Case Report
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Immunosuppressive-Free Renal Allograft Function After Allogeneic Hematopoietic Stem Cell Transplantation: A Case Report

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Abstract

Objective. We describe a rare case of satisfactory renal allograft function without immunosuppressive therapy following allogeneic hematopoietic stem cell transplantation (alloHSCT). **Case Report.** The patient was a 64-year-old male who had undergone a kidney transplant from a sibling donor in 2007. After 16 years, he required alloHSCT for acute myeloid leukemia (AML), with the same sibling serving as the donor for both transplants. HLA was a 50% match. Post-alloHSCT, immunosuppressive therapy was discontinued, and the renal allograft function remained stable. The patient later developed severe complications and succumbed to infection. Insights into the precise tolerance mechanisms were limited because laboratory evaluation for chimerism was not performed. **Conclusion.** There is potential for immunosuppressive-free renal allograft function after alloHSCT. This case underscores the significant risk of infection-related mortality. To achieve the best outcome, rigorous patient selection, tailored conditioning regimens, robust infection prevention strategies, and the possibility of combined transplantation for carefully selected patients are needed.

Key Words: Kidney Transplantation ▪ Allogeneic Transplantation ▪ Immunosuppression.

Introduction

The best way to treat chronic kidney failure is a kidney transplantation from a living or deceased donor. Successful maintenance of graft function requires immunosuppressive therapy, the use of which has unwanted effects. These include: susceptibility to infections, the rise of malignant diseases, de novo diabetes, dyslipidemia, neurotoxicity, and chronic allograft nephropathy due to the impact of immunosuppressive drugs (1). If the patient somehow develops transplantation tolerance, there is no need for immunosuppressive therapy.

Transplantation tolerance is the stable acceptance of a transplanted organ without ongoing immunosuppression. It represents a critical milestone in transplant medicine. Several mechanisms for achieving tolerance exist, such as durable hematopoietic chimerism and regulatory T-cell therapy. The coexistence of donor and recipient hematopoietic cells within the recipient's immune system is hematopoietic chimerism. In this situation, an environment where the transplanted organ is recognized as "self" is created. Combined kidney and alloHSCT is a unique therapeutic strategy that may induce transplantation tolerance. At the same time, the long-term complications of immunosuppressive therapy are avoided. This type of transplantation, combined kidney and alloHSCT transplantation, is rarely performed and is typically limited to patients with concurrent renal and hematologic conditions. The first described cases were in patients with multiple myeloma.

Patients with combined kidney and alloHSCT transplantation have highly variable outcomes that are influenced by different factors, such

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as: pre-transplant conditioning regimens, HLA compatibility, and recipient health status (2, 3). Aggressive conditioning regimens can lead to renal allograft damage and infections; malignancies remain significant risks.

As far as we know, there have previously not been any patients with combined transplantation of kidney and alloHSCT in Bosnia and Herzegovina.

We present the first case of a patient who underwent allogeneic hematopoietic stem cell transplantation 16 years after a kidney transplant from a living relative.

Case Report

We present the case of a male patient, 64 yrs old, whose primary renal disease was unknown, and who spent five years on hemodialysis before a living related kidney transplant was performed in 2007. After his kidney transplantation, he was regularly monitored by a nephrologist, and his immunosuppressive regimen consisted of cyclosporine (100 mg and 75 mg) and mofetil mycophenolate 250 mg 2×4. He was on steroid-free protocols of immunosuppressive therapy after careful evaluation. His levels of cyclosporine were kept in the range of 100-150 μmol/l during regular checkups. He did not want to switch to tacrolimus therapy because of personal reasons.

On January 2023 the patient was admitted to hospital due to malaise, weight loss and profuse sweating. A complete hematological work-up was performed: bone marrow aspiration puncture with myelogram, immunophenotype, and cytogenetic analysis, showing that it was a case of acute myeloid leukemia/AML M4-M5/FAB. It was mutually agreed that the patient should be prescribed induction chemotherapy according to the Idarubicin/Cytarabin 3+7 protocol. A previous assessment of renal allograft function was performed. He was discharged on day 23 of therapy and recovered. Aspiration puncture control was performed, and disease remission confirmed. After that, the first consolidation with high-dose cytarabine was prescribed. A nephrologist was consulted for correction of the immunosuppressants. HLA typing was performed for the recipients in Sarajevo, and for the donor procedure, it was performed in a transplantation center abroad. The results of HLA typing are shown in Table 1. The patient was transferred to a center abroad for allogeneic bone marrow stem cell transplantation. This was performed in May 2023 with a preconditioning regimen consisting of cyclophosphamide and busulfan, but data about the intensity and dosage of the preconditioning regimen were impossible to obtain.

