RESEARCH ARTICLE

A FATAL OUTCOME OF A NEONATAL DILATED CARDIOMYOPATHY: EVOLUTIVE NEONATAL LUPUS OR EARLIER CHILDHOOD-ONSET SYSTEMIC LUPUS? A CASE REPORT

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Abstract
Neonatal lupus is a rare congenital syndrome resulting from placental passage of maternal antibodies against SSA/Ro and/or SSB/La to the fetus. It is a generally benign condition, the cardiac involvement determining the prognosis. NNL is rarely manifested by isolated cardiomyopathy. The subsequent evolution towards systemic lupus is rare and unpredictable. We report the case of a daughter from a non-consanguineous marriage with healthy parents who presented a dilated cardiomyopathy in the first months of her life complicated by several outbreaks of heart failure. The spontaneous evolution was marked by the occurrence of skin lesions of the face and arms at the age of 10 years, then by the installation of episodes of hydrous retention at the age of 12 years complicated by an acute renal insufficiency with a rapid fatal outcome at the age of 15 years. ANA antibodies rate was at the threshold of positivity, antiDNA and ANCA were not detectable. C3 rate was low. Although a genetic cause can never be ruled out, the diagnosis was a systemic erythematous lupus SLE (an evolution of an eventual NNL or a childhood-onset systemic lupus). We propose a decision tree for the management of neonatal cardiomyopathy NCMP as a synthesis of the literature. The search for anti SSA/SSB must be part of the check-up usually requested at the time of pregnancy. In addition, we must strengthen the knowledge of the medical profession, especially in the proximity health centers, on rare diseases for a better management of patients.

Introduction:

Case Report
The patient was a 15 years-old Moroccan girl. She was the third eldest of 4 healthy children. The parents were healthy without any consanguinity. As a family story, was drawn a maternal uncle who died because of an unknown cardiopathy. She was born at 39 weeks of gestation. At birth, she was 3.9kg weight with normal oxygen saturation. At 3 months, she was hospitalized because of the first episode of heart failure following bronchitis. No specific investigations had been performed then. She remained asymptomatic and had a normal neuro-development. At 30 months, she was hospitalized due to the first episode of heart failure following bronchitis. No specific investigations had been performed then. She remained asymptomatic and had a normal neuro-development. At 30 months, she was brought to pediatric department of our hospital because of coughing and fever. A harsh holosystolic murmur (Levine 2nd degree) was found. ECG showed left ventricular hypertrophy with normal atrio-ventricular conduction (figure 3). Chest x-rays revealed pulmonary congestion and cardiac enlargement (CTR 60%).
Echocardiography showed dilated cardiomyopathy with severe depressed LV contraction (EF 30%) and functional mitral regurgitation grade II. Although she stuck with Digoxin, she consulted many times for coughing and fever. Soon after she began primary school, she was lost to follow up. At the age of 10, she presented a skin rash on the face and forearms, triggered by the cold, but did not consult a doctor. At 12 years of age, she was referred by her pediatrician to our cardiology department for dyspnea class III of NYHA. 3rd heart sounds were heard. Echocardiography showed biventricular dilated cardiomyopathy (EF =38%), severe mitral regurgitation MR, right ventricle RV systolic dysfunction with tricuspid regurgitationTR grade III and SPAP=56mmHg (figure 4). All measurements are summarized in table 1. Coronary angiography revealed no abnormality of large vessels (Figure 1). Symptoms improved after treatment with diuretics and conversion enzyme inhibitors CEI, but only for few months. She manifested episodes of hydric retention with normal seric creatinin. She was irregularly followed. At 15 years, she was urgently hospitalized because of an acute renal failure with arthritis; seric creatinin was 47mg/l and urea =2,18g/l, alcalin reserve =13 and Kaliemny= 6 mEq/l. Measurement and differentiation of kidneys were normal at echography. She underwent three short period hemodialysis (1H30). She also received three 500 mg intravenous bolus of Solu-Medrol as an auto immune disease was suspected (systemic erythematous lupus). Anti native DNA and ANCA antibodies weren’t detectable. Anti nuclear antibodies ANA’s level was at the threshold of positivity; laboratory data are summarized in table 2. Echocardiography showed no aggravation of ventricular functions, calculated EF was 43%. Despite reducing of seric creatinin to 38mg/l, Diuresis didn’t recover. So she had the fourth hemodialysis, unfortunately, it was interrupted because of an acute chest pain which was immediately followed by a cardiac arrest. She died despite cardiopulmonary resuscitation maneuvers. She didn’t have a Kidney biopsy.

Limitations:
We were not able to complete immunological assessment (measure of Ro/SSA, Lo/SSB and anti cardiolipin antibodies, anti RNP) neither in the patient nor in the healthy mother.

Discussion:-
We described a case of neonatal dilated cardiomyopathy DCMP followed by skin and renal damage in childhood. DCMP are defined as a myocardial disorder characterized by dilated left ventricular chamber and systolic dysfunction, it can also extend to the right ventricle. These pathologies pose a threefold problem: etiological as the causes are diverse and can only be identified in 34% of cases (11,12); Therapeutic and prognostic because they are the main cause of heart transplantation in children despite the different therapeutic means available (5,6,11,12). Even for their classification, it’s complex; moreover, there is no consensus; while the AHA subdivides cardiomyopathies into primary and secondary groups, the ESC has proposed a distinction between genetic and non-genetic. If we refer to the latest AHA classification (5) which divides cardiomyopathies into two large groups: primary (genetic, mixed, acquired) and secondary, we would have classified our patient before the age of 10 years as a possible primary CMP but after as a secondary CMP as long as the cardiac involvement was associated with generalized systemic disorders.

