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Linagliptin-Associated Alopecia and Bullous Pemphigoid

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ABSTRACT

Bullous pemphigoid is a chronic autoimmune blistering disease. Recently, several reports suggested dipeptidyl peptidase 4 (DPP-4) inhibitors, also known as gliptins, were a potential cause of drug-induced bullous pemphigoid but not of both bullous pemphigoid and alopecia areata together. Here we describe the case of a 68-year-old man with type 2 diabetes mellitus who developed new onset diffuse alopecia on the scalp with diffuse tense bullae over his body a few months after linagliptin was introduced for better control of his diabetes.
DPP-4 inhibitors are not known to increase the risk of alopecia. To the best of our knowledge, this is the first report of linagliptin-associated alopecia areata and bullous pemphigoid, which may help demonstrate if there are any links between DPP-4 inhibitors and alopecia.

LEARNING POINTS

- This is the first report of linagliptin-associated alopecia areata and bullous pemphigoid (BP), which may help demonstrate a link between DPP-4 inhibitors and alopecia.
- Since the time of onset of BP after initiation of a DPP-4 inhibitor varies, a high index of suspicion is needed for diagnosis.
- Early diagnosis is essential as DPP-4 inhibitor withdrawal has a significant effect on disease remission.

KEYWORDS

Gliptin, drug, bullous pemphigoid

INTRODUCTION

Bullous pemphigoid (BP) is an autoimmune disease where autoantibodies target structural proteins at the dermal–epidermal junction. Two hemidesmosomal proteins, 230 kDa protein and 180 kDa antigen, have been identified as the major targets of BP autoantibodies. BP manifests with tense blisters on the skin[1]. It is poorly understood although many trigger factors have been identified, such as contrast material injection, surgical procedures, mechanical trauma, insect bites, thermal burns, radiotherapy and ultraviolet exposure associated with pre-existing psoriasis[2]. Linagliptin is one of the new dipeptidyl peptidase-4 (DPP-4) inhibitors used in the treatment of type 2 diabetes mellitus (DM). DPP-4 inhibitors have been recently implicated in inducing BP, but the mechanism is not entirely clear. DPP-4 inhibitors may induce anti-basement membrane zone antibodies or other structurally similar antibodies, leading to sub-epidermal bullae and BP[3]. Many recent case reports show that use of DPP-4 inhibitors is a risk factor for BP onset, but there is no evidence of an association with alopecia.

CASE DESCRIPTION

A 68-year-old Caucasian man with a complex medical history including type 2 DM presented to the emergency department with a 3–4-week history of generalized pruritus, new onset diffuse alopecia and diffuse bullae over his trunk, arms and legs. The patient initially had developed bullae and blisters over his legs. Simultaneously, he noticed a significant loss of his scalp and beard hair as well as his eyebrows. This was

European Journal of Case Reports in Internal Medicine

accompanied by intense pruritus over the abdomen and back for approximately 2 weeks prior to the development of the bullae. The intense itching, development of further bullae, and almost complete alopecia prompted the patient to present to the emergency department.

A review of his history did not reveal any drug allergies and he denied a family history of autoimmune conditions. He had not travelled anywhere recently and did not present with any constitutional symptoms or myalgias. His home medications included linagliptin, allopurinol, amlodipine, atorvastatin, furosemide, hydralazine, levothyroxine, pantoprazole, rivaroxaban, terazosin and insulin.

His vital signs were all within normal limits: he was afebrile at 36.8°C, his heart rate was 59 bpm, blood pressure was 118/73 mmHg, and oxygen saturation was 98% on room air. Physical examination revealed bullae over his back, abdomen and both lower legs and measuring approximately 1–3 cm in diameter (*Fig. 1*). He also had numerous smaller bullae over both flanks, upper arms and lower legs and measuring approximately 0.5–1 cm in diameter. There was no specific dermatomal distribution and no oral ulcerations or mucositis. The patient had diffuse alopecia on his scalp, eyebrows and beard. There was no erythema, scaling or scarring associated with the hair loss (*Fig. 2*).

