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Case Report

Multipotent mesenchymal stromal cell therapy for a neonate with congenital diaphragmatic hernia and adhesive small bowel obstruction

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ABSTRACT

Background. In the last decade, therapy using multipotent mesenchymal stromal cells (MSCs) has offered hope for regenerating the lungs of preterm babies with chronic lung disease. Due to similar disease mechanisms, it is logical to explore the potential impact of MSC therapy on pulmonary hypoplasia in congenital diaphragmatic hernia. Furthermore, MSCs may also contribute to the regeneration of the intestines affected by adhesive small bowel obstruction in patients with congenital diaphragmatic hernia.

Case presentation. A female newborn, delivered at 32 weeks and six days gestational age, was diagnosed with a left congenital diaphragmatic hernia. After surgical repair and respiratory/nutritional support for 39 days, she was still dependent on a ventilator and total parenteral nutrition. Two MSC treatments were given a week apart: 10 million cells/kg intratracheally and 5 million cells/kg intravenously. She was extubated, and her enteral nutrition improved after the treatment. No side effects were detected. We present the first documented case using MSCs derived from the umbilical cord to simultaneously treat pulmonary hypoplasia and adhesive small bowel obstruction of congenital diaphragmatic hernia.

Conclusion. Although MSC treatment is very promising for pulmonary hypoplasia and adhesive small bowel disease of congenital diaphragmatic hernia, much more needs to be learned about potential side effects, appropriate dosage, and the optimal method of administration.

Key words: mesenchymal stromal cell, congenital diaphragmatic hernia.

Congenital diaphragmatic hernia (CDH) is one of the most challenging diseases of the neonatal period, with a mortality rate of up to 60%.[1] Pulmonary hypertension and pulmonary hypoplasia, leading to respiratory failure, are the significant causes of death. Long-term ventilatory support adds diffuse alveolar damage, inflammation, and interstitial fibrois to pulmonary hypoplasia.[2] There is little to offer newborns after birth, aside from managing pulmonary hypertension, providing ventilatory support / extracorporeal membrane oxygenation (ECMO), and offering nutritional support[3,4], Multipotent mesenchymal stromal cell (MSC) therapy has emerged as a promising approach for the regeneration of hypoplastic lungs in the last decade in preterm babies.[5] MSC therapy has also been used for the treatment of hypoplastic lungs in CDH antenatally in animal models.[6-8] Nevertheless, limited experience is conveyed postnatally, particularly among humans.[9]

Another severe cause of mortality and morbidity in patients with CDH is adhesive small bowel obstruction (ASBO), which occurs mainly

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after midline laparotomy and patch repair.[10,11] Increased circulating adhesion molecules in CDH patients with pulmonary hypertension seem to contribute to the process.[12] An 11 to 20% incidence of ASBO has been reported in CDH survivors.[13] Occasionally, ASBO progresses to necrotizing enterocolitis (NEC).[13,14] NEC may occur even before surgery.[15] It is one of a neonate's most significant life-threatening diseases.[16] Also, severe morbidities, like strictures, adhesions, cholestasis, short bowel syndrome, and neurological sequelae, are possible. Conventional treatment is limited to supportive care and, at times, surgery intervention.[17] MSC treatment has gained interest in treating NEC like other neonatal disorders.[18]

We present a case of a newborn with CDH, pulmonary hypoplasia, ASBO, and NEC who showed improvement following MSC treatment.

Case presentation

A female newborn born at 32 weeks six days gestational age with a birthweight of 2,000 grams was diagnosed with a CDH at 29 gestational weeks. She was intubated right after delivery and transferred to the neonatal intensive care unit. Her first chest X-ray is seen in Fig. 1. The abdominal and cranial ultrasounds, as well as the echocardiogram, showed no other associated anomalies. At four days old, she underwent surgery to repair a left diaphragmatic hernia. During the surgery, her stomach, spleen, cecum, ascending colon, transverse colon, and intestines were found in the left hemithorax. The left lung was hypoplastic, and a patch repair was performed. Following the surgery, she was placed on a high-frequency oscillator ventilator for eight days and then on synchronized intermittent mandatory ventilation (SIMV). A follow-up echocardiogram on the fourth day revealed a non-significant patent ductus arteriosus (PDA), which closed spontaneously after three days, and a patent foramen ovale (PFO). The pressure in the right ventricle, calculated from the tricuspid valve, was 40 mmHg. She had feeding intolerance for ten days and had ileal perforation (Fig. 2) on the 10th day, for which she had a second operation (primary repair). Two extubation attempts failed because of pulmonary hypoplasia, pneumothorax of the left lung, and ventilator-associated pneumonia. Minimal enteral feeding attempts failed, and an abdominal X-ray revealed pneumatosis intestinalis on the 31st day. The family was offered the option of MSC treatment. With the consent of the family and approval from the Republic of Türkiye Ministry of Health, Organ and Tissue Unit, MSCs were administered at doses of 10 million cells/kg intratracheally and 5 million cells/kg intravenously, twice on the 39th and 45th postnatal days. Fig. 3 illustrates the chest X-ray taken ten days after the initial treatment. The patient's respiratory, nutrition,

