Microscopic polyangiitis necrotizing glomerulonephritis associated with pregnancy: case with a 20-year clinical course and review of the literature

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Abstract

A 29-year-old woman with past medical history of hypertension was referred to our hospital for the evaluation of kidney dysfunction (serum creatinine 1.0 mg/dL), proteinuria (0.54 g/gCre), and microscopic hematuria. Renal biopsy before the first pregnancy was supportive for benign nephrosclerosis with no evidence of vasculitis. After her second pregnancy and delivery when she was 32 years old, she developed proteinuria of 3.2 g/gCre, hematuria, and elevated serum creatinine level of 2.6 mg/dL. Second renal biopsy revealed necrotizing glomerulonephritis and her serum MPO-ANCA was positive, leading to the diagnosis of MPA/renal-limited vasculitis (RLV). Interestingly, frozen preserved serum from 4 years earlier also tested positive for MPO-ANCA. Despite intensive treatment, hemodialysis was required 10 years later due to progressive deterioration of renal function. At that time, she developed pericarditis, bloody cardiac tamponade, and pulmonary alveolar hemorrhage, resulting in a diagnosis of systemic vasculitis MPA. She received living donor kidney transplantation at the age of 44 years, after which serum creatinine has been stable around 1.1 mg/dL without proteinuria or hematuria and MPO-ANCA has remained negative. The association of vasculitis with pregnancy and delivery is not well documented, especially in patients with MPA. Here, we report this MPO-ANCA positive woman developing MPA necrotizing glomerulonephritis after her second pregnancy and a 20-year clinical course.

Keywords Microscopic polyangiitis · Pregnancy · Delivery · Necrotizing glomerulonephritis · MPO-ANCA

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis is a necrotizing vasculitis with few or no immune deposits that predominantly affects small vessels and is associated with ANCA targeting myeloperoxidase (MPO)

or proteinase 3 (PR3) [1]. Microscopic polyangiitis (MPA) involves various organs such as the kidney, lung, nervous system, head and neck region, skin, heart, and eye. The kidney is the organ most often affected in MPA patients [2, 3]. Most renal-limited disease in patients with ANCA-associated vasculitis is classified as MPA, apart from a few cases of renal-limited disease preceding systemic vasculitis due to granulomatosis with polyangiitis (GPA) [4]. The mean age of onset for MPA is 65 years in the UK and 71 years in Japan, and MPO-ANCA tends to be positive rather than PR3-ANCA [2].

The association of vasculitis with pregnancy and delivery is not well documented, especially in patients with MPA, probably because this disease is uncommon and has a relatively high age of onset. There have been eight reports describing a total of 15 pregnancies in nine women with MPA [5–12], including two reports about the onset of MPA

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1st RBx
(Age 29)

2nd RBx
(Age 33)

3rd RBx
(Age 41)

Fig. 1 Histological features of three renal biopsies (RBx) obtained during the clinical course. 1st renal biopsy: PAS staining shows a slight increase of mesangial matrix (A), protein casts, and slight interstitial fibrosis (B). No atrophy of tubules was noted. 2nd renal biopsy: C Masson trichrome staining shows fibrinoid necrosis in a glomerulus (yellow arrow). D PAM staining shows cellular crescent formation, an increase of Bowman's epithelial cells, and attachment of the glomerulus to Bowman's capsule. C, D Support the diagnosis of necrotizing glomerulonephritis. E PAS staining shows atrophy of renal tubules, flattening of the tubular epithelium, infiltration of lymphocytes, macrophages and plasma cells, and hyaline sclerosis in the intralobular arteries (red arrow). The findings were consistent with changes due to hypertension. F Electron microscopy (EM) shows accumulation of vesicles in a podocyte (black arrow). G EM shows subendothelial edema (magnified in the upper right corner), which is compatible with changes due to pregnancy. 3rd renal biopsy: H PAS staining shows segmental sclerosis, which is consistent with secondary effects of the necrotizing changes seen in the 2nd biopsy. Global sclerosis is seen in 13 out of 18 glomeruli. I PAM staining shows collapse of glomeruli, rupture of the basement membrane, and ballooning of epithelial cells. J Tubules show foamy degeneration and atrophy. Moderate to severe interstitial cellular infiltration (mainly lymphocytes) is seen. K EM shows no subendothelial edema, unlike the 2nd biopsy

