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Familial collapsing glomerulopathy: Clinical, pathological and immunogenetic features

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Familial collapsing glomerulopathy: Clinical, pathological and immunogenetic features.

Background. Collapsing glomerulopathy (CG) is an aggressive form of glomerular injury frequently seen in association with HIV infection, although it is also recognized in non-HIV patients as a primary disease. Until now, the occurrence of CG in a familial pattern has not been reported.

Methods. We studied five members of a family (siblings), admitted for evaluation of proteinuria and nephrotic syndrome. They had no other family history of renal disease. Blood samples for major histocompatibility complex (MHC) analysis were obtained from the five siblings, both parents and four relatives.

Results. Renal biopsy performed in four out of the five siblings revealed capillary collapse and retraction with visceral epithelial cell swelling and reabsorption droplets, consistent with CG. Two of the patients had suggestive symptoms of systemic lupus erythematosus, such as arthritis, rash, hair loss, moderate leukopenia and lymphopenia, low titers of antinuclear antibodies (ANA) and anti-SSA/Ro antibodies, but no immune complex deposition on renal biopsy. IgG serology for parvovirus B19 (PVB-19) was positive only in two siblings but polymerase chain reaction (PCR) was negative. Immunogenetic analysis showed that all patients shared the same MHC haplotype inherited from the mother.

Conclusions. CG can present in a familial pattern. Since a similar MHC haplotype was observed in affected and non-affected members of the family, we conclude that the environment plays an important role in the development of the disease.

Collapsing glomerulopathy (CG) is a well-defined form of glomerular injury. In 1986, Weiss et al described six cases with nephrotic syndrome, progressive irreversible renal failure and characteristic histopathological changes [1]. Histopathological changes in this disease consist of glomerular capillary retraction or collapse and visceral epithelial cell swelling accompanied by tubular cystic dilatation and interstitial fibrosis [1]. Clinically, patients present nephrotic syndrome with profuse proteinuria and a rapid course to end-stage renal failure or death due to complications of nephrotic syndrome [2]. The diagnosis of primary CG requires a lack of evidence for human immunodeficiency virus (HIV) infection, since HIV-nephropathy can be morphologically and clinically indistinguishable [2–8]. The presentation of renal disease in a familial pattern has been described in a variety of entities that includes: autosomal recessive polycystic kidney disease [9], thin basement membrane disease [10] and Alport disease [11], all of them recognized as hereditary renal diseases, as well as in families with focal and segmental glomerulosclerosis (FSGS) [12]. Nevertheless, it has not been reported in patients with collapsing glomerulopathy. We report the clinical, pathological and immunogenetic findings in a family with collapsing glomerulopathy.

Key words: familial nephrotic syndrome, renal disease, glomerular injury, inheritance, MHC haplotype, HIV infection.

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METHODS

Patients

Five members of a family (siblings) with no other family history of renal disease were admitted for clinical evaluation. The patients belonged to a Mexican-Mestizo population and had no evidence of HIV infection or intravenous drug use. Four of these patients underwent a renal biopsy that fulfilled diagnostic criteria for collapsing glomerulopathy. Other family members including both parents and four relatives (two grandparents, one uncle, and one aunt) were screened for abnormal urinary sediment and protein excretion; their levels of serum creatinine, electrolytes, and cholesterol were determined. All of the results were either normal or negative. An immunogenetic evaluation also was performed.

Histological diagnosis

The diagnosis of CG was based on light microscopy findings of focal and segmental, or global glomerular capil-

Table 1. Major clinical and laboratory data in the five patients

Patient	Gender/age	Proteinuria *g/day*	Symptoms	ANA
1 III-7	F/21	4.8	Edema arthralgias	1:160
2 III-9	F/22	6.5	Edema arthralgias	Neg
3 III-11	M/20	5.3	Edema Fatigue	Neg
4 III-8	F/14	8.0	Edema arthralgias	1:640
5 III-10	M/7	Trace	None	Neg

Abbreviations are: ANA, antinuclear antibodies; Neg, negative.

