

Pulmonary hypertension associated with congenital heart block and neonatal lupus syndrome: A series of four cases

Lupus

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Abstract

Objective: Neonatal lupus syndrome has multisystemic manifestations among which pulmonary involvement has been rarely reported. We describe the clinical presentation, management, and outcome of a series of four neonates who developed reversible pulmonary hypertension associated with auto-immune congenital complete heart block.

Method: Data from the French registry of neonatal lupus syndrome were retrospectively reviewed.

Results: Between 2000 and March 2020, 231 children were included in the French registry, four/73 followed in our institution developed pulmonary hypertension. Diagnosis was suspected on transthoracic echocardiography at a median age of 42 days [range 10-58], and confirmed by right heart catheterization in all; 2 of them were paced at time of diagnosis and 2 were not. All had some degree of hypoxemia and respiratory distress. Hypoxemia was always reversible under O² et NO. Lung CT demonstrated ground glass anomalies in all. One patient had a lung biopsy consistent with pulmonary hypertension secondary to lung disease. Management included immunosuppressive therapy in 3 associated with sildenafil in 2. Pulmonary hypertension resolved in all at a median age of 4 weeks [range 3-6] after treatment initiation and after one year for the one child who did not receive specific treatment.

Conclusion: Clinical, hemodynamical, imaging and histological findings advocate for pulmonary hypertension associated with respiratory disease as a rare manifestation of neonatal lupus syndrome.

Keywords

Cardiovascular disease, anti-DNA antibodies, pregnancy

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Introduction

Immune-mediated congenital complete heart block (CHB) is a well-defined consequence of antenatal exposure to maternal anti-SSA/Ro and/or anti-SSB/La autoantibodies.¹ After birth, the persistence of maternal anti-SSA and/or anti-SSB antibodies passively transferred to the foetus can cause skin rash, hepatic or neurologic manifestations in the children. While the complete atrio-ventricular block is irreversible, with rare exception, other clinical or biological signs of neonatal lupus syndrome will resolve as soon as the maternal antibodies are cleared from the child's circulation.

Pulmonary hypertension (PH) is a rare complication of systemic lupus erythematosus (SLE) in adulthood.

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To our knowledge, only rare cases of pulmonary manifestations associated with auto-immune CHB have been reported in neonates, with only one case of PH.²⁻⁵ We report here the clinical presentation and outcomes of four neonates referred to our institution for autoimmune CHB and who had associated PH.

Patients and methods

Patients

Inclusion criteria for this study were (1) a liveborn child enrolled in the French registry of neonatal lupus syndrome by March 2020 for a CHB associated to maternal anti-SSA and/or anti-SSB antibodies, (2) followed in our institution, and (3) with confirmation of pulmonary hypertension (PH) by a right heart catheterisation (RHC). The French registry of neonatal lupus was established in 2000 with Institutional Review Board approval and collect fetuses or children with neonatal lupus syndrome born to mothers with anti-SSA and/or anti-SSB antibodies.¹

Methods

We retrospectively analysed the clinical records including the pre-natal and post-natal echocardiographies, neonatal clinical condition, the hemodynamic findings at right heart catheterisation, and follow-up notes of these patients. Maternal serological screening identified anti-SSA/Ro and/or anti-SSB/La antibodies.

Follow-up

After birth, standard care included pacemaker implantation in accordance with the current guidelines^{6,7} or a close follow-up planned on a weekly basis for the first month and then monthly for the 3 following months or until pacemaker implantation. The follow-up includes clinical evaluation, Holter-ECG and transthoracic echocardiography (TTE). Pulmonary artery (PA) pressures are estimated on tricuspid regurgitation velocity and on pulmonary regurgitation velocity if present. When tricuspid regurgitation velocity is above 2.8 m/s after 10 days of life and with arterial duct closed, patients had right heart catheterization in order to confirm the diagnosis of PH, to characterize the type of PH, to assess the severity of haemodynamic impairment and to test vasoreactivity of the pulmonary circulation. Right heart pressures (right atrium, right ventricle, pulmonary artery and wedge pressures) were recorded, cardiac output was estimated with the Fick principle by collecting pressures and blood samples for oximetry from the superior vena cava (SVC), from the inferior vena cava (IVC) and from the PA as well as in the aorta.

