【 CASE REPORT 】

Anti-glomerular Basement Membrane Glomerulonephritis During the First Trimester of Pregnancy

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Abstract:
 A 28-year-old woman was admitted during the eighth week of her pregnancy because her clinical course was consistent with rapid progressive glomerulonephritis (RPGN). Anti-glomerular basement membrane antibody (anti-GBM Ab) and myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) were positive, and the anti-GBM Ab titer being extremely high. She was treated with hemodialysis, plasma exchange and prednisolone. She survived the illness; however, neither the fetus nor her kidney function could be rescued. She had human leukocyte antigen (HLA)-DRB1*1502:01, which differs from the DRB1*1501 associated with anti-GBM GN. When patients have particular symptoms, we should check the urine and serum creatinine to exclude RPGN, even in cases of pregnancy.

Key words: 1st trimester of pregnancy, anti-glomerular basement membrane glomerulonephritis (anti-GBM GN), rapid progressive glomerulonephritis (RPGN), plasma exchange (PE), HLA-DRB1*1502:01

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Introduction

Anti-glomerular basement membrane glomerulonephritis (anti-GBM GN), also called Goodpasture's syndrome, is an autoimmune-mediated disorder, and patients with anti-GBM antibody disease develop rapidly progressive glomerulonephritis (RPGN), leading to severe kidney deterioration. Despite various aggressive treatments, the prognosis of anti-GBM GN is very poor, often leading to renal failure and/or death (1). Once anti-GBM GN patients begin dialysis, they usually remain dialysis-dependent (2). Anti-GBM GN is well known to occur in young and elderly patients (3) and is a rare cause of renal insufficiency in young patients, especially in association with pregnancy.

We herein report a case of anti-GBM GN disease requiring dialysis that presented in early pregnancy.

Case Report

A 28-year-old woman was introduced to our hospital because of generalized edema associated with a reduced urine output in the eighth week of pregnancy. She had no abnormality recorded in her previous medical examinations. This was her first pregnancy, and she had had no miscarriages. At a medical examination one year earlier, her serum creatinine level had been 0.64 mg/dL, and urine protein and urine occult blood were negative. There was no familial history of renal disease. She had had gross hematuria, a fever, nausea and diarrhea for about three weeks. She visited a local obstetrics clinic and was treated with amoxicillin for a suspected urinary tract infection. Treatment with antibiotics did not improve her symptoms, and she was referred urgently to our hospital because of severe kidney dysfunction.

On a clinical examination, she had bilateral pitting pedal edema, abdominal fullness, due to ascites fluid, and anemia.

Table 1.   Laboratory Findings on Admission.

Peripheral blood tests		Na	123 mEq/L	KL-6	115 U/mL
WBC	13,000 /μL	K	6.6 mEq/L	SP-A	8.3 ng/mL
Neu	87.1 %	Cl	88 mEq/L	SP-D	17.2 ng/mL
Ly	5.2 %	Ca	7.9 mg/dL		
Mo	6.7 %	IP	7.6 mg/dL	Urinalysis	
Eo	0.8 %	CRP	15.5 mg/dL	Protein	2+
RBC	339×10⁴ /μL	Blood sugar	99 mg/dL		0.17 g/day
Hb	9.4 g/dL	HbAlc (NGSP)	5.4 %	Occult blood	3+
Ht	27.5 %	IgG	1,020 mg/dL	Sugar sediment	-
Platelet	53.7×10⁴ /μL	IgA	108 mg/dL	RBC	>100 HPF
Blood chemistry tests		IgM	141 mg/dL	WBC	0 HPF
TP	5.9 g/dL	MPO-ANCA	16.1 U/mL	hyaline cast	1-4 HPF
Alb	2.5 g/dL	PR3-ANCA	<1.0 U/mL	granular cast	1-4 HPF
T-Bil	0.3 mg/dL	Anti-GBM Ab	>680 U/mL	Urine chemistry	
AST	16 U/L	ANA	<40 times	NAG	15.3 U/L
ALT	15 U/L	Anti-DNA Ab	<2 times	β2MG	57,815 ng/mL
LDH	179 U/L	Anti-cardiolipin-beta2 glycoprotein 1 complex Ab	negative		
CPK	97 U/L				
UA	8.2 mg/dL				
BUN	62.5 mg/dL	antiphospholipid Ab	negative		
Cr	12.52 mg/dL				

