SWISS SOCIETY OF NEONATOLOGY

Would you recognize the leopard?

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Title figure:
Leopard (Panthera pardus) (source: Thomas M. Berger,
AfriCat Foundation, Namibia)

INTRODUCTION

Second only to trisomy 21, Noonan syndrome (NS) is a common syndromic cause of congenital heart disease (CHD). It is well known for its association with pulmonary stenosis, which indeed is the most common cardiovascular phenotype of NS; it is present in 50 – 60% of cases. In addition, other forms of CHD can be found in patients with NS: hypertrophic cardiomyopathy (HCM) occurs in 20% and secundum atrial septal defects occur in 6 – 10% of patients (1).

We report the case of a male infant, who was born by normal spontaneous vaginal delivery in a birthing home at 39 6/7 weeks of gestation. He adapted well with Apgar scores of 8, 9, and 10 at 1, 5 and 10 minutes, respectively. His birth weight was 3600 g (P50), birth length was 49 cm (P10) and head circumference was 33 cm (P5).

At the age of 3 hours, the infant was noted to have mild desaturations (SpO_2 88 – 93 %) and central cyanosis was apparent during two episodes of vomiting. The baby was therefore transferred to the neonatal intensive care unit (NICU) at the University Children's Hospital of Basel for further evaluation and monitoring.

On admission, the infant had signs of respiratory distress and required support with heated and humidified high flow (HHHF) therapy and supplemental oxygen. Findings on chest X-ray were felt to be compatible with retained fetal lung fluid (Fig. 1). In addition, clinical examination was remarkable for a 3/6 systolic murmur. Admission laboratory examinations showed an abnormal lactate concentration (7.4 mmol/l), thrombocytopenia (68 G/l) and a slightly elevated C-reactive protein concentration (14 mg/l). Blood cultures were obtained, and antibiotic therapy was started. Blood cultures remained negative. Respiratory support could be stopped after three days.

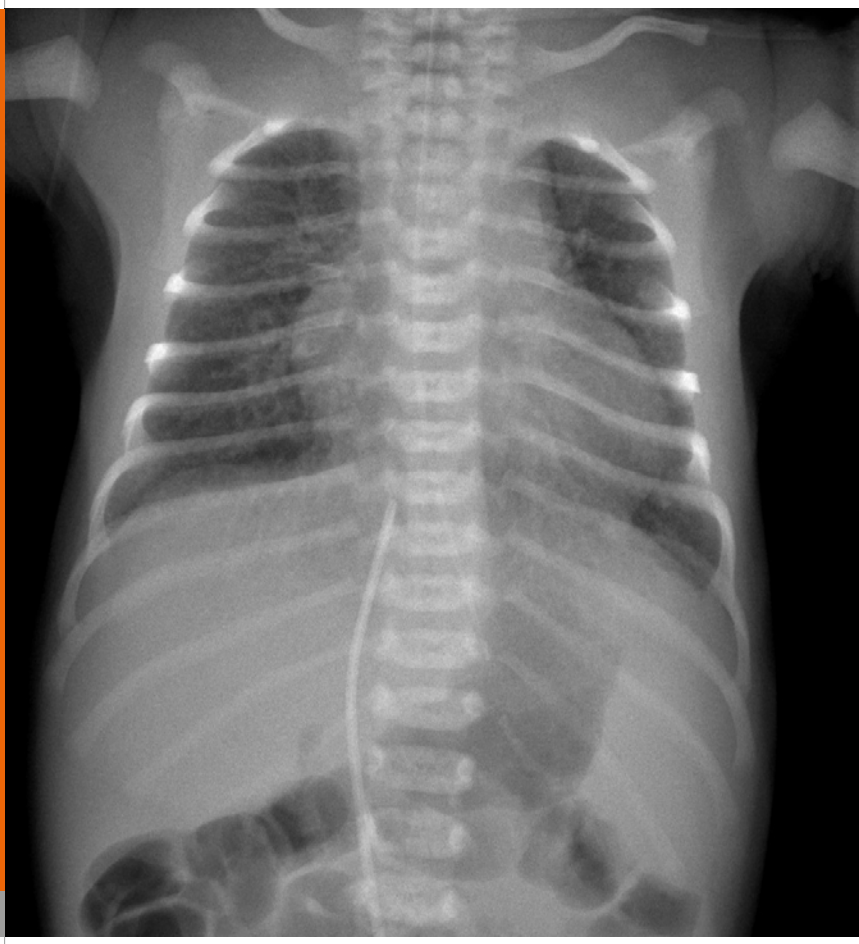

Fig. 1

Babygram following admission to the NICU: prominent cardiothymic silhouette, mildly increased pulmonary interstitial markings; UVC in central position.

