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Luspatercept in myelodysplastic syndrome with ring sideroblasts: a case report of intrapulmonary vascular dilatation syndrome causing protracted inexplicable hypoxia

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Running head: Luspatercept MDS-RS: case of IPVD

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Myelodysplastic syndrome with ring sideroblasts (MDS-RS) is an MDS subtype characterized by ineffective erythropoiesis leading to profound anemia.[1] It is frequently associated with pathogenic SF3B1 mutations and lower risk disease.[2] Morphologically, the bone marrow demonstrates erythroid precursors with abnormal mitochondrial iron accumulation.[3] Today, red blood cell (RBC) transfusion dependent MDS-RS patients with SF3B1 mutations are commonly treated with Luspatercept and achieve transfusion independence lasting eight weeks or longer at a rate of 38% when used after erythroid-stimulating agent failure.[4,5] This case report describes a patient with MD-RS who was successfully treated with Luspatercept, achieving durable transfusion independence, but then developed hypoxia due to intrapulmonary shunting attributed to Luspatercept. The case report was written in accordance with the ethical standards of Canada. Informed consent was obtained from the patient.

The patient is a gentleman in his 80s diagnosed with MDS-RS and unilineage dysplasia in August 2015. Karyotype from a bone marrow biopsy/aspirate completed in November 2020 was notable for a 20q deletion. Samples had been banked and when next generation sequencing was available, he was confirmed to harbour an SFB31 mutation. The mutation was a single nucleotide variant, NM_012433.4:c.2098A>G (p.Lys700Glu), variant allele frequency 43%. At the time of diagnosis, the patient was deemed low-risk by the Revised International Prognostic Scoring System. His EPO level was 57.9 mU/mL and his hemoglobin ranged between 100 and 110 g/L. Between diagnosis and January 2021, the patient was treated with increasing doses of Epoetin alfa monotherapy for symptomatic anemia and maintained a hemoglobin level between 90 and 100 g/L. By January 2021 his hemoglobin dropped below 80 g/L despite 80,000 units of weekly Epoietin alfa. He commenced regular RBC transfusions of 2 units every two weeks for symptomatic anemia. His Epoetin alfa was discontinued. Once funded in Ontario, Canada, the patient commenced Luspatercept in June 2021 and the dose was quickly escalated to 1.75 mg/kg. He achieved and maintained transfusion independence while on Luspatercept as of September 2021 with hemoglobin ranging between 90 and 100 g/L.

On August 12th 2024, the patient presented to hospital with symptoms of fever and shortness of breath. He was admitted to the intensive care unit (ICU) with hypoxemic respiratory failure secondary to a community acquired pneumonia. His peak oxygen requirements in the ICU were high-flow nasal cannula at 50 liters per minute (LPM) and 60% FiO2. He was treated with empiric antibiotics and steroids. He improved clinically and was transferred to the ward after 5-days. While his oxygen requirements improved overall, the patient remained hypoxic. He required 2 to 4 liters per minute (LPM) at rest. There was evidence of platypnea orthodexia syndrome as his oxygen requirements would increase up to 6 LPM upright and 10 LPM with exertion.

Respirology was consulted on August 27th, 2024. An arterial blood gas (pH 7.45/$PaCO_2$ 30 mmHg/PaO_2 71 mmHg) demonstrated a markedly elevated A-a gradient of 205.2 (approximated with an FiO2 of 44% while on 6 LPM). The differential diagnoses for the persistent hypoxia and elevated A-a gradient included V/Q mismatch, hepatopulmonary syndrome, right-to-left shunting, and intrapulmonary shunting. A CT Chest ruled out pulmonary embolism, large pulmonary arteriovenous malformations, and showed radiographic improvement of his prior pneumonia consolidations. An abdominal ultrasound was negative for findings suggestive of hepatopulmonary syndrome. A transthoracic echocardiogram (TTE) with contrast returned abnormal with grade 2+ bubbles in the left heart after 2 to 3 cardiac cycles, followed by grade 3+ bubbles after 5 cardiac cycles. These findings were in-keeping with a moderate (grade 3) right-to-left shunt. A cardiac MRI demonstrated normal right-sided heart function with no evidence of an intracardiac shunt. These investigations were completed by August 30th.