Ab: antibody, Alb: albumin, ALT: alanine aminotransferase, ANA: antinuclear antibody, ANCA: antineutrophil cytoplasmic antibody, AST: aspartate aminotransferase, β2MG: beta-2 microglobulin, BUN: blood urea nitrogen, Ca: calcium, CPK: creatine phosphokinase, Cr: creatinine, CRP: C-reactive protein, DNA: deoxyribonucleic acid, Eo: eosinophils, Hb: hemoglobin, Ht: hematocrit, Ig: immunoglobulin, IP: Inorganic phosphorus, K: potassium, KL-6: Krebs von den Lungen-6, LDH: lactate dehydrogenase, Ly: lymphocytes, Mo: monocytes, MPO: myeloperoxidase, Na: sodium, NAG: N-acetyl-beta-D-glucosaminidase, Neu: neutrophils, NGSP: National Glycohemoglobin Standardization Program, PR3: proteinase3, RBC: red blood cells, SP-A: Surfactant Protein A, SP-D: Surfactant Protein D, T-Bil: total-bilirubin, TP: total protein, UA: uric acid, WBC: white blood cells

Her blood pressure was 134/81 mmHg, her pulse rate was 89/minute and her body temperature was 37.7℃. She had no hemosputum or hypoxemia, and the remainder of her systemic examination findings, including those for her chest, were within normal limits.

The laboratory findings on admission are shown in Table 1. She had severe renal dysfunction with urinary abnormality, severe inflammation, anemia, hypoproteinemia, hyperkalemia, hyperphosphatemia and hyperuricemia. Anti-GBM Ab and myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) were positive, with the anti-GBM Ab titer (>680 U/mL) being extremely high, unlike the MPO-ANCA titer (16.1 U/mL). Both anti-nuclear Ab (ANA) and PR3-ANCA were negative. There was no reduction in the complement value and no monoclonal protein. Ultrasound imaging of the abdomen showed her right kidney to be 10.5 cm ×4.0 cm and left kidney to be 10.6 cm × 4.3 cm, with bilateral increased echogenicity. Chest X-ray showed no interstitial pneumonia or alveolar hemorrhaging, which are typically seen in Goodpasture's syndrome. The values of Krebs von den Lungen-6 (KL-6), Surfactant Protein A (SP-A) Surfactant Protein D (SP-D) were within normal limits.

Her clinical course suggested RPGN with severe renal dysfunction due to anti-GBM GN. In an effort to rescue her fetus and her kidney function, she was treated with hemo-dialysis and plasma exchange (PE) and started on 30 mg/day of prednisolone. Her clinical course is shown in Fig. 1. On admission, obstetric ultrasound findings showed five weeks of gestation, which differed from the estimated 8 weeks of gestation from her last menstruation, and miscarriage was strongly suspected. After reconfirmation, a fetal heartbeat could not be detected, so dilatation and curettage were performed on the 15th day of admission. All of our efforts were then directed to saving her kidneys and life.

She was examined by a renal biopsy on the 24th day of admission. The biopsy revealed 27 glomeruli, of which 1 had segmental necrosis with nuclear debris and hyaline thrombi within glomerular capillaries. There were fibrocellular crescents in 26 glomeruli. The underlying tufts did not show significant endocapillary proliferation. Lymphocyte infiltration around the tubulointerstitium was found near the glomerulus (Fig. 2A) and mainly formed fibrocellular crescents (Fig. 2B). Immunofluorescence staining revealed linear IgG (Fig. 2C) and C3 staining along glomerular capillary loops. IgA, IgM and C1q were negative, and fibrinogen was weakly positive. A diagnosis of crescentic glomerulonephritis was made, which was consistent with anti-GBM GN disease with diffuse global glomerulosclerosis. Based on the kidney biopsy result, we suspected a low probability of improving her renal function. Although plasma exchange was performed 14 times and immunosuppressive therapy contin-
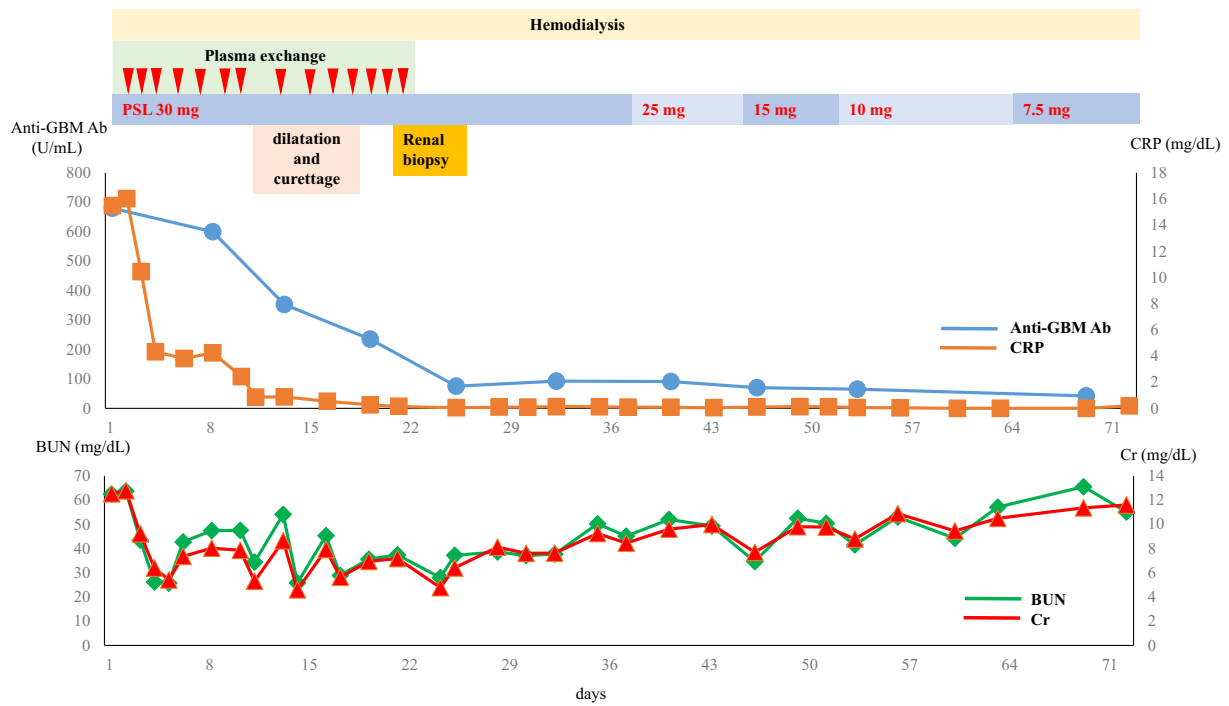
Figure 1.   Clinical course of the patient.

