Case Report: Lessons Learned From Subsequent Autologous and Allogeneic Hematopoietic Stem Cell Transplantations in a Pediatric Patient With Relapsing Polychondritis

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Background: Autologous hematopoietic stem cell transplantation (autoHSCT) is increasingly being recognized as a treatment option for severe refractory autoimmune diseases (AD). However, efficacy is hampered by high relapse rates. In contrast, allogeneic HSCT (alloHSCT) has high potential to cure AD, but is associated with significant morbidity and mortality, and data in AD are limited. Experience with autoHSCT in relapsing polychondritis, a rare episodic inflammatory disorder characterized by destruction of cartilage, is scarce and alloHSCT has not been described before.

Case Presentation: Here, we present a case of a 9-year-old girl who was diagnosed with relapsing polychondritis, with severe airway involvement requiring a tracheostomy. The disease proved to be steroid-dependent and refractory to a wide array of disease-modifying anti-rheumatic drugs and biologicals. After an autoHSCT procedure, the disease became inactive for a short period of time, until the patient experienced a relapse after 31 days, accompanied by repopulation of effector/memory CD8+ T cells. Because of persistent inflammation and serious steroid toxicity, including severe osteoporosis, growth restriction, and excessive weight gain, the patient was offered an alloHSCT. She experienced transient antibody-mediated immune events post-alloHSCT, which subsided after rituximab. She ultimately developed a balanced immune reconstitution and is currently still in long-term disease remission, 8 years after alloHSCT.

Conclusion: This case adds to the few existing reports on autoHSCT in relapsing polychondritis and gives new insights in its pathogenesis, with a possible role for CD8+ T cells. Moreover, it is the first report of successful alloHSCT as a treatment for children with this severe autoimmune disease.

Keywords: case report, relapsing polychondritis, autologous hematopoietic stem cell transplantation, allogeneic hematopoietic cell transplantation, autoimmune disease, cytotoxic T cells
INTRODUCTION

In the past 25 years, autologous hematopoietic stem cell transplantation (autoHSCT) has been used to treat severe refractory autoimmune diseases (AD) in adults and children (1, 2). The aim of autoHSCT is to reset the immune system by eliminating autoreactive T and B cells with high-dose immunosuppression and promoting the generation and outgrowth of an immune system with a new self-tolerant immune repertoire. An increasing amount of evidence supports autoHSCT in a wide range of AD, including multiple sclerosis (MS), systemic sclerosis (SSc), and Crohn’s disease (3–6). While some patients achieve long-term remission, others experience reactivation of their disease post-autoHSCT (7). In contrast, allogeneic HSCT (alloHSCT) has a higher curative potential, but is associated with significant morbidity and mortality, including graft-versus-host-disease (GvHD) and viral reactivations. Experience with alloHSCT in refractory AD is therefore limited and mainly restricted to pediatric practice, with immune cytopenias as the predominant indication (8, 9). Here, we report a case of a girl with severe steroid-dependent relapsing polychondritis, a rare inflammatory disorder characterized by recurrent episodes of inflammation and deterioration of cartilaginous structures. This patient’s disease was refractory to azathioprine, methotrexate, infliximab, cyclophosphamide and anakinra, and relapsed one month after autoHSCT. This relapse was concurrent with the repopulation of effector/memory CD8+ T cells. After unsuccessful treatment attempts with tacrolimus, tocilizumab and abatacept, long-term remission was eventually induced by alloHSCT. This unique case adds to the scarcely available literature on autoHSCT in relapsing polychondritis, provides insights in the pathogenesis of this disease, and is the first report of successful alloHSCT as a rescue treatment for children with this severe autoimmune disorder.

CASE DESCRIPTION

An 8-year-old girl was admitted to the Intensive Care Unit (ICU) twice in October 2010 with acute respiratory distress due to an upper airway obstruction. At laryngoscopy, a subglottic stenosis was seen and blood results showed an iron deficiency anemia. In the preceding months, she had experienced weight loss and fever, with no response to antibiotic treatment. Granulomatosis with Polyangiitis was initially considered as diagnosis, but antineutrophil cytoplasmic antibodies (ANCA) test results were negative. Methylprednisolone pulse therapy was administered during the second admission with marked improvement of the patient’s condition, and she was discharged home with oral steroids and azathioprine. However, during steroid tapering the girl again developed an inspiratory stridor, as well as a saddle nose and pain complaints at the costochondral junctions. She was diagnosed with relapsing polychondritis at the end of December 2010, upon which the steroid dosage was increased, azathioprine was switched to methotrexate (MTX) and infliximab was started. Nevertheless, the patient was readmitted to the ICU shortly thereafter because of acute respiratory distress requiring intubation, and a tracheostomy was performed. Moreover, she developed arthritis of the temporomanibular joint, fever, and increased costochondral pain, with rising C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels. Methylprednisolone pulse therapy ameliorated symptoms and lowered inflammation markers, but exacerbations were still frequent. Consequently, intravenous cyclophosphamide was started, and infliximab was withdrawn. In the following 6 months, she received monthly doses of 750mg/m² cyclophosphamide. Although no exacerbations occurred, disease remission was not achieved as she had persistent complaints of pain in the chest, jaws and limbs, accompanied by elevated CRP levels (61–111 mg/L). Anakinra was added to the regimen of MTX and steroids in July 2011, because of a few successful case reports, but had no effect. An F-18-FDG positron emission tomography (PET) scan confirmed persistent disease activity in the cartilage of the larynx, bronchial tree and ribs. Because of this persistent inflammation and the inability to taper the steroids below 1 mg/kg/d, causing side effects such as steroid-induced Cushing syndrome, the patient was referred to our center for an autoHSCT, with the aim of resetting the immune system and restoring self-tolerance.