We do not have data on the incidence of DCMP in Morocco or Africa. Incidence of DCMP in the USA has been estimated at 0.57 cases per 100000 per year (11, 12). It most occurs in the first year of life with about 20% presenting in the neonatal period (12). Clinical presentation often includes signs of heart failure, symptoms severity correlates with the degree of ventricular dysfunction. A good history should be taken to look for consanguinitis and also to identify a history of DCMP, thromboembolic events or sudden death before the age of 30-35 years; it should also inquire wether family members show signs of inherited metabolic disease. A through physical examination should be carried out and must be supplemented by an ophthalmological examination. A well-behaved history combined with a complete physical examination allows for a better diagnostic orientation.

The most common cause of neonatal DCMP is myocarditis, and neuro muscular disease (5, 6, 11, 12). The diagnostic process must be sequential. Transthoracic echocardiography is the key test; it allows the diagnosis of DCMP to be made and congenital heart disease to be ruled out. Segmental kinetic disorders associated with EKG abnormalities point to myocarditis.

Lab tests constitute an unavoidable step in the etiological investigation (figure b). Cardiovascular magnetic resonance (MRI) offers the double advantage of allowing a high spatial resolution characterization of the myocardium on the one hand and, on the other hand, to explore the coronary arteries in a non-invasive and non-irradiating way (5).
The existence of a first-degree relative with documented DCM, thromboembolism or sudden cardiac death under the age of 30-35 years is suggestive of a familial form of DCM. The reported prevalence of familial DCMP in children (1/20) is probably underestimated. It turned out that 20 to 48% of the DCMP classified as idiopathic are of genetic origin, with AD inheritance being the predominant pattern of transmission, while X-linked AR, and mitochondrial inheritance are less common (5). AD-transmitting DCMP are either pure isolated or associated with conductive tissue abnormalities; the latter may lead to juvenile-onset muscular dystrophies (5).

In X-linked forms as well as forms linked to mutations in the mitochondrial t-RNA, DCMP is associated with neurosensory, musculoskeletal and metabolic damage (5, 12).

Thus, more than 40 genes have been identified as harboring mutations that cause DCMP (12). The genetic investigation must lead to the genetic counseling.

Endomyocardial biopsy can be used, although it is technically more difficult to perform in children than in adults; it could be crucial to the diagnosis and determination of the etiology (12).

Let’s get back to our case. A neonatal dilated cardiomyopathy unfortunately not exploited during 10 years of evolution because of the lack of qualified centers in the place of residence of the girl’s family; DCMP being classified as post-infectious. Following these events, skin eruption appeared triggered by spontaneous cold remission in the cheeks and forearms, which were not declared by the patient’s family. Finally, arthritis and the renal damage started with episodes of hydro-sodic retention and evolved abruptly, despite regular monitoring of serum creatinine and proteinuria, towards acute renal failure with a fatal outcome.

We were not able to complete the etiological assessment and no biopsy was performed. However, it seems that it is probably a systemic disease associating lesions of vasculitis rather than small vessels. According to the EULAR/ACR CLASSIFICATION CRITERIA FOR SLE(30), she was classified as SLE with a score of 21 (malar rash: 6 + arthritis: 6 + proteinuria: 6 + deficient complement C 3: 3). We have issued 2 diagnosis hypotheses:

The first hypothesis was a priori the possibility of a neonatal lupus having evolved towards a systemic erythematous lupus.

Neonatal lupus NNL is a rare congenital syndrome caused by placental passage of maternal Ig G type antibodies, often anti-Ro/SSA; anti-La/SSB or both to the developing fetus. Mothers may have SLE, Sjogren syndrome or other autoimmune symptoms, or may be entirely asymptomatic (15, 26). The exact incidence of NNL is unknown with a slight female dominance (15), the likelihood of having a child with NNL increases in mothers who have already had previous affected children (15). It is often a benign syndrome regressing spontaneously after 2 to 12 months (21); some infants develop only skin lesions (2, 3, 4); others present only heart symptoms (7, 24), and less often, some infants develop both (1, 22).

Conduction disorders represent the most frequent cardiac manifestation and can be detectable in utero between 17 and 24 weeks of gestation, all degrees can be observed, complete heart block CHB being the most feared because irreversible (14,29). CHB can be associated with fetal myocarditis and lead to hydrops and death in utero (26). Note that even blocks of 1st and 2nd degree can evolve to a 3rd degree even after the total disappearance of maternal antibodies from the circulation of the newborn (7).

Cardiomyopathy may occur in the absence of CHB as it could be seen in the course of CHB even after early successful pace maker implantation. Some studies found higher sera levels of anti Ro in cardiac NNL compared with Cutaneous NNL (8).

Table 3 shows some further other cardiac manifestations of NNL that has been reported in literature.

Infants with neonatal lupus may also have hematologic and hepatobiliary anomalies: thrombocytopenia, anemia, neutropenia, splenomegaly and hepatomegaly. A cholestatic hepatitis may also occur, fortunately, asymptomatic transient elevation of the liver enzymes is the most common hepatic disorder. Again, most of these non-cardiac abnormalities resolve themselves within the first six months of an affected infant’s life when the maternal antibodies are cleared from the infant’s circulation (15, 21, 26).
Although extremely rare, some infants with neonatal lupus may present macrocephaly with or without hydrocephaly (20).

Our patient had severe mitral regurgitation by a dual mecanism: ring dilatation with thickening and restriction of valve movements. Heart valve disease have been frequently reported in patients having Antiphospholipid syndrome APS with or without SLE. However, we don't know which of the 2 conditions predisposes the most to this type of lesions (8, 9).

