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MEMBRANOUS NEPHROPATHY ASSOCIATED WITH DIABETES MELLITUS: REPORT OF FOUR CASES AND REVIEW OF LITERATURE

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Abstract: Case reports of 4 patients with membranous nephropathy (MN) associated with diabetes mellitus are presented. The clinical characteristics of each of the patients differed. We determined the incidence of MN in a total of 292 patients with diabetes mellitus who underwent renal biopsy between 1982 and 1995: it was 1.4 % for the group of all patients, and 4.8 % for patients with overt proteinuria. Clinicopathologic features of MN observed in diabetic patients are discussed in the context of a review of the literature.

Index Terms

diabetes mellitus, membranous nephropathy

INTRODUCTION

Diabetic patients may be thought to have another primary glomerular disease if they have heavy proteinuria despite diabetes of only short duration. It has been reported that several types of glomerulonephritis are superimposed on diabetic nephropathy[1-8]. In particular, the association of membranous nephropathy (MN) with diabetes has been mentioned in some case reports[9-18], but detailed profiles were not given. We review the clinicopathologic features of MN observed in diabetic patients in our series, and discuss them with respect to the literature.

CASE REPORTS

Case 1

A 63-year-old woman suffering from massive proteinuria and edema was admitted to our hospital in November 1985. She was well until 7 years earlier, when glucosuria was first detected by her home doctor. Her diabetes was controlled with dietary therapy, but massive proteinuria and high blood pressure were discovered during the preceding ten months. There was no history of numbness or visual disturbance. On physical examination, blood pressure was 160/74 mmHg, and the pulse rate 72/min and regular. The head, neck, chest and abdomen were normal. There was pitting edema over both lower extremities. Neurologic examination was normal. Funduscopic examination disclosed no evidence of hypertensive change or diabetic retinopathy. Urinary protein excretion was 1.7 g/day and creatinine clearance was 88 ml/min. Total protein concentration was 6.4 g/dl with an albumin fraction of 3.2 g/dl. HbA_1 was 8.1 %. Tests of antinuclear antibody (ANA), hepatitis B surface antigen (HBs-Ag), and treponema pallidum hemagglutination assay (TPHA) were negative. Carcinoembryonic antigen (CEA) was normal (Table 1, 2). Light microscopy of a renal biopsy specimen revealed MN. Immunofluorescent examination revealed strong granular staining on glomerular capillary

walls for IgG and C3.

Case 2

A 40-year old man complaining of precordial pain was admitted to the coronary care unit of our hospital in September 1992. A diagnosis of acute myocardial infarction was made, and coronary angiography revealed a 100 % stenosis of the anterior discending coronary artery. Diabetes mellitus was first detected as an abnormal 75 g-OGTT during hospitalization. Blood pressure was 106/70 mmHg with a pulse rate of 90/min. No peripheral edema was evident. Neurologic examination was normal. The ocular fundi displayed no microaneurysm or exudate. Findings of urinalysis were as follows: protein 2+ ; glucose 2+ ; occult blood 2+ ; and hyaline casts in the sediment. Laboratory investigation revealed a urinary protein of 2.1 g/day, creatinine clearance 117 ml/min, total protein 6.4 g/dl, serum albumin 4.1 g/dl, and HbAlc 8.3 %. Serological test were negative (Table 1, 2). Light microscopy of a renal biopsy specimen revealed MN. Immunofluorescent examination revealed granular staining on glomerular capillary walls for IgG and C 3.

