

CASE REPORT

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Remitting Seronegative Symmetrical Synovitis with Pitting Edema in a Patient with Diabetes Mellitus Receiving Saxagliptin

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ABSTRACT We described a rare case of RS3PE associated with DPP-4 inhibitor (saxagliptin) therapy in a diabetic patient with no evidence of another underlying pathology. To the best of our knowledge, this is the first case report of RS3PE associated with saxagliptin. The patient presented with acute onset of swelling and pain in multiple peripheral joints, swelling of the dorsum of the hands and feet occurred a month after the initiation of saxagliptin. Laboratory results were remarkable for elevated acute phase reactants. The diagnosis of RS3PE was made through exclusion and was based on acute onset of pitting edema, synovitis shown by ultrasound and magnetic resonance investigation, absence of joint erosions and negative rheumatoid factor. Patient showed a good response to low dose of steroids with a complete and sustained remission. The development of RS3PE following introduction of drug should suggest this drug as a possible trigger for the development of RS3PE.

Keywords: Saxagliptin; diabetes mellitus; edema; synovitis

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) is a rare clinical syndrome characterized by a symmetrical tenosynovitis of the hands, wrists and pitting edema over upper and lower extremities.¹ RS3PE occurs commonly in elder men and usually has a benign course. The etiology of RS3PE syndrome is not fully understood although the association between RS3PE and late-onset rheumatoid arthritis, polymyalgia rheumatica was debated widely.^{1,2} RS3PE is reported to be seen secondarily to malignancy, several disorders or drugs.²⁻⁶ In the literature, we encountered two cases of RS3PE syndrome that are related with the use of DPP-4 inhibitor

medication (sitagliptine and vildagliptine).⁶ Saxagliptin is a relatively novel DPP-4 inhibitor and this is the first case report of the RS3PE in a patient receiving saxagliptin treatment.

CASE REPORT

A 51-year-old man presented to our clinic with an acute onset of swelling in multiple peripheral joints (metacarpophalangeal, proximal interphalangeal and wrist joints) and the dorsum of the hands and feet (Figure 1). The patient had hyperlipidemia and type 2 diabetes, diagnosed 7 years ago. He was on metformin, pre-mixed insulin, saxagliptin and rosuvastatin.

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FIGURE 1: Edema of the dorsum of the hands and wrists was observed before treatment.

tatine treatment. He had received insulin therapy for 4 years. To achieve adequate glycemic control, saxagliptin has been added recently to the antidiabetic therapy. The onset of symptoms started acutely 4 weeks after the initiation of saxagliptin treatment. The patient described also morning stiffness lasting about half an hour, however previous joint pain, fever, trauma, rash, burning sense in micturition or diarrhea were not accompanying. His medical history was not remarkable. The patient denied any drug allergy. Physical examination showed tenosynovitis on metacarpophalangeal, proximal interphalangeal and wrist joints bilaterally. The patient had pitting edema on the back of both hands and wrist joints (Figure 1). Skin of the hands was not warm but there was moderate tenderness. Physical examination was otherwise normal. Laboratory evaluation revealed high erythrocyte sedimentation rate (ESR) (57 mm/h) and C-

reactive protein (CRP) (58 mg/d; normal range <3) levels. Diabetes was well controlled with a glycated hemoglobin A_{1C} level of 6.6%. Complete blood count, total protein, albumin and creatinine phosphokinase levels were normal. There was not abnormality in urine analysis. Pathologies that caused edema including kidney and liver disease, heart failure or edema due to malnutrition were excluded. Antinuclear antibodies, anti-neutrophil cytoplasmic antibody, rheumatoid factor and anti-citrullinated peptide antibody resulted negative. Investigations for infectious, including hepatitis B and C, parvovirus, human immunodeficiency virus and malignancy screening test results were all negative. We also ruled out rheumatological disorders such as giant cell arteritis, polymyalgia rheumatica, rheumatoid arthritis (RA), viral arthralgia or polyarthritis due to endocarditis. X-ray examination of the patient's hands did not indicate any bone erosions. Doppler ultrasound revealed extensor tenosynovitis of both hands. Magnetic resonance imaging (MRI) revealed only soft-tissue swelling, tenosynovitis without any evidence of joint destruction (Figure 2). We established the diagnosis of RS3PE according to clinical appearance of pitting edema, additional radiological examination and negative serology. We assumed saxagliptin as a cause of RS3PE because there was no evidence of underlying pathologies related to RS3PE and the onset of symptoms occurred within a month after initiation of treatment. Saxagliptin treatment was discontinued. After two weeks, we initiated corticosteroid treatment (20 mg daily) since we did not observe