Based on the above-described clinical findings, echocardiography was performed on the first day of life and demonstrated diffuse left ventricular hypertrophy (Fig. 2). Over the course of the next few days, increasing left ventricular outflow tract obstruction was documented (Fig. 3), and escalating doses of propranolol were required (final dose of 4 mg/kg/day on day of life six).

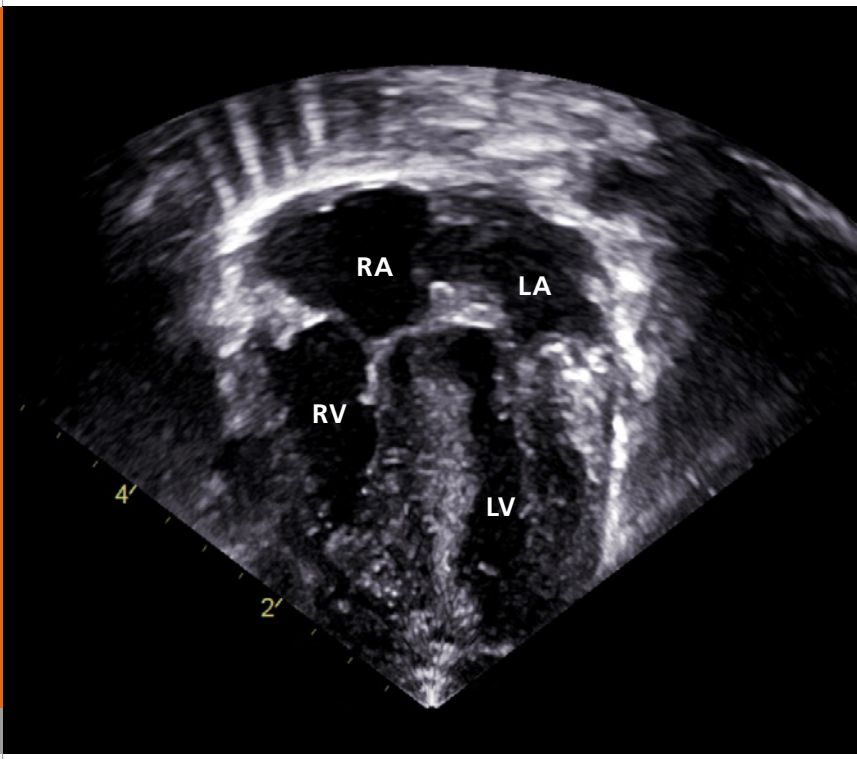

Fig. 2

Echocardiography, 4 chamber view (DOL 2): significant hypertrophy of both ventricles, left more than right (LA: left atrium, LV: left ventricle, RA: right atrium, RV: right ventricle,).

