

Pregnancy-induced complications in IgA nephropathy

A case report

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Abstract

Rationale: IgA nephropathy is one of the most common causes of renal hypertension. The clinical management of IgA renal patients during pregnancy is challenging, as complex pathophysiological changes may occur that affect both the patient's prognosis and the outcome of the pregnancy.

Patient concerns: A 36-year-old woman with a family history of hypertension and at least one year of untreated mild high blood pressure was admitted to our hospital in the 28th week of pregnancy. She suffered from hypertensive disorder complicating pregnancy (HDCP) with renal insufficiency and stillbirth. Treatment with duplex antihypertensive drugs did not improve her blood pressure and she presented with abnormal renal function.

Diagnoses: A renal biopsy led to the diagnosis of a grade IV IgA nephropathy (Lee's grading system) with renal hypertension.

Interventions: The prescribed treatment regimen consisted of low dose cyclophosphamide 0.2 g per day for two days, followed by daily oral administration of 30 mg prednisone, 30 mg Nifedipine extended-release tablets and 80 mg Telmisartan to regulate the blood pressure.

Outcomes: The medication with a combination of antihypertensive and immunosuppressive drugs led to a clinical improvement with a nearly normal renal function and a stable blood pressure during the one-year follow-up.

Lessons: This case underlines that 1) the pregnancy outcomes of patients with IgA nephropathy are variable and depend on the renal function, blood pressure, status of urine proteins and the renal histological grade, and 2) especially female patients of childbearing age with hypertension need to be carefully examined to determine the cause of hypertension to avoid damage to target organs and complications during pregnancy.

Abbreviations: 24h-UPQ = 24 h urinary protein quantification, ABPM = ambulatory blood pressure monitoring, BUN = blood urea nitrogen, CKD = chronic kidney disease, CRE = creatinine, CT = computed tomography, EF = ejection fraction, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease, HDCP = hypertensive disorder complicating pregnancy, IVST = interventricular septum thickness, K⁺ = potassium ion, NR = normal range, NT-proBNP = N-terminal pro-B-type natriuretic peptide, PIH = pregnancy-induced hypertension, UCG = ultrasound echocardiography, UR = urine routine.

Keywords: hypertension, hypertensive disorder complicating pregnancy (HDCP), IgA, nephropathy, pregnancy complications, renal hypertension, stillbirth

1. Introduction

Hypertension is one of the leading causes of heart disease, stroke, kidney disease, and death worldwide. In contrast to essential

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Ethical statement: The Ethics Committee of the First Affiliated Hospital of Xi'an Jiao Tong University approved this study. Informed consent was obtained from the patient.

The authors have no conflicts of interest to disclose.

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hypertension with no identifiable cause, secondary hypertension is defined by the presence of an identifiable underlying primary cause, such as endocrine diseases, tumors, or kidney diseases. Renal hypertension is a form of secondary hypertension that is mainly caused by renal parenchymal lesions and renal artery disease. Nearly half of all cases with malignant hypertension with renal parenchymal disease are caused by IgA nephropathy. IgA nephropathy, also called Berger disease, is a term describing primary glomerulonephritis without systemic diseases. The disease is characterized by IgA depositions in the glomerular mesangial area and is associated with typical clinical symptoms like hematuria and proteinuria, and in a minority of patients also with hypertension. IgA nephropathy can occur at any age, but there is an increased susceptibility in men in their 2nd and 3rd decade. The global incidence rate of IgA nephropathy is 2.5 per 100,000 per year.^[1] IgA nephropathy is the most frequently diagnosed primary glomerular disease with approximately 30% and 40% of cases, and the leading primary glomerulopathy causing end-stage renal disease (ESRD). Notably, there are regional differences in the incidence and prevalence rates, with IgA glomerulonephritis being the most common cause of primary glomerular diseases in the Asia-Pacific region.^[2]

Pregnancy can induce complex pathological changes in IgA nephropathy patients; it can aggravate the deterioration of renal function and in consequence lead to increased blood pressure, forming a vicious cycle that affects ultimately the prognosis of the disease. To date, there are only few clinical reports of IgA nephropathy with pregnancy-induced complications. Diagnosis and treatment of these patients is challenging, which is why we report and analyze here one case with IgA nephropathy with pregnancy-induced complications. We hope that our case report will help to improve the clinical management of pregnant women with IgA nephropathy.

