal iron storage diseases occurring intrauterine or shortly after birth and resulting in fatality; or cholestasis with conjugated hyperbilirubunemia and minimal transaminase elevations occuring in a few weeks after birth and eventually resolving; and mild or moderate transaminase elevations occurring a few weeks or months after birth and resolving can found in liver manifestation in NLE [21]. Liver involvement is caused by maternal autoantibodies [6], [7], [18], [21]. Sunlight exposure is very limited in a newborn, so photosensitivity is more commonly demonstrated after phototherapy for neonatal hyperbilirubinemia. Study in NLE at Siriraj hospital Bangkok, Thailand, there is one neonate developed skin lesions after phototherapy [14], [22].

In our case, there were increasing level of aminotransferase and hyperbilirubinemia in both babies and only the first baby underwent phototherapy. The condition of both babies improved following comprehensive management.

IV. Summary

Two case reports of NLE has been presented. The diagnosis established based on clinical presentation and maternal auto antibody on neonate. Organ involvement can occur as single or multiple manifestations.

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