during pregnancy [11, 12], but there have been no reported MPO-ANCA positive individual who developed MPA after delivery. Others have reported two patients with MPA-like clinical features during pregnancy. However, one patient did not satisfy the Chapel Hill Consensus Conference criteria for MPA [13], and the other probably had secondary vasculitic symptoms due to MRSA sepsis [14], as also pointed out elsewhere [11]. Furthermore, it was reported that MPA was diagnosed after delivery in 20 patients, but the age of onset, clinical characteristics, histological findings, and especially the MPO-ANCA titer before the pregnancy were unknown since the study was based on an anonymous self-reported questionnaire [9]. Here, we report a case which developed MPA necrotizing glomerulonephritis after the second pregnancy in an MPO-ANCA positive woman with a clinical course of 20 years.

Case presentation

A 29-year-old Japanese woman was referred to our hospital with an elevated serum creatinine level (1.0 mg/dL), mild proteinuria [0.54 g per gram of creatinine (g/gCre)], and positive microscopic hematuria [<5 red blood cells per high power field (RBCs/HPF)]. Hypertension was pointed out at the age of 20, although no treatment was practiced. Renal biopsy before the first pregnancy demonstrated no evidence of vasculitis and only mild mesangial matrix deposition and slight interstitial fibrosis was admitted (Fig. 1A, B). Therefore, at this point, we considered this case as benign nephrosclerosis. One year later, she developed gestational toxicosis during her first pregnancy. During the years between age 29

and 32, medical records showed no proteinuria or hematuria. These evidences suggested no active renal disease during this period. At the age of 32 years, after her second pregnancy and delivery, serum creatinine was elevated to 2.6 mg/dL and microscopic hematuria became evident. At this point, the patient was admitted to our hospital as described as follows. The patient's entire clinical course is presented in Fig. 2.

The patient was 153 cm tall and weighed 54 kg, with a blood pressure of 139/78 mmHg, pulse rate of 98 /min, and temperature of 37.0 °C. Physical examination revealed no significant abnormalities. Although laboratory tests showed slight elevation of CRP to 0.4 mg/dL, the levels of gamma globulin (IgG, IgA, and IgM) and complement (C3, C4, and CH50) were normal, and antinuclear antibody, double-stranded DNA antibody, and PR3-antineutrophil cytoplasmic antibody (ANCA) were negative. MPO-ANCA was elevated to 80 enzymatic units (EU). Urinalysis revealed proteinuria (3.2 g/gCre), while the sediment contained >100 RBCs/HPF and granular casts. The second renal biopsy showed fibrinoid necrosis in a glomerulus (Fig. 1C), cellular crescent formation (Fig. 1D), global nephrosclerosis in five out of seven glomeruli, and the interstitium displayed moderate fibrosis with infiltration of lymphocytes, plasma cells, and macrophages. The glomeruli were pauci-immune. Together, these changes were consistent with MPA necrotizing glomerulonephritis. Moreover, hyaline sclerosis of intralobular arteries was observed, which suggested damage associated with hypertension (Fig. 1E). Electron microscopy revealed endothelial injury accompanied by subendothelial edema (Fig. 1G), which was probably associated with her recent pregnancy. Therefore, MPA/renal-limited vasculitis (RLV) was diagnosed and she was immediately treated with intravenous cyclophosphamide pulse therapy, oral prednisolone, and oral cyclosporin A. Although no guidelines were published at the time, cyclophosphamide and prednisolone was selected because these were widely used. In addition, cyclosporin A was selected because there were positive reports for ANCA-associated vasculitis at that time [15–17]. Nowadays, cyclosporin A is known to suppress T cells and T cells are reported to have a pathophysiological role in ANCA-associated vasculitis [18]. Consequently, her serum creatinine decreased to 2.2 mg/dL, proteinuria declined to 0.5 g/gCre, and MPO-ANCA became undetectable. Interestingly, testing of frozen preserved serum from the time of the first kidney biopsy 4 years earlier revealed that MPO-ANCA was also positive (22 EU).

