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Case report

Vancomycin-induced linear IgA bullous dermatosis: reports and factors that may influence pathogenesis

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Abstract

Linear IgA bullous dermatosis (LABD) is a rare autoimmune blistering disease. LABD is considered mostly idiopathic, but some cases have been reported to be drug-induced, mainly associated with vancomycin (VCM).

We present two cases of LABD possibly associated with VCM used for cardiac surgery prophylaxis; in the presented cases, the eruptions occurred only after VCM withdrawal, therefore leaving a question about the relationship between VCM and LABD in these cases.

We reviewed previous reports of VCM-induced LABD and analyzed the following parameters: gender, age, recent medical history, concurrent medication, latency period, progression after withdrawal, time to resolution, treatment, and rechallenge.

Results: The causal relationship between VCM and LABD was often unclear; patients frequently had concurrent medication and symptoms frequently began and/or progressed after VCM withdrawal. Among the 46 reviewed patients in addition to our two cases (n=48), 20 (42%) had recent history of cardiac procedure, cardiac infection, congestive heart failure, or aortic aneurism.

Conclusion: Further investigation is needed to ascertain the association between LABD, VCM, and heart disease.

Keywords: Linear IgA bullous dermatosis, vancomycin, cardiac

Introduction

Linear IgA bullous dermatosis (LABD) is a rare autoimmune bullous disease, characterized by linear deposition of IgA autoantibodies against basement membrane zone (BMZ) antigens [1, 2]. Several target antigens have been identified, namely BP180, BP230, LAD285, ColVII, and laminin-332. LABD target antigens are also present in other autoimmune BMZ blistering disorders, which may explain the frequent clinical overlap. As an example, bullous pemphigoid (BP), pemphigoid gestationis (PG), and LABD react to BP180 antigen. However, in BP and PG IgG antibodies bind the MCW-1 epitope in the NC16A domain, whereas in LABD IgA antibodies recognize LABD97 and LAD1 epitopes [3, 4, 5, 6].

Most LABD cases are classified as idiopathic. However, autoimmunity, malignancies, infections, trauma, ultraviolet radiation, and drugs have been reported as triggers [1, 7, 8]. Exposure to VCM has been considered the trigger in about half of drug-induced LABD cases [9], but other drugs have been implicated, namely captopril, lithium, sulfamethoxazole-trimethoprim, phenytoin, furosemide, atorvastatin, amiodarone, and diclofenac [1, 9, 10].

We present two cases of LABD with possible involvement of VCM, although with a peculiar time-course, and review the literature on this subject.

Case synopsis

Case 1

A 72-year-old man received VCM and amikacin for seven days as a standard prophylaxis regimen for coronary bypass surgery and biological aortic valve prosthesis placement. Seven days after VCM suspension, the patient developed tense hemorrhagic bullae on the palms, trunk, neck, and face, with oral blisters and conjunctival erythema (Figure 1). Despite oral prednisolone (0.5 mg/kg/day), his condition initially worsened then slowly improved to complete resolution within three weeks, allowing corticosteroid withdrawal in two months. Histopathology showed dermal–epidermal detachment with partial re-epithelization, and a neutrophilic infiltrate forming microabscesses in the papillary dermis (Figure 2), with linear IgA deposition along the dermal–epidermal junction.