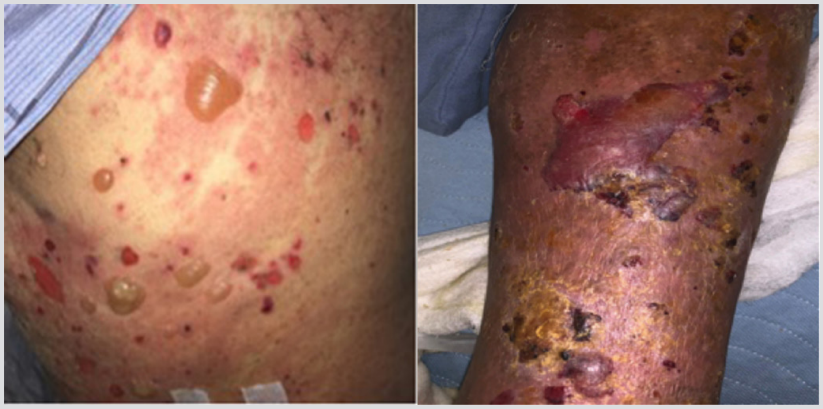

Figure 1. Diffuse tense bullae and blisters on the patient's initial presentation to hospital

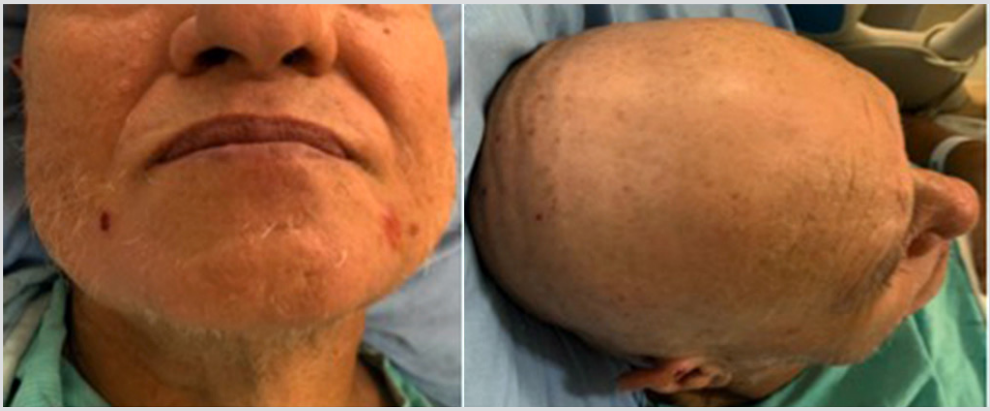

Figure 2. Diffuse alopecia on the scalp and jaw with no erythema, scaling or scarring

Investigations

Initial laboratory investigations revealed an elevated creatinine level of 300 mmol/l (baseline in the mid-200s) with normal electrolytes. The patient also had an elevated CRP level of 12.6 mg/l, his white blood cell count was normal at 10.3 g/l, and haemoglobin concentration was 110 g/l.

Hospital course

Skin biopsies performed on admission showed sub-epidermal blisters with multiple eosinophils highly suggestive of BP (*Fig. 3*). Eosinophils are commonly seen in BP, but the diffuse eosinophilia seen in the biopsy specimen raised the possibility of drug-induced BP. Direct immunofluorescence showed deposition of IgG and C3 along the basement membrane confirming BP (*Fig. 4*). Interestingly, linagliptin had been introduced a few months before the onset of cutaneous eruptions. At that point, linagliptin was highly suspected as the cause of BP and alopecia and therefore was discontinued. The patient was started on prednisone 40 mg with significant improvement of his skin lesions. He was then followed by the dermatology department and was started on mycophenolic acid (720 mg by mouth twice a day as a steroid-sparing agent) and topical clobetasol cream. At his 6-month follow-up, 80–90% of his skin lesions had resolved and his hair had grown back (*Fig. 5A,B*).