Note that valve abnormalities reported in SLE and APS are similar, varying from thickening and/or vegetation to severe valve distorsion and dysfunction (8, 9).

Can neonatal lupus turn into systemic lupus?
According to literature, some children who had NNL might develop later auto immune diseases, but it is not known whether the risk is lower or higher compared to the general population (15).
What immunological workup is required to support the diagnosis?
• Antinuclear antibodies ANA: a positive ANA test indicates that it may be an autoimmune disorder but not necessarily lupus. A negative rate does not eliminate the diagnosis either.
• Antibodies to double-stranded DNA (anti-dsDNA) : are present in 50% of lupus cases, their absence does not rule out the diagnosis.
• Antibodies to histone : sometimes detectable in SLE, but are more often found in drug-induced lupus; in this case, anti histone usually Disappear as soon as the drug is discontinued.
• Antibodies to phospholipids (aPLs) : The most commonly measured aPLs are lupus anticoagulant, anticardiolipin antibody, and anti-beta2 glycoprotein I. Nearly 30 percent of people with lupus will test positive for antiphospholipid antibodies. Note that Phospholipids found in lupus are also found in syphilis, and the blood test cannot always tell the difference between the two diseases.
• Antibodies to RNP : Anti-RNPs are detectable in many autoimmune conditions and will be at very high levels in people, whose symptoms combine features of several diseases, including lupus.
• Antibodies to Ro/SS-A and La/SS-B: These antibodies are often found in people with Sjögren’s syndrome. Anti-Ro antibodies will be particularly found in people with cutaneous lupus
• Antibodies to Sm : Found in 30-40 percent of people with lupus, their presence signs the diagnosis.

Other blood tests,which are indirect indicators of inflammation, autoimmunity or hypercoagulability:

* Complement: C3, C4, CH50 which are consumed in auto immune diseases especially when kidney damage is associated.
* C-reactive protein (CRP)
* Erythrocyte sedimentation rate (ESR or "sed" rate)
* Prothrombin time (PT)
* Partial thromboplastin time (PTT)
* Modified Russell viper venom time (RVVT), platelet neutralization procedure (PNP), and kaolin clotting time (KCT).

How should we treat NNL?
Children with NNL must be cared for and followed up in qualified care centers with various specialties. The treatment differs according to the nature and severity of the manifestations.
• DCMP: The main goals of treatment include symptom control and prevention of disease progression and complications including congestive HF, arrhythmias, sudden death and thromboembolic events. Guidelines for drug therapy in neonates are largely based on consensus and extrapolation from data on children and adults (12, 28). Despite the number of available molecules and devices, the prognosis remains cautious: one third of children die (28). Cardiac transplantation is the last resort in the event of treatment failure, severe failure to thrive, intractable arrhythmias and severe limitation to activity (28).
• Pace maker implantation is usually indicated in CHB especially in slow rates and persistant symptoms like poor exercise tolerance, cardiomegaly, long QRS or QT durations, ectopy, syncope or structural or functional heart disease (14). First and second heart blocs require regular EKG monitoring.
• Cutaneous, hematologic and hepatobiliary manifestations usually resolve with no need to specific medication (26). Can we prevent NNL?
To date no treatment has succeeded in reversing a CHB or a DCMP in NNL. However, the maternal use of fluorinated steroids during pregnancy has shown some efficacy in treating second degree heart block and cardiac disease beyond the atrioventricular node, however, their safety isn’t assured (13, 16). Intravenous immunoglobulin (IVIG) has been studied for prevention of disease, and has been used in treatment of associated cardiomyopathy (13, 16). The use of Hydroxychloroquine (HXQ) may protect against recurrence of disease in a subsequent pregnancy (18).

We recommend a systematic screening for anti SSA and anti SSB during pregnancy to predict the risk of giving birth to a child with NNI.

Second hypothesis: was it an early childhood-onset systemic lupus (cSLE)?

Childhood-onset SLE (cSLE) is a rare disease with an incidence of 0.3-0.9 per 100,000 children-years and a prevalence of 3.3-8.8 per 100,000 children (40). Most forms of cSLE meet 4 or more of the American college of Rheumatology classification criteria (30). CSLE can affect any organ system. Glomerulonephritis and central nervous system involvement seem to occur more often in cSLE than in adult- SLE (31, 40). Table 4 summarizes the frequencies of the common manifestations of cSLE and table 7 shows a comparision between adult-SLE and c- SLE. Most studies report a median age of onset of cSLE between 11-12 years; the disease is quite rare under the age of 5 years. As in adult onset SLE, approximately 80% of patients with cSLE are female (40). Some studies reported a higher incidence of myocardial and pericardial manifestations in cSLE compared to a SLE (36). Bundhun et al have published a meta-analysis that raised significant differences between childhood-onset and adult-onset SLE. While cSLE was associated with significantly higher incidence of neurological involvement, renal involvement, oral ulcers, malar rash, vasculitis, fever, ocular, and hematological manifestations, pulmonary involvement, Raynaud phenomenon, and photosensitivity were significantly higher with adult-onset SLE. However, no significant difference was observed in gastrointestinal involvement, cardiovascular involvement, discoid rash, psychosis, alopecia, serositis, and arthritis (31).

As the diagnosis isn’t usually easy especially in the absence of skin lesions, the current laboratory tests such as urinalysis, quantitative proteinuria, complete blood count, ESR, C-reactive protein, antidouble-stranded DNA antibodies, and the complement components C3 and C4 are clearly insufficient for identifying or monitoring the disease activity. Thus, significant progress has been made in the field of biological diagnosis of cSLE (34, 37).

