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Levofloxacin-Associated Bullous Pemphigoid in a Hemodialysis Patient After Kidney Transplant Failure

Authors' Contribution:

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Patient: Female, 27-year-old
Final Diagnosis: Levofloxacin-associated bullous pemphigoid
Symptoms: Worsening bullous rash
Medication: —
Clinical Procedure: —
Specialty: Dermatology • Nephrology

Objective: Rare disease

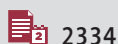
Background: Patients with end-stage renal disease (ESRD) who require dialysis can develop a variety of skin conditions, such as pruritus, xerosis, skin infections, and autoimmune reactions. Bullous pemphigoid (BP) is an autoimmune bullous disorder with an increasing incidence. It can be caused by over 90 medications, but levofloxacin-induced BP in hemodialysis patients has not yet been reported. This report is of a 27-year-old woman with ESRD on hemodialysis who developed BP after levofloxacin treatment.

Case Report: A 27-year-old woman with hemodialysis after kidney transplantation failure was started with levofloxacin for suspected urinary tract infection 1.5 months prior to admission. Her urinary tract infection symptoms were improved after 3 weeks of levofloxacin treatment, but a serious rash developed, presenting with progressive bullous throughout the body and facial involvement. A thorough workup showed a remarkably elevated hemidesmosomal antigen, BP180 (116 RU/mL), and cutaneous indirect immunofluorescence on human salt-split skin substrate was positive for serum basement membrane zone IgG with an epidermal pattern. Skin biopsy direct immunofluorescence staining showed continuous linear C3 deposition along the basement membrane zone. Prednisone 60 mg daily was started with a taper schedule. She no longer had new skin rash during a follow-up of over 3 months.

Conclusions: To the best of our knowledge, this is the first case of levofloxacin-induced BP in a patient undergoing hemodialysis. This report highlights the importance of recognizing skin reactions associated with ESRD in dialysis patients, the correct diagnosis by biopsy and histopathology, and the correct and timely management.

Keywords: Levofloxacin • Allografts • Renal Dialysis • Pemphigoid, Bullous

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Background

Dermatological diseases are not uncommon in patients with advanced chronic kidney disease, including those with end-stage renal disease (ESRD) and renal transplant, presenting with a wide spectrum of cutaneous abnormalities, such as itching, Lindsay's nails, xerosis cutis, hyperpigmentation, nephrogenic systemic fibrosis, severe deforming necrotizing lesions, and non-melanoma skin cancer [1]. Autoimmune blistering disorders include pemphigus and pemphigoid [2]. Pemphigus has 3 major types, pemphigus vulgaris, pemphigus foliaceus, and paraneoplastic pemphigus, and is characterized by autoantibodies directed against epidermal surface proteins leading to the loss of cell-to-cell adhesion [3]. Bullous pemphigoid (BP), the most common type of autoimmune bullous skin disease, has been reported in patients with ESRD and dialysis [4,5]. BP is caused by circulating autoantibodies against the specific hemidesmosomal antigens (ie, BP180 and BP230) located at the dermo-epidermal junction, thus causing complete separation of the epidermis from the dermis and development of tense blisters over an erythematous or urticarial base [3,6].

The incidence of BP is increasing and is currently reported between 4 and 22 per 1 000 000 person-years in Europe [7-9]. A recent systematic review and meta-analysis study shows that a global incidence of BP was 41.9 per 1 000 000 person-years (95% confidence interval [CI]: 41.4-42.4) [10]. Several forms of BP have been well characterized, including localized, mucous membrane predominant, pemphigoid gestation, and drug-associated BP (DABP). It has been reported that over 90 medications can cause BP, such as diuretics (eg, furosemide), antihypertensives (eg, angiotensin-converting enzyme inhibitors, beta-blockers, and Ca²⁺ channel blockers), antitumor agents (eg, adalimumab, efalizumab, and etanercept), and antibiotics (penicillin, amoxicillin, and metronidazole) [9,11-13]. Quinolone-induced BP has been rarely reported, and only 2 cases were related to ciprofloxacin during treatment for urinary tract infection [14,15] and 1 case was related to levofloxacin for pneumonia [16].

As outlined above, patients with ESRD who require dialysis can develop a variety of skin conditions, ranging from itching and skin infections to autoimmune reactions. This report is of a 27-year-old woman with ESRD on hemodialysis who developed BP after levofloxacin treatment.