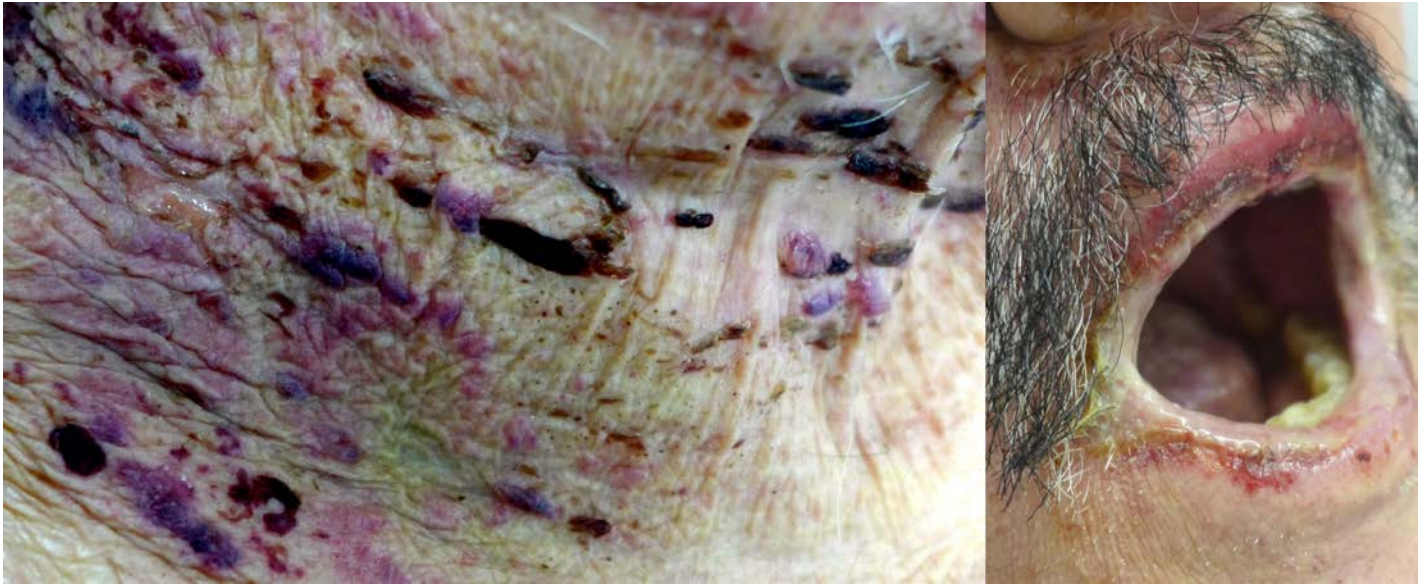


Figure 1. Linear IgA bullous dermatosis. Hemorrhagic bullae and erosions on the neck, and mucosal involvement presenting blisters and crusts on the lips.

