Shimane J. Med. Sci., Vol. 16 pp. 33 - 35, 1998

MINIMAL CHANGE NEPHROTIC SYNDROME POSSIBLY INDUCED BY TROGLITAZONE ADMINISTRATION IN A CASE OF NON-INSULIN DEPENDENT DIABETES MELLITUS

Tadashi SHIMIZU, Masateru NISHIKI, Soichi KURIOKA, Hiroyuki YAMAMOTO and Yuzuru KATO

First Division, Department of Medicine, Shimane Medical University, Izumo 693-8501, Japan

(Accepted September 9, 1998)

We describe a case of minimal nephrotic syndrome (MCNS) which was possibly induced by troglitazone administration in non-insulin dependent diabetes mellitus (NIDDM). A 68-year-old female patient with NIDDM had been poorly treated with gliclazide (40mg/day) for last four years when HbA1c levels were ranged from 7.0 to 8.2%, whereas such complications as diabetic retinopathy and overt nephropathy were not associated and serum CPR levels were preserved. In order to reduce insulin resistance, troglitazone, a new hypoglycemic agent, was started in a dose of 200mg b.i.d. However, she noticed edematous swelling in her lower extremities after two weeks and severe albuminuria (6.2g/day) developed after one month, which was persisted for the following 6 weeks although she had no previous history of proteinuria or hematuria. She was then admitted to our hospital and diagnosed by renal biopsy as MCNS associated with early-stage diabetic nephropathy. She was treated with prednisolone in combination with intensive insulin therapy. Her nephrotic state was rapidly improved. Recurrence of albuminuria was not recognized after taping off of prednisolone. These findings suggest that MCNS might be induced by troglitazone in a patient with NIDDM under the longer-term treatment with gliclazide.

Key words: nephrotic syndrome / NIDDM / troglitazone / gliclazide

It has been reported that immune complex glomerulonephritis may be superimposed with diabetic nephropathy (1,2). However, minimal change nephrotic syndrome (MCNS) is rarely associated in a diabetic patient with early-stage diabetic nephropathy (3). It is also known that some therapeutic agents may induce nephrotic syndrome in which MCNS is occasionally found by histological examination. Troglitazone, newly developed as an insulin action enhancer, is a useful hypoglycemic agent in the treatment of NIDDM who are not well controlled by sulphonylureas (4). In this report, we describe the first case of NCNS which was associated with non-insulin dependent diabetes mellitus (NIDDM) shortly after the start of troglitazone treatment in combination with gliclazide, a hypoglycemic agent of sulphonylurea.

CASE REPORT

A 68-year-old woman was admitted to our hospital for severe albuminuria. She was diagnosed as NIDDM at the age of 57 years and had been treated with gliclazide (40mg/day) for the last 4 years. However, plasma glucose levels were not well controlled and HbA1c levels were ranged from 7 to 8%. Two months before the admission, her treatment was modified to add troglitazone, a new hypoglycemic agent, to reduce insulin resistance for one month (4). However, she noticed edematous swelling in her lower extremities after two weeks and sever albuminuria (6.2g/day) developed after one month, which was persisted for the following 6 weeks, although she had no previous history of proteinuria or hematuria.

Physical examination revealed that her body temperature was 36.0℃ and heart rate was 88/min, regular. Blood pressure was slightly increased as 142/88 mmHg. There was no rash or eruption at all. There was pitting edema in lower extremities, but pleural effusion or ascites was not found. Funduscopic examination revealed no diabetic change in the retina.

Laboratory findings were characterized by severe albuminuria (6.8g/day), hypoalbuminemia (1.9g/dl) and hypercholesteremia (328mg/dl). Blood urea nitrogen and serum creatinine levels remained within the normal range (15mg/dl and 0.7mg/dl, respectively). CBC, liver functions and serum electrolytes were normal. There was no serological abnormality and lymphocyte stimulating test was negative for either troglitazone or gliclazide.

Transcutaneous renal biopsy was performed three months after the onset of nephrotic syndrome. Light microscopic studies demonstrated that all of 31 glomeruli obtained had minor abnormalities with slightly increased mesangial matrix and that there was focal lymphoid infiltration in the interstitium (Fig. 1). Immunofluorescence studies did not detect any glomerular deposition of IgG, IgA, IgM, C3, C4, C1q and fibrinogen. Electromicroscopic studies demonstrated marked foot process effacement with villous proliferation (Fig. 2). There was no electron-dense deposit in any location. These histological findings were summarized as MCNS complicated with early-stage diabetic nephropathy.

As shown in Fig. 3, oral administration of prednisolone was started in an initial dose of 60mg/day and then the severe albuminuria was favorably decreased. Plasma glucose levels were strictly controlled by intensive insulin therapy during the prednisolone therapy. The patient was discharged after tapering off of prednisolone. Recurrence of severe proteinuria was not recognized thereafter.