Two years after initiation of treatment (when she was 34 years old), MPO-ANCA increased to 100 EU, so mizoribine (200 mg/day) was started. When she was aged 37 years, serum creatinine increased to 3.0 mg/dL and proteinuria to 1.0 g/gCre, so methylprednisolone pulse therapy (500 mg/day for 3 days) was administered. Unfortunately, serum

Fig. 2 The patient's 20-year clinical course. Despite administration of IVCY, steroids, cyclosporin A, and mizoribine, hemodialysis was required due to progressive deterioration of renal function. After kidney transplantation, serum creatinine, proteinuria, and the MPO-ANCA titer all improved. At the top of the graph, corticosteroid and immunosuppressant therapy is shown. Red arrows show methylpred-

nisolone (mPSL) pulse therapy. Black arrows show each event. Asterisk shows occurrence of pericarditis, cardiac tamponade, and alveolar hemorrhage. MPO-ANCA is shown as enzymatic units (EU, normal range <20) until age 45, and as U/mL (normal range <3.5) from age 45. IVCY intravenous cyclophosphamide, MMF mycophenolate mofetil

creatinine and proteinuria did not improve; therefore, third renal biopsy was performed to confirm that the deterioration of renal function was due to ANCA-associated vasculitis. This showed focal segmental glomerulosclerosis, which was consistent with scarring due to vasculitis, and no other pathologic changes were noted (Fig. 1H–J). Subendothelial edema, which was thought to be secondary to pregnancy at the time of the second renal biopsy, could not be detected (Fig. 1K). The serum creatinine level continued to increase despite additional therapy such as cyclophosphamide pulse therapy, intravenous tocilizumab, and further methylprednisolone pulse therapy as shown in Fig. 1. Tocilizumab was recently reported to be effective for MPA [19, 20].

At the age of 43 years, she developed fever of 38 °C (100 °F), cough, and dyspnea. Detailed investigation by electrocardiography, echocardiography, CT scanning, bronchoscopy, and pericardiocentesis revealed pericarditis, bloody cardiac tamponade, and pulmonary alveolar hemorrhage, leading to a diagnosis of systemic vasculitis MPA. Hemodialysis was commenced, and methylprednisolone pulse

therapy was administered. 14 months later (when she was 44 years old), ABO mismatched living donor kidney transplantation was performed with the donor being her mother. Mycophenolate mofetil, tacrolimus, and prednisolone were used for maintenance of immunosuppression. 5 years after the transplantation, serum creatinine is stable around 1.1 mg/dL, with MPO-ANCA titer and proteinuria being negative and with no evidence of relapse.

Discussion

In the present patient, MPO-ANCA was retrospectively found to be positive 4 years before the diagnosis of MPA/RLV. It is considered that MPO-ANCA has pathogenic role in the development of MPA, as reviewed elsewhere [18, 21]. Moreover, recently a study has revealed the significance of MPO-ANCA epitope in the pathogenesis of MPA [22]. Although there is no study confirming the precedence of MPO-ANCA positivity in a MPA prone individual, the

finding that positive MPO-ANCA test prior to disease onset as shown in this case is of importance. In fact, increase of MPO-ANCA value or seroconversion of MPO-ANCA from negative to positive is suggestive of relapse in renal MPA [23].

Since the diagnostic criteria have changed during the patient's 20-year clinical course, we retrospectively validated the diagnosis of this case using the algorithm of Watts et al. for ANCA-associated vasculitis and polyarthritides nodosa [24]. This algorithm first differentiates eosinophilic granulomatosis with polyangiitis (EGPA) according to the American College of Rheumatology (ACR) and Lanham criteria, and then differentiates GPA by the ACR criteria, Chapel Hill Consensus Conference (CHCC) criteria, and GPA surrogate markers [24]. Finally, MPA/RLV is diagnosed by exclusion. At the time of her second renal biopsy, this patient did not have asthma, eosinophilia, neuropathy, chest X-ray changes, sinusitis, or histologically proven eosinophilic vascular infiltration, which suggest that the ACR and Lanham criteria for EGPA were not fulfilled. The patient also did not have