lary collapse, prominence of visceral epithelial cells by hypertrophy or hyperplasia with prominent periodic acid-Schiff (PAS) positive droplets and tubulointerstitial changes. All cases presenting at least one glomerulus with features of capillary collapse, as previously described [1], were considered to have CG. Two to three cores of renal tissue were processed for light and electron microscopy and direct immunofluorescence, according to standard techniques [13]. Sections for light microscopy were stained with hematoxylin and eosin (H&E), PAS, Mallory trichrome and Jones' methenamine silver staining. An average of 15 ± 6 (range 7 to 23) glomeruli per level of section in each sample were examined. All biopsies were evaluated for the presence of immune deposits by direct immunofluorescence (IF). One core of frozen renal tissue was stained with fluorescein isothiocyanate (FITC)-bound monoclonal antibodies against IgG, IgM, IgA, C1q, C3, albumin and fibrinogen (Dako Corporation, Palo Alto, CA, USA). Three to five glomeruli were examined per case. Fluorescence intensity was evaluated in a semiquantitative form on a scale of 0 to 3+, where: 0 = negative, 1+ = weak, 2+ = moderate, and 3+ = strong. Electron microscopy examination was performed in all cases looking for the presence of tubuloreticular structures in the cytoplasm of endothelial cells of glomerular capillary loops and capillaries of the interstitium. At the ultrastructural level we also analyzed wrinkling of the capillary loop basement membrane, visceral epithelial cell foot processes obliteration, and the presence of droplets and vacuoles within the podocytes. All renal biopsies were examined by an experienced renal pathologist.

DNA extraction

Genomic DNA from whole blood was extracted by standard techniques [14].

MHC typing

Generic variants of human lymphocyte antigen (HLA)-A, HLA-B, HLA-DR, HLA-DQA and HLA-DQB in five siblings, both parents and four relatives were determined by polymerase chain reaction with sequence specific primers (PCR-SSP; Pel-Freez, Brown Deer, WI, USA) and electrophoresis in 2% agarose gel with ethidium bromide. Interpretation of the results was carried out using a computer program designed for such purpose (Pel-Freez).

RESULTS

The clinical history of the patients is presented in Table 1.

Patient 1 (III-7). A 21-year-old woman was admitted to the hospital in June 1997 with an 18-month history of edema of the hands and legs. She also complained of arthralgias involving the knees and ankles. Physical examination revealed palpebral edema, hair loss, photosensitivity, Raynaud's phenomenon, and synovitis in metacarpophalangeal joints, proximal interphalangeal joints, and knees. Laboratory tests revealed serum creatinine at 0.89 mg/dL, and creatinine clearance at 42.3 mL/min. Urinalysis showed granular and hyaline casts, and albuminuria 4.8 g/24 h. Other tests revealed cholesterol 232 mg/dL, triglycerides 190 mg/dL, lymphopenia 1.3×10^9, erythrocyte sedimentation rate (ESR) 50 mm/h, antinuclear antibodies (ANA) 1:160, anti-SSA/Ro positive, CH50 160 (80-320 mg/dl), C3 99 (>75 mg/dL), and C4 13 (>13 mg/dL). Screening tests for HIV, parvovirus B19 (PVB-19), and hepatitis B and C virus (HBV and HCV) infection were negative. A diagnosis of systemic lupus erythematosus (SLE) was suspected and prednisone (1 mg/kg/day for 3 months) was started after the renal biopsy was performed.

Patient 2 (III-9). A 22-year-old female was admitted in August 1997, with an 18-month history of fatigue, hair loss, arthralgias in hands, knees and ankles. On admission, hypertension (150/100 mm Hg), malar rash and generalized edema were detected. Urinalysis revealed erythrocytes 3+, proteinuria 6.5 g/day, serum creatinine 1.18 mg/dL, creatinine clearance 137 mL/min, cholesterol 279 mg/dL, and triglycerides 175 mg/dL. Antinuclear antibodies, anti-DNA antibodies (*Crithidia lucilae*), HIV screening, anti-PVB-19 serology (IgG and IgM) and DNA (PCR) in peripheral blood, were normal or negative. She received captopril 25 mg/day for six months. A renal biopsy was performed.