PH was defined as mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg and classified as pre-capillary if pulmonary artery wedge pressure (PAWP) was ≤ 15 mmHg.⁸ Pulmonary vasoreactivity testing was performed with a combination of oxygen (FiO₂ 100%) and inhaled nitric oxide (NO). A positive acute response was defined as a reduction of the mPAP ≥ 10 mmHg. Pulmonary vascular resistance (PVR) was then calculated at basal and O₂/NO status. During follow-up, PA pressures were evaluated on TTE based on tricuspid or pulmonary regurgitation velocity.

Lung CT-pulmonary angiography to evaluate diameters of the common pulmonary trunk and lung parenchyma were performed as a part of our routine work-up in patients with pulmonary hypertension but also to establish the presence of lung disease and to characterize the severity of the lesions.

Presentation of data

Quantitative variables were expressed as mean \pm standard deviation (SD) in case of normal distribution, otherwise as median [range minimum-maximum], and qualitative variables as number of patients (percentages).

Results

Between January 2000 and March 2020, 231 children had been included in the French registry of neonatal lupus syndrome including 73 fetuses followed in our institution from the prenatal period. During postnatal follow-up, PH was considered highly likely on echocardiography in four/73 infants regularly followed at our institution. The first diagnosis was made in 2006 and the last one in 2020.

Patient 1

CHB was diagnosed during pregnancy and was well tolerated. He was born at term by vaginal delivery after spontaneous labour with a birth weight of 3 kg. At birth, heart rate was 60 bpm and adaptation to extrauterine life was uneventful. Given the perfect tolerance of the bradycardia, pacemaker implantation was not indicated during the hospital stay and TTE was normal at this time without PH. Immediate post discharge period was uneventful with stable mean heart rate at Holter monitoring and satisfactory growth. At 1-month of age, typical lupus cutaneous lesions appeared and were successfully treated by local steroids. At 2 months of life, the child was hospitalized for mild respiratory distress. On admission, estimated systolic PAP was 45 mmHg on TTE. Bronchiolitis was first suspected as the child had suggestive symptoms. Three weeks later, the patient deteriorated with increased respiratory distress and marked

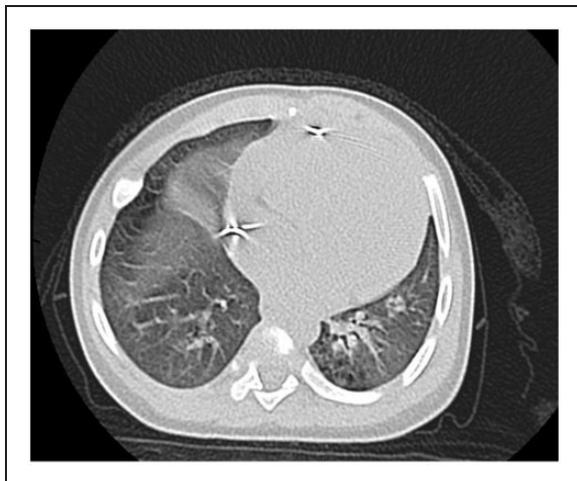


Figure 1. Lung CT scan.

Lung CT scan of patient 1 show hazy increased opacity of the lung, with preservation of bronchial and vascular margins typical of ground glass opacities.

desaturation with SpO₂ of 80% on room air. Viral tests were all negative refuting the initial diagnosis. Twelve-lead ECG confirmed CHB with heart rate at 48 bpm. TTE showed aggravated PH with estimated systolic PAP of 70 mmHg with preserved right and left ventricular functions. Data of RHC are shown in table. Lung CT scan displayed diffuse ground glass opacities without any other abnormality (Figure 1). Because of severe bradycardia associated with PH, an epicardial mono-chambered pacemaker was implanted. During the surgery, a bronchoalveolar lavage was performed, that did not add pertinent information. Corticosteroids therapy was discussed but finally, not given. Regular TTE during the following months kept on showing PH. Gradually pulmonary pressure decreased despite the lack of treatment. PH resolved at 1 year of age and never relapsed. Ten years follow-up was uneventful except for the replacement of leads and pacemaker at age 9 years.