European Journal of Case Reports in Internal Medicine

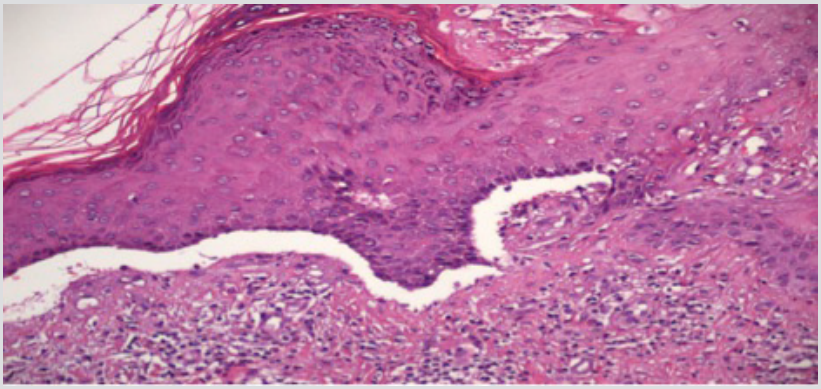

Figure 3. Sub-epidermal blister with multiple eosinophils

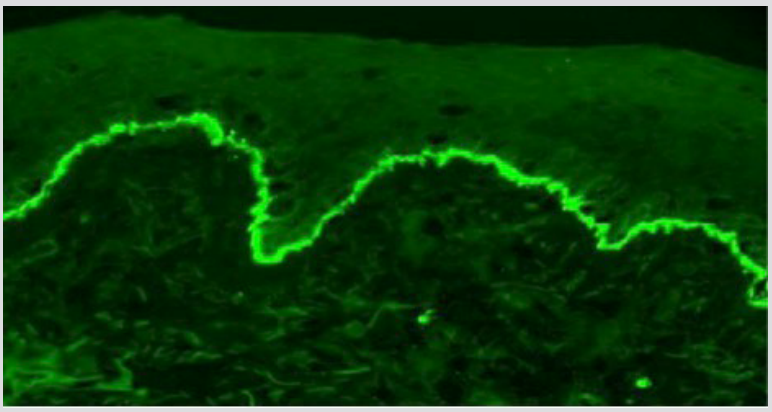

Figure 4. Direct immunofluorescence revealed deposition of IgG and C3 along the basement membrane

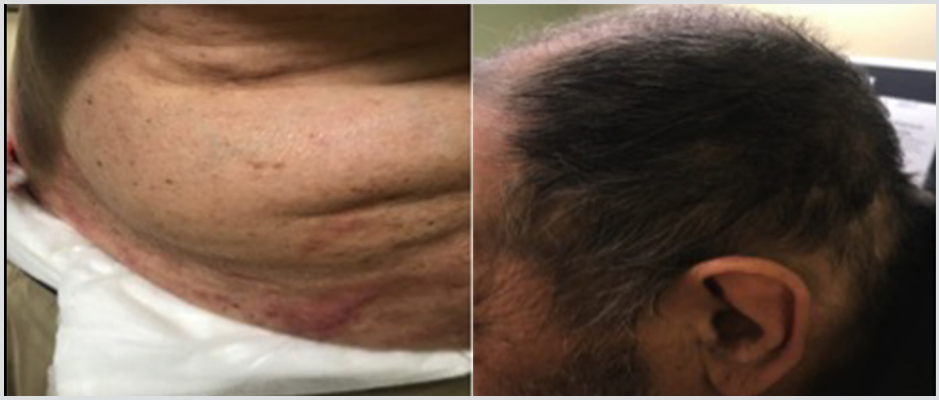

Figure 5. Almost complete remission of skin lesions and alopecia 6 weeks after treatment

DISCUSSION

BP is not uncommon and has an incidence of 0.2–3/100,000 person-years with a higher incidence in older age groups. A UK study estimated the incidence there was 1.4/100,000 person-years[4]. There is a wide variation in mortality rate, with a 1-year mortality rate of 13–41% in Europe and 11–23% in the USA[5]. The classic manifestation of BP is diffuse tense blisters, but clinical presentation can also include diffuse urticarial or dermatitis plaques[6].