ued, anuria persisted, and her kidney function did not improve; she could not discontinue hemodialysis despite a reduction in the anti-GBM Ab titer (42.3 U/mL) and C-reactive protein (CRP) on the 71st hospital day. On that day, her serum blood urea nitrogen (BUN) was 55.1 mg/dL and creatinine 11.6 mg/dL (Fig. 1). The high titer level of anti-GBM Ab persisted, and no improvement in the kidney function could be expected, but fortunately, there were no signs of respiratory symptoms or the development of lung lesions, which was important in deciding to withdraw treatment. Her life was saved; however, give the loss of her renal function, renal transplantation in the near future is desirable.

Discussion

There are only a few case reports of anti-GBM GN disease during pregnancy in the literature, especially in the early phase of pregnancy (4). We summarized the reports of anti-GBM GN in pregnancy in Table 2 (5-13). There have been some reports of a severe renal outcome and prognosis in pregnancy (5-7, 9). For example, Qin et al. reported both maternal and fetal death in a case of Goodpasture's syndrome during pregnancy (5).

However, there have been some reports in which the kidney function was rescued by aggressive treatment with corticosteroid, immunosuppressive agents and PE (8, 10-13). Vasiliou et al. described a 34-year-old woman who presented with RPGN with anti-GBM GN at 18 weeks of pregnancy, and her baby was born alive after 27 weeks of gestation (10). She was treated with acute dialysis for renal failure and received intensive treatment with PE, corticosteroid and azathioprine, resulting in the partial recovery of her kidney function. A renal biopsy showed 80% crescentic GN

with linear immune fluorescence. Yankowitz et al. reported the case of a 28-year-old woman with anti-GBM GN 3 months before pregnancy who was treated with intensive hemodialysis along with corticosteroid and delivered at 37 weeks of gestation (11). Anti-GBM Ab, which had been negative during pregnancy, was detected again after delivery. Sprenger-Mähr et al. described the case of a 30-year-old woman with anti-GBM GN and who was treated with PE, corticosteroid, cyclophosphamide and rituximab and delivered at 38 weeks of gestation (12). Although the differences between the reports with good and poor renal prognoses are unclear, it seems that anti-GBM GN requires aggressive treatment, even during pregnancy. In our case, the anti-GBM antibody titers were very high, even during pregnancy, and did not become negative after treatment. She also obtained a very poor renal recovery with immunosuppression, along with intensive plasma exchange and hemodialysis.

