Kidney Medicine

Alogliptin-Induced Minimal Change Nephrotic Syndrome and Interstitial Nephritis

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Alogliptin is one of the dipeptidyl peptidase-4 inhibitors used to treat patients with type 2 diabetes. Little is known about the nephrotoxicity associated with alogliptin, such as nephrotic syndrome or interstitial nephritis. We report a biopsy-proven rare case of minimal change nephrotic syndrome and interstitial nephritis induced by alogliptin. A 68-year-old man who had been prescribed alogliptin was hospitalized for nephrotic syndrome. On admission, serum creatinine level was elevated with increased urinary β_2-microglobulin and *N*-acetyl-β-D-glucosaminidase excretion. Kidney biopsy revealed minor glomerular abnormalities and interstitial nephritis, and gallium-67 scintigraphy showed uptake in both kidneys. A drug lymphocyte stimulation test for alogliptin was positive. With discontinuation of alogliptin treatment alone, serum creatinine level normalized in parallel with urine β_2-microglobulin and *N*-acetyl-β-D-glucosaminidase levels. In addition, complete remission of nephrotic syndrome was observed. Drug-induced dual pathology has not been previously reported with alogliptin. In summary, clinicians should keep in mind that alogliptin can induce minimal change nephrotic syndrome and interstitial nephritis.

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INTRODUCTION

Alogliptin is one of the dipeptidyl peptidase-4 (DPP-4) inhibitors used to treat patients with type 2 diabetes mellitus.[1] Alogliptin accounts for nearly 10% of prescription of DPP-4 inhibitors in Japan. DPP-4 inhibitors enhance insulin production by inhibiting the degradation of glucagon-like peptide-1, which regulates glucose metabolism.[2] Severe side effects of DPP-4 inhibitors have been reported, including hypoglycemia, acute pancreatitis, and hypersensitivity reactions.[1] Allergic reactions, such as rash, itching, and hives, also have been reported. However, alogliptin-induced kidney disease has not previously been reported. The dose of alogliptin varies according to kidney function.[3] In many cases, physicians prescribe alogliptin without considering nephrotoxicity as long as the dose is adjusted.

Minimal change nephrotic syndrome (MCNS) is a common form of nephrotic syndrome. Although most cases of MCNS occur due to primary or idiopathic causes, various drugs have also been reported to induce MCNS.[4] MCNS cases are usually treated with steroids, and spontaneous remission is rare. Acute interstitial nephritis (AIN) is another common cause of acute decreased kidney function. To our knowledge, this is the first case report describing the incidence of both MCNS and interstitial nephritis induced by alogliptin, prescribed at its appropriate dose. We also report that stopping oral alogliptin treatment alone attenuated both nephrotic syndrome and renal interstitial damage markers without requiring corticosteroid treatment. Such spontaneous remission is rare.

CASE REPORT

A 68-year-old man was admitted to our hospital due to anasarca. He had a history of type 2 diabetes mellitus, hypertension, and cerebral infarction and had been on treatment with only alogliptin (25 mg/d) and clopidogrel (75 mg/d) for 14 months. He had no history of allergies. Serum creatinine (Scr) level was 0.75 mg/dL with no proteinuria and hematuria at 1 year before admission.

On admission, vital signs were as follows: blood pressure, 131/77 mm Hg; temperature, 35.9°C; pulse rate, 107 beats/min; and respiratory rate, 20 breaths/min. The patient did not present with skin rash but had extensive peripheral edema. Dipstick urinalysis revealed proteinuria (4^+) and hematuria (±). Spot urine protein-creatinine ratio was 26.3 g/gCr. Urinary excretion of β_2-microglobulin and N-acetyl-β-D-glucosaminidase (NAG) were markedly elevated (22,470 μg/gCr and 118.5 U/gCr, respectively). Scr level was elevated at 1.55 mg/dL, and serum total protein and albumin levels were low at 5.3 g/dL and 1.4 g/dL, respectively. Based on these results, we made a diagnosis of nephrotic syndrome. His serum corrected calcium and angiotensin-converting enzyme levels were 10.8 mg/dL and 33.9 (reference range, 7.0-25.0) U/L, respectively. Serum immunoglobulin E (IgE) level was elevated (332; reference range, <170 U/mL). No eosinophilia was detected. Protein electrophoresis of serum and urine detected no monoclonal protein. Serum free light chain κ:λ ratio was normal (1.56; reference range, 0.26-1.65). Bence-Jones protein was not detected in urine. Computed tomography of the chest revealed right hilar lymph node enlargement. Gallium-67 scintigraphy revealed uptake in the hilar lymph nodes and both kidneys (Fig 1A).

