Remitting Seronegative Symmetrical Synovitis and Pitting Edema Syndrome After Administration of a Dipeptidyl Peptidase-4 Inhibitor, Alogliptin, in a Patient With Type 2 Diabetes

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Case Report

Remitting Seronegative Symmetrical Synovitis and Pitting Edema Syndrome After Administration of a Dipeptidyl Peptidase-4 Inhibitor, Alogliptin, in a Patient With Type 2 Diabetes

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A 57-year-old Japanese man with type 2 diabetes presented with bilateral pitting edema and pain of the hands and feet two months after being initiated on a dipeptidyl peptidase-4 (DPP-4) inhibitor, alogliptin. Laboratory tests showed elevated levels of C-reactive protein, matrix metalloproteinase-3 and vascular endothelial growth factor, and a negative rheumatoid factor. The computed tomography scan showed swelling in the dominant right wrist joint, and joint ultrasonography showed synovial swelling. He was diagnosed with remitting seronegative symmetrical synovitis and pitting edema (RS3PE) syndrome. Alogliptin was discontinued and prednisolone was initiated, thereafter, his symptoms quickly improved. As for his glycemic control, his hemoglobin A1c (HbA1c) went from an initial 9.1% to 8.3% once alogliptin was initiated. However, after being diagnosed with RS3PE syndrome, his treatment was changed from alogliptin to metformin, and his HbA1c remained between 6% and 7%. The diagnosis of RS3PE syndrome should be considered if pitting edema and arthralgia in the extremities are observed after initiating patients with type 2 diabetes on DPP-4 inhibitors.

Keywords: DPP-4 inhibitor, alogliptin, diabetes, RS3PE syndrome

Introduction

Remitting seronegative symmetrical synovitis and pitting edema (RS3PE) syndrome is characterized by the development of synovitis and pitting edema in both hands and feet, a negative rheumatoid factor (RF), and a good prognosis.[1] Dipeptidyl peptidase-4 (DPP-4) inhibitors are widely used in patients with type 2 diabetes, and although rare, adverse effects including pancreatitis, pemphigoid and the development of immune disorders have been reported.[2,3] Moreover, the use of DPP-4 inhibitors has been associated with the development of RS3PE syn-

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Table 1. Laboratory data on admission.

<Blood count>		*<Biochemistry>*		*<Tumor markers>*	
WBC	6,810 /μL	TP	7 g/dL	CEA	3.4 ng/mL
RBC	342×10^4 /μL	Albumin	2.2 g/dL	CA19-9	< 2 U/mL
Hemoglobin	9.9 g/dL	AST	15 U/L	SCC	0.6 ng/mL
Hematocrit	30.2 %	ALT	18 U/L		
Platelet	40.3×10^4 /μL	LDH	143 U/L	*<Culture test>*	
		BUN	12.6 mg/dL	Blood culture	(-)
<Urinalysis>		Creatinine	0.65 mg/dL	Urine culture	(-)
Urine sugar	4+	eGFR	97.4 mL/min/1.73 m^2		
Urine protein	-	UA	3.3 mg/dL	*<Immunological test>*	
Urine microalbumin	9.6 mg/g・Cr	Sodium	132 mEq/L	Anti-nuclear antibody	(-)
		Potassium	4.3 mEq/L	RF	(-)
<Glucose metabolism>		Chlorine	97 mEq/L	Anti-citrullinated peptide antibody	(-)
Casual blood glucose	312 mg/dL	Correction Ca	10.6 mg/dL	MMP-3	154.2 ng/mL
HbA1c	9.9 %	Iron	30 μg/dL	VEGF	879 pg/mL
Urine C-peptide	218.7 μg/day	TIBC	134 μg/dL		
C-peptide index	1.36	Ferritin	931 ng/mL		
		<Inflammatory indicators>			
		CRP	13.86 mg/dL		
		ESR 60 min	132 mm		

WBC, white blood cell; RBC, red blood cell; HbA1c, hemoglobin A1c; TP, total protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; UA, uric acid; TIBC, total iron binding capacity; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; SCC, squamous cell carcinoma; RF, rheumatoid factor; MMP-3, matrix metalloproteinase-3; VEGF, vascular endothelial growth factor.

drome,[4-18] although the mechanism remains unclear. We report a case of RS3PE syndrome, diagnosed after being initiated on a DPP-4 inhibitor, alogliptin. Furthermore, we discuss the association between DPP-4 inhibitors and the development of RS3PE syndrome based on a review of domestic and international cases.

