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Case Report

Idiopathic Nodular Glomerulosclerosis: Case studies

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ABSTRACT

An Idiopathic Nodular Glomerulosclerosis (ING) patient was admitted to our hospital. In order to further understand ING and its treatment options, we have performed a detailed global screening and analysis of all published ING case reports. Amongst the cases, 55.56% (n=90) of the patients suffered from severe renal impairment, with an average eGFR (epidermal growth factor receptor) of 33.51mL/min/1.73m2 (n=90) and an average creatinine level of 3.22 mg/dL (n=89). Apart from the aforementioned indicators of ING, we have also found that 76.63% (n=107) of the patients were smokers, 93.63% (n=110) were diagnosed with hypertension, 57.52% (n=113) were obese and 45.13% (n=113) of them had dyslipidaemia. We have further identified that within 5 years of hypertension diagnosis, 58% (n=27) of the patients were also diagnosed with ING. Furthermore, 56.75% (n=50) were also found to have extra renal vascular disease. Most importantly, we found that glucocorticoid or immunosuppressant treatments was not effective, or even possibly deteriorate kidney impairment; and a poor control of blood pressure was detrimental to kidneys. Such findings could shed light on the early detection and the development of effective ING treatment.

Keywords: Idiopathic nodular glomerulosclerosis; Hypertension; Smoking; Hypertensive nephropathy; Diabetic nephropathy

INTRODUCTION

Nodular glomerulosclerosis was first described in 1936 as a hallmark change of diabetic nephropathy [1]. It is worth-noting that not all the patients with nodular glomerulosclerosis had diabetes. Until 1999 some experts proposed that cases of nodular glomerulosclerosis without diabetes or IGT (impaired glucose tolerance) should be separated from nodular glomerulosclerosis. These cases are then termed as ING [2]. Therefore, apart from excluding diabetes or IGT, the diagnostic criteria of ING also include that the nodular glomerulosclerosis is not due to any other types of diseases, in particular immune-related ones.

Under light microscopy, nodular mesangial sclerosis with a lobular pattern, increased mesangial matrix, ischemic damage, endothelial hyperplasia, tubular atrophy accompanied with interstitial fibrosis can be observed. Furthermore, renal arteriolar wall thickening and hyalinization can also be seen. These features are also shared by nodular diabetic glomerulosclerosis. However, what separates ING from nodular diabetic glomerulosclerosis or other immune-related diseases are as follows: Firstly, in ING, the immunopathological staining is non-specific. Secondly, in serology tests, the kappa/lambda ratio, C3 and C4 complements are normal; while anti-nuclear antibody, ribonucleoprotein antibody (RNP), Smith antibody (anti-Smith), double-stranded DNA antibody (anti-dsDNA), anti-nuclear cytoplasmic antibodies (ANCAs), antiglomerular basement membrane antibodies (anti-GBM), direct Coombs and indirect Coombs antibodies are in general negative. Thirdly, immunostaining of renal biopsy samples, in particular, Immunoglobulin M, Immunoglobulin A, Complement factor C3, Complement factor C1q, Fibrinogen/fibrin related antigens, albumin, κ-, λ-Congo red staining are all negative. Last but not least, by electron microscopy, features including ischemic shrinkage of the glomerular basement membrane, proliferation of mesangial cells can be observed with no electron dense deposits or structural abnormalities.

CASE REPORT

A 69-male with was admitted to our hospital with macroalbuminuria, hypoalbuminemia, edema and elevated serum creatinine (SCr) level. He has already been smoking for at least 20 years, and had a background of hyperuricemia (1 year) and had undergone cholecystectomy. 3 years ago, he was diagnosed with hypertension (blood pressure 150/80 mmHg), elevated SCr level (110 μmol/L) and the urine protein test was positive. Subsequently he was treated with valsartan/hydrochlorothiazide 80/12.5 mg q.d as well as Corbrin capsule 2g t.i.d. During the following year,

