Diabetes Mellitus with Membranous Nephropathy and H.pylori Infection: A Case Report

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Abstract. Early membranous nephropathy with diabetes mellitus is often easily misdiagnosed as diabetic nephropathy. Tacrolimus is a common drug for the treatment of membranous nephropathy, and *CYP3A5* gene plays an important role in its metabolism. The decreased expression activity of *CYP3A5* gene leads to the increased blood concentration of tacrolimus and adverse reactions. We report the case of diabetes mellitus with early membranous nephropathy and H.pylori infection in a 55-year-old female. Our patient was diagnosed with membranous nephropathy by renal puncture. Due to the slow metabolism of *CYP3A5*, tacrolimus was reduced to avoid side effects. After eradication of H.pylori, the patient's urine protein decreased and the prognosis of membranous nephropathy was good. There was no discomfort during the follow-up period after the patient was discharged.

Keywords: Diabetes Mellitus; CYP3A5 Gene; Tacrolimus; Membranous Nephropathy.

1. Introduction

Renal damages brought by diabetes mellitus can be divided as diabetic nephropathy and non-diabetic nephropathy, whose differential diagnosis can be realized by Renal biopsy pathology, diabetic retinopathy, microalbuminuria, and hematuria during the course of diabetes, etc. Membranous nephropathy (MN) is one of the most common types of nephrotic syndrome. About 75% of MN is of undetermined cause, known as idiopathic membranous nephropathy (IMN), and there is more than 20% of secondary membranous nephropathy (SMN). Anti-phospholipase A2 receptor (PLA2R) was positive in 70% of IMN patients. [1, 2] PLA2R antibodies (PLA2R-AB) are associated with disease activity and can be used as biomarkers for monitoring and predicting outcomes in MN patients. [3]

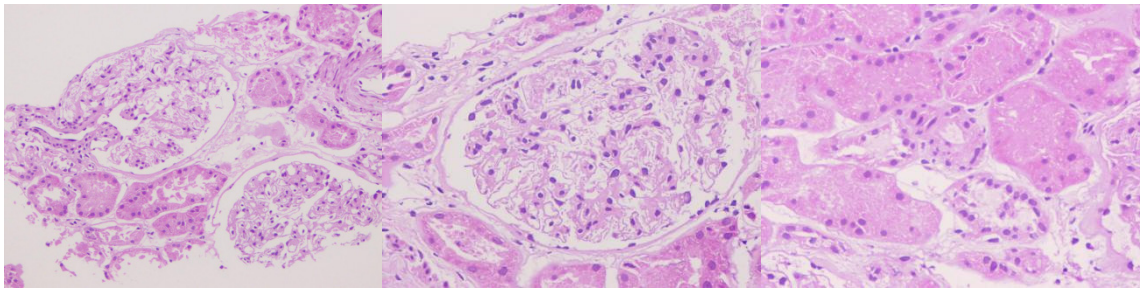
Tacrolimus (macrolide immunosuppressive agent) is currently a commonly used immunosuppressive agent clinically used for the treatment of MN. However, due to the narrow therapeutic window and large individual difference under the effective dose, different blood concentrations will appear when the same dose of tacrolimus is given, resulting in liver and kidney function impairment, nausea, vomiting, hyperglycemia and other adverse reactions. H.pylori (HP) infection is the main cause of peptic ulcer and can also lead to chronic active gastritis. Eradication of HP can significantly improve gastric mucosal inflammation, delay or prevent gastric mucosal atrophy and the existence and development of intestinal metaplasia. For some patients, the atrophy can be reversed, or even intestinal metaplasia can be reversed, to reduce the risk of gastric cancer. We report a case of diabetes mellitus with *CYP3A5* slow metabolism idiopathic membranous nephropathy and HP infection.

2. Case Description

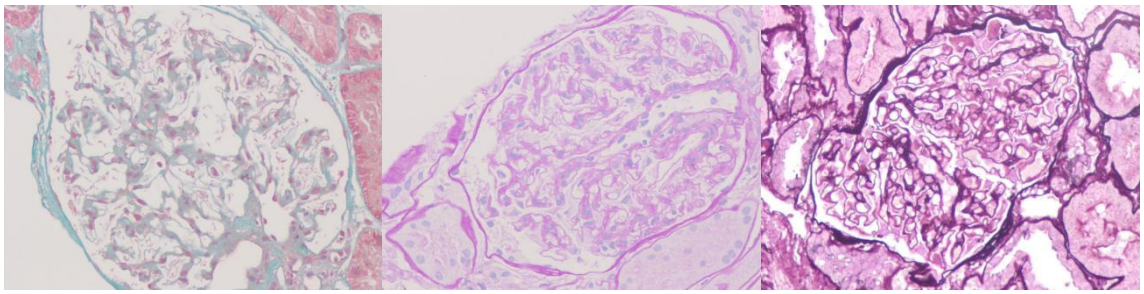
Female, 55 years old, with a 3-year history of diabetes mellitus. The patient was presented to our hospital for the first time on 1 March 2022 with "lower extremity edema", measured by albumin at 30.6 g/l, creatinine at 39 umol/l, blood glucose at 7.68 mmol/l and glycated hemoglobin at 6.2%. Urine routine: urine protein 2+, urine glucose-,urine ketone body-. Ophthalmic examination: The blood vessels ran normally, and there were no microangiomas and a small amount of hard infiltration in the fundus retina. Anti-PLA2R antibody test was negative, and 24hr urine protein quantification