DPP-4 inhibitors are a class of oral hypoglycaemic agents which can be used to treat type 2 DM. DPP-4 inhibitors work by increasing glucagon-like peptide-1 and glucose-dependent insulin-trophic polypeptide which leads to increased insulin and inhibits glucagon. Sitagliptin was the first agent of this class to be approved by the FDA in 2006[7]. The DPP-4 enzyme has many functions including biological roles in pro-inflammatory pathways[8]. DPP-4 is also known as CD26 and is widely expressed in various cell types throughout the body including the skin, but the role of the DPP-4 enzyme in autoimmune pathogenesis has not yet been clearly elucidated[9, 10]. A large observational study has indicated that the use of DPP-4 inhibitors is associated with an overall 75% increase in the risk of inflammatory bowel disease in patients with type 2 DM[9]. However, another large observational study indicated that DPP-4 inhibitor combination therapy appears to be associated

European Journal of Case Reports in Internal Medicine

with a decreased risk of autoimmune diseases, including rheumatoid arthritis, compared with non-DPP-4 inhibitor combination therapy[11]. A few months after starting linagliptin, our patient developed alopecia areata totalis and a skin eruption shown to be BP by histological examination and immunofluorescence. Several cases of linagliptin-induced BP have been reported (Table 1). However, none of those cases described both alopecia areata and BP simultaneously due to linagliptin.

CONCLUSION

This is the first report of linagliptin-associated alopecia areata and BP and may indicate a link between DPP-4 inhibitors and alopecia. Although DPP-4 inhibitors are known to be associated with BP, the pathogenesis is still not completely understood. Early diagnosis is essential as agent withdrawal has a significant effect on disease remission.

Author	Patient age and gender	DPP-4i	Length of time before BP onset	Clinical presentation	Treatment	Outcome
Mendonça et al.[12]	82 M	Linagliptin	45 Days	Pruritic cutaneous eruption. No mucosal involvement	Prednisone taper over 6 months and etamethasone-gentamicin cream	Followed for 6 months, no further exacerbations following linagliptin withdrawal
	77 F	Vildagliptin/ metformin	NA	Mucosal involvement at onset; afterwards, mucosal and cutaneous	Prednisone 1 mg/kg/day	Lost to follow-up
	72 F	Vildagliptin/ metformin	3 Months	Pruriginous tense bullae over a urticarial base. No mucosal involvement	Prednisone 1 mg/kg/day	Followed for >8 months, no further exacerbation
Sakai et al.[13]	76 F	Linagliptin	9 Months	Tense bullae over whole body. No mucosal involvement	Topical dexamethasone valerate; minocycline 100 mg daily was added for a while	Complete remission was achieved at 16 weeks after the discontinuation of linagliptin
Haber et al. [3]	60 M	Linagliptin	4 Months	Pruritus and erythematous tense bullae on the limbs. No mucosal involvement	Topical corticosteroid	No clinical recurrence of BP during 3 months of follow-up
	70 F	Linagliptin	3 Months	Pruritus and tense bullae on the trunk. No mucosal involvement	Topical clobetasol propionate	Followed for 5 months with no clinical recurrence of BP
García et al. [14]	74 F	Vildagliptin/ metformin	12 Months	Pruritic bullous skin lesions on the trunk. No mucosal involvement	Oral prednisone for 3 weeks+topical clobetasol	No clinical recurrence after 3 years of follow-up
Yoshiji et al. [15]	81 M	Linagliptin	9 Months	Erythematous tense bullae over entire body. No mucosal involvement	20 mg prednisone, then tapered off	Complete remission 6 weeks after agent withdrawal
	86 M	Linagliptin	9 Months	Erythematous tense bullae over entire body. No mucosal involvement	Started on 20 mg/day prednisolone, which was tapered to 2 mg/day over 10 months	Complete remission 4 weeks after agent withdrawal
	83 F	Linagliptin, sitagliptin	15 Months	Erythematous tense bullae. No mucosal involvement	Prednisolone (15 mg/day), then replaced by IVIG after 3 days because of poor control of BP	Complete remission 2 weeks after agent withdrawal
	86 F	Vildagliptin	6 Months	Erythematous tense bullae. No mucosal involvement	Started on 40 mg/day prednisolone and then received IVIG due to poor control of skin symptoms	Complete remission 4 weeks after agent withdrawal
	63 M	Anagliptin	5 Months	Erythematous bullous eruptions over entire body. No mucosal involvement	Prednisolone (20 mg/day), tapered and stopped within 14 days	Complete remission 2 weeks after agent withdrawal
Guliani et al. [16]	69 M	Teneligliptin/ metformin	4 Months	Erythematous, itchy, fluid-filled lesions. No mucosal involvement	Topical clobetasol propionate	The skin lesions improved in a month. Duration of follow-up unknown