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blood pressure and SCr levels were well controlled, but urine protein level fluctuated between 2+ and 3+. Concurrently, a drop in hemoglobin level was occasionally observed. Hence, the patient was treated with polysaccharide iron complex and erythropoietin. 2 years ago, intermittent pitting edema could be observed at both lower extremities of the patient. Furosemide was then prescribed to reduce edema. Despite the fact that the furosemide treatment was effective, at the same time the SCr level of the patient gradually increased to 180 μmol/L. 2 months ago, his edema worsened and his blood pressure was beyond control, with a sharp rose in SCr (200 μmol/L) and urine protein (6+) levels. Therefore, his treatment was adjusted as follows: Adalat 30 mg q.d or Zanidip 10 mg q.d, Almarl 10 mg b.i.d. At the same time, due to heavy proteinuria, he was diagnosed with chronic nephritis and was treated with prednisone 20mg q.d. However, the patient discontinued prednisone a month later because of fever, gum swelling and pain. Oral antibiotics were therefore prescribed and both gum swelling and pain was relieved in two to three weeks. However, his edema aggravated. Therefore, he came to our hospital for further treatment.

At the point when this patient was admitted into our hospital, his blood pressure was elevated (150/100 mmHg) and edema was observed in both of his lower extremities. His body mass index (BMI) was 24 kg/m2. Mild anemia (hemoglobin: 87g/L), hypoproteinemia (albumin: 22.8g/L), high proteinuria (6.45g/24h), hypercholesterolemia (cholesterol 7.96mmol/L), and impaired renal function (SCr: 237μmol/L) were also found. No abnormalities were found in serological tests. Negative results were also found against human immunodeficiency virus (HIV), hepatitis panel (Hepatitis A, B, and C), cryoglobulin level, and hepatitis C virus polymerase chain reaction (HCV PCR). Furthermore, glycated hemoglobin test and serum thyroid function were normal (5.1%). Pleural effusion (1.7cm) was seen under ultrasonography and the sizes of both kidneys were normal. The right kidney was 11.2cm×5.4cm and the left one was 10.4cm×5.6cm. There were no obvious abnormalities in electrocardiogram, Doppler ultrasonography scan and computed tomography scan.

According to the aforementioned results, the patient was diagnosed with chronic kidney disease, nephrotic syndrome, renal hypertension, and renal anaemia. However, the patient refused to undergo renal needle biopsy, and therefore the treatment was formulated according to experience: prednisone acetate 40mg q.d, calcium carbonate D3 1 tablet b.i.d, famotidine 20mg b.i.d., torasemil 20mg q.d, clopidogrel bisulphate 25mg b.i.d., recombinant human erythrophin injection 10000U q.w, folic acid 10mg t.i.d., polysaccharide iron complex capsule 0.15g q.d, alorolol hydrochloride 10mg b.i.d. and levamlodipine benzoylate tablet 2.5mg q.d After one week, the patient developed pulmonary bacterial infection, increased proteinuria (12.44g/24h), elevated serum creatinine (SCr: 252μmol/L), more severe hypoproteinemia (albumin: 24.6g/L), and increased random blood glucose. After anti-infective treatment, the patient agreed to further tests and renal biopsy.

Under light microscope, some of the glomeruli appeared enlarged, and with slightly cellular proliferation. Among those glomeruli, there was 1 that was globally sclerotic, 4 with discarded glomerulosclerosis, and 1 with amplified matrix synthesis by mesangial cells. Most of the glomerular mesangium was expanded, and a trend to nodularity was observed. Some of the mesangial segments were negative in periodic acid-Schiff (PAS) and periodic acid methenamine silver (PAM) staining's. The basement membrane was moderately thickened with a moderate capillary dilation or constriction. An accumulation of eosinophilic sediments could be seen in the endothelium and the mesangial segment. Vacuolar degeneration and granular degeneration were observed in renal tubular epithelial cells. In the renal tubules, multifocal tubular atrophy, interstitial fibrosis (about 35%), and mild tubular hypertrophy was observed. Focal renal tubular epithelial cells were flat with shorter cilia, while some of these cells were shredded. The tubule lumen was moderately dilated and the renal interstitium was moderately swollen. The walls of some arterioles were thickened (Figures 1A and 1B). Under electron microscope, a glomerulus with segmental sclerosis was observed with features like increased proliferation of mesangial cells, basement membrane shrinkage with mild thickening, and partial capillary occlusion at the matrix. Most of the epithelial cell foot processes were fused. No dense deposits or abnormal substructures were observed. Renal tubules atrophy and collagen fibres proliferation could be observed in the renal interstitium (Figure 1C). Immunostainings were performed on the renal biopsy samples. 6 glomeruli could be observed, in which 2 of them were globally sclerotic. The glomerular capillary wall and renal tubular basement membrane were both exclusively immunopositive against Immunoglobulin G (Figure 1D). Based on the above clinical examinations and pathological tests, nodular mesangial glomerulosclerosis was diagnosed.

