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BULLOUS PEMPHIGOID INDUCED BY VILDAGLIPTIN

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Introduction

Bullous pemphigoid (BP) is an autoimmune blistering disease that typically affects the elderly. A skin biopsy from a fresh blister stained with haematoxylin and eosin yields subepidermal clefting and an inflammatory infiltrate mainly consisting of eosinophils in addition to lymphocytes, plasma cells, and histiocytes. The characteristic direct immunofluorescence (IF) picture is a linear deposition of autoantibodies of IgG type (and less commonly IgA, IgM and IgE) and/or C3 along the basement membrane zone (BMZ). The two main autoantigens are BP230 (BPAg1) and BP180 (BPAg2, collagen XVII).

BP may be localized or generalized. It may involve both skin of extremities and trunk and mucosa. Tense blisters occur over normal or erythematous skin. It can be associated with drugs (spironolactone, enalapril, furosemide, chloroquine, beta blocker, TNF-alpha blocker therapy, ampicillin), UV irradiation, and X-ray therapy. ,

There is a number of reports on BP induced by DPP-IV inhibitors (vildagliptin, sitagliptin, saxagliptin). The enzyme DPP-IV degrades glucagon like peptide 1 (GLP-1), which is a potent stimulator of insulin production and secretion.

DPP-IV is expressed by diverse tissues including skin. It is also known as CD26 which is a cell surface glycoprotein on lymphocytes with an intrinsic enzymatic activity.

We present a case of BP induced by vildagliptin.

Case report

A 59 yr old male patient who had recently diagnosed type 2 DM had initial haemoglobin A1c level of 12.90%. His past medical history was nonsignificant for hypertension, cerebrovascular disease, malignancies, and autoimmune diseases. Baseline renal and liver function tests and TSH level were normal.
Initial therapy with premix biphasic aspart insulin bid was switched to metformin and vildagliptin 50/1000 mg bid combination therapy after A1c level dropped to 5.7% at 9 months of insulin therapy,

Five months after vildagliptin was started, tense vesicles 8-10 in number with an erythematous base developed over forearms and lower extremities (Figure 1). Nikolsky's sign was absent. Mucosa was not involved. Fever was absent. Eosinophil count was normal. Histologic examination of the lesions yielded BP (Figure 2). Direct and indirect IF was unavailable.

Oral antidiabetic drugs were discontinued. He was followed up with diet alone. He did not adhere to the therapy of oral deflazacort, azathioprine, and topical steroid. But the lesions regressed spontaneously after cessation of antidiabetic medication. A1c was 5.7% 5 months after discontinuation of vildagliptin and metformin.

