Clinical Case Report

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Spontaneous remission of membranous glomerulonephritis with successful fetal outcome

A case report and literature review

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Abstract

Membranous glomerulonephritis (MGN) represents an immunologically mediated disease characterized by deposition of immune complexes in the glomerular subepithelial space. Persistent proteinuria at diagnosis predicts poor prognosis. Pregnancy with MGN is a risk of fetal loss and may worsen maternal renal function.

Here, we report a lady with MGN and proteinuria achieved spontaneous remission and successful fetal outcome naive to any medications. The 26-year old woman had 1-year history of persistent proteinuria (5.5–12.56 g/24 hours) and biopsy-proven MGN. Histopathological characteristics included glomerular basement membrane spikes, subepithelial monoclonal IgG immunofluorescence, and diffuse electron dense deposits. She was sticking to a regular morning exercise routine without any medications. After successful delivery of a full-term baby girl, the mother had improved proteinuria (0.56 g/24 hours) and albuminuria (351.96 g/24 hours contrasting 2281.6 g/24 hours before pregnancy). The baby had normal height and body weight at 4 months old.

We identified more pregnancies with MGN in 5 case reports and 5 clinical series review articles (7–33 cases included). Spontaneous remission of maternal MGN with good fetal outcome rarely occurred in mothers on immunosuppressive therapy.

Mothers naive to immunosuppressive therapy may achieve spontaneous remission of maternal membranous glomerulonephritis and successful fetal outcome. Theoretically, fetus might donate stem cells to heal mother's kidney.

Abbreviations: GBM = glomerular basement membrane, MGN = membranous glomerulonephritis, PAS = periodic acid–Schiff, PLA2R = phospholipase A2 receptor, PLA2R-AB = anti-PLA2R autoantibodies.

Keywords: membranous glomerulonephritis, nephrotic syndrome, pregnancy, proteinuria, stem cell

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Y-MH, H-RZ, and LZ contributed equally to this work.

Authorship: Research idea and study design: Y-MH, LZ, and H-RZ; data acquisition: LZ and H-RZ; data analysis/interpretation: Y-MH and H-RZ; statistical analysis: K-KY; Attending physician: J-XL; Revision of the manuscript, approval of the submission and supervisor: H-LZ. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. H-LZ takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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1. Introduction

Membranous glomerulonephritis (MGN) is one of the most common forms of nephrotic syndrome histopathologically characterized by thickening glomerular basement membrane (GBM) and subepithelial deposition of immune complexes.[1] Clinical presentations of MGN include generalized edema and asymptomatic proteinuria. MGN can be idiopathic, accounting for estimated 70% to 80% of cases[2] and secondary to infections, cancer, systemic lupus erythematosus, and drug intoxication. Deterioration in renal function and development of end-stage renal disease occur in approximately 40% of the patients with idiopathic MGN.[2] The amount of proteinuria at the diagnosis of MGN is an important determinant of prognosis.

The impact of pregnancy with MGN on the maternal and gestational outcomes remains unclear. On the one hand, pregnancy could influence the maternal kidney problems. On the other hand, the kidney disease could impact the gestational outcomes. Pregnancy with MGN is associated with increased fetal loss and, in some instances, a progressive loss of maternal renal function.[3] Presence of persistent proteinuria during the pregnancy is an important risk for poor fetal and poor maternal outcomes.[4] Spontaneous remission of MGN with successful maternal and fetal outcomes has rarely been reported. Here, we present a case report of spontaneous disease remission without medication, followed by literature reviews concerning the impact of pregnancy with MGN on the maternal and fetal outcomes.

2. Case report

2.1. The pregnant lady

The 26-year-old Chinese lady was an immigrant from the Inner Mongolia and incidentally found in the 8th week of pregnancy. She had being lived on cow milk products for 24 years in Inner Mongolia before she married a man in Guilin. As an aboriginal inhabitant, fresh milk and milk products were her favorite. She had 1-year history of renal biopsy-proven MGN with persistent proteinuria (2.5–5.5 g/24 hours). The lady was admitted to the Affiliated Hospital of Guilin Medical University in March 2014.

2.2. Clinical history and initial laboratory data

The patient was first admitted to the People's Hospital of Guilin with complaints of generalized edema in her face and legs in March 2013. No other abnormalities had previously been detected on her annual physical examinations.

The results of physical examination revealed normal, except for 2+ pitting pretibial edema and lower eyelids swelling. Laboratory measurements were as follows: total serum protein, 44.8 g/L (normal 60–80 g/L); albumin, 24.6 g/L (normal 35–50 g/L); total cholesterol, 7.91 mmol/L (normal 3.1–6.0 mmol/L), triglycerides, 1.22 mmol/L (normal 0.48–1.6 mmol/L), high-density lipoprotein, 1.49 mmol/L (normal 1.0–1.9 mmol/L); and low-density lipoprotein, 4.43 mmol/L (normal 2.1–3.36 mmol/L). The levels of liver enzymes, blood electrolytes, and the results of blood routine examination were basically within the normal ranges. Urinalysis showed the presence of urine dipstick protein of 3+, 24-hour urine protein level of 5.5 g/day (normal 0.04–0.23), blood urea nitrogen of 2.65 mmol/L (normal 3.2–7.5 mmol/L), and creatinine of 55.5 μmol/L (normal 44–115 μmol/L).