Table 1. HLA Typing for Donor and Recipient before AlloHSCT

HLA Locus	Donor Alleles	Recipient Alleles
HLA-A	02	02, 26
HLA-B	50	38, 57
HLA-C	06	06, 12
HLA-DRB1	04	11, 13
HLA-DQB1	03	03, 06

After the procedure, his immunosuppressive maintenance therapy for kidney allograft was halted, and he was followed up at our center from September 1, 2023. According to the nephrologist's recommendations, he was not on immunosuppressive therapy for his renal allograft. His immunosuppressive therapy before and after alloHSCT is shown in Table 2.

Table 2. Immunosuppressive Therapy before and after AlloHSCT

Time Point	Medication	Dosage
Pre-alloHSCT	Cyclosporine	100 mg morning /75 mg evening
Pre-alloHSCT	Mycophenolate Mofetil	250 mg twice daily
Post-alloHSCT	None	N/A

On one occasion after that, in November 2023, he was hospitalized at our center, due to bicytopenia and a drop in hemoglobin values. A hematological work-up was performed, and no relapse of the disease was confirmed during this hospitalization. His laboratory results are shown in Table 3.

Table 3. Laboratory Results from January to December

Laboratory values	January	September	November	December
Creatinine (μmol/l)	95	89	112	97
Urea (mmol/L)	10.8	6.2	5.3	18
Uroprotein (g/d)	0.17	0.47	-	2.2
Creatinine clearance (ml/min)	110	95	-	94
White blood count (109/L)	68	3.8	5.76	3.4
Red Blood count (109/L)	2.92	2.55	2.17	2.81
Hemoglobin (g/L)	91	99	88	88
Platelet (109/L)	83	130	75	33
CRP (mg/L)	27.7	11.4	74.2	112

Three weeks later, he was re-hospitalized due to febricity. Upon admission, blood samples, as well as urine and sputum were obtained. Physical inspection revealed ascites. Diagnostic ultrasound (US) and computed tomography were performed. The ascites was evacuated several times. According to the US scan, a polypoid mass on the stomach was verified, but gastroscopy did not confirm this due to the patient's deteriorating condition. Color Doppler ultrasound of the renal allograft showed normal findings. Trends of laboratory values are shown in Figure 1. Urine output was satisfactory.

Viral testing, including cytomegalovirus (CMV) PCR and Epstein-Barr virus (EBV) PCR, were performed with negative results. Microbiology results showed the presence of Klebsiella pneumoniae ESBL and Acinetobacter baumannii in his sputum and Escherichia coli in his urine. Broad-spectrum antibiotic therapy, including carbapenems and colistin, was introduced. Despite the therapy, the patient's condition continued to deteriorate, and three weeks after admission and 24 weeks after the alloHSCT, he died. No post-mortem examination was conducted.

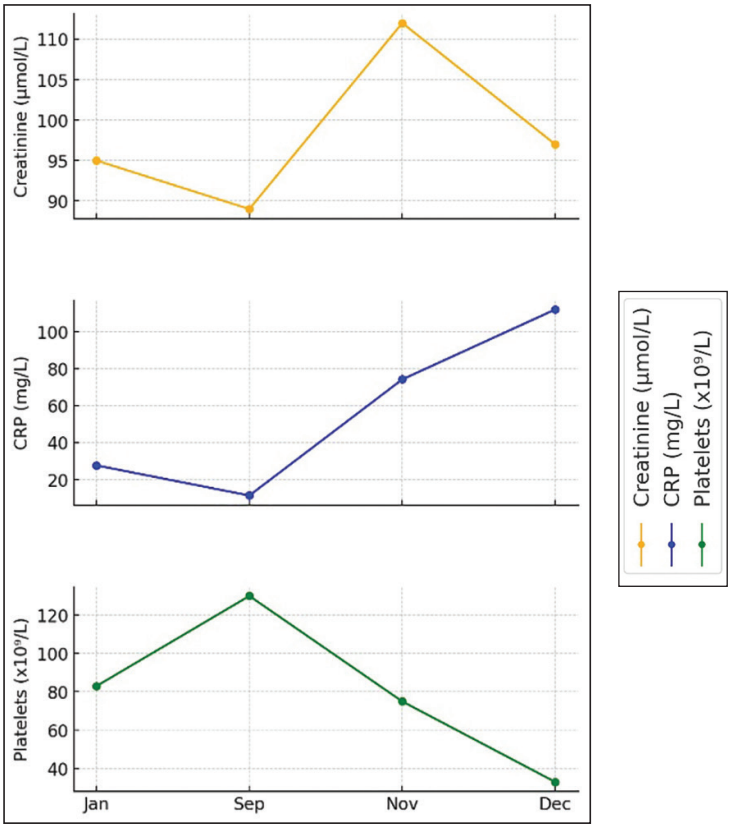

Figure 1. Trends of key laboratory values from January to December 2023.