Case 3

A 73-year-old man was admitted to our hospital in June 1995 for massive proteinuria. Three years before admission, he was found to have high blood pressure, glucosuria and proteinuria at an annual medical check up. Hypertension was managed with Enalapril maleate and Nicardipine hydrochloride. Massive proteinuria continued throughout the above period. On admission, blood pressure was 152/88 mmHg with a pulse rate of 72 per min. Physical examination demonstrated no abnormalities in the neck, chest or abdomen. No evidence of peripheral edema was detected. Neurologic examination was normal. Funduscopic examination revealed simple diabetic retinopathy (grade A 2). Urinalysis disclosed the following: protein 2+ ; glucose(−) ; occult blood (−) ; and hyaline casts in the sediment. Laboratory investigation showed a urinary protein of 1.2 g/day, creatinine clearance 56 ml/min, total protein 6.8 g/dl, serum albumin 4.1 g/dl, and HbA_1c 4.7 %. Serological tests were negative (Table 1, 2). Light microscopy of a renal biopsy specimen revealed MN. Immunofluorescent examination revealed strong granular staining of glomerular capillary wall for IgG and C3.

Table 1. Summary of present four cases

Items	Case			
	1	2	3	4
Age(yo)	63	40	73	62
Gender	F	M	M	M
Duration of diabetes(yr)	7	unknown	3	10
Hypertension	(+)	(−)	(+)	(+)
Retinopathy	0	0	A2	A2
Treatment	Diet	Diet	Diet	OHA

OHA : oral hypoglycemic agent

Table 2. Laboratory findings for present four cases

Items	Case			
	1	2	3	4
UP(g/day)	1.8	2.1	1.2	3.4
Hematuria	(−)	(+)	(−)	(−)
Ccr(ml/min)	88	117	56	89
HbA_1c(%)	8.1	8.3	4.7	5.9
TPHA	(−)	(−)	(−)	(−)
HBs-Ag	(−)	(−)	(−)	(−)
HCV-Ab	ND	(−)	(−)	(−)
CEA(ng/ml)	1.5	ND	ND	2.9

ND : not determined

Case 4

A 62-year old man with a 10-year history of diabetes was admitted to our hospital in July 1994. At age 52, he was admitted to an another hospital for retinal detachment, at which time glucosuria was first detected. At that time, arthralgia developed in the shoulder and elbow with increasing deformities of the hands. A diagnosis of rheumatoid arthritis was made, but no anti-rheumatic drug was prescribed. In February 1993, he was found to have hypertension and 1+ proteinuria. Since December 1993, he had been receiving 180 mg daily of Loxoprofen sodium and 300 mg daily of Bucillamine for treatment of rheumatoid arthritis. The degree of proteinuria had increased to 3+ by June 1994. On physical examination, the blood pressure was 170/94 mmHg, and the pulse rate 72/min and regular. The head, neck, chest and abdomen were normal. There was pitting edema over both lower extremities. Deep tendon reflexes were decreased. Funduscopic examination revealed simple diabetic retinopathy (grade A 2). Laboratory investigation showed a urinary protein of 3.4 g/day, creatinine clearance 89 ml/min, total protein 6.1 g/dl, serum albumin 3.2 g/dl, and HbA_1c 5.9 %. Serological testing for rheumatoid factor revealed high titer (Table 1, 2). Light microscopy of a renal biopsy specimen revealed MN superimposed on advanced diabetic nephropathy (Fig. 1). Immunofluorescent examination revealed granular staining on glomerular capillary walls for IgG.

Clinical data and the incidence of membranous nephropathy associated with diabetes mellitus

The clinical and laboratory characteristics for these 4 patients are summarized in Tables 1 and 2. There were 3 males and one female, aged 40 to 73 (mean, 59) years. Three of the

