INTERNAL MEDICINE

□ CASE REPORT □

Successful Delivery in a Patient with Antineutrophil Cytoplasmic Antibody-associated Glomerulonephritis

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Abstract

We herein report a case of spontaneous pregnancy and preterm delivery in a 29-year-old patient with myeloperoxidase-antineutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis. Her basal serum creatinine level before pregnancy was 1.4 mg/dL and her urinary protein level was approximately 2 g/day. The proteinuria and hematuria increased during pregnancy, and the patient was admitted to our hospital and treated with prednisolone (PSL). At 27 weeks of gestation, she delivered a live infant weighing 848 g via cesarean section. No relapse of ANCA-associated glomerulonephritis occurred.

Key words: ANCA-associated glomerulonephritis, GFR, pregnancy, delivery, immunosuppressant

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Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis usually develops in elderly people. Therefore, pregnancy in patients with ANCA-associated glomerulonephritis is rare, and information regarding the management of ANCA-associated glomerulonephritis during pregnancy is limited. Moreover, pregnancy in patients with a low estimated glomerular filtration rate (eGFR) for any reason accelerates declines in the kidney function accompanied with a high rate of obstetrical complications (1-8).

In this report, we present a case of spontaneous pregnancy and preterm delivery in a patient with myeloperoxidase (MPO)-ANCA-associated glomerulonephritis with a low eGFR. At 27 weeks of gestation, the patient delivered a live infant via cesarean section.

Case Report

A 29-year-old pregnant Japanese woman was admitted to our hospital in 2011 at nine weeks of gestation due to increased proteinuria and hematuria. The proteinuria and hematuria were first detected in 2000 at an annual health examination conducted in high school (Fig. 1). The patient was admitted to the hospital for a further evaluation. The serum creatinine (sCr) level was 0.9 mg/dL and the MPO-ANCA level was 10 EU (normal: <10 EU at that time). A kidney biopsy was performed, in which 94% of the glomeruli (16 of 17 glomeruli) were found to have crescent formation with minor immunoglobulin deposition (Fig. 2). The patient was diagnosed with MPO-ANCA-associated glomerulonephritis and treated with methylprednisolone (m-PSL) pulse therapy followed by oral prednisolone (PSL) therapy. Thereafter, the proteinuria, hematuria and kidney function recovered to the normal ranges, and the dose of PSL was gradually tapered. In 2009, the patient suffered a

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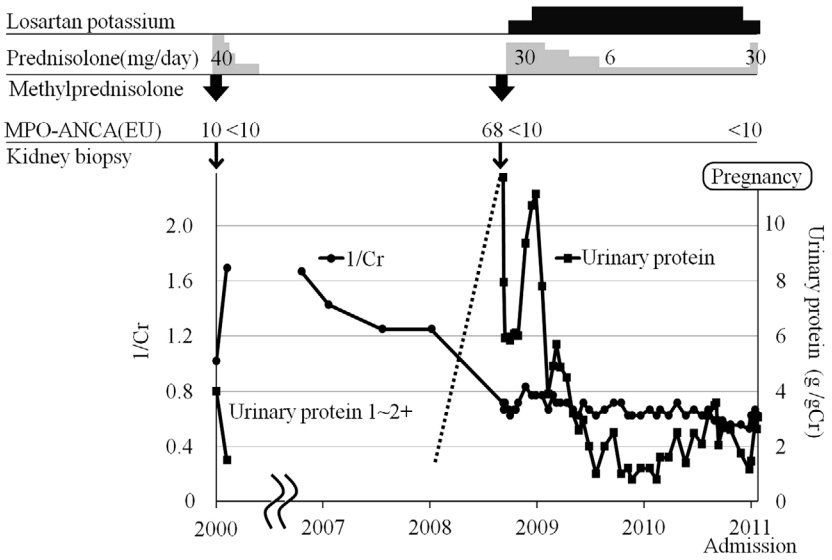

Figure 1. **The patient's clinical course before admission. ● indicates 1/Cr and ■ indicates urinary protein. The scale of 1/Cr is shown on the left and the scale of urinary protein is shown on the right.**

