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Persistent Renal Activity Despite Systemic Remission After Hematopoietic Stem Cell Transplantation in Lupus Nephritis

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INTRODUCTION

Systemic lupus erythematosus (SLE) remains one of the most prevalent autoimmune diseases. Despite the advances in immunosuppressive therapies, a considerable proportion of patients continue to be refractory to conventional treatments. In this context, autologous hematopoietic stem cell transplantation (HSCT) has emerged as a promising strategy aimed at resetting the immune system and inducing long-term remission.[1–4] The potential role of HSCT in SLE was first demonstrated by Marmont in 1998,[5] and subsequent studies have further supported its efficacy and safety, reporting 5-year disease-free survival rates between 70% and 85%.[6,7] However, most studies have included mixed SLE populations, with only a fraction of patients presenting with lupus nephritis (LN), and treatment protocols remain heterogeneous.[8,9] More recent research focusing on patients with LN suggests that, although initial remission rates following HSCT can reach up to 80%, long-term disease-free survival at 5 years drops to approximately 50%.[S1] Here, we present 2 cases of patients with refractory LN who underwent HSCT and achieved complete immunologic and extrarenal response, but with persistent renal activity. Informed consent was obtained from both participants, and approval was granted by the Institutional Review Board (Ethics Committee of Hospital Universitario 12 de Octubre).

RESULTS

Case 1 is a 14-year-old Hispanic woman from Colombia who was diagnosed with SLE in 2015, presenting with arthralgias; oral ulcers; nephrotic syndrome (proteinuria: 14 g/24 h); and positive for antinuclear antibody, anti-dsDNA, anti-SSA/Ro, and anti-SSB/La, with low complement levels. A renal biopsy showed class III LN. She received 3 pulses of IV steroids (500 mg) and mycophenolate (MMF) but relapsed in October 2016 with recurrent nephrotic syndrome. MMF was replaced with 6 monthly doses of IV cyclophosphamide (750 mg) with partial remission. A new flare in March 2017 led to a second renal biopsy showing class III + V LN (activity index 4/24, chronicity index 4/12). She was treated with 3 pulses of IV steroids (500 mg) and 2 doses of 1 g rituximab. In August 2017, she arrived in Spain and was admitted with a new SLE flare. Despite intensive immunosuppression with high-dose steroids, Euro-Lupus cyclophosphamide, tacrolimus, MMF, and belimumab, she continued to experience LN flares. In November 2021, a third kidney biopsy showed class IV + V LN (activity index 3/24, chronicity index 6/12). Due to persistent clinical, immunological, and renal activity, the case was discussed in a multidisciplinary committee, and she underwent autologous HSCT on March 17, 2022, without notable complications. Under immunosuppression with prednisone, tacrolimus, and MMF, she achieved

Table 1. Renal biopsies and main treatments

	Biopsy	Date	Histologic results	Activity/chronicity index	Treatment
Case 1	1st biopsy	June 2015	Class III	Unknown	Cs, MMF, CYC
	2nd biopsy	March 2017	Class III + V	AI: 4/24 CI: 4/12	Cs, Rituximab, CYC, MMF, tacrolimus, belimumab
	3rd biopsy	November 2021	Class IV + V	AI: 3/24 CI: 6/12	Autologous HSCT
	Autologous HSCT	March 2022			Conditioning with CYC and thymoglobulin
	4th biopsy	February 2024	Class V	AI: 1/24 CI: 4/12	Voclosporin
Case 2	1st biopsy	October 2022	Class IV + V	AI: 7/24 CI: 0/12	Cs, MMF, tacrolimus, CYC, rituximab
	2nd biopsy	August 2023	Class IV + V	AI: 13/24 CI: 3/12	Autologous HSCT
	Autologous HSCT	February 2024			Conditioning with CYC and thymoglobulin
	3rd biopsy	January 2025	Class IV + V	AI: 3/24 CI: 2/12	Cs, MMF, tacrolimus

AI, activity index; CI, chronicity index; Cs, corticosteroids; CYC, cyclophosphamide; HSCT, hematopoietic stem cell transplantation; MMF, mycophenolate mofetil.

full clinical and immunologic remission but partial renal response, with a reduction of proteinuria to a nadir of 4 g/24 h. In February 2024, a new kidney biopsy showed class V LN (activity index 1/24, chronicity index 4/12). At her most recent follow-up, she remains in extrarenal and immunological remission, with improved albumin (3.1 g/dl), resolution of hematuria, but persistent proteinuria of 5 g/24 h.