Case Description

A 57-year-old Japanese man was admitted to our hospital with bilateral pitting edema, pain of both hands and feet, fever, and general malaise. He had a history of duodenal ulcer and schizophrenia. His family history revealed that his mother had myelodysplastic syndrome, and his father had multiple myeloma. He had a history of smoking 20 cigarettes a day between the ages of 20 and 40 years but had quit, and he did not consume alcohol regularly. He was diagnosed with type 2 diabetes at the age of 45 years. After having received temporary insulin treatment, at the age of 52 years he regularly followed up at a local clinic and his hemoglobin A1c (HbA1c) levels were maintained between 6% and 7% without medication. At the age of 57 years, in February, his postprandial blood glucose and HbAlc levels had increased to 301 mg/dL and 9.1%, respectively. Therefore, he was referred to our hospital and we initiated him on alogliptin, 25 mg/day. One month after the initiation of alogliptin, his HbA1c level decreased to 8.3%. He developed wrist joint pain and pitting edema on the dorsal side of both hands and feet, after alogliptin initiation, which led him to consult at a local clinic. He took a nonsteroidal anti-inflammatory drug for three months; however, the pain and edema of the extremities worsened, and he developed a fever of 38.0°C. He was then admitted to our hospital for further examination and treatment.

On admission, his physical examination revealed clear consciousness, a body mass index of 24.3 kg/m^2, body temperature of 38.1°C, pulse rate of 104 bpm and blood pressure of 140/93 mmHg. No abnormalities were noted in the head, neck, or thoracoabdominal region. There was pitting edema of the extremities and pain in both wrist joints. Palpation of the dorsalis pedis arteries revealed diminished blood flow bilaterally, but the ankle reflexes and vibration sensations were normal.

The results of the laboratory blood test performed on admission are shown in **Table 1**. The leukocyte count

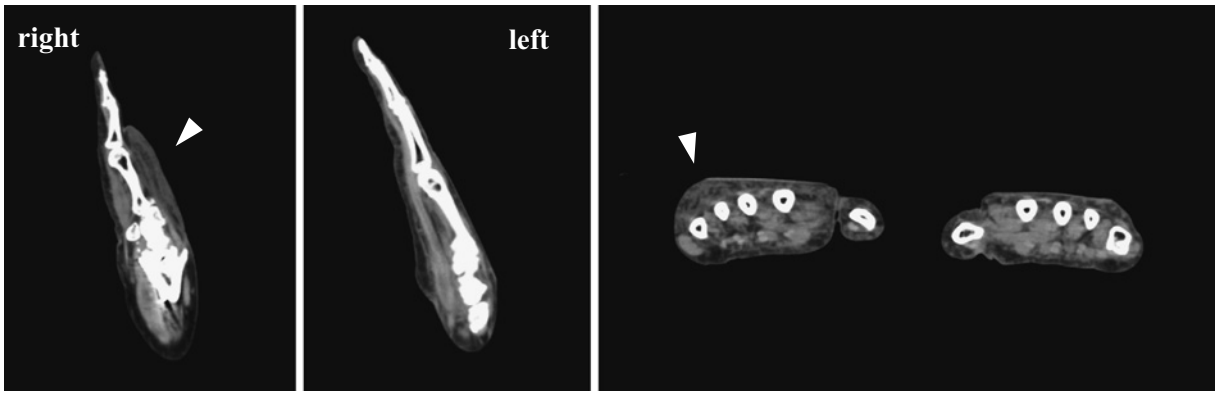

Figure 1. Computed tomography of both hands.
Swelling is observed in both hands. The white arrow indicates the severe swelling and turbidity of adipose tissue in right hand.

was 6,810/μL and the C-reactive protein (CRP) level was 13.86 mg/dL, indicating a severe inflammatory response. Although the level of total serum protein was normal, the level of serum albumin was markedly low. Normocytic normochromic anemia, with normal serum iron levels and total iron-binding capacity, and high levels of serum ferritin suggested secondary anemia associated with chronic inflammation. His random blood glucose and HbA1c levels were 312 mg/dL and 9.9%, respectively. The tumor markers were within the normal ranges.