Especially if combined, some new biomarkers summarized in table 5 appear superior to the current tools available to rheumatologists to monitor cSLE and its course. Moreover, the IFN-I signature was present in 57% of patients with cSLE and was associated with increased expression of TLR7 and cytosolic nucleic acid binding receptors in Wahadat et al’s studies (35).

Does the fact of having made 2 diagnosis hypotheses have therapeutic implications?

The care of a child or adolescent with SLE requires a multidisciplinary approach. Pharmacologic treatment is often aggressive, but tailored to the severity and extent of disease manifestations. Only aspirin, prednisone and belimumab are actually approved by the Federal Drug Agency (FDA) for use in patients with cSLE (40). The use of multiple immunosuppressants on an “off-label” basis is the reality. Many therapeutic regimens which can be associated may be proposed based on corticosteroids, Non steroid anti inflammatory drugs, immusuppressive agents or anti alkylant. For patients with glomerulonephritis, the choice of immunosuppressant depends on the histologic classification, in addition to other patient factors including race/ethnicity (for example hispanic and african-american patients may respond better to mycophenolate mofetil compared to cyclophosphamide) (40 ). Concomitant control of Hypertension, peripheral edema and proteinuria with fluid restriction, low salt diet, and antihypertensives are important for optimal outcome. Angiotensin converting enzyme (ACE) inhibitors are particularly effective for reducing proteinuria. Although prescribed by some physicians, there are no recommendations for the use of lipid lowering statins in cSLE. Newer therapies are showing promise for the next generation of SLE patients. Rituximab, Belimumab that has not yet been studied for use in cSLE (40). Table 6 shows different treatments available with main indications.
Tables and Figures

Table 1: Cardiac measurements assessed by echography.

| Parameter        | Value |
|------------------|-------|
| LVEDD (mm)       | 57    |
| LVESD (mm)       | 43    |
| DIVS (mm)        | 6     |
| DPW (mm)         | 5     |
| LVEF (%)         | 38    |
| RVDD (mm)        | 35    |
| LAA (cm²)        | 27    |
| DIVS (mm)        | 26.8  |
| ROS MR (cm²)     | 50    |
| SPAP (mmHg)      | 56    |

(LVEDD: left ventricle end diastolic diameter, LVESD: left ventricle end systolic diameter, DPW: diastolic posterior wall thickness, DIVS: diastolic interventricular septum, LVEF: left ventricle ejection fraction, DRVD: diastolic right ventricle diameter, LAA: left atrium area, RAA: right atrium area, ROS/MR: regurgitating orifice surface/MR: mitral regurgitation, SPAP: systolic pulmonary artery pressure)

Table 2: A summary of laboratory tests results in the reported case.

| Biologic parameter | Value     | Normal value       |
|--------------------|-----------|-------------------|
|                    | (2017)    | (2018) After dialysis |
| Hb (g/dl)         | 15.1      | 15.1 12-14.5       |
| RC (106/mm3)      | 5.1       | 6.1 4-5.4          |
| WC (/mm3)         | 9570      | 9560 4000-10000    |
| Platelets (/mm3)  | 229000    | 223000 150000-40000 |
| Creatinin (mg/l)  | 8.1       | 47 38 6-14         |
| Potassium (mEq/l) | 4.3       | 6.1 6 3.8-5        |
| Urea (g/l)        | 2.18      | 1.97 0.12-0.38     |
| Uricemia (mg/l)   | 131       | 110 26-70          |
| Glycemia (g/l)    | 0.7       | 0.5 0.70-1.10      |
| Alcalin reserve (mmol/l) | 11        | 13 22-29          |
| AAN                | 80        |                   |
| Ac antiDNA db     | <5U OMS   |                   |
| ANCA               | <20       |                   |
| C3 (g/l)          | 0.63      | 0.90-1.80         |
| CH50 (U/ml)       | 42        | >32               |

Table 3: Cardiac manifestations of neonatal lupus (10, 17, 22, 24).

- Atrioventricular block
- QT- interval prolongation
- Sinus bradycardia
- Cardiomyopathy / heart failure
Myocarditis
Ventricular septal defect
Atrial septal defect
Patent foramen ovale
Patent ductus arteriosus
Valvular abnormalities: Pulmonary stenosis; pulmonary valve dysplasia; fusion of the chordae tendineae of tricuspid valve.

Table 4: Common manifestations of childhood onset systemic lupus (40).

| Constitutional Symptoms |
|-------------------------|
| Fever, fatigue, anorexia, weight loss, alopecia and arthralgias |
| Lymphadenopathy, hepatosplenomegaly |

| Mucocutaneous |
|---------------|
| Malar, or butterfly rash |
| Dacryostasis |
| Oral and or nasal hyperemia to painless oral ulcers of the hard palate, shallow nasal septal ulcers, nasal septal perforation |

| Musculoskeletal |
|----------------|
| Arthralgias and arthritis, avascular necrosis, bone fragility fractures |

| Renal disease |
|---------------|
| Minimal proteinuria; microscopic hematuria, nephrotic-range proteinuria, urinary casts, severe hypertension, peripheral edema, renal insufficiency or acute renal failure |

The classification of glomerulonephritis in SLE: Class I (minimal mesangial), Class II (mesangial proliferative), Class III (focal proliferative), Class IV (diffuse proliferative), Class V (membranous lupus nephritis), Class VI (advanced sclerosing lupus nephritis).