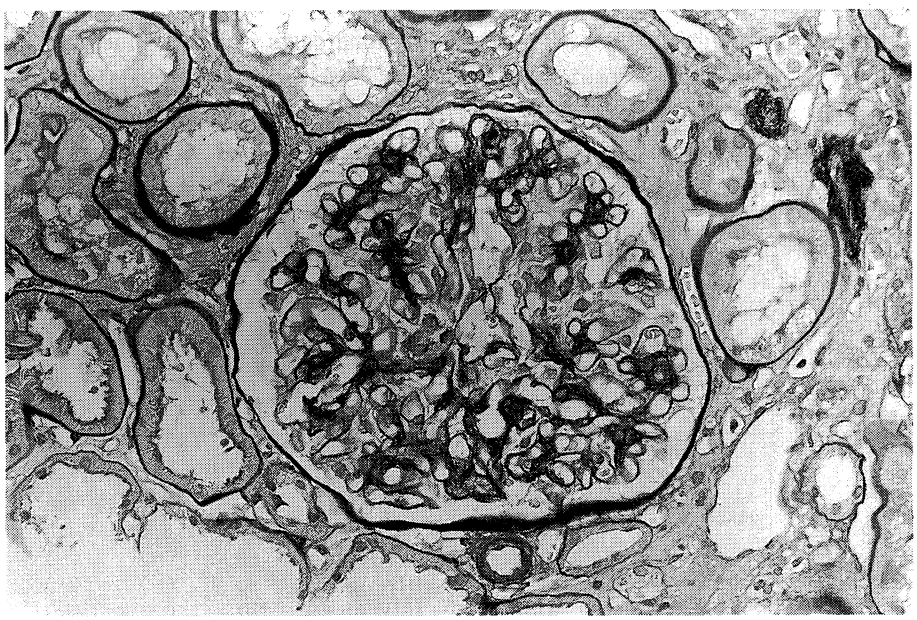

Fig. 1. Light microscopic findings of a renal biopsy specimen in the case 4 (PAS stain, ×200).

patients had hypertension, one had hematuria. None of them received insulin therapy. Mean creatitine clearance was 87 ml/min, and mean protein excretion was 2.1 g/day. The mean duration of diabetes was 6.6 years.

We attempted to determine the incidence of MN associated with diabetes mellitus in a total of 292 consecutive diabetic patients who had undergone renal biopsy in the First Department of Internal Medicine of Nara Medical University between 1982 and 1995 (Fig. 2). We found 30 patients with non-diabetic renal disease (10.3 %) and 4 with MN (1.4 %) in this entire group