2.3. Histopathological examination

She was hospitalized to have percutaneous kidney biopsy performed on the 21st March, 2013. Renal tissues were obtained by core needle biopsy under ultrasound control on the basis of written informed consent from the patient. One third each of the renal biopsy specimen was processed for histochemical stains (HE, periodic acid-Schiff [PAS], periodic Schiff-methenamine, and Masson trichrome) with light microscopy; immunofluorescence stains for the monoclonal IgG, IgA, IgM, C1q, and C3c; and ultrastructural examination with transmission electron microscopy (Supplementary methods, http://links.lww.com/MD/B76).

PAS stain with light microscopy showed diffused thickening of GBM (Figs. 1–4). Mesangial expansion, proliferation, and

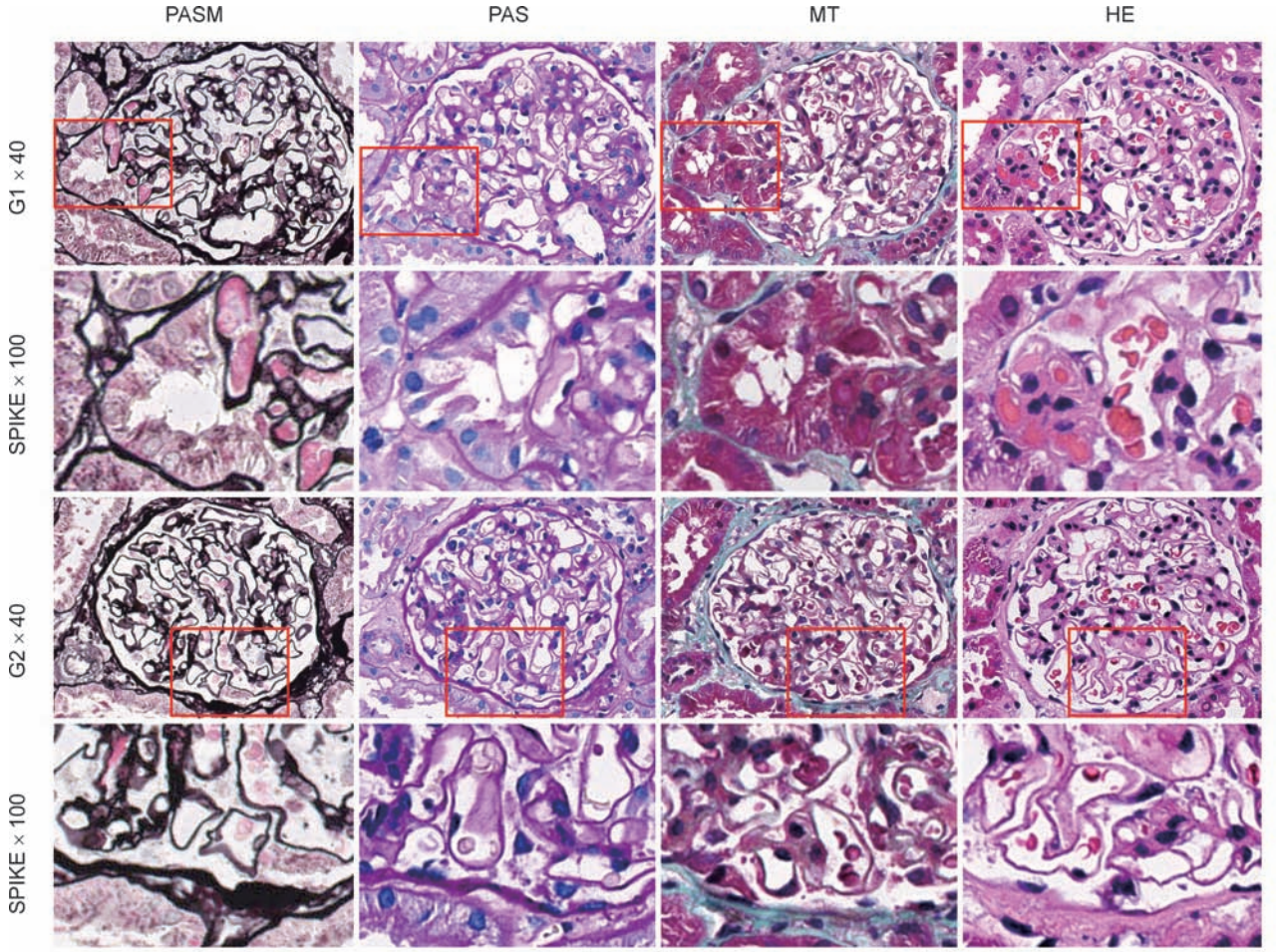

Figure 1. Diffuse glomerular basement membrane thickening with formation of spikes due to subepithelial deposits of immune complexes. Serial sections of the renal biopsy were sequentially stained with PASM, PAS, MT, and HE, and observed by light microscopy. The characteristic glomerular wall thickening and spikes are more evident by PASM compared to other stains. In the 1st glomerulus (G1), the spikes appear adjacent to the glomerular urinary pole. In the second glomerulus, the spikes form adjacent to Bowman capsule. The square frames of the two glomeruli (original magnification × 400) indicate the spikes shown at higher magnification in the 2nd and 4th panels (original magnification × 1000). PAS = periodic acid–Schiff, PASM = periodic Schiff-methenamine.