| Neuropsychiatric Involvement |
|-----------------------------|
| Headache, mood disorder, cognitive dysfunction, psychosis, seizures |

| Hematologic Features |
|----------------------|
| Cytopenia |
| Antiphospholipid antibodies |

| Gastrointestinal Involvement |
|-----------------------------|
| Abdominal pain and discomfort, Abdominal vessel vasculitis, sterile Peritonitis, pancreatitis, Elevated liver enzyme tests |

| Cardiopulmonary Features |
|--------------------------|
| Serositis, myocarditis, non-infective (Libman-Sacks) endocarditis, interstitial pneumonitis, pulmonary hemorrhage and pulmonary hypertension |

| Vascular Manifestations |
|-------------------------|
| Cutaneous vasculitis, retinal vasculitis, thrombotic thrombocytopenic purpura, |
Table 5: New biomarkers for diagnosis of childhood onset systemic lupus (34).

| Biomarker                                                                 | Interest                          |
|--------------------------------------------------------------------------|-----------------------------------|
| Monocyte chemoattractant protein-1 (MCP-1)                                | Lupus nephritis (LN)              |
| Neutrophil gelatinase-associated lipocalin (NGAL)                        | LN                                |
| Transthyretin, orosomucoid (or α-1 acid glycoprotein [AGP])              | LN                                |
| Ceruloplasmin (CP), and lipocalin-type prostaglandin B synthase (L-PDGS or B-trace protein) | LN                                |
| Colony-stimulating factor 1 (CSF 1)                                      | LN                                |
| MicroRNAs (miRNAs)                                                       | LN+adult SLE                      |
| Type 1 interferon (IFN)                                                  | SLE                               |
| Cellular adhesion molecules, vascular cell adhesion molecule-1 (VCAM-1)   | SLE                               |
| and E-selectin complement components C3 and C4                          | LN/REMISSION                      |
| Antiribosomal P antibodies                                               | Lupus psychosis                   |
| Antiganglioside antibodies                                               | Cognitive dysfunction             |
| Adipokine cytokines                                                      | Cardiovascular lupus              |

Table 6: Available treatments for childhood onset systemic lupus with their indications (39, 40).

| Therapeutic agent                          | Type (mechanism) | Main indication                                          | Main side effects                                                                 |
|--------------------------------------------|------------------|----------------------------------------------------------|-----------------------------------------------------------------------------------|
| Hydroxychloroquine                         | Anti malarial    | Mild symptom particularly arthritis and rash            | Cardiac, digestive, ocular                                                        |
| Chloroquine                                |                  |                                                          |                                                                                   |
| Non steroid anti inflammatory drugs NSAID  |                  | Musculoskeletal manifestations                           | Digestive                                                                         |
| Oral and iv corticosteroids                |                  | Rapid disease control                                    | Digestive, non ischemic bone necrosis, hypercorticism, induced diabetes, induced hypertension |
| Methotrexate                                | Immunosuppressants IS | Isolated persistent arthritis |                                                                                   |
| Azathioprine                               | IS               | Arthritis, vasculitic rash, persistent cytopenia, serositis |                                                                                   |
| Mycophenolate mofetil                      | IS               | Lupus nephritis Maintenance of other significant manifestations |                                                                                   |
| Cyclophosphamide                           | Alkylants        | Life threatening symptoms                                | Toxicities: infertility, infection, cancer                                          |
Table 7: Comparison between adult onset – SLE and childhood onset – SLE (31, 36).

| Clinical manifestations | Adult onset SLE | Childhood onset SLE |
|-------------------------|-----------------|---------------------|
| Fever                   | higher          |                     |
| Vasculitis              | higher          |                     |
| Pulmonary               | higher          |                     |
| Neurological (seizures) | higher          |                     |
| Renal                   | higher          |                     |
| Cardiovascular          | similar         |                     |
| Hematological (cytopenia)| higher        |                     |
| Gastrointestinal        | similar         |                     |
| Neuropsychiatric        | similar         |                     |
| Musculoskeletal         | similar         |                     |
| Arthritis               | similar         |                     |
| Malar rash              | higher          |                     |
| Discoid rash            | similar         |                     |
| Raynaud syndrome        | higher          |                     |
| Photosensitivity        | higher          |                     |
| Oral ulcers             | similar         | higher              |
| Alopecia                | similar         |                     |
| Serositis               | similar         |                     |
| Myositis                | similar         |                     |
| Ocular                  | higher          |                     |

Figure 1: Coronary incidences in our reported case (left: RAO10, 1°/CRA 34, 5°. MIDDLE: LAD 11, 4°/CRA 42°; RIGHT: LAD 45, 2°).
Management of neonatal dilated cardiomyopathy

**Known immunologic profile mother anti Ro/La**

- Routin follow up of pregnancy
- In utero fetal monitoring: TEE, ECG (2nd-3rd trimester)
- Bradycardia
- HXQ+
  - Monitor fetus / NB
  - Alive newborn
  - Risk factors? Slow HR, syncope, ectopy, long QRS/QT, heart
  - PM
  - Close monitoring
  - Regular TEE

**Unknown immunologic profile mother anti Ro/La**

- Concomittant treatment of HF (ph+nonph)
  - Lab tests: anti Ro/La, ANA, antiDNA, APA, RNP, Sm, UB, BCC, CRP, SR, VIH, VHC; hemoc, creat, gly, HbA1C, E, Pr, GOT, GPT, B, CPK, aldolases
  - TSH, CORT8, PTH, GH, MU, L-carnitine, D3

- And/or Skin lesions
  - Ro/La+
  - NNL
  - Plasmapheresis
  - Iv IG
  - Devices

- Inflammation
- Metabolic anomaly

- MRI
  - Normal
  - Specific etiology

- Dysmorphism
- Neurologic manifestations

- Genetic assessment
Figure 2: A proposed decision tree for management of neonatal dilated cardiomyopathy

Abbreviations: TEE thrans thoracic echography; EM endomyocardic; ph : pharmacological; nonph: non pharmacological; HF heart failure; UB urinary bandelette; BCC blood cell count; RS rheumatoid serology; MU microalbuminuria; E electrolytes; B bilirubin; Pr protein; cort8 cortisol 8h, hemoc hemocultures; gly glycemia; creat creatin; GH growth hormone; PTH Parathormon; iv IG intravenous immunoglobulin; MRI magnetic resonance imaging; NB new born; CHB complete heart block; iv CS intravenous corticosteroid; HXQ hydroxychloroquine; LGHB left heart block; PM pace maker. HR heart rate.

