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Severe pulmonary arterial hypertension in congenital sideroblastic anemia from PUS1 mutation – a case report

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Abstract

Background Myopathy, lactic acidosis and inherited sideroblastic anemia (MLASA) are a group of rare intriguing disorders with wider pathophysiological implications. One of the causes of MLASA is the mutation in PUS1 gene that encodes for pseudouridine synthase. This PUS1 mutation results in MLASA in which anemia and myopathy predominate. Severe pulmonary arterial hypertension has not been previously reported in patients with PUS1 gene mutation.

Case report A 17 year old girl with congenital sideroblastic anemia presented with worsening of breathlessness. Severe pulmonary artery hypertension was documented on investigations. A homozygous variant in exon 3 of gene PUS1,(chromosome 12:g.131932301 C > T c.430 C > T) was found on sanger sequencing.

Conclusion We document severe pulmonary arterial hypertension in a patient of congenital sideroblastic anemia from PUS1 gene. We hypothesis that cross talk with TGFb pathways might occur in PUS1 mutation, and that might cause severe PAH. This observation might have therapeutic implications.

Keywords MLASA, Pulmonary hypertension, Genetics, Mitochondria

Introduction

Myopathy, lactic acidosis and inherited sideroblastic anemia (MLASA) are known to occur from mutations in PUS1 (pseudouridine synthase 1), YARS2, Mt-ATP6, and few other genes [1]. The PUS1 encodes pseudouridine synthase that converts uridine into pseudouridine after the nucleotide has been incorporated into several cytosolic and mitochondrial t RNA. The mutation in PUS1 gene result in impaired protein synthesis due to disrupted posttranscriptional modification in mitochondrial and cytosolic t RNA functions. In MLASA, the clinical phenotype varies markedly and the symptoms are often seen in few systems only despite a mutation involving mitochondrial function. In MLASA1 mutation, mostly the skeletal myopathy and sideroblastic anemia predominate. Pulmonary arterial hypertension (PAH), to the best of our knowledge, has not been reported in patients with MLASA1.

Herein, we report a 17 year. old girl with congenital sideroblastic anemia in MLASA1 and severe PAH, and speculate on the clinical implications of such an occurrence.

Case report

A 17 year old girl presented with worsening breathlessness and anemia for the last 2 years. She was borne of a term pregnancy and had delayed motor milestones in the

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infancy and early childhood. The patient required blood transfusion twice for anemia at the age of 4 years, but was asymptomatic thereafter until 16 years of age, when progressive breathlessness developed. She had moderate scholastic performance in the school and had average physical capacity and growth. She attained menarche at 14 years of age. There was no history of seizures, diarrhoea, or muscle weakness. Her elder brother had similar history of blood transfusion requirements in early childhood but was asymptomatic subsequently. There was no consanguinity in the parents. In last 2 years, the patient had received blood transfusion 12 times with haemoglobin dropping to 6–7 gm%. A hematologic evaluation identified sideroblastic anemia on bone marrow examination. Next generation sequencing on the extracted DNA from blood revealed a homozygous variant in exon 3 of gene PUS1,(chromosome 12:g.131932301 C>T c.430 C>T). A missense variant "C" to "T" detectd at nucleotide 430 leading to change in amino acid sequence from Arginine to Tryptophan at codon 144 that was highly pathogenic. The same variation was validated using Sanger sequencing (Fig 1a).

When presented to cardiology services, the patient was dyspnoeic, with tachycardia, and systemic desaturation. Her Arterial blood gases showed pH 7.46, pO2-46 mm Hg, pCO2 38 mm Hg, serum lactate 2.5 mmol/L. The serum electrolytes, renal and liver functions were normal. The Creatine Phosphokinase was 46 U/L (normal-29-168 U/L), and serum ferritin was 1598 ng/ml (normal-20-200ng/ml). The serum uric acid was 8.8 mg/dl. Abdominal ultrasound showed a single spleen. The ECG showed right ventricle hypertrophy, and the echocardiogram showed significant pulmonary arterial hypertension with mild tricuspid regurgitation. Contrast echocardiogram did not show any evidence of a right to left shunt or pulmonary arteriovenous fistula. The left