Because there was no evidence of immune disorders, the amount of prednisone acetate prescribed was reduced. ARB/ACEI was not used due to high SCr level. levamlodipine benzenesylate 5mg b.i.d and bisoprolol fumarate 2.5mg q.d were administered to control blood pressure, and tolasemide was used to reduce edema. Smoking cessation, diet control and moderate exercise were also recommended. Prednisone was stopped half a month after discharge, and the postprandial blood glucose level returned to normal. 3 months later, there was still no edema after the discontinuation of diuretics. Serum albumin, uric acid and blood lipid levels returned to normal, whereas the SCr level did not increase significantly (216 μmol/L). The patient was followed up for one and a half to two years. During the period of time, no edema was observed, and his blood pressure and blood glucose were well controlled; whereas the urine protein level remained stable at 2+. However, the serum creatinine was gradually increased (SCr: 260 μmol/ L).

DISCUSSION

ING is a rare disease without clearly distinguishable clinical features. Therefore, it is often that when ING could be identified or diagnosed, the disease has already advanced to the stage where renal function was at least moderately reduced. Therefore, we believe that it is important to diagnose the disease as early as possible. In order to better understand ING, we have performed a global screening and analysis of ING case reports (from 1999, the year which ING was proposed, till now) with an aim to collect as many cases as possible. We have eventually compiled in total 38 ING case report articles and 113 existing ING cases via PubMed, Google scholar and CNKI (Table 1).

Serious renal damages can often be observed in ING patients, including the one mentioned in our case report. According to our data analysis, 55.56% (n=90) had severe renal impairment or the kidney was in the end stage, with an average eGFR of 33.51 mL/ min/ 1.73 m2 (n=90), and average SCr was 3.22 mg/dL (n=89). Therefore, ideally ING should be identified as soon as possible. Here, we have summarized a number of possible risk factors that may aid the diagnosis of ING. For example, hypertension (93.63%, n=110) and dyslipidemia (77.27%, n=66) were often found in ING