Patient 2

Diagnostic of CHB was made during pregnancy. She was born at 37 weeks of gestation by caesarean section, with a birth weight of 2.5 kg. After birth, ECG confirmed CHB with a stable heart rate of 60 bpm and she did not require pacemaker implantation. At this time, a large persistent arterial duct with equalization of pulmonary pressure was noted on TTE. Ten days after birth, she had polypnea (respiratory rate 50/min) and was cyanotic on room air (oxygen saturation 80%). Clinical examination was otherwise unremarkable. Initial blood sample showed hepatic cholestasis with slightly prolonged activated partial thromboplastin

time. During hospital stay, acute haemolytic anaemia was noticed. On TTE, estimated systolic PAP pressure was 80 mmHg with a mean PAP pressure of 45 mmHg, despite spontaneous arterial duct closure. These findings were confirmed by RHC (see Table 1). Lung CT scan displayed isolated segmental unilateral ground glass opacities. As she had a multiorgan involvement of neonatal lupus, she was treated with two doses of intravenous immunoglobulin (1 g/kg each) and with intravenous bolus of methylprednisolone (20 mg/kg for 3 consecutive days) to reduce the autoimmune and inflammatory activation. Oral steroids therapy was continued after this initial treatment (initially 2 mg/kg/day then 1 mg/kg/day). Concomitantly, sildenafil was started (4 mg/kg/day). A dual chamber was implanted during the same admission. The pacemaker was programmed on a VVI mode because early post-operative atrial lead failure. A lung biopsy was performed at time of surgery for pacemaker implantation that showed proximal and distal intra-acinary medial hypertrophy without intimal proliferation and a mild infiltrate with a mix of macrophages, lymphocytes and eosinophilic leucocytes (Figure 2). Of note, dilated lymphatic vessels surrounding proximal and distal pulmonary arteries were observed. A small territory of parenchymal inflammation was observed, and distal pulmonary arteries exhibited non obstructive intimal damage only in this part of the lung (Figure 2(C)).

During the hospitalization, bilirubin levels, haemolytic anaemia and pulmonary pressure all normalized after 20 days of treatment. Steroids were slowly tapered down and stopped after 4 months. She was weaned of sildenafil treatment after 10 months. At this period, a control RHC was performed showing complete resolution of PH as shown in Table 1. After 9 years of follow up, no recurrence of PH was reported.

Patient 3

She was born at 36 weeks of gestation by caesarean section due to intrauterine growth retardation with a birth weight of 2 kg and a heart rate of 40 bpm. An epicardial unipolar mono-chambered pacemaker was implanted immediately after birth due to low heart rate. Post-operative TTE did not show sign of PH. During out-clinic close follow-up, mild desaturation (SpO₂ 90%) was noted on day 21 with paced heart rate of 130 bpm, while she had no sign of respiratory distress or hemodynamic compromise. NT-pro-brain natriuretic peptide level was high 3500 ng/mL. TTE showed elevated pulmonary pressure with normal right and left ventricular functions. RHC confirmed PH (see Table 1). Lung CT scan shown only segmental bilateral ground glass opacities. Typical cutaneous lesions appeared. She was initially treated with two

Table 1. Patients' characteristics.

	Patient 1	Patient 2	Patient 3	Patient 4
Gestational age at CHB diagnosis (weeks)	29	23	22	22
Maternal autoantibodies status (blood level not available)	Anti-SSA + anti-SSB	Anti-SSA + anti-SSB	Anti-SSA	Anti-SSA
Clinical Maternal status	Asympto.	Asympto.	SLE	Asympto.
Maternal steroid treatment during pregnancy for CHB	Dexamethasone 8 mg per day	None	Betamethasone 8 mg per day	Betamethasone 4 mg per day
GA at initiation (week)/cumulative dose (mg)	29/196		22.5/534	23/348
Heart rate before birth (bpm) ^a	57	57	45	50
LV function before birth	Normal	Normal	Normal	Normal
Gestational age at birth (weeks)	39	37	36	35
Gender	M	F	F	F
Birth weight (kg)	3	2.5	2	1.6
Heart rate at birth (bpm)	60	60	40	43
LV function at birth	Normal	Normal	Normal	Normal
Time of PM impl. (days)	87	30	birth	birth
Age at PH diagnosis (days)	85	10	21	53
PM at the time of PH	No	No	Yes	Yes
Main clinical findings	Low SaO ₂ Tachypnoea	Low SaO ₂ Tachypnoea	Low SaO ₂	Low SaO ₂
Lung CT – Ground glass opacities RHC	Diffuse	Segmental-unilateral	Segmental-bilateral	Segmental- bilateral
PAP (s/d-m) (mmHg)	65/25-40	104/30-59	37/12-25	48/23-35
PAo (s/d-m) (mmHg)	90/40-60	98/60-73	78/44-60	86/53-67
PWP (mmHg)	8	13	13	13
PVRi (Wood unit.m ²)	17.8	16	4.8	12.9
PVRi with O ₂ +NO°	3.6	8.1	0.9	7.5
PVR/SVR	0.5	0.72	0.23	-
SaO ₂ (baseline/O ₂) %	98/100	60/100	90/100	89/100
SvO ₂ (baseline/O ₂) %	46/87	23/75	58/84	75/83
Other signs of NLS	Cutaneous rash	Hepatic cytolysis Anemia	Cutaneous rash	None
PH therapy	None	ImmunoS + sildenafil	ImmunoS	ImmunoS + sildenafil