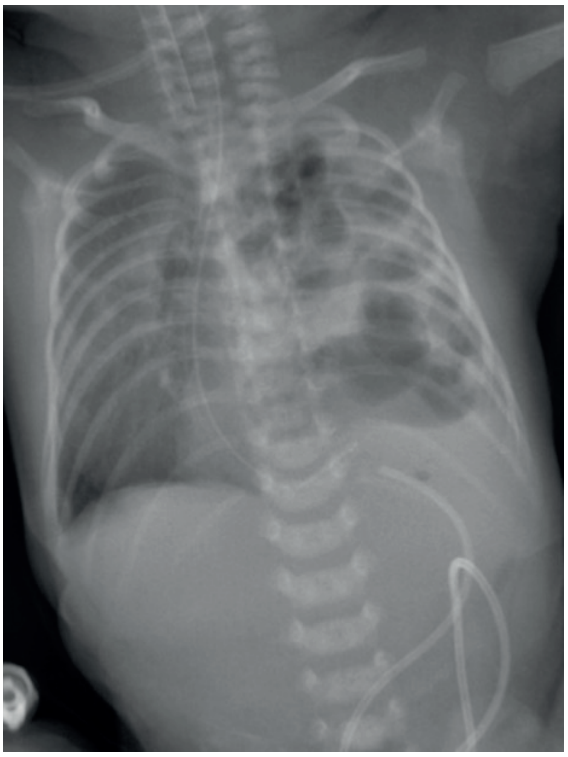

Fig. 1. The first radiographic imaging of the patient. The loops of the intestine are found in the left hemithorax, with the mediastinum shifted to the right. The umbilical catheter trace is displaced to the left due to the shifting of the abdominal organs. The abdominal cavity contains very little gas.

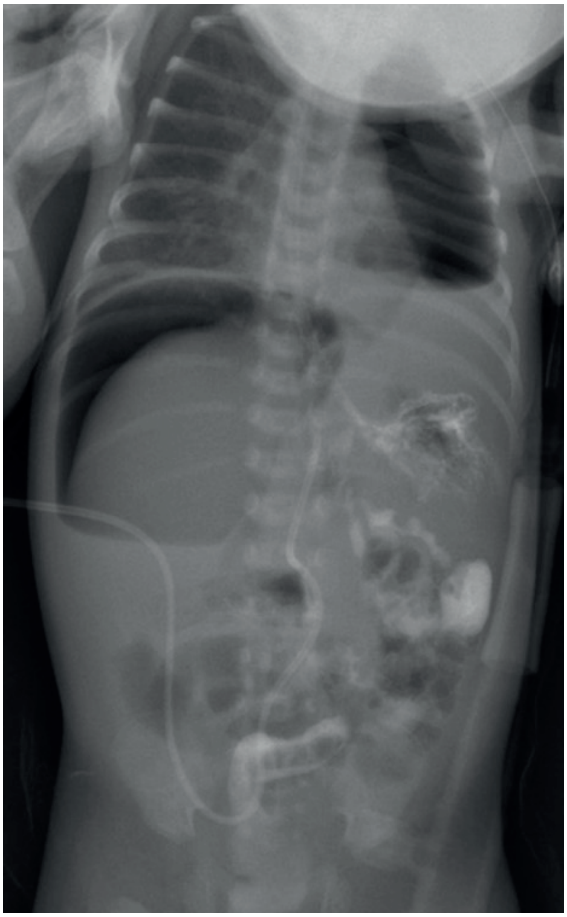

Fig. 2. The radiographic imaging of the patient on the tenth day. Subdiaphragmatic free air is present due to intestinal perforation. The left lung is hypoplastic, and the right lung appears hazy.

and clinical status before and after MSC treatment are seen in Fig. 4. The ventilation of both the left and right lung had improved, and the intestinal loops appeared normal. The patient was discharged on the 50th day.

Follow-up examinations at seven months revealed a minor delay in fine motor skills, and no tumors were found on a computed tomography (CT) scan of the chest or on abdominal ultrasound. The family provided written informed consent to publish this case report.