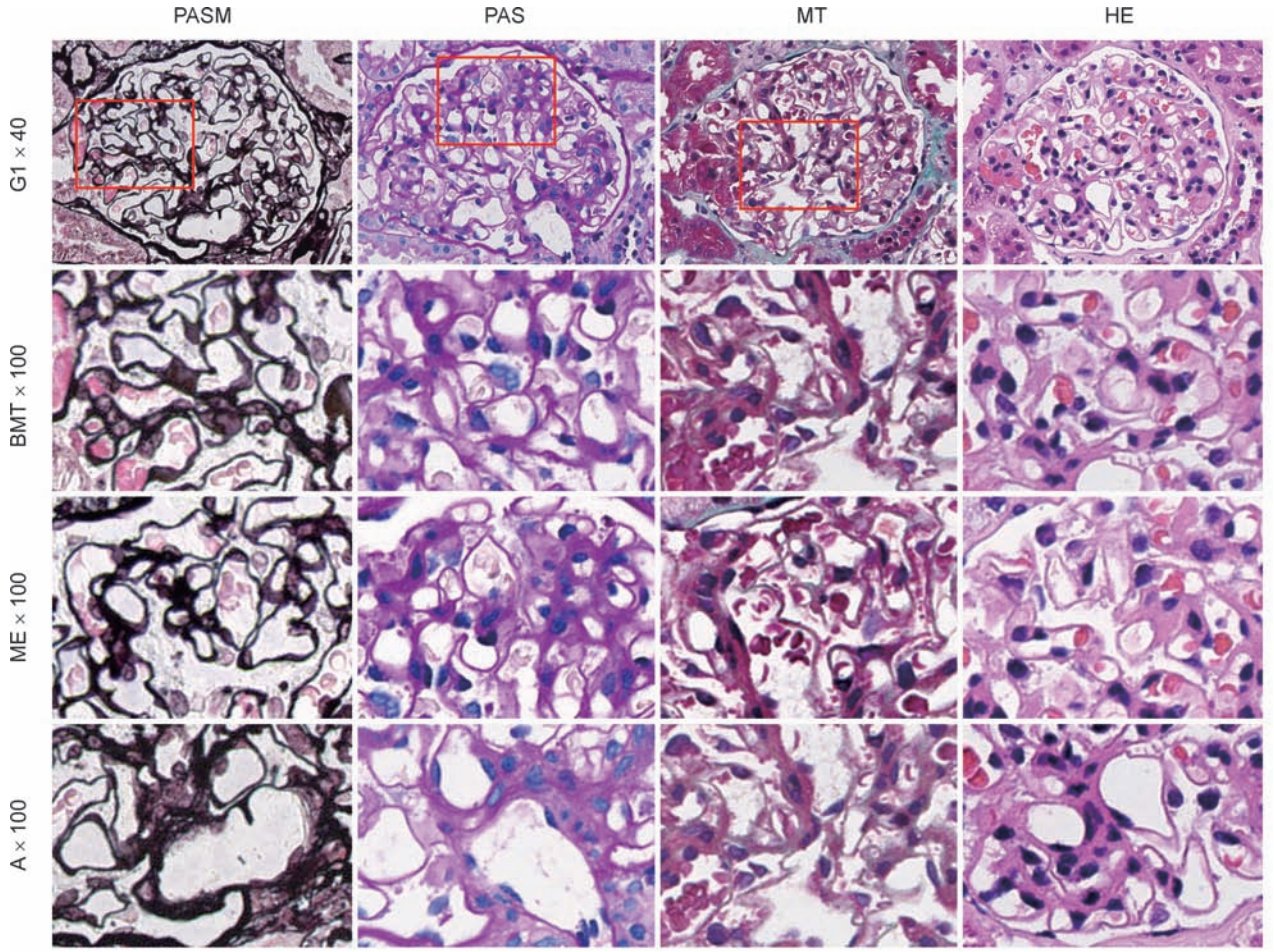

Figure 2. Histopathologic changes of glomerular arterioles and mesangial areas other than diffuse glomerular basement membrane thickening. Serial sections of the renal biopsy were sequentially stained with PASM, PAS, MT, and HE, and observed by light microscopy. The characteristic glomerular membrane thickening is consistently more evident by PASM compared to other stains. In the glomerulus, no mesangial expansion (ME) is seen whereas the efferent arteriole shows mild hyalinosis. The square frames of the glomerulus (original magnification × 400) indicate the histopathological changes shown at higher magnification in the 2nd, 3rd, and 4th panels (original magnification × 1000). HE = hematoxylin-eosin, MT = Masson's trichrome, PAS = periodic acid–Schiff, PASM = periodic Schiff-methenamine.

sclerosis, and hyalinosis of glomerular arterioles and intralobular arteries were not significant.