Figure 1

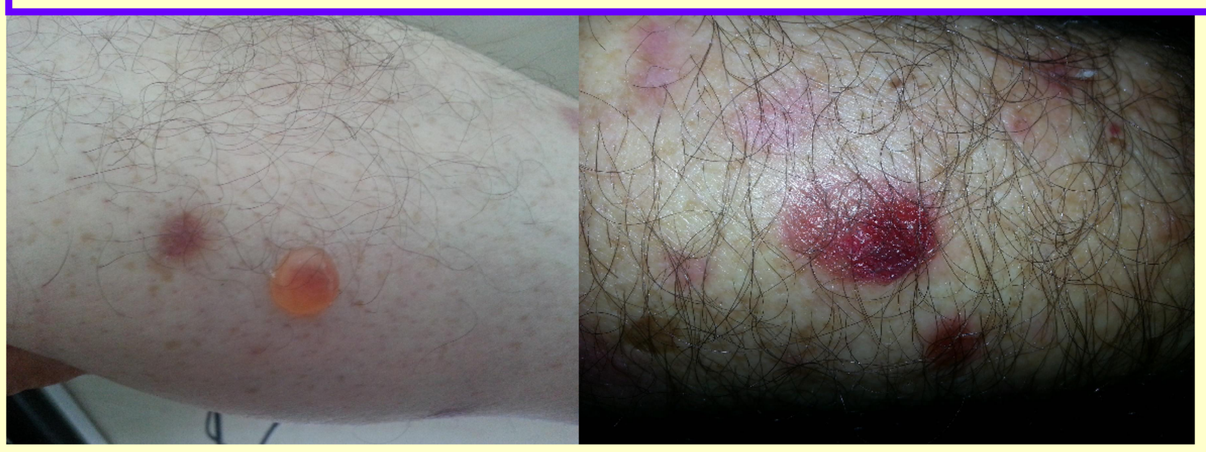
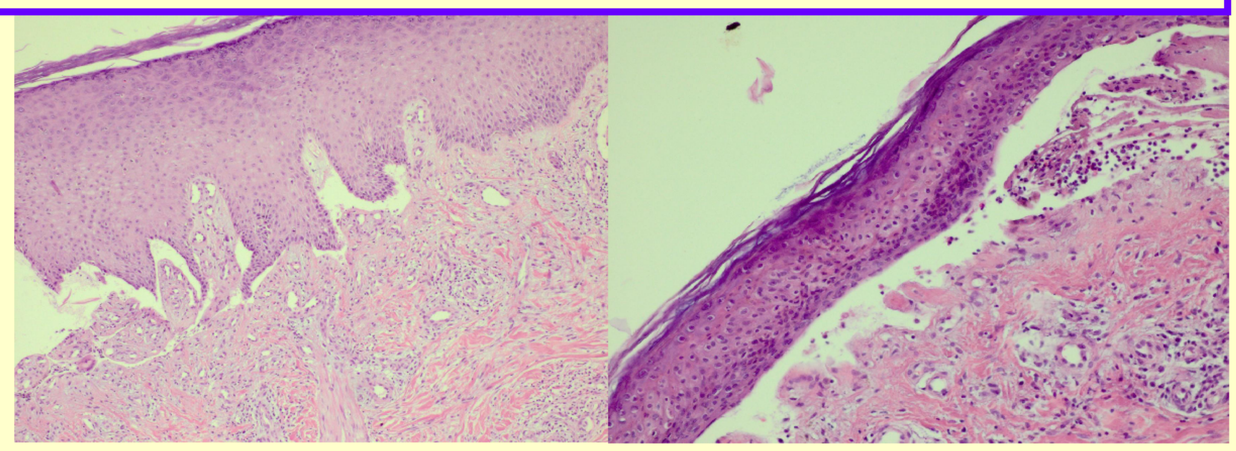


Figure 2. H&E stain (left: 20x, right: 10x)



Discussion

Although skin lesions were not observed at an increased incidence in clinical trials, in postmarketing surveillance there is a wide spectrum of adverse skin reactions including Steven Johnson syndrome induced by gliptins.

In the literature the onset of gliptin induced BP lesions took 10 days to 2 years. Elder males predominate. Most of the patients were on combination therapy with metformin. The lesions improve dramatically after cessation DPP-IV inhibitors avoiding necessity for systemic treatment. Our case bears these features of gliptin induced BP. This is the first case of BP induced by DPP-IV inhibitors in Turkey.

A group of data support the role of gliptins in BP.

Gliptins may modify the immune response by eosinophil activation in the skin and lymphocyte infiltration. These reactions cause blister formation. It was shown that inhibition of DPP-IV enhance CCL11/eotaxin mediated recruitment of eosinophils into the dermis and promote skin homing of lymphocytes.

Gliptins may alter the antigenic properties of the epidermal basement membrane zone. Proteinase activation level plays an important role in the processing and/or destruction of B180 antigen. B180 is the core target of autoimmunity.

DPP-IV does not have significant gelatinase activity. Gelatinase activity is important for processing of B180. Gliptins may modify the activity of allied proteases such as separase which in turn affect epidermal basement zone. Seprase, which is highly homologous to gelatinase, has marked gelatinase activity.

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Clinical Cases - thyroid/others
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