Case Report

A 27-year-old female with hemodialysis was admitted for evaluation of a worsening bullous rash and shortness of breath over the last 3 days. Her past medical history was notable for ESRD secondary to inherited focal segmental glomerulosclerosis with

INF2 mutation and living unrelated kidney transplantation in October 2013. Subsequently, allograft failure occurred due to rejection related to non-compliance with anti-rejection medications. Her allograft failure was caused by acute cellular and antibody-mediated rejection via biopsy approval. She had restarted in-center hemodialysis in December 2017. Her condition was maintained on anti-rejection medications, including tacrolimus and prednisolone, while she was on dialysis. However, she was not compliant with anti-rejection medications. She had a long history of hypertension and chronic anemia, with a baseline hemoglobin between 10.3 and 11.4 g/dL. Her home medications mainly included tacrolimus 4 mg every morning and 3 mg every evening, prednisolone 5 mg daily, carvedilol 25 mg twice a day, lisinopril 5 mg daily, cholecalciferol 1000 unit daily, folate 1 tablet daily, calcium carbonate 1000 mg with meals and 1500 mg at bedtime, sevelamer 800 mg with meals, darbepoetin alfa 40 mcg intravenous (i.v.) and iron sucrose 100 mg i.v. once a week, and paricalcitol 2.5 mcg i.v. and etelcalcetide 5 mg i.v. with each dialysis treatment.

One and one-half months prior to admission (**Figure 1**), she reported having flank pain and frequency, urgency, and voiding small volumes of gross hematuria for 4 days, associated with a low-grade temperature of 38°C and a notable drop of hemoglobin from the baseline >10 to 7.5 g/dL. She sought treatment with primary care, and urinary tract infection was suspected. She was started on levofloxacin 500 mg every 48 h for 10 days. Although she no longer had fever and the flank pain improved, she still had hematuria. An ultrasound of the transplanted kidney indicated allograft pyelonephritis. Her levofloxacin was extended for another 10 days with the same dose. Thereafter, the hematuria was not improved. A urine culture showed mixed flora. An indium-111 white blood cell (WBC) scan showed inflammation in the right lower quadrant renal allograft, and possibly partial recovery. Subsequently, she continued levofloxacin 250 mg every 48 h to complete a total of 4 weeks of therapy.

One week prior to admission, she noted the onset of a macular rash on the wrist, which subsequently blistered. She stated that the rash was intensely pruritic, but not painful. She also reported numerous lesions throughout the body and facial involvement, but denied any rashes in the mouth. She had a history of shingles. She was started on valacyclovir 500 mg once a day for potential herpes zoster. Meantime, swab polymerase chain reaction (PCR) testing for varicella-zoster virus (VZV) and herpes simplex virus (HSV) was performed, and the results were negative. In the 3 days prior to admission, she reported that her rash was worsening and was occasionally accompanied by chest pain and shortness of breath. She had several episodes of vomiting and denied any diarrhea, cough, and sore throat. She denied melena and hematochezia.