Discussion

Proper function of a renal allograft is possible without immunosuppression in patients after bone marrow transplantation and is the result of newly established transplantation tolerance. That is: "the lack of destructive immune responses to a transplanted organ in the absence of immunosuppression", as first described by Oven et al. (4) and later by Medawar et al. (5). So far, the

most promising ways to achieve successful transplantation tolerance in humans are regulatory cell therapy and hematopoietic chimerism. We present a case highlighting the convergence of kidney transplantation and alloHSCT as a therapeutic strategy. Also, this case emphasizes the challenges associated with long-term outcomes, such as infection-related complications.

However, to achieve tolerance and durable chimerism, it is necessary to determine the state in which donor hematopoietic cells are present in the recipient organism (6). This may be achieved by allogeneic bone marrow transplantation (BMT) or allogeneic hematopoietic stem cell transplantation (HSCT) (7). To accomplish any chimerism, a preconditioning regimen is necessary. Preconditioning consists of myeloablative regimens in which high-dose total irradiation is used in combination with chemotherapeutic drugs. Still, this approach carries the most significant risk of developing complications: infections and graft versus host disease (GvHD). In the absence of malignant disease, the risk of GvHD is not justified, so different non-myeloablative regimens have been developed (8).

Solid organ transplantation is a unique challenge. Immunosuppression could lead to the development of end-stage organ failure and malignancies, which require a second transplant. One to three percent of patients with liver and kidney, 3–9% of heart and lung transplant patients, and up to 10% of intestinal or multi-organ transplant patients develop post-transplant lymphoproliferative disease (PTLD). Acute myeloid leukemia develops in 0.2% of recipients of solid organs (9). Our patient belonged to the small group of patients who developed acute myeloid leukemia after 16 years of immunosuppressive therapy.

The outcome of patients with combined transplantations depends on several factors: 1) the histocompatibility of the transplanted organs, 2) the sensitivity of the solid organ graft to conditioning the regime necessary for HCT and the effects of long-term immunosuppression, infection complications, and relapse rate after HCT (10). The donor of hematopoietic stem cells (HSC) usually has an HLA that matches the recipient, not the transplanted organ. Therefore, alloHSCT can lead to graft rejection. If the donor of the stem cells and the solid organ kidney are the same, tolerance may develop.

The most studied mechanisms of transplantation tolerance involve hematopoietic chimerism and regulatory T-cell (Treg) activity. In this case, the donor was the same for the renal allograft and the hematopoietic stem cells. This resulted in a shared immune environment. In a situation where both donor and recipient hematopoietic cells coexist, mixed chimerism develops, where the immune system recognizes the renal graft as "self," thereby preventing rejection. Expansion of donor-derived Tregs may suppress alloreactive T-cell responses. That further contributes to tolerance. Although Treg function was not evaluated in this case, existing studies suggest their critical role in preventing graft rejection in immunosuppression-free conditions. Also, preconditioning regimens may lead to the depletion of alloreactive T-cells or render them inactive, reducing the possibility of rejection. Despite the absence of immunosuppressive therapy, the stable renal function in this patient post-alloHSCT suggests the successful integration of these mechanisms. It should be stressed that the lack of solid evidence, such as laboratory confirmation of chimerism or Treg profiling, limits definitive conclusions. Future cases should include these evaluations to better explain the mechanisms underlying tolerance.

Studies with combined transplantation are scarce, and results are sporadically reported (11). This reflects differences in patient selection, transplant protocols, and post-transplant management. The European Society for Blood and Marrow Transplantation reported on 28 patients with combined transplantation, of whom 12 patients had a transplanted kidney. Patients with a transplanted kidney were more prone to organ failure compared to those with liver transplants. The overall survival (OS) was 75% at 3 months, 60.2% at 12 months, 45.1% at 36 and 40.1% at 60 months. The European Society for Blood and Marrow Transplantation study highlighted infection-related complications

as the leading cause of mortality. It was mainly within the first year post-transplant. These findings align with our case, where the patient died due to sepsis six months after alloHSCT. Also, the same study noted that loss of graft function was the second most common cause of mortality, emphasizing the challenges of maintaining long-term renal allograft function in patients with combined transplantation (12). Preserved renal graft function without immunosuppressive therapy, observed in our patient, underscores the potential for tolerance in such cases. However, the lack of chimerism testing in this case limits a more profound understanding with complete evidence.