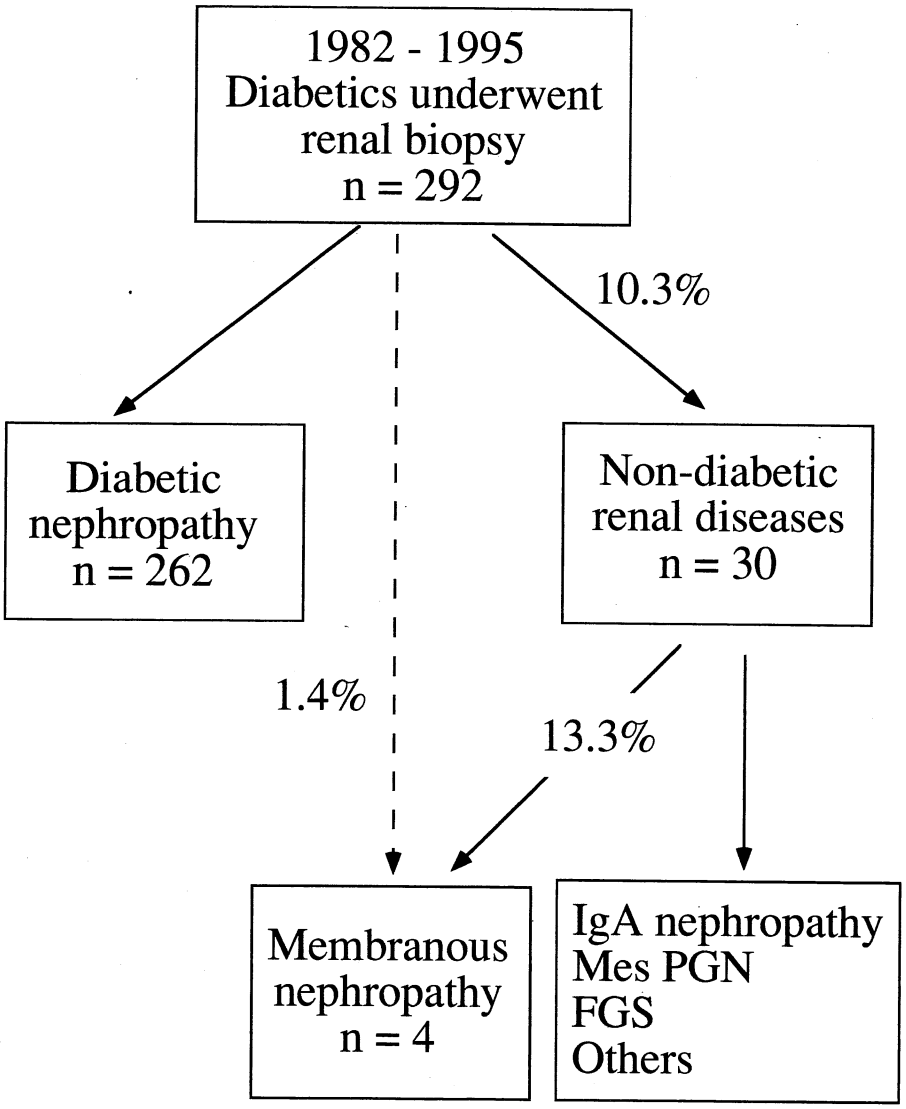

Fig. 2. Incidences of non-diabetic renal diseases and membranous nephropathy in diabetics in our series.
Mes PGN : mesangial proliferative glomerulonephritis
FGS : focal glomerulosclerosis

of patients. When subjects were classified into subgroups with and without overt proteinuria, the incidence of MN in the overt proteinuric group was 4.8 %.

DISCUSSION

The first case report of MN occurring with diabetes mellitus was published by Warms et al[9]. Since then, a few reports of MN associated with diabetes mellitus have been published[10-18], but details concerning clinical characteristics and the renal histopathology of MN are limited. In a review of the literature, we found reports of 36 other diabetic patients with MN (Table 3). We analyzed the 36 previously reported cases and the 4 present ones. Seventeen out of 36 cases (47.2 %) had a short duration of diabetes of less than 10 years, and 12 of 34 cases (35.3 %) received insulin therapy. Twenty-three of 38 cases (60.5 %) had hypertension, 13 of 23 (56.5 %) had hematuria, and 32 of 40 (80.0 %) had proteinuria in the nephrotic range. Mean urinary protein excretion was 9.1 g/day, and mean serum creatinine was 1.35 mg/dl. These findings differ markedly from those of typical diabetic nephropathy. In diabetic patients, the incidence of proteinuria exhibits a good correlation with the duration of diabetes mellitus. Proteinuria becomes apparent much later, on average 17 years after diagnosis of diabetes[19]. High levels of serum creatinine or decrease in Ccr are usually associated with nephrotic syndrome of diabetic nephropathy. Diabetic retinopathy was present in only 9 of 33 cases (27.3 %) for which ophthalmoscopic findings were described. It is commonly believed that retinal microangiopathy is a reflection of the same pathological process that occurs in the kidney. Therefore, renal biopsy should be considered in diabetic patients with overt proteinuria who do not have diabetic retinopathy.

The cause of MN in diabetic patients remains unclear. The possibility exists that immunoglobulin demonstrated in the patient's glomeruli might represent insulin-anti-insulin complexes, as has been previously suggested. Furuta et al.[16] reported that granular deposits of insulin were detected along the glomerular capillary wall with an immuno-peroxidase technique using anti-porcine insulin antibody in 3 out of 7 diabetic patients with MN. Since porcine insulin is a heterologous peptide for humans, immune complex deposition may cause MN in some diabetic patients. However, 22 of 34 (64.7 %) patients had not received insulin (Table 3). Several underlying diseases and environmental agents can produce secondary membranous nephropathy. We cannot exclude the possibility that in some patients MN was caused by systemic diseases, since sufficient clinical information was not available in some previously reported cases. However, the most common secondary causes of MN, including syphilis, hepatitis B, hepatitis C and carcinoma of the colon, were discussed in our series. Therefore, it seems reasonable to conclude that most of the cases of MN reported in patients with diabetes mellitus should be considered idiopathic MN. On the other hand, bucillamine administration is frequently associated with the development of proteinuria, usually due to MN[20]. Notably, the 4 th of our patients had received bucillamine for RA. Massive proteinuria developed after treatment with this agent, and resolved when it was withdrawn. It appears likely that MN developed due to bucillamine treatment in this unusual case.