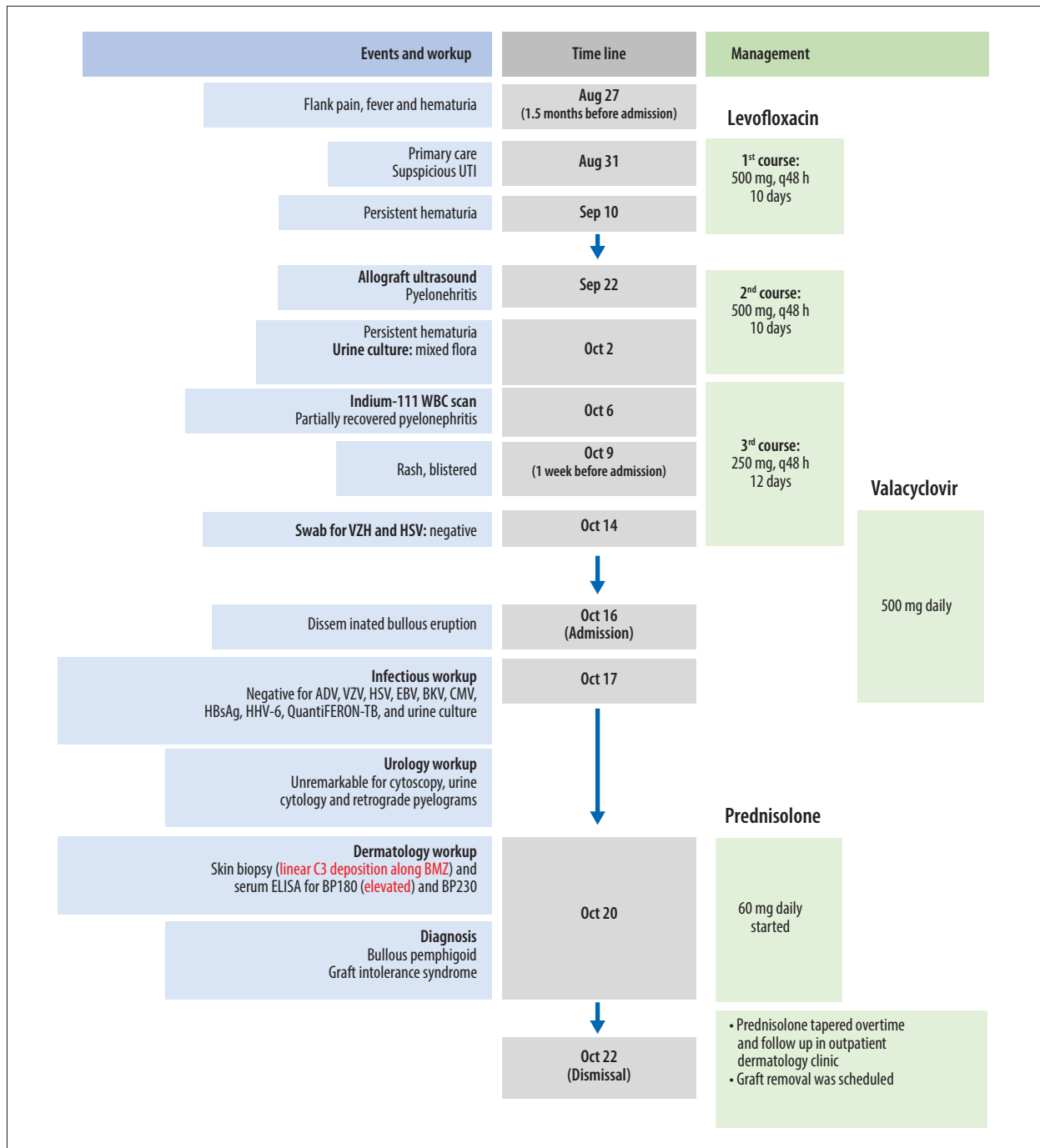


Figure 1. Timeline of disease course, diagnostic workup, and management of the patient. UTI – urinary tract infection; WBC – white blood cell; VZV – varicella-zoster virus; HSV – herpes simplex virus; ADV – adenovirus; EBV – Epstein-Barr virus; BKV – BK virus; CMV – cytomegalovirus; HBsAg – hepatitis B surface antigen; HHV – human herpesvirus; TB – tuberculosis; BMZ – basement membrane zone; ELISA – enzyme-linked immunosorbent assay; BP – bullous pemphigoid.

On admission, her vital signs were blood pressure of 168/126 mmHg, heart rate of 112 beats/min, respiratory rate of 20 breaths/min, and temperature of 37°C. She was alert and oriented. The lower extremities were warm and negative for myalgias. A skin examination showed diffuse vesicular lesions,

not photo distributed, on an erythematous base in different stages of healing and crusting. Large bullous lesions were noted over the upper extremities (Figure 2A). She did not have any intraoral lesions or signs of angioedema. The rest of the physical examination was unremarkable. Although the swab