was 2047.58mg/day. Taken the patient's history of type 2 diabetes mellitus into consideration, a preliminary diagnosis of type 2 diabetic nephropathy was made. Two days after symptomatic treatment, the condition did not improve and the edema of the lower limbs did not improve. Considering that the history of type 2 diabetes is short, there was no significant lesion in fundus retina, and hypoproteinemia and hyperlipidemia exist, the possibility of diabetes mellitus combined with other nephropathy exists (or not excluded). Immunofluorescence examination of the renal biopsy revealed a total of 6 glomeruli with a granular distribution along the capillary wall: IgG+++, IgA-, C3-F-, IgM-, C1Q-, Kappa++ and Lambda+++. HE and special staining (Fig.1): a total of 13 glomeruli were found, showing complete fibrosis in 3 glomeruli, mild diffuse thickening of the glomerular capillary wall and swelling of podocytes. There was no proliferation in the glomerular mesangial area, 1 – 3 mesangial cells/mesangial area, no expansion of the mesangial matrix, and no proliferation of endothelial cells. Masson staining showed scattered deposits of eosinophilic protein. Renal tubular small focal atrophy, renal tubular epithelial cell swelling, vacuolation degeneration, a small amount of protein cast visible, renal interstitial small focal fibrosis, a small amount of lymphocytes, mononuclear cell infiltration, interstitial small vessel wall mild segmental thickening. Electron microscopic results of renal biopsy (Fig.2): There was no proliferation and expansion of glomerular mesangial cells and mesangial matrix, and the basement membrane of the capillary wall was slightly thickened. More electron density deposits and segmental nailing were observed under the epidermis. Diffuse podoid fusion of podoid cells can be seen. The renal tubular epithelial cells were swollen, and the organelles were swollen. There was no obvious thickening of the basement membrane or focal interstitial edema.

Diagnosis confirmed by comprehensive renal biopsy results: Early membranous nephropathy, IMN.



a. Renal tissue HE b. Glomerular HE c. Renal interstitial arteriole HE



d. Masson e. PAS f. Hexamine silver

a. renal tissue HE, 200X; b. glomerular HE, 400X; c. renal interstitial arteriole HE; d. Masson,400X; e.PAS,400X; F. hexamine silver, 400X.

Fig 1. Renal biopsy pathology

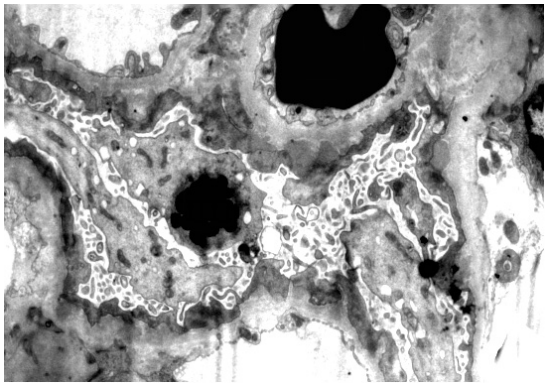


Fig 2. Renal biopsy electron microscope 800X

According to the KDIGO 2020 guideline, the patient was still in a low-risk phase and self-healing was possible in early membranous nephropathy. Therefore, the patient went through regular re-examination every month to observe changes in the course of the disease. Her condition was stable on re-examination in the first month with albumin at 31.4g/l, creatinine at 50 umol/l, and 24h urine protein quantification of 2637.51mg/day. Follow-up in the second month: albumin at 27.9g/l, creatinine at 54 umol/l, 24 urine protein quantitation of 5416.32mg/day, and the elevated urine protein reached medium risk. Re-examination in the third month: albumin at 26.2g/l, creatinine at 50 umol/l, urine protein quantification of 5989.8mg/day. Due to persistently elevated proteinuria, 24mg methylprednisolone/day (24mg qd) with 1.5mg tacrolimus every 12 hours (1.5mg q12h) was administered orally.