The true prevalence of glomerular disease superimposed on diabetes mellitus is difficult to estimate. Kasinath et al.[1] performed renal biopsy in 122 diabetic patients who presented with proteinuria, and found 10 (8.2 %) with non-diabetic glomerular disease. However, there was

only one case of MN in Kasinath's study. Yum et al.[2] found 8 patients (44.4 %) with primary glomerulonephritis and one (5.6 %) with MN among 18 diabetic patients. However, this series may not represent the true incidence of glomerulonephritis as a complication of diabetes. Chihara et al.[3] reported 36 (21.9 %) of 164 diabetic patients with various types of glomerulonephritis as complications, and 8 (4.9 %) of them were diagnosed as having MN. Walderr et al.[7] examined 210 consecutive diabetic patients who came to autopsy during 3 years, and reported that IgA nephropathy was present in only one case and MN was not found. The presence of MN has been mentioned in the large studies of diabetic patients noted above, with

Table 3. Case reports of membranous nephropathy occuring with diabetes

Author	Age /Sex	Duration of diabetes (yr)	Insulin therapy	Hyper-tension	Hemat-uria	UP (g/day)	Scr (mg/dl)	Retino-pathy
Warms, et al. (1973)	56 F	20	(+)	(−)	(+)	11.3	1.2	(−)
Wass, et al. (1978)	35M	14	(+)	ND	ND	17.2	ND	(+)
Kato (1978) & Kobayashi (1981)	67M	8	(−)	(−)	ND	10.0	1.5	(−)
	56 F	9	(−)	(+)	ND	7.1	0.6	(−)
	42M	5	(−)	(−)	ND	5.8	0.7	(−)
Rao, et al. (1980)	66 F	20	(−)	(+)	(+)	8.0	0.7	(−)
	42M	14	(+)	(+)	(−)	9.0	1.2	(+)
	32M	15	(+)	(+)	(+)	35.0	4.9	(+)
Kasinath, et al. (1983)	75 F	20	ND	(+)	(−)	3.2	0.8	(−)
Yum, et al. (1984)	64M	8	ND	(+)	(+)	8.0	1.5	(−)
Zhu, et al. (1989)	52 F	4	(−)	(+)	(+)	6.4	0.9	(−)
Yoshikawa, et al. (1990)	27M	12	(+)	(+)	(+)	9.7	4.1	(+)
	50 F	20	(+)	(+)	ND	2.5	ND	(+)
	64M	10	(−)	(+)	ND	4.0	2.0	(−)
	60 F	unknown	ND	(−)	(−)	15.0	1.5	(−)
	67M	11	ND	(−)	ND	4.5	ND	(−)
	76M	15	(−)	(−)	(−)	11.0	0.9	(−)
	67M	5	(−)	(−)	(+)	2.1	ND	(−)
	45M	17	(+)	(+)	ND	2.0	1.5	(−)
	72 F	13	(−)	(+)	(−)	11.0	2.0	(−)
	56 F	6	(−)	(+)	(+)	3.8	1.0	(−)
	12 F	10	(+)	(−)	(+)	5.0	1.0	(−)
	69 F	16	(−)	(+)	(+)	4.3	1.0	(−)
	63M	1	(−)	(−)	(−)	5.1	1.4	(−)
	58M	4	(−)	(+)	(−)	8.0	1.8	(+)
	50M	2	(−)	(−)	(+)	5.0	1.7	(−)
Furuta, et al. (1992)	51M	2	(+)	(−)	ND	33.0	0.8	ND
	65M	15	(+)	(+)	ND	20.0	1.5	ND
	34M	5	(+)	(+)	ND	43.0	0.9	ND
	40M	unknown	(−)	(+)	ND	5.0	0.9	ND
	41 F	2	(−)	(−)	ND	4.0	0.7	ND
	59M	unknown	(−)	(+)	ND	5.0	0.9	ND
	71 F	2	(−)	(+)	ND	9.0	1.5	ND
Uchida, et al. (1994)	71 F	10	(+)	ND	(+)	8.4	2.1	(+)
Nitta, et al. (1996)	30M	4	ND	(−)	ND	6.7	0.8	(−)
	68 F	12	ND	(−)	ND	3.9	0.9	(−)
Present cases	63 F	7	(−)	(+)	(−)	1.8	1.1	(−)
	40M	unknown	(−)	(−)	(+)	2.1	0.7	(−)
	73M	3	(−)	(+)	(−)	1.2	0.9	(+)
	62M	10	(−)	(+)	(−)	3.4	0.8	(+)

