An Atypical Case of Wolf’s Isotopic Response Manifesting as Bullous Pemphigoid in a Patient with Longstanding Psoriasis Vulgaris

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ABSTRACT
Wolf’s isotopic response refers to the occurrence of a new, unrelated skin disorder over areas of skin which were previously affected by another skin disorder. To date, a case of Wolf’s isotopic response in a patient with psoriasis vulgaris as the primary dermatological condition has yet to be reported. We describe an occurrence of Wolf’s isotopic response in a 72-year-old patient with longstanding psoriasis vulgaris, who presented with itchy blisters of 2 months. She had been started on linagliptin 5 months prior to the occurrence of the blisters. On examination, tense bullae and healing erosions were observed. They were Nikolsky’s negative and were confined to the psoriatic plaques, which were located predominantly over the trunk and lower limbs. Mucosal and acral surfaces were spared. Neither targetoid lesions nor pustules were present. A punch biopsy was performed on a blister over the left thigh, with both histology and direct immunofluorescence results consistent with the diagnosis of bullous pemphigoid. Anti-BP180 antibodies were positive, while anti-BP230 antibodies was negative.

The concept of Immunocompromised Cutaneous Districts (ICDs) described by Ruocco et al may explain the occurrence of Wolf’s isotopic response in our patient. Psoriasis vulgaris is a cause of chronic lymphedema, which contributes to the formation of these ICDs. Moreover, our patient was on linagliptin, a Dipeptidyl Peptidase-4 Inhibitor (DPPi). The use of DPPis has been shown to precede bullous pemphigoid eruptions. The association between psoriasis vulgaris and bullous pemphigoid has previously been demonstrated, with the onset of psoriasis vulgaris preceding that of bullous pemphigoid in the majority of cases. However, unlike in our case, the distribution of blisters in previously reported cases was not confined to psoriatic skin. Advancements in the understanding of the pathogenesis of psoriasis vulgaris may shed light onto the differing distribution of subsequent bullous pemphigoid eruptions.

INTRODUCTION
Wolf’s Isotopic Response (WIR) refers to the occurrence of a new, unrelated skin disorder over areas of skin which were previously affected by another skin disorder [1]. The occurrence of the initial skin disorder does not influence the incidence of a subsequent disease – it merely results in the localization of the secondary disorder to previously affected sites [1]. Although the pathophysiology behind the response has yet to be fully elucidated, it is hypothesized that the localization effect observed is due to the immune response induced by the initial disorders at those particular sites.

Since the introduction of the concept in 1995 [1], the use of the term has expanded beyond post-herpetic cases. The phenomenon has since been reported in patients with primary lesions caused not just by viral infections [2], but also autoimmune conditions and even vaccination sites [3]. To date, a case of Wolf’s isotopic response in a patient with psoriasis vulgaris as the primary dermatological condition has yet to be reported. We describe an atypical occurrence of Wolf’s isotopic response in a patient with longstanding psoriasis vulgaris.

**CASE REPORT**

The patient was a 72-year-old female who presented with itchy blisters of 2 months. She had chronic plaque psoriasis without joint involvement, which affected her scalp, trunk and limbs, for which she was prescribed 0.1% mometasone cream, 50mcg/g calcipotriol ointment, cocois ointment and 25% coal tar shampoo. At the time of the visit, she had never received any phototherapy, oral immunosuppressants or biologic therapy for her psoriasis. Her other medical conditions included diabetes mellitus, hypertension, hyperlipidemia and osteoarthritis. She had been on linagliptin for 5 months prior to the occurrence of the blisters.

On examination, we noted psoriatic plaques over her frontal scalp, trunk, back and thighs. The active psoriatic Body Surface Area (BSA) involvement was 30%. All of her nails were dystrophic with distal onycholysis. Tense bullae and healing erosions, which were Nikolsky’s negative, were confined to the psoriatic plaques. They were located predominantly over the trunk and lower limbs, with sparing of the mucosal and acral surfaces. Neither targetoid lesions nor pustules were present (Figures 1-3).

A punch biopsy was performed on a blister over the left thigh (Figure 4). Histology showed a subepidermal blister. There was superficial perivascular and interstitial infiltrate of lymphocytes with increased numbers of eosinophils, in association with dermal edema. Direct immunofluorescence showed bright linear deposits of IgG and C3 along the Basement Membrane Zone (BMZ). Indirect immunofluorescence on salt-split skin revealed a roof pattern. ELISA showed anti-BP180 antibodies to be positive at >200RU/mL (positive: >/=20 RU/mL), while anti-BP230 antibodies was negative at <2RU/mL (negative: <20 RU/mL). The full blood count did not reveal any eosinophilia.

The patient was advised to stop taking linagliptin, and was prescribed 0.1% mometasone ointment and loratadine. Two weeks later, the patient no longer had new blisters, and existing erosions were healing well.

**DISCUSSION**

A popular concept that seeks to explain the occurrence of Wolf’s isotopic response is that of immunocompromised cutaneous districts [4]. Ruocco et al delineated a number of pathologies that lead to the formation of these districts, one of which is chronic lymphedema. It is postulated that the compromised lymphatic drainage of affected areas contributes to the localization of the subsequent skin conditions to these same sites in Wolf’s isotopic response [4], although the specific mechanism is not well understood. Psoriasis vulgaris is one such cause of chronic lymphedema [4]. Given the chronicity and extent of the psoriasis vulgaris in our patient, it is not far-fetched to consider chronic lymphedema as a possible explanation for the occurrence of Wolf’s isotopic response.
Although the psoriatic lesions were not fully healed, there may have been sufficient chronic lymphedema or epithelial damage that resulted in sensitization to the BP180 antigen, especially in the context of linagliptin use.

The use of Dipeptidyl Peptidase-4 Inhibitors (DPPIs) such as linagliptin has been shown to precede the eruption of Bullous Pemphigoid (BP) [5]. Although linagliptin is infrequently featured in reports of association between the use of DPPIs and subsequent incidence of bullous pemphigoid [6], the occurrence of the Autoimmune Blistering Disease (AIBD) in such cases has nonetheless been recorded [7]. Izumi et al had previously demonstrated the association between treatment with DPPIs and non-inflammatory bullous pemphigoid, which has milder symptoms and signs as well as reduced numbers of eosinophils seen on histology [8], although this was not the case in our patient. This discrepancy in bullous pemphigoid subtype may be explained by an idea put forth by Haber et al in a report of a similar case of linagliptin-induced bullous pemphigoid in a patient with psoriasis – existing psoriasis may have a synergistic effect on DPPIs-induced reactions by causing an increased number of DPP-4 receptors in keratinocytes [7]. The presence of a roof pattern on indirect immunofluorescence also makes the diagnosis of anti-p200 pemphigoid, which can be seen in patients with chronic plaque psoriasis, less likely.

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The secondary condition of bullous pemphigoid in our patient is also uncommonly seen in Wolf’s isotopic response. While there exist reported cases of bullous pemphigoid occurring as a secondary condition [9], none of the patients in these cases presented with psoriasis vulgaris as the primary
condition. The association between psoriasis vulgaris and bullous pemphigoid has previously been demonstrated, with the onset of psoriasis vulgaris preceding that of bullous pemphigoid in the majority of cases [10]. This same temporal relationship is observed in our patient. However, unlike in our case, the distribution of blisters in previously reported cases was not confined to psoriatic skin — the blisters arose on both psoriatic and normal skin. Advancements in the understanding of the pathogenesis of psoriasis vulgaris may shed light onto the differing distribution of subsequent bullous pemphigoid eruptions.

REFERENCES