Severe Bullous Pemphigoid Onset after Jugular Catheter Placement in a Patient on Hemodialysis

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Abstract
Pruritus is highly prevalent in the dialysis population. Its etiology however remains often unclear with uremic pruritus primarily suspected unless compelling evidence of another cause. Although bullous pemphigoid (BP) is considered idiopathic, there are growing data in the literature on BP provoked by different factors, such as medications or surgical procedures. These secondary dermatoses are described as rather mild conditions and more frequent in the elderly Caucasian. We herein describe a newly dialyzed African man of 76 years old, treated by a sulfonylurea such as an antidiabetic drug, who developed a severe BP after jugular catheter placement.

Introduction
Pruritus is highly prevalent in the dialysis population with wide variations, ranging from 5 to 75\% of all hemodialysis patients. Its etiology remains often unclear with uremic pruritus being primarily suspected unless compelling evidence of another cause [1]. This could harm the early diagnosis and medical care of other cutaneous diseases.

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Bullous pemphigoid (BP) mainly affects elderly people, and it is considered an idiopathic autoimmune subepidermal blistering skin disorder characterized by a humoral response to the BP230 and BP180 self-antigens [2]. Recent studies have shown that the incidence of BP is increasing [3]. Clinically, BP is usually characterized by tense blisters located mainly on the flexural surfaces of the extremities and trunk, with severe pruritus in almost all cases. Although BP is considered idiopathic, there are growing data in the literature on BP provoked by different factors, such as medications, UV, or skin injuries, caused by trauma or surgical procedures.

The association of BP with renal insufficiency, renal transplantation, or dialysis is not common. There are few reports on this association in the literature for patients requiring dialysis after the placement of an arteriovenous fistula (AVF) [4–8] or, more recently, after the placement of a peritoneal catheter [9]. We report a case of severe BP associated with jugular catheter placement in a hemodialysis patient.

**Case Report**

We report the case of a 75-year-old patient with end-stage kidney disease secondary to hypertension and type 2 diabetes. A kidney biopsy showed Kimmestiel-Wilson nodules along with chronic tubulointerstitial lesions. The patient is on hemodialysis through a tunneled right internal jugular catheter.

The patient is also known for left-ventricle dilatation secondary to chronic hypertension, neuro- and retinopathy secondary to type 2 diabetes, renal and iron deficiency anemia, and chronic hepatitis C virus (HCV). His medications per day are gliquidone (sulfonylurea) 45 mg, gabapentine 100 mg, trazodone 50 mg, and lorazepam 2.5 mg. Hypertension is controlled using bisoprolol 5 mg, olmesartan 40 mg, and amlodipine 10 mg. During dialysis, the patient is treated by erythropoietin, iron supplements along with B and D vitamins, and a phosphorus chelator. HCV is treated by a glecaprevir-pibrentasvir association.

Soon after the placement of the jugular catheter during the first dialysis session, the patient developed nonspecific general pruritus. At the time, his predialytic blood urea was around 145 mg/dL with an 87% urea reduction rate, indicating good dialysis efficacy. Laboratory results showed Hb: 9.9 g/dL, Ht: 30.2%, uric acid: 6.2 mg/dL (normal value [NV]: 3.5–7.2), phosphorus: 1.39 mmol/L (NV: 0.75–1.39), calcium: 2.13 mmol/L (NV: 2.20–2.55), magnesium: 1.05 mmol/L (NV: 0.63–1.50), PTH: 258 ng/L, and albumin: 35 g/L (NV: 40–49).

Pruritus was considered uremic, and our patient first received antihistamines with little effect. A pruriginous skin rash soon appeared around the catheter insertions site. Our patient received topical corticosteroids for suspected eczematiform dermatitis, with good cutaneous evolution. After the treatment was stopped, pruritus returned despite antihistamines. Erosive lesions on the chest drew dermatologists toward bullous impetigo, and topical oxacillin was added. Yet, the pruritus returned. As new blisters appeared regularly around the jugular catheter, expanding to the torso, neck, and face (Fig. 1); the patient was hospitalized to maximize treatment compliance and perform cutaneous biopsies. A tiny blister formed itself upon pressure on the patient’s chest during the usual care of the dialysis catheter. The direct Nikolsky’s sign raised suspicion for BP.

