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CASE REPORT

Oral Prednisolone, Apremilast and Human Umbilical Cord Mesenchymal Stem Cells in the Management of Pemphigus Foliaceus

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Abstract: This case report showed a 60-year-old male with Pemphigus foliaceus (PF), complicated by hypertension, diabetes, and hepatitis B, for whom traditional treatments posed potential risks. The regimen included prednisone, human umbilical cord mesenchymal stem cells (UC-MSCs), and apremilast, showing several advancements: UC-MSCs addressed PF and comorbidities without reported side effects, accelerated steroid tapering substantially compared to apremilast monotherapy, and held superior benefits over hematopoietic stem cells. Over a 4-month follow-up, there was a marked improvement in the patient's condition, normalization of autoantibody levels, and an increase in regulatory T cells. Further research and extended monitoring are warranted to ascertain the findings' validity and applicability.

Keywords: autoimmune bullous diseases, stem cells, apremilast, regulatory T cells

Introduction

Pemphigus foliaceus (PF), which is a chronic autoimmune bullous disease caused by the detachment of keratinocytes mediated by anti-desmoglein (Dsg) autoantibodies, mainly affects the skin with positive Nikolsky sign and rupture-prone bullae walls, impacting patients' lives considerably.[1] Current standard therapies for PF include systemic glucocorticoids, immunosuppressive agents such as mycophenolate mofetil (MMF), and rituximab.[1] However, these treatments present substantial risks, particularly for patients with comorbid conditions. Prolonged glucocorticoid use can exacerbate hypertension and hyperglycemia, while immunosuppressants heighten susceptibility to infections. Although rituximab has demonstrated efficacy, its use is contraindicated in patients with hepatitis B virus (HBV) due to the risk of viral reactivation.[2] These limitations highlight the critical need for safer adjunctive therapeutic options. Therefore, it's extremely tough to pick a proper treatment plan for elderly patients with comorbidities and highly urgent to reduce the dosage of glucocorticoids.

Here, we report a case of PF complicated by hypertension, type 2 diabetes mellitus, and a history of HBV infection. The patient was effectively treated with a combination regimen comprising prednisone, human umbilical cord mesenchymal stem cells (UC-MSCs) and apremilast. UC-MSCs, with immunomodulatory and multi - directional differentiation capabilities, have been employed in the treatment of autoimmune diseases as well as other diseases like diabetes and hepatitis B, with no obvious side effects reported so far.[3–5] Given the scarcity of previous reports on UC-MSCs for treatment, apremilast, a PDE-4 inhibitor with a relatively slow onset but comparatively high safety profile, was combined for treatment.

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Case Report

A 60-year-old man presented with erythema and erosions on his back for 3 months, which had extended to his face and anterior chest over 2 months (Figure 1a and b). The patient had a medical history of hypertension, type 2 diabetes mellitus, and a resolved HBV infection. Hypertension was effectively controlled with valsartan dispersible tablets (80 mg once daily), while diabetes was managed with pioglitazone hydrochloride and metformin hydrochloride tablets (15 mg twice daily), The HBV infection was resolved, as indicated by negative hepatitis B surface antigen (HBsAg) and positive hepatitis B surface antibody (HBsAb) and hepatitis B core antibody (HBcAb) serology, with no requirement for antiviral therapy. No adjustments were made to the treatment regimen during UC-MSCs therapy. Physical examination showed erythema, erosions and crusts on his head, face and back. The pemphigus disease area index (PDAI) was 6 points. The anti-desmoglein (Dsg) 1 antibody level was 59.16 U/mL (MBL, Nagoya, Japan; normal range <20 U/mL), while anti-