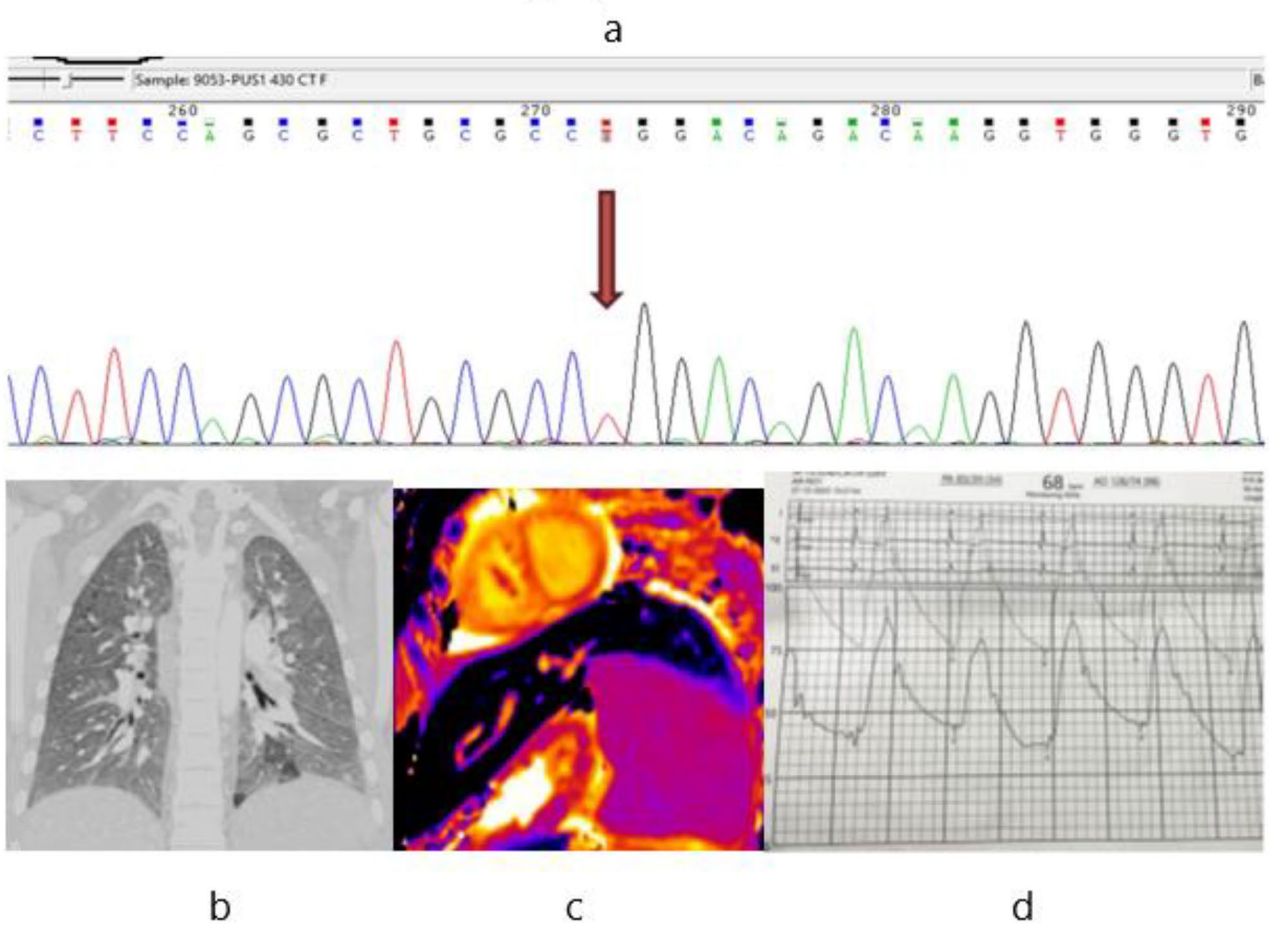

Fig. 1 **a**: Sanger sequencing (electrophoregram)showing the homozygous nucleotide change C>T at c.430 in PUS1 gene. The variation was confirmed by sequencing with both forward and reverse primers. **b**: Coronal CT image (lung window) showing dilated pulmonary arteries and mosaic attenuation with tiny cysts in the periphery. **c** - T1 myocardial map sagittal oblique image depicting the decrease T1 values of the liver parenchyma (408ms; reference mean normal value for same age and gender:820 ms) suggestive of iron deposition within the liver parenchyma (yellow asterisk). **d**: shows aortic and pulmonary artery pressure tracings during cardiac catheterisation. Pulmonary artery pressure is 83/39(54) mm Hg on 100% oxygen by mask. Aortic pressure is 126/74(96) mm Hg

