J Nepal Health Res Counc 2021 Jul-Sep;19(52): 644-6

DOI: https://doi.org/10.33314/jnhrc.v19i3.3433

Late Onset Dipeptidyl Peptidase -4 Inhibitor Associated Seronegative Rheumatoid Arthritis

Binit Vaidya,[1] Bhojraj Adhikari,[2] Manisha Bhochhibhoya,[1] Shweta Nakarmi[1]

ABSTRACT

Drug-induced arthritis is not an uncommon scenario. DPP-4 inhibitors could potentially cause adverse-events mediated by cytokine-induced inflammation leading to arthritis. The activity of the DPP-4 enzyme could be inversely related to the development of rheumatoid arthritis, explaining the increased inflammatory activity with its inhibition by a drug. We discuss a 72-year-old gentleman with twenty-three years of history of type 2 diabetes mellitus, who after 6 years of treatment with a DPP-4 inhibitor, developed features of inflammatory arthritis and fulfilled the criteria for seronegative rheumatoid; which eventually subsided after stopping the drug.

Keywords: DDP-4 inhibitor; diabetes mellitus; Nepal; rheumatoid arthritis; seronegative

INTRODUCTION

Musculoskeletal symptoms are known adverse-effect of many therapeutic agents.[1, 2] Rheumatologists need to remain abreast with these side-effects. There are previous reports of dipeptidyl peptidase4 inhibitor (DPP-4i) related arthritis.[3] Sitagliptin, saxagliptin, linagliptin, and alogliptin are members of DPP-4i used to treat type 2 diabetes mellitus (T2DM). DPP-4 iuse is associated with occurrence of arthralgia, arthritis, or even reactivation of rheumatoid arthritis (RA).[4] We describe a male patient who developed seronegative RA after treatment with sitagliptin.

CASE REPORT

A 72-year-old male with a twenty-three years history of type 2 diabetes mellitus (DM 2) presented to the rheumatology clinic at the National Center for Rheumatic Diseases, Kathmandu, Nepal with complaints of pain and swelling in multiple joints for 6 weeks. It was gradual in onset, affecting mainly bilateral wrist joints, metacarpo-phalangeal (MCP) joints, and proximal interphalangeal (PIP) joints. He had significant early morning stiffness of more than 30 minutes. Polyarthritis was associated with weight loss of about 5 kilograms (kg) in the past 3 months. There was no history of fever, night sweat, psoriasis, back pain, enthesitis, red-eye, headache, jaw claudication, dysuria, hematochezia, preceding infection, or familial autoimmune arthritis. On examination, the patient had 15 swollen and 17 tender joints. Vitals were stable.

He was diagnosed type 2 DM in 1996 A.D., which was controlled by single oral hypoglycemic, metformin 500 milligram (mg) once daily. After 6 years, the dose was increased to 500mg twice a day. In 2013 A.D, along with metformin 1gm two times a day, DPP-4i (sitagliptin) 100 mg once a day was added. In subsequent years, the doses of these drugs were adjusted along with the addition of long-acting insulin (Lantus, 10-20 units).

Laboratory reports showed elevated erythrocyte sedimentation rate (ESR) 53 mm and C- reactive protein (CRP) 62mg/L. Rheumatoid factor (RF), anti-cyclic citrullinated peptide antibody(anti-CCP), and anti-nuclear antibody(ANA) were negative. Human leukocyte antigen (HLAB27 by polymerase-chain reaction) was negative. Complete blood count (CBC), kidney function test (KFT), and liver function test (LFT) were within normal range. Random blood sugar (RBS) was 194 mg/dL and glycated hemoglobin(HbA1c) was 8.2%. The work-up for paraneoplastic syndrome was done with negative results (Table 1).

High-frequency musculoskeletal ultrasonography (MSUS) examination with the application of power doppler was performed for the affected joints (Figure 1a, b and 2a, b). MSUS definition and quantification of synovitis were done using a scoring system developed by European League Against Rheumatism (EULAR) - Outcome Measures in Rheumatology (OMERACT) ultrasound taskforce.[5] MSUS examination showed grade 2 synovitis of wrist and MCP joints along with tenosynovitis of flexor tendons. Thus the provisional diagnosis of seronegative RA was made according to 2010 ACR/EULAR criteria with a total score being 7/10.[6] Crystal induced arthropathy, diabetic cheiro-arthropathy (no classic payer or table top sign)

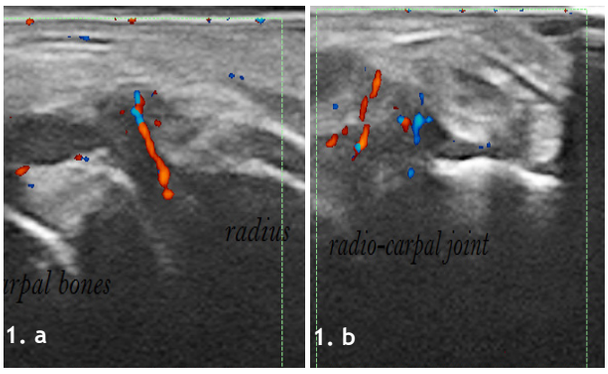
Correspondence: Dr Binit Vaidya, National Centre for Rheumatic Diseases, Nepal.
Email: drbinitvaidya@gmail.com, Phone: +97714464288.

and, paraneoplastic syndrome as the differential diagnosis were ruled out.