Figure 3: Electrocardiogram of the reported case.

Figure 4: Some transthoracic echography anomalies in reported case (from left to right: mitral regurgitation in 2c apical incidence; dilated cardiomyopathy in 4C apical incidence; altered S wave in tissue Doppler of mitral valve; dilated ventricules in TM).

Conclusion:
The reported case illustrates the lack of knowledge of our practitioners on certain rare pathologies, which leads to a delay in diagnosis with fatal outcomes.

A DCMP in the context of NNL might have evolved better if we had earlier associated plasmapheresis and IVIG (1) with the pharmacological treatment of heart failure.

If it was rather a cSLE, early aggressive treatment with corticosteroids and/ or IS and HXQ may have prevented renal damage (40).

We suggest that the systematic search for anti La/Ro antibodies must be integrated into the pregnancy check-up. At the end of the article, we propose a decision tree for the management of NDCMP represented by the figure a.
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References: -
1 Rumancik B, Haggstrom AN, Ebenroth ES. Neonatal lupus with left bundle branch block and cardiomyopathy: a case report. BMC Cardiovasc Disord. 2020 Jul 29; 20(1):352. doi: 10.1186/s12872-020-01637-4.
2 Blake SC, Daniel BS. Cutaneous lupus erythematosus: A review of the literature. Int J Womens Dermatol. 2019 Jul 31;5(5):320-329. doi: 10.1016/j.ijwd.2019.07.004. eCollection 2019 Dec.
3 Nahidi Y, Meibodi NT, Javidi Z, Moghimi HR. Annular Erythematous Plaques on the Face, Trunk and Extremities of an Infant. Indian J Dermatol. 2015 May-Jun; 60(3):316-8. doi: 10.4103/0019-5154.156411.
4 Dickey BZ, Holland KE, Drolet BA, Galbraith SS, Lyon VB, Siegel DH, Chiu YE. Demographic and clinical characteristics of cutaneous lupus erythematosus at a paediatric dermatology referral centre. Br J Dermatol. 2013 Aug; 169(2):428-33. doi: 10.1111/bjd.12383.
5 Barry J. Maron, Chair; Jeffrey A. Towbin, Gaetano Thiene Charles Antzelevitch, Domenico Corrado, Donna Arnett, Arthur J. Moss, Christine E. Seidman, James B. Young. Contemporary Definitions and Classification of the Cardiomyopathies an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation. 2006; 113:1807-1816.
6 Perry Elliott, Bert Andersson, Eloisa Arbustini, Zofia Bilinska, Franco Cecchi, Philippe Charron, Olivier Dubourg, Uwe Ku‘ hl, Bernhard Maisch, William J. McKenna, Lorenzo Monserrat, Sabine Pankuweit, Claudio Rapezzi, Petar Seferovic, Luigi Tavazzi, and Andre Keren. Classification of the cardiomyopathies: a position statement from the European society of cardiology working group on myocardial and pericardial diseases. European Heart Journal (2008) 29, 270–276. doi: 10.1093/eurheartj/ehm342.
7 Modern KG, Miller TD, Tazelaar HD. Cardiac involvement in systemic lupus erythematosus. Mayo Clin Proc. 1999 Mar; 74(3):275–84. Doi: 10.4065/74.3.275.
8 Tincani A, Rebaioli CB, Taglietti M, Shoenfeld Y. Heart involvement in systemic lupus erythematosus, antiphospholipid syndrome and neonatal lupus. Rheumatology (Oxford). 2006 Oct; 45 Suppl 4:i8-13. doi: 10.1093/rheumatology/kel308.
9 Bazyar Z, Moaref A, Amirghofran AA, Nazarinia M, Kojuri J. A Woman with Systemic Lupus Erythematosus and Odd Valvular Presentation: A Case Report. Am J Case Rep. 2019 Nov 19; 20:1705-1708. doi: 10.12659/AJCR.917743.
10 Yi-qun Li , Qian Wang, Yan Luo, Yan Zhao. Neonatal lupus erythematosus: a review of 123 cases in China. International Journal of Rheumatic Diseases.
11 Paulo Soaresa, Gustavo Rochaa, Susana Pissarraa, Henrique Soaresa, Filipa Flôr-de-Limaa, Sandra Costaa, Cláudia Mourab, Sofia Dôriac, Hercíliu Guimarãesa. Neonatal dilated cardiomyopathy. Port Cardiol. 2017; 36(3):201----214.
12 Jeffrey A. Towbin, April M. Lowe, Steven D. Colan., Lynn A. Sleeper, E. John Orav, Sarah Clunie, Jane Messere, Gerald F. Cox, Paul R. Lurie, Daphne Hsu, Charles Canter, James D. Wilkinson, Steven E. Lipshultz, Incidence, Causes, and Outcomes of Dilated Cardiomyopathy in Children. JAMA, October 18, 2006—Vol 296, No. 15.
13 Izmirly P, Saxena A, Buyon JP. Curr Opin Rheumatol. 2017 Sep; 29(5):467-472.https://www.ncbi.nlm.nih.gov/pubmed/28520682
14 Brito-Zeron P, Izmirly PM, Ramos-Casals M, Buyon JP, Khamashita MA. The clinical spectrum of autoimmune congenital heart block. Nat Rev Rheumatol. 2015; 11:301-312. http://www.ncbi.nlm.nih.gov/pubmed/25800217
15 Morel N, Georgin-Lavialle S, Levesque K, et al. Neonatal lupus syndrome: literature review. Rev Med Interne. 2015; 36:159-166.http://www.ncbi.nlm.nih.gov/pubmed/25240481
16 Saxena A, Izmirly PM, Mendez B, Buyon JP, Friedman DM. Prevention and treatment of in utero of autoimmune-associated congenital heart block. Cardiol Rev. 2014; 263-267. http://www.ncbi.nlm.nih.gov/pubmed/25050975
17 Izmirly PM, Buyon JP, Saxena A. Neonatal lupus: advances in understanding pathogenesis and identifying treatments of cardiac disease. Curr Opin Rheumatol. 2012; 24:466-472. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3749830/
• 18 Izmirly PM, Costedoat-Chalumeau N, Pisoni CN, et al. Maternal use of hydroxychloroquine is associated with a reduced risk of recurrent anti-SSA/Ro-antibody-associated cardiac manifestations of neonatal lupus. Circulation. 2012; 126:76-82. https://www.ncbi.nlm.nih.gov/pubmed/22626746