Silver stain of periodic Schiff-methenamine highlighted the irregular GBM thickening due to subepithelial deposits to form spikes (Figs. 1–4). The spikes were not evident by stains of HE, PAS, and Masson trichrome.

Immunofluorescence microscopy demonstrated strong global granular GBM reactivity for IgG (3+, Fig. 5). Immunofluorescence for IgA, IgM, C1q, and C3c was not significant.

Electron microscopy pinpointed diffuse, irregular, and numerous electron-dense deposits along the GBM in subepithelial spaces (Fig. 6).

Tubular changes mainly occurred in the proximal convoluted tubules and were characterized by loss of tubular brush border and formation of lipid peroxidation (Fig. 3). Characteristic changes in interstitial compartments were lipid-laden foam cell infiltration (Fig. 4).

3. Diagnosis

All the stained slides for light microscopy and micrographs of immunofluorescence stains and transmission electron microscopy were checked by 3 distinguished renal pathologists independently working at the General Hospital of People's Liberation Army (Beijing), the KingMed Diagnostic (Guangzhou), and the University Affiliated Hospital (Guilin). All the 3 pathologists reviewed the clinical manifestations of this case and uniformly issued a pathology report of idiopathic MGN. The diagnosis of idiopathic MGN was based on the histopathological characteristics after differentiation from glomerular changes secondary to neoplasms, infections, and any other autoimmunity diseases.

3.1. Clinical follow-up

The lady with MGN insisted on taking no medications because of the concerns of adverse drug effects on pregnancy. Physical examination at the Affiliated Hospital of Guilin Medical University showed her body temperature 36.8 °C, pulse rate 85 beats per minute, and blood pressure 111/65 mm Hg. In her 1st trimester (8th week), urine protein shot up 12.56 g/day and edema was generalized simultaneously with the onset of hypoalbuminemia (Fig. 7). She consulted 3 leading national experts of clinical nephrology who strongly recommended termination of the pregnancy. Nonetheless, the patient determined to carry on her baby without using any medications. Instead, she often walked for 3 hours in the morning and kept

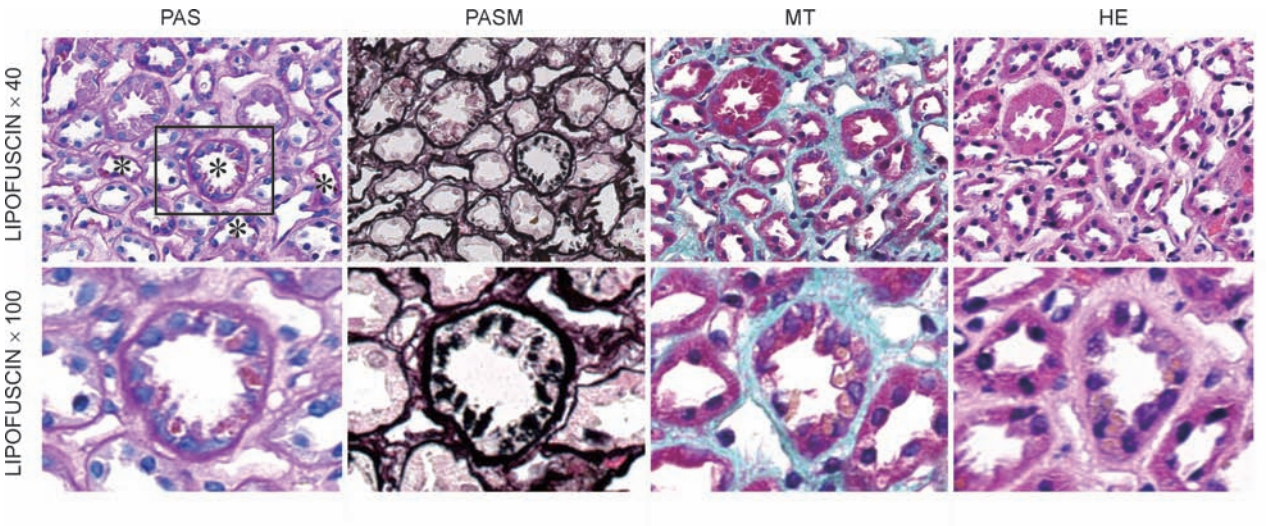

Figure 3. Lipofuscin pigments in the renal tubular cells. Serial sections of the renal biopsy were sequentially stained with PAS, PASM, MT, and HE, and observed by light microscopy. Lipofuscin pigments in the tubular cells are consistently more evident by PAS (asterisk) compared to other stains. The square frame of the tubule (original magnification × 400) indicates the pigments shown at higher magnification in the 2nd panel (original magnification × 1000). PAS = periodic acid–Schiff, PASM = periodic Schiff-methenamine.

talking to her fetus during lower abdominal pain and vaginal bleeding.