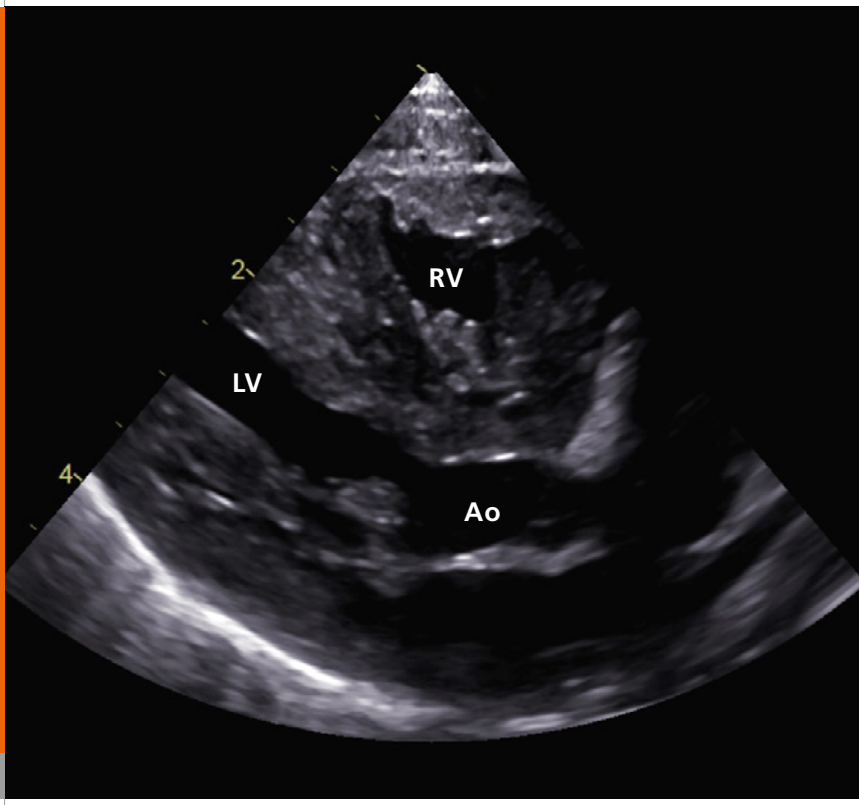

Fig. 3

Echocardiography, long axis view (DOL 10): hypertrophy of both ventricles and increasing left ventricular outflow tract obstruction (Ao: aorta, LV: left ventricle, RV: right ventricle).

There were no obvious dysmorphic signs, and, in addition to the cardiorespiratory abnormalities, only mild muscular hypotonia was found. Family history was negative for cardiac diseases, and the first child of the young family, a girl, was healthy.

A number of potential underlying causes of HCM were excluded over the first few days, including inborn errors of metabolism, infantile M. Pompe and mitochondriopathies. Ultimately, a genetic work-up revealed a de novo mutation in the *PTPN11 (protein tyrosine phosphatase non-receptor type 11) gene*, c.836>C, p.(Tyr279Ser), consistent with the diagnosis of NS with multiple lentigines.

The patient was discharged home on DOL 20, still requiring nasogastric tube feedings. At regular follow-up visits, increasing left ventricular outflow tract obstruction was documented (Fig. 4). At the age of 5 months, muscle resection and extension of the left ventricular outflow tract obstruction were performed. Postoperatively, propranolol therapy had to be continued.

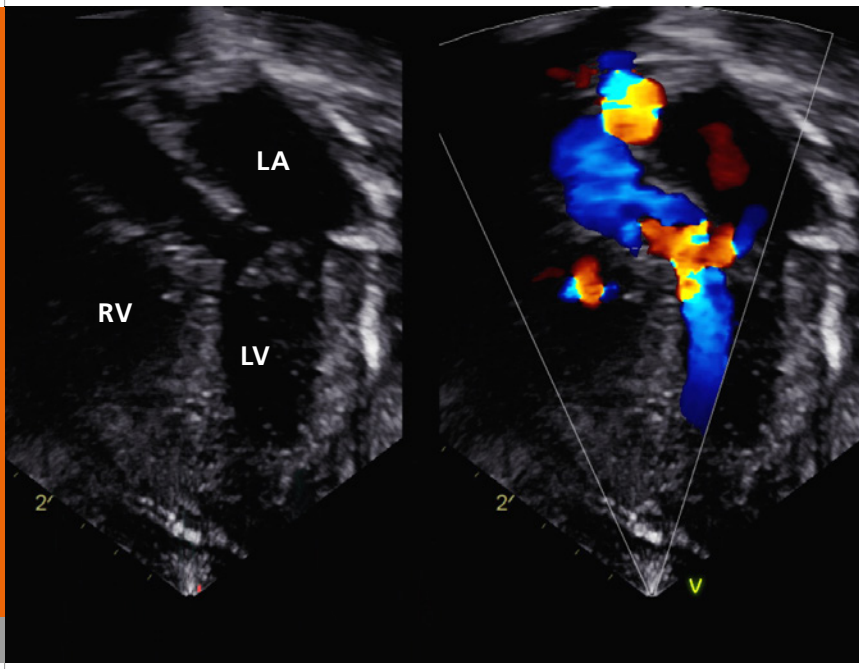

Fig. 4

Echocardiography, 4 chamber view (week 4 of life): marked hypertrophy of both ventricles (LA: left atrium, LV: left ventricle, RV: right ventricel).

