



## CORRESPONDENCE

# First allogeneic hematopoietic stem cell transplantation in RASGRP1 deficiency: long-term follow-up

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**TO THE EDITOR:**

RAS guanyl-releasing protein 1 (RASGRP1) is a guanine-nucleotide-exchange factor that is involved in lymphocyte development and function [1]. RASGRP1 converts the small GTPase RAS from an inactive GDP-bound state to an active GTP-bound state in response to lymphocyte activation. Activated RAS initiates a MAP-kinase cascade which leads to cytoskeletal reorganization and transcription of effector molecules [1, 2].

RASGRP1 deficiency was defined in human in 2016 [1]. It is shown to cause a combined type of primary immunodeficiency (PID) with susceptibility to Epstein-Barr virus infections [1]. Up to now, less than ten different cases of RASGRP1 deficiency have been defined [1–5]. The main clinical findings of patients include recurrent upper and lower respiratory infections, susceptibility to viral and opportunistic infections, hepatosplenomegaly, lymphadenopathy, EBV-associated lymphoproliferation, B cell lymphoma, and autoimmune features such as autoimmune cytopenia [1, 2, 4, 5].

RASGRP1 is shown to be involved in dynamic reorganization of the cytoskeleton. It is highly expressed in T cells, and to a lesser extent in B and natural killer cells [4]. The immunophenotypic characteristics of the patients include CD4+ T cell lymphopenia, elevated numbers of CD8+ T cells, decreased B cell counts, naive CD4+ and CD8+ T cells, and impaired T cell proliferation response [2, 3, 5].

Early diagnosis in patients with combined immunodeficiency is critical and hematopoietic stem cell transplantation (HSCT) might be considered to be a curative treatment [3]. Here we present the first allogeneic hematopoietic stem cell transplantation (HSCT) in RASGRP1 deficiency in detail and report the results of long-term follow-up. The present case was also reported as the first human in whom RASGRP1 deficiency was shown to cause primary immunodeficiency in 2016 [1].

A 4-year-old boy was admitted with the history of recurrent infections and pneumonia leading to bronchiectasis. He also had a cleft lip repair. He was the ninth child of consanguineous parents and three older siblings had died in the first two years of life possibly due to immunodeficiency-related infections. During the follow-up, severe failure to thrive (weight and height below the third percentiles), mild mental retardation, recurrent upper and lower respiratory infections, and finger clubbing became evident. At the age of 8 years, the patient underwent right middle and upper pulmonary lobectomy due to severe bronchiectasis. Monthly intravenous immunoglobulin (IVIG) therapy was started at the age of 12 years as he had idiopathic CD4+ lymphopenia

and suffered recurrent upper and lower respiratory tract infections. At the age of 14 years, he was diagnosed with RASGRP1 deficiency due to stop-gain mutation in *RASGRP1* (c. C726T, p. Arg246\*) after detailed immunological analysis and functional test of the patient [1]. At the age of 15 he had dysphagia for a few weeks and hypertrophied adenoid were noted in his physical examination. He underwent partial adenoidectomy and the pathological examination revealed Epstein-Barr virus (EBV) positive pediatric nodal marginal zone lymphoma. Metastatic work-up with fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET-CT) showed FDG uptake in adenoid region, lymph nodes in bilateral cervical, right paratracheal and left hilar regions and bilateral a few subpleural small nodules. He was staged as II and R-CHOP regimen was started with the dose reduction of 25%. After 3 courses of chemotherapy complete response was documented by PET-CT.

After chemotherapy given for lymphoma, the patient underwent HSCT from his HLA identical cousin at the age of 16. Reduced intensity conditioning (RIC) regimen including busulfan (11.2 mg/kg), fludarabine (180 mg/m<sup>2</sup>), anti-thymocyte globulin (rabbit; 30 mg/kg) was preferred due to severe comorbidities. Cyclosporine A and methotrexate (day +1, +3, +6) were used as graft versus host disease (GVHD) prophylaxis. The source of stem cells was bone marrow and the number of nucleated cells was 3.9 × 10<sup>8</sup>/kg and CD34 (+) cells was 1.6 × 10<sup>6</sup>/kg. The patient received acyclovir, fluconazole, and trimethoprim-sulfamethoxazole for prophylaxis against herpes simplex and varicella-zoster viruses, fungal infection and infection with *Pneumocystis jiroveci*, respectively. Intravenous immunoglobulin was administered weekly at a standard dose of 400 mg/kg from day -1 to day +21 and depending on IgG levels thereafter. Intravenous glutamine, enoxaparin, ursodeoxycholic acid, and vitamin E were given for venoocclusive disease (VOD) prophylaxis. Neutrophil and thrombocyte engraftment was achieved on day +20 and on day +21 respectively. Chimerism analysis showed 96% donor profile at the third month, and 100% at the sixth month after HSCT. Acute/chronic GVHD or VOD were not observed during the post-transplant period. The patient developed pulmonary infection on day +8 and treated with broad spectrum antibacterial and antifungal agents. The patient had been hospitalized (for 3–14 days) for pneumonia five times within 18 months after HSCT. Afterwards he did not have any infections requiring hospitalization. Twenty-eight months after HSCT IVIG is stopped. On the 50<sup>th</sup> month of HSCT the patient was infected with SARS CoV-2 and was hospitalized for three days. Then he was discharged to complete the antibiotic treatment for prevention of secondary bacterial infection at home, and he has fully recovered. The detailed laboratory characteristics of the patient before and after transplantation are given in Table 1. The patient is now well in the last follow-up with full donor chimerism 65 months after HSCT.