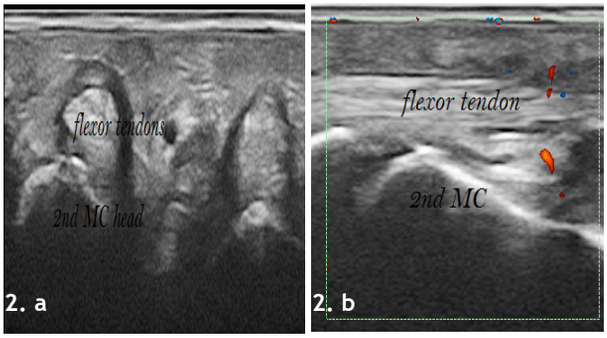
Table 1. Results of laboratory and radiological tests.

Investigations (Method)	Results	Reference range
CEA*	0.5 ng/ml	(<5)
CA-19-9†	0.2 U/ml	(0-37)
PSA‡	0.82 ng/ml	(<4.0)
Urine RME§	Within normal range	
USG abdomen and pelvis‖	Mild prostatomegaly	
Chest X-ray PA view¶	No abnormality detected	
Mantoux test (Dose: 10 TU)	<10 mm induration at 72 hours	(<10 mm)
PBS**	Normochromic, Normocytic	

*Abbreviations: *CEA:Carcinoembryonic antigen; †CA-19-9: Carbohydrate antigen 19-9; ‡PSA: Prostrate- specific antigen; §Urine RME: Urine routine and microscopic examination;‖USG: Ultrasonography; ¶PA view: Poster anterior view; **PBS: peripheral blood smear*



Figures 1. a, b. MSUS of wrist joint.



Figures 2 a, b. MSUS of flexor surface of hand at the level of MCP joint.

TREATMENT

Initially presenting symptoms were inflammatory in nature, supported by pain and swelling of joints, raised inflammatory markers (CRP and ESR), thus sitagliptin was continued. Treatment was started for seronegative RA with hydroxychloroquine 200 mg per oral twice a day, and etoricoxib.

Follow-up

On subsequent follow-up, the intensity of pain decreased (negative squeeze test at MCP and PIPs) but there were skin changes with subungual hyperkeratosis and plantar hyperkeratosis. Skin histopathology report suggested spongiotic dermatosis suggestive of eczema and no features of psoriasis. The CRP level decreased to 5.7 mg/L and ESR was within the normal range. The patient was kept under hydroxychloroquine 200 mg bid and vitamin D with NSAID for the next 3 months. He had a flare of arthritis in 1 month when NSAIDs were tapered. Before going for methotrexate, we opted to give one more course of NSAIDs and evaluate the response of withdrawal of DPP-4 inhibitors. Sitagliptin was changed to repaglinide 4 mg once a day along with metformin 1 gm twice a day, acarbose 50 mg and 25 mg and insulin (Lantus,12 units). Over the next 6 weeks, his symptoms gradually disappeared.

At 3 months follow-up, the patient had no pain or swelling. He was off medication for 3 weeks as he had gastrointestinal intolerance due to hydroxychloroquine. His CRP and ESR and other parameters in a routine blood test were within range. The normalization of acute-phase reactants (CRP and ESR) and subsequent improvement in clinical symptoms after cessation of DPP-4 inhibitor led to the conclusion that seronegative RA was induced by DPP-4 inhibitor which was started 6 years before the appearance of acute arthritis. The patient had remained in drug-free remission after another 3months (total of 6months of drug cessation).

DISCUSSION

Medications could cause musculoskeletal related adverse effects like joint pain and inflammatory arthritis. One group of medication that has been reported to cause inflammatory arthritis is DPP-4i.[3]

The clinical studies have shown mixed results.[7]Multiple case reports have suggested that DPP-4 inhibitors may be associated with 3.77 times increased risk of developing arthritis/arthralgia. Resolution of joint symptoms after discontinuation of the offending medication has been described.[3,4,7] A washout period of 3months for disappearance of symptoms after discontinuation has been reported.[8]

We described a case of suspected inflammatory arthritis following the use of Sitagliptin. The mechanism behind DPP-4 inhibitor-related arthralgia is also being studied. In chronic inflammatory autoimmune diseases like RA, DPP-4 may have multiple roles like stimulating cellular immunity and inhibiting chemokine function.[9] The activity of DPP-4 is thought to be inversely related to RA, and inhibiting DPP-4 may contribute to RA development.[5] DPP-4 protects articular cartilage against invasion by fibroblast in RA and, the plasma level of DPP-4 is spontaneously decreased and is inversely related to the CRP level.[10]

CONCLUSIONS

Patients receiving treatment with DPP-4ishould be carefully monitored for the development of arthritis irrespective of the duration of treatment.

ACKNOWLEDGEMENTS

We would like to thank Dr Sudarshan Bhakta Mathema for his cooperation in providing relevant information.

Author Affiliations

[1]National Center for Rheumatic Diseases, Kathmandu, Nepal

[2]Bharatpur Hospital, Bharatpur, Chitwan, Nepal

Competing interests: None declared

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