Asympto.: asymptomatic; CHB: congenital heart block; ImmunoS: immunosuppressive therapy; LV: left ventricular; PH: pulmonary hypertension; PM implant.: pacemaker implantation; NLS: neonatal lupus syndrome.

^aHeart rate before birth at the nadir.

doses of intravenous immunoglobulin (1 g/kg each), a unique dose of intravenous steroid (methylprednisolone: 1 mg/kg) followed by oral steroids. Sildenafil was not added to the anti-inflammatory treatment. Steroids were slowly decreased when PA pressure normalised on TTE after 1 month and a half of treatment. Discontinuation of PH therapy was possible after 6 months. After 4.7 years, no event was noted, except for a device replacement at 4 years of age.

Patient 4

She was born by caesarean section at 35 + 3 weeks of gestation with severe intra-uterine growth retardation

and a birth weight of 1.585 kg. Heart rate was 43 bpm. Because of the severe intrauterine growth retardation, a temporary external pacemaker was implanted first followed by implantation of a single chamber epicardial pacemaker on day 28 at a weight of 2.28 kg. She was extubated five days after pacemaker implantation. Transient self-resolving oxygen desaturation episodes were reported (SpO₂ 80% without dyspnoea) in the following days. While echocardiogram performed at day 35 did not report any PH, the echocardiogram done at day 53, showed PH with estimated mean PAP of 50 mmHg with right ventricle dysfunction (TAPSE 5 mm). At that time, the patient was still hospitalized in the neonatal ward because of failure to