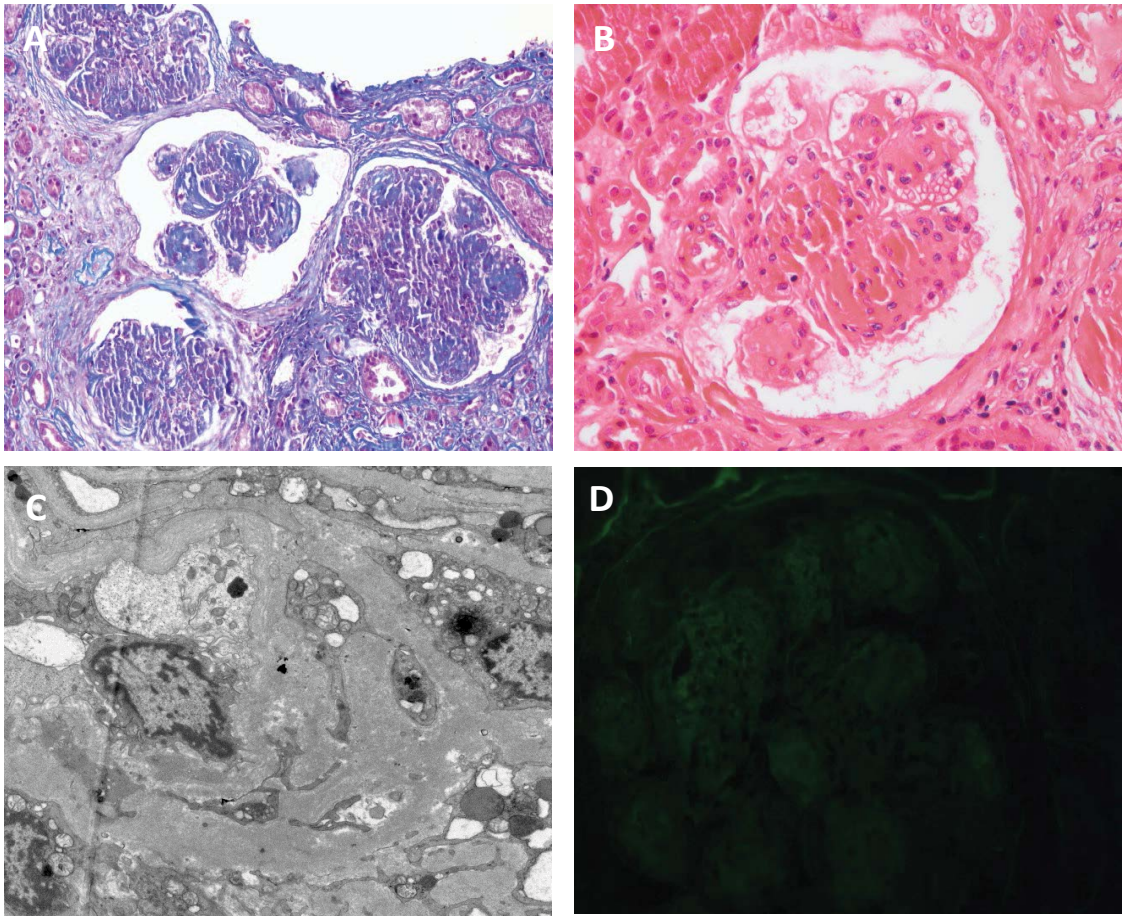

Figure 1: Renal biopsy：Light microscopy (A: ×200, Masson, B: ×400, HE): The mesangial area widened and showed nodular changes. Mild thickening of basement membrane with mild expansion or narrow of part of capillary lumen. Scanning electron microscopy (C: ×8000): basement membrane with mild thickening, epithelial cell foot processes were fused, partial capillary occlusion. Immunofluorescence (D: ×600): weak positive for anti-IgG.

Table 1: Global screening and analysis of ING case reports. [2,3,12–15,17,22–26,4,27–36,5,37–44,6–11].

	Cases	Smoke			Hypertension		Kidney Function		Obesity		Others	Treatment	Medication	
Reference	Age/Sex	Smoker	Pack-Year	Duration of smoking	Smoker/ Hypertension	Duration of Hypertension	eGFR/ ml/ min/1.73m2	S-Cre mg/dl	Obesity?	Dyslipidemia?	Other medical history	Anti-Hypertension	Immuno supression	Evaluation
Hanna et al.,in 2020 [25]	59F	N	N	N	N Y	U	10	4.4	U	U	vd1/isd1	Y	Y[1]	→
Solares et al., in 2020 [26]	44 F	Y	25	U	Y Y	2	13	4	N	Y	vd2	U	N[2]	U
Feng et al., in 2019 [28]	60 F	N	N	N	N Y	2	61	1	ov	Y	vd3\isd2	Y	Y[2]	↓
Gilberto and Lilian, in 2018	23 F	N	N	N	N N	N	38	U	U	N	U	ACEI\ARB	Y	→
Nakamura et al., in 2018 [29]	59 M	Y	40	40	Y Y	2	123	0.8	ov	Y	COPD	ACEI\ARB	N	U
Onteddu et al., in 2018 [11]	58 M	Y	U	U	Y Y	10	36	2.4	ov	U	HCV	Y\DIU	N	↑
Hamrahian et al., in 2018 [6]	54 M	Y	U	U	Y Y	U	35	2.5	ob	U	U	N	Y	U
	61 M	Y	U	U	Y Y	U	36	2	ov	U	U	U	U	U
	52 M	N	N	N	N Y	U	59	1.6	ob	U	U	U	U	U
	53 M	Y	U	U	Y Y	U	17	4	ov	U	U	U	U	U
	69 M	N	N	N	N Y	U	45	1.9	U	U	U	U	U	U
	76 F	N	N	N	N Y	U	38	1.7	N	U	U	U	U	U
	72 M	Y	U	U	Y Y	U	58	1.3	ov	U	U	U	Y	U
	73 M	Y	U	U	Y Y	U	31	2.2	ov	U	U	N	U	U
	27 F	N	N	N	N Y	U	154	0.6	ob	U	U	U	U	U
	81 M	Y	U	U	Y Y	U	26	2.5	ov	U	U	U	U	U
	57 M	Y	U	U	Y Y	U	18	4.4	ov	U	U	U	U	U
	73 F	Y	U	U	YY	U	35	1.8	U	U	U	U	U	U