Patient 3 (III-11). A 20-year-old male was admitted to the hospital in October 1997 with a six-month history of edema of pelvic extremities and fatigue. He had a positive history for smoking (2 packages/day), cocaine and marihuana consumption, and alcoholism (3 oz/day). On admission he was found hypertensive (BP 140/95 mm Hg). Urinalysis revealed proteinuria 5.3 g/day, urinary sediment did not show granular or red blood cell casts, serum creatinine was 0.89 mg/dL, creatinine clearance 109 mL/min, cholesterol 194 mg/dL, triglycerides 169 mg/dL, C3 117 mg/dL (normal >75 mg/dL), C4 25

mg/dL (nl >13 mg/dL). Antibodies to HIV, HBV and HCV were negative. Anti-PVB-19 IgG was positive (5.3) and anti-PVB-19 IgM negative. He was treated with captopril 50 mg/day for eight months. A renal biopsy was performed.

Patient 4 (III-8). A 14-year-old female was admitted in January 1998. Her prior medical history was unremarkable; however, two months before admission she developed cough and hyaline rhinorrhea and was treated with penicillin for seven days. Two weeks later she noticed frothy urine. Two days before admission she developed dyspnea and edema of both legs. On admission, physical examination revealed BP 124/76 mm Hg, rash, photosensitivity, and edema of both legs. Laboratory tests showed proteinuria 8 g/day, serum creatinine 0.85 mg/dL, creatinine clearance 67 mL/min, lymphopenia 1.3×10^9, and antinuclear antibodies homogeneous and in a fibrillar pattern 1:640. PVB-19 serology (IgG and IgM) and DNA (PCR) were negative. A diagnosis of SLE was suspected, and she was started on prednisone 1 mg/kg/day for one year, and captopril 50 mg/day for one year. Before starting any treatment, a renal biopsy was performed.

Patient 5 (III-10). A 7-year-old male was admitted to the hospital in March 1998 because of the family history of renal disease. Medical history was positive for neurodermatitis affecting the neck, arms and legs. He was asymptomatic. Urinalysis revealed microscopic hematuria and trace proteins; urinary sediment showed no cellular casts; serum creatinine was 0.7 mg/dL, creatinine clearance 97.7 mL/min, cholesterol 190 mg/dL, and triglycerides 150 mg/dL. Anti-PVB-19 antibodies (IgG) were positive (5.8), while IgM antibodies and DNA (PCR) were negative. Serology for HIV, HBV and HCV was not performed.

Follow-up

Patients were lost to follow-up in this institution. Clinical data at the last outpatient visit, two years after renal biopsy, showed that all patients had persistent proteinuria in the nephrotic range (<10 g/day) without progression to end-stage renal disease (ESRD; serum creatinine <2 mg/dL). The youngest sibling was seen at the outpatient visit one year later (April 1999); he had trace proteinuria and microhematuria in the urinalysis.

Pathological examination

Renal biopsy material from four siblings was available. Histological examination in all cases revealed the presence of glomerular capillary collapse and retraction of the tuft with obliteration of the capillary lumen and prominence of the visceral epithelial cells.

Patient 1. Renal biopsy presented ten glomeruli at light microscopy (LM). Two glomeruli were globally sclerosed and two glomeruli appeared globally collapsed. In the collapsed glomeruli, visceral epithelial cells appeared prominent and numerous (hypertrophy and hyperplasia) and contained large hyaline droplets (Fig. 1). The rest of the glomeruli showed prominent visceral epithelial cells, the capillary loops were open, and basement membranes appeared fine and delicate. Interstitial fibrosis was present and scored Grade II (>25 and <40%) with sparse mononuclear cell infiltration. Direct immunofluorescence against IgG, IgM, IgA, C1q, C3, kappa and lambda was negative for immune-complex deposition in five non-collapsed glomeruli. One collapsed glomerulus showed diffuse irregular staining for IgM and vacuoles of albumin within the visceral epithelial cells. Albumin was present also in vacuoles within the tubular cells.