nasal, oral, subglottic, or retro-orbital involvement, and no granulomatous changes were noted in the biopsy specimen, so the ACR criteria, CHCC criteria, and GPA surrogate markers were not fulfilled. Therefore, the positive surrogate marker for renal vasculitis (positive urinalysis), positive MPO-ANCA, and histologically proven necrotizing glomerulonephritis led to the diagnosis of MPA/RLV. Symptoms that developed subsequently in this patient, such as cardiac tamponade and alveolar hemorrhage, indicate that the vasculitis was no longer limited to the kidneys, leading to a diagnosis of systemic vasculitis MPA. Her later symptoms were compatible with those of MPA as described in previous reports [2, 25]. Other conditions that may cause MPA-like symptoms, such as malignancy, infection, medications, and other rheumatic or vasculitic diseases, were not observed.

We have extensively reviewed and compared the three renal biopsy histologies in this case as shown in Table 1. Only mild increase in serum creatinine, proteinuria, and microscopic hematuria were seen in the first renal biopsy. The histology showed no sign of vasculitis in glomeruli,

Table 1 Comparison of extensive histologies in three renal biopsies in the present case

	First renal biopsy	Second renal biopsy	Third renal biopsy
Laboratory data			
Serum creatinine, mg/dL	1.0	2.6	3.3
Proteinuria, g/gCre	0.5	3.2	1.3
Hematuria, RBC/HPF	< 5	> 100	> 100
Histological classification of ANCA associate vasculitis ^a	No evidence of vasculitis	Sclerotic	Sclerotic
Number of glomeruli			
Total glomeruli	3	7	18
Global sclerosis	0	5	13
Segmental sclerosis	0	2	3
Crescent formation	0	1 (cellular)	0
Glomerular necrotic lesion	0	1	0
Glomerular infiltrate	0	0	1 (foam cell, granular cell)
Light microscopy			
Arteriole			
Arteriolar vasculitis	None	None	None
Hyaline change due to hypertension	Mild	Mild	Moderate
Interstitium			
Rate of interstitial fibrosis	Below 25% (protein cast present)	50%	Over 75%
Inflammatory cells	None	Lymphocytes, plasma cells, and macrophages	Lymphocytes, plasma cells, foam cells, and eosinophils
Immuno fluorescent	Negative	Negative	Negative
Electron microscopy	Mild mesangial matrix deposition	Mild mesangial matrix deposition, subendothelial edema, diffuse foot process effacement	Partial foot process effacement

Finding from light microscopy (glomeruli, arteriole, interstitium), immunofluorescent, and electron microscopy as well as laboratory data are presented

^aRefer to [27] for histological classification of ANCA associate vasculitis

Table 2 Previous reports of pregnancy in MPA patients

Case no.	Age at diagnosis of MPA	Age at conception	MPA activity before pregnancy	Medication before pregnancy	MPA relapse after delivery	References
1	22	32	Remission	None	None	
2	36	41	Remission	CS, AZA	CS, AZA	
3	25	31	Remission	CS, AZA	AZA	
4		31	Remission	AZA	None	
5	Not recorded	26 (twin)	Remission	CS, CYC, AZA	None	
6						
7	19	36	Remission	CS, AZA	CS	
8	17	35	Remission	MMF, AZA	CS, AZA	
9	25	25	N/A	None	PE, IVCY, mPSL pulse	
10	38	38	N/A	None	PE, IVCY, mPSL pulse	

Case no.	Fetal or newborn status	Pregnancy duration	MPA relapse after delivery	References
1	Neonatal pulmonary hemorrhage and renal involvement (responded to high-dose steroid therapy and plasma exchange)	33 weeks	Not recorded	[5]
2	Good health	38 weeks	Not recorded	[6]
3	Miscarriage at 6 weeks	N/A	None	[7]
4	3500 g, good health	39 weeks	None for 35 months	
5	2290 g, good health	36 weeks + 0 days (twin)	Relapse after 62 months	[8]
6	1860 g, cheilognathopalatoschisis, minor VSDs			
7	2900 g, good health	38 weeks + 3 days	Not recorded	[10]
8	2700 g, good health	38 weeks + 3 days	Not recorded	
9	1440 g, single pelvic kidney	35 weeks	Not recorded	[11]
10	Dilation and curettage	N/A	None for 9 months	[12]