AutoHSCT

In November 2011, the patient received an autoHSCT (5.85 x 10^6 CD34+ cells/kg body weight) after stem cell mobilization with cyclophosphamide and recombinant granulocyte colony stimulating factor (G-CSF) and a conditioning regimen consisting of antithymocyte globulins (ATG) 10 mg/kg in 4 days (-10, -10, -9, -7), cyclophosphamide 120 mg/kg in 2 days (-7, -6) and fludarabine 150 mg/m² in 4 days (-5, -4, -3, -2). After the autoHSCT, which was uncomplicated, all symptoms disappeared, CRP level normalized, and an F-18-FDG PET scan 3 weeks post-HSCT scan showed complete remission. Oral steroids were gradually tapered to 0.3 mg/kg/d. However, 31 days after autoHSCT the patient experienced a relapse of costochondral pain and CRP level increased again to 156 mg/L. Flow cytometric immunophenotyping showed repopulation of specifically CD8-positive (+) T cells (Figure 1). Of all CD8 T cells, 91.3% were of the effector/memory type (CD27+CD45RA- CD27-CD45RA+) and 8.7% were naïve (CD27-CD45RA+). Almost all (97.2%) had an activated phenotype (CD38+HLA-DR+). A viral infection was considered as a potential trigger for this repopulation, but analysis of the CD3+ T cell Receptor (TCR)-Vbeta repertoire showed a polyclonal pattern and quantitative PCR measurements for Epstein-Barr virus (EBV), cytomegalovirus (CMV), Human Herpesvirus 6 (HHV6), and adenovirus were negative.

In contrast to the CD8+ T cells, the CD4+ T cell and B cell (CD19+) counts remained low. Absolute numbers of Natural Killer (NK) cells (CD3 CD16+56+) and neutrophils started rising early after autoHSCT (Figure 2). Steroid dosage was increased to 1.3 mg/kg/d, after which CD8+ T cell, NK cell and CRP levels rapidly declined. In addition, tacrolimus was started as a steroid-sparing agent, with the aim of slowing down CD8+ T cell repopulation so that new thymic output could arise and induce self-tolerance. In the
following year, steroid dosage could be reduced to 0.3 mg/kg/d, but several attempts at further tapering resulted in disease flares, as illustrated by the CRP elevations in Figure 3. Tacrolimus had to be withdrawn due to renal toxicity and the patient suffered from serious steroid-induced side effects, including severe osteoporosis, growth restriction, hypertension and Cushingoid features with excessive weight gain. After approximately 300 days post-HSCT, new thymic output appeared as reflected by rising CD8+ and CD4+ T cell numbers with a 48% and 44% naïve phenotype, respectively. However, also in this new situation further tapering of steroids resulted in a disease flare (day 325, Figure 3). This confirmed that autoHSCT had failed to restore self-tolerance. In search of a novel treatment strategy, tocilizumab was started in November 2012, which led to clinical improvement and made further steroid tapering possible (0.08 mg/kg every other day), until the patient relapsed again in April 2013. This relapse was characterized by a return of clinical symptoms (costochondral pain, loss of appetite) and increased activity on an F-18-FDG PET scan. CRP level was probably not elevated at this time due to the masking effect of tocilizumab (10). After an unsuccessful attempt with abatacept, we concluded that for this patient with steroid-dependent relapsing polychondritis with severe steroid toxicity there were no other treatment options left, except for alloHSCT. During the screening process for alloHSCT, fludarabine was given in order to be able to decrease the steroid dosage.