In the 13th week of gestation, test of 24-hour urine protein level declined to 3 g/day with urine albumin extraction rate of 2281.6 mg/24 hours. She was encouraged by the laboratory findings and persisted on walking in the morning. By September 2014 (31 weeks of gestation), her body temperature was 36.7 °C, pulse rate 89 beats per minute, and blood pressure 115/69 mm Hg. Serum measurements were as follows: total protein, 57.2 g/L; albumin, 36.1 g/L; total cholesterol, 5.59 mmol/L; triglycerides, 3.29 mmol/L; high-density lipoprotein, 3.14 mmol/L; and low-density lipoprotein, 1.24 mmol/L. Cardiotocography revealed normal fetal heart rate and uterine activity. Prenatal ultrasound tests also showed normal placenta location, amniotic fluid volume (6.4 cm), head presentation, and umbilical cord.

During the 10 months of pregnancy, her edema and proteinuria substantially waned (Fig. 8). Her lower abdominal pain and vaginal bleeding gradually disappeared.

The delivery was realized at the Guilin Women and Children's Hospital. Laboratory tests showed significant improvement in serum lipid and albumin profile (Fig. 7). A baby girl was born by spontaneous vaginal delivery at 40 weeks of gestation. Her birth weight was 2.2 kg. Apgar scores at 1 and 5 minutes were consistently 10. She was breastfed exclusively whereas her height and body weight at 4 months old reached normal (Fig. 9).

The mother was discharged to home on the 3rd postpartum day. Figure 7 showed at 1 month postpartum her improvement in

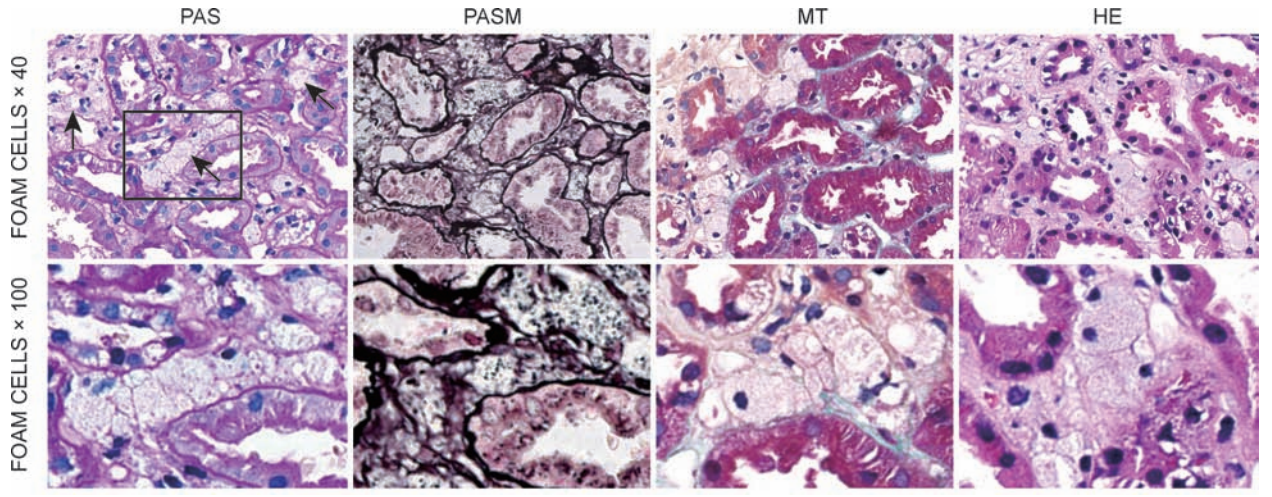

Figure 4. Lipid-laden foam cells in the renal interstitium. Serial sections of the renal biopsy were sequentially stained with PAS, PASM, MT and HE, and observed with light microscopy. Parches of lipid-laden form cells (arrow) are shown by all the histochemical stains. The square frame of PAS stain (original magnification × 400) indicates the foamy cells shown at higher magnification in the 2nd panel (original magnification × 1000). PAS = periodic acid–Schiff, PASM = periodic Schiff-methenamine.

