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LETTER TO THE EDITOR

PEDIATRIC PULMONOLOGY WILEY

Nonmyeloablative hematopoietic stem cell transplantation in a patient with hereditary pulmonary alveolar proteinosis

To the Editor,

Pulmonary alveolar proteinosis (PAP) is a syndrome characterized by the abnormal accumulation of alveolar surfactant protein in alveolar spaces, which interferes with gas exchange.[1] PAP is a heterogeneous group of disorders classified as primary (autoimmune and hereditary), congenital, and secondary PAP. Hereditary PAP is detected in children related with mutations in genes encoding macrophage granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor subunits (CSF2RA-CSF2RB).[1]

Here, we report an 18-year-old boy with the CSF2RA mutation who had a very severe course and responded well to allogenic hematopoietic stem cell transplantation (HSCT), but died 8 months posttransplant of pneumoniae and sepsis while under intense immunosuppression due to graft-versus-host disease (GVHD). The patient was diagnosed as having PAP at 4 years of age through a histopathologic examination of lung biopsy. He was the second child of consanguineous parents. PAS-positive material accumulation was observed in biopsy and bronchoalveolar lavage (BAL) materials. Chest X-ray showed bilateral opaque consolidation. Chest computed tomography (CT) scanning showed diffuse ground-glass opacity with interlobular septal thickening. GM-CSF autoantibody was negative and CSF2RA mutation was detected (homozygous deletion of exons 2–13 of the CSF2RA gene) in Molecular Genetics Laboratory, Institute of Laboratory Medicine, Singen/Germany, proved the diagnosis of hereditary PAP. Father and mother of him did not carry this mutation and the pedigree of the family is shown in Figure 1. Lung lavage therapy via flexible bronchoscopy had started since his first diagnosis, which had been performed at least four times per year for 14 years. Due to worsening pulmonary symptoms, he had been receiving lung lavage every 1 or 2 months for the last 2 years. Pulmonary function tests (PFT) revealed decreasing pulmonary capacity with worsening restrictive findings (FEV1:18%, FVC:14%, FEV1/FVC:117%). Oxygen therapy was initiated at 2 L/min, which was increased to 4 L/min at his last visit. A decision was made to perform HSCT with a purpose of getting functional macrophages from the donor, which might stabilize or improve pulmonary symptoms because of the worsening pulmonary findings despite continuing lung lavages. With special permission from the national and other health authorities, this experimental transplant was performed in June 2017 from his human leukocyte antigen (HLA) 10/10-matched father. Two doses of bone marrow–derived mesenchymal stem cells (MSCs) from the same donor were given intravenously 3 weeks apart (before conditioning and at Day 0, 4 h before HSCT) to support the regenerative capacity of the lung, and to subside the ongoing inflammation in the lungs, both of which would help to enhance the engraftment and success rate of allogeneic HSCT.

A reduced intensity conditioning (RIC) regimen was chosen to decrease the transplant-related toxicity and the risk of mortality because of his significant comorbidities, including impaired lung function, pulmonary hypertension, and the risk of invasive infections. A conditioning regimen consisting of fludarabine (30 mg/m^2/d for 5 days), melphalan (70 mg/m^2/d for 2 days) and antithymocyte globulin (ATG-Fresenius: 7.5 mg/kg/d for 4 days) was administered. Cyclosporine A and methotrexate were used for GVHD prophylaxis.

Neutrophil and platelet engraftment were achieved on day + 14 and day + 38, respectively. Whole blood chimerism analysis showed 94% and 96% donor profile on day + 23 and + 170, respectively. Interestingly, a significant improvement of breath sounds was evident on the day of neutrophil engraftment and his oxygen requirement gradually decreased. His exercise capacity increased gradually and he no longer required continuous oxygen therapy except for pulmonary infection periods. On his chest X-ray, alveolar infiltration disappeared.

His chest X-ray and CT at just before HSCT, 3 months of HSCT, are shown in Figure 2A–D. He no longer needed bronchoalveolar lavage because BMT and BAL fluid was clear at the bronchoscopy performed at posttransplant + 4 months.

During the posttransplant period, he developed Grade II-III acute GVHD (skin and liver involvement) and received cyclosporine, steroids, and mycophenolate mofetil. Cytomegalovirus (CMV) reactivation was also observed during the same period. On Day + 75, he developed cytopenia, which was attributed to CMV infection and/or acute GVHD. At posttransplant day + 100, he had a symptom of hoarseness and was diagnosed as having biopsy-proven vocal cord aspergillus infection associated with pulmonary nodules. On Day + 210, he was hospitalized with worsening pneumoniae and died a month later of sepsis and multiorgan failure despite antifungal, antibacterial treatment, and mechanical ventilatory support.