The outcomes of the infants of mothers with anti-GBM GN during pregnancy are generally poor, often resulting in stillbirth and both natural and artificial abortion (7, 8, 13). Nilssen et al. reported a 19-year-old woman who was treated with RPGN with anti-GBM GN in the second trimester of pregnancy and had a stillbirth at 28 weeks of gestation (7). Nair et al. described the case of a 23-year-old woman who presented with Goodpasture's syndrome during the 13th week of pregnancy (8). She was started on corticosteroid and cytotoxic agents, along with intensive PE and alternate day hemodialysis. Her pregnancy was terminated at 15 weeks. The patient improved dramatically with treatment, her renal function normalized, and her anti-GBM Ab became undetectable. However, some reports have described successful deliveries of live infants, despite poor kidney outcomes. Al-Harbi et al. reported a 30-year-old woman with
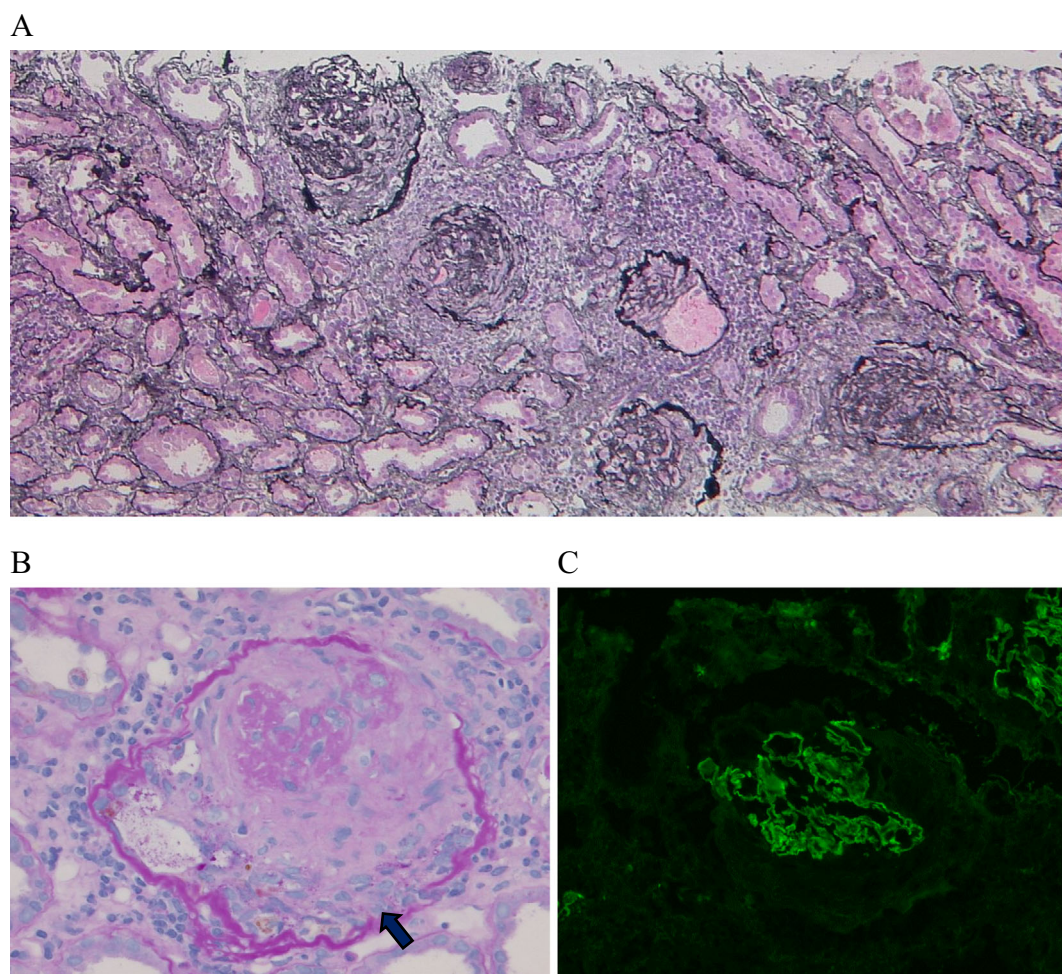
A

B

C

Figure 2. Histological findings in the kidney. (A) Fibrocellular crescents in the glomeruli and lymphocyte infiltration around the tubulointerstitium, near the glomerulus [Periodic Acid-Methenamine Silver (PAM) staining ×100]. (B) The fibrocellular crescents, indicated by an arrow [Periodic Acid Schiff (PAS) staining ×400]. (C) Immunofluorescence staining revealed linear staining along the glomerular capillary loops (IgG staining ×400).

Table 2. Maternal and Fetal Outocomes and Treatments in Anti-GBM GN in Pregnancy.