2. Case report

A 36-year-old woman diagnosed with hypertension was admitted to our hospital. At age 25, she had a successful pregnancy without complications. At first admission, the patient had complained about dizziness for two days and was diagnosed with high blood pressure (150/90 mm Hg, normal range [NR] < 140/90), but had no further complaints for 1 year. Due to a history of hypertension from the maternal side of her family, the complaints were not taken seriously by the patient, so that she refused any further diagnostic testing and did not take any medication. Three months later she became pregnant, but did not monitor her blood pressure regularly. At the 28th week of pregnancy, she suddenly felt a weakening of fetal movement and lower abdominal discomfort. Upon examination, her blood pressure was high (220/130 mm Hg, NR < 140/90). Laboratory tests revealed increased urinary protein levels (3⁺, NR 0), increased occult blood (3⁺, NR 0), high 24 hours urinary protein quantification (24h-UPQ) levels (2.266 g/24h, NR 0–0.15), increased blood urea nitrogen (BUN) (9.94 mmol/L, NR 2.8–7.2), elevated creatinine (CRE) levels (160.9 μmol/L, NR 35–71), and high blood potassium ion (K⁺) levels (6.61 mmol/L, NR 3.5–5.5). The estimated glomerular filtration rate (eGFR) was low (33.41 mL/min, NR > 90). The N-terminal pro-B-type natriuretic peptide (NT-proBNP) level was high (2073 pg/μL, NR 0–400). The result of echocardiography showed a left ventricular diastolic dysfunction with preserved ejection fraction (EF) (77%, NR > 50). Furthermore, an obstetric ultrasound determined the death of the fetus. Based on the test results the diagnosis was stillbirth, hypertensive disorder complicating pregnancy (HDCP) and severe chronic hypertension complicated with preeclampsia and renal insufficiency. After lowering the blood pressure, sedation, improvement of the renal function and correction of the electrolyte imbalance, labor was induced and a dead female baby was delivered. To reduce the blood pressure after discharge, Nifedipine extended-release tablets (30 mg/d) and Carvedilol (25 mg/d) were prescribed, but the patient did not monitor her blood pressure regularly as we had advised. Two months later, the patient complained again of dizziness with a high blood pressure (180/110 mm Hg, NR < 140/90), despite taking the prescribed medication. Due to the treatment resistance and the high blood pressure, further diagnostic workup was focused on target organs. The results revealed increased urinary protein levels (3⁺, NR 0), raised occult blood (3⁺, NR 0), high 24h-UPQ (2.395 g/24h, NR 0–0.15), high serum β₂-MG (2451.6 μg/L, NR < 2300), high urinary β₂-MG (568.3 μg/L, NR < 154), raised BUN (8.5 mmol/L, NR 2.8–7.2) and CRE (102.0 μmol/L, NR 35–71). The NT-proBNP level was slightly elevated (661.40 pg/μL, NR 0–400). The echocardiography showed a left ventricular diastolic dysfunction with normal EF (72%, NR > 50). The ambulatory blood pressure monitoring (ABPM) showed a

nondipper hypertension with the increased average blood pressure during the day (172/109 mm Hg, NR < 130/80), and both the systolic pressure load ratio as well as the diastolic pressure load ratio were high (100%, 98.3%, NR < 50). Results from the carotid artery ultrasonography showed a plaque formation in the right subclavian artery and the right vertebral artery diameter was thin. The renal ultrasound showed spots in the renal parenchyma of both kidneys and in the left kidney a renal cyst with calcification was found. Results of the computer tomography (CT) showed no apparent abnormality in the bilateral adrenal gland, all other routine examinations were normal.

Based on these results, we suspected that the patient suffered from renal hypertension, and did further nephro-dynamic imaging. The result suggested that she had stage 3 chronic kidney disease (CKD) with mildly impaired renal perfusion and parenchymal function (eGFR: 51.99 mL/min, L=22.25 mL/min; R=29.74 mL/min, NR > 90). Finally, a renal biopsy was taken. The result showed that 29 glomeruli were found in total in the renal biopsy section, of these 19 presented with glomerulosclerosis and one with a small fibrous crescent under the light microscope. Other glomeruli presented with a mild hyperplasia of mesangial cells and mesangial stroma, and moderate to severe focal segmental hyperplasia with eosinophil deposition was found in the mesangial area. Vacuoles and granular degeneration could be observed in the renal tubular epithelial cells and multifocal atrophy and visible protein of tubular type were present. The renal interstitium presented with multiple fibrosis with infiltrates of lymphocytes and monocytes. Arteries were small with thick walls and hyaline degeneration. The immunofluorescence staining revealed prominent IgA⁺⁺⁺ depositions in the mesangial area, and the clumps were furthermore negative for IgG, IgM, C1q, and FRA but positive for C3. A focal proliferative sclerosing IgA nephropathy (grade IV according to Lee's grading system, Fig. 1) could be identified. The final diagnosis was therefore a grade IV IgA nephropathy (Lee's grading system) with renal hypertension. The newly prescribed treatment regimen consisted of low dose cyclophosphamide 0.2 g per day for 2 days, followed by daily oral administration of 30 mg prednisone, 30 mg Nifedipine extended-release tablets and 80 mg Telmisartan to regulate the blood pressure after the biopsy.