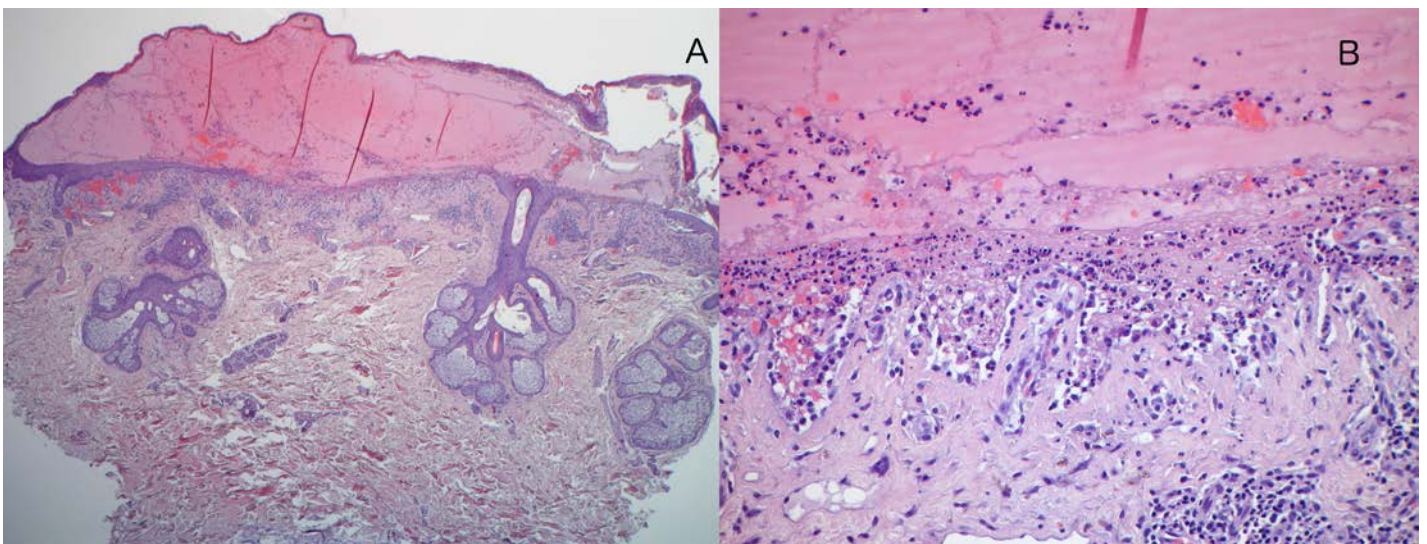


Figure 2. A. (Low Power H&E-x25) Dermal–epidermal detachment, with partial reepithelization. B. (High Power H&E-x200) Extensive neutrophilic infiltrate in papillary dermis.

Case 2

A 50-year-old man was prophylactically treated with VCM and amikacin during five days for coronary bypass surgery and aortic valve replacement with a mechanical prosthesis. Seventeen days after VCM withdrawal, the patient developed erythematous patches around the sternotomy scar and erythema and tense blisters around the saphenectomy scar. Cutaneous lesions soon generalized, exhibiting the characteristic “string of pearls sign” (Figure 3), and oral and genital erosions developed. Skin biopsy showed subepithelial detachment, a neutrophilic and eosinophilic dermal infiltrate, and linear IgA and

C3 deposition along the dermal–epidermal junction (Figure 4). Indirect immunofluorescence using a salt-split skin substrate detected anti-BMZ antibodies on the epidermal side, and ELISA identified BP180 antibodies. The condition worsened despite oral steroids (methylprednisolone 0.5 mg/kg/day) but improved quickly on dapsone (100 mg/day), with complete resolution in four weeks. Corticosteroids and dapsone were discontinued in three months with no recurrence.



Figure 3. Linear IgA bullous dermatosis. Tense blisters and bullae on the saphenectomy scar, and the “string of pearls” sign-circular red patches with blisters on the periphery, located on the right leg.