	78 F	Y	U	U	YY	U	29	1.8	ob	U	U	U	U	U
	47 M	N	N	N	N Y	U	24	3	ob	U	U	U	U	U
	56 M	N	N	N	N Y	U	48	1.6	ob	U	U	U	U	U
	48 M	Y	U	U	Y Y	U	23	3.7	N	U	U	U	U	U
	47 M	Y	U	U	Y Y	U	21	3.4	N	U	U	U	U	U
Mollae e et al., in 2017 [9]	36 F	Y	3	11	Y Y	9	5	10.9	U	N	vd4	U	U	↓
Kuri et al., in 2016 [30]	34 F	N	N	N	N Y	0	4	12.1	ob	U	d	U	U	U
Balafa et al., in 2016 [12]	58 M	Y	70	U	Y Y	20	18	3.6	N	N	HCV	CCB	N	↑
A raujo et al., in 2016 [23]	64 M	Y	U	U	Y Y	5	34	2.1	ob	Y	e	DIU	Y	→
Lopez -Revuelta et al., in 2015 [5]	53 M	Y	40	13	Y N	N	42	1.6-1.8	N	Y	HIV	CCB\BB	N	U
	74 M	Y	U	U	Y Y	20	4	12	ob	Y	vd5	DIU	N[2]	U
Chandragiri et al., in 2016 [13]	46 M	N	N	N	N Y	1	63	13	ob	Y	g	ACEI\ARB	N	↑
	45 F	N	N	N	N N	N	5	8.9	N	U	U	N	N	U
Kikuta et al., in 2015 [31]	45 M	Y	22	U	Y Y	5	129	0.7	ov	Y	U	ACEI\ARB	Y	↑
Batal et al., in 2014 [24]	28 F	Y	14	8	Y Y	0.25	23	2.6	U	U	U	N	Y[3]	↑
	77 M	Y	59	U	Y Y	3	14	4.5	U	U	U	N	Y[3]	↓
	53 M	Y	53	U	Y Y	0.16	22	3.2	U	U	U	ACEI/ARB	Y	↑
Wu et al., in 2014 [4]	62 M	Y	35	U	Y Y	5	34	2.4	ov	Y	U	U	U	U
	65 M	Y	30	U	Y Y	15	9	8	ov	N	U	U	U	U
	32 M	Y	12	U	Y Y	0.5	38	1.4	ob	N	U	U	U	U
	68 M	Y	30	U	Y Y	7	30	1.7	ov	Y	U	U	U	U
	44 M	Y	15	U	Y Y	3	29	2.3	ob	N	U	U	U	U
	70 M	Y	40	U	Y Y	0.5	16	3.8	ov	N	U	U	U	U
	62 M	Y	15	U	Y Y	7	73	1.1	ob	Y	U	U	U	U
	55 F	Y	25	U	Y Y	0.5	14	4.6	ov	Y	U	U	U	U
	32 F	Y	10	U	Y Y	0.5	14	3.4	N	Y	U	U	U	U
	21 M	Y	5	U	Y Y	U	31	2.2	ob	N	U	U	U	U
	71 M	Y	30	U	y u	4	34	2	ob	Y	U	U	U	U
	21 M	Y	10	U	y y	0	18	3.5	ov	N	U	U	U	U
	16 M	N	N	N	N N	N	21	3.1	ov	N	U	U	U	U
	51 M	Y	15	U	Y Y	2	20	3.1	ov	Y	U	U	U	U
	43 M	Y	15	U	Y Y	0.5	9	7.8	ob	Y	U	U	U	U
	56 F	N	N	N	N Y	10	8	8	ob	N	U	U	U	U
	59 M	Y	20	U	Y Y	5	9	6.6	ob	Y	U	U	U	U
	55 M	Y	15	U	Y Y	5	8	6.9	ov	Y	U	U	U	U
	62 F	N	N	N	N Y	3	7	7	ov	N	U	U	U	U
	65 M	Y	15	U	Y Y	5	10	5.8	ov	N	U	U	U	U
Sumnu et al., in 2012 [33]	43 M	Y	18	U	Y Y	8	37	21	U	Y	HCV	Y	N	U
Baradhi et al., in 2012 [14]	58M	Y	20	20	Y Y	18	87	10	ob	Y	vd6	Y/BB/DIU	N[S]	↑
Uchida et al., in 2012 [34]	53 F	N	N	N	N N	N	24	23	N	Y	U	ACEI/ARB	N[S]	U
Predosa et al., in 2011	65 M	Y	40	U	Y Y	12	36	20	N	Y	U	U	U	U
Tomohiro et al., in 2010	27 M	Y	20	13	Y Y	2	64	12	ob	Y	U	Y/DIU	N	↑ ↓
Kasmani et al., in 2010	82 F	N	N	N	N Y	U	31	17	U	Y	h	U	U	U
Li and Verani , in 2008 [3]	57 M	Y	54.2[m]	U	Y Y	U	82	1	ob	Y	U	U	U	U
	67 F	Y	54.2[m]	U	Y Y	U	14	3.4	ob	U	U	U	U	U
	73 M	Y	54.2[m]	U	Y Y	U	18	3.5	ob	U	U	U	U	U
	48 F	N	N	N	N Y	U	7	6.8	N	U	U	U	U	U
	68 F	N	N	N	N Y	U	30	2.1	ob	U	U	U	U	U
	76 M	Y	54.2[m]	U	Y Y	U	16	4	ov	U	U	U	U	U

