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Atypical presentation and management of a neonate with alveolar capillary dysplasia: A case report

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May 01, 2024

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To the Editor,

Alveolar capillary dysplasia with misalignment of capillary veins (ACD/MCV) is a rare interstitial lung disease caused by maldevelopment of alveoli and capillaries. Neonates typically present with intractable pulmonary hypertension within the first 48 hours of life and have a very short life expectancy [1]. However, atypical cases have been described with a late, less fulminant clinical presentation and prolonged survival on pulmonary vasodilators, providing a window for bilateral lung transplantation [2].

Case presentation

Our patient is a female neonate born at 37 weeks of gestation, weighing 3080 gr after an uncomplicated pregnancy. She was admitted to the neonatal intensive care unit (NICU) at the age of two hours due to pneumothorax, which was managed conservatively and absorbed. On the second day of life, she was intubated due to worsening respiratory distress. Over the next several days, unsuccessful extubation trials were attempted. Eventually, she was weaned off oxygen on the 11th day. However, on postnatal day 16, significant respiratory deterioration was noted. Echocardiography revealed moderate pulmonary hypertension, and sildenafil and dopamine were initiated. The patient's clinical condition and echocardiography findings gradually deteriorated. High-frequency oscillatory ventilation (HFOV) was commenced with a fraction of inspired oxygen (fiO2) up to 1.0. As our patient continued to deteriorate (maximum oxygenation index OI:32 on day 23), we used intravenous iloprost as a pulmonary vasodilator, titrated up to 20 ng/kg/min in combination with levosimendan up to 0.1 mcg/kg/min, to improve cardiac contractility and reduce afterload and pulmonary resistance. Of note, nitric oxide was unavailable in our center at this time. Although gradual improvement in pulmonary hypertension was noticed, our patient developed severe pulmonary edema, which was managed with a continuous intravenous infusion of furosemide titrated up to 0.4mg/kg/h. Intravenous medications were gradually withdrawn, and we could switch to conventional ventilation on the day of life 34. The infant was extubated ten days later.

Computed tomography of the lungs showed bilateral symmetrical ground-glass opacification, and genetic testing with whole exome sequencing (WES) revealed a heterozygous missense variant of the FOXF1 gene (c.229T>C;p.Phe77Leu) in exon 1.

Our patient remained stable on a high-flow nasal cannula (HFNC) until the 68th day when she was rein-

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tubated, and echocardiography revealed severe pulmonary hypertension. On the 72nd day of life, she was transferred to another NICU at the request of her parents. She remained intubated, treatment with pulmonary vasodilators was continued, and finally, a tracheostomy was performed. She eventually died at five months of age. The parents have consent to report the medical details of the neonate.

Discussion

ACD/MPV is a rare and almost universally lethal condition caused by an abnormal development of the pulmonary blood vessels. The clinical picture of ACD/MVP resembles that of persistent pulmonary hypertension of the newborn (PPHN), and the initial therapeutic approach is similar. The response to pulmonary vasodilators is not sustained in typical cases, and despite escalating care, patients die in the neonatal period[3]. However, atypical cases with reactive pulmonary vasculature that overcame the pulmonary hypertension crisis with pulmonary vasodilators have rarely been reported, as in our case[1].

Various pulmonary vasodilators have been used to manage ACD/MPV, including inhaled nitric oxide (iNO), prostanoids, and phosphodiesterase (PDE) inhibitors [3]. Our center was not equipped with iNO, so we initially used PDE inhibitors. However, our patient progressively deteriorated. Eventually, she showed gradual improvement with high-dose intravenous iloprost and levosimendan.

The potential usefulness of prostacyclins in ACD/MPV cases has been described. It has been previously reported that these patients may benefit from higher-than-usual doses of intravenous epoprostenol[4]. We used intravenous iloprost, a synthetic analogue of PGI2, titrated up to 20ng/kg/min, well above the usual neonatal range, without significant adverse effects.

There is limited data regarding the use of levosimendan in neonates, mostly in cardiac surgery patients. A few case series have reported its use in neonates with heart failure and pulmonary hypertension without structural heart disease, concluding that it is safe and effective[5]. Our patient showed marked improvement with no side effects.

Despite improvement in pulmonary hypertension, our patient developed severe pulmonary edema, requiring continuous infusion of furosemide. This complication of pulmonary vasodilators in infants with ACD/MPV has been previously described and reinforces the diagnosis. It is probably due to combined capillary and post-capillary obstruction[1].

Histopathological examination is considered the gold standard for diagnosis. Characteristic histopathological features of the lung tissue include significantly reduced and misplaced alveolar capillaries, medial hypertrophy of the small pulmonary arteries, and misplaced pulmonary veins [2,3]. Although it has been proposed that atypical cases may be associated with an uneven distribution of disease and areas of normal lung parenchyma, the evidence is still inconclusive[1,2].

Genetic testing may obviate the need for a biopsy, which is not always feasible in critically ill patients. However, a negative result does not preclude the diagnosis. The FOXF1 gene, which encodes a transcription factor crucial for the lung and other organs' mesenchymal development, was found to be involved in the pathogenesis of AVD/MPV[1,3]. A heterozygous pathogenic variant in the FOXF1 gene was identified in our patient using WES.

Conclusion

ACD/MPV should be suspected in any infant presenting with severe hypoxemia and pulmonary hypertension without an apparent causative factor. As there is no curative treatment, managing these patients is challenging. However, some infants, as our patient, may benefit from pulmonary vasodilators to overcome pulmonary hypertension crisis, thus providing a time window for life-saving lung transplants. Inhaled nitric oxide, the only FDA-approved drug for neonatal pulmonary hypertension, can be used in patients with ACD/MPV, although it is not always effective and not universally available due to the high cost of equipment. Therefore, it is crucial to identify alternative agents that are both safe and effective for use in neonates. In our case, due to the unavailability of iNO, we had to use alternative off-label pulmonary vasodilators for neonatal use

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and dosages beyond the usual neonatal range. Our patient's pulmonary hypertension crisis was successfully resolved by levosimendan and high-dose intravenous iloprost without any adverse effects. These drugs may provide a therapeutic option for pulmonary hypertension in patients with ADV/MPV when iNO is ineffective or unavailable.

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Funding : This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.