Though blood samples showed no obvious signs of infection, a computed tomography (CT) scan showed swelling predominantly on the dorsum of the right hand (**Figure 1**), suggesting cellulitis, therefore treatment with cefazolin (2 g/day) was initiated. On the 5th day of taking the antibiotics (i.e., the 5th day of hospitalization), the swelling and pain in both hands and feet and fever showed little improvement; the CRP level remained high and the results of the two consecutive blood cultures, as well as urine culture, were negative. An inflammatory condition other than infection was suspected; therefore, antibiotic use was discontinued on the 7th day, and the patient was initiated on a non-steroidal anti-inflammatory drug. Results of the tests for anti-nuclear antibodies, RF, and anti-cyclic citrullinated peptides (anti-CCP) antibodies were negative, but levels of matrix metalloproteinase-3 (MMP-3) and vascular endothelial growth factor (VEGF) were elevated (**Table 1**). Joint ultrasonography revealed synovial swelling of the right wrist joint, thus, we diagnosed him with RS3PE syndrome.

Since previous case reports provided evidence of an association between DPP-4 inhibitor administration and RS3PE syndrome diagnosis,[4-18] we discontinued alogliptin and replaced it with metformin, 1,000 mg/day. The fever resolved on the 3rd day (the 10th day of hospitalization), after the discontinuation of alogliptin. The edema then gradually improved, and the patient was discharged on the 20th day after admission, although the inflammatory reaction and edema did not completely disappear. On the 7th day after discharge, he was initiated on prednisolone, 15 mg/day; his CRP and serum albumin levels rapidly returned to normal, and the pain and edema in his extremities rapidly disappeared. Prednisolone was then tapered down to 6 mg/day, over the next 6 months, and there was no recurrence of RS3PE syndrome (**Figure 2**).

Discussion

In this case, we diagnosed the patient with RS3PE syndrome based on the following findings: 1) pitting edema of both hands and feet with general fatigue and fever, 2) elevated CRP levels, erythrocyte sedimentation rate, MMP-3 and VEGF levels, 3) a negative RF test result, 4) synovial swelling of the right wrist joint, and 5) prompt improvement of the symptoms and inflammatory reaction in response to steroid therapy. In the diagnosis of RS3PE syndrome, it is important to differentiate it from elderly-onset rheumatoid arthritis (EORA) and polymyalgia rheumatica (PMR). In this case, both RF and antinuclear antibodies were negative. PMR was considered, but the male onset, relatively small joint lesions, and lack of myalgia made it unlikely. As for EORA, the patient's age of