At 1-year follow-up, we repeated the diagnostic workup of UR and 24h-UPQ and found a nearly normal renal function. Furthermore, there were no more complaints of dizziness and the blood pressure was stable at 140/90 mm Hg. Clinical details are shown in Table 1.

3. Discussion

The clinical management of IgA nephropathy with pregnancy-induced complications is challenging and only few reports have described this issue to date. Here we present a patient that was difficult to diagnose and treat. It took a lot of time and effort from the first symptoms of high blood pressure to reach the diagnosis of IgA nephropathy, which was further complicated by pregnancy. We observed that she had high blood pressure and reduplicated abnormal urinalysis, renal function and electrolyte levels during her second pregnancy, which could not be explained by simple pregnancy-induced hypertension (PIH). After the delivery, the abnormal urine parameters and a treatment resistant hypertension persisted. Therefore, we suspected an underlying primary disease, most likely a kidney disease, causing the high blood pressure. After further diagnostic workup and a renal

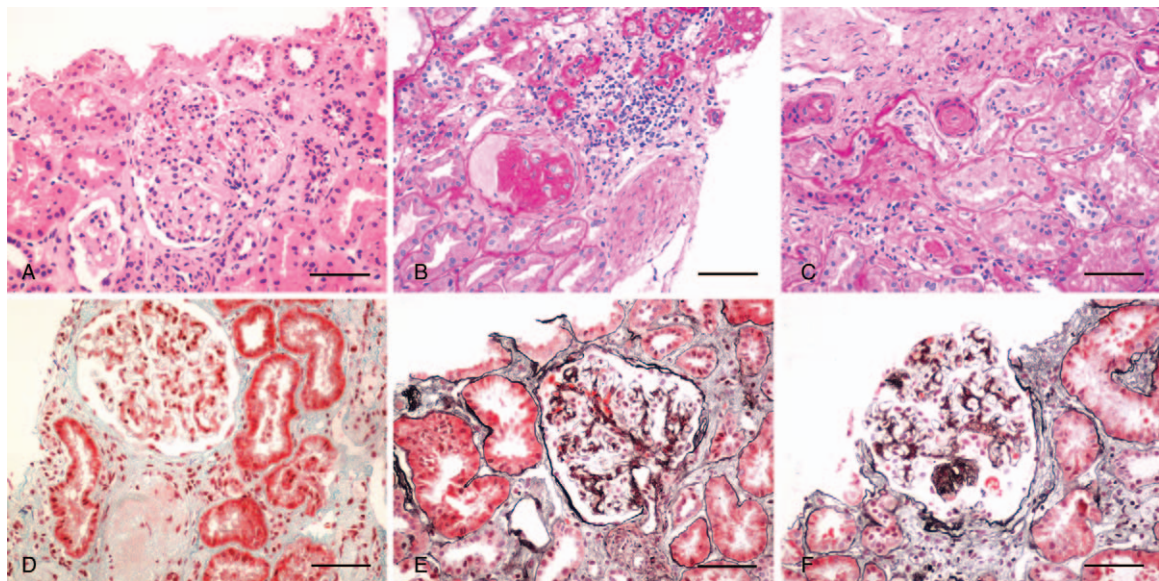


Figure 1. Kidney tissue section (200× magnification, scale bar=100 μm). (A) HE staining. (B and C) PAS staining. (D) MASSON staining. (E and F) Six ammonium silver staining. PAS=Periodic Acid-Schiff staining.

biopsy we identified an IgA nephropathy (Lee's grade IV) as the underlying cause of the hypertension.

Common clinical parameters that are tested to determine the prognosis of IgA nephropathy are the level of proteinuria, hypertension and serum creatinine, and the pathological indicators are the presence of glomerular sclerosis, interstitial renal tubular injury, vascular lesions, and pathological severity of Lee's grade III-V.^[3] Although reports have shown that the renal function in IgA nephropathy deteriorated significantly faster in male than in female patients,^[4] pregnancy is a very complex physiological process that can severely affect the renal function. This is in line with our findings, as our patient with IgA nephropathy presented with a high coagulation and glomerular hyperfiltration state during her second pregnancy, which could accelerate the deterioration of renal function. The state of impaired renal function could have promoted sodium retention, which could have increased the blood pressure and exacerbated the deterioration of renal function in return. The result was a severe preeclampsia, death of the fetus, and the termination of the pregnancy. Although the severe pre-eclampsia ended with the termination of the pregnancy, other factors such as inflammation, immune imbalance, severe hypertension, and other factors during

the pregnancy may have promoted the progression of IgA nephropathy, causing severe, treatment-resistant hypertension. Immunosuppressive and antihypertensive treatments were administered after the final diagnosis which led to clinical recovery of the patient. At 1-year follow-up, her blood pressure had decreased gradually with the improvement of the renal function.