The biopsy (Fig. 2) showed a unilocular sub-epidermal bulla containing fibrin, mononucleated inflammatory cells, eosinophils, and few neutrophils. The roof of the bulla was partially necrotic. Its floor typically showed a preserved papillary outline, focally covered by sheets of regenerating epidermis. An inflammatory infiltrate of lymphocytes and eosinophils surrounded the vessels of the superficial dermis, assuming a band-like configuration. Eosinophils focally infiltrated the spongiotic regenerating epidermis. Because of the clinical context,
a nonautoimmune bullous drug reaction consequent to severe edema and/or to interface dermatitis was considered in the differential diagnosis. However, direct immunofluorescence showed linear deposition of IgG and C3 along the basal membrane of the epidermis, while immunohistochemistry for type IV collagen indicates that the dermal epidermal cleavage occurred in the most superficial parts of the basal membrane. These findings are consistent with an autoimmune BP. This and other bullous skin diseases may also represent adverse drug reactions. Treatment was therefore readapted with superpotent topical corticosteroids as first-line treatment.
We reviewed our patients’ chronic medications stopping the gliquidone and anti-HCV treatment because they are potential causes of BP. Since lesions were stretching, our patient was kept hospitalized to allow maximum compliance with topical treatment. By avoiding the use of oral corticosteroids, we ensured better control of his destabilized diabetes since stopping gliquidone. With daily whole-body topical corticosteroids, our patient recovered completely. He was sent to a revalidation center 6 months after the start of itching, 4 months after the first blister, and 3 months after the accurate diagnosis. He still shows cutaneous stigmas of his dermatosis (postinflammatory depigmentation), but his daily activities could resume.

Even if we considered the placement of the central line as the triggering factor, it could not be removed. AVF would develop too slowly, and endovascular fistula was not technically possible.

**Discussion**

Pruritus is highly prevalent in the hemodialysis population. In a report from one of the largest trials (the Dialysis Outcomes and Practice Patterns Study [DOPPS]), between the years 1996–2001 and 2012–2015, wide variation in the percentage of patients with moderate to extreme pruritus was reported, ranging from 5% to 75% with Belgian reported rate at 38%. Pruritus is associated with a 17% higher mortality risk, which appears to be mediated in large part through disturbances in sleep quality [1]. High urea levels, iron deficiency anemia, inflammation, as well as metabolic disturbances such as hypercalcemia, hyperphosphatemia, and secondary hyperparathyroidism have been reported to be associated with pruritus [1].

Since it is extremely common, we assume that pruritus presenting in dialysis patients is uremic pruritus unless there is unequivocal and compelling evidence of another cause. Features suggestive of uremic pruritus include onset at the time of dialysis initiation, persistence of symptoms, or markedly elevated calcium/phosphate, PTH, and/or blood urea nitrogen levels [10].

As previously mentioned, BP in dialysis patients is a rarity. Since 1997, among all the cutaneous complications of dialysis, BP has only been described in 8 patients with fistula [4–8, 11, 12]. Of those 8, only 2 BP resulted from recent fistula confection or catheter placement.

BP was once thought to be an idiopathic disorders [2], but growing data suggest many possible triggering factors, such as ultraviolet rays, medication, and skin injury. Localized BP has been reported in the clinical settings of radiotherapy, surgical wounds, trauma, or burns [6]. The pathogenetic mechanisms through which external agents could provoke or exacerbate BP are not clear. According to some authors, trauma induced tissue disruption leads to consequent exposure of otherwise masked antigens and development of autoantibodies. Other authors suggest the preexistence of low titers of circulating autoantibodies in predisposed individuals. In these subjects, damaged tissue could release a variety of proinflammatory factors that may contribute to the recruitment of inflammatory cells and circulating antibodies, activation of granulocytes, and complement, leading to the formation of bullae [13].

BP has been associated with different internal disorders, particularly diabetes mellitus [14] or the use of certain drugs. There is growing epidemiological evidence of the association between BP onset and gliptin therapy [15], which could represent, as diabetes mellitus, a risk factor rather than an etiological factor. BP can also be secondary to sulfonylurea, even though they are considered significantly safer than gliptin concerning BP onset [16]. Many drugs used in the dialyzed population have been associated with BP. There are epidemiological data to support associations between enalapril, ampicillin, spironolactone, furosemide, statins neuroleptics, and BP.

Lee et al. [16] have calculated an incidence rate of 0.31 per 1,000 person-year in people under sulfonylurea, with an increased risk more evident over the age of 65 years and in
Caucasians. Even though our patient is African, he is 76 years old and has been treated by gliquidone (a sulfonylurea) for years.