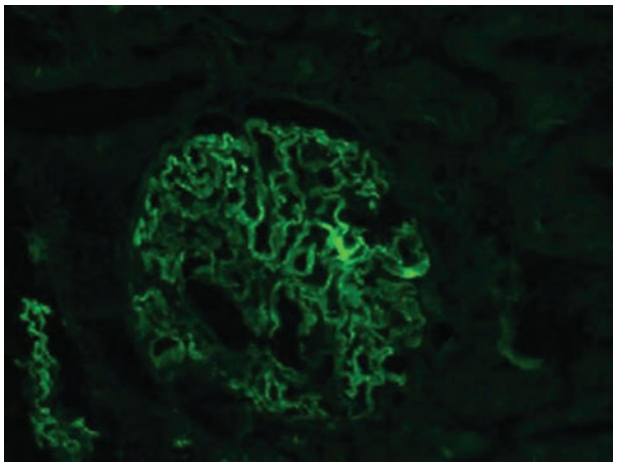

Figure 5. Diffuse granular capillary loop staining for IgG. Serial sections of the renal biopsy were sequentially stained for IgG, IgM, C1q, and C3c, and observed by immunofluorescence microscopy. The immunofluorescence deposition for IgG (original magnification × 400) is granular and diffuse along the basement membranes of the glomerular capillary loops. Immunofluorescence for IgA, IgM, C1q, and C3c is not significant.

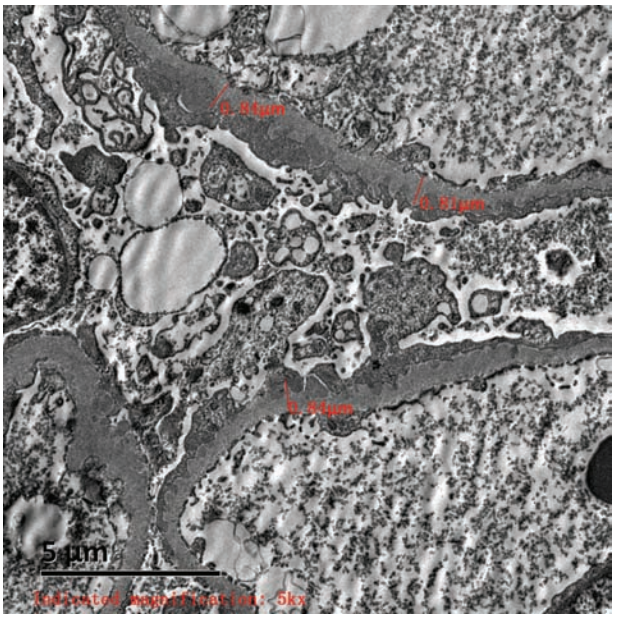

Figure 6. Diffuse subepithelial deposition of electron dense substances. Electron microscopy illustrates numerous darker electron dense immune deposits seen scattered within the thickened basement membrane. The subepithelial deposits by electron microscopy correspond to the spikes seen with the silver stain.

Changes of laboratory measurements during pregnancy

Gestation period	progestation (March 2013)	8th week (March 2014)	13rd week (May 2014)	31st week (September 2014)	40th weeks (Parturition)	postpartum (December 2014)	Reference value
Proteinuria, g/24 h	5.5	12.56	3			0.56	0.04-0.23
Microalbuminuria, mg/24 h			2281.6			351.96	
TC (mmol/l)	7.91	6.62		5.59	5.77		3.1-6
TG (mmol/l)	1.22	0.95		3.29	3.78		0.48-1.6
HDL (mmol/l)	1.49	5.39		3.14	3.35		1-1.9
LDL (mmol/l)	4.43	2		1.24	1.47		2.1-3.36
TP (g/l)	44.8	59.6		57.2	60		60-80
ALB (g/l)	24.6	28.83		36.1	37.8		35-50
SCr (μmol/l)	55.5	37.8		39.1	48.6		44-130

TC. Total cholesterol; TG. Triglyceride; HDL. High density lipoprotein; LDL. Low density lipoprotein; ALB. Serum albumin; SCr. Serum creatinine.

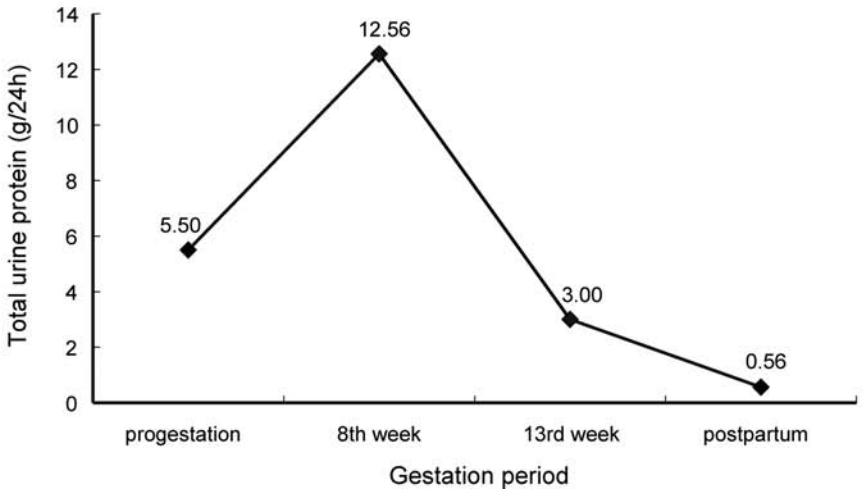

Figure 7. Changes of laboratory measurements during pregnancy.