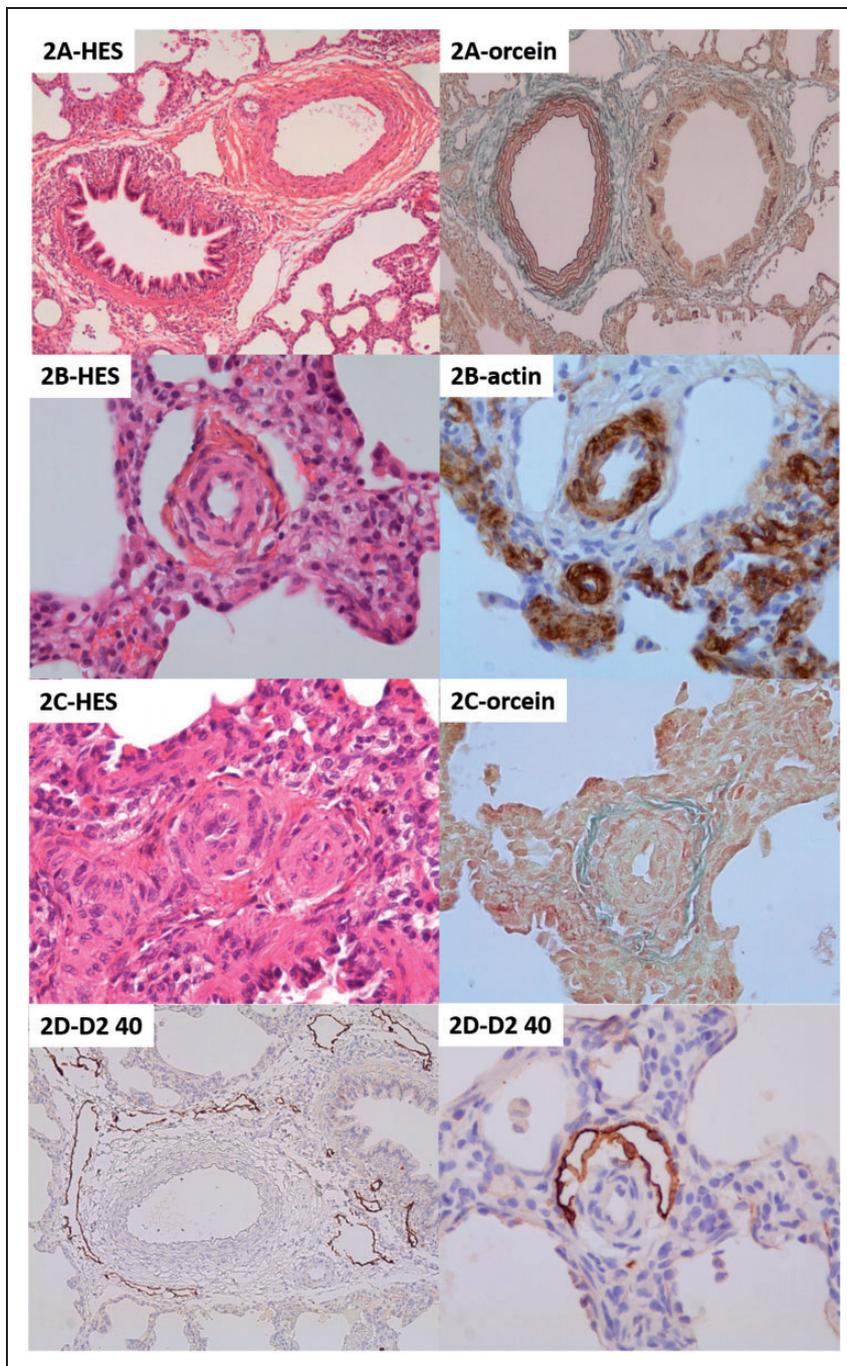


Figure 2. Histological lesions of proximal and distal intra-acinar pulmonary arteries.

A: HES and orcein coloration showing increased wall thickness of terminal bronchial artery without intimal damage

B: HES coloration and actin immunostaining showing alveolar duct artery with abnormal extension of smooth muscle cells but normal endothelial layer

C: intimal lesions of distal intra-acinar arteries associated with parenchymal inflammation

D: D2 40 immunostaining underlying that dilated lumen surrounding proximal and distal pulmonary arteries are lymphatic vessels

thrive. No other signs of systemic involvement were present and clinical examination was unremarkable. Based on our previous experience, she was treated with two doses of intravenous immunoglobulin (1 g/

kg each) and intravenous steroid therapy (20 mg/kg) for 3 consecutive days, followed by oral steroid (2 mg/kg/day). Sildenafil was also introduced (10 mg/kg/day). The RHC (Table 1) and CT scan, that