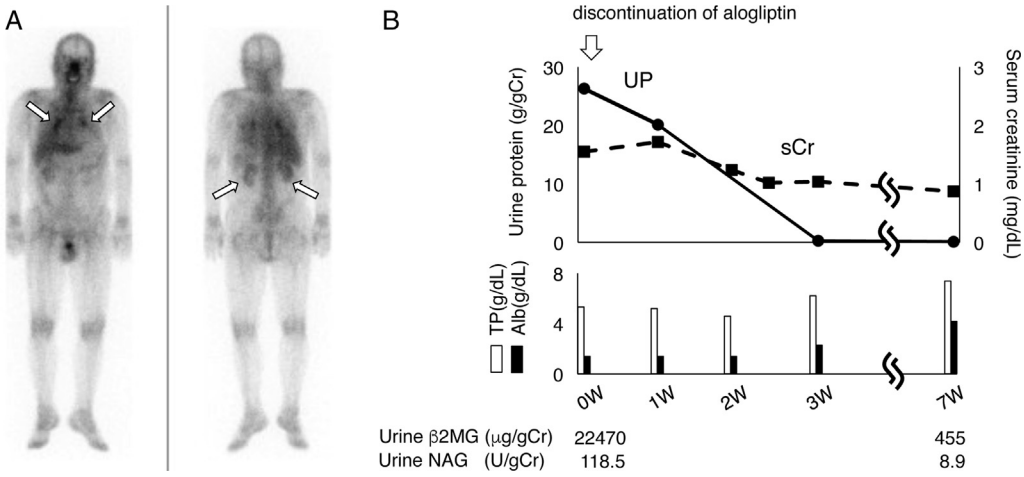

Figure 1. (A) Gallium-67 scintigraphy shows uptake in the hilar lymph nodes and both kidneys. (B) With discontinuation of alogliptin treatment, urine protein (UP) excretion and serum creatinine (sCr), serum total protein (TP), serum albumin (Alb), urinary β_2-microglobulin (β2MG), and *N*-acetyl-β-D-glucosaminidase (NAG) levels were all attenuated at 7 months.

We then suspected the possibility of sarcoidosis and thus investigated cardiac, ocular, and renal lesions. Cardiac sarcoidosis was not detected using cardiac magnetic resonance imaging. Ocular sarcoidosis was also not detected using fluorescent angiography. Moreover, a kidney ultrasound showed that the kidneys were of normal size with no dilation of the urinary tract and no kidney stones.

However, kidney biopsy revealed diffuse lymphocyte infiltration in the interstitium and tubulointerstitial fibrosis. Eosinophils and plasma cells were not identified (Fig 2A-C). Glomeruli were normal with no crescents (Fig 2D). Granulomas were observed, but they were not noncaseating (Fig 2E). Immunofluorescence staining was nonspecific for IgG and negative for IgA, IgM, C3, C4, C1q, and fibrinogen. Staining for κ and λ light chains was equivalent (data not shown). Electron microscopy showed widespread foot-process fusions (Fig 2F). We also performed Ziehl-Neelsen staining on the kidney biopsy specimen, which provided negative results (data not shown).

Altogether, a diagnosis of MCNS and interstitial nephritis was made. Because we suspected delayed drug-induced hypersensitivity reactions, drug lymphocyte stimulation tests for alogliptin and clopidogrel were performed. The result for alogliptin was positive (stimulation index, 270%; a positive result is >180%) and for clopidogrel was negative (stimulation index, 70%). Test results for antinuclear antibody, anti-Sjögren syndrome A, anti-Sjögren syndrome B antibody, perinuclear antineutrophil cytoplasmic antibody (ANCA), cytoplasmic ANCA, and anti–glomerular basement membrane antibody were all negative.