In the re-examination of the fourth month, the patient's edema was gradually resolved, but the patient felt that she had poor appetite with fatigue, intermittent upper abdominal pain, no vomiting and no fever since she had taken tacrolimus for one month. Re-examination results showed that albumin was at 35.1g/l, creatinine at 58.7umol/l, 24h urine protein quantification at 1909.12mg/day, and blood concentration of tacrolimus at 20.21ng/ml, which was higher than normal level. It was suspected that the disease was due to side effects of tacrolimus. The patient was therefore given a reduced dose of tacrolimus to 1.0mg in the morning and 0.5mg in the evening. Two weeks after medication, the gastrointestinal symptoms of the patient did not improve, and she felt nausea and fatigue worsened. Taking the gastrointestinal lesions into account, a gastroscopic pathological examination was performed. The results revealed: chronic atrophic gastritis (C-1), multiple superficial ulcers were found in the gastric angle and antrum, and a positive C14 expiratory test. Pathological results of gastric antrum: moderate chronic active inflammation of superficial mucosa, small amount of inflammatory exudation visible, and special staining showed negative HP. Meanwhile, results of re-examination of blood concentration of tacrolimus showed that the concentration was 14.5ng/ml. Hormone and tacrolimus decrease (methylprednisolone 16mgqd, tacrolimus 0.5mg q12h) were given, together with eradication of HP treatment and acid suppression. Symptomatic treatments such as glucose-reducing, renal protection, hormone continuation and immunosuppressive agents were given at the same time. Re-examination after one month of treatment revealed an albumin measurement of 35.3g/l, creatinine measurement of 52umol/l, and 24h urine protein quantification of 1948.29mg/day. Urine protein did not increase, indicating that the condition was under control and MN was in a stable phase. The patient was asked to continue her re-examination once a month.

3. Discussion

For diabetic patients, the differentiation between diabetic nephropathy and MN is of great clinical significance, especially for IMN and diabetic nephropathy with proteinuria as the main manifestation. For the identification between diabetic nephropathy and IMN, if a patient with type 2 diabetes

presents with the following conditions, including: a) active urinary sediment abnormalities (hematuria, proteinuria with hematuria, cylindruria); b) rapid decrease in glomerular filtration rate (eGFR) within a short period of time; c) without diabetic retinopathy; d) when there is rapid increase in urinary albumin creatinine ratio (UACR) within a short period of time or the development of nephrotic syndrome, the combination of diabetes mellitus with other chronic kidney disease should be considered. Pathologic diagnosis is the golden standard for diabetic nephropathy, but renal puncture pathology examination is an invasive examination, and has limitations, contraindications and risks of potential complications such as bleeding and infection [4], so routine renal puncture biopsy is generally not performed in diabetic patients. Renal puncture pathology is feasible when the etiology is difficult to identify. In recent years, the detection of PLA2R-AB has played an important role in the diagnosis of IMN. The latest 2021 KDIGO guidelines recommend the use of PLA2R-AB as a biological indicator for the diagnosis of MN. PLA2R-AB is elevated before the production of proteinuria and decreases before its resolution, and correlates with disease activity. Therefore, PLA2R-AB can also be used as a biomarker for monitoring and predicting regression in patients with MN [3].

The clinical criteria for the diagnosis of IMN are, a) massive proteinuria (urine protein greater than or equal to 3.5g/24h) b) hypoproteinemia (blood albumin less than 30g/l) c) edema and d) hyperlipidemia; among which the first two are necessary for the diagnosis. However, the patient was initially diagnosed with diabetic nephropathy at the time of first examination because she did not meet the criteria for massive proteinuria and hypoproteinemia, and had a negative PLAR-AB, combined with a history of diabetes. However, after symptomatic treatment for diabetic nephropathy failed, the possible presence of diabetes combined with other nephropathies was considered, and a renal puncture pathology was quickly performed to confirm the diagnosis of MN. The negative PLA2R-AB test in this patient's serum may be related to the binding of the antibody to the antigen in the kidney with high affinity. This is because antibodies can be detected only when the binding site is saturated and then the antibody enters the circulation [5]. Therefore, this may be the cause of PLA2R-AB (-) in this patient.

According to the phenotypes of *CYP3A5* *3 in the CPIC guidelines, the population can be divided into tacrolimus fast metabolism type (*1/*1), medium metabolism type (*1/*3) and slow metabolism type (*3/*3). Decreased *CYP3A5* gene activity may result in increased blood concentration of tacrolimus and increased adverse reactions. During tacrolimus treatment, the patient's blood concentration was abnormally increased, and it was possible that this patient was of the tacrolimus slow metabolism type. However, due to the fact that *CYP3A5* gene detection is not routine in the current clinical application of tacrolimus, the drug amount can only be reduced tentatively based on monitoring the blood concentration of tacrolimus in patients. In our opinion, it is necessary to detect the *CYP3A5* gene during the clinical treatment of IMN, which is instructive for adjusting tacrolimus administration and precise treatment.

24h proteinuria in patients with MN was associated with HP infection to a certain extent, and eradication of HP was significant for reducing proteinuria in patients with MN. [6, 7] HP eradication therapy can help to reduce proteinuria and improve the prognosis of MN. In the selection of treatment regimen, since the patient suffered from diabetes, membranous nephropathy and HP infection at the same time, and needed to take multiple drugs, personalized medication was conducted in consideration of possible renal burden on the patient. The two-way therapy, namely, acid inhibitor PPI+ high-dose amoxicillin was selected for the treatment of HP infection, and the condition was well controlled.

In summary, in the differential diagnosis of diabetic nephropathy and membranous nephropathy, renal biopsy should be performed in time for the condition that the etiology is difficult to determine, so as to avoid delaying the optimal treatment timing. When tacrolimus is applied, it is necessary to monitor the blood concentration and adjust the dosage in time. When patients suffering from multiple chronic diseases at the same time need combined medication, the joint use of drugs to enhance the therapeutic effect or reduce the toxic and side effects should be applied.

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