ventricular systolic function was normal, but the right ventricle was mildly dilated and showed reduced contractility. After stabilisation, she underwent a chest CECT that showed features of pulmonary hypertension with ground glass and mosaic perfusion in the lung fields, but was not otherwise diagnostic of any specific entity (Fig 1b). There was no evidence of pulmonary thromboembolism. Patient could not cooperate for pulmonary function tests or DLCo measurement due to dyspnoea. Tests for autoimmune disorders were negative. A cardiac MRI showed mild iron overload in the liver, but there was no obvious myocardial iron overload (Fig. 1c). Cardiac catheterization documented severe PAH with pulmonary artery pressures of 114/58(78) mm Hg and aortic pressure of 120/75(96) mm Hg. (Fig. 1d). On 100% oxygen with mask, the Pulmonary artery pressures dropped to 83/40(54) mm Hg. The Left ventricular end diastolic pressure was 10 mm Hg and the right atrial pressures were 14 mm Hg. The calculated Pulmonary vascular resistance index was 19 wood units.mm2 on room air that dropped to 12 wood units on Oxygen. Vasoreactivity testing with nitric oxide was not done due to non availability, but the pulmonary arterial pressures were responsive to oxygen. The patient was treated with pulmonary vasodilator therapy with ambrisentan and tadalafil, and amlodepin (in view of oxygen responsiveness). She continued to be symptomatic requiring low flow oxygen to maintain oxygen saturation. The oxygen saturation on room air would drop to 75-84% without any hypercarbia. Her transfusion requirements were intermittent, and empirical treatment with pyridoxine, and danazol did not change it remarkably. The patient was evaluated for a bone marrow, and lung transplant, but the family declined the same.

Discussion and conclusion

We document severe PAH in a patient with PUS1 mutation and congenital sideroblastic anemia. Hemolysis associated pulmonary hypertension is well known in patients with sickle cell anemia, B thalassemia, paroxysmal nocturnal hemaglobinuria, and congenital dyserythropoietic anemia ; diseases associated with intravascular hemolysis and ineffective erythropoiesis. However, severe PAH in patients with congenital sideroblastic anemia is not recognised. The PAH in our patient was disproportionately high and a main clinical facet. The mechanisms of pulmonary hypertension in hemolytic anemia may be multiple and are being investigated. Nitric oxide deficiency from the intravascular hemolysis, vascular injury from hemolysis induced release of adenosine deaminase and arginase from red blood cells, and post capillary pulmonary hypertension from left ventricular dysfunction due to iron overload and anemia are some of the postulated mechanisms. In addition, there could be increased TGFb pathways in some MLASA [2].

PAH is integral part of the rare HUPRA syndrome (hyperuricemia, pulmonary hypertension, renal failure and alkalosis) that results from mutation in seryl t RNA synthase 2 gene (SARS-2 gene) affecting mitochondrial t RNA functioning [2]. Patients with the mutation in YARS-2 gene, a MLASA-2 syndrome have respiratory difficulties, but donot have prominent PAH [1]. Pseudouridylation is the most abundant modification found in RNA and has wide pathogenetic importance. Whether any common link in PUS1 mutation and seryl t RNA functioning that might result in PAH is speculative.

MLASA are very rare disorders but provide opportunities to uncover basic pathophysiological clues for disease states. Although involving mitochondrial function, the phenotypic variability in clinical features might result from compensatory changes involving ribosomal proteins and also from pleiotropic effects of the involved genes. Even so, severe PAH in PUS1 mutation and in SARS-2 mutation that involve t-RNA function may be important from the pathogenesis of PAH. The sMAD signalling is increased in patients with haemolytic anemia. The SARS2 gene has been shown to influence VEGF and hence the pathways of PAH. Similar role of PUS1 gene needs to be explored.

Seryl t RNA modulates VEFGA functioning [3] that interacts with SMAD signalling and might be influential in causing PAH. Amelioration in pulmonary hypertension and anemia are reported with the use of recombinant fusion proteins that reduce SMAD signalling in congenital sideroblastic anemia [4], as well as in idiopathic PAH [5]. Whether there could be any cross talk between the Smad signalling pathways that are important for PAH pathogenesis and PUS1 related post transcriptional alterations can only be speculated at present but might have therapeutic potential for the rare MLASA disorders.

Conclusion

we document severe pulmonary arterial hypertension in a patient with PUS1 gene mutation causing congenital sideroblastic anemia that has not been previously reported. We speculate that there could be a crosstalk between SMAD signalling and PUS1 related post transcriptional alterations as a cause for pulmonary arterial hypertension.

Abbreviations

MLASA	Myopathy, lactic acidosis and inherited sideroblastic anemia
HUPRA	(hyperuricemia, pulmonary hypertension, renal failure and alkalosis)
PAH	Pulmonary arterial hypertension

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Author contributions
SSK synthesised the idea and wrote the Ms. JS, VS, RC, RP were involved in clinical care of the patient and contributed critically to the Ms.SV did the genetic testing. All authors read and approved the Ms.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Consent for publication
Written informed consent for the clinical details to be published is available from both the parents.

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
Ethical approval and review was waived off as it is a single case report as per our local ethical committee requirements.

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