Figure 8. Remission of edema during pregnancy.

proteinuria (0.56 g/24 hours) and albuminuria (351.96 mg/24 hours after delivery in contrast to 2281.6 mg/24 hours before pregnancy).

3.2. Literature reviews

We have identified more pregnancies with MGN in 5 case reports and 5 clinical review articles. Tables 1 and 2 summarize the characteristics of neonates and pregnant women with MGN. In the pooled analysis, the rate of fetal loss consisted of 3.3% abortion and 3.3% perinatal mortality in the pregnant mothers with MGN on immunosuppressive therapy. Moreover, 6.6% of preterm delivery and 10% of low birth weight were recorded. In other 3 reports without information of the specific medications, the rate of fetus loss was as high as 24%. Successful delivery was reported in 7 of the 9 pregnancies (77.8%) naive to any drug treatment. In the 5 case reports of pregnancy with MGN, all mothers but 1 received drug treatment during gestation. Three out of 4 neonates were healthy in contrast to 1 therapeutic abortion at the 21st week of pregnancy. Vaginal delivery and exclusive breastfeeding were reported in 1 mother. Spontaneous remission of maternal MGN with good fetal outcome rarely occurred in mothers on immunosuppressive therapy.

4. Discussion

For the 1st time, we report a case of spontaneous remission of proteinuria MGN with successful fetal outcomes naive to any medications. Although the presence of persistent proteinuria during the pregnancy predicts poor fetal and poor maternal outcomes,[4] this lady with persistent proteinuria is exceptionally successful with regular morning exercise. Findings from our literature review also highlight the point that spontaneous remission of maternal MGN with good fetal outcome rarely happens in the mothers on immunosuppressive therapy.

Mechanisms underlying spontaneous remission of MGN and successful fetal outcomes without any medication are not fully understood. Theoretically, fetus can donate stem cells to heal the mother's kidney. In human and animal pregnant experiments, fetal cells are capable to traffic to the mother's circulation. The traffic cells are described as microchimerism now increasingly being recognized for their healing, reparative, and regenerative potentials.[5] Indeed, Lee et al[6] have found that microchimeric cells are pluripotent stem cells that can be efficiently induced to repair damages. For example, mouse fetuses can release sufficient number of stem cells to repair their mother's heart.[7] The discovery could explain why half the women with heart problems during or just after pregnancy recover spontaneously. Previous studies have shown fetal stem cells in other damaged organs of pregnant women, including the brain, liver, kidney, lung, and endocrine disorders.[8–10,11] Furthermore, fetuses also produce cells that are known to protect the mother against breast cancer.[12] In the present study, spontaneous remission of MGN might in part relate to the healing capacity of stem cells from the fetus. Therefore, the fetal stem cells in the mother may represent an evolutionary mechanism that the fetus promotes its own survival by protecting its mother's health.

The mother in the study has resided in Inner Mongolia, the largest source of fresh milk and milk products in China, for more than 20 years. As an aboriginal inhabitant, fresh milk and milk products are always her favorite dietary choice. Based on the findings from the prior studies, the presence of antibovine serum albumin antibody and bovine serum albumin antigen in

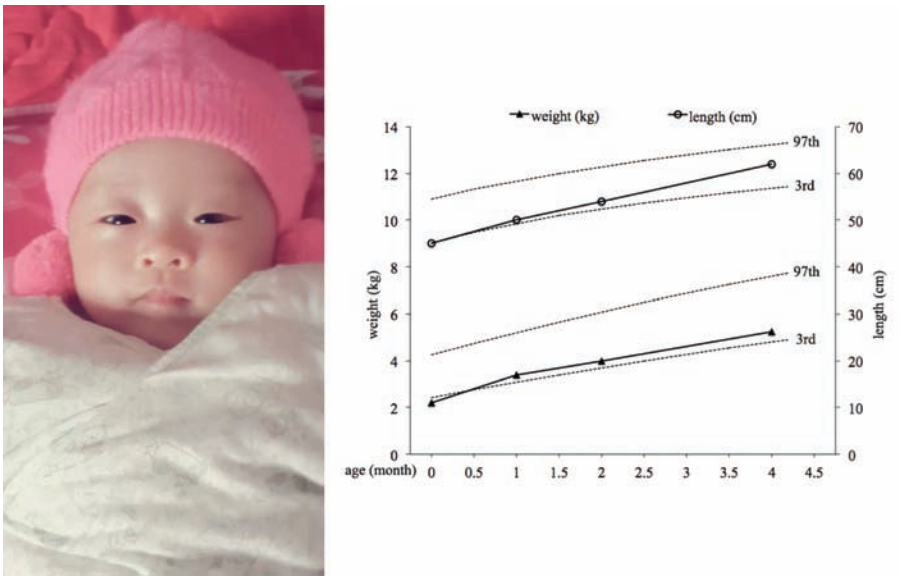

Figure 9. The 2-month-old infant girl and her growth chart.

circulation could facilitate the deposition in glomerular subepithelial space to form the characteristic spikes in MGN.[13,14] Cow's milk is a major source of bovine serum albumin. Mothers with prolonged exposure to milk may be at risk for the development of idiopathic MGN. Discontinuation and reduction in milk albumin intake may also help to achieve spontaneous remission of MGN. On the other hand, high levels of circulating antibovine serum albumin antibodies and circulating cationic bovine serum albumin are found in 4 out of 9 children with MGN.[14] Improvement may be sustained by eliminating cow's milk and beef protein from the diet.