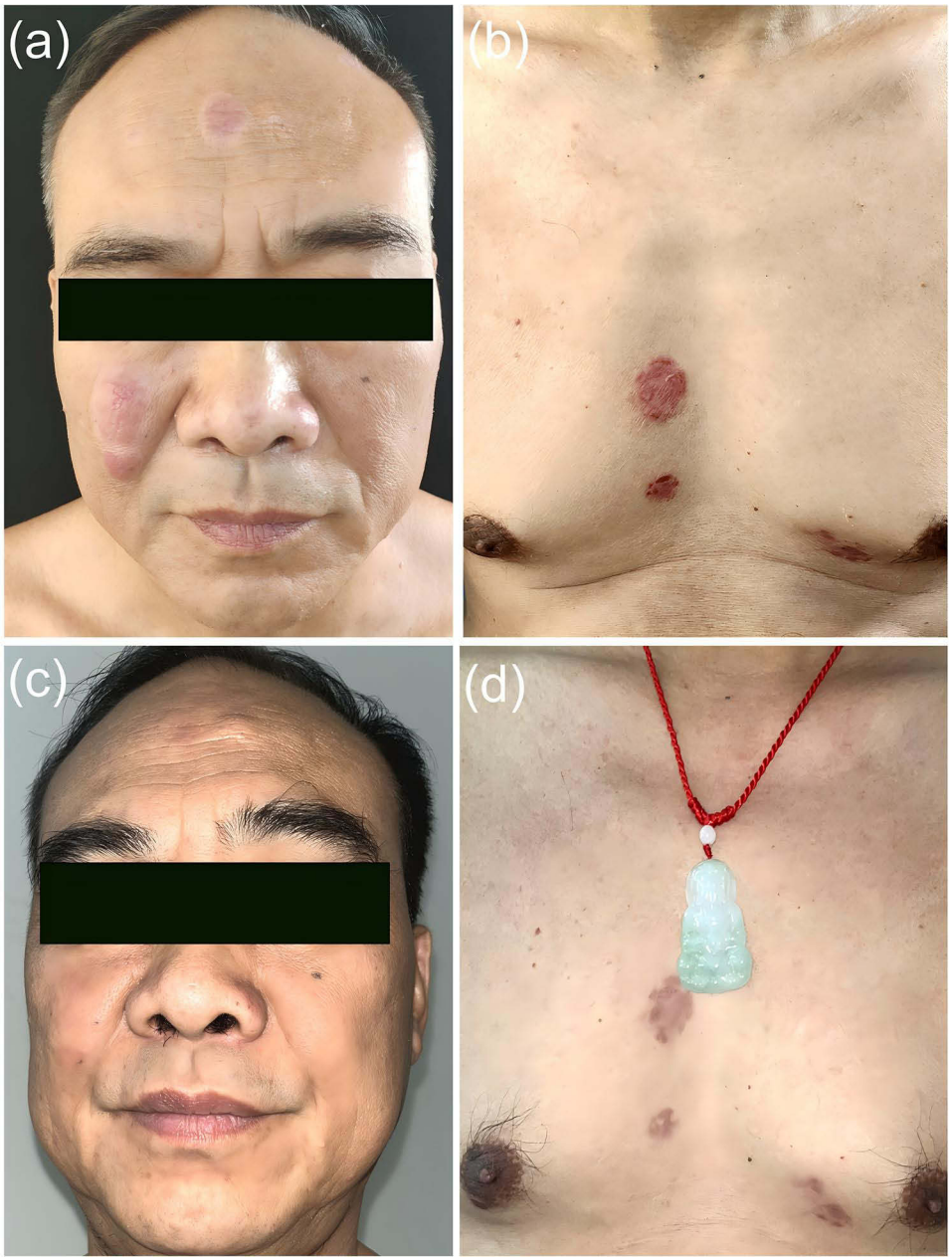

Figure 1 Facial (**a**) and anterior chest (**b**) manifestations prior to UC-MSCs (week 0). Facial (**c**) and anterior chest (**d**) manifestations after six intravenous injections of UC -MSCs (week 6). UC-MSCs, Human Umbilical Cord Mesenchymal Stem Cells.

