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CASE REPORT

Autologous Epstein–Barr virus-specific adoptive T-cell therapy in a patient with lupus nephritis

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Abstract

Objectives. Dysregulation of Epstein–Barr virus (EBV)-specific cellular immunity has been hypothesised as one of the contributing factors in the pathogenesis of systemic lupus erythematosus (SLE). Lupus nephritis is a major risk factor for overall morbidity in SLE. Immune-based strategies directed to EBV have been proposed as potential therapeutic strategy for SLE and lupus nephritis. **Methods.** Autologous EBV latent antigen-specific $CD4^+$ and $CD8^+$ T cells were expanded *in vitro* and adoptively transferred to a lupus nephritis patient. **Results.** This adoptive immunotherapy had no immediate adverse effects, and the patient was subsequently treated with the anti-CD20 antibody, obinutuzumab. The patient showed a reduction in anti-dsDNA antibodies and improved glomerular filtration rate but remained nephrotic. These observations were coincident with a reduction in anti-viral and global T-cell activation. **Conclusion.** To our knowledge, this is the first report of the use of EBV-specific adoptive immunotherapy to treat a patient with lupus nephritis.

Keywords: autoimmune diseases, lupus nephritis, systemic lupus erythematosus, T cell therapy

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multi-system autoimmune disorder affecting predominantly women of reproductive age, with a female-to-male ratio of 9.1.[1] It is a chronic disease with a relapsing and remitting course. The 2019 European Alliance of Associations for Rheumatology and American College of Rheumatology classification criteria for SLE utilises 20 different clinical and immunological criteria or biopsy-proven class III/IV lupus nephritis to diagnose SLE.[2] Multiple genetic and environmental factors and the interplay between these factors are responsible for the pathogenesis of

SLE. Sunlight, silica dust exposure, smoking and Epstein–Barr virus (EBV) infection are major environmental factors found to be associated with SLE.[3]

Epstein–Barr virus is a ubiquitous human herpesvirus associated with a wide range of diseases including B cell and epithelial malignancies, as well as autoimmune diseases.[4,5] EBV infection is generally acquired in the early years of human life, although seroconversion can occur in later parts of life.[6] At the time of primary infection, transmission of EBV occurs through saliva.[6] Rarely, infection can spread through blood transfusion, organ transplantation and semen. EBV establishes latent infection in resting memory B cells, and these latently infected B cells express limited viral genes, which allows these cells to escape host immune surveillance.[7] The reactivation of EBV can be demonstrated serologically through the detection of viral capsid antigen (VCA)-specific antibodies in peripheral blood and saliva.[8] Antibodies against EBV-encoded early antigen (EA) can be detected in peripheral blood after primary infection, and these antibodies can persist for a period of 6 months to 2 years.[9]

Previous studies have hypothesised a causal relationship between EBV infection and SLE.[10–16] This is evidenced by clinical studies in SLE patients, who show higher levels of antibodies to VCA and EA, increased viral load and higher frequencies of latently infected B cells when compared to healthy individuals.[17] These EBV-infected B cells display unusual expression of EBV-encoded latent antigens, including EBV nuclear antigen-1 (EBNA1) and latent membrane protein-1.[18] This increased expression is also coincident with high levels of anti-EBNA1 antibodies and is associated with transition to active clinical disease activity and flare.[19] Several studies have also shown that antibodies directed to EBNA1 protein cross-react with SLE autoantigens including Ro/SSA, spliceosomal proteins Sm B, Sm D1, and RNP A and dsDNA.[20] While the precise reason for increased EBV reactivation in SLE patients is not known, it has been proposed that dysregulated virus-specific cellular immunity against EBV may be a contributing factor for SLE pathogenesis.[21] Indeed, Kang and colleagues showed that patients with SLE have an increased frequency of EBV-specific memory $CD69^+$ $CD4^+$ T cells and a decreased frequency of virus-specific $CD69^+$ $CD8^+$ T cells producing IFN-γ and TNF[22]. These observations and other studies suggest that EBV-specific T-cell-mediated immune control may be defective in SLE patients.[23–25] In this study, we have treated a patient with lupus nephritis with *in vitro*-expanded autologous EBV-specific $CD8^+$ and $CD4^+$ T cells directed to EBV latent antigens.

