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RS3PE SYNDROME WITH SUBSEQUENT PMR CAUSED BY LONG-TERM DPP-4 INHIBITOR USE

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ABSTRACT

Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) syndrome has been reported in patients treated with dipeptidyl peptidase-4 inhibitors (DPP-4i). We experienced a case of RS3PE syndrome in a 73-year-old man with a history of type 2 diabetes, who developed RS3PE as a side effect of vildagliptin. Further to this, the patient developed polymyalgia rheumatica (PMR), the first such case associated with long-term DPP-4i use.

KEYWORDS

RS3PE syndrome, dipeptidyl peptidase (DPP-4), side effect, polymyalgia rheumatica (PMR)

LEARNING POINTS

- RS3PE syndrome and PMR are rare diseases that cause painful extremities in adults. We need to know if it occurs by DPP-4i.
- RS3PE syndrome and PMR can be complicated with malignancy or giant cell arteritis. However, we must rule out side effects of drugs at first from the standpoint of medical resources.

INTRODUCTION

Glucagon-like peptide-1 (GLP-1), a small intestine incretin that promotes insulin secretion, is degraded by the enzyme dipeptidyl peptidase-4. DPP-4i increase the amount of available GLP-1, promoting insulin secretion to lower blood glucose levels. They remain a popular choice of anti-diabetic agent, with $10.5 billion spent on these medicines in 2018 in the US[1].

Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) syndrome has been reported as a complication of diabetes[2-4]. It has also been reported in patients treated with DPP-4i[5]. In this report, we present a case of a type 2 diabetic patient with no prior rheumatology history treated with vildagliptin and DPP-4i, who developed R3SPE syndrome with subsequent onset of PMR.

CASE DESCRIPTION

A 73-year-old man patient was admitted to our hospital due to painful extremities. Four months before admission he noted fever, lost 10 kg of body weight, had oedema, and pain at dorsal hands and feet bilaterally. He had a 23-year history of type 2 diabetes mellitus. His medication regimen consisted of glimepiride 1 mg, metformin 1,500 mg, empagliflozin 10 mg and miglitol 75 mg, as well as vildagliptin 100 mg.

Vital signs were as follows: blood pressure, 137/61 mm Hg; pulse, 101 beats/min; body temperature, 38.2°C; respiratory

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rate, 13 breaths/min; SpO_2 98% on ambient air.

On physical examination, the distal extremities revealed slow-pitting oedema *(Fig. 1)* with pain rated at 5/10 at bilateral distal interphalangeal, proximal interphalangeal, metacarpophalangeal and carpometacarpal joints. Symmetric weakness was seen in iliopsoas, tibialis anterior and gastrocnemius muscles.

Blood tests revealed elevated C-reactive protein (CRP) and matrix metalloproteinase-3. Serum glucose was 207 mg/dLl and HbA1c was 8.4%. There was no abnormality showing during a malignancy survey.

During this exploration, we found four reports of RS3PE syndrome due to vildagliptin, with no clear report of other medications linked to RS3PE. Given the lack of evidence for an equally plausible competing aetiology, the patient was diagnosed with RS3PE syndrome induced by vildagliptin. We discontinued his glimepiride and metformin on admission. On the sixth hospital day, empagliflozin was discontinued. Musculoskeletal ultrasonography was performed and peripheral synovitis and oedema were observed in the lower limbs[2,3]. On the seventh hospital day vildagliptin was discontinued, with only miglitol continued. Subsequent to stopping vildagliptin, the patient noted substantial improvement in pain and oedema on the tenth hospital day. The Adverse Drug Reaction Probability (Naranjo) Scale was 6 points, which is probably from the drug side effect[6]. On the twenty-seventh hospital day, distal limb musculoskeletal ultrasonography was performed again, showing complete resolution of inflammation and oedema. The patient gradually recovered and was discharged.

Three months after discharge, he reported tenderness and heat in bilateral shoulders. On lab evaluation, inflammatory markers were again elevated (CRP 3.4 mg/dl, erythrocyte sedimentation rate 43 mm/hour). Given that these findings were typical for PMR, we referred him to the Department of Rheumatology. Subsequent musculoskeletal ultrasonography revealed subcutaneous oedema and joint fluid around both shoulder joints. Doppler imaging was taken of the long head of the biceps brachii muscle which identified tenosynovitis, confirming that he met four Bird criteria for diagnosis of PMR (age ≥65; bilateral shoulder pain and/or stiffness; morning stiffness for >1 hour; bilateral upper arm tenderness) and five EULAR/ACR provisional criteria by echo (morning stiffness >45 minutes; absence of abnormal rheumatoid factor or cyclic citrullinated peptide; one shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis)[7,8]. He was prescribed 15 mg of oral prednisolone daily and there was gradual resolution of all symptoms.

DISCUSSION

RS3PE syndrome is characterised by remitting, symmetrical, seronegative, rapid-onset synovitis, and pitting oedema of the hands and feet. Other features include absence of bone erosion, limited wrist and finger joint movement without pain, inflammation, subcutaneous oedema, increased blood flow in the synovial tissue on MRI and high serum vascular endothelial growth factor (VEGF>1,000 pg/ml). Our case satisfies the following diagnostic criteria for RS3PE: marked pitting oedema on the back of bilateral hands, age>50 and seronegativity[2,9,10].