Dsg3 antibody was normal range. Skin biopsies showed superficial crusting, epidermal hyperplasia, and papillary vascular hyperplasia in the dermis with a few lymphocytes infiltration around, indicating that the patient's skin lesions were relatively superficial. Direct immunofluorescence (DIF) revealed IgG deposits between the acanthocytes. Serological tests indicated positive HBcAb and HBsAb. The primary diagnosis was PF, with comorbid hypertension, type 2 diabetes mellitus, and resolved hepatitis B virus infection. His treatment was initiated with prednisone at a dosage of 0.5 mg/kg once daily (40 mg once daily) combined with apremilast at 30 mg twice daily. With the disease under control, the prednisone was reduced to 25 mg once daily over 2 months. However, a few new lesions occurred during this period. Due to comorbid hypertension and diabetes, and concerns about glucocorticoid risks, the patient incorporated UC-MSCs with informed consent. The clinical-grade UC-MSCs were supplied by the R&D Center, Wuhan Hamilton Biotechnology Co., Ltd. Intravenous infusion with UC-MSCs was given at 50×10^6 per session, once weekly for 6 times. Since the first intravenous infusion, there has been a notable improvement without new lesions (Figure 1c and d), as evidenced by a reduction in the levels of anti-Dsg1 autoantibody to normal level and a decrease in the prednisone from 25 mg to 10 mg. As of now, after 4 months of follow-up, the patient is stable with no recurrence and no side effects from apremilast and UC-MSCs. Treg and iTreg cells increased to 6.31% and 5.12% respectively (normal value 0.6–5.09% and 0.1–2.05%).

Discussion

The patient explicitly declined treatment with rituximab and MMF due to safety concerns. While rituximab has demonstrated efficacy in the management of pemphigus, its use is associated with a significant risk of HBV reactivation in carriers. Similarly, MMF, which is metabolized to mycophenolic acid, has been shown to directly enhance HBV replication in vitro, thereby increasing the risk of viral reactivation in this HBV carrier.[6] In contrast, UC-MSCs not only lack the immunosuppressive toxicity associated with conventional therapies but also exhibit potential hepatoprotective effects. Through immunomodulatory properties and tissue repair mechanisms, UC-MSCs may contribute to improved liver function in patients with HBV-related conditions.[5]

The successful deployment of UC-MSCs in managing diseases like psoriasis and lupus without notable side effects, along with the promising outcomes from Han et al's use of cytotoxic T-lymphocyte antigen 4 (CTLA4)-overexpressing adipose tissue mesenchymal stem cells (ATMSCs) to treat a dog with steroid-refractory PF, bolsters our consideration for utilizing UC-MSCs in treating this patient.[7]

UC-MSCs demonstrate therapeutic potential in type 2 diabetes by enhancing β-cell function and insulin sensitivity, aligning with our patient's stable glycemic control.[8] Additionally, UC-MSCs may mitigate cardiovascular remodeling in hypertension, supporting their use in comorbid populations.[9] A meta-analysis of 19 trials confirmed UC-MSCs' safety, with transient fever as the primary adverse event.[10] Notably, our patient experienced no adverse events during or after treatment, highlighting individualized tolerability.

Patients' autoreactive B cells play a crucial role in producing autoantibodies that form the basis of the pathogenesis.[1] UC-MSCs have been shown to inhibit the proliferation of naive B cells and suppress B lymphocyte differentiation through the production of interleukin-1 receptor antagonist (IL-1RA), consequently leading to a reduction in plasma cell and antibody production.[11] IL-1RA may improve dysfunctional Breg cells in pemphigus patients by enhancing IL-10 production.[11,12] UC-MSCs can also arrest B-lymphocytes in the G0/G1 phase of the cell cycle by activating MAPK pathways such as p38, thereby inhibiting the proliferation and maturation of B-lymphocytes.[4]