Patient 2. Renal biopsy had twelve glomeruli per section by LM. One glomerulus was globally sclerosed. Two glomeruli showed retraction of the glomerular tuft that appeared collapsed (Fig. 2). Visceral epithelial cells were prominent and contained hyaline droplets and blebs. The rest of the glomeruli showed no abnormalities by light microscopy. Interstitial fibrosis was present and scored Grade II (>25 and <40%) with sparse mononuclear cell infiltration. Direct immunofluorescence against IgG, IgM, IgA, C1q, C3, kappa and lambda was negative for immune complex deposition in four glomeruli. Albumin was present in vacuoles in the tubular cells.

Patient 3. Renal biopsy contained 23 glomeruli per section at LM. One glomerulus was globally sclerosed. Two glomeruli appeared collapsed. One of them with areas of early segmental sclerosis and damage to the visceral epithelial cells that appeared swollen and contained vacuoles and blebs (Fig. 3). The rest of the glomeruli showed prominence of visceral epithelial cells. Direct immunofluorescence against IgG, IgM, IgA, C1q, C3, kappa and lambda was negative for immune-complex deposition in the three non-collapsed glomeruli examined. Two collapsed glomeruli showed equivocal staining against IgM and vacuoles of albumin within the visceral epithelial cells. Tubular cells showed vacuoles of albumin as well.

Patient 4. Renal biopsy presented seven glomeruli per section at LM. One glomerulus was globally sclerosed. Two glomeruli were globally collapsed and showed the characteristic damage to the visceral epithelial cells that appeared prominent and contained vacuoles and blebs (Fig. 4). Direct immunofluorescence against IgG, IgM IgA, C1q C3, kappa and lambda was negative.

None of the cases presented interstitial tubular cystic dilation.

Electron microscopy examination

Ultrastructural examination in the four cases revealed diffuse obliteration of visceral epithelial cell foot processes in all glomeruli examined. Collapsed glomeruli presented wrinkling of the glomerular basement mem-

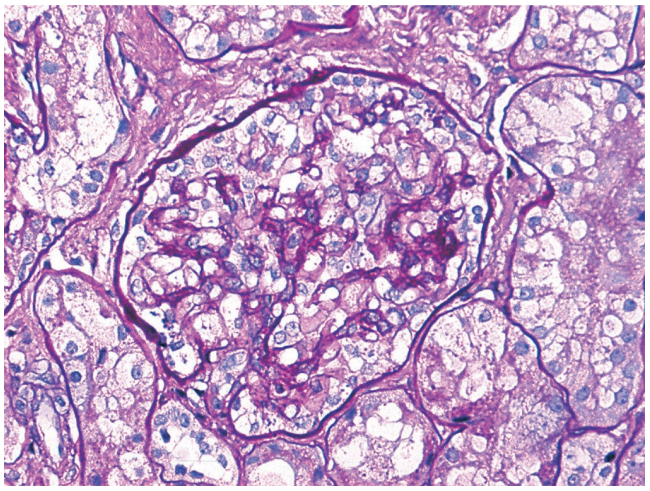

Fig. 1. Renal biopsy of patient 1. Glomerulus shows characteristic capillary collapse and prominence of visceral epithelial cells that contain blebs and vacuoles (PAS stain, ×400).

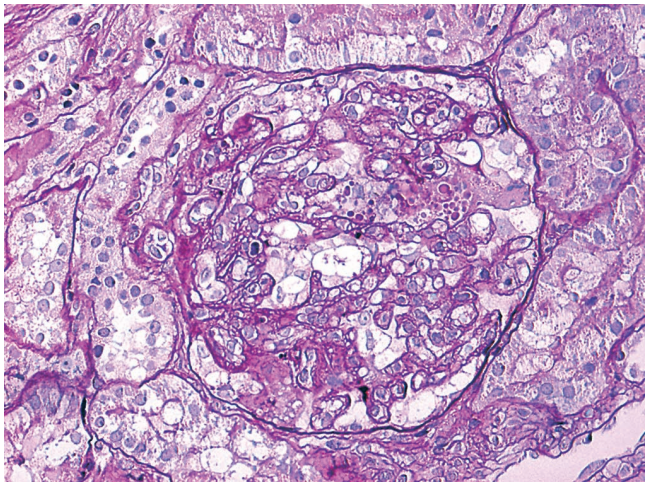

Fig. 2. Renal biopsy from patient 2. Periodic acid-Schiff positive hyaline droplets within hypertrophied visceral epithelial cells can be seen (×400).