Correspondence: Masateru Nishiki, M.D., First Division, Department of Medicine, Shimane Medical University, Izumo 693-8501 Japan. Phone: 0853-20-2183 Fax: 0853-23-8650

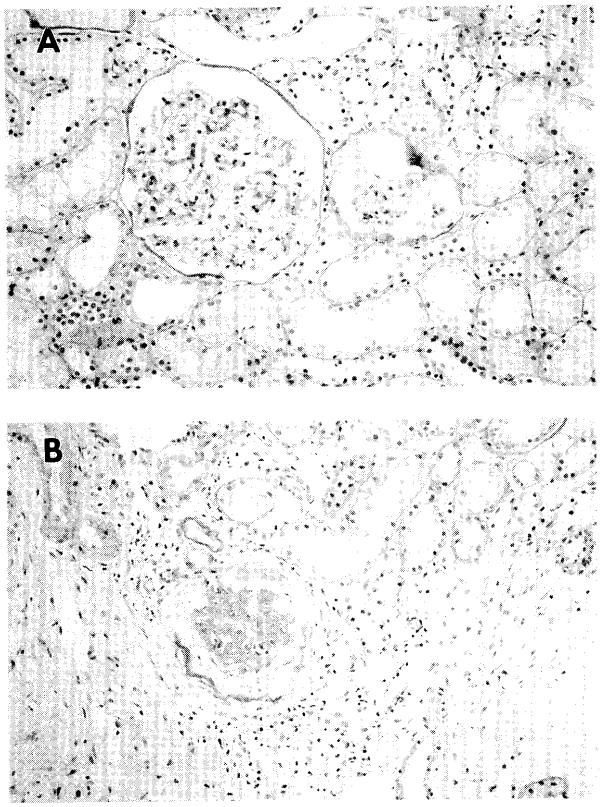

Fig. 1. Histopathological findings of the renal specimen biopsied (× 200).
A: There are no remarkable changes in the glomerulus at the light microscopic level.
B: Edema and cellular infiltration are detected at the renal interstitial region.

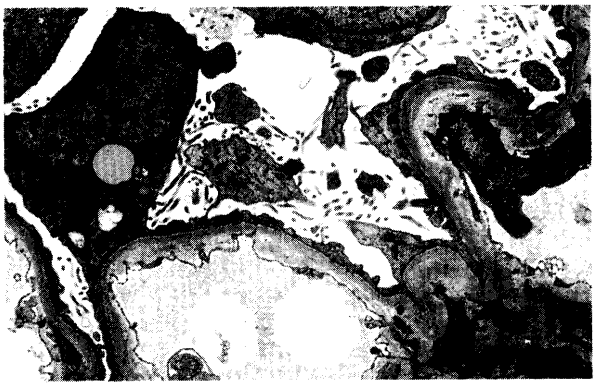

Fig. 2. Electron microscopic findings of a part of glomerulus (× 2000). There are marked foot process effacement with villous proliferation. There are no electron dense deposit in any location.

DISCUSSION

The present case was characterized by nephrotic syndrome appeared shortly after the start of troglitazone administration in order to obtain better control of plasma glucose which had not been well maintained by the treatment with gliclazide. Troglitazone is a newly established hypoglycemic agent to enhance insulin sensitivity acting through peroxisome proliferative-activated receptor gamma (PPARgamma) (5) and was recently documented to cause idiosyncratic hepatocellular injury in some diabetic patients (6). However, it has not been

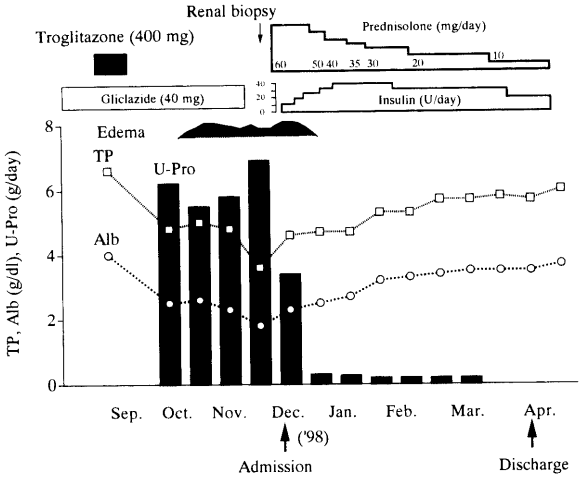

Fig. 3. Summary of the clinical course in a patient with NIDDM. Severe proteinuria occurred one month after the administration of troglitazone and was improved by prednisolone therapy in combination with insulin. Hypoalbuminemia associated with edema remained corrected even after the interruption of prednisolone. Minimal change nephrotic syndrome was revealed by renal biopsy which was performed immediately before prednisolone administration.

ever reported that nephrotic syndrome was induced by the drug. Allergic reactions were not demonstrated in the present case.