A study from Japan reported on 19 patients with combined hematopoietic stem cell transplantation (HSCT) and solid organ transplantation, where nine patients had a kidney transplant. Eight of the kidney transplant patients experienced renal dysfunction during and after HSCT, with a worsening of renal function within one year after transplantation. All of them required dialysis, and three of them experienced rejection of the renal allograft. Five of the nine patients died within the first year after HSCT. In this study, 5-year OS in patients undergoing alloHSCT was 41.7% for non-malignant diseases but just 23.1% for those with a malignant disease. Median survival time was 10.7 months for all patients (13). In our case, the patient did not need any form of renal replacement therapy, and he was without any sign of malignancy, which is different from the Japanese study. His survival was shorter than the average median survival time reported by Japanese authors: 7 months vs. 10.5 months (13). This difference may be attributed to several factors, such as the conditioning regimen (cyclophosphamide and busulfan) used in our case, and HLA matching. The Japanese study highlighted a high incidence of rejection in kidney recipients, a complication not observed in our patient. This could be explained by the fact that the same donor for both the kidney and alloHSCT facilitated a degree of immune tolerance.

The latest French study presented excellent overall survival of 94% for a 5-year period, with excellent kidney graft survival (14). The survival rates and complications reported in European and Japanese studies show critical differences in patient outcomes based on geographic regions, transplant protocols, and post-transplant care. The French study demonstrates the potential for excellent outcomes with proper patient selection and optimized care, contrasting data from European and Japanese studies, which reported high early mortality due to infections and graft rejection.

The patient we have presented died 24 weeks after allogeneic HSCT transplantation due to infection complications. This result correlates with previous findings from The European Society for Blood and Marrow Transplantation. His kidney allograft function remained stable without immunosuppressive therapy (12). This highlights the critical need for robust infection prevention and management strategies in the early post-transplant period.

The main limitation of our case is the absence of laboratory analyses to confirm chimerism, such as B and T lymphocyte testing. Those tests would provide direct evidence of tolerance mechanisms. In this case, the absence of an established infection monitoring protocol limited the ability to manage complications preemptively. Strategies, such as routine viral load and microbiological testing with prophylactic antimicrobial therapies, could mitigate this risk in future cases. Also, no postmortem examination was performed to identify the exact cause of death. Without autopsy, there was no possibility to determine the extent of residual disease and infection. This article contributes to the body of evidence by demonstrating the feasibility of maintaining stable renal graft function without immunosuppression, even with early mortality due to infection.

Conclusion

In conclusion, we have provided a report of a rare case of a patient with acute myeloid leukemia who successfully underwent alloHSCT from a related donor 16 years after having received a related kidney transplant. Later, he died due to infectious complications. Our experience, in this case, supports the findings from European data of the high

risk of death in the first year post-alloHSCT due to infective complications. This case underscores the need for personalized approaches in cases like this. We recommend several key procedures for future practice in similar cases. First, donor-recipient compatibility should be maximized. Preferably, the same donor should be used for kidney and alloHSCT transplants. Infection management should include comprehensive screening for latent infections (e.g. CMV, EBV), a prophylactic strategy, and a rigorous prophylactic antimicrobial regimen (e.g., fungal, bacterial, and viral infections). Routine microbiological surveillance should be standard practice to enable early infection detection and intervention. Post-transplant monitoring should be done weekly during the first three months, and it is essential to address complications promptly. Chimerism monitoring is obligatory to understand the tolerance mechanism and for guidance for immunosuppressive management. To ensure ongoing graft stability, an assessment of creatinine, proteinuria, and Doppler ultrasonography should be performed monthly. Our case shows that combined transplantation is feasible, and this approach could be used but with high caution, and in a highly selected group of patients.

What Is Already Known on This Topic:

Combined kidney transplanttion is done in rare circumstances and in highly selected patients. These cases are rarely reported. Mortality is high, mainly in the first year post-transplant and due to infections.

What This Case Adds:

There have not been any reports to date of patients with combined kidney and alloHSCT in Bosnia and Herzegovina, and this is the first report of that type. Even with post-transplant complications that developed after the second transplantation, the patient had a normal-functioning renal allograft. This is an example of how tolerance was developed and how a renal allograft could be functional without maintenance immunosuppressive therapy.