RESULTS AND CONCLUSION

The patient was a 46-year-old woman with SLE diagnosed 24 years ago when she presented with mucocutaneous and musculoskeletal manifestations, leukopenia and a high titre-positive antinuclear antibody (1:> 2560—speckled pattern). Complement proteins were low and SLE-specific antibodies (anti-dsDNA antibody, anti-Smith antibody) were positive at the time of diagnosis. Ten years after her initial SLE diagnosis, she was diagnosed with presumed lupus nephritis after she presented with nephrotic-range proteinuria. Three years later, she came under our care, at which time she had been taking mycophenolate 1000 mg twice a day, prednisolone 5 mg daily and hydroxychloroquine 200 mg twice a day. She developed gastrointestinal side effects on mycophenolate. Mycophenolate was converted to azathioprine in the context of prenatal planning. She had a kidney biopsy for worsening proteinuria to 2.7 g per day and haematuria with dysmorphic red blood cells that showed a combination of class III and V lupus nephritis. She was commenced on multi-target therapy with the addition of tacrolimus in 2012 because of persistent subnephrotic proteinuria.

In 2017, the patient achieved complete remission of lupus nephritis; kidney indices were stable with less than 0.5 g per day of proteinuria. At this stage, azathioprine was stopped and tacrolimus and prednisolone continued. In 2020, she developed worsening proteinuria and rising dsDNA titres. Rituximab was initially considered but deferred because of the SARS-CoV-2 outbreak, and the patient resumed azathioprine at 100 mg daily. However, the proteinuria did not improve despite escalating doses of azathioprine over 12 months, and rituximab was eventually administered at a dose of 1 g at Days 0 and 14. Four months after rituximab administration, B-cell subsets remained undetectable at 0×10^9 cells L^{-1} and dsDNA titres fell to 19 IU mL^{-1} (reference range: < 7 IU mL^{-1}) from 73 IU mL^{-1} prior to treatment. However, the patient remained nephrotic and had a repeat kidney histology that showed class V lupus with minimal scarring. The kidney function started deteriorating over the subsequent months and dsDNA titres rose to 391 IU mL^{-1}. Repeat EBV serology showed IgG EBNA positive (first time tested) and VCA