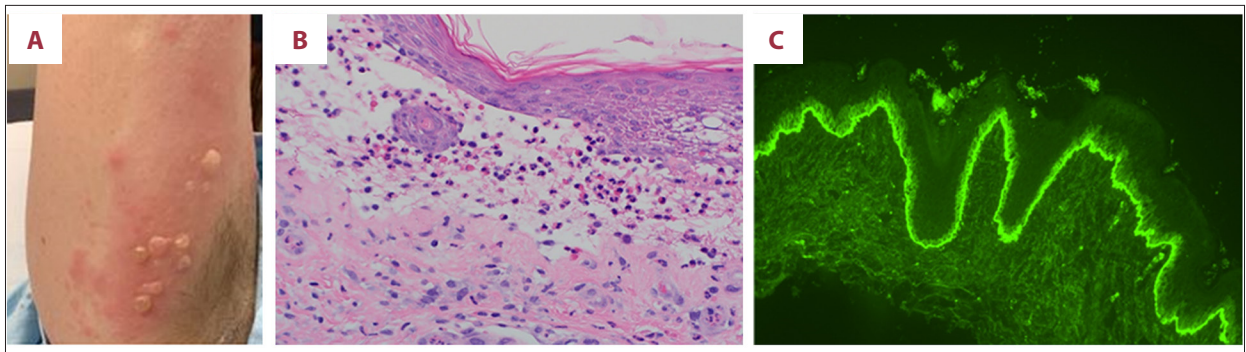


Figure 2. Representative skin lesions and histological findings of bullous pemphigoid on skin biopsy. (A) Multiple vesicular and tense bullae lesions over the upper arm presented on admission. (B) Hematoxylin and eosin staining of skin biopsy showed eosinophilic spongiosis, subepidermal cleft and mixed dermal inflammation with numerous eosinophils and neutrophils (magnification: 400×). (C) Direct immunofluorescence staining of skin biopsy revealed strong deposition of linear complement 3 along the basement membrane zones (magnification: 400×).

PCR test for VZV and HSV was negative, there was still concern about disseminated herpes zoster, as the patient was immunosuppressed. Drug-induced and idiopathic autoimmune blistering diseases, such as porphyria or pseudo porphyria, bullous impetigo, pemphigus vulgaris and BP, were considered. Levofloxacin and valacyclovir were discontinued, and cetirizine 10 mg 4 times a day and hydroxyzine 25 mg at bedtime was initiated until further evaluation was completed.

The laboratory examination revealed a hemoglobin level of 7.3 g/dL. Serum quantitative beta-human chorionic gonadotropin and QuantiFERON-tuberculosis Gold testing was negative. Testing for urine BK virus, urine culture, urine mycobacterial culture, and urine cytology were negative. A repeated PCR test from skin vesicles was negative for VZV and HSV. PCR testing for the SARS-CoV-2 virus was negative. Drainage bacteria culture of the skin lesion was negative. An electrocardiogram and chest computed tomography (CT) scan were unremarkable. An abdominal CT scan indicated graft pyelonephritis. A repeated transplant kidney ultrasound showed continued mild hydronephrosis with evidence of allograft pyelonephritis. A cystoscopy with retrograde pyelograms of the transplant and native kidneys were unremarkable.

Serum enzyme-linked immunosorbent assay (ELISA) showed remarkably elevated BP180 (116 RU/mL) and negative BP230 (<2 RU/mL). Cutaneous indirect immunofluorescence testing on human salt-split skin substrate was positive for serum basement membrane zone IgG with an epidermal pattern. Hematoxylin and eosin (H&E) staining of a skin-shave biopsy on the right upper anterior arm showed eosinophilic spongiosis, subepidermal cleft, and mixed dermal inflammation with numerous eosinophils and neutrophils (Figure 2B). Skin direct immunofluorescence staining was negative for IgG, IgM, IgA, and fibrinogen, but revealed continuous linear C3 deposition along the basement membrane zone (Figure 2C). Considering

the history of medications, a diagnosis of DABP likely caused by levofloxacin was made. Prednisone 60 mg daily was started with a taper schedule. She no longer had new skin rash during a follow-up of over 3 months.

Discussion

This report highlights the importance of early diagnosis of DABP, as recognition and prompt cessation of the offending agent produce a rapid improvement. So far, only 1 case of levofloxacin-associated BP has been reported [16]. Here, we reported the first case of levofloxacin-induced BP in a patient undergoing hemodialysis. Our patient mainly presented with blistered bullae. BP is the most frequent autoimmune bullous disorder [17]. The patient would be quite young to have classic BP, as it most frequently occurs in the elderly, with average age of onset >60 years [6]. A significant feature of this patient was a recent change of medication list, as she was taking levofloxacin for a suspected urinary tract infection. DABP tends toward younger age groups, and can resemble other entities, such as erythema multiforme or pemphigus [9]. The diagnosis of BP relies on skin immunopathologic findings and elevated BP180/BP230 autoantibodies [6]. In our patient, positive staining for C3 along the basement membrane zone, highly elevated serum BP180, and positive IgG on human salt-split skin substrate with an epidermal pattern were consistent with the features of BP. Negative staining for cell surface IgG ruled out pemphigus vulgaris, another rare autoimmune bullous skin disorder. Pemphigus vulgaris is characterized by painful blistering of skin and mucous membranes. Histological features of pemphigus vulgaris are defined as intra-epidermal acantholysis on H&E staining and intercellular deposition of IgG and/or C3 at the surface of epidermal keratinocytes on direct immunofluorescence staining [18-20]. Following discontinuation of levofloxacin and treatment with prednisone, her symptoms improved and no new skin lesions

appeared. As such, BP was very likely induced by levofloxacin in this patient. The underlying mechanism of levofloxacin-associated BP remains unclear, yet it has been hypothesized that levofloxacin may have acted as a hapten in the affected patients with a result of the formation of an autoantibody against BP180 and thus leading to the development of BP [16].