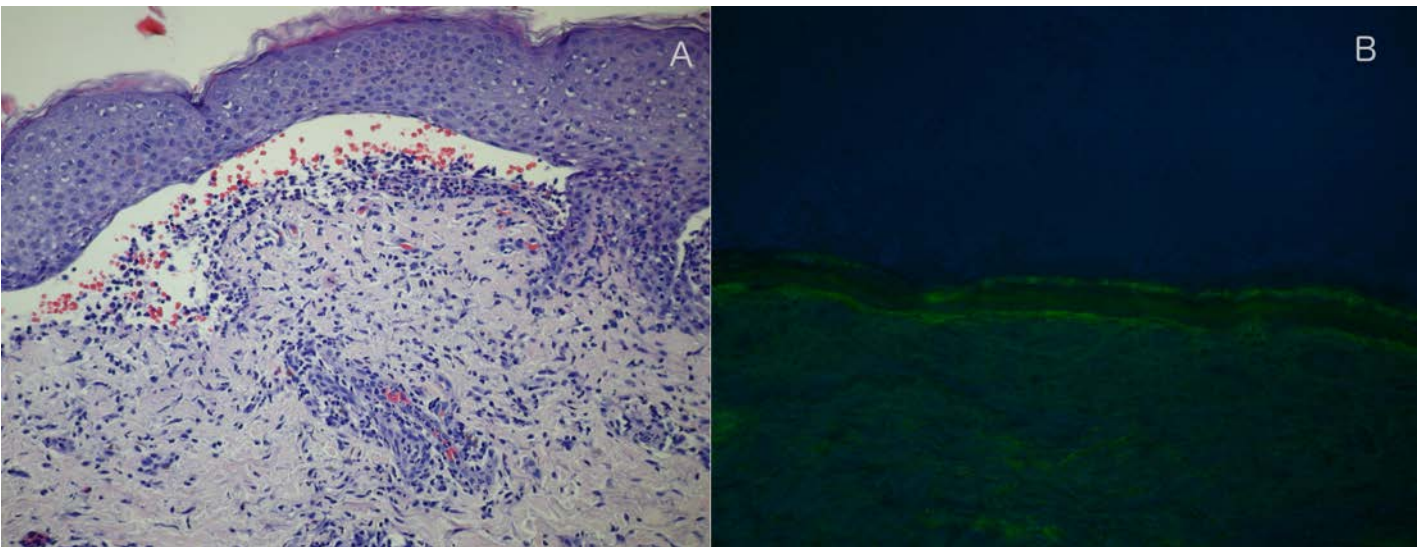


Figure 4. A. (High Power H&E-x100) Dermal–epidermal detachment in association with a neutrophilic and eosinophilic infiltrate. B. (High Power, DIF-x100) Linear deposition of IgA along the dermal–epidermal junction.

Methods

A PubMed database search was performed using the keywords: “linear IgA disease,” “linear IgA bullous disease,” and “linear IgA bullous dermatosis” in association with “vancomycin”. We found 58 potentially relevant articles published between August 1988 and March 2015, of which 35 articles met the inclusion criteria: 1) articles written in English and 2) LABD diagnosis based on histology and direct immunofluorescence. These comprised 27 case reports and 8 case series; including our two patients, 48 individuals were evaluated. Data were extracted from the full-text articles and analyzed for gender, age, recent medical history, concurrent medication, latency period, progression after withdrawal, time to resolution, treatment, and rechallenge, in order to consider the association between adult LABD and either VCM or others factors.

Results

The mean age of the 48 patients was 67.5 years (range 32–91) with no gender difference (22 female and 26 male patients). Table 1 describes the vancomycin-induced linear IgA bullous dermatosis cases.

The period between onset of VCM and first skin symptoms, reported in 43 cases, ranged from 1 to 22 days (mean 10.5 days). In seven cases, cutaneous lesions developed after VCM suspension (3–17 days), and in one other case occurred three days after a single VCM dose [11].

Table 1.