European Journal of Case Reports in Internal Medicine

Author	Patient age and gender	DPP-4i	Length of time before BP onset	Clinical presentation	Treatment	Outcome
Takama et al. [17]	86 F	Linagliptin, anagliptin	6 Weeks	Multiple blisters on both legs. No mucosal nvolvement	Initially topical clobetasol propionate. On day 185, BP relapsed so prednisone 7.5 mg and mizoribine started	Complete remission on day 220. Then no relapses up to day 297
Maki et al. [18]	70 M	Teneligliptin	4 Weeks	Multiple blisters on the trunk. No mucosal involvement	None	Followed up for 2 months with no clinical recurrence of BP
Harada et al. [19]	78 M	Sitagliptin	3 Years	Cutaneous blisters on the bilateral limbs and abdomen	Prednisolone 20 mg	Died on day 14
Esposito et al. [20]	73 F	Linagliptin	5 Months	Diffuse bullous rash	IV methylprednisolone (1 mg/kg/day for 10 days, then tapered) and azathioprine (100 mg/day) for 12 weeks	Still in remission at 1-year follow-up
Maki et al. [18]	70 M	Teneligliptin	4 Weeks	Multiple blisters on the trunk. No mucosal involvement	None	Followed up for 2 months with no clinical recurrence of BP
Harada et al. [19]	78 M	Sitagliptin	3 Years	Cutaneous blisters on the bilateral limbs and abdomen	Prednisolone 20 mg	Died on day 14
Esposito et al. [20]	73 F	Linagliptin	5 Months	Diffuse bullous rash	IV methylprednisolone (1 mg/kg/day for 10 days, then tapered) and azathioprine (100 mg/day) for 12 weeks	Still in remission at 1-year follow-up
Keseroglu et al. [21]	61 F	Vildagliptin/metformin	10 Months	Pruritic vesiculobullous lesions. No mucosal involvement	Topical clobetasol	Remission within 3 weeks. No further follow-up mentioned
Béné et al. [22]	86 F	Vildagliptin/metformin	2 Months	Erythematous bullous eruption, with bullae on healthy skin and extensive erosions on the body	Topical clobetasol	Condition improved after withdrawal of vildagliptin. Duration of follow-up not mentioned
	79 M	Vildagliptin/metformin	37 Months	Generalized erythematous vesicular bullous eruption	Topical clobetasol	The lesions recurred at 3 months but improved after discontinuation of vildagliptin. The duration of follow-up not mentioned
	77 F	Vildagliptin	26 Months	Pruriginous bullous eruption	Topical clobetasol	Condition improved after withdrawal of vildagliptin. The duration of follow up not mentioned
Aouidad et al. [23]	61 M	Vildagliptin/metformin	5 Months	Pruritus and bullous haemorrhagic lesions over an erythematous base disseminated on the trunk and the limb	Topical corticosteroid	Complete remission 2 weeks after agent withdrawal
Pasmatzi et al. [24]	59 F	Vildagliptin/metformin	2 Months	Diffuse bullous eruption mostly on an erythematous base	0.5 mg/kg/day methylprednisolone which was tapered over 8 weeks	Complete remission 10 weeks after agent withdrawal
	67 M	Vildagliptin/metformin	2 Months	Diffuse bullous eruption mostly on an erythematous base	200 mg/day doxycycline for 4 weeks	Complete remission 8 weeks after agent withdrawal
	64 M	Linagliptin	6 Months	Cutaneous and severe mucosal involvement	0.3 mg/kg/day oral prednisolone	Improvement of only cutaneous lesions 2 weeks after agent withdrawal. Mucosal lesions improved 2 weeks after starting prednisone. No further follow-up

Table 1. Characteristics of previous dipeptidyl peptidase-4 inhibitor (DPP-4i)-induced bullous pemphigoid (BP)

European Journal of Case Reports in Internal Medicine

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