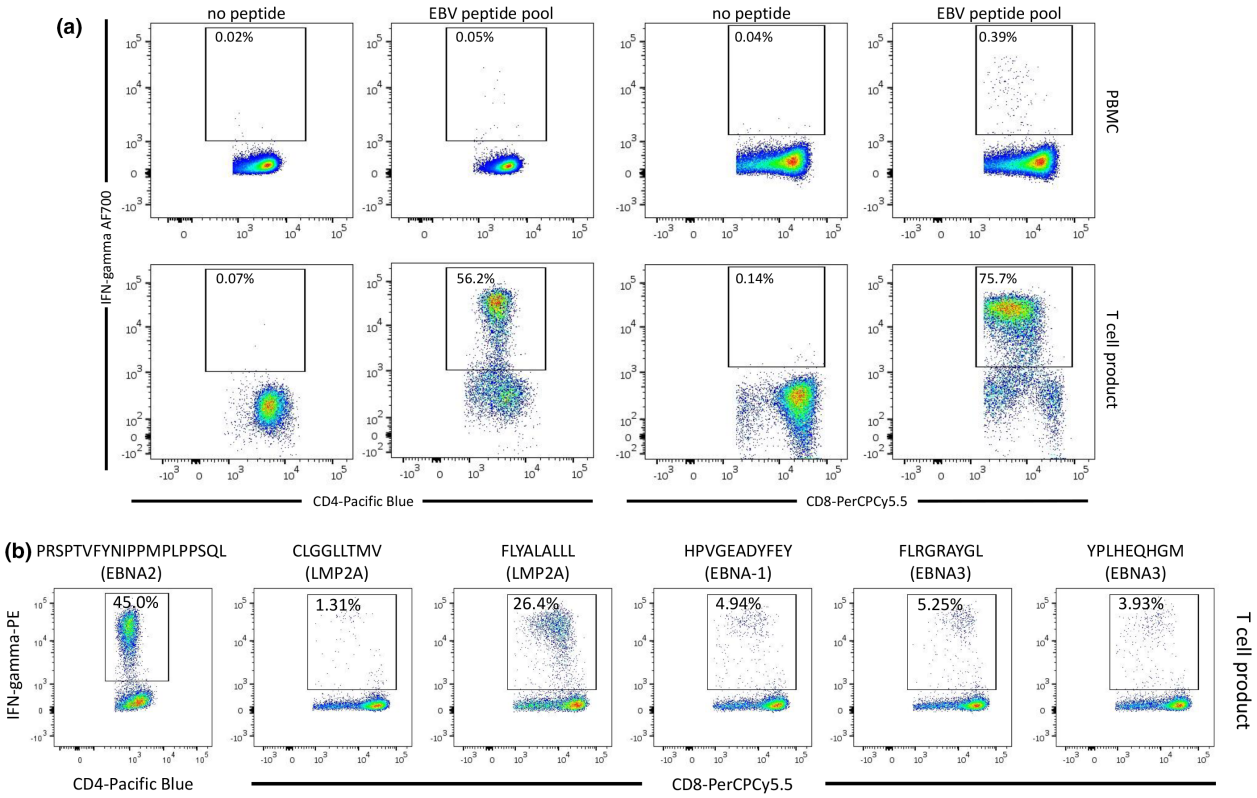

Figure 1. Characterisation of *in vitro*-expanded autologous EBV-specific T cells from a patient with lupus nephritis. **(a)** EBV-specific $CD4^+$ and $CD8^+$ T-cell reactivity against pooled EBV peptide epitopes. **(b)** EBV-specific $CD4^+$ and $CD8^+$ T-cell reactivity to HLA class II and class I-restricted individual EBV peptide epitopes. Briefly, *in vitro*-expanded T cells were incubated with either pooled or individual HLA class I and class II-restricted synthetic peptide epitopes for 4 h in the presence of GolgiPlug (Brefeldin A). T cells were stained for surface expression of CD3, CD4 and CD8, fixed and permeabilised, then assessed for the intracellular expression of IFN-γ. Data were acquired using an LSRFortessa (BD Biosciences), then analysed using FlowJo software.

IgG remained positive, with negative IgM. EBV viral load was not detected in peripheral blood. The unremitting lupus nephritis and virological profile suggested she could be a potential candidate for EBV-specific adoptive immunotherapy.

We sought and were approved by the Australian Therapeutic Goods Administration (TGA) to access autologous T-cell therapy via the Special Access Scheme Category B pathway. Approval for this adoptive T-cell therapy was granted by the Royal Brisbane and Women's Hospital's *ad hoc* multidisciplinary Clinical, Ethical and Legal Review Group. Peripheral blood from the patient was collected and processed to manufacture EBV-specific T-cell therapy in the TGA-licensed cell therapy manufacturing facility Q-Gen Cell Therapeutics. Briefly, peripheral blood mononuclear cells isolated from whole blood were stimulated with a pool of HLA class I- and class II-restricted peptide epitopes from EBV-encoded latent antigens and then cultured for 14 days in the presence of recombinant interleukin 2. After 14 days, these *in vitro*-expanded T cells were harvested and assessed for EBV-specific reactivity and microbiological contamination. EBV-specific reactivity was performed in triplicate using a standard intracellular cytokine assay. Data presented in Figure 1a show an increase in EBV-specific $CD4^+$ and $CD8^+$ T cells following expansion. These T cells revealed strong reactivity against multiple EBV epitopes restricted through HLA class I and class II alleles (Figure 1b). Microbiological testing showed no evidence of any infectious pathogen.

While awaiting T-cell therapy, the patient developed lymphopenia, and azathioprine was stopped. The $CD19^+$ and $CD20^+$ B-cell count was 0.03×10^9 cells L^{-1} and $< 0.01 \times 10^9$ cell L^{-1}, respectively, before T-cell administration. The patient received three T-cell infusions at fortnightly intervals with no immediate adverse