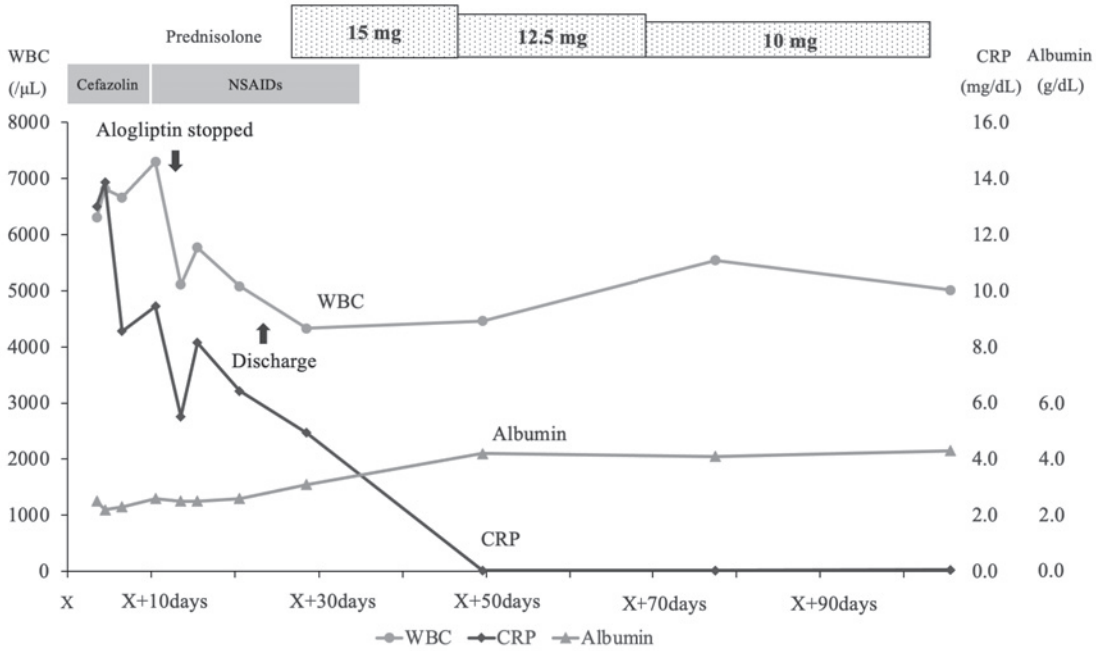

Figure 2. Clinical course.
The circles indicate white blood cells, the squares indicate CRP, and the triangles indicate albumin.
WBC, white blood cell; CRP, c-reactive protein; NSAIDs, non-steroidal anti-inflammatory drugs.

less than 60 years met the exclusion criteria for the disease.

Factors associated with the development of RS3PE syndrome include parvovirus infection, malignant tumors, multiple myeloma, DPP-4 inhibitors, and anti-programmed cell death protein-1 antibodies.[19-21] Although diabetes, *per se*, with and without insulin therapy has also been implicated in the mechanism of RS3PE syndrome development[22-24] the clinical course of the patient suggested a strong association between RS3PE syndrome development and alogliptin administration. It has been shown that human leukocyte antigen (HLA)-B7 is positive in approximately half of the patients diagnosed with RS3PE syndrome, and HLA-CW7 and HLA-DQW2 are involved in its mechanism.[25, 26] However, in our patient, HLA-B7, HLA-CW7, and HLA-DQW2 were not detected.

The first case of RS3PE syndrome associated with a DPP-4 inhibitor was reported in Japan in 2012;[4] since then, 21 Japanese cases have been reported, as listed in **Table 2**.[5-18] The fact that the most common DPP-4 inhibitor associated with RS3PE syndrome was sitagliptin (**Table 2**), does not necessarily indicate a stronger association between sitagliptin intake and RS3PE syndrome diagnosis than other DPP-4 inhibitors. Sitagliptin was the first DPP-4 inhibitor marketed in Japan and is still the most prescribed DPP-4 inhibitor. The average age of onset of RS3PE syndrome was 73 years and the incidence was slightly higher in men than in women. From the 21 Japanese cases reported, the period from DPP-4 inhibitor administration to RS3PE syndrome onset was less than 2 months, and the number of cases was as high as 9 (42.9%). The most common symptom was edema of both hands, 19 cases (90.5%). In our case, edema of both hands was also observed within 2 months after alogliptin administration.

All the Japanese cases, other than ours, showed that symptoms improved despite continuing treatment with a DPP-4 inhibitor, suggesting that RS3PE syndrome was not only caused by the effects of DPP-4 inhibitors.[27] Patients with type 2 diabetes who developed RS3PE syndrome after starting treatment with DPP-4 inhibitors have been reported in other countries,[28, 29] however, most cases are from Japan, suggesting that racial differences play a potential role in the development of RS3PE syndrome associated with the use of DPP-4 inhibitors.

The mechanisms implicated in the pathogenesis of RS3PE syndrome associated with DPP-4 inhibitors are

Table 2. Twenty two case reports of RS3PE syndrome involving DPP inhibitors in Japan.