	50 F	Y	54.2[m]	U	Y Y	U	32	1.8	ob	U	U	U	U	U
	74 F	N	N	N	N Y	U	23	2.6	N	U	U	U	U	U
	52 M	Y	54.2[m]	U	Y N	N	29	2.5	ov	U	U	U	U	U
	70 F	Y	54.2[m]	U	Y Y	U	19	3.1	ob	U	U	U	U	U
	57 F	Y	54.2[m]	U	Y Y	U	24	2.2	ob	U	U	U	U	U
	76 F	N	N	N	N Y	U	26	2	ob	U	U	U	U	U
	57 F	Y	54.2[m]	U	Y Y	U	19	2.7	ov	U	U	U	U	U
	71 M	Y	54.2[m]	U	Y Y	U	40	1.8	ob	U	U	U	U	U
	67 F	N	N	N	N Y	U	21	2.4	ov	U	U	U	U	U
Sanai et al., in 2007 [37]	78 M	U	U	U	U Y	U	25	2.6	N	U	U	U	U	↓
Park et al., in 2007 [38]	39 M	Y	10	U	Y Y	10	28	2.7	U	Y	U	U	U	U
Liang et al., in 2007 [39]	66 F	Y	50	52	Y Y	1	31	1	N	Y	vd7	ACEI/ARB/ BB/DIU	Y	↑ ↓
Suneja et al., in 2007 [8]	48 F	Y	40	24	Y Y	20	17	3.1	N	Y	i	BB/DIU	Y[4]	U
Nasrand D Agati , in 2007 [7]	70 F	Y	60	20	Y Y	U	15	3.2	ob	U	vd8	BB/DIU	N	U
Sanchez J uan et al., in 2006 [17]	56 M	Y	U	U	Y N	N	126	0.7	ov	Y	U	ACEI/ARB	U	↑
	39 M	y	U	U	Y Y	U	79	1.1	U	Y	vd9	ACEI/ARB	N	Other
Kuppachi et al., in 2006 [40]	77 F	y	60	U	Y Y	25	39	1.4	U	Y	j	ACEI/ARB	N[S]	U
Chang et al., in 2004 [41]	50 M	y	5	U	Y Y	0.2	16	2.7	U	Y	U	U	U	U
Jo et al., in 2002 [42]	46 M	N	N	N	N Y	U	50	1.6	ov	Y	k	U	U	U
Markowitz et al., in 2002 [22]	U	Y (20)	52.9 ± 6.9	U	Y Y (20)		U	U				ACEI/ARB	N	U
	U	N	N	N	N Y	15.1±3.4	U	U	ob(3/23)	Y(18/20)U(3)	vd10(10/23)	U	U	U
	U	U	U	U	U		U	U				U	U	U
	U	U	U	U	U		U	U				U	U	U
Yeh et al., in 2001 [43]	72 F	N	N	N	N Y	8	31	1.7	U	U	I	U	U	U
Abdi et al., in 1999 [27]	56 M	U	U	U	U Y	23	12	5.2	N	U	HCV	N	Y[S]	↓
Herzenberg et al., in 1999 [2]	70 M	U	U	U	U Y	10	12	5	ob	U	vd11	CCB	N	U
	58 M	U	U	U	U Y	10	60	1.3	ob	Y	U	U	U	U

