OBSERVATIONS

RS3PE in Association With Dipeptidyl Peptidase-4 Inhibitor: Report of Two Cases

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE), first described by McCarty (1), is characterized by symmetrical pitting edema of the hands and feet; tenderness, swelling, and/or limited motion of the joints; fatigue; and fever (1,2). It commonly occurs in elderly people (1,2). We have recently encountered two cases of RS3PE that developed shortly after the initiation of a dipeptidyl peptidase-4 (DPP4) inhibitor and resolved markedly upon cessation of it.

Case 1 was a 74-year-old woman with a 30-year history of type 2 diabetes who presented with edema of the hands, low grade fever, and malaise, which developed 5 weeks after switching from 20 mg gliclazide to 50 mg sitagliptin. Physical examination revealed severe pitting edema at the dorsum of the hands and mild edema at the fingers of both hands and the dorsum of the feet. Mild arthralgia was also present at the wrists and knees. Glycohemoglobin A1C (HbA_{1c}) was 7.2% (National Glycohemoglobin Standardization Program equivalent). Case 2 was a 71-year-old man with a 1-year history of type 2 diabetes who noticed pitting edema of the dorsum of the hands and the feet 8 weeks after starting 100 mg vildagliptin. HbA_{1c} was 5.7%.

In cases 1 and 2, C-reactive protein (CRP; reference range <9.5 nmol/L) was 1,313 and 13 nmol/L, respectively, and erythrocyte sedimentation rate was 86 and 23 mm/hour, respectively. Rheumatoid factor, anticyclic citrullinated protein antibody, antinuclear factor, and anti-DNA antibody were negative in both cases. Neither patient had a history of drug allergy and collagen vascular disorders. In case 1, expression of CD26, a lymphocyte membrane protease with DPP4 activity, was found in 38% of the peripheral lymphocytes, which was within the normal range (3). The symptoms and signs, and the laboratory data established diagnosis of RS3PE (1,2). Under a presumptive judgment that DPP4 inhibitor use was related to RS3PE, the DPP4 inhibitor was discontinued in both cases. In case 1, the symptoms and signs ameliorated markedly after 7 days, and CRP was 837 nmol/L. Because edema had not completely disappeared, 20 mg prednisolone was initiated 25 days after cessation of sitagliptin, which was followed by complete resolution of edema and the near-normalization of CRP at 76 nmol/L. In case 2, striking improvement of symptoms and signs and normalization of CRP (8 nmol/L) had occurred within 10 days of cessation of vildagliptin.

DPP4 inhibitors are relatively new oral hypoglycemic agents that elevate plasma active glucagon-like peptide 1 and thereby amplify glucose-induced insulin release by the pancreatic β-cells. This is the first report of the occurrence of RS3PE in patients receiving a DPP4 inhibitor. Although the cause-result relationship cannot decisively be established, the temporal sequence of events strongly suggests that the DPP4 inhibitor could have been causally related to development of RS3PE. As a possible side effect of a combination of metformin and DPP4 inhibitor, bullous pemphigoid was reported by two groups (4,5). Given our observations for these two cases, heightened awareness is suggested in assessing possible dermatological side effects of DPP4 inhibitors, and extensive epidemiological analysis of it may be warranted if other cases are observed.

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DOI: 10.2337/dc11-1995

Acknowledgments—No potential conflicts of interest relevant to this article were reported.

K.Yamau. is the guarantor of this article. K.Yamau. and Y.S. researched data, followed up the patients, and wrote the manuscript. T.A. researched data, participated in discussion, and reviewed and edited the manuscript. T.K., T.H., K.Yamas., and Y.F. participated in discussion.

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