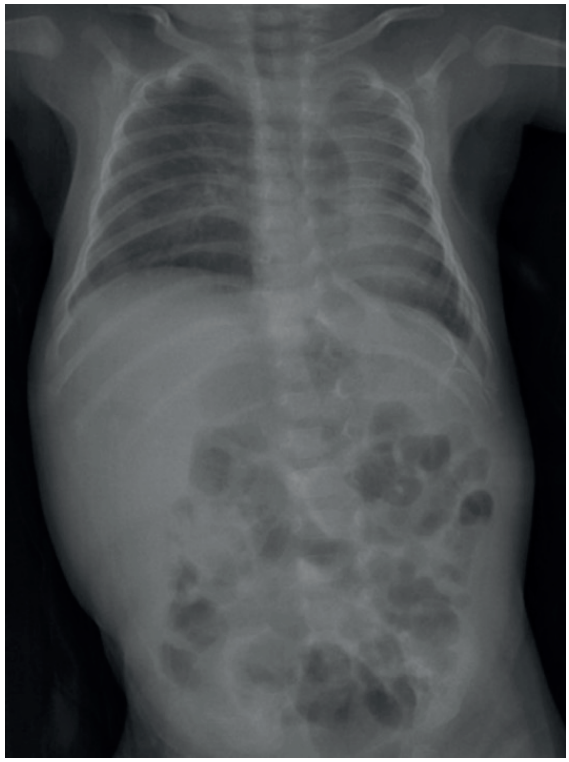

Fig. 3. The patient's radiographic imaging after ten days of the initial mesenchymal stromal cell treatment. The ventilation of both the left and right lung has improved. The appearance of the intestinal loops is normal.

Discussion

Mesenchymal stromal cells (MSCs) hold tremendous potential in regenerative medicine. MSCs offer numerous benefits, including anti-inflammatory, anti-apoptotic, anti-oxidative, anti-fibrotic, pro-angiogenic, and anti-microbial effects. They can transform into damaged tissue cells and treat various medical conditions.[19] Mesenchymal stromal cells have broad biodistribution and poor homing efficiency to most target tissues because they are plastic adherent and entrapped in other organs' capillaries.[20] Their primary regeneration method involves releasing regenerative compounds such as cytokines, growth factors, and microRNAs, crucial to the

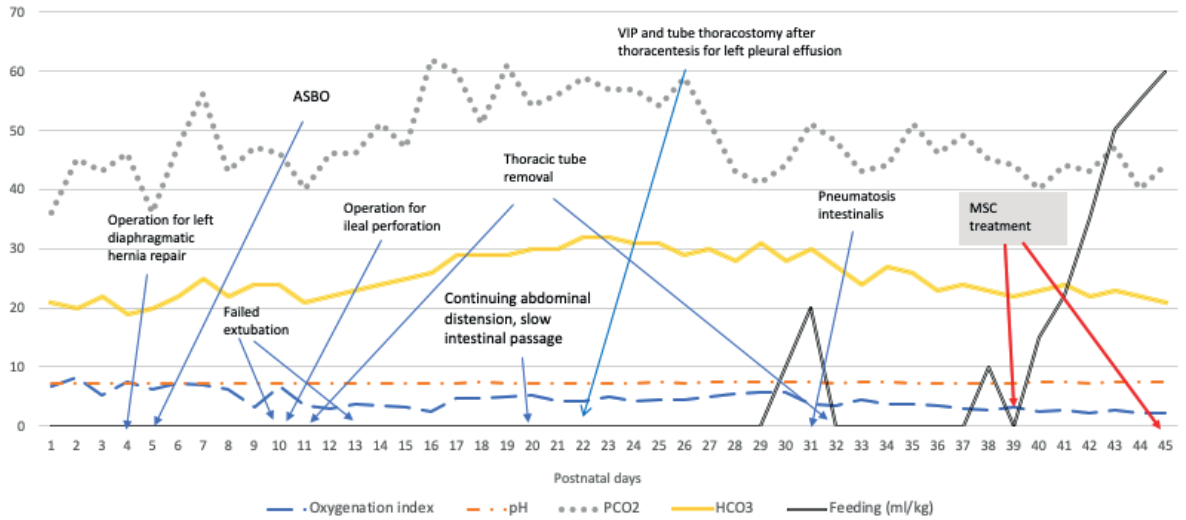

Fig. 4. The patient's respiratory, nutrition, and clinical status before and after MSC treatment.