Note: Y: Yes, N: No, U: Unknown, M: Male, F: Female, COPD: Chronic Obstructive Pulmonary Disease, HCV: Hepatitis C, HIV: Human Immunodeficiency Virus, sus: soft vitiligo and blood vessel meandering, ob: obesity, ov: overweight, vd1-11: vascular disease, vd1: evidence of healing thrombotic microangiopathy, vd2:- peripheral arterial disease, vd3/isd2: sjogren's syndrome and immune thrombocytopenic purpura, vd4: pulmonary hypertension, vd5: nephroangiosclerosis, and super imposed cholesterol atheroembolism, vd6: myocardial infraction, vd7: extra renal vascular disease, vd8: bilateral severe peripheral artery disease with a chronic non healing right foot ulcer, vd9: prostatitis and varicose veins of the lower extremities, vd10: 10 patients with extra renal vascular disease, and 4 patients with gout, vd11: coronary artery disease, a: steroid induced diabetes mellitus, c: vitreous hemorrhages and cataracts in both eye, d: hypothyroidism, e: leukoderma and COPD, g: appendicectomy, h: permanent atrial fibrillation, and osteoarthritis, i: kidney transplant, j; pancreatic mass and hyperamylasemia, k: pediatric glomerulonephritis, i: diffuse type nesidioblastosis and suspicious rheumatoid arthritis, m: mean of pack year, ACE: Angiotensin converting enzyme inhibitors, ARB: Angiotensin II Receptor blockers, CCB: Calcium Channel Blockers, BB: Beta Blockers, Metoprolol, Atenolol, DIU: Furosemide, Hydrochlorothiazide, spironolactone, Y4: Eculizumab, Y2: Hydroxycholoroquine, Y3:- Cyclophosphamide, Y4: mycophenolate, CsA, and prednisone, Y5: Azathioprine, N1: Allopurino, Ns: stains, ↑: efficacy, →: inefficacy, ↓: harmful.

patients. Other risk factors include smoking (76.63%, n=107) and overweight (n=27) /obesity (n=35). These data are similar to the study by other researchers [3-6].

