Bullous pemphigoid with prominent mucosal involvement in the setting of renal allograft rejection

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INTRODUCTION

Bullous pemphigoid (BP) is a blistering disorder characterized by autoantibodies to skin basement membrane zone components, specifically collagen XVII (BPAg2/BP180) and BP230 (BPAg1). Most cases of BP are idiopathic; however, a small proportion of BP cases are medication-induced. There have also been reports of BP after renal allograft rejection.[1-17] Here, we present 2 cases of renal allograft rejection associated BP involving oral mucosal lesions. Our literature review suggests that mucosal involvement may be relatively common in BP associated with renal allograft rejection.

Abbreviations used:

BP: Bullous pemphigoid
HSV: herpes simplex virus

CASE REPORTS

Case 1

A 34-year-old African American woman with end-stage renal disease due to type I diabetes mellitus underwent kidney and pancreas allogeneic transplant at age 28 years. Apart from an episode of acute grade 3 pancreatic rejection that responded to solumedrol and thymoglobulin, her posttransplant course was uncomplicated. Her creatinine was stable on an immunosuppression regimen of tacrolimus 5 mg twice a day, mycophenolate mofetil 360 mg twice a day, and prednisone 5 mg daily.

Six years posttransplant and 1 week after stopping tacrolimus due to difficulties refilling medication, she presented to the emergency department with nausea, poor oral intake, left lower quadrant pain, and rash. She was found to have elevated serum creatine (5.48 mg/dL) and nephrotic range proteinuria concerning for acute renal rejection. Renal biopsy demonstrated Banff IB/2A acute cellular and antibody-mediated rejection.

On examination, she had multiple 4 to 8 mm dusky-centered erythematous vesicles affecting the lower extremities, scattered erythematous erosions on the lower back and abdomen, and buccal mucosa erosions (Fig 1). She was empirically started on IV acyclovir for suspected disseminated herpes simplex virus (HSV). Skin biopsy from a left thigh vesicle demonstrated a subepidermal vesicular dermatitis with eosinophils (Fig 2). On direct immunofluorescence, there was diffuse linear deposition of C3 and IgG at the basement membrane zone with C3 predominating. Serum enzyme-linked immunosorbent assay (ELISA) analysis detected elevated BP180 antigen, consistent with a diagnosis of BP. Serum BP230 antigen tests were negative. HSVI, HSVII, and

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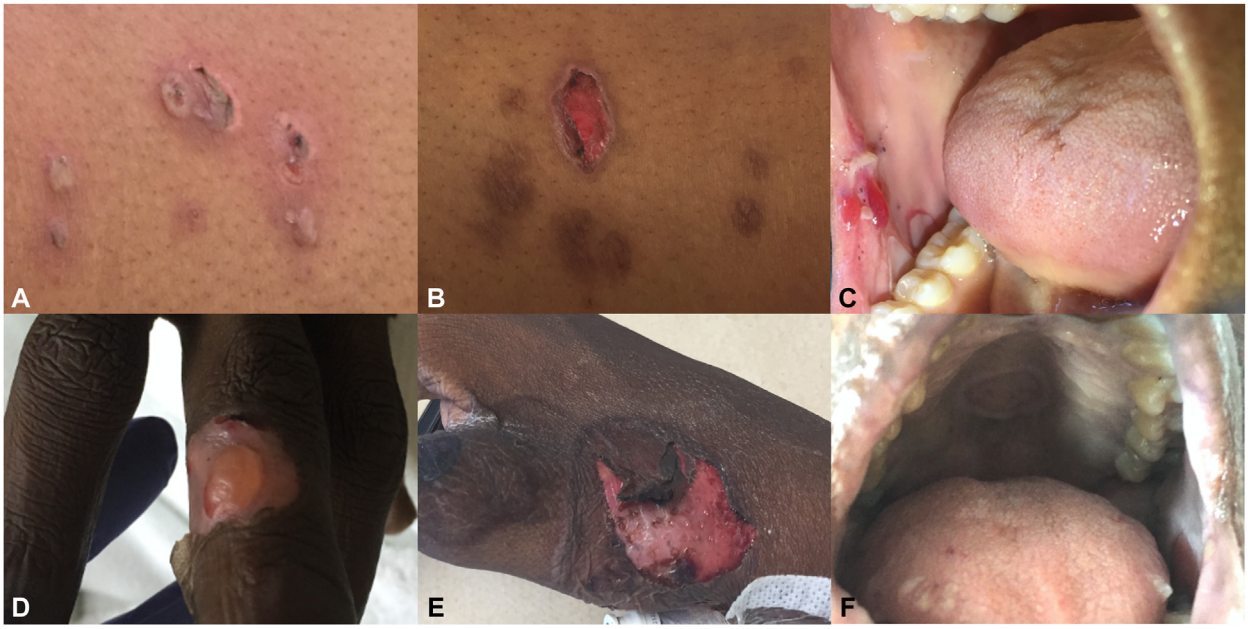

Fig 1. Clinical images of cutaneous and oral mucosal lesions. Images from patient 1 including **(A)** middle portion of the thigh, **(B)** upper portion of the thigh, and **(C)** oral mucosal lesions. Images from patient 2 including **(D)** 2nd digit, **(E)** dorsal aspect of the thumb, and **(F)** hard palate lesions.