DISCUSSION

Hypertrophic cardiomyopathy (HCM) is rare in children with an overall annual incidence of 4.7/1'000'000. It is more often seen in infants (incidence 30/1'000'000) than beyond infancy (incidence among 1 to 18-year-old children 3.2/1'000'000) (2). Long-term prognosis depends mainly on the age at presentation and etiology.

HCM in children is most commonly caused by mutations in the cardiac sarcomere protein genes, but inborn errors of metabolism, neuromuscular disorders and malformation syndromes can also lead to HCM. In a retrospective study from the United Kingdom, 37 % of 687 patients with HCM aged less than 16 years of age had a syndromic form, and in 18.3 % of all patients, NS (or RASopathies, see below) was the underlying cause. RASopathies were significantly more often diagnosed in infants than older children (42 % versus 11.2 %, respectively, $p < 0.0001$) (3).

NS, which was characterized by the pediatric cardiologist Jacqueline Noonan in 1963, is a non-chromosomal genetic multi-system disorder with an estimated incidence between 1:1'000 and 1:2'500 live births. It is characterized by short stature, mild facial dysmorphia, developmental delay in a subset of patients, learning difficulties, CHD, renal anomalies, lymphatic malformations and bleeding anomalies (including deficiency of factor XI, von Willebrand`s disease, thrombocytopenia and platelet function defects) (4).

NS and related disorders (as NS with multiple lentigines, Costello syndrome, cardio-facio-cutaneous syndrome) are autosomal dominant traits with significant phenotypic overlap. Mutations causing these disorders alter proteins relevant for the RAS signaling pathway. Therefore, these disorders are collectively known as RASopathies (5). The RAS-MAPK signaling cascade is an important signal transduction pathway by which extracellular ligands induce cell proliferation, differentiation, survival and metabolism. This pathway plays an important role in growth factor and cytokine signaling as well as cancer pathogenesis (the term RAS is derived from rat sarcoma) (1, 4).

In 50 % of patients with NS, mutations in the PTPN11 gene on chromosome 12, which encodes the non-receptor protein tyrosine phosphatase SHP-2, are found; they are more often seen in familial cases (59 %) than in sporadic cases (37 %) (6). However, there are at least eight candidate genes in the RAS-MAPK signaling pathway that are involved in the pathogenesis of NS or closely related conditions (1).

Frequently, the prenatal history of patients with NS is unremarkable. Occasionally, polyhydramnios, pleural effusions, hydronephrosis, distended jugular lymphatic sacs or cystic hygroma can be seen (1, 4). Often, birth weight and length are within normal limits. The phenotype changes significantly with increasing age (4).

Up to 80 – 90 % of patients with NS have cardiovascular involvement, with valvar pulmonary stenosis being the most common abnormality (50 – 60 %), followed by HCM. In NS, HCM is diagnosed early in life (50 % are diagnosed by 6 months of age). This is far earlier than in other pediatric forms of HCM. Children with NS-associated HCM are also more likely to have congestive heart failure when diagnosis is made, and they often present with significant left ventricular outflow obstruction. Young age at presentation with congestive heart failure is strongly associated with increased mortality by 2 years of age (70 % when diagnosed at less than 6 months of age versus 5 % when diagnosed later and congestive heart failure is absent) (5).

In our patient, NS with multiple lentigines (formerly known as LEOPARD syndrome) was diagnosed, which is a rare variant of NS with specific mutations in the PTPN11 gene (4). Its distinctive feature is the presence of lentigines (small hyperpigmented skin lesions that occur with increasing age). The acronym LEOPARD syndrome stands for: (L)entigines, (E)lectrocardiographic conduction defects, (O)cular hypertelorism, (P)ulmonary stenosis, (A)bnormalities of genitalia (as cryptorchism), (R)etarded growth, (D)eafness. HCM is present in about 80 % of patients with NS with multiple lentigines – the highest rate among the RASopathies – and left ventricular outflow tract obstruction (as seen in our patient) occurs in about half of these cases (5).

The prognosis of HCM in NS with multiple lentigines is variable. Rare cases with rapid progression have been described, but in most children the course appears to be relatively benign (5).

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