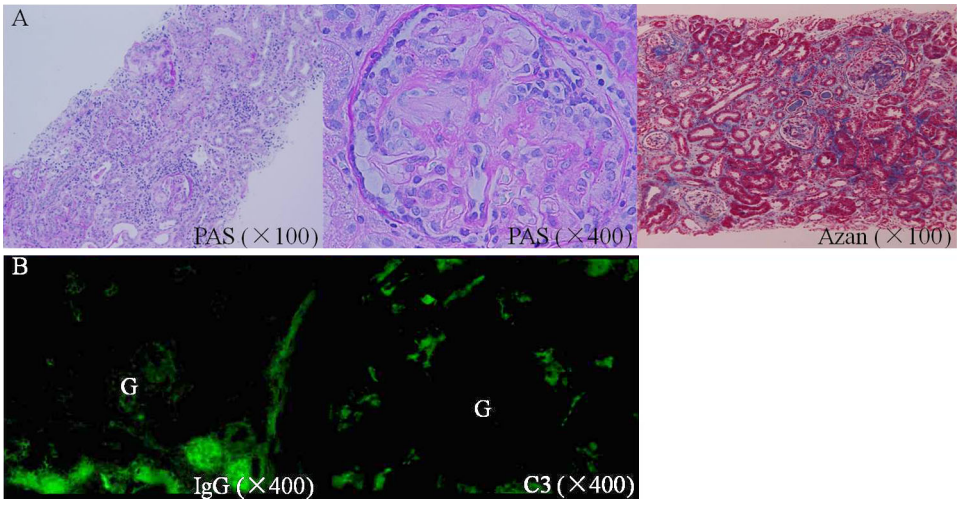

Figure 2. **Histopathology of the kidneys. (A) Light microscopic findings of a kidney biopsy performed in 2000 showing crescent formation and small round cell infiltration in the interstitium. PAS: periodic acid-Schiff. (B) Immunofluorescence microscopy showing no significant deposits of IgG or C3. G: glomerulus**

relapse. The MPO-ANCA level was 68 EU and a second kidney biopsy demonstrated 82% crescentic glomerulonephritis (18 of 22 glomeruli). The patient was again treated with m-PSL pulse therapy followed by oral PSL therapy (gradually tapered to 6 mg/day). Although the activity of MPO-ANCA-associated glomerulonephritis was controlled to some extent, the patient's proteinuria, hematuria and kidney insufficiency did not recover completely (urinal protein: approximately 2 g/day, urinary erythrocyte: 1 to 9 per high power field, sCr: 1.4 mg/dL). In 2011, pregnancy was confirmed, and the proteinuria and hematuria increased. In addition, erythrocyte casts were observed. After the PSL dose was increased from 6 to 30 mg/day by a previous physician, the patient came to our hospital.

On admission to our hospital, the patient was 156 cm tall and weighed 43 kg. Her blood pressure was 118/72 mmHg and her body temperature was 36.8℃. There were no significant findings on physical examination. A chest X-ray and electrocardiogram were normal. The laboratory data obtained on admission are shown in Table 1. On urinalysis, the level of occult blood was 2+ according to a dipstick test, and the urinary sediment contained 30 to 49 erythrocytes per high power field with no erythrocyte casts. A 24-hour urine collection contained 3.0 g of protein and 6,286 μg of β2-microglobulin. The blood and serum laboratory data were as follows: hemoglobin: 9.9 g/dL, total protein: 6.0 g/dL, albumin: 3.8 g/dL, blood urea nitrogen: 31 mg/dL, sCr: 1.6 mg/dL, eGFR: 32 mL/min/1.73 m^2 and C-reactive pro-

Table 1. Laboratory Data on Admission

Urinalysis		Blood chemistry		Blood chemistry	
pH	6.5	Total protein	6.0 g/dL	Fasting plasma glucose	90 mg/dL
Protein	2+ (3 g/day)	Albumin	3.8 g/dL	Hemoglobin A1c(JDS)	4.7 %
Occult blood	2+	Na	135 mEq/L	Fe	96 mg/dL
RBC	30-49 /HPF	K	4.3 mEq/L	TIBC	264 mg/dL
RBC cast	−	Cl	102 mEq/L	Ferritin	29 ng/mL
NAG	8.9 IU/L	Ca	8.7 mg/dL	Erythropoietin	13.9 mIU/mL
β2-microglobulin	2,668 ng/mL	P	3.2 mg/dL	Serology	
24h CCr	40.1 mL/min	BUN	31 mg/dL	CRP	0 mg/dL
Complete blood cell count		Cr	1.6 mg/dL	IgG	690 mg/dL
WBC	14,600 /μL	Uric acid	6.6 mg/dL	IgA	169 mg/dL
RBC	351 $\times 10^4$/μL	Total bilirubin	0.5 mg/dL	IgM	180 mg/dL
Hemoglobin	9.9 g/dL	AST	11 IU/L	IgE	744 IU/mL
Hematocrit	29.4 %	ALT	11 IU/L	C3	74 mg/dL
Platelet	14.6 $\times 10^4$/μL	LDH	154 IU/L	C4	22 mg/dL
Coagulation		γ-GTP	25 IU/L	CH50	50 IU/mL
FDP	35.6 μg/mL	Total cholesterol	200 mg/dL	MPO-ANCA	<10 EU
FDP D-dimer	14.9 μg/mL	Triglyceride	115 mg/dL	PR3-ANCA	<10 EU

NAG; N-acetyl-β-D-glucosaminidase, CCr; creatinine clearance, FDP; fibrin degradation products, AST; aspartate aminotransferase, ALT; alanine aminotransferase, LDH; lactate dehydrogenase, γ-GTP; γ-glutamyl transpeptidase, TIBC; total iron binding capacity, MPO / PR3-ANCA; myeloperoxidase / serine proteinase 3anti-neutrophil cytoplasmic antibody.