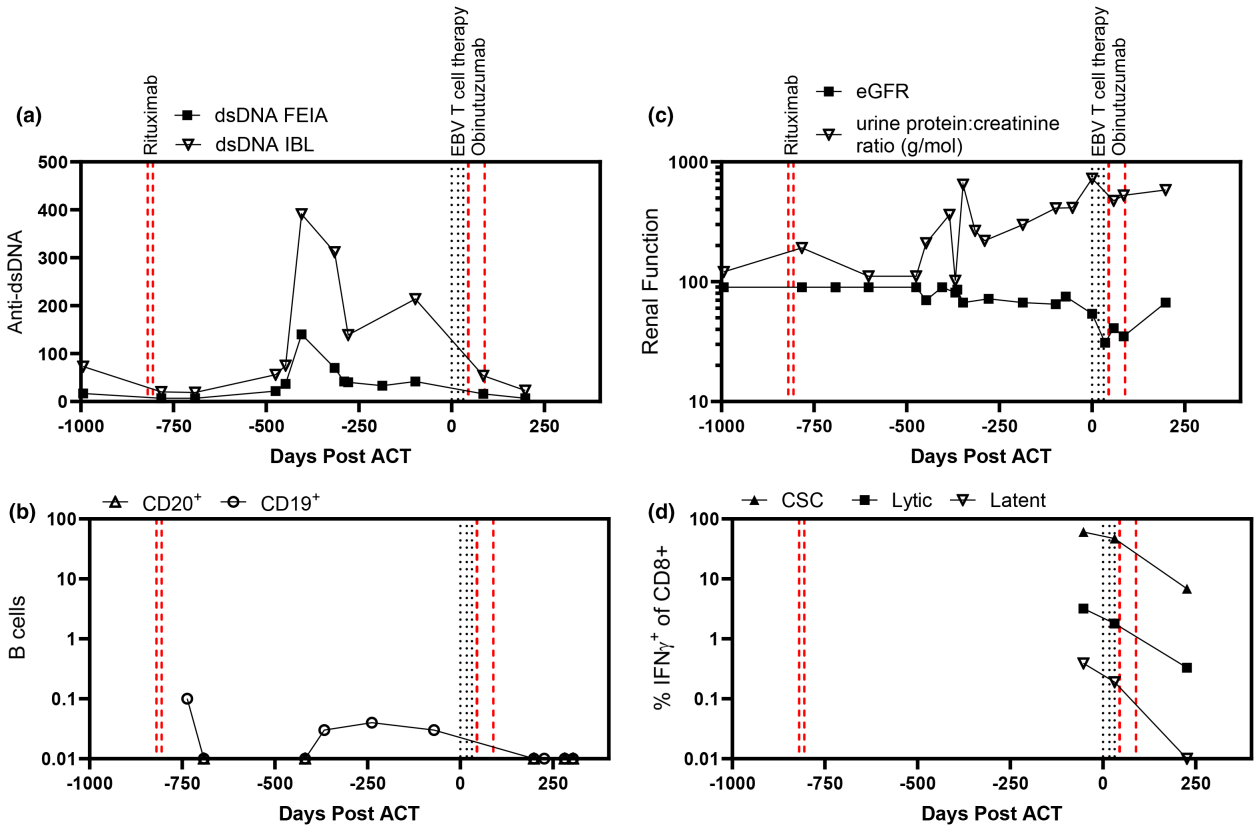

Figure 2. Clinical follow-up of a lupus nephritis patient before and after adoptive T-cell therapy (ACT). **(a)** Anti-dsDNA antibodies, **(b)** $CD19^+$ and $CD20^+$ B cells, **(c)** eGFR and urine protein to creatinine ratio and **(d)** frequency of EBV latent and lytic antigen-specific T cells. The dotted lines in the graphs indicate infusion of rituximab, EBV-specific T-cell therapy and obinutuzumab.

events. A day after the third infusion, the patient presented with norovirus gastroenteritis that was symptomatic with hypotension, diarrhoea and worsening kidney function (peak Cr 218 μmol L^{-1}). She was stabilised with symptomatic therapy and tacrolimus cessation. After careful consideration, further T-cell infusions were stopped in view of her persistently low immune cell counts and infectious complications, in the absence of a tangible renal response.

In the following 6 months, the patient gained 20 kg in weight and continued to exhibit features of nephrotic syndrome. She received three escalating doses of obinutuzumab (100 mg, 900 mg and 1 g). Immunological analysis showed a reduction in anti-dsDNA antibody levels (Figure 2a) while $CD19^+$ and $CD20^+$ B cell counts remained suppressed (Figure 2b). All other lymphoid subsets ($CD3^+$, $CD4^+$, $CD8^+$ T cells and $CD16^+$ NK cells) showed minimal change before or after the T-cell therapy (data not shown). After obinutuzumab therapy, the patient showed improvement in glomerular filtration rate (GFR) but continued to have nephrotic syndrome (Figure 2c). Although the urine protein-to-creatinine ratio showed a marginal reduction following T-cell administration, this ratio returned to high levels indicative of continued renal dysfunction (Figure 2c). Interestingly, T-cell responses to EBV-encoded latent and lytic antigens in the patient's peripheral blood declined after adoptive T-cell therapy (Figure 2d). This decline was also coincident with reduced global T-cell activation as measured using a cell stimulation cocktail. We were not able to assess the circulating half-life of administered adoptive T cells following infusion.