**AlloHSCT**

Almost two years post-autoHSCT, after patient and parents both agreed, the now 11-year old patient received a cord blood transplant (5/6 HLA match, 0.12 x 10⁶ CD34+ cells/kg body weight) after reduced intensity conditioning with busulfan at a cumulative AUC of 60 in 3 days (-5, -4, -3), fludarabine 160 mg/m2 in 4 days (-5, -4, -3, -2), and early alemtuzumab as serotherapy. Alemtuzumab (1 mg/kg in 3 days) was chosen because of the prior ATG during the conditioning for autoHSCT (risk of anti-ATG-antibody formation).
and for maximal recipient lymphodepletion. It was given very early (day -21 – day -19) to not impact immune recovery post-transplant. GvHD prophylaxis consisted of prednisolone, ciclosporin and mycophenolate mofetil (MMF). The early post-alloHSCT course was uncomplicated with remission of inflammation and symptoms, no serious toxicity, early and stable engraftment, and full donor chimerism. The earlier established benchmark of a CD4 count of >50 x 10⁶/L within 100 days, correlating with survival in pediatric alloHSCT, was easily reached (11, 12). New thymic output, as reflected by rising naïve CD4⁺ and CD8⁺ T cell counts, was observed 285 days post-alloHSCT (Figure 4). Both T cell (total) counts reached normal reference limits 332 days post-alloHSCT. The patient developed several immune-mediated events during immune reconstitution, including Graves’ disease and donor-induced autoimmune hemolytic anemia and thrombocytopenia, which were treated with steroids, MMF, and intravenous immunoglobulins (IVIGs), and only subsided after a rituximab course (375 mg/m² weekly, 3x). These events were considered unrelated to her prior auto-immune disease and were of temporary nature. Six years post-alloHSCT, the last immunosuppressive medication (MMF) was withdrawn and recently, the tracheostomy tube was removed and the trachea was reconstructed successfully. She has received hormone replacement therapy because of secondary growth restriction and hypergonadotropic hypogonadism. The patient is currently still in long-term disease remission, 8 years after alloHSCT.

**DISCUSSION**

Relapsing polychondritis is a rare episodic inflammatory disorder involving immune-mediated destruction of cartilaginous structures. Disease onset is most likely between the ages of 40 and 60, but the disease has been described in children as well (13, 14). Laryngeal chondritis occurs in more than half of patients, and chronic laryngotraheobronchial involvement represents advanced disease with poor prognosis and increased mortality risk. Treatment has not been standardized and, although symptom control can be achieved, it usually does not prevent disease progression (15, 16). Only three (adult) cases that received autoHSCT have been published, two of which reported complete remission after 18 and 21 months follow-up (17, 18). The third case was reported in a retrospective study on rituximab in relapsing polychondritis and had previously received autoHSCT, indicating that no remission was achieved (19). No reports on alloHSCT in relapsing polychondritis currently exist. Little is known about the pathogenesis of relapsing polychondritis, although there is some evidence of cell-mediated autoimmunity playing a role (20). Besides the strong association with the genetic allele HLA-DR4, T cells have been found in affected cartilage, and T cell responses specific to collagen type II peptides were reported (21–24). Also, decreased regulatory T cell (Treg) counts and a less diverse TCR repertoire were observed in patients with relapsing polychondritis compared to healthy
controls (25, 26). However, the presence of autoantibodies directed against collagens and other cartilage matrix components suggests that humoral autoimmunity is involved as well (27, 28). This case report provides further insights in the pathogenesis, as the relapse after autoHSCT was concurrent with an increase in CD8+ T cells, suggesting that this cytotoxic cell type plays a role in relapsing polychondritis.

The rationale behind autoHSCT in AD is that after depletion of autoreactive T and B cells, a reset and naïve immune system can be regenerated from the stem cell graft, although the exact mechanisms by which self-tolerance is induced are still unknown. It is thought that successful induction of disease remission after autoHSCT relies primarily on the complete renewal of the CD4+ TCR repertoire through thymopoiesis, a process that can require at least 6 months and sometimes years, with a particularly important role for Tregs (1, 29–31). Reconstitution of CD8+ T cells occurs earlier, within 1 to 6 months post-autoHSCT, due to proliferation of either cells contained within the graft or residual cells that escaped the pre-transplant conditioning therapy (32–40). Conserved T cell clones have been demonstrated after autoHSCT in both SSc and MS patients (36, 38). In patients with MS, the expansion of pre-existing CD8+ T cell clones was not associated with a different clinical outcome, suggesting that these clones were either not autoreactive, or no longer able to induce disease activity post-autoHSCT (36, 39, 40). In our patient, however, the increase in CD8+ T cells on day 31 post-transplantation was accompanied by rising CRP levels and a relapse in symptoms, strongly suggesting that these were expanding autoreactive T cells that had not been eliminated by the lymphodepleting conditioning regimen and were able to induce disease reactivation. Whether this can be contributed to insufficient lymphodepletion is unclear, as cases with persisting or re-emerging autoreactive immune cells without concomitant clinical relapse have also been described, indicating that other mechanisms besides lymphodepletion are involved in obtaining disease control after autoHSCT (41–44). Indeed, “reprogramming” of residual autoreactive cells towards a more anti-inflammatory/ regulatory phenotype and the restoration of regulatory networks have been proposed to also take part in the process of restoring self-tolerance (44–48). We may thus speculate that the expanding CD8+ T cells in our patient not only escaped the lymphodepleting regimen, but also escaped the immunomodulatory effects of the autoHSCT, resulting in clinical relapse. A viral infection triggering the rise in CD8+ T cells cannot be ruled out, even though the patient did not show any related symptoms and the most common post-HSCT viral reactivations were tested negative by quantitative PCR.