Three weeks after stopping oral alogliptin treatment, both proteinuria and Scr levels were improved (0.29 g/gCr and 1.04 mg/dL, respectively; Fig 1B). Total serum protein and albumin levels also gradually increased and improved at 7.4 g/dL, and 4.2 g/dL, respectively, at the 7-week follow-up. β_2-Microglobulin and NAG levels also improved (455 μg/gCr and 8.9 U/gCr, respectively) at the 7-week testing (Fig 1B).

DISCUSSION

In this report, we demonstrate for the first time the possibility of alogliptin inducing both MCNS and interstitial nephritis. Although it has been reported that MCNS can be induced as a secondary reaction to various drugs, including nonsteroidal anti-inflammatory drugs, lithium, and D-penicillamine,[4] no reports have been published describing MCNS induced by DPP-4 inhibitors. Although spontaneous remission of MCNS is rare, the symptoms of nephrotic syndrome in this case spontaneously improved with discontinuation of alogliptin treatment alone. Other secondary causes of MCNS are infections, neoplasms, and other kidney diseases.[4] However, our patient had no symptoms of infectious diseases. Computed tomography and gallium-67 scintigraphy revealed no malignancies. Based on these findings, we strongly speculate that this was a case of alogliptin-induced MCNS.

Kidney biopsy also revealed interstitial nephritis, which is mainly caused by drugs and sarcoidosis.[5] Common causative drugs are antibiotics, nonsteroidal anti-inflammatory drugs, anticonvulsants, and diuretics.[6] However, our patient was not taking these drugs. Therefore, based on the results of kidney biopsy, gallium-67 scintigraphy, and the drug lymphocyte stimulation test, we diagnosed AIN induced by alogliptin, which to our knowledge is the first case reported in literature.

According to the Gell and Coombs classification, drug-induced AIN is a delayed hypersensitivity reaction of type IV.[7] The administration period before the occurrence of AIN varies depending on the drug (ranging from 7 days to 18 months).[8,9] In this case, AIN might have developed at 14 months after beginning alogliptin treatment. AIN is reported to have classic symptoms, such as fever,