Based on our analysis, there are also a couple of interesting data that are related to the risk factors. For example, 58% (n=29) of the patients, including the one in our case report, were diagnosed with ING within 5 years (on average, 1.6 years, n=27) of their hypertension diagnosis. On the other hand, we could also possibly rely on the medical history of patients to aid the diagnosis of ING. For example, 56.75% of the ING patients have had a history of extrarenal vascular disease, whereas 4 of the cases were HCV antigen (HCVAg) positive, and 2 of the patients also got chronic obstructive pulmonary disease (COPD). Interestingly, 3 patients developed hypertension very rapidly after they have started smoking, and they were also diagnosed with ING within a very short period of time after the hypertension diagnosis. Coincidentally, these patients also suffered from extrarenal vascular disease [7-9]. Therefore, it is possible that these factor combined are the key to the development of ING, which could be similar mechanism.

The patient in our case report received ACEI/ARB treatment with the aim to control blood pressure and reduce hyperalbuminuria, and under such treatment renal damages were limited. Due to the elevated SCr level, we switched from ACEI/ARB to CCB during the treatment. Intriguingly, the severity of renal damages was restored to a steady level after the blood pressure was under control. According to our data, we have identified 12 cases that included anti-hypertensive medications in the treatment and they were all effective in controlling ING. [10,11]. For example, 23.5% of ING patients (n=17) did not receive ACEI treatment for blood pressure control, and in approximately one year these

patients developed end-stage kidney disease [12-19]. According to study by Markowitz et al, 53.8% of patients (n=13) received ACEI treatment and their ING conditions were remarkably stabilized [20]. Therefore, according to our case report as well as various literature, it is clear that the control of blood pressure is crucial and very likely beneficial in the treatment of ING [21, 22].

As mentioned in the case report, we administered glucocorticoid to minimize proteinuria, but unfortunately the patient developed several adverse symptoms afterwards. Therefore, we stopped the use of glucocorticoid as we suspected that the culprit of these undesirable effects was glucocorticoid. Surprisingly, after our data analysis, only 20.5% (n=39) of the case reports stated that glucocorticoid was included in the treatment of ING. There were 7 case reports that assessed the glucocorticoid treatment outcomes. In 3 of the cases the condition deteriorated after the treatment and in 1 case glucocorticoid was not effective. Indeed, there were also 3 cases that were seemingly effective, but in 2 out of the 3 effective cases the patients developed immune-related disease [23,24] . From these cases, we can clearly observe that glucocorticoid is not a conventional treatment option against ING, and the use of glucocorticoid might not be beneficial, or even potentially harmful, to ING patients. We have also identified 2 cases which the patients simultaneously suffered from ING and other immune diseases [25,26]. They were treated with other immunosuppressant's but the outcome was again not effective or even detrimental. There were also two interesting cases that the patients received kidney transplantation and then diagnosed with ING [27]. As organ transplant recipients have to take immunosuppressant's throughout a long period of time as to minimize the chance of transplant rejection [28], it would be worthwhile to further investigate into the relationship between ING and the usage of immunosuppressant's, especially if immunosuppressant's would increase the chance of ING development [32]. Therefore, based on the above observations and analysis, we would suggest that glucocorticoid or other immunosuppressant's should be avoided in ING treatments.

CONCLUSION

ING is a rare disease without distinctive clinical features, and it is very difficult to identify ING at an early stage. At the point when ING can be clearly diagnosed, it is often that the kidneys of the patients are already severely damaged. When kidney damage can be observed, physicians should not rule out the possibility of ING if patients have a background of smoking, hypertension (especially when the diagnosis is within 5 years), obesity, dyslipidemia, or extra renal vascular disease. In the aspect of ING treatment, we have found that the use of antihypertensive drugs and a good management of blood pressure are beneficial to ING patients. Contrastly, we do not suggest the use of glucocorticoids (possible immunosuppressant's) in ING treatment.

CONFLICT OF INTEREST

The authors have no relevant conflict of interest to disclose. Ethics approval and consent to participate the study was approved by the Ethics Committee of the Institute of Chengdu City No.1 People's Hospital, and all participants including patient written informed consent. The study was performed in accordance with approved national guidelines.

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