• 19 Izmirly PM, Saxena A, Kim MY, et al. Maternal and fetal factors associated with mortality and morbidity in a multi-racial/ethnic registry of anti-SSA/Ro-associated cardiac neonatal lupus. Circulation. 2011; 124:1927-1935.https://www.ncbi.nlm.nih.gov/pubmed/21969015

• 20 Boros CA, Spence D, Blaser S, Silverman ED. Hydrocephalus and macrocephaly: new manifestations of neonatal lupus erythematosus. Arthritis Rheum. 2007; 57:261-266. http://www.ncbi.nlm.nih.gov/pubmed/17330304

• 21 Lee LA. Neonatal lupus erythematosus: clinical findings and pathogenesis. J Investig Dermatol Symp Proc. 2004; 9:52-56.http://www.ncbi.nlm.nih.gov/pubmed/14870986

• 22 Zuppa AA, Delogu AB, De Rosa G, et al. Neonatal lupus: different neonatal expression in siblings. Arch Pediatr. 2004; 11:936-9.http://www.ncbi.nlm.nih.gov/pubmed/15288086

• 23 Dorner T, Feist E, Pruss A, et al. Significance of autoantibodies in neonatal lupus erythematosus. Int Arch Allergy Immunol. 2000; 123:58-66.http://www.ncbi.nlm.nih.gov/pubmed/11014972

• 24 Garcia S, Campos-de-Carvalho AC. Neonatal lupus syndrome: the heart as a target of the immune system. An Acad Bras Cienc. 2000; 72:83-89.http://www.ncbi.nlm.nih.gov/pubmed/10932109

• 25 De Bandt M, Palazzo E, Belmatoug N, et al. Outcome of pregnancies in lupus: experience at one center. Ann Med Interne. 2000; 151:87-92.http://www.ncbi.nlm.nih.gov/pubmed/10855360

• 26 Femia AN, Callen JP, Vleugels RA. Neonatal and Pediatric Lupus Erythematosus. Medscape. Updated: Jun 08, 2016. Available at: http://emedicine.medscape.com/article/1006582-overview Accessed September 11, 2018.

• 27 Daniele Masaroni, Fabio Valente, Marta Rubino, Rossella Vastarella, Rita Gravino, Alessandra Rea, Maria Giovanna Russo, Giuseppe Pacileo, Giuseppe Limongelli. Pediatric Heart Failure: A Practical Guide to Diagnosis and Management. Pediatrics and Neonatology (2017) 58, 303e312.

• 28 Sérgio Laranjo, Conceicão Trigo, Fátima F. Pinto, Dual etiology of dilated cardiomyopathy: The synergistic role of vitamin D deficiency. Rev Port Cardiol. 2014; 33(3):179.e4-179.e4.

• 29 Mohammed AltWajry, Waled AlMane, Sulaiman M Al-Mayouf, Electrocardiographic disturbances in children with systemic lupus erythematosus. International Journal of Pediatrics and Adolescent Medicine 5 (2018) 127e130.