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Conflict of Interest: The authors declare that they have no conflict of interest.

References

1. Ghanta M, Dreier J, Jacob R, Lee I. Overview of Immunosuppression in Renal Transplantation [Internet]. Current Issues and Future Direction in Kidney Transplantation. InTech; 2013. [cited 2024 Jul 30]. Available from: http://dx.doi.org/10.5772/54865.
2. Kawai T, Sachs DH, Sprangers B, Spitzer TR, Saidman SL, Zorn E, et al. Long-term results in recipients of combined HLA-mismatched kidney and bone marrow transplantation without maintenance immunosuppression. Am J Transplant. 2014;14(7):1599-611. doi: 10.1111/ajt.12731. Epub 2014 Jun 5.
3. Hariharan S, Israni AK, Danovitch G. Long-Term Survival after Kidney Transplantation. N Engl J Med. 2021;385(8):729-43. doi: 10.1056/NEJMra2014530.
4. Owen RD. Immunogenetic consequences of vascular anastomoses between bovine twins. Science. 1945;102(2651):400-1. doi: 10.1126/science.102.2651.400.
5. Billingham RE, Brent l, Medawar PB. Actively acquired tolerance of foreign cells. Nature. 1953;172(4379):603-6. doi: 10.1038/172603a0.
6. Leventhal J, Abecassis M, Miller J, Gallon L, Tollerud D, Elliott MJ, et al. Tolerance induction in HLA disparate living donor kidney transplantation by donor stem cell infusion: durable chimerism predicts outcome. Transplantation. 2013;95(1):169-76. doi: 10.1097/TP.0b013e3182782fc1.
7. Podestà MA, Sykes M. Chimerism-Based Tolerance to Kidney Allografts in Humans: Novel Insights and Future Perspectives. Front Immunol. 2022 Jan 5;12:791725. doi: 10.3389/fimmu.2021.791725.
8. Kawai T, Cosimi AB, Colvin RB, Powelson J, Eason J, Kozlowski T, et al. Mixed allogeneic chimerism and renal allograft tolerance in cynomolgus monkeys. Transplantation. 1995 Jan 27;59(2):256-62.
9. El Jurdi N, DeFor T, Adamusiak AM, Brunstein CG, Pruett T, Weisdorf DJ. Hematopoietic Cell and Solid Organ Transplantation in the Same Patient: Long-Term Experience at the University of Minnesota. Transplant Cell Ther. 2021 Jan;27(1):87.e1-87.e6. doi: 10.1016/j.bbmt.2020.09.005. Epub 2020 Sep 17.
10. Salisbury EM, Game DS, Lechler RI. Transplantation tolerance. Pediatr Nephrol. 2014 Dec;29(12):2263-72. doi: 10.1007/s00467-013-2659-5. Epub 2013 Nov 10.
11. Doney KC, Mielcarek M, Stewart FM, Appelbaum FR. Hematopoietic Cell Transplantation after Solid Organ Transplantation. Biol Blood Marrow Transplant. 2015 Dec;21(12):2123-2128. doi: 10.1016/j.bbmt.2015.08.004. Epub 2015 Aug 10.
12. Basak GW, Wiktor-Jedrzejczak W, Labopin M, Schoemans H, Ljungman P, Kobbe G, et al. Allogeneic hematopoietic stem cell transplantation in solid organ transplant recipients: a retrospective, multicenter study of the

EBMT. Am J Transplant. 2015 Mar;15(3):705-14. doi: 10.1111/ajt.13017. Epub 2015 Feb 3.

13. Shinohara A, Oshima K, Fuji S, Umeda K, Kako S, Kurokawa M, et al. Hematopoietic Stem Cell Transplantation in Solid Organ Recipients with Emphasis on Transplant Complications: A Nationwide Retrospective Survey on Behalf of the Japan Society for Hematopoietic Stem Cell Transplantation Transplant Complications Working Group. Biol Blood Marrow Transplant. 2020 Jan;26(1):66-75. doi: 10.1016/j.bbmt.2019.08.021. Epub 2019 Sep 5.
14. Ziliotis MJ, Vauchy C, Deconinck E, Berceanu A, Büchler M, Caillard S, et al. Kidney Transplantation After Allogeneic Hematopoietic Cell Transplantation. Kidney Int Rep. 2024 Jan 30;9(4):1127-1131. doi: 10.1016/j.ekir.2024.01.048.