Notably, the patient's cardiac function changed during the preeclampsia, as she suffered from diastolic heart failure with high NT-proBNP and preserved EF value. Her heart function had improved 2 months after delivery, but the cardiac diastolic dysfunction still persisted. At the 1-year follow-up, she had no cardiac discomfort and refused to repeat the UCG, which is why no follow-up data on cardiac function is available. Several studies have suggested an association between HDCP (especially preeclampsia) and cardiac diastolic dysfunction,^[5-7] but whether a diastolic dysfunction during pregnancy is a predictor for postpartum diastolic dysfunction and future congestive heart failure is still unknown. Therefore, it is of great clinical importance to record and analyze these co-occurrences during the long-term follow-up of these patients.

The clinical management of hypertensive women of childbearing age is challenging and has great clinical significance. Before

Table 1

Part of the patient's admission and follow-up examination results.

Monitoring index	Obstetrics	Cardiology	Nephrology	Follow-up		Normal range
	0 month	2 months	2 months	6 months	12 months	
BP, mm Hg	220/130	190/110	160/100	140/90	130/80	<120/80
UP, g/L	3+	3+	3+	—	—	—
24h-UPQ, g/24h	2.266	2.395	1.495	0.291	0.121	0–0.15
OB, cells/μL	3+	3+	3+	—	—	—
URBCC, /μL	137.10	80.56	85.0	35.0	18.0	0–23.8
CRE, μmol/L	160.9	76.0	102.0	88.0	65.0	35–71
BUN, mmol/L	9.94	5.14	8.50	7.62	6.98	2.8–7.2
eGFR, mL/min×1.73 m ²	33.41	79.39	56.54	67.03	95.08	>90

24h-UPQ = 24 h urine protein quantitation, BP = blood pressure, BUN = blood urea nitrogen, CRE = creatinine, eGFR = estimated glomerular filtration rate, OB = occult blood, UP = urine protein, URBCC = urine red blood cell count.

pregnancy, patients should undergo an appropriate evaluation including a thorough screening for factors of secondary hypertension. There are only few studies on pregnancy in patients with nephritis, although these patients are difficult to manage clinically. Successful pregnancy is usually possible for patients with IgA nephropathy, but may be associated with high risks for the patient and the fetus if the patient has persistent severe hypertension, a glomerular filtration rate of < 70 mL/min or has serious renal vascular or renal interstitial lesions. A prospective cohort study showed that elevated urinary protein levels during pregnancy might be a suitable risk indicator for an adverse pregnancy outcome in patients with IgA nephropathy.^[8] Therefore, female patients with IgA nephropathy who want to become pregnant should be strictly evaluated for their renal function, blood pressure, urine protein levels and renal pathology, and clinicians should provide individualized guidelines for the patients. Unfortunately, our patient has lost her second child due to complications of her disease.

We suggest to monitor the blood pressure of HDCP patients regularly during pregnancy. Importantly, the blood pressure standards for PIH patients differ from those for HDCP patients. Blood pressure guidelines suggest for PIH patients^[9–11] that if the systolic blood pressure is between 150 and 160 mm Hg or if the diastolic blood pressure is up to 100 to 110 mm Hg, antihypertensive drugs are indicated. Patients with chronic hypertension are more at risk of damage to their target organs and are more susceptible to organism decompensation and preeclampsia after pregnancy, even if all the functional values are within the normal range. Therefore, lower threshold and target values for the blood pressure are required for patients with chronic hypertension, and should not exceed 140/90 mm Hg. The aim for the management of the blood pressure in pregnant HDCP patients is to minimize any damage to target organs while maintaining blood perfusion to the uterine placenta.

Previous clinical studies did not find any effect of pregnancy on the long-term outcome of IgA nephropathy patients with preserved renal function.^[12–14] Our findings were in line with these results, because after 1 year of regular treatment, the blood pressure, urine test results, and renal function had returned to normal levels in our patient. This underlines the importance of a thorough prepregnancy evaluation for patients with IgA nephropathy.

4. Conclusions

Due to complex pathophysiological changes during pregnancy, patients with IgA nephropathy patients may suffer from complications and variable pregnancy outcomes. Important factors that affect the prognosis are renal function, blood pressure, urine protein levels, and the pathology of the renal tissue. Therefore, patients with hypertension need to be thoroughly investigated for secondary factors to clarify the

cause of hypertension before any damage to target organs occurs. This is especially important for female patients during their childbearing years, even if they have a family history of hypertension. Taken together, this will help clinicians to make a comprehensive assessment of the patient and to provide the patient with individualized guidance, which will improve the prognosis of the disease and prevent the occurrence of adverse events.

Author contributions

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