In the two years post-autoHSCT, complete T cell reconstitution was never observed, most likely due to extensive steroid treatment (49–52). After alloHSCT, however, full thymopoietic recovery and T cell reconstitution did occur, despite the extensive immunosuppression and two transplants. While alemtuzumab can cause unintentional lymphodepletion of the graft due to its prolonged half-life, it is highly unlikely that this occurred in our patient, since we chose to administer alemtuzumab very early pre-transplant for this reason and lymphocyte recovery post-transplant was not delayed (53). The development of a more
balanced immune reconstitution over time may have contributed to the subsiding of the secondary immune-mediated diseases post-alloHSCT. Although a significant fraction of patients with AD relapse after autoHSCT, many do become responsive to conventional treatment again (54). Our patient, too, required less steroids for symptom control after transplantation compared to before. Nevertheless, further tapering proved impossible and in the end she had to undergo alloHSCT due to persistent inflammation and severe steroid toxicity. AlloHSCT in AD has curative potential as it replaces a patient’s dysfunctional immune system with an allograft from a healthy donor. Whereas autoHSCT is increasingly being adopted as a treatment option in severe AD, there is limited experience with alloHSCT in these patients, and data are scattered (2, 55). Both long-term complete remissions and relapses have been reported after alloHSCT (2, 56–58). Because alloHSCT is associated with significant morbidity and mortality, including GvHD, it is currently only recommended for patients with refractory, life-threatening autoimmune disease. Data from the EBMT registry revealed that of the 128 patients who received alloHSCT for refractory autoimmune disease between 1997 and 2014, 20.8% had developed grade II–IV acute GvHD at 100 days post-transplant, and 27.8% had developed chronic GvHD at 5 years. Transplant-related mortality (TRM) and relapse rate were both 20% at 5 years (8). In contrast, the 5-year TRM in the 1,951 patients who underwent autoHSCT between 1994 and 2015 was 5% and the relapse rate was 46% (9). Thus, autoHSCT appears safer than alloHSCT, but has a higher risk of relapse. However, when comparing these two types of transplantation, it is important to note the recent advances that have been made in the field of alloHSCT. Novel conditioning approaches using reduced intensity regimens and individualized dosing strategies have been shown to optimize lymphodepletion and influence TRM, and improved diagnostics, treatment and prophylaxis have reduced infectious complications post-alloHSCT (8, 11, 12, 59–61). Multivariate analysis with EBMT registry data identified age <18 years and more recent year of transplant to be significantly associated with improved progression-free survival and lower TRM in patients with refractory AD (8). Thus, alloHSCT is becoming safer and may become a sensible option for patients with severe refractory AD, children in particular. In autoHSCT, too, younger age was associated with lower TRM and improved survival, stressing the importance of timely consideration of HSCT (9).

In any case where HSCT is considered – autologous or allogeneic – for the treatment of AD, a thorough evaluation is required by an experienced transplantation team to weigh the risks of the transplantation against the burden of the disease. Careful selection and screening of patients, including evaluation of cardiopulmonary fitness and viral serological status, are vital in this process, as well as involving the patient and family early in the decision (2, 62).

CONCLUSION

The case we presented here provides unique evidence of HSCT in relapsing polychondritis, as well as new insights in its pathogenesis, suggesting a possible role for CD8+ T cells. Moreover, it supports alloHSCT as a sensible option in the treatment of severe relapsing polychondritis, especially in pediatric cases with serious steroid toxicity and proven failure of autoHSCT. However, as clearly not every patient with multi-refractory autoimmune disease is able to deal with the toxicity of two sequential stem cell transplantations, physicians will have to carefully weigh the risks and chances of autoHSCT versus alloHSCT for patients with severe AD.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

SV wrote the case report. MJ, JS, and CL critically reviewed and revised the report. JS and CL were also involved as treating physicians in this case. All authors issued final approval for the final version to be submitted.

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