The case study presented here offers proof of principle that autologous EBV-specific T-cell therapy can be safely administered to patients with lupus nephritis. While the patient was diagnosed with norovirus a day after the third infusion, no adverse events were recorded after the first two infusions. Because of continuing nephrotic syndrome, the patient was treated with humanised anti-CD20 antibody (obinutuzumab).[26] After completing these

immunotherapies, the patient showed a reduction in anti-dsDNA antibodies and improved GFR. However, her urine protein to creatinine ratio remained high, indicative of ongoing renal dysfunction. While it is tempting to speculate that adoptive immunotherapy with autologous EBV-specific T cells may have contributed to a reduction in anti-dsDNA antibodies, it is not possible to dissociate the clinical impact of adoptive T-cell therapy and obinutuzumab therapy. It is important to note that the patient had undetectable $CD20^+$ B cells before obinutuzumab therapy. However, it has been reported that obinutuzumab has greater tissue penetration than rituximab, suggesting that it could impact B-cell populations in tissue sites.[27] While EBV-specific T cells may have killed auto-reactive EBV-immortalised B cells, leading to a reduction in autoantibodies in peripheral blood, these immunotherapies had a limited impact on renal function. Previous studies by Nantes University Hospital have assessed the potential therapeutic benefit of autologous EBV-specific cytotoxic T cells for the treatment of SLE.[28] Nine SLE participants were recruited to the study. Patients with lupus nephritis and cerebral lupus were excluded from the study. The response to adoptive T-cell therapy was equivocal, and there were no significant side effects of the therapy (personal communication). More recently, CD19 CAR T cells have been successfully used for the treatment of SLE, and many of these patients have shown long-term disease resolution.[29] One of the potential limitations of CD19 CAR T-cell therapy is the long-term global elimination of B cells, which may compromise the humoral immunity of the patients. Specific targeting of EBV-infected auto-reactive B cells through adoptive EBV-specific T-cell therapy offers a safe and targeted strategy to potentially improve clinical symptoms of lupus patients. It will be important to assess the therapeutic potential of EBV-specific T cells in a formal clinical trial across the broad clinical spectrum of lupus patients. EBV-specific T-cell therapy may be more effective for patients who are either newly diagnosed or have not progressed to late-stage disease.

METHODS

Manufacture of EBV-specific T cells

Peripheral blood mononuclear cells from the patient were stimulated with HLA class I- and class II-restricted peptide epitopes from EBV-encoded latent antigens.[30] These T cells were then cultured in RPMI 1640 medium supplemented with 5% human AB serum and recombinant interleukin 2 (IL-2; 200 IU mL^{-1}) for 14 days. After 14 days, these *in vitro*-expanded EBV-specific T cells were cryopreserved in Albumex 4 (CSL Behring, Melbourne, Australia) containing 10% dimethyl sulfoxide (WAK-Chemie Medical, Steinbach, Germany). Antigen specificity of these *in vitro*-expanded EBV-specific T cells was determined using intracellular cytokine assay as outlined below.

Intracellular cytokine assays

To assess EBV-specific reactivity, *in vitro* expanded T cells and PBMC were stimulated with EBV-specific peptide epitopes, then $CD4^+$ T cells and $CD8^+$ T cells were assessed for the expression of interferon gamma (IFN-γ), tumor necrosis factor (TNF), IL-2 and/or the mobilisation of CD107a, as previously described.[31,32] Flow cytometric acquisition was performed using a BD LSR Fortessa cell analyser with the FACSDiva software (BD Biosciences, Melbourne, Australia). Post-acquisition analysis was also performed using the FlowJo software (FlowJo, Ashland, Oregon, USA).

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AUTHOR CONTRIBUTIONS

Dwarakanathan Ranganathan: Conceptualization; investigation; writing – original draft; writing – review and editing. **Saskia Leibowitz:** Data curation; investigation; writing – original draft; writing – review and editing. **George T John:** Conceptualization; investigation; writing – original draft; writing – review and editing. **Michelle A Neller:** Data curation; writing – original draft; writing – review and editing. **George R Ambalathingal:** Data curation; writing – review and editing. **Leone Beagley:** Data curation; writing – review and editing. **Archana Panikkar:** Data curation; writing – review and editing. **Shannon Best:** Data curation; writing – review and editing. **Jyothy Raju:** Data curation; writing – review and editing. **Hilary Reddiex:** Data curation; writing – review and editing. **Sharad Ratanjee:** Data curation; writing – review and editing. **Monica Suet Ying Ng:** Data curation; writing – review and editing. **Corey Smith:** Data curation; writing – original draft; writing – review and editing. **Rajiv Khanna:**

Conceptualization; investigation; supervision; writing – original draft; writing – review and editing.

CONFLICT OF INTEREST

RK and CS are listed as inventors on patents for adoptive T-cell therapy for autoimmune diseases.

DATA AVAILABILITY STATEMENT

All data are available from the corresponding authors upon reasonable request.

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