Case	Paper [First author, year]	Gender	Age	Hospitalization history	Concurrent medication	Latency period (days)	Progression after VCM withdrawal (days)	Treatment
1	Nasr, 2014	M	76	Pneumonia, bacteremia, renal cell carcinoma	Omeprazole, aspirin, atorvastatin, bisoprolol, piperacillin, tazobactam	8	Y (3)	N
2	Zenke, 2014	M	62	Brainstem hemorrhage, endocarditis	Rifampicin, sulfamethoxazole, trimethoprim, tazobactam, piperacillin	10	NW	SS
3	Kakar, 2014	F	91	Acute cholecystitis, sepsis	Piperacillin, tazobactam, ceftazidime, ampicillin, sulbactam, amoxicillin, clavulanic acid	16	NR	N
4	Tashima, 2014	M	84	Osteomyelitis	NR	12	Y	SS, IM
5	Selvaraj, 2013	F	70	Orthopedic surgery, sepsis	Piperacillin, tazobactam	5	N	N
6	Jawitz, 2011	F	NR	NR	Piperacillin, tazobactam	5	N	TS
7	Bustillo, 2011	M	77	Endocarditis	Gentamicin, ampicillin	days	N	N
8	Jheng-Wei, 2011	F	41	Meningitis	Ceftriaxone	10	Y (3)	N
9	Le Merlouett, 2011	F	77	Bacteremia	Strontium ranelate	16	N	N
10	MacDonald, 2010	M	32	Accident, ventilator-acquired pneumonia	Piperacillin, tazobactam	10	N	NR
11	Walsh, 2009	M	76	Bacteremia	NR (VCM at supratherapeutic levels)	19	Y	TS, Dialysis for VCM washout
12		M	77	Endocarditis	Gentamicin, ampicillin	days	N	N
13	Billet, 2008	M	70	Obesity surgery, perihepatic abscess, sepsis	Levofloxacin, metronidazole, meropenem, linezolid, caspofungin	NR (but after VCM suspension)	Y	SS, dapsone
14		F	61	Sigmoidectomy, wound infection, renal transplant recipient	Meropenem	13	N	TS
15	Eisendle, 2006	M	65	Arterial popliteal reconstruction, sepsis, transplant recipient (liver and renal)	Imipenem	8	Y (skin lesions only appeared 2 days after VCM suspension)	SS
16	Navi, 2006	M	73	Pleural effusion, congestive heart failure, implantable cardiac defibrillator	Carvedilol, lisinopril, furosemide, cefazolin, spironolactone, amlodipine, simvastatin	3 (VCM only during the procedure)	N	N
17	Coelho, 2006	F	67	Pneumonia	Meropenem	13 (3 days after VCM suspension)	Y (5)	SS
18	Waldman, 2004	F	77	Coronary bypass, pneumonia, sepsis	Aztreonam, cefazolin, ciprofloxacin, ceftazidime, tobramycin, clindamycin	6	N	Dapsone
19	Joshi, 2004	F	48	Hysterectomy, pelvic abscess, sepsis	Furosemide	10	N	N
20	Armstrong, 2004	M	81	Aortic aneurysm surgery, sternal wound drainage	N	3	N	N
21	Solky, 2004	M	46	Pneumonia	NR	12	N	N
22	Dellavalle, 2003	M	74	Cerebral vascular accident, urinary infection, pneumonia	Piperacillin, tazobactam, ciprofloxacin	4 (1 month before VCM treatment)	Y (10)	N
23	Palmer, 2001	F	75	Infection of varicose ulcer	Ciprofloxacin, lactulose, dalteparin, furosemide, co-codamol, morphine	6	Y	SS, dapsone
24		F	86	Femur fracture	Amoxicillin	1 (2 weeks before VCM treatment)	N	SS
25		F	78	Coronary bypass, mesenteric occlusion, sternotomy wound infection	Ciprofloxacin, fusidate	15	N	TS
26	Wiadrowski, 2001	F	69	Endocarditis, pneumonia	Cephalothin, cephalixin, gentamicin, ceftriaxone, roxithromycin, aspirin, furosemide, ciprofloxacin	8	N	N
27	Hughes, 2001	M	77	Intracranial hemorrhage	Dexamethasone, famotidine, phenytoin, digoxin, enalapril, acetaminophen, levaquin	11	NR	N
28	Klein, 2000	F	65	Heart stroke, coronary bypass	Clonidine, hydrochlorothiazide	20 (14 days after VCM suspension)	Y	N
29		M	70	Congestive heart failure, gangrene	Clonidine, diclofenac, methylidopa, furosemide, digitalis, dopamine, hydrochloride, enalapril, maleate, nicardipine, isosorbide, rifampin, heparin	10	NR	N
30	Nousari, 1999	F	74	Endocarditis	Gentamicin, aztreonam	13	N	N
31		F	41	Endocarditis	Gentamicin	2 (previous VCM treatment)	N	N
32	Bernstein, 1998	F	60	Enterocutaneous infected fistula	Imipenem, gentamicin	10	NR	SS
33		F	71	Pneumonia	Nafcillin	8 (7 days after VCM suspension)	NR	SS
34	Nousari, 1998	M	65	Subarachnoid hemorrhage, sepsis	Gentamicin, ticarcillin, ranitidine, nitroglycerin, nimodipine, phenytoin	7	Y (2)	NR
35	Bitman, 1996	F	NR	Leg ulcer, previous femoral-peroneal bypass	Furosemide, aspirin, insulin, ticarcillin	7	N	NR
36	Whitworth, 1996	M	63	Cardiac catheterization, urinary infection, transitional cell bladder carcinoma	Ampicillin	1	Y	SS, TS
37	Richards, 1995	F	72	Bladder carcinoma	Hydrochlorothiazide, heparin, metronidazole, ceftriaxone, amphotericin, trimethoprim, sulfamethoxazole, metoprolol, oxycodone	12	Y	NR
38	Gueissmann, 1995	F	79	Leg ulcer infection	Tobramycin	8	N (with no new lesions after 2 days)	NR
39	Kuechle, 1994	M	69	Coronary bypass, sternal wound infection	Rifampin	14	NR	N
40		M	74	Coronary bypass, sternal wound infection	Morphine, digoxin, furosemide, diltiazem, hydrochloride, cephazolin, captopril	9	NR	N
41		M	67	Coronary bypass, sternal wound infection	Digoxin, levofloxacin, meperidine, promethazine, triazolam, quinidine, isosorbide	14	NR	Dapsone
42	Piketty, 1994	M	53	Dissecting aortic aneurysm, groin cellulitis	Amiodarone, furosemide, beta-blocker	15	N	TS
43	Carpenter, 1992	M	54	Bowel perforation	Ceftazidime, metronidazole, ranitidine	10	N	NR
44		F	72	Ovarian adenocarcinoma, intra-abdominal abscess	Clindamycin, gentamicin, ranitidine	7	Y (2)	NR
45		M	54	Osteomyelitis	N	14	N (VCM was continued for additional 3 weeks after eruption with no progression)	NR
46	Baden, 1988	M	68	Coronary bypass, bacteremia	Verapamil, diltiazem, digoxin, atenolol, furosemide, cefizoxime, procainamide, nitroglycerine, heparin	9	Y (2)	N