			Maternal		Fetal outcomes				Treatments
Reference numbers	Age	Onset week of pregnancy, weeks	Kidney outocomes	Respiratory symptoms	Livebirth	Weeks gestation	Small for gestational age	PE	Medicine
5	17	13	Maternal death	Hemoptysis	Maternal death			(-)	corticosteroid
6	21	12	HD, RTx	Normal	(+)	35	NR	(+)	corticosteroid, CY
7	19	19	HD, RTx	Normal	(-); SB	28	SB	(+)	corticosteroid, CY
8	23	13	Full recovery	Dyspnea	(-); TA	15	TA	(+)	corticosteroid, CY
9	30	28	HD	Dyspnea	(+)	34	(+)	(+)	corticosteroid
10	34	18	Partial recovery	Hemoptysis	(+)	27	(+)	(+)	corticosteroid, AZA
11	28	Prepregnancy	Normal	Hemoptysis, Dyspnea	(+)	37	(-)	(+)	corticosteroid, CY
12	30	13	Normal	Hemoptysis	(+)	38	(+)	(+)	corticosteroid, CY, RT
13	17	6	Full recovery	Normal	(-); SA	8	SA	(+)	corticosteroid,CY
This case	28	8	HD	Normal	(-); SA	8	SA	(+)	corticosteroid

AZA: azathioprine, CY: cyclophosphamide, HD: hemodialysis, PE: plasma exchange, RT: rituximab, RTx: renal transplantation, SA: spontaneous abortion, SB: stillbirth, TA: therapeutic abortion, NR: not reported

acute kidney injury at 28 weeks of gestation who was treated with intensive hemodialysis along with corticoster-oid (9). The patient did not recover bad kidney function and required regular maintenance hemodialysis, but she delivered

at 34 weeks of gestation. In summary, pregnant women complicated with anti-GBM GN are unlikely but still able to deliver a newborn baby, although many such infants have low birth weights.

The titers of anti-GBM Ab decline in response to immunosuppression and plasma exchange. Plasma exchange is generally considered low risk in pregnancy (14). Anti-GBM Ab binds human placental antigens (15); however, the clinical outcome of this phenomenon is controversial (4). Deubner et al. discussed a protective aspect of the placental binding of anti-GBM antibodies, resulting in decreased transfer to the fetus and reduced maternal total anti-GBM Ab levels (6). However, anti-GBM Ab binding to the placenta might increase the risk of placental dysfunction if not treated aggressively. Anti-GBM Ab comprises IgG antibodies and is transported across the placenta via placental transporters. There is the possibility that the fetus may be exposed to maternal IgG antibodies, including anti-GBM antibodies. In the present patient, no placenta was observed in the uterine contents, and anti-IgG staining of the uterine contents was not apparent.

We investigated the human leukocyte antigen (HLA) genotypes through an external examination center (LSI Medience Corporation, Tokyo, Japan). HLA-DRB1*1501 is known to have a strong relationship with anti-GBM GN pathogenesis (16-18). HLA-DR15 confers a markedly increased disease risk; an autoreactive CD4+ T-cell self-epitope, derived from the α3 chain of type IV collagen, is expanded in patients with Goodpasture syndrome (19). The present patient had HLA-DRB1*1502:01, which was not consistent with the previous report. The only difference between DRB1*1501 and DRB1*1502 is the 86th amino acid in pocket 4; here, a valine residue in HLA-DRB1*1501 is substituted by a glycine residue in DRB1*1502 (17). However, the relationship between HLA-DRB1*1502:01 and the pathogenesis of the anti-GBM GN in this case was not clear.

We need to consider the relationship between pregnancy and renal failure. First, we discuss the relationship with hypertensive disorders of pregnancy (HDP) (20). Because this case had <20 weeks of gestation, it did not meet the definitions of pre-eclampsia, gestational hypertension or superimposed pre-eclampsia. In addition, the findings of a renal biopsy did not reveal endothelial injury, which is typical of HDP (21, 22). While anti-GBM GN may have been exacerbated by pregnancy or developed during pregnancy, the anti-GBM Ab before pregnancy had not been measured, so we could not determine the pathogenesis of this disease.

Unfortunately, the patient's kidney function did not recover, and her fetus was stillborn. We consider it necessary to pay attention to the subjective symptoms of anti-GBM GN, which include a fever, macrohematuria, general fatigue and systemic edema, in the early stage of the disease. In particular, such a serious disease might exist in a pregnant woman who is diagnosed as a urinary tract infection. We should not ignore the possibility of RPGN and should check the urine and serum creatinine contents to avoid a misdiagnosis. We hope that this case report will improve awareness of a potential anti-GBM GN diagnosis and its appropriate treatment during pregnancy.

Informed consent was obtained from the patient described in this case report.

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

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