ND : not determined

Table 4. Incidence of membranous nephropathy in diabetics

Author	Duration of the study (yr)	Diabetic subjects	Non-diabetic renal disease	Membranous nephropathy
Kasinath, et al. (1983)	23	122	10 (8%)	1 (0.8%)
Yum, et al. (1984)	9	18	8 (44)	1 (5.6)
Chihara, et al. (1986)	16	164	36 (22)	8 (5.0)
Amoah, et al. (1988)	11	109	23 (21)	5 (4.6)
Lynn, et al. (1988)	10	53	12 (23)	2 (3.8)
Nakamoto, et al. (1990)	10	133	16 (12)	8 (3.0)
Waldherr, et al. (1992)	3	210	1 (0.5)	0 (0)
Richards, et al. (1992)	10	68	25 (37)	3 (4.4)
Our series	14	292	30 (10)	4 (1.4)

an incidence ranging from 0.8 to 5.4 % (Table 4). In a review of the renal biopsy material from 292 diabetic patients at our clinic during the past 14 years, we encountered 30 cases of non -diabetic renal disease (10.3 %) and 4 of MN (1.4 %). In our series of diabetic patients, subjects were not selected based on the presence of proteinuria. This may account for the low incidence of primary glomerulonephritis.

In conclusion, MN in diabetic patients is reported to occur infrequently. However, renal biopsy shound be considered whenever clinical findings do not fit the natural course of diabetic nephropathy.

REFERENCES

1) **Kasinath, B. S., Mujais, S., Spargo, B.** and **Katz, A. I.**: Non-diabetic renal disease in patients with diabetes mellitus. Am. J. Med. **75**: 613-617, 1983.

2) **Yum, M., Maxwell, D. R., Hamburger, R.** and **Kleit, S. A.**: Primary glomerulonephritis complicating diabetic nephropathy. Hum. Pathol. **15**: 921-927, 1984.

3) **Chihara, J., Takebayashi, S., Taguchi, T., Yokoyama, K., Harada, T.** and **Naito, S.**: Glomerulonephritis in diabetic patients and its effect on the prognosis. Nephron **43**: 45-49, 1986.

4) **Amoah, E., Glickman, J. L., Malchoff, C. D., Sturgall, B. C., Kaiser, D. L.** and **Bolton, W. K.**: Clinical identification of nondiabetic renal disease in diabetic patients with type I and type II disease presenting with renal dysfunction. Am. J. Nephrol. **8**: 204-211, 1988.

5) **Lynn, K. L., Bailey, R. R., Frendin, T. J., Swainson, C. P.** and **Walker, R. J.**: Renal disease in diabetics. Aust. NZ. J. Med. **18**: 764-767, 1988.