In addition to the bovine serum albumin, the other possible target antigens associated with idiopathic MGN are the podocyte proteins M-type phospholipase A2 receptor (PLA2R) and neutral

Table 1

Summary of the 5 case reports.

Number	First author	Year	Diagnosis	Maternal age (years)	Renal biopsy	MGN duration before pregnancy	Drug treatment
1	Bates[1]	1996	Hepatitis B-associated membranous glomerulonephritis	19	Yes	8 years	Unclear
2	Katzir[2]	2004	Primary membranous glomerulonephritis	23	Yes	8 years	Yes
3	Sebestyen[3]	2008	Primary membranous glomerulonephritis	33	Yes	5 years	Yes
4	Szucs[4]	2010	Primary membranous glomerulonephritis	27	Yes	10 years	Yes
5	Aoshima[5]	2013	Primary membranous glomerulonephritis	37	Yes	NS → pregnancy → MGN	Yes

Drugs	Obstetric history	Gestational duration (weeks)	Mode of delivery	Condition of neonate	Breastfeed	Maternal remission/outcomes
Unclear	G1P1	40	Induction	Unclear	Unclear	Partial
Methylprednisolone, prednisone	G1P1	34	Cesarean	Healthy	Unclear	Partial
Methylprednisolone, azathioprine, antihypertensive, diuretic, anticoagulant therapy, and supplementation with fresh frozen plasma and albumin received	G3P2	33	Cesarean	Healthy (required pharynx oxygen for only 2 days)	Unclear	Complete remission at 3 months postpartum; relapse during 4-year follow-up; eventually hemodialysis 3 times a week
Amlodipine	G1P1	39	Vaginal	Healthy	Exclusive breastfeeding	Stable renal function
Prednisolone, methylprednisolone, prednisolone	G2P1	21	Elective Abortion	_	_	Partial

References in the table were listed in the supplementary references, http://links.lww.com/MD/B76. MGN = membranous glomerulonephritis, NS = nephrotic syndrome.

Table 2

Summary of the 5 review articles.

Number	First author	Year	Diagnosis	Renal biopsy	Drug treatment	Pregnancies	Condition of fetus	Maternal remission/outcomes
1	Noel[6]	1979	Primary membranous glomerulonephritis	Yes	No	9 (7 women)	One abortion, one anencephalic child, 7 successful delivery	One with increased level of proteinuria, the other 6 with no modification of clinical status
2	Surian[7]	1984	Primary and secondary membranous nephropathy	Yes	Unclear	8	Unclear	1 With reversible deterioration of renal function, no complications reported in the remaining 7 ladies
3	Barcelo[8]	1986	Membranous glomerulonephritis	Yes	Unclear	9 (7 women)	7 Full-term, 2 pre-term, no still births and abortion	3 With increased blood pressure, 2 with increased proteinuria, no declined renal function was noted in the others
4	Packham[9]	1987	Membranous glomerulonephritis	Yes	Unclear	33 (24 women)	24% (8) Fetal loss, 43% (14) prematurity rate and 33% (11) live birth rate with full-term deliveries	During 6 months postpartum follow up: 9% (3) with hypertension, 18% (6) with increased proteinuria, 12% (4) with stable proteinuria, 36% (12) remission of proteinuria
5	Malik[10]	2002	Primary membranous glomerulonephritis	Yes	Yes	30	6.6% (2) Fetal loss (include 3.3% spontaneous abortion, 3.3% prenatal mortality); 90% live birth rate (include 10% low-birth-weight babies, 10% cesarean section, 6.6% preterm delivery)	1 Develop renal insufficiency after 6 years follow up

References in the table were listed in the supplementary references, http://links.lww.com/MD/B76.

endopepdidase. Antibodies to neutral endopeptidase have been found in the subepithelial deposits in a subset of patients with antenatal MGN.[15] PLA2R has been identified as a major target antigen of idiopathic MGN in adults.[16] Circulating anti-PLA2R autoantibodies (PLA2R-AB), primarily of the IgG4 subclass, bind to PLA2R to form the subepithelial immune complex deposits. The prevalence of PLA2R-AB was found in 52% to 78% of adults with biopsy-proven primary MGN.[17–19] In these patients, serum level of the autoantibodies has correlated strongly with clinical status and proteinuria.[18] In patients with secondary MGN or other renal diseases, the autoantibodies are generally absent. Therefore, the PLA2R-AB may serve as an indicator for the diagnosis of primary MGN and response to treatment. In this case report, we do not have the data of autoantibodies to PLA2R and neutral endopepdidase due to the limited kidney biopsy specimen. The exact target antigens in this case are not clear.

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