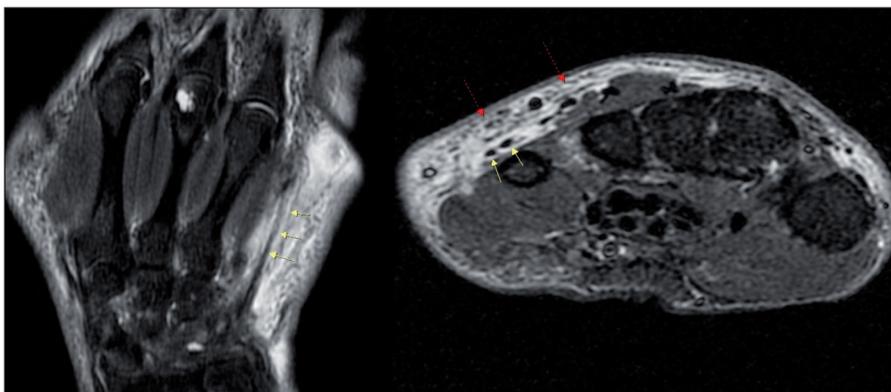


FIGURE 2: Dorsal hand swelling (red dot arrow), mild synovitis, tenosynovitis of the extensor tendons (yellow arrow) of the dorsal hand axial and coronal short inversion time inversion recovery (STIR) images of the left wrist (TR/TE 3000/33; TI= 90; Slice= 4 cm; matrix= 256x192).



FIGURE 3: Edema of the dorsum of the hands and wrists improved after the corticosteroids treatment.

a sufficient improvement in symptoms. Clinical findings showed dramatic response to prednisone; all of the symptoms relieved within four weeks (Figure 3). The patient has been in regular follow up for the last 48 months and no residual disability or deformity and no malignancy was detected.

DISCUSSION

This is the first report describing the association of RS3PE with saxagliptin. RS3PE is a rare clinical entity identified by symmetrical tenosynovitis of the hands and wrists and swelling of the back of hands and feet.¹ The entity occurs commonly in elder men and usually has a benign course. Most cases of RS3PE syndrome are idiopathic, although the syndrome has been associated with malignancy, rheumatologic diseases and some drugs.²⁻⁶ In a meta-analysis evaluating 331 cases of RS3PE, it was shown that the relation of RS3PE with malignancy and rheumatologic diseases were 16.31% and 6.65% respectively.² The drugs reported in relation with RS3PE are insulin, DPP-4 inhibitors, rifampicin and nivolumab.⁴⁻⁶ In the present case the clinical presentation and disease course of RS3PE due to saxagliptin showed a course similar to those related to the other etiologies but with the onset of disease at young age. Yamauchi et al. reported two diabetic patients who developed RS3PE while taking DPP-4 inhibitors.⁶ One of them developed the condition at 5th week after starting sitagliptin and the other patient developed RS3PE at 8th week after the vildagliptin was administered. Clinical improvement was achieved within

several days after discontinuation of the DPP-4 inhibitors in both patients. Prednisone was required for resolution of the inflammation in the patient who was receiving sitagliptin. Similarly to the case with sitagliptin in our patient, the symptoms of the disease improved partially and it was necessary to initiate corticosteroid treatment. Except treatment with DPP-4 inhibitors, in diabetic patients, RS3PE was reported in association with insulin treatment and diabetes itself.^{4,7,8} Oyama reported four patients with type 2 diabetes who developed RS3PE syndrome but among these patients there was a history of malignancy in two of the patients.⁸ Sakoda described a patient at age of 59 who developed type 1 diabetes mellitus and RS3PE syndrome simultaneously.⁷ Although RS3PE was accepted to be related to a newly developed type 1 diabetes, authors did not ignore the possibility that the infectious agent may be the initial trigger for autoimmune process implicated in pathogenesis of type 1 diabetes together with RS3PE. Mainali and colleagues reported RS3PE syndrome associated with insulin therapy, regardless of its type.⁴

DPP-4 enzyme, also known as a lymphocyte cell surface protein CD26, is an enzyme that degrades numerous peptides and plays a potential role in modulating immune system especially inhibiting proliferation of T cell and cytokine production.^{9,10} Prolonged inhibition of DPP-4 by DPP-4inhibitors may influence immune system in different ways. Some studies suggested a favorable potential role of DPP-4 inhibitors as a novel therapy for several inflammatory diseases while a few studies reported cases of rheumatoid arthritis like inflammatory arthritis potentially related to the use of DPP-4 inhibitors.^{9,11,12} These conflicting results indicate the need for further studies to better understand the role of DPP-4 inhibitors on immune system.

The pathogenesis of RS3PE is unknown. It is argued that vascular endothelial growth factor (VEGF) has been implicated as a contributing factor responsible for both synovitis and subcutaneous edema in RS3PE.¹³ Arima and colleagues showed elevated levels of VEGF in RS3PE patients compared with controls. Samikannu and colleagues experimentally showed that the improvement of islet vascularization

through the VEGF-A/VEGF-R2 via stabilization of Glp-1 by DPP-4 inhibition.¹⁴ The authors suggested that VEGF-DPP-4-Glp-1 may also control systemic availability of VEGF necessary and advocated the possibility of additional pro-angiogenic pathways activated by DPP-4 inhibitors. Recently, it was found that sitagliptin causes vascular leakage in the retina increasing stromal cell-derived factor-1 α (SDF-1 α). Activated by DPP-4 inhibitor, SDF-1 α is responsible for disrupting of endothelial cell-to-cell junctions leading to vascular leakage.¹⁵ We speculated that a similar mechanism may be involved in the pathogenesis of RS3PE but we could not demonstrate this conclusively in our patient.