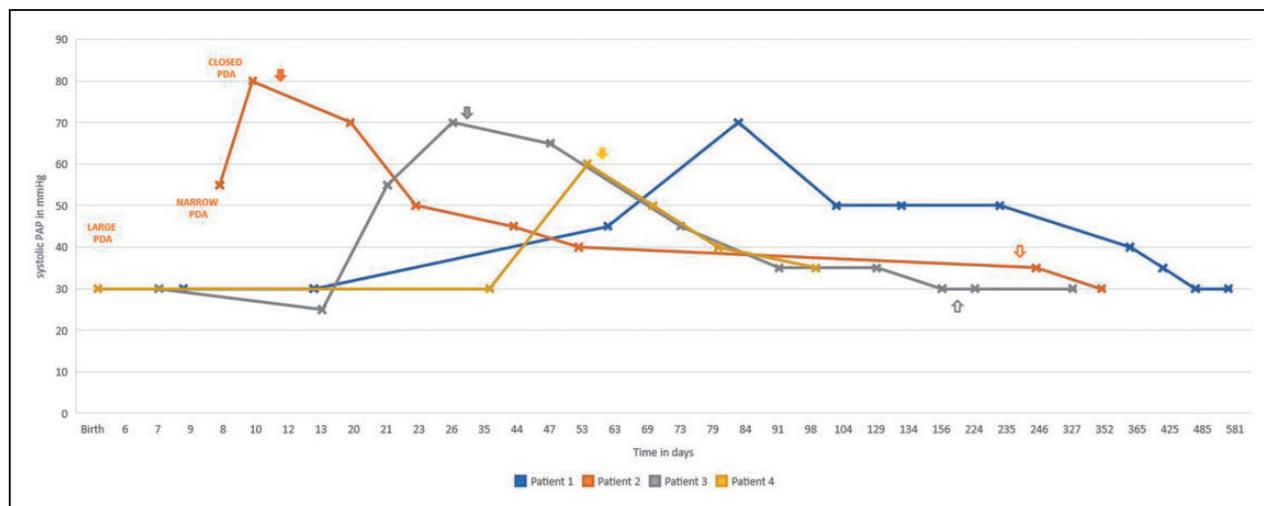


Figure 3. Longitudinal profile of echocardiographic findings.

Evolution of echocardiography based estimated systolic pulmonary arterial pressure over time. AD: arterial duct. PAD: persistent arterial duct. Solid arrow: treatment initiation. Empty arrow: treatment withdrawal.

displayed solely segmental bilateral ground glass opacities, were done while on PH treatment. PH normalized 3 weeks after treatment introduction, steroids could be rapidly decreased and stopped. At the time of submission, the patient was 7 months old and about to be weaning from sildenafil.

The Figure 3 summarize the TTE findings over time for the 4 patients.

Discussion

We report four cases of neonatal PH associated with complete autoimmune CHB. To our knowledge only one other case has been describe in the literature by Komori et al.,⁵ but pulmonary involvement suggestive of interstitial lung disease has nevertheless been reported in neonates exposed to maternal auto-antibodies during pregnancy.^{2,3}

Physiopathology of PH in those neonates is unknown. Komori and al suggested that delayed adaptation of the pulmonary vessels, majored by bradycardia, can be the case of PH.⁵ This hypothesis is not consistent with our clinical observation since PH was delayed from birth. PH was suspected at a median of 42 days [range 10-58] based on TTE and confirmed by RHC in all 4. Three patients had a free interval where pulmonary pressure was described as normal on TTE, suggesting that PH developed secondarily as cutaneous manifestation of neonatal lupus syndrome does. A true free interval was not observed for the fourth patient since she had initially a large persistent arterial duct. However, it is worth mentioning that the right ventricle pressure of this patient has decreased along with the

arterial duct narrowing and increased again after complete arterial duct closure.

The role of left heart dysfunction can be discussed. RHC in our patients confirmed the pulmonary arterial hypertension without significant contribution of left heart dysfunction. Still, pulmonary wedge pressure was slightly above the normal value (12–13 mmHg).⁸ This mild increase in pulmonary wedge pressure was not due to left ventricular systolic dysfunction but could be explained by the bradycardia in the two non-paced patients and potentially to the asynchrony between atrial and ventricular contraction due to the single chamber pacing in the two paced patients.

The clinical symptoms particularly hypoxemia and respiratory distress, lung imaging and the only pulmonary biopsy findings were consistent with associated lung disease that might also have contributed to the development of PH. At time of diagnosis of PH, three patients had basal oxygen desaturation that normalized with O²/NO, the fourth patient had only transient oxygen desaturation episodes. Desaturation is known to induce reactive pulmonary hypertension by constriction of hyper-muscularized distal pulmonary arteries as observed at lung biopsy. Of note, all patients had ground glass anomalies at CT scan in favour of primary parenchymal lung disease. No other radiological signs of PH could be described on CT potentially because of the young age of the patients and the short delay that did not allow for vascular remodelling and neo-vessels development. During RHC, acute vaso-reactivity testing was considered positive in all patients with the limitation of the technique in infants and neonates.

Finally, inflammatory component of PH is possibly contributing to the development of the disease in our patients. Despite the fact that therapy of pulmonary arterial hypertension associated with SLE in adults remains elusive particularly regarding the place of immunosuppressant,⁹ we decided to treat the three later patients with high dose steroids. The first one did not receive such treatment because of suspected infection, but the outcome was identical indicating a spontaneous improvement of the inflammatory process. Still, it is to note that pulmonary pressure normalization took much longer in this non-treated patient. Indeed, PH resolved at a median of 4 weeks [range 3–6] after treatment introduction in the 3 treated patients but only at 1 year of age for the non-treated patient.