Case 2 is a 23-year-old Hispanic woman from Honduras who was diagnosed in her own country with SLE onset in March 2022, presenting with arthritis, alopecia, and cutaneous lesions. Serological studies showed hypocomplementemia and positive for antinuclear, anti-dsDNA, anti-Sm, and anti-RNP/Sm antibodies. She was treated with intravenous steroid pulses and oral hydroxychloroquine. Six months later, she presented to our emergency department with new LN onset (impaired renal function, nephrotic syndrome, and microscopic hematuria). A first kidney biopsy on October 2022 revealed class IV + V LN (activity index 7/24 and chronicity index 0/12). She received 3 intravenous steroid pulses followed by oral prednisone, MMF, and tacrolimus. Nephroprotective therapy (angiotensin-converting enzyme inhibition and sodium-glucose cotransporter 2 inhibition) was initiated. The patient achieved clinical remission and partial renal response, with normalization of serum creatinine and improved proteinuria and hematuria. However, in February 2023, following SARS-CoV-2 vaccination, she experienced a flare with increased proteinuria and hypoalbuminemia; therefore, new pulses of IV steroids, cyclophosphamide in Euro-Lupus protocol and intravenous belimumab were administrated. The patient showed poor renal response, with continued nephrotic syndrome, microscopic hematuria, and persistent immunologic activity. Compassionate use of rituximab was administered with limited effect. A second kidney biopsy in August 2023 confirmed class IV + V LN (activity index 13/24, chronicity index 3/12). Subsequently, cyclophosphamide was reinitiated following the National Institutes of Health protocol, again without renal response. The case was discussed in a multidisciplinary session and after failing to qualify for a chimeric antigen receptor T-cell trial, autologous HSCT was performed on February 20, 2024. Post-HSCT, she achieved clinical and immunological remission. However, renal involvement persisted. A third biopsy in January 2025 showed persistent class IV + V LN (activity index 3/24, chronicity index 2/12); thus, MMF was added to steroids and tacrolimus. As of the most recent follow-up, the patient remains in extrarenal and immunologic remission, with improved plasma albumin (3.2 g/dl), resolution of hematuria, but persistent proteinuria (4.7 g/24 h) (Tables 1 and 2 and Supplementary Table S1).

DISCUSSION

We report 2 cases of young patients with severe, refractory LN who underwent autologous HSCT. Both patients had accumulated extensive immunosuppression and demonstrated resistance to multiple conventional therapeutic regimens, including cytotoxic agents, calcineurin inhibitors, biologic therapies (rituximab and belimumab), and combined approaches. In this context, HSCT was considered as an attempt to reestablish immune self-tolerance. Following HSCT, both patients achieved complete clinical and immunological remission characterized by normalization of complement levels, disappearance of anti-dsDNA and ANA antibodies, and resolution of extrarenal symptoms. These outcomes support the concept of autologous HSCT as an effective immune reset, eliminating autoreactive clones and reprogramming immune tolerance. Despite immunologic remission, both patients exhibited nephrotic-range