RS3PE related to saxagliptin had a good prognosis and showed no recurrence of symptoms. The potential effects of DPP-4 inhibitors on immune system and vascular permeability remain to be elucidated.

Informed Consent

Informed consent was obtained from the patient to publish their case "Remitting seronegative symmetrical synovitis with pitting edema in a patient with diabetes mellitus receiving saxagliptin: a case report."

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Aylia Mehmedova Yeşilova, Müge Bilge, Gizem Aya, Recep Yılmaz Bayraktarlı, Mine Adas; **Design:** Aylia Mehmedova Yeşilova, Müge Bilge; **Control/Supervision:** Mine Adas, Recep Yılmaz Bayraktarlı; **Data Collection and/or Processing:** Aylia Mehmedova Yeşilova, Müge Bilge, Gizem Ayan; **Analysis and/or Interpretation:** Aylia Mehmedova Yeşilova, Müge Bilge, Gizem Ayan; **Literature Review:** Aylia Mehmedova Yeşilova, Müge Bilge, Gizem Ayan; **Writing the Article:** Aylia Mehmedova Yeşilova, Müge Bilge, Gizem Ayan; **Critical Review:** Mine Adas, Recep Yılmaz Bayraktarlı.

REFERENCES

- McCarty DJ, O'Duffy JD, Pearson L, Hunter JB. Remitting seronegative symmetrical synovitis with pitting edema. RS3PE syndrome. *JAMA*. 1985;254(19):2763-7. [[Crossref](#)] [[PubMed](#)]
- 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(3):404-15. [[PubMed](#)]
- Russell EB. Remitting seronegative symmetrical synovitis with pitting edema syndrome: follow up for neoplasia. *J Rheumatol*. 2005;32(9):1760-1. [[PubMed](#)]
- 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;15:119-22. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
- Gauci ML, Baroudjian B, Laly P, Madelaine I, Da Meda L, Vercellino L, et al. Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome induced by nivolumab. *Semin Arthritis Rheum*. 2017;47(2):281-7. [[Crossref](#)] [[PubMed](#)]
- 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(2):e7. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
- Sakoda H, Ito S, Kanda H, Fujishiro M, Osuga J, Tsukamoto K, et al. Association between type 1 diabetes mellitus and remitting seronegative symmetrical synovitis with pitting edema: a case report. *Diabetes Res Clin Pract*. 2011;91(2):e43-4. [[Crossref](#)] [[PubMed](#)]
- Oyama K, Taniguchi JI, 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(1):e5-8. [[Crossref](#)] [[PubMed](#)]
- Reinhold D, Biton A, Goihl A, Pieper S, Lendeckel U, Faust J, et al. Dual inhibition of dipeptidyl peptidase IV and aminopeptidase N suppresses inflammatory immune responses. *Ann N Y Acad Sci*. 2007;1110:402-9. [[Crossref](#)] [[PubMed](#)]
- Abbott CA, Yu DM, Woollatt E, Sutherland GR, McCaughan GW, Gorrell MD. Cloning, expression and chromosomal localization of a novel human dipeptidyl peptidase (DPP) IV homolog, DPP8. *Eur J Biochem*. 2000;267(20):6140-50. [[Crossref](#)] [[PubMed](#)]
- Saito T, Ohnuma K, Suzuki H, Dang NH, Hatano R, Ninomiya H, et al. Polyarthropathy in type 2 diabetes patients treated with DPP4 inhibitors. *Diabetes Res Clin Pract*. 2013;102(1):e8-12. [[Crossref](#)] [[PubMed](#)]

12. Crickx E, Marroun I, Veyrie C, Le Beller C, Schoindre Y, Bouilloud F, et al. DPP4 inhibitor-induced polyarthritis: a report of three cases. *Rheumatol Int.* 2014;34(2):291-2. [[Crossref](#)] [[PubMed](#)]
13. 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(11):1653-5. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
14. Samikannu B, Chen C, Lingwal N, Padmasekar M, Engel FB, Linn T. Dipeptidyl peptidase IV inhibition activates CREB and improves islet vascularization through VEGF-A/VEGFR-2 signaling pathway. *PLoS One.* 2013;8(12):e82639. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
15. Lee CS, Kim YG, Cho HJ, Park J, Jeong H, Lee SE, et al. Dipeptidyl peptidase-4 inhibitor increases vascular leakage in retina through VE-cadherin phosphorylation. *Sci Rep.* 2016;6:29393. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]