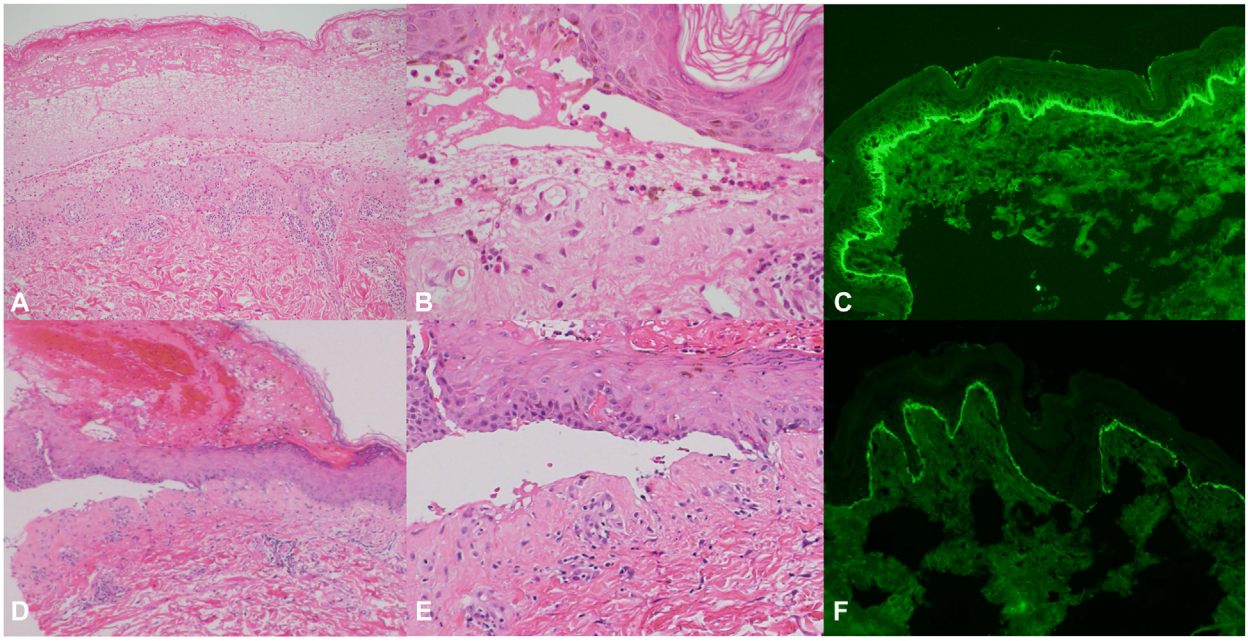

Fig 2. Histological and immunofluorescence images of skin lesions. Skin biopsy from patient 1 shows a subepidermal blister with eosinophils (hematoxylin-eosin stain; original magnifications: **A,** ×40; **B,** ×200) and diffuse linear C3 deposition at the basement membrane zone on direct immunofluorescence **(C)**. Skin biopsy from patient 2 shows a pauci-inflammatory subepidermal blister with scant inflammatory cell infiltrate (hematoxylin-eosin stain; original magnifications: **D,** ×40; **E,** ×100) and diffuse linear C3 deposition at the basement membrane zone on direct immunofluorescence **(F)**.

varicella-zoster virus immunohistochemical tissue stains as well as lesional HSV and varicella-zoster virus polymerase chain reaction (PCR) swabs were also negative.

Table I. Literature review of cases of bullous pemphigoid in the setting of renal allograft rejection

References	Year	Age at presentation	Sex	Rejection type	Mucosal lesions	BP status
Feehally et al[1]	1982	12	F	Chronic	Yes	Resolution with nephrectomy
Simon and Winkelmann[2]	1986	63	M	Chronic	No	Resolution with corticosteroids (oral prednisone)
Ross and Ahmed[3]	1989	28	M	Chronic	Yes	Resolution with corticosteroids (oral prednisone)
Yamazaki et al[4]	1998	9	M	Chronic	No	Resolution with graft atrophy
Morelli and Weston[5]	1999	15	F	Chronic	No	Resolution with corticosteroids (oral prednisone)
Tessari et al[6]	2002	47	F	Chronic	No	Resolution with nephrectomy
Chen et al[7]	2009	52	M	Chronic	Yes	Lesions resistant to systemic therapies; patient died of sepsis
Sofi et al[8]	2010	46	M	Acute	No	Resolution with corticosteroids and mycophenolate
Liaw et al[9]	2011	27	M	Chronic	No	Resolution with nephrectomy
Davis et al[10]	2011	13	M	Chronic	No	Resolution with nephrectomy
Mammen et al[11]	2011	12	M	Chronic	Yes	Resolution with nephrectomy
Devaux et al[12]	2011	56, 61	M	Chronic	No	Resolution twice with nephrectomy
Rodríguez-Caruncho et al[13]	2011	42	M	Chronic	No	Resolution with nephrectomy
Peruzzo et al[14]	2013	28	F	Chronic	Yes	Resolution with corticosteroids (oral prednisone) and azathioprine; received second kidney transplantation
Green et al[15]; Abdul Salim et al[16]	2015	44	F	Chronic	No	Resolution with corticosteroids
Koratala et al[17]	2018	63	M	Acute, with new MN	No	Resolution with corticosteroids (oral prednisone)
Present case 1	2018	34	F	Acute	Yes	Resolution with corticosteroids (oral prednisone) and rituximab
Present case 2	2019	50	M	Chronic	Yes	Improvements with nephrectomy, undergoing corticosteroid taper