No	Author (year)	Age	Sex	DPP-4 inhibitor	Time to onset	Type of diabetes	Symptoms
1	Yamauchi K (2012)[4]	74	F	Sitagliptin	5 weeks	Type 2	Edema of both hands and feet, Joint pain of elbow and knee
2	Gocho N (2013)[5]	79	F	Sitagliptin	5 months	Type 2	Edema of upper and lower limb, Joint pain of fingers
3	Iida M (2013)[6]	70s	F	Sitagliptin	1 year 6 months	Type 2	Edema of both hands and feet, Pain of upper and lower limb
4	Murakoshi M (2014)[7]	64	M	Sitagliptin	1 month	Type 2	Edema and pain of both hands
5	Murakoshi M (2014)[7]	75	M	Sitagliptin	2 months	Type 2	Swelling and pain of both wrists
6	Sawada T (2014)[8]	78	M	Sitagliptin	1 year 7 months	Type 2	Edema and arthralgia of both hands
7	Gonai M (2016)[9]	87	M	Sitagliptin	6 months	Type 2	Edema and pain of both hands
8	Arii K (2016)[10]	76	F	Sitagliptin	1 year 2 months	Type 2	Edema and joint pain of both hands
9	Yamada Y (2017)[11]	71	F	Sitagliptin	-	Type 2	Edema of both hands and feet, Arthralgia and muscle pain
10	Kikuno S (2018)[12]	79	M	Sitagliptin	3 years 4 months	Type 2	Swelling and edema of both hands
11	Sako O (2019)[13]	67	M	Sitagliptin	5 years	Type 2	Edema and arthralgia of both hands and feet
12	Hidaka N (2019)[14]	73	M	Sitagliptin	3 weeks	Type 2 (steroid)	Edema of both feet
13	Hidaka N (2019)[14]	81	F	Sitagliptin	1 month	Type 2	Edema of both feet
14	Hidaka N (2019)[14]	63	M	Sitagliptin	2 years	Type 2	Edema of both hands
15	Yamauchi K (2012)[4]	71	M	Vildagliptin	2 months	Type 2	Edema of both hands
16	Nagakura R (2012)[15]	79	F	Vildagliptin	2 months	Type 2	Edema of both hands, Joint pain of knee
17	Hidaka N (2019)[14]	55	F	Vildagliptin	1 month	Type 2 (steroid)	Edema of both hands and feet
18	Hidaka N (2019)[14]	72	M	Vildagliptin	1 month	Type 2	Edema of both hands and feet
19	Kato K (2020)[16]	71	M	Vildagliptin	-	Type 2	Edema and arthralgia of both hands
20	Murakami N (2017)[17]	60	M	Linagliptin	1 year	Type 2	Swelling and arthralgia of both hands and feet
21	Hidaka N (2019)[14]	79	F	Linagliptin	1 year 4 months	Type 2	Edema and arthralgia of both hands
22	Yoshioka Y (2018)[18]	-	-	Alogliptin	-	Type 2	-

unclear. DPP-4 is a type II transmembrane protein that plays an important role in the regulation of $CD26^+$ T cell activation.[30, 31] It degrades stromal cell-derived factor-1 (SDF-1), which is an adipocytokine. DPP-4 inhibitors could increase SDF-1 levels, causing increased levels of inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor-α via an increase in fibroblasts.[32] Elevated SDF-1 increases leukocyte migration and increases vascular endothelial growth factor (VEGF) level.[33] This results in increased vascular permeability and edema.[34, 35] Furthermore, an increased level in SDF-1, VEGF, and inflammatory cytokines promotes synovial destruction and proliferation, resulting in increased MMP-3 and CRP levels.[32]

In conclusion, we treated a 57-year-old Japanese man with type 2 diabetes who experienced RS3PE syndrome after being treated with a DPP-4 inhibitor, alogliptin. RS3PE syndrome resolved after the discontinuation of the DPP-4 inhibitor, followed by the initiation of prednisolone treatment. When pitting edema in both hands and feet are observed in patients with type 2 diabetes after the administration of DPP-4 inhibitors, a careful examination considering RS3PE syndrome as a possible cause is recommended.

Conflicts of Interest: The authors declare that they have no conflicts of interest.

Author Contributions: SM wrote the paper; JO and TB edited the paper; MS, TM, YH, ST, NY, HK, and MH collected information; TB approved the final draft of the paper. All authors read and approved the final manuscript.

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