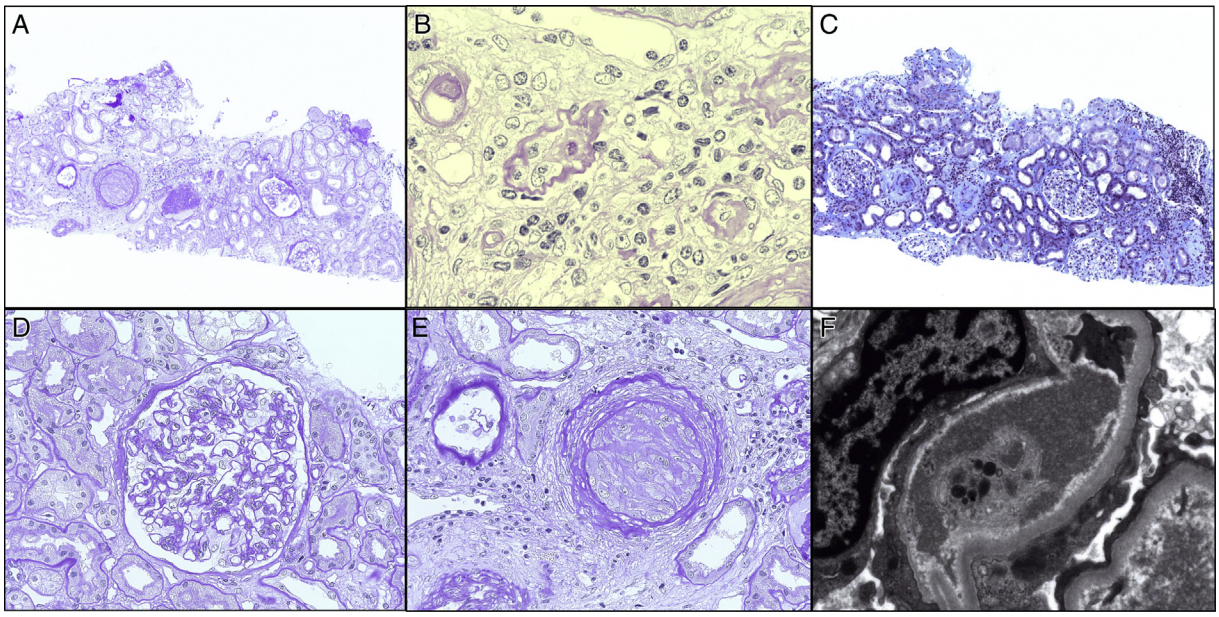

Figure 2. (A, B) Periodic acid–Schiff and (C) Masson trichrome staining reveal diffuse lymphocyte infiltration in the interstitium and tubulointerstitial fibrosis (A, C: original magnification, ×100; B: original magnification, ×1,000). (D) Glomeruli were almost normal; (E) granulomas were observed, but not noncaseating epithelioid cell (D, E: periodic acid–Schiff staining; original magnification, ×400). (F) Electron microscopy shows widespread foot-process fusions (original magnification, ×8,000).

arthralgia, and rash.[10] However, these symptoms were not present in our case, possibly because these are recognized in only 10% of AIN cases.[10] As shown in Figure 1A, gallium-67 scintigraphy was useful in the diagnosis of AIN.[11] In addition, urinary β_2-microglobulin and NAG are reported to be useful markers of renal interstitial damage. These markers and Scr levels were remitted with the discontinuation of alogliptin treatment alone.

Sarcoidosis was diagnosed using the clinical, radiologic, and histopathologic findings and exclusion of other granulomatous diseases.[12] In the present case, the patient did not have clinical symptoms and noncaseating epithelioid cell granulomas in the kidneys, often seen in sarcoidosis.[13] Therefore, although it cannot be denied completely, we believe that the possibility of our patient having sarcoidosis is less likely. The granulomatous inflammation is caused by various diseases, including tuberculosis, hematologic malignancy, and eosinophilic granulomatosis with polyangiitis.[14] Caseating granulomas are typical of tuberculosis.[14] Based on Ziehl-Neelsen staining on the kidney biopsy specimen and no typical symptoms, the possibility of tuberculosis is less likely.

Multiple myeloma is a cancer of plasma cells, accounting for ~10% of hematologic malignancy. Monoclonal protein is produced by clonal plasma cells in multiple myeloma. Decreased kidney function and proteinuria are common complications.[15] Based on immunofluorescence staining, serum and urine protein electrophoresis, and serum free light chain κ:λ ratio, the possibility of myeloma is less likely. However, the possibility of hematologic malignancy cannot be completely denied because we did not perform lymph node biopsy or bone marrow biopsy.

Eosinophilic granulomatosis with polyangiitis is a systemic necrotizing vasculitis with asthma and eosinophilia, characterized by granulomas and eosinophilic infiltration.[16] Myeloperoxidase ANCA is positive in 40% to 60% of patients with eosinophilic granulomatosis with polyangiitis.[16] In this case, the patient was ANCA negative, with no blood and tissue eosinophilia and asthma. Therefore, we considered that eosinophilic granulomatosis with polyangiitis is less likely.

Drug lymphocyte stimulation tests are used for auxiliary diagnosis of drug allergies. The stimulation index is defined as the value of ^{3}H-thymidine uptake with antigen/without antigen.[17] Although a previous report suggested that the positivity of drug lymphocyte stimulation tests was ~40%,[18] results would be different depending on the suspect drugs. Few reports have investigated the sensitivity and specificity of drug lymphocyte stimulation tests in the diagnosis of allergy to alogliptin. However, the clinical spontaneous resolution following discontinuation of alogliptin treatment makes the case convincing. The Naranjo adverse drug reaction possibility scale is a method for estimating the probability of adverse drug reaction.[19] In this case, the score was 7, which meant probable adverse drug reaction.

It is important to note that alogliptin has been reported to have a renoprotective effect in patients with type 2 diabetes mellitus.[20] Therefore, in many cases physicians prescribe alogliptin without considering its potential nephrotoxicity. In view of the case presented here, it is imperative that physicians pay attention to the renal

parameters, such as urinalysis findings and Scr levels, in similar cases after prescribing alogliptin.

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