VCM therapy was frequently maintained for one or two weeks until the diagnosis was confirmed by direct immunofluorescence. Thereafter, VCM was withdrawn in all cases except one, in which the patient nevertheless achieved complete clinical remission with systemic corticosteroids [6]. Lesions improved on VCM suspension in 21/40 cases (52%), but disease progressed after VCM withdrawal in 18/40 (45%) cases; there was no reference to this aspect in 8/48 cases (17%). In four cases, VCM was accidentally reintroduced a few days after its withdrawal; of these, 2/4 developed bullous lesions on reintroduction [12, 13].

VCM was clearly the single drug in two cases, whereas concomitant medication was reported in 90% (43/48) of patients, mostly other antibiotics in 38/43 (88%) and furosemide in 11/43 (26%). Apart from concomitant drugs, 20 patients (42%) had a recent history of cardiac surgical procedure or heart disease (9 coronary bypass, 1 implantable cardiac defibrillator, 1 cardiac catheterization, 6 endocarditis, 2 aortic aneurysm dissection, and 1 congestive heart disease). Table 1 shows the vancomycin-induced linear IgA bullous dermatosis cases.

Discussion

The clinical and immunopathological features of VCM-induced LABD are indistinguishable from the idiopathic form, although the former is classically reported to cause lower morbidity and to be more transient. We presented two typical LABD cases, developing 7 and 17 days respectively after VCM withdrawal, in a time course different from that classically described in drug-induced LABD. The expected course is: onset 3–15 days after drug introduction, improvement on subsequent withdrawal, and resolution within 2–3 weeks without systemic therapy [2, 9, 10]. On the contrary, our two cases presented here required prolonged systemic therapy, one with corticosteroids and dapsone. We therefore questioned the relationship between LABD and VCM and looked for other possible triggers for this autoimmune blistering disorder.

Most algorithms for assessing the causality of an adverse drug reaction (ADR), namely the WHO–UMC and Naranjo algorithms [14], rely on previous descriptions of the ADR. These are: the absence of other causes, and suspicious timing of events such as the onset of ADR upon drug administration, clinical improvement after drug withdrawal, and relapse after rechallenge. However, in the reviewed cases of VCM-induced LABD, these algorithms were only applied in one case [15]. Moreover, one patient maintained VCM and was successfully treated with systemic steroids [6] and 18/40 (45%) cases showed clinical deterioration following VCM withdrawal (excluding eight cases in which improvement or deterioration after VCM withdrawal was not stated). In addition, 14/40 cases (35%) required systemic therapy (excluding eight cases in which therapy was not mentioned). Furthermore, 43/48 patients (90%) received concomitant drugs, which further hampers the evaluation of the relationship between VCM and LABD. The data do not clearly support a role for VCM according to the WHO–UMC and Naranjo algorithms, although a drug-induced autoimmune reaction may certainly progress after the trigger has been removed [5].