ASBO, adhesive small bowel obstruction; CPAP, continuous positive airway pressure; HCO_3, bicarbonate (mEq/L); HFO, high-frequency oscillation; MSC, mesenchymal stromal cell; PCO_2, partial carbon dioxide pressure (mmHg); SIMV, synchronized mandatory ventilation; VAP, ventilator-associated pneumonia.

body's natural healing processes. So, despite poor engraftment, MSCs are still effective.[21] There are several ways to increase engraftment and improve the therapeutic effect, such as administering multiple doses, delivering MSCs close to the targeted organ, and priming MSCs with hypoxia or biochemical agents to increase homing.[22-25] Entrapment primarily occurs in the lungs[26], which is advantageous when the lung is the desired site.

Therefore, intravenous and endotracheal routes have proven successful in treating chronic lung disease in preterm babies such as bronchopulmonary dysplasia (BPD). In a phase II trial, MSC treatment for BPD successfully used a dose of 1x10 million cells/kg administered intratracheally. Clinical trials have shown that an IV dose of 1-10 million/kg MSC is also effective for treating BPD. Up to three doses have been used for the treatment of BPD.[5] A recent meta-analysis revealed that MSC therapy also shows promise for treating NEC. However, more data is needed regarding the optimal dose or timing of MSC treatment in NEC for humans.[18] In a specific case of a patient who was born preterm at 32 weeks and had been on a ventilator for 46 days, MSC treatment was the only option to treat both lung and small bowel conditions simultaneously. Patients with respiratory failure associated with pulmonary hypoplasia and pulmonary hypertension in CDH may also benefit from MSC treatment, given the shared pathophysiology of BPD and CDH.[27,28] Also, it is reasonable to explore the potential use of MSC treatment in treating ASBO progressing to NEC due to its promising results in treating NEC in animal studies.[18] As a result, we decided to administer 1x10 million cells/kg intratracheally and 5 million cells/kg intravenously to target both the lungs and intestines and overcome lung capillary entrapment.

The patient experienced prolonged difficulty tolerating feeding due to ASBO and was unable to be taken off the ventilator because of abdominal distension and pre-existing pulmonary hypoplasia. This led to a cycle of recurrent infections and pneumothoraces. Arterial blood gas tests revealed increasing bicarbonate levels, similar to those in patients with BPD. Following the initial MSC treatment, the patient's feeding tolerance improved. Subsequently, a gradual decline in bicarbonate levels was noted. After the second treatment, the patient was successfully weaned from the ventilator, and the total parenteral nutrition

was discontinued (Fig. 3). At seven months old, she weighs 8 kg with no residual respiratory or nutritional deficiencies. According to age-appropriate developmental standards, her results on the Denver neurodevelopmental test fall within the normal range except for a minor delay in fine motor skills. A follow-up computed tomography of the chest at seven months revealed well-expanded lungs. This is the first documented case of successfully treating pulmonary hypoplasia and ASBO/NEC simultaneously in CDH patients.

When considering potential side effects, it is essential to note that MSCs do not have major histocompatibility complex antigens, which helps to reduce concerns related to graft-versus-host disease. However, there have been reports of thromboembolism in adult patients and a microembolism phenomenon in a newborn after amnion-derived MSC transfusion.[29,30] Ongoing concerns persist regarding potential tumorigenicity, especially with repeated doses, even though MSC therapy is also used in tumor treatment.[31,32] However, human MSCs from the umbilical cord showed no signs of malignant transformation after up to 15 passages in vitro.[33] Umbilical cord-derived MSC therapy may also be a source of viral and mycoplasma infections, as it is a blood product.[34] To the best of our knowledge, no long-term side effects have been reported in newborns. In our specific case, no adverse effects were observed, and a chest CT scan at seven months of age did not reveal any tumors. The use of MSC exosomes (acellular therapy) for BPD has gained recent interest due to concerns regarding the potential adverse effects of MSCs and the observation that MSCs primarily exert their regenerative effects through paracrine signaling. Acellular therapy has been found to exhibit similar effects as MSCs.[35] We only had access to cellular MSC therapy, but acellular therapy may also benefit CDH and related complications. It is uncertain whether this particular patient would have been able to discontinue using the ventilator or TPN without the therapy. Additionally, the optimal dosage and the contribution of MSC therapy to long-term outcomes of CDH are currently unknown. Nevertheless, we advocate for further investigations of MSC therapy for CDH patients. Given the lack of data, we hope this case will encourage additional research.

Ethical approval

The competent authority (Republic of Türkiye Ministry of Health, Organ and Tissue Unit) approved the stem cell therapy used in the patients presented in this article. The family provided written informed consent to publish this case report.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: ŞY; data collection: ŞY; analysis and interpretation of results: ŞY, AK; draft manuscript preparation: ŞY, AK. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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