On September 2nd the patient developed symptoms of a viral illness and tested positive for COVID-19, presumably acquired in hospital. He was treated with x5 days of Remdesivir and Dexamethasone. Even with COVID-19 treatment and resolution, his oxygen requirements were unchanged at 2 to 4 LPM at rest and 10 LPM with exertion. At this point, with no clear cause identified, Respirology felt that his dyspnea and hypoxia were multifactorial and due to his MDS-RS related anemia, ICU admission for pneumonia, and COVID-19 infection. They recommended that he continue with physiotherapy and incentive spirometry to improve his respiratory function over time. The patient was discharged home on September 11th with home oxygen and outpatient follow-up. He continued to receive his Luspatercept every 3 weeks and was maintaining a hemoglobin between 80 to 90 g/L.

Unfortunately, the patient required re-admission on September 13th due to ongoing symptoms of shortness of breath in the absence of infectious symptoms. Further investigations were pursued to determine the etiology of his right-to-left shunt and hypoxia. A transesophageal echocardiogram (TEE) demonstrated an intermediate sized patent foramen ovale (PFO). However, a PFO of this size was unlikely to explain this degree of hypoxia with symptom onset later in life. Nevertheless, he underwent right heart catheterization, which demonstrated no significant bubbles and RV pressures of 33/7 mmHg, confirming that the right-to-left shunt was not PFO mediated. With no plausible cardiac cause for his right-to-left shunt, an intrapulmonary etiology was suspected. An oxygen shunt study was completed, demonstrating a rise from a PaO_2 of 47 mmHg on room air to 169 mmHg with administration of 100% oxygen, confirming a large shunt. With investigations thus far negative for alternative causes, the right-to-left shunt was attributed to intrapulmonary vascular dilatation syndrome (IPVD). The timeline and investigations are summarized in Figure 1.

It was hypothesized that the IPVD was related to the Luspatercept and perhaps unmasked by the prior pneumonia. Luspatercept was held commencing September 26th. The patient was discharged home on September 30th with home oxygen at moderate to high rates. He had complete resolution of his hypoxia and platypnea orthodeoxia syndrome after missing two doses of Luspatercept (6 weeks). He achieved oxygen saturations of >95% on room air.

Respirology repeated investigations as an outpatient in June 2025 to reassess for right-to-left shunting. The patient completed a 6-minute walk test on room air and demonstrated normal pulse oximetry. A repeat TTE with contrast demonstrated marked improvement with only grade 1 right-to-left shunting, conceivably a false positive or physiologic finding. In addition to the clinical resolution of his hypoxia, these investigations confirmed physiologic resolution of the right-to-left shunt. Unfortunately, within two weeks of discontinuing Luspatercept, the patient resumed RBC transfusion dependence at a rate of 2 units every two weeks and remains transfusion dependant today.

Luspatercept is an Activin Receptor Type IIB (ACTRIIB) fusion protein, which acts as a ligand trap for transforming growth factor beta (TGF-β) family of ligands.[6] TGF-β family ligands are ligands for activin receptors, a type of serine/threonine kinase receptor.[7] Activin receptors are involved in a broad range of cellular functions, including cell growth and cell differentiation. Relevant to MDS, Luspatercept prevents TGF-β family ligands from binding endogenous ACTRIIB and blocks downstream SMAD2/3 signaling, which interferes with late-stage erythroid maturation. Disruption of this pathway by Luspatercept enables erythroid maturation and effectively improves anemia/transfusion dependence in MDS patients.[8] MDS-RS patients with SF3B1 mutations are particularly responsive.[7,4]