The underlying pathogenic mechanisms involved in triggering autoimmune blistering diseases are still not fully defined. Drugs may induce autoantibodies to BMZ antigens by cross-reactivity, or by altering or exposing epitopes, which may explain why drug-induced LABD can also occur after the withdrawal of the suspected drug. Nevertheless, other triggering factors, such as infection or tissue injury, may also occur along with the drug-induced mechanisms [1, 2, 5].

In summary, the relationship between VCM and LABD is not entirely consistent in several of the reviewed cases. Fortuna *et al.* also addressed these discrepancies and questioned the existence of VCM-induced LABD, [16], although most authors strongly support this association [17].

Apart from the use of VCM, a substantial proportion (20/48; 42%) of the reviewed LABD cases followed a cardiac procedure, congestive heart failure, endocarditis, or aortic aneurism dissection, which may indicate that an underlying heart disorder may also be a contributory factor for LABD. In the remaining cases, although no direct cardiac procedure was reported, most patients suffered from severe conditions that, *per se*, can induce heart damage as a result of lower cardiac output and anoxia. Supporting this hypothesis, one LABD case was described seven days after amlodipine therapy, and in the setting of coronary disease, amlodipine is a potential risk factor for inducing myocardial infarction [18]; and another case of LABD was reported following cardiac transplant, with no reference to the use of VCM [19]. Nevertheless, as VCM is commonly used in cardiac procedures and endocarditis, this may be a confounding factor [20].

In this context, and by analogy with BP in which diseases involving the central nervous system are overrepresented [21, 22], we suggest a possible relationship between LABD and cardiac injury. Surgical or other technical procedures, infection, or anoxia may expose BP180 and BP230 antigens present in cardiac tissue [23,24] and may induce IgA autoantibodies involved in LABD. IgA and IgG anti-BP180 can occur concomitantly in LABD and BP, which raises the question of whether LABD and PB represent two poles of the same clinical spectrum [25].

In adult LABD the association with VCM is unquestionably overrepresented. Nevertheless, further data collection, ultimately as part of a multi-center prospective study using consistent diagnostic procedures and algorithms would be welcome to clarify this relationship and explain cases that show considerable delay between VCM withdrawal and LABD onset, as in those presented here. Moreover, it would be desirable to ascertain the hypothesized association of adult LABD with cardiac injury in idiopathic or drug-induced cases, namely in those unrelated to VCM.

Conclusion

In the reviewed VCM-induced LABD cases, there may be a less than clear causal relationship between LABD and VCM. In 90% (43/48) of cases, patients received concomitant medication. A substantial proportion showed clinical deterioration after VCM withdrawal (45%) and required systemic therapy (35%). Furthermore, seven patients developed LABD after VCM suspension (3–17 days).

However, the appearance of LABD after VCM withdrawal does not exclude VCM as a cause; this evolution is consistent with other examples of drug-induced autoimmune diseases such as lupus erythematosus and pemphigus vulgaris, in which the autoimmune reaction may progress despite the elimination of the trigger drug, although this has not been described as a common pattern in drug-induced LABD.

VCM was used in the two presented cases; the patients also had cardiac surgery. Including these two patients, we observed that 42% of the reviewed LABD cases followed a cardiac event (nine coronary bypass, one implantable cardiac defibrillator, one cardiac catheterization, one congestive heart disease, six endocarditis, and two aortic aneurism dissection). We hypothesize that cardiac injury can also contribute to LABD pathogenesis, although we recognize that VCM is preferentially used to treat endocarditis, or in prophylaxis for cardiac surgical procedures, and therefore represents a confounding factor.

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