BP, Bullous pemphigoid; *MN*, membranous nephropathy.

The patient's BP lesions were not controlled with the transplant rejection regimen described above. She was given clobetasol 0.05% gel and ointment for symptom relief but was subsequently rehospitalized for worsening oral BP flare with hemoptysis and epistaxis. She was given prednisone 80 mg daily with magic mouth wash (aluminum-magnesium-hydroxide with simethicone, diphenhydramine, and lidocaine) and clobetasol ointment, and she was discharged with a steroid taper. However, ongoing flares resulted in reescalation to 80 mg prednisone daily. To minimize steroid burden, she was treated with 2 rituximab transfusions and transitioned to a 5 mg prednisone maintenance dose. Her last reported lesion occurred 4 months after the rituximab transfusions and >1 year out she continues to have no new lesions.

Case 2

A 50-year-old African American man with end-stage renal disease presumably due to hypertensive nephrosclerosis underwent 2 allogeneic kidney transplants in 1999 and 2013, complicated by focal segmental glomerulosclerosis and graft failure. He has been on hemodialysis since 2018.

In 2019, the patient developed rashes on his hands and face that progressed to fluid filled blisters; he also noted oral mucosal involvement (Fig 1). He was given mupirocin (nasal blisters) and topical betamethasone ointment (oral blisters). An abdominal vesicle punch biopsy demonstrated pauci-inflammatory subepidermal vesicular dermatitis with a scant inflammatory cell infiltrate (Fig 2). Immunostaining demonstrated diffuse linear C3 deposition but not IgG deposition at the basement membrane zone. Serum testing was positive for BP180 antibodies but negative for BP230, desmoglein-1 and desmoglein-3 antibodies consistent with BP.

He began an oral prednisone taper starting at 80 mg and saw a decrease in blisters but with some residual activity. We suspected the patient's BP was

driven by his rejected kidney graft due to persistent BP lesions on 80 mg prednisone. After surgical nephrectomy, the patient's BP steadily improved. He is currently well controlled with 20 mg of prednisone daily and 0.05% betamethasone topical ointment and is undergoing a prednisone taper.

DISCUSSION

These 2 cases add to the available reports of patients developing BP after renal allograft rejection, the etiology of which is unknown. Previous reports have hypothesized that autoantibodies causing BP lesions may be formed within the immunological milieu occurring at the site of graft rejection.[1,4,6,11] Sofi et al[8] suggested that the alpha-5 chain of type-IV collagen, which is present in both the renal and epidermal basement membranes, may be a common immunologic target to explain this phenomenon.[8] Indeed, BP blisters resolved in all reported patients who underwent graft nephrectomy supporting the hypothesis that an immunologic process targeting the allograft contributes to the etiology of BP lesions in these patients.

After a literature review of renal allograft rejection associated BP, we noticed an unusually high rate of mucosal involvement compared with idiopathic cases. Including the 2 patients presented in this report, 7 of 18 (38.9%) available cases have documented mucosal lesions (Table I). Limitations of this estimate include reporting bias and small sample size, which precludes statistical analyses. Reported prevalence of mucosal lesions in idiopathic BP ranges from 17.1%[18] to 18.9%[19] (56/328 and 18/95, respectively).

The pathophysiologic understanding of mucosal lesions in BP is very limited. Recent studies demonstrated that mucosal involvement is associated with more extensive cutaneous blister severity, younger age, and less peripheral eosinophilia.[18,19] Clapé et al[19] demonstrated that mucosal lesions were associated with disease severity and were also more common in patients negative for anti-BP230 antibodies, as was the case for both our patients. Finally, mucosal involvement in BP has been associated with higher steroid dose requirements, although it is unclear if this association is confounded by cutaneous BP severity.[18]

The observation of prominent oral lesions in BP after renal transplant rejection has important implications. First, mucosal involvement should not reduce clinical suspicion for BP in this setting. Second, the observation of frequent oral mucosal lesions may help uncover a distinct etiology of BP after renal allograft rejection. However, it remains unclear if mucosal involvement is related to cutaneous BP severity after renal allograft rejection. Further investigation is required to clarify the etiology of BP in renal allograft rejection and to understand what factors mediate mucosal involvement.

Conflicts of interest

None disclosed.

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