CS corticosteroid, AZA azathioprine, CYC cyclophosphamide, IVCY intravenous cyclophosphamide, PE plasma exchange, mPLS methylprednisolone, VSD ventricular septal defect, N/A not applicable

arterioles, nor in interstitium even by electron microscopy. The histology was compatible with benign nephrosclerosis which changes are due to chronic hypertension. In fact, it has recently been reported that renal biopsy proven benign nephrosclerosis can have microscopic hematuria, proteinuria, and elevated serum creatinine [26]. Although, we must admit the limitation of this diagnosis; the possibility of latent ANCA-associated vasculitis could not be completely denied because the number of glomeruli obtained was only three. In the second renal biopsy, vasculitic changes were evident with glomerular crescent formation and necrotic lesion, and moderate interstitial fibrosis was found. These findings show that the vasculitis had developed between the first and second renal biopsy. The third renal biopsy revealed focal segmental glomerulosclerosis consistent with scarring changes by vasculitis. Progressive fibrosis in the interstitium and high rate of global sclerosis indicated that the kidney falls in the category of end stage renal disease.

There is little in the literature about pregnancy/delivery in women with MPA, but the available reports are summarized in Table 2. Eight reports describe a total of 15 pregnancies in nine women with MPA [5–12], and there are only two reports of patients developing MPA during pregnancy [11, 12]. (Note that the identical cases were reported in two different articles [5, 28].) Among the 15 pregnancies, descriptions of six pregnancies in two women are lacking (other than one preterm delivery) [9]. Therefore, Table 2 shows summarized information of ten fetus in nine pregnancies (twin was recorded in one pregnancy). One miscarriage, and one dilation and curettage made eight newborns in seven pregnancies. All the MPA patients were in remission, and no flare-up of MPA was reported in already diagnosed MPA patients. Immunosuppressive therapy during pregnancy was either none, corticosteroids alone, azathioprine alone, or combination therapy. Preeclampsia developed in three out of seven pregnancies and preterm delivery occurred in two out of seven pregnancies. Complications reported in the newborn infants were ventricular septal defect, cheilognathopalatoschisis, single pelvic kidney, and low birth weight. In three of seven pregnancies (42.9%), there were no complications in either the mother or the newborn infant. Conversely, physicians and obstetricians should be aware that more than half of the pregnancies were associated with preeclampsia and/or congenital anomalies or low birth weight. On the other hand, it is of note that pregnancy itself did not cause flare-up of MPA.

Our patient developed MPA after two pregnancies/deliveries, and MPO-ANCA was positive at least 4 years before the onset. Excluding exceptional cases of new onset MPA during pregnancy from previous reports as shown in Table 2, hypothesis that pregnancy is protective might be possible, because no flare-up of vasculitis was seen during pregnancy in these past reports. It is true that the burden of pregnancy

was observed in the second renal biopsy as shown by subendothelial edema in the present case, although we cannot deny the possibility that the patient might have developed MPA earlier without her two pregnancies/deliveries. Because MPO-ANCA, which is thought to be pathogenic, remains positive in pregnant MPA patients [6, 10], other unknown factors could be involved in modifying the activity of MPA during pregnancy. Yet, because the evidence regarding MPA and pregnancy is very limited, medical doctors should make case by case decisions.

In summary, we encountered an MPO-ANCA positive individual who developed MPA necrotizing glomerulonephritis after pregnancy and delivery. The present case provides evidence that MPO-ANCA positive women can develop MPA after pregnancy. Piling up of evidence is expected and associations between MPA and pregnancy should further be elucidated in the future.

Compliance with ethical standards

Conflict of interest All the authors have declared no competing interest.

Human and animal rights This article does not contain any studies with human participants performed by any of the authors.

Informed consent Informed consent was obtained from this patient.

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