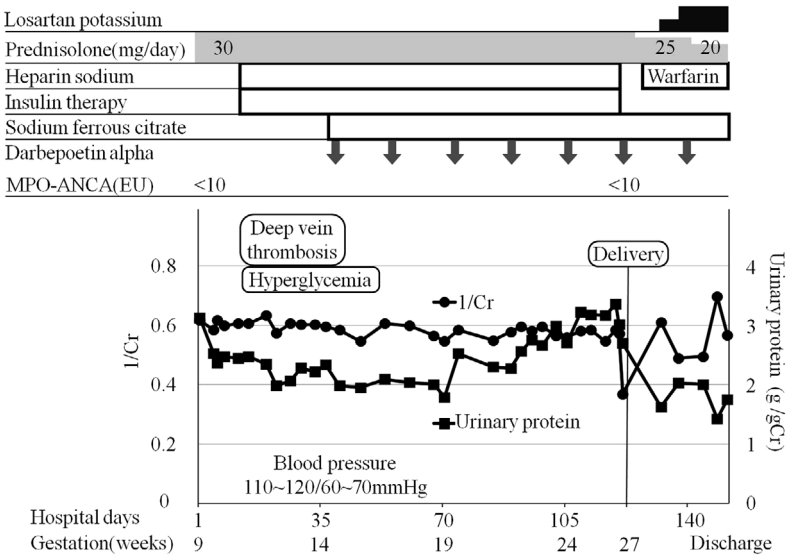

Figure 3. The patient's clinical course after admission. ● indicates 1/Cr and ■ indicates urinary protein. The scale of 1/Cr is shown on the left and the scale of urinary protein is shown on the right.

tein: 0 mg/dL. The 24-hour creatinine clearance was 40.1 mL/min/1.73 m^2. The fibrin degradation product (FDP) level was 35.6 μg/mL and the FDP D-dimer level was 14.9 μg/mL. The serum IgG level was 690 mg/dL, and no MPO-ANCA or proteinase 3 (PR3)-ANCA were detected.

After admission, the patient continued to receive PSL therapy at a dose of 30 mg/day, and the urinary protein level decreased to 2 g/day (Fig. 3). However, after 20 weeks of gestation, the urinary protein level gradually increased. In addition, deep vein thrombosis was observed in the right lower extremity on ultrasonography, and hyperglycemia was detected following the increase in the dose of PSL. Although she was adequately informed about the risk of pregnancy and delivery, the patient wished to continue her pregnancy. Therefore, she was treated with continuous intravenous infusion of heparin sodium to prevent thrombosis, and the FDP level gradually decreased. Insulin therapy was introduced to treat the hyperglycemia. Moreover, the patient

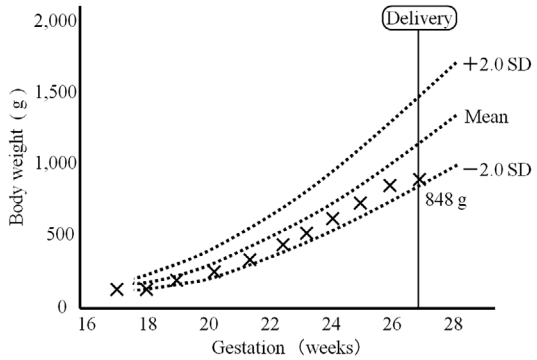

Figure 4. Intrauterine fetal growth curve before delivery. × indicates the body weight of the fetus.

was treated with oral sodium ferrous citrate and subcutaneous darbepoetin alpha for progressive anemia caused by iron deficiency and kidney insufficiency. The hemoglobin level remained around 9 g/dL following the administration of these therapies.

The patient's fetus exhibited normal growth on routine fetal ultrasonography (Fig. 4). However, at 27 weeks of gestation, the patient was suddenly threatened with premature delivery and delivered a live female infant weighing 848 g via cesarean section. The infant exhibited no apparent physical abnormalities. After delivery, the dose of PSL was gradually tapered to 20 mg/day, and the patient was treated with losartan potassium and warfarin potassium instead of heparin sodium. Twenty-nine days after delivery, the patient was discharged from our hospital, and no relapse of ANCA-associated glomerulonephritis occurred.