Clinically, drug-induced BP is similar to idiopathic disease, although the lesions are often polymorphic, mimicking other drug-induced bullous dermatoses such as erythema multiform, eczematous dermatitis, and porphyria cutanea tarda. In drug-induced disease, mucous membranes are often involved, thereby blurring the distinction between bullous and mucosal variants of pemphigoid. In some patients, there appears to be overlap between BP and pemphigus vulgaris. Because the secondary variants of BP are histologically similar to the idiopathic forms, clinical correlation is necessary to assess their etiology [17].

Our patient initially developed his dermatosis around his central line soon after its placement. From then on, the blistering disease expanded on the patient’s back, torso, abdomen, arms, hands, and face with the more numerous lesions around catheter’s exit site (shown in Fig. 1).

The two main hypothesis were that the BP was secondary to catheter placement as it was recently described in peritoneal dialysis and/or secondary to his sulfonylurea therapy. Sulfonylurea are proven etiologies of BP. The disease dynamics and its resolution without catheter removal suggest that BP would be related to skin trauma rather than an allergic-type reaction to the catheter. Having been treated with gliquidone for years was presumably a predisposing factor with the catheter placement being the triggering factor.

According to the latest recommendations, whole-body topical treatment using superpotent corticosteroids are validated as first-line treatment and should be prioritized for extensive BP. Professionals should taper doses when disease is controlled (when no new blisters occur within 3 weeks of adequate treatment). Tetracyclines can be added as second-line treatment to avoid the use of oral corticosteroids as it has been proven noninferior to systemic corticosteroids [18]. There is evidence that high-dose systemic steroid therapy is effective in patients with extensive disease. However, this therapy has been associated with higher mortality and increased side effects compared with the whole-body topical use [19, 20]. No trial has ever studied the effect of stopping a potentially causative drug on BP progression. The latest European recommendations do not even mention it. Recently, a German consensus of experts suggest that it should be considered if the disease does not respond to first-line treatment [21]. Indeed, in most cases where an association between antidiabetic drug or diuretics and BP has been established, the drug had to be discontinued to obtain resolution of BP or avoid recurrence of the disease. It is noteworthy that in the only case report describing BP secondary to catheter placement, the catheter had not been removed, and the patient recovered fully with topical treatment [9]. In our case, the addition of doxycycline achieved disease control.

BP provoked by external factors like medications or skin injury is described as a mild condition in terms of prognosis and response to therapy, and the cutaneous lesions are usually localized. Patients in the literature were treated with prednisone alone [6] or in combination with azathioprine [7] and tetracycline [4], whereas two remaining patients achieved topical corticosteroids only (clobetasol, betamethasone) with success [5, 8]. Most of those 7 patients had coexisting hypertension and diabetes mellitus. Even though our patient suffered from an unusually severe BP, topical superpotent corticosteroids and doxycycline, along with antimicrobial wound contact layer, and emollients could cure the BP completely.

**Conclusion**

The onset of pruritus at the start of dialysis is usually attributed to the uremic state. A nonuremic cause of pruritus should be considered quickly among dialysis patients whose symptoms are refractory to common treatments such as topical emollients and analgesic agents, oral antihistamines, or gabapentin. Dialysis patients cumulate usually many treatments
that are risk factors for BP, especially older diabetic patients. Central line placement should be considered a risk factor for the development of BP. Clinicians should therefore closely monitor the evolution of any worsening pruritus after catheter placement or AVF confection in a diabetic patient under oral antidiabetic drugs.

**Statement of Ethics**

Written informed consent was obtained from the patient for publication of this case report and accompanying images. The study received approval from the Brugmann University Hospital Committee on November 9, 2021.

**Conflict of Interest Statement**

The authors declare no conflict of interest.

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**Author Contributions**

We declare each author in full agreement with what is written in the article. Lucas Jacobs wrote the study. Frederic Collart offered his supervision in the writing and content. Francesco Feoli and Pascal Bruderer performed the anatomopathological examination and offered further addition to the text. Ivan Grozdev offered guidance regarding dermatology in the text. Edouard Cubilier and Semra Top offered significant additions in the text regarding clinical evolution.