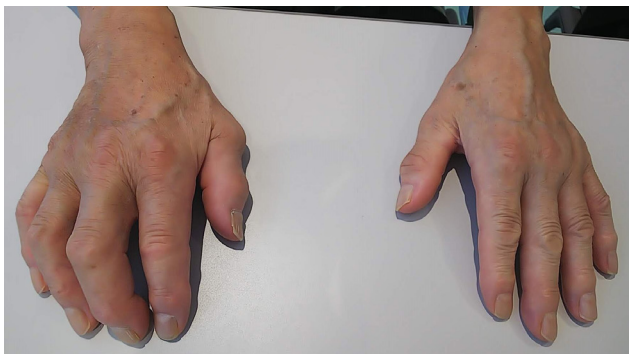

Figure 1. Distal portion of the extremities revealed slow-pitting oedema

RS3PE syndrome has been reported as a complication of diabetes[5] and as a side effect of DPP-4i[10]. In June 2015, it was added as a side effect to the package insert of DPP-4i in Japan. The US Food and Drug Administration also warned of joint pain when taking DPP-4i[11]. Cases involving oral administration of sitagliptin, saxagliptin, linagliptin and alogliptin have been reported, with joint symptoms disappearing within one month after discontinuation[10].

As DPP-4 is associated with various immune functions an association with collagen diseases such as PMR has been hypothesised, though details of this mechanism remain unknown. DPP-4 is a component of the CD26 molecule, a co-stimulatory molecule involved in T-cell activation, present on the surface of lymphocyte T cells, vascular endothelium, skin, intestines, and kidneys. As CD26 contains DPP-4 on the outer cell membrane, cleaving chemokines, and peptides (such as incretins) and playing a role in T-cell activation, there are concerns about its effects on immune system function. DPP-4 inhibition may contribute to increases in stromal-derived factor 1 (SDF-1) and VEGF expression, implicated in the synovial inflammation characteristic of RS3PE syndrome[12]. Diabetic patients have high blood levels of SDF-1 and a higher risk of rheumatoid arthritis; as such, the risk of developing RS3PE syndrome is also considered elevated in diabetic patients compared to healthy individuals[13].

DPP-4i are common type 2 diabetes treatments. Accordingly, the incidence of RS3PE syndrome – currently rare – as well as other rheumatic illness is expected to increase. No previous literature has reported an association between RS3PE syndrome caused by long-term use of DPP-4 inhibitors with subsequent development into PMR. The later emergence of other rheumatic complications suggests that continued monitoring is important for RS3PE syndrome patients, even after discontinuation of the DPP-4i.

CONCLUSION

DPP-4i are commonly administered to patients with type 2 diabetes and may be associated with a wider range of side effects than previously known. This case reports an

association between DPP-4i and both RS3PE syndrome and PMR, a novel finding. Physicians prescribing this class of medicines should remain vigilant regarding the occurrence of rheumatic side effects in general, and RS3PE syndrome in particular.

REFERENCES

1. Research and Markets. Dipeptide Peptidase 4 (DPP-4) Inhibitors Market - Growth, Trends, and Forecast (2019 - 2024). 2015 [cited 2019 Apr 20]. Available from: https://www.researchandmarkets.com/reports/4758263/dipeptide-peptidase-4-dpp-4-inhibitors
2. McCarty DJ, O'Duffy JD, Pearson L, Hunter JB. Remitting seronegative symmetrical synovitis with pitting edema. RS3PE syndrome. *JAMA* 1985;**254**:2763–2767.
3. Karmacharya P, Donato AA, Aryal MR, Ghimire S, Pathak R, Shah K, et al. RS3PE revisited: a systematic review and meta-analysis of 331 cases. *Clin Exp Rheumatol* 2016;**34**:404–15.
4. Mainali NR, Schmidt TR, Alweis R, George DL. Novel development of remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome due to insulin therapy. *Am J Case Rep* 2014;**15**:119–122.
5. Oyama K, Taniguchi J-I, Goto R, Matsui K. Remitting seronegative symmetrical synovitis with pitting edema syndrome in individuals with type 2 diabetes mellitus or impaired glucose tolerance. *Diabetes Res Clin Pract* 2015;**110**:e5–e8.
6. Naranjo CA, Busto U,Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method of estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;**30**:239–245.
7. Bird HA, Esselinckx W, Dixon AS, Mowat AG, Wood PH. An evaluation of criteria for polymyalgia rheumatica. *Ann Rheum Dis* 1979;**38**:434–439.
8. Dasgupta B, Cimmino MA, Maradit-Kremers H, Schmidt WA, Schirmer M, Salvarani C, et al. 2012 provisional classification criteria for polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. *Ann Rheum Dis* 2012;**71**:484–492.
9. Olivieri I, Salvarani C, Cantini F. RS3PE syndrome: an overview. *Clin Exp Rheumatol* 2000;**18**:S53–S55.
10. Yamauchi K, Sato Y, Yamashita K, Funase Y, Kaneko T, Hashimoto T, et al. RS3PE in association with dipeptidyl peptidase-4 inhibitor: report of two cases. *Diabetes Care* 2012;**35**:e7.
11. FDA Drug Safety Communication. Drug Safety and Availability. FDA Drug Safety Communication: FDA warns that DPP-4 inhibitors for type 2 diabetes may cause severe joint pain. 2015 [cited 2019 Apr 21]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-dpp-4-inhibitors-type-2-diabetes-may-cause-severe-joint-pain
12. Arima K, Origuchi T, Tamai M, Iwanaga N, Izumi Y, Huang M, et al. RS3PE syndrome presenting as vascular endothelial growth factor associated disorder. *Ann Rheum Dis* 2005;**64**:1653–1655.
13. Fadini GP, Boscaro E, Albiero M, Menegazzo L, Frison V, de Kreutzenberg S, et al. The oral dipeptidyl peptidase-4 inhibitor sitagliptin increases circulating endothelial progenitor cells in patients with type 2 diabetes: possible role of stromal-derived factor-1alpha. *Diabetes Care* 2010;**33**:1607–1609.