In hereditary PAP, because of the genetic deficiency and diminished expression or function of the alpha or beta subunits of the GM-CSF receptor, alveolar macrophages are unable to remove the surfactant lipoproteins from the alveolar space. There is no known curative therapy of congenital and hereditary PAP to date. Therapeutic lung lavage has been the only treatment option for PAP since 1963.[1]

Some experimental studies have been performed in animal models studying the effect of HSCT therapy in PAP.[2,3] In macrophage transplantation studies conducted in animals, Trapnell et al.[1]

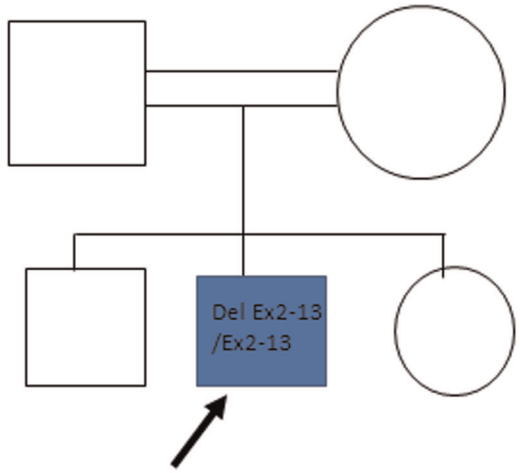

FIGURE 1 Family pedigree of the patient

found that transplanted macrophages persisted for more than 1 year after transplantation and retained therapeutic efficacy throughout this period. Clinical trials on pulmonary macrophage transplantation in patients with hereditary PAP is being planned.[1] In the literature, there are two case reports in which HSCT in hereditary PAP is described. The first was about a patient with GM-CSF-Rα-deficient PAP who underwent HSCT and died of a viral infection before full immune reconstruction.[4] The other case report is about a child with mutations causing CSF2RA allele loss and underwent HSCT from an HLA-matched unrelated donor at the age of 6.3 years. Curative treatment was achieved in this case with successful HSCT.[5]

In the present case, he was diagnosed with hereditary PAP because of detected CSF2RA mutation and negative GM-CSF autoantibody. The protein encoded by this gene is the alpha subunit of the heterodimeric receptor for colony-stimulating factor 2, which controls the production, differentiation, and function of granulocytes and macrophages. Hematopoietic stem cell transplantation was performed for our patient due to his progressive lung disease and severe respiratory failure despite lung lavages for 14 years. Moreover, myeloablative HSCT may further aggravate respiratory insufficiency and pulmonary hypertension, and may lead to an increased risk for infection. Therefore, in this case, an RIC regimen was chosen to decrease transplantation-associated comorbidity with the goal of obtaining functional macrophages. Moreover, it was speculated that the achievement of mixed chimerism would be sufficient to ameliorate pulmonary symptoms. The posttransplant course was complicated by multiple infections including CMV viremia, aspergillosis, and viral respiratory infections, Grade II-III GVHD with occasional episodes of exacerbation, and pneumonia and sepsis that eventually led to death. Acute GVHD is the leading cause of mortality and morbidity in HSCT setting.[6,7] The likelihood of GVHD is directly related to the degree of HLA disparity between patients and donors, but moderate to severe acute GVHD occurs in roughly 40% of patients receiving HLA-identical grafts.[6] Even in HLA identical siblings who have the lowest risk for GVHD, the incidence of Grade II–IV GVHD was found as 28% in a large registry-based study.[7]

In the present case, the significant improvement in the respiratory status and successful engraftment after transplantation suggest that allogeneic HSCT with an MSC cotransplant may be considered as a promising treatment option in patients with PAP. Further studies are needed on macrophage transplantation or genetically corrected patient-specific monocytes and macrophage transplantation in congenital PAP.

