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 β₂-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 β₂-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.

© 2019 The Authors. Published by Elsevier Inc. on behalf of the National Kidney Foundation, Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
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 non-caseating (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 cytoplasmatic 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. β₂-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, 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. 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. Common causative drugs are antibiotics, nonsteroidal anti-inflammatory drugs, anticonvulsants, and diuretics. 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. The administration period before the occurrence of AIN varies depending on the drug (ranging from 7 days to 18 months). In this case, AIN might have developed at 14 months after beginning alogliptin treatment. AIN is reported to have classic symptoms, such as fever,
arthralgia, and rash. However, these symptoms were not present in our case, possibly because these are recognized in only 10% of AIN cases. As shown in Figure 1A, gallium-67 scintigraphy was useful in the diagnosis of AIN. In addition, urinary β₂-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. In the present case, the patient did not have clinical symptoms and noncaseating epithelioid cell granulomas in the kidneys, often seen in sarcoidosis. 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. Caseating granulomas are typical of tuberculosis. 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. 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. Myeloperoxidase ANCA is positive in 40% to 60% of patients with eosinophilic granulomatosis with polyangiitis. 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 3H-thymidine uptake with antigen/without antigen. Although a previous report suggested that the positivity of drug lymphocyte stimulation tests was ~40%, 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. 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. 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...

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

ARTICLE INFORMATION

Authors’ Full Names and Academic Degrees: Hisato Shima, MD, PhD, Takuya Okamoto, BM, Manabu Tashiro, MD, PhD, Tomoko Inoue, MD, PhD, Chiaki Masaki, BM, Hiroaki Tada, MT, Norimichi Takamatsu, PhD, Kazuhiro Kawahara, MD, Kazuyoshi Okada, MD, PhD, Toshio Doi, MD, PhD, Jun Minakuchi, MD, PhD, and Shu Kawashima, MD.

Authors’ Affiliations: Departments of Kidney Disease (HS, MT, TI, KO, TD, JM, SK) and Laboratory (TO, CM, HT, NT), Kawashima Hospital, Tokushima; and Kamojima-Kawashima Clinic, Yoshinogawa, Tokushima, Japan (KK).

Address for Correspondence: Hisato Shima, MD, PhD, Department of Kidney Disease, Kawashima Hospital, 1-39 Kitasakicho-cho, Tokushima, Tokushima 770-0011, Japan. E-mail: h.shima@khg.or.jp

Support: None.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Acknowledgements: We thank Editage for technical assistance in editing a draft of this manuscript.

Peer Review: Received January 17, 2019. Evaluated by 2 external peer reviewers, with direct editorial input from an Associate Editor and the Editor-in-Chief. Accepted in revised form March 4, 2019.

REFERENCES

1. Jarvis CI, Cabrera A, Charron D. Alogliptin: a new dipeptidyl peptidase-4 inhibitor for type 2 diabetes mellitus. Ann Pharmacother. 2013;47(11):1532-1539.

2. Schott G, Martinez YY, Ediriweera de Silva RE, et al. Effectiveness and safety of dipeptidyl peptidase 4 inhibitors in the management of type 2 diabetes in older adults: a systematic review and development of recommendations to reduce inappropriate prescribing. BMC Geriatr. 2017;17(suppl 1):226.

3. Dineen L, Law C, Scher R, Pyon E. Alogliptin (Nesina) for adults with type-2 diabetes. Pharm Ther. 2014;39(3):186-202.

4. Glassock RJ. Secondary minimal change disease. Nephrol Dial Transplant. 2003;18(suppl 6):vi52-vi58.

5. Joss N, Morris S, Young B, Geddes C. Granulomatous interstitial nephritis. Clin J Am Soc Nephrol. 2007;2(2):222-230.

6. Shah S, Carter-Monroe N, Atta MG. Granulomatous interstitial nephritis. Clin Kidney J. 2015;8(5):516-523.

7. Rajan TV. The Gell-Coombs classification of hypersensitivity reactions: a re-interpretation. Trends Immunol. 2003;24(7):376-379.

8. Shima H, Tashiro M, Yamada S, et al. Cilostazol-induced acute tubulointerstitial nephritis accompanied by IgA nephropathy: a case report. BMC Nephrol. 2018;19(1):52.

9. Perazella MA, Markowitz GS. Drug-induced acute interstitial nephritis. Nat Rev Nephrol. 2010;6(8):461-470.

10. Baker RJ, Pusey CD. The changing profile of acute tubulointerstitial nephritis. Nephrol Dial Transplant. 2004;19(1):8-11.

11. Graham F, Lord M, Froment D, Cardinal H, Bollee G. The use of gallium-67 scintigraphy in the diagnosis of acute interstitial nephritis. Clin Kidney J. 2016;9(1):76-81.

12. Spagnolo P, Luppi F, Roversi P, Cerri S, Fabbri LM, Richeldi L. Sarcoidosis: challenging diagnostic aspects of an old disease. Am J Med. 2012;125(2):118-125.

13. Iannuzzi MC, Rybicki BA, Teirstein AS, Teirstein, Sarcoidosis. N Engl J Med. 2007;357(21):2153-2165.

14. Shah KK, Pritt BS, Alexander MP. Histopathologic review of granulomatous inflammation. J Clin Tuberc Other Mycobact Dis. 2017;7:1-12.

15. Korbet SM, Schwartz MM. Multiple myeloma. J Am Soc Nephrol. 2006;17(9):2533-2545.

16. Gioffredi A, Maritati F, Oliva E, et al. Eosinophilic granulomatosis with polyangiitis: an overview. Front Immunol. 2014;5:549.

17. Naniwa T, Maeda T, Mizoshiha T, et al. Alendronate-induced esophagitis: possible pathogenic role of hypersensitivity to alendronate. Intern Med. 2008;47(23):2083-2085.

18. Takikawa H, Sakisaka S, Aiso M, et al. Recent status of drug-induced liver injury: an analysis of 366 cases between 2002 and 2006. Kanzo. 2007;48:517-521.

19. Gallagher RM, Kirkham JJ, Mason JR, et al. Development and inter-rater reliability of the Liverpool adverse drug reaction causality assessment tool. PLos One. 2011;6(12):e28096.

20. Esaki H, Tachi T, Goto C, et al. Renoprotective effect of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes mellitus. Front Pharmacol. 2017;8:835.