• 30 Martin Aringer, Karen Costenbader, David Daikh, Ralph Brinks, Marta Mosca, Rosalind Ramsey-Goldman, Josef S. Smolen, David Wofsy, Dimitrios T. Boupamas, Diane L. Kamen, David Jayne, Ricard Cervera, Nathalie Costedoat-Chalumeau, Betty Diamond, Dafina D. Gladman, Bevra Hahn, Falk Hiepe, Søren Jacobsen, Dinesh Khanna, Kirsten Lerstrøm, Elena Massarotti, Joseph McCune, Guillermo Ruiz-Irastorza, Jorge Sanchez-Guerrero, Matthias Schneider, Murray Urowitz, George Beretsias, Bimba F. Hoyer, Nicolai Leuchten, Chiara Tani, Sara K. Tedeschi, Zahi Touma, Gabriela Schmajuk, Branimir Anic, Florence Assan, Tak Mao Chan, Ann Elaine Clarke, Mary K. Crow, László Czirjak, Andrea Doria, Winfried Graninger, Bernadett Halda-Kiss, Sarfaraz Hasni, Peter M. Izmirly, Michelle Jung, Gábor Kumánovics, Xavier Mariette, Ivan Padjen, José M. Pego-Reigosa, Juanita Romero-Diaz, Ilhgo Rúa-Figueroa Fernández, Raphaéle Seror, George H. Stumvoll, Yoshiya Tanaka, Maria G. Tektónidou, Carlos Vasconcelos, Edward M. Vital, Daniel J. Wallace, Sule Yavuz, Peter M. Izmirly, Michelle Jung, Gábor Kumánovics, Xavier Mariette, Ivan Padjen, José M. Pego-Reigosa, Juanita Romero-Diaz, Ilhgo Rúa-Figueroa Fernández, Raphaéle Seror, George H. Stumvoll, Yoshiya Tanaka, Maria G. Tektónidou, Carlos Vasconcelos, Edward M. Vital, Daniel J. Wallace, Sule Yavuz, Peter M. Izmirly, Michelle Jung, Gábor Kumánovics, Xavier Mariette, Ivan Padjen, José M. Pego-Reigosa, Juanita Romero-Diaz, Ilhgo Rúa-Figueroa Fernández, Raphaéle Seror, George H. Stumvoll, Yoshiya Tanaka, Maria G. Tektónidou, Carlos Vasconcelos, Edward M. Vital, Daniel J. Wallace, Sule Yavuz, Pier Luigi Meroni, Marvin J. Fritzler, Ray Naden, Thomas Dörner, and Sindhu R. Johnson. 2019 European League against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. Arthritis & Rheumatology Vol. 71, No. 9, September 2019, pp 1400–1412. doi:10.1002/art.40930.

• 31 Bundhun PK, Kumari A, Huang F. Differences in clinical features observed between childhood-onset versus adult-onset systemic lupus erythematosus: A systematic review and meta-analysis. Medicine (Baltimore). 2017 Sep; 96(37):e8086. doi: 10.1097/MD.0000000000000808.

• 32 Brunner HI, Holland MJ, Beresford MW, Ardon SP, Appenzeller S, Silva CA, Flores F, Goilav B, Avar Aydin PO, Wenderfer SE, Levy DM, Ravelli A, Khubchandani R, Avcin T, Klein-Gitelman MS, Ruperto N, Feldman BM, Ying J; Paediatric Rheumatology International Trial Organisation and Pediatric Rheumatology Collaborative Study Group. American College of Rheumatology Provisional Criteria for Clinically Relevant Improvement in Children and Adolescents with Childhood-Onset Systemic Lupus Erythematosus. Arthritis Care Res (Hoboken). 2019 May; 71(5):579-590. doi: 10.1002/acr.23834.

• 33 Holland MJ, Beresford MW, Feldman BM, Huggins J, Norambuena X, Silva CA, Susic G, Szajnbok F, Uziel Y, Appenzeller S, Ardon SP, Avcin T, Flores F, Goilav B, Khubchandani R, Klein-Gitelman M, Levy D, Ravelli A, Wenderfer SE, Ying J, Ruperto N, Brunner HI; PRINTO and PRCSG Investigators. Measuring Disease Damage and Its Severity in Childhood-Onset Systemic Lupus Erythematosus. Arthritis Care Res (Hoboken). 2018 Nov; 70(11):1621-1629. doi: 10.1002/acr.23531.
• 34 Abulaban KM, Brunner HI. Biomarkers for childhood-onset systemic lupus erythematosus. Curr Rheumatol Rep. 2015 Jan; 17(1):471. doi: 10.1007/s11926-014-0471-2.
• 35 Wahadat MJ, Bodewes ILA, Maria NI, van Helden-Meeuwsen CG, van Dijk-Hummelman A, Steenwijk EC, Kamphuis S, Versnel MA. Type I IFN signature in childhood-onset systemic lupus erythematosus: a conspiracy of DNA- and RNA-sensing receptors?
• 36 Chang JC, Xiao R, Mercer-Rosa L, Knight AM, Weiss PF. Child-onset systemic lupus erythematosus is associated with a higher incidence of myopericardial manifestations compared to adult-onset disease. Lupus. 2018 Nov; 27(13):2146-2154. doi: 10.1177/0961203318804889. Epub 2018 Oct 14.
• 37 Brunner HI, Gulati G, Klein-Gitelman MS, Rouster-Stevens KA, Tucker L, Ardoin SP, Onel KB, Mainville R, Turnier J, Aydin POA, Witte D, Huang B, Bennett MR, Devarajan P. Urine biomarkers of chronic kidney damage and renal functional decline in childhood-onset systemic lupus erythematosus. Pediatr Nephrol. 2019 Jan; 34(1):117-128. doi: 10.1007/s00467-018-4049-5. Epub 2018 Aug 29.
• 38 Afzali P, Isaeian A, Sadeghi P, Moazzami B, Parvaneh N, Robatjazi M, Ziaee V. Complement deficiency in pediatric-onset systemic lupus erythematosus. J Lab Physicians. 2018 Apr-Jun; 10(2):232-236. doi: 10.4103/JLP.JLP_171_17.
• 39 Gomes RC, Silva MF, Kozu K, Bonfá E, Pereira RM, Terreri MT, Magalhães CS, Sacchetti SB, Marini R, Fraga M, Carvalho LM, Barbosa CM, Carneiro-Sampaio M, Silva CA. Features of 847 Childhood-Onset Systemic Lupus Erythematosus Patients in Three Age Groups at Diagnosis: A Brazilian Multicenter Study. Arthritis Care Res (Hoboken). 2016 Nov; 68(11):1736-1741. doi: 10.1002/acr.22881. Epub 2016 Oct 6.
• 40 Deborah M. Levy, and Sylvia Kamphuis. Systemic Lupus Erythematosus in Children and Adolescents. Pediatr Clin North Am. 2012 April; 59(2): 345–364. doi:10.1016/j.pcl.2012.03.007.