Table 2. Detailed serologic data at the time of each biopsy

		1st biopsy	2nd biopsy		3rd biopsy		4th biopsy	Last test
Case 1	Date	June 2015	March 2017		November 2021	March 2022 Autologous HSCT	February 2024	May 2025
	Histology OMS classification	Class III	Clas III + V		Class IV + V		Class V	
	Cr (mg/dl)	Unknown	1.58		1.47	1.76	0.89	1.01
	eGFR (ml/min)	Unknown	49		52	38	>90	81
	Albumin (g/dl)	Unknown	2.3		1.7	1.8	3.1	3
	Proteinuria (g/24 h)	14	31.67		10.58	11.08	3.17	5.49
	Microhematuria (RBC/HPF)	Unknown	53		5	38	1	0
	ANA	+	+		+	+	Negative	Negative
	Anti-DNA	+	+ (1/50)		+ (1/25)	+ (1/25)	Negative	Negative
	C3/C4 (mg/dl)	Unknown	24 / 3.4		68 / 18	81.4 / 27.3	105 / 32.2	97.6 / 22.5
Case 2	Date	October 2022	August 2023	February 2024 Autologous HSCT	January 2025			May 2025
	Histology OMS classification	Clas IV + V	Clas IV + V		Clas IV + V			
	Cr (mg/dl)	0.91	1.6	1.01	0.65			0.58
	eGFR (ml/min)	>90	41	82	>90			> 90
	Albumin (g/dl)	2.5	2.6	2.7	3.3			3.2
	Proteinuria (g/24 h)	6.28	11	13.27	5.44			4.7
	Microhematuria (RBC/HPF)	5	176	8.6	0			0
	ANA	+ (1/160)	+ (1/160)	Negative	Negative			Negative
	Anti-DNA	+ (1/50)	+ (1/50)	Negative	Negative			Negative
	C3/C4 (mg/dl)	18 / 2.9	35.8 / 13.7	95.8 / 40	83.2 / 26.5			96.5 / 23

ANA, antinuclear antibody; Cr, creatinine; eGFR, estimated glomerular filtration rate; RBC/HPF, red blood cells / high power field.

proteinuria, and repeat kidney biopsies performed post-HSCT demonstrated persistent histological activity as class IV and V LN. These findings raise important questions regarding the true extent of HSCT's impact on renal-targeted immunity. One possibility is that though autologous HSCT achieves an effective immune reset at the systemic level, it may not fully eradicate local immune dysregulation within the renal microenvironment. Histologic evidence suggests that memory B and T cells may persist within renal tissue, protected from systemic immune modulation and immunosuppressive therapies, perpetuating local inflammation even after systemic disease quiescence.[S2,S3] In addition, histologic recovery in the kidney may require extended time. Glomerular remodeling and full resolution of renal inflammation are slow processes, particularly in patients with preexisting chronic damage, as reflected in chronicity indices (4/12 and 2/12). Nonetheless, the persistence of histologic inflammation despite systemic immunological quiescence remains an open and unresolved question, as shown in our biopsies with activity index of 1/24 and 3/24.

Interestingly, our results contrast with previous data reporting complete renal remission rates of 60% to 80% following HSCT,[6,7,S1] potentially because of differences in patient selection, conditioning protocols, remission definitions, and follow-up duration. Despite these limitations, HSCT has demonstrated long-term safety and feasibility,[S4] and standardized protocols allow reproducibility across centers. In addition, CD19-targeted chimeric antigen receptor T-cell therapy has recently emerged as a promising strategy aiming to achieve a deep immune reset by selectively depleting autoreactive B-cell populations.[S5,S6] Given its safety and potential efficacy, there is growing interest in introducing HSCT earlier in treatment, before irreversible organ damage occurs.

In summary, our cases highlight that though autologous HSCT can induce a robust immune reset with sustained extrarenal remission, persistent renal activity remains a major clinical and biochemical challenge. Further investigation is needed to elucidate the mechanisms underlying intrarenal immune persistence and to develop novel therapeutic strategies targeting the renal microenvironment to achieve full renal remission in patients with severe LN.

DISCLOSURE

All the authors declared no competing interests.

PATIENT CONSENT

The authors declare that they have obtained consent from the patients discussed in the report.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Patients and transplant characteristics.

Supplementary References.

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