Bone Morphogenetic Proteins (BMP) are members of the TGF-β superfamily and also targeted by Luspatrercept.[7] Animal models deficient in BMP-9 have demonstrated the development of IPVDs and

hypoxia due to impaired activin receptor signaling, highlighting the role of BMP in maintaining normal pulmonary vasculature.[8,9] Disruptions of TGF-β/SMAD and related BMP signaling pathways have been implicated in disorders characterized by pulmonary vascular malformations, such as hemorrhagic hereditary telangiectasia.[10,11] TGF-β/SMAD and related BMP signaling pathways are key regulators of blood vessel development and mutations affecting these pathways can result in abnormal vascular proliferation and dilatation.[12] We hypothesize that disruptions to the TGF-β and related BMP signaling pathways by Luspatercept resulted in the development of IPVD, unmasked by the patient's infectious/inflammatory insult. Microscopic pulmonary vascular malformations and IPVD could explain the intrapulmonary shunt and hypoxia observed in the patient. In support of this, Sotatercept, an activin signalling inhibitor used for the treatment of pulmonary arterial hypertension, had been shown to induce telangiectasis in up to 10% of patients.[13]

In the MDS literature related to Luspatercept, the phase 2 dose finding study did not report respiratory symptoms or hypoxia as a treatment-emergent adverse effect.[4] In the phase 3 study, grade 3-4 severity dyspnea was reported as an adverse event experienced by 15% of patients, but there were no reports of hypoxia and anemia as competing causes.[5] Literature review identified two recent case reports that documented severe but reversible hypoxia with features of platypnea-orthodexia syndrome due to intrapulmonary shunting and IPVD in patients with MDS on Luspatercept.[14,15] Similar to our case, both case reports documented a comprehensive diagnostic work-up to rule-out alternative etiologies and resolution of the hypoxia occurred within 6-8 weeks of discontinuing Luspatercept. Together, these case reports support a drug-induced mechanism of hypoxia by Luspatercept.

IPVD syndromes triggered by Luspatercept may be extremely rare adverse events or clinically undetectable in most patients. Nevertheless, physicians should be mindful of this potential pathophysiology in cases of protracted inexplicable hypoxia in patients with MDS treated with Luspatercept.

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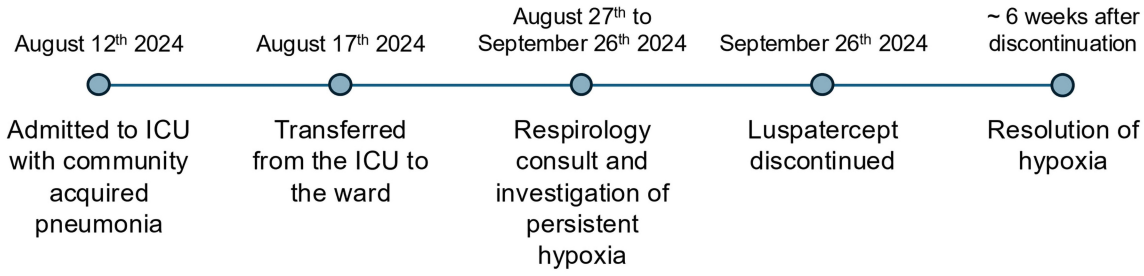
Figure 1. Timeline and diagnostic evaluation of hypoxia. (A) Clinical timeline of events. (B) Arterial blood gas results that demonstrated an elevated A-a gradient. (C) Key findings of pertinent investigations completed to rule out alternative causes of hypoxia and right-to-left shunt.

A



B

ABG on FiO_2 of 44%	
pH	7.45
$PaCO_2$	30 mmHg
PaO_2	71 mmHg

A-a gradient of 205 mmHg

C

CT Chest	Abdominal US	TTE with contrast	Cardiac MRI	TEE	Rt heart cath
○ Negative for pulmonary embolism ○ Improvement of prior pneumonia consolidations	○ Negative for findings suggestive of hepato-pulmonary syndrome	○ Moderate (grade 3) right-to-left shunt	○ Normal right-sided heart function ○ No evidence of intracardiac shunt	○ Intermediate sized patent foramen ovale	○ RV pressure 33/7 mmHg ○ No significant bubbles, PFO unlikely to be causing shunt