In pemphigus patients, the proportion of Treg cells in peripheral blood is significantly reduced, and the balance between Th17 and Treg cells is disrupted. Treg cells mainly control inflammation and immune responses to self-antigens, while Th17 cells promote inflammatory responses and skin damage. UC-MSCs inhibit Th17 differentiation by promoting IL-10 and PGE2 while suppressing IL-17, IL-22, and IFN-γ.[4] They also balance Th17/Treg by increasing Treg levels through TGF-β secretion.[4] The addition of treg in this patient aligns with these findings. Due to limited prior reports on using UC-MSCs for treatment, the PDE-4 inhibitor apremilast, known for its safety, was used. In HBV carriers, apremilast poses a low reactivation risk and does not require antiviral prophylaxis, making it safer than traditional agents.[13] Apremilast has been reported as effective in managing mild PF.[14] In a previous case, a patient required 5 months to reduce their prednisone dosage from 25 mg to 15 mg daily. However, with the addition of UC-MSCs, the

patient in our case was a notable decrease in the prednisone from 25 mg to 15 mg in 6 weeks. No significant abnormalities in blood, liver, or kidney function were noted. Apremilast, by inhibiting PDE activity and increasing cAMP levels, suppresses the synthesis of pro-inflammatory factors such as TNF-α and promotes the synthesis of anti-inflammatory factors like IL-10.[15] Furthermore, it can also regulate the balance of Th17/Treg cells, thereby being used to treat chronic inflammatory diseases.[16]

Research indicates that autologous hematopoietic stem cell transplantation (ASCT) or allogeneic hematopoietic stem cell transplantation (allo-HSCT), while efficacious for refractory pemphigus, is more intricate and has more stricter patient selection criteria compared to UC-MSCs therapy.[17,18] The deep immunosuppression required in the pretreatment phase raises the risk of infection, and allogeneic transplants pose a risk of graft-versus-host disease (GVHD). In contrast, UC-MSCs treatment, with its low immunogenicity and potential to treat GVHD, offers a simpler and more accessible alternative.[4]

Although there are currently few reported cases, in this patient, the skin lesions have been significantly improved, and glucocorticosteroids have been successfully and rapidly reduced. Moreover, various aspects such as the normalization of autoantibody levels and the increase in the detection of Treg cells can all prove the effectiveness of the treatment. Furthermore, UC-MSCs possess the characteristic of multi-directional differentiation, which might be beneficial for the repair of skin damage in patients with pemphigus. The findings of this study are limited by its single-case design, which restricts generalizability, and the short follow-up period (4 months) that precludes assessment of long-term outcomes. Additionally, larger cohort studies are warranted to validate the efficacy and safety of UC-MSCs in patients with complex comorbidities.

Conclusion

This case underscores the potential of UC-MSCs as a novel adjunctive therapy in the management of PF, particularly in patients with multiple comorbidities where conventional immunosuppressive therapies pose significant risks. The combination of UC-MSCs and apremilast facilitated a substantial reduction in glucocorticoid dosage while effectively controlling disease activity, normalizing autoantibody levels, and increasing regulatory T cells. Notably, the absence of adverse effects, including the risk of HBV reactivation, highlights the safety profile of this therapeutic approach in patients with a history of viral infections and metabolic disorders. Future research should focus on larger, controlled clinical trials to validate the long-term efficacy, safety, and immunomodulatory mechanisms of UC-MSCs in PF. Further investigations are also needed to explore the broader applicability of UC-MSCs in autoimmune diseases, particularly their role in enhancing immune tolerance and tissue repair. The integration of UC-MSCs into existing treatment protocols may offer a safer and more effective alternative for patients with complex medical profiles, warranting continued research and clinical evaluation.

Abbreviations

PF, Pemphigus foliaceus; UC-MSCs, Human Umbilical Cord Mesenchymal Stem Cells; Dsg, desmoglein; CTLA4, cytotoxic T-lymphocyte antigen 4; ATMSCs, adipose tissue mesenchymal stem cells; ASCT, autologous hematopoietic stem cell transplantation; allo-HSCT, allogeneic hematopoietic stem cell transplantation.

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Disclosure

The authors report no conflicts of interest in this work.

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