Discussion

The most compelling part of this process was that the patient had a low eGFR with massive proteinuria. In this case, the eGFR decreased from 32 to 25 mL/min/1.73 m^2 during pregnancy. Increasing evidence suggests that the presence of a certain degree of kidney insufficiency before pregnancy is a risk factor for accelerated decline in the kidney function during pregnancy. Jones et al. reported the outcomes of 82 pregnancies in 67 patients with primary kidney diseases. The rate of pregnancy-related maternal kidney dysfunction was 43%. The mean ± SD sCr concentration increased from 1.9±0.8 mg/dL in the early phase of pregnancy to 2.5±1.3 mg/dL in the third trimester. In addition, the frequency of hypertension rose from 28% at baseline to 48% in the third trimester, and the rate of high-grade proteinuria (>3 g/day) rose from 23% to 41% (1). Two other studies showed similar results. Patients with high sCr levels (>1.4 mg/dL) demonstrate more rapid decreases in eGFR during pregnancy (2, 3). Moreover, Imbasciati et al. reported the findings of a prospective analysis of 49 women with an eGFR <60 mL/min/1.73 m^2. An accelerated rate of eGFR loss after delivery was observed in the subgroup of women with both an eGFR <40 mL/min/1.73 m^2 and proteinuria >1 g/day before pregnancy (4). Therefore, pregnancy should be avoided in patients with a low eGFR and a high level of proteinuria.

In addition to maternal kidney function loss, the rate of obstetrical complications increases in pregnant patients with moderate to severe kidney insufficiency. Our patient delivered a small infant at 27 weeks of gestation. More than 70% of pregnant women with a sCr level >2.5 mg/dL experience preterm delivery, and more than 40% develop preeclampsia (5). Similarly, a low eGFR increases the risk of preterm delivery, cesarean section and admission to neonatal intensive care (normal eGFR vs. low eGFR; 5 vs. 44%, 25 vs. 44%, 1 vs. 26%, respectively) (6). The three major risk factors for complications in offspring have been reported to be a low eGFR, hypertension and proteinuria. The combination of these risk factors multiplies the risks for offspring (7, 8). Further improvements in management of delivery are required.

In our case, during early pregnancy, the level of proteinuria and hematuria were increased and erythrocyte casts were detected. Therefore, the disease activity was suspected to be aggravated. The British Society for Rheumatology and British Health Professionals in Rheumatology guidelines recommend that minor relapses, relapses without a threatened vital organ function, should be treated with an increased dose of PSL (30 mg/day) (9). Moreover, the Japanese "clinical practice guideline for ANCA-associated vasculitis" recommends increasing the dose of PSL to a level that induces remission when the patient relapses. According to these guidelines, we increased the dose of PSL from 6 to 30 mg/day in our patient. Fortunately, the ANCA titers did not increase, and our patient exhibited no clinical manifestations associated with a relapse of ANCA-associated glomerulonephritis.

There is limited information regarding whether ANCA-associated glomerulonephritis itself influences the outcome of pregnancy or whether pregnancy affects the course of ANCA-associated glomerulonephritis. Case reports of pregnancies in patients with ANCA-associated glomerulonephritis are shown in Table 2. Of these cases, four patients successfully delivered infants. Two of the patients underwent cesarean section, and the remaining four patients underwent abortion, including two spontaneous abortions. Moreover, two patients relapsed during pregnancy. Obtaining additional information regarding pregnant patients with ANCA-associated glomerulonephritis is necessary.

In conclusion, both a low eGFR and the presence of ANCA-associated glomerulonephritis carry high risks during pregnancy. All patients with low eGFR values should be made aware of the risks for long-term kidney function problems and complications for their offspring before pregnancy. Careful monitoring for this disease and its complications during pregnancy is essential. Accumulating further experience and studies is necessary for improving the management of ANCA-associated glomerulonephritis during pregnancy and delivery.

Table 2. Clinical and Laboratory Findings Associated with Pregnancies in Patients with ANCA Associated Glomerulonephritis

Case / Age	Obstetrical outcome	Kidney / Pulmonary involvement	Relapse	Treatment
1 / 24 y	1 : induced abortion			none
	2 : spontaneous abortion		-	PSL 10mg
	3 : normal delivery		-	PSL 10mg
2 / 32 y	1 : spontaneous abortion	kidney insufficiency (Cr 1.8)		none
	2 : normal delivery (39w)	kidney insufficiency (Cr 1.0)	-	PSL 10mg
3 / 21 y	induced abortion		-	PSL 5mg
4 / 34 y	cesarean section (33w)	alveolar hemorrhage respiratory insufficiency	+	PSL
5 / 33 y	cesarean section (33w)	respiratory insufficiency	+	PSL 30mg
6 / 29 y (present case)	cesarean section (27w)	kidney insufficiency (Cr 1.4)	-	PSL 30mg

y; years old, w; gestation weeks, PSL; prednisolone.

The authors state that they have no Conflict of Interest (COI).

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