Differential diagnoses should be considered in this patient. Notably, only 1 medication, lisinopril, on her home medication list has been reported to be probably associated with BP [9,21]. For our patient, lisinopril-associated BP was much less likely as this is her home medication and has been taken for more than 10 years. DABP should be highly considered in patients with a recent change of medication list, especially those medications highly implicated in BP. A systematic review suggested that 89 drugs were associated with BP, and the strongest evidence for DABP is observed with gliptins, programmed cell death protein-1 and programmed death ligand-1 inhibitors (ie, nivolumab, pembrolizumab, atezolizumab, and durvalumab), loop diuretics (in particular, furosemide), and penicillin and derivatives [9]. In addition, a literature survey study shows that 12 cases of BP have been reported in patients receiving hemodialysis, and 5 in patients receiving peritoneal dialysis [4]. This survey study suggested that the skin injury and nifedipine and icodextrin exposures might be the potential factors directly or indirectly affecting the onset of BP [4]. Just recently, a case report study suggested that SARS-CoV-2 infection was likely associated with BP [22]. Our patient's SARS-CoV-2 test was negative. Therefore, these factors outlined above were not present in our patient, further supporting the diagnosis of levofloxacin-associated BP.

Immunosuppressants are used for therapy in patients with BP [23]. Corticosteroids are considered as the first-line medications [23]. In our patient, prednisolone monotherapy sufficiently caused remission.

Additionally, she had a history of prior kidney transplantation, with subsequent allograft failure due to non-compliance of anti-rejection medication. Weaning immunosuppression leads to late sensitization after kidney transplant failure, and can unleash an immune response to residual donor tissue, particularly in peritoneal dialysis patients [24]. Therefore, maintenance of immunosuppressive therapy after transplant failure should be considered for those patients seeking another transplant who are likely to undergo subsequent transplantation quickly through living donation or early relisting. Unfortunately, our patient was deactivated from the transplant list a year prior to this admission due to non-compliance with the immunosuppression. Graft failure or loss is mainly caused by primary nonfunction, arterial or venous thrombosis, and hyperacute or early refractory acute rejection [25]. In this patient, allograft failure was hypothesized to be secondary to cellular and antibody

mediated rejection that was thought to be related to her non-compliance with anti-rejection medications. A retained failed transplant might be a source of a chronic inflammatory state, potentially leading to unfavorable outcomes, such as graft intolerance syndrome [26]. To date, the incidence and risk factors of graft intolerance syndrome are unknown. Graft intolerance syndrome usually occurs within the first year of returning to dialysis therapy in patients with failed renal allografts left in situ. A study showed that of 149 patients with failed renal allografts, more than one-third of patients (37%, n=55) developed graft intolerance syndrome during the follow-up period (28±35 months; ranging from 1 to 173 months) [26]. The potential immunologic predictors for graft intolerance syndrome were explored. But, none of these factors, such as number of human leukocyte antigen mismatches, acute rejection episodes, maximum pre-transplantation panel reactive antibodies, duration of allograft function, immunosuppressants, and re-transplantation condition, was found to be related to the occurrence of graft intolerance syndrome [26].

Our patient's recent manifestations of fever, graft tenderness, gross hematuria, and acute anemia (hemoglobin dropped from the baseline >10 to 7.3 g/dL) strongly suggested the formation of graft intolerance syndrome. In such patients, allograft nephrectomy is the only or best treatment [24,27,28]. A retrospective cohort study showed that older donor age, shorter graft survival, and the number of rejections can be used to predict the need for graft nephrectomy [29]. Recently, renal graft embolization was shown to be an effective technique as an alternative treatment strategy in patients with clinical signs of intolerance syndrome, with a success rate >80%, low morbidity, and short hospital stay [28,30]. For our patient, allograft nephrectomy was postponed in the setting of active pemphigoid to a time when her skin condition improved. This report highlights that immunosuppressants should be continued if patients with allograft kidney failure seek another transplantation. Yet, if there are signs and symptoms of rejection in the failed allograft, kidney graft intolerance syndrome should be suspected.

Conclusions

To the best of our knowledge, this is the first case of levofloxacin-induced BP in a hemodialysis patient. This report has highlighted the importance of recognizing skin reactions associated with ESRD in dialysis patients, the correct diagnosis by biopsy and histopathology, and the correct and timely management.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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