There has been only one report in which MCNS was associated with diabetic patients without diabetic glomeruloscrelosis (3). In that case, nephrotic syndrome abruptly appeared within one month after the administration of acarbose, another hypoglycemic agent to inhibit alpha-glucosidase. Although the authors suspected that MCNS was induced by acarbose, there was no clearly established cause-and-effect relationship between acarbose and nephrotic syndrome. In the present case, histological studies of the renal tissue revealed MCNS associated with early-stage diabetic nephropathy. Allergic reactions were not demonstrated in the present case. If we could speculate similarly in the present case, it is possible that troglitazone administration in combination with gliclazide may be close related to the acute onset of MCNS although the mechanisms for the episode remain to be further elucidated. Matsuda M *et al.* (3) reported that MCNSt was treated with cyclosporin A in their patient because of high potential side effects of steroids. Our patient was favourably improved by steroid without any serious side effect.

Some agents have been reported to cause MCNS (7,8). Lithium-induced MCNS was presumably unrelated to immune complex formation, indicating that lithium therapy might have interfered with the filtration barrier by altering the normal fixed anionic changes of the glomerular capillary wall (8). It was also reported that acarbose treatment prevented from a reduction in the number of anionic sites in glomerular basement membrane (GMB) in streptozotocin-induced diabetic rats, which might ameliorate an increased permeability of GMB leading to albuminuria (9). However, the effect of troglitazone on the glomerular capillay wall was not well elucidated. Recent animal study demonstrated that troglitazone treatment rather decreased the diabetes-associated albuminuria in Streptozotocin-induced diabetic rats for 12 weeks (10). Authors

speculated that an inhibitory action of troglitazone on protein kinase C (PKC) may be responsible for the prevention of the increase in urinary albumin excretion. In our patient, it was unclear whether the enhanced activation of PKC was present or not. Troglitazone was shown to negligibly affect endothelial cell proliferation *in vitro* although it inhibits cytokine-induced endothelial cell mitogenesis (11). We therefore propose that renal condition should be carefully monitored in a diabetic patient treated with troglitazone, and that renal biopsy should be performed in the case in which renal lesion was presumed to be drug-associated.

In summary, we describe the first case of MCNS which was revealed after troglitazone treatment in combination with gliclazide in NIDDM, which was also associated with early diabetic nephropathy. Since gliclazide had been used without any considerable side effect for four years before the start of troglitazone therapy, it is likely that MCNS was possibly induced by troglitazone in the present case.

ACKNOWLEDGMENTS

This work was supported in part by grants from the Ministry of Education and Culture, Japan, the Ministry of Health and Welfare, Japan, and the Foundation of Renal Disorders. We also thank Ms. A. Kanayama for her technical assistance and Ms. A. Kawakami for her secretarial help.

REFERENCES

1) Yum M, Maxwell DR, Hamburger R and Kleit SA (1984) Primary glomerulonephritis complicating diabetic nephropathy. *Hum Pathol* 15: 921-927.
2) Waldherr R, Ilkenhans C and Ritz E (1992) How frequent is glomerulonephritis in diabetes mellitus type II ? *Clin Nephrol* 37: 271-273.
3) Matsuda M, Hayashi Y, Shikata K, Makino H, Shikata Y, Sugimoto H, Akiyama K, Kushiro M and Ota Z (1997) A case of early-stage diabetic nephropathy complicated by minimal change nephrotic syndrome treated with cyclosporin A. *Nephron* 75: 490-491.
4) Iwamoto Y, Kosaka K, Kuzuya T, Akanuma Y, Shigeta Y and Kaneko T (1996) Effect of combination therapy of troglitazone and sulphonylureas in patients with Type 2 diabetes who were poorly controlled by sulphonylurea therapy alone. *Diabet Med* 13: 365-370.
5) Iijima K, Yoshizumi M, Ako J, Eto M, Kim S, Hashimoto M, Sugimoto N, Liang YQ, Sudoh N, Toba K and Ouchi Y (1998) Expression of peroxisome proliferator-activated receptor gamma (PPARgamma) in rat aortic smooth muscle cells. *Biochem Biophys Res Commun* 247: 353-356.
6) Sparano N and Seaton TL (1998) Troglitazone in type II diabetes mellitus. *Pharmacotherapy* 18: 539-548.
7) Brezin JH, Katz SM, Schwartz AB and Chinitz JL (1979) Reversible renal failure and nephrotic syndrome associated with non-steroidal anti-inflamma tory drugs. *N Engl J Med* 301: 1271-1273.
8) Richman AV, Maseo HL, Rifkin SI and Acharya MK (1980) Minimal change disease and the nephrotic syndrome associated with lithium therapy. *Ann Inter Med* 92: 70-71.
9) Sato H and Shiina N (1997) Effect of an alpha-glucosidase inhibitor on glomerular basement membrane anionic sites in streptozotocin induced mildly diabetic rats. *Diabet Res Clin Pract* 37: 91-99.
10) Fujii M, Takemura R, Yamaguchi M, Hasegawa G, Shigeta H, Nakano K and Kondo M (1997) Troglitazone (CS-045) ameliorates albuminuria in streptozotocin-induced diabetic rats. *Metabolism* 46: 981-983.
11) Gralinski MR, Rowse PE and Breider MA(1998) Effects of troglitazone and pioglitazone on cytokine-mediated endothelial cell proliferation *in vitro*. *J Cardiovasc Pharmacol* 31: 909-913.