Previous studies in adult raised controversies about the benefit of adding pulmonary arterial hypertension specific molecules to immunosuppressant therapy. We decided to add sildenafil in the two more severe patients (supra-systemic PH, RV dysfunction) and their favourable outcome supports this strategy. Pulmonary pressures normalized in all our patients. It suggests that the role of the maternal antibodies was key in the development of PH in our patients even if the cause of PH could have been described as multifactorial. Even if, we did not monitor the antibodies blood levels, their natural clearance from the neonatal circulation has been described. We relied on this to withdraw all immunosuppressant treatment and PAH-specific drug after the first year. The full reversibility of this rare form of pulmonary arterial hypertension was also observed in the only reported observation.⁵

Reversibility of PH in our patients is also supported by histological findings showing increased wall thickness without intimal fibrosis. Dilated lymphatic vessels observed at lung biopsy in our patient has also been described in PH associated with inflammatory process.¹⁰ Finally, we could not assess in this short series if the type of antibodies, their levels or high disease activity in the mother were risk factors for the development of pulmonary hypertension. Among the mothers only one was symptomatic for SLE.

The prevalence of PH in SLE varies between 0.5 and 17.5%. This complication of SLE in adult has not been reported as a cardiac manifestation of neonatal lupus erythematosus in large series of neonates exposed to maternal antibodies during gestation.^{11,12} In our series, diagnosis of PH was made during systematic follow-up in two infants and because of tachypnoea in the two other patients. Other manifestations of neonatal lupus syndrome included cutaneous involvement in 2 patients, and hepatic and haematological involvement in one. One patient did not have any sign of neonatal lupus syndrome other than CHB and PH. In children with CHB, echocardiography is routinely

performed. In neonates exposed to maternal autoantibodies during pregnancy but without cardiac manifestation, TTE is not done routinely. Therefore, PH can be underdiagnosed in the absence of respiratory distress or awareness of possible pulmonary involvement. Indeed, whilst we cannot assume incidence of PH in these neonates who passively received maternal antibodies, this rare condition might be underdiagnosed in this population for different reasons such as non-specific symptoms, spontaneous reversibility, or absence of cardiac monitoring. This observation advocates for close cardiac follow-up of every neonate exposed to maternal autoantibodies during pregnancy, especially when they develop neonatal lupus syndrome.

In conclusion, we believe that this case series illustrates a rare situation of reversible PH due to inflammatory process possibly secondary to passive transfer of maternal autoantibodies to their offspring. This delayed onset parenchymal lung disease associated with reversible PH might be a new manifestation of neonatal lupus, that is underdiagnosed particularly in those without CHB who might not have systematic neonatal screening. Finally, the favourable outcome raises the discussion about the interest of combining immunosuppressant with PAH-specific therapy to avoid severe events related to PH in these fragile infants.

Key messages

Neonatal lupus syndrome is caused by passive transplacental passage of maternal anti-SSA and/or anti-SSB antibodies. It includes cardiac neonatal lupus, skin rash and less commonly haematological, hepatic or neurological manifestations. Pulmonary manifestation is seldom described.

Based on this report, pulmonary hypertension, hypoxemia and respiratory distress due to transient lung disease seem to be unrecognized symptoms of neonatal lupus syndrome.

Pulmonary involvement might be underdiagnosed when not associated to congenital heart block as cardiac follow-up is, then, not routinely done.

This observation advocate for close cardiac follow-up of every neonate exposed to maternal autoantibodies during pregnancy even in absence of cardiac manifestation of neonatal lupus syndrome.

Immunosuppressant treatment and pulmonary arterial hypertension specific drug administration should be considered in case of pulmonary hypertension associated with neonatal lupus syndrome.

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Ethical approval

The French registry of neonatal lupus has obtained Institutional Review Broad approval in 2000.

Contributorship

AM and NM designed the article. AM and ME acquired the data. ML, SM-M and PB interpreted the data. NC-C made substantial modifications. DB drafted and revised the manuscript.

All authors approved the manuscript.

Clinical contributors

Dr Julien Strinemann and Dr Marine Driessen, Dr Muriel Nicloux, Dr Laureline Berteloot, Prof. Christophe Delacourt and Prof. Pierre Quartier.

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Data sharing statement

Data sharing is possible upon acceptance by our institution.

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