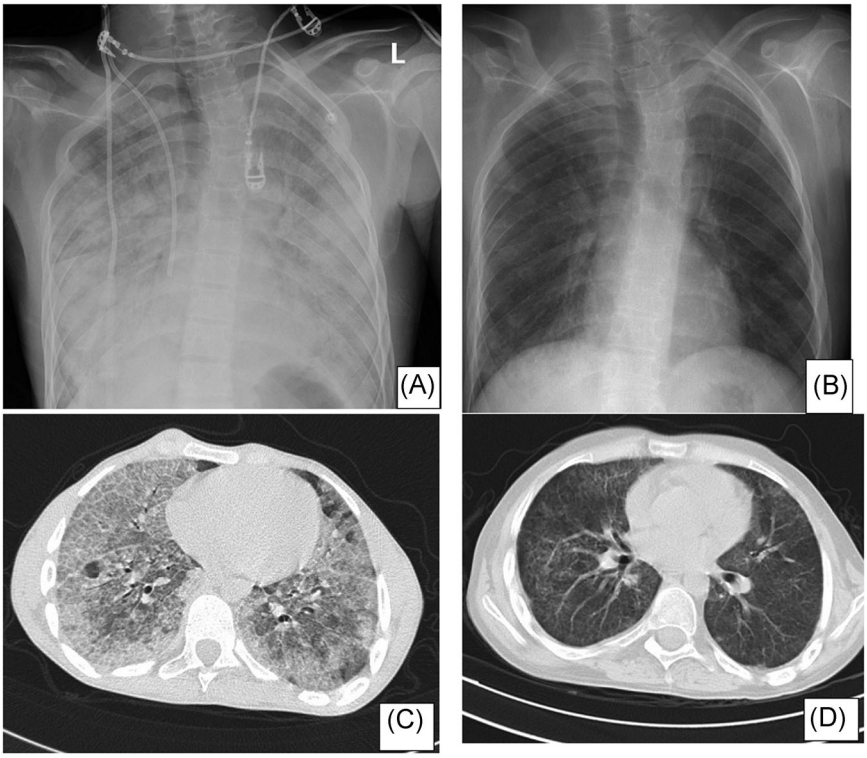

FIGURE 2 (A) Chest X-ray before HSCT showed bilateral air-space disease. (B) Chest X-ray 3 months after HSCT showed marked radiological improvement. (C) Chest CT before HSCT showed bilateral ground glass opacification with interlobular septal thickening (crazy paving pattern). (D) Chest CT 3 months after HSCT showed decreased ground glass appearance and marked radiological improvement. CT, computed tomography; HSCT, hematopoietic stem cell transplantation

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Uğur Özçelik, Selin Aytaç, Barış Kuşkonmaz, Visal Okur, and Duygu Uçkan Çetinkaya designed this case report. Selin Aytaç, Barış Kuşkonmaz, Visal Okur, and Duygu Uçkan Çetinkaya performed HSCT. Ates Kara, Ugur Özcelik, Deniz Dogru, Ebru Yalçın, Nural Kiper, Nagehan Emiralioğlu, Sanem Eryılmaz Polat, and Mina Gharibzadeh Hızal have followed up this case during the hospitalization period and outpatient clinic. Uğur Özçelik, Nagehan Emiralioğlu, Deniz Doğru, Ebru Yalçın, Barış Kuşkonmaz, and Nural Kiper reviewed the manuscript and contributed important reagents. Uğur Özçelik, Selin Aytaç, Barış Kuşkonmaz, and Visal Okur searched the literature and wrote the paper.

Ugur Ozcelik MD[1]
Selin Aytac MD[2]
Baris Kuskonmaz MD[2,3]
Ebru Yalcin MD[1]
Deniz Dogru MD[1]
Visal Okur MD[2,3]
Ateş Kara MD[4]
Mina Hizal MD[1]
Sanem Eryılmaz Polat[1]
Nagehan Emiralioglu MD[1]
Nural Kiper MD[1]
Duygu Uckan Çetinkaya MD[2,3]

[1]*Department of Pediatric Pulmonology, Faculty of Medicine, Hacettepe University, Ankara, Turkey*
[2]*Department of Pediatric Hematology, Faculty of Medicine, Hacettepe University, Ankara, Turkey*
[3]*Bone Marrow Transplantation Unit, Department of Pediatric Hematology, Faculty of Medicine, Hacettepe University, Ankara, Turkey*
[4]*Department of Pediatric Infectious Infectious Disease, Faculty of Medicine, Hacettepe University, Ankara, Turkey*

Correspondence
Ugur Ozcelik, MD, Hacettepe University Faculty of Medicine, Ihsan Dogramaci Children's Hospital, Sıhhiye, Ankara, Turkey.
Email: uozcelik@hacettepe.edu.tr

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ORCID

Deniz Dogru http://orcid.org/0000-0001-9931-9473
Mina Hizal http://orcid.org/0000-0002-6922-4948
Nagehan Emiralioglu http://orcid.org/0000-0002-1405-8401

REFERENCES

1. Trapnell BC, Nakata K, Bonella F, et al. Pulmonary alveolar proteinosis. *Nature Rev*. 2019;5:16.
2. Nishinakamura R, Wiler R, Dirksen U, et al. The pulmonary alveolar proteinosis in granulocyte macrophage colony-stimulating factor/interleukins3/5 beta c receptor deficient mice is reversed by bone marrow transplantation. *J Exp Med*. 1996;183:2657-2662.
3. Suzuki T, Arumugam P, Sakagami T, et al. Pulmonary macrophage transplantation therapy. *Nature*. 2014;514:450-454.
4. Martinez-Moczygemba M, Doan ML, Elidemir O, et al. Pulmonary alveolar proteinosis caused by delation of the GM-CSFRα gene in the X chromosome psudoautosomal region 1. *J Experimental Med*. 2008;205:2711-2716.
5. Frémond ML, Hadchouel A, Schweitzer C, et al. Succesful haematopoietic stem cell transplantation in a case of pulmonary alveolar proteinosis due to GM-CSF receptor deficiency. *Thorax*. 2018;73:590-592.
6. Jagasia M, Arora M, Flowers MED, et al. Risk factors for acute GVHD and survival after hematopoietic cell transplantation. *Blood*. 2012;119:296-307.
7. Eapen M, Horowitz MM, Klein JP, et al. Higher mortality after allogeneic peripheral-blood transplantation compared with bone marrow in children and adolescents: the Histocompatibility and Alternate Stem Cell Source Working Committee of the International Bone Marrow Transplant Registry. *J Clin Oncol*. 2004;22:4872-4880.