**Data Availability Statement**

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

**References**

1. Pisoni RL, Wikströ m B, Ekler SJ, Akizawa T, Asano Y, Keen ML, et al. Pruritus in haemodialysis patients: international results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant*. 2006 Dec; 21(12):3495–505.
2. Schmidt E, Zillikens D. Pemphigoid diseases. *Lancet*. 2013 Jan 26;381(9863):320–32.
3. Joly P, Baricault S, Sparsa A, Bernard P, Bédane C, Duvert-Lehembre S, et al. Incidence and mortality of bullous pemphigoid in France. *J Invest Dermatol*. 2012 Aug;132(8):1998–2004.
4. Freeman BD, Rubin BG. Bullous pemphigoid after prosthetic vascular graft placement. *Surgery*. 1998 Jul;124(1):112–3.
5. Kamada N, Ino N, Hatamochi A, Shinkai H. A case of bullous pemphigoid in a patient on hemodialysis. *J Dermatol*. 1998 Apr;25(4):246–9.
6. Pardo J, Rodriguez-Serna M, Mercader P, Fortea JM. Localized bullous pemphigoid overlying a fistula for hemodialysis. *J Am Acad Dermatol*. 2004 Aug;51(2 Suppl):S131–2.
7 Peruzzo J, Dias Pinheiro Dantas L, Zampese M. Bullous pemphigoid associated with chronic renal allograft rejection. J Am Acad Dermatol. 2013 Jun;68(6):e192–3.
8 Yosudian PD, Dobson CM, Ahmad R, Azurdia RM. Trauma-induced bullous pemphigoid around venous access site in a haemodialysis patient. Clin Exp Dermatol. 2002 Jan;27(1):70–2.
9 Giunzioni D. Development of bullous pemphigoid after tenckhoff catheter placement in a peritoneal dialysis patient. Case Rep Dermatol. 2020 Apr;12(1):42–6.
10 Zucker I, Yosipovitch G, David M, Gafter U, Boner G. Prevalence and characterization of uremic pruritus in patients undergoing hemodialysis: uremic pruritus is still a major problem for patients with end-stage renal disease. J Am Acad Dermatol. 2003 Nov;49(5):842–6.
11 Osipowicz K, Kalinska-Bienias A, Kowalewski C, Wozniak K. Development of bullous pemphigoid during the haemodialysis of a young man: case report and literature survey. Int Wound J. 2017 Feb;14(1):288–92.
12 Jang JW, Song CH, Jung YJ, Kim TL, Seo H-M, Kim YG, et al. A case of localized bullous pemphigoid associated with an arteriovenous fistula. Indian J Dermatol. 2020 Nov–Dec;65(6):547–8.
13 Dănescu S, Chiorean R, Macovei V, Sitaru C, Baican A. Role of physical factors in the pathogenesis of bullous pemphigoid: case report series and a comprehensive review of the published work. J Dermatol. 2016 Feb;43(2):134–40.
14 Geller S, Kremer N, Zeeli T, Sprecher E. Bullous pemphigoid and diabetes mellitus: are we missing the larger picture? J Am Acad Dermatol. 2018 Aug;79(2):e27.
15 Tasanen K, Varpuluoma O, Nishie W. Dipeptidyl peptidase-4 inhibitor-associated bullous pemphigoid. Front Immunol. 2019;10:1238.
16 Lee H, Chung HJ, Pawar A, Patorno E, Kim DH. Evaluation of risk of bullous pemphigoid with initiation of dipeptidyl peptidase-4 inhibitor vs second-generation sulfonylurea. JAMA Dermatol. 2020 Oct 1;156(10):1107–14.
17 Calonje JE, Brenn T, Lazar A, Bilings S. McKee's pathology of the skin. 5th ed. Elsevier; 2019.
18 Williams HC, Wojnarowska F, Kirtschig G, Mason J, Godec TR, Schmidt E, et al. Doxycycline versus prednisolone as an initial treatment strategy for bullous pemphigoid: a pragmatic, non-inferiority, randomised controlled trial. Lancet. 2017 Apr 22;389(10079):1630–8.
19 Feliciani C, Joly P, Jonkman MF, Zambruno G, Zillikens D, Ioannides D, et al. Management of bullous pemphigoid: the European Dermatology Forum consensus in collaboration with the European Academy of Dermatology and Venereology. Br J Dermatol. 2015;172(4):867–77.
20 Oren-Shabtai M, Kremer N, Lapidoth M, Sharon E, Atzmony L, Nosrati A, et al. Treatment of bullous pemphigoid in people aged 80 years and older: a systematic review of the literature. Drugs Aging. 2021 Feb;38(2):125–36.
21 Schmidt E, Sticherling M, Sárdy M, Eming R, Goebeler M, Hertl M, et al. S2k guidelines for the treatment of pemphigus vulgaris/foliaceus and bullous pemphigoid: 2019 update. J Dtsch Dermatol Ges. 2020 May;18(5):516–26.