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**Table 1.** The laboratory characteristics of the patient before and after transplantation.

Patient/Age	12 years old	17 years old (+1 years of HSCT)	18 years old (+2 years of HSCT)	21 years old (+5.5 years of HSCT)
Complete Blood Count				
ALC (cells/mm <sup>3</sup> )	2700	1500	2600	2700
(normal range)	(1000–5300)	(1400–3300)	(1400–3300)	(1400–3300)
Immunoglobulins				
Ig A (g/dl)	640 (67–433)	341 (139–378)	275 (139–378)	318 (149–378)
Ig G (g/dl)	1720 (835–2094)	1640 (913–1884)	1300 (913–1884)	930 (913–1884)
Ig M (g/dl)	218 (47–484)	139 (88–322)	120 (88–322)	149 (88–332)
Ig E (U/l)	12,4			
Lymphocyte subsets				
CD3 (%)	75 (60–76)	77 (56–84)	69 (56–84)	70 (56–84)
(cells/mm <sup>3</sup> )	1125 (800–3500)	1155 (1000–2200)	1794 (1000–2200)	1890 (1000–2200)
CD4 (%)	<b>13 (31–47)</b>	<b>23 (31–52)</b>	<b>22 (31–52)</b>	31 (31–52)
(cells/mm <sup>3</sup> )	<b>195 (400–2100)</b>	<b>345 (530–1300)</b>	572 (530–1300)	837 (530–1300)
CD8 (%)	58 (18–35)	54 (18–35)	48 (18–35)	30 (18–35)
(cells/mm <sup>3</sup> )	870 (200–1200)	810 (330–920)	1248 (330–920)	810 (330–920)
CD19 (%)	9 (13–27)	15 (6–23)	18 (6–23)	15 (6–23)
(cells/mm <sup>3</sup> )	135 (200–600)	225 (110–570)	468 (110–570)	405 (110–570)
CD16 + 56 (%)*	11 (4–17)	6 (3–22)	12 (3–22)	13 (3–22)
(cells/mm <sup>3</sup> )	165 (70–1200)	90 (70–480)	312 (70–480)	405 (70–480)
CD45RA	55			
CD45RO	51			
TCR αβ	62			
TCR γδ	17			

Reference values are shown in paranthesis, abnormal values are indicated in bold.

HSCT hematopoietic stem cell transplantation.

\*Impaired NK-cell cytotoxicity was detected.

More than 400 distinct PID diseases have now been described and many new genetic causes of PIDs are being described each year by the help of the next-generation sequencing studies [6]. Early HSCT is the only potentially curative option for many of the PIDs. Whilst incremental enhancements in transplantation techniques have gradually improved survival outcomes over time, some of these new applications are likely to radically alter our approach to treat PID diseases [7]. The present patient is the first case who underwent HSCT with the diagnosis of RASGRP1 deficiency. It is shown that the HSCT restores the function of RASGRP1 indirectly with the recovery of the clinical features and immunologic characteristics.

Optimal conditioning regimen for HSCT in PID has yet to be defined and also is a matter of debate. A variety of conditioning regimens has been used in different forms of PIDs with varying success [7, 8]. Optimal conditioning regimes may be disease specific in PIDs. Some patients with PID experience significant organ damage before transplant that could complicate the use of myeloablative conditioning which increases the risk of transplant-related mortality [7, 8]. That is why a RIC regimen may be preferable to minimize toxicity. On the other hand, RIC regimen carries a higher risk of mixed donor chimerism and a higher rate of viral infections [8]. Since the present case had lobectomy secondary to bronchiectasis, RIC regimen is preferred which successfully resulted in full donor chimerism.

Many studies suggest that HSCT should be considered as early as possible before development of significant organ damage, life-threatening infections, or malignancies in PID [9]. Although performed at a relatively later age and after the treatment of lymphoma, HSCT provided full donor chimerism and an IVIG-free

long-term survival in the present case. Despite SARS CoV-2 infection, he recovered without serious pulmonary involvement.

There are seven patients described with RASGRP1 deficiency and lymphoproliferative malignancy including our patient [2, 4, 5, 10]. This is the only reported marginal zone lymphoma and the oldest among the seven. All reported cases have B cell lymphoproliferative neoplasms and are associated with EBV. Two patients retrospectively diagnosed with RASGRP1 deficiency underwent autologous HSCT due to Hodgkin and non-Hodgkin lymphoma were reported to be in remission [3, 5].

When we take into account the risk of life-threatening infections and lymphoma HSCT is the curative treatment in the present patient with a background of a rare form of combined immunodeficiency causing cytoskeletal dysfunction, especially in T cells.

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#### DATA AVAILABILITY

The authors confirm that all data underlying the findings are fully available without restriction. All data are included within the manuscript.

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## AUTHOR CONTRIBUTIONS

BK analyzed and interpreted the patient data regarding the hematological disease and the transplant and wrote the manuscript. BA performed the oncological assessment of the patient data and was contributor in writing the manuscript. DA and IT performed the immunological evaluation and were contributors in writing the manuscript. FVO and DUC analyzed the transplant data and were contributors in writing the manuscript. All authors read and approved the final manuscript.

## COMPETING INTERESTS

The authors declare no competing interests.

## ADDITIONAL INFORMATION

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