6) **Nakamoto, Y.** and **Wakui, H.**: Policy and practice of treatment of diabetic patients complicated by primary glomerular diseases. Kidney and dialysis **29**: 587-590, 1990. (*in Japanese*)

7) **Waldherr, R., Ilkenhans, C.** and **Ritz, E.**: How frequent is glomerulonephritis in diabetes mellitus type II? Clin. Nephrol. **37**: 271-273, 1992.

8) **Richards, N. T., Greaves, I., Lee, S. J., Howie, A. J., Adu, D.** and **Michael, J.**: Increased prevalence of renal biopsy findings other than diabetic glomerulopathy in type II diabetes mellitus. Nephrol. Dial. Transplant. **7**: 394-399, 1992.

9) **Warms, P. C., Rosenbaum, B. J., Michelis, M. F.** and **Haas, J. E.**: Idiopathic membranous glomerulonephritis occuring with diabetes mellitus. Arch. Intern. Med. **132**: 735-738, 1973.

10) **Wass, J. A., Watkins, P. J., Dische, F. E.** and **Parsons, V.**: Renal failure, glomerular disease and diabetes mellitus. Nephron **21**: 289-296, 1978.

11) **Kato, N., Harada, A., Iida, H., Onoyama, K., Fujimi, A., Uzawa, H.** and **Omae, T.**: Studies on three cases

of idiopathic membranous glomerulonephropathy associated with diabetes mellitus. Kumamoto Med. J. **31**: 110-119, 1978.

12) **Rao, K. V.** and **Crosson, J. T.**: Idiopathic membranous glomerulonephritis in diabetic patients. Arch. Intern. Med. **140**: 624-627, 1980.

13) **Kobayarhi, K., Harada, A., Onoyama, K., Shimamatsu, K., Maeda, T., Fujimi, S.** and **Omae, T.**: Idiopathic membranous glomerulonephritis associated with diabetes mellitus. Nephron **28**: 163-168, 1981.

14) **Zhu, L. Z., Makino, H., Tanoguchi, S., Kumagaya, I., Shikata, K., Takaoka, M., Ota, Z.** and **Yoshino, S.**: Diabetic nephropathy associated with membranous nephropathy. Kidney and dialysis **27**: 1113-1117, 1989. (*in Japanese*)

15) **Yoshikawa, Y., Truong, L. D., Mattioli, C. A., Ordonez, N. G.** and **Balsaver, A. M.**: Membranous glomerulonephritis in diabetic patients; a study of 15 cases and review of the literature. Modern Pathol. **3**: 36-42, 1990.

16) **Furuta, T., Seino, J., Saito, T., Sato, H., Agatsuma, J., Ootaka, T., Satoh, T.** and **Yoshinaga, K.**: Insulin deposits in membranous nephropathy associated with diabetes mellitus. Clin. Nephrol. **37**: 65-69, 1992.

17) **Uchida, K., Shindo, T., Kondo, T., Yuasa, S.** and **Matzuo, H.**: A case of membranous nephropathy in the elderly accompanied with diabetic retinopathy and nephropathy. Kidney and dialysis **37**: 1207-1210, 1994. (*in Japanese*)

18) **Nitta, K., Yumura, W., Hara, Y., Honda, K., Kubota, K., Ozu, H., Naito, T., Sanaka, T.** and **Nihei, H.**: Two cases of prednisolone-responsive nephrotic syndrome associated with diabetes mellitus and idiopathic membranous nephropathy. J. Tokyo Wom. Med. Coll. **66**: 55-61, 1996.

19) **McCrary, R. F., Pitts, T. O.** and **Puschett, J. B.**: Diabetic nephropathy: natural course, survivorship and therapy. Am. J. Nephrol. **1**: 206-218, 1981.

20) **Baba, N., Nomura, T., Sakemi, T., Uchida, M.** and **Watanabe, T.**: Membranous glomerulonephritis probably related to bucillamine therapy in two patients with rheumatoid arthritis. Jpn. J. Nephrol. **33**: 629-634, 1991.