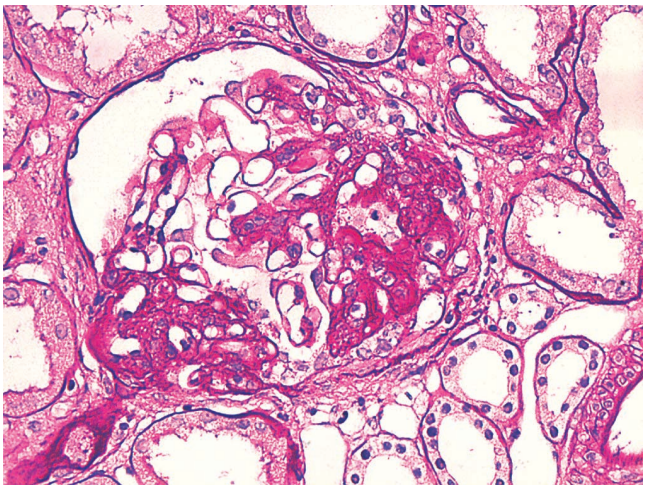

Fig. 3. Renal biopsy from patient 3. Capillary collapse and retraction. Visceral epithelial cells appear prominent and contain vacuoles. A segmental area of sclerosis is also seen (PAS stain, ×400).

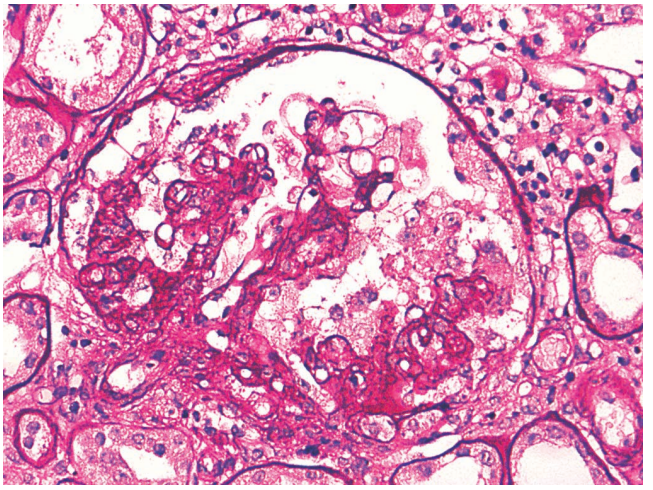

Fig. 4. Renal biopsy from patient 4 showing capillary collapse and retraction of the glomerular tuft. Visceral epithelial cells appear prominent and contain vacuoles and blebs (×400).

branes. Visceral epithelial cells contained numerous vacuoles, blebs and droplets. Electron dense deposits suggestive of immune complex deposition were not identified. The presence of tubuloreticular structures was identified in two cases: case 1 and case 4. In these two patients the tubuloreticular structures were seldom present within the endothelium lining the capillary loops.

Immunogenetics

Segregation analysis of MHC haplotypes in the family showed the following results:

(*1*) The four siblings with CG and the youngest brother without renal disease shared the same MHC haplotype (HLA-A24, B14, DR1, DQA1*0101, DQB1*0501) inherited from the mother (III-7, III-8, III-9, III-10 and III-11 in Fig. 5).

(*2*) The patients with collapsing glomerulopathy (patients 1 and 4; III-7 and III-8, respectively, in Fig. 5) shared the A74, B8, DR1, DQA1*0101, DQB1*0501 haplotype and both presented several clinical manifestations resembling systemic lupus erythematosus (SLE-like).

(*3*) The screening of the mother's sister (II-6), who had a clinical diagnosis of rheumatoid arthritis (RA), showed the HLA-A24, B14, DR1, DQA1*0101, DQB1*0501 haplotype.

DISCUSSION

This study describes a family with renal disease where histological examination of their renal biopsies revealed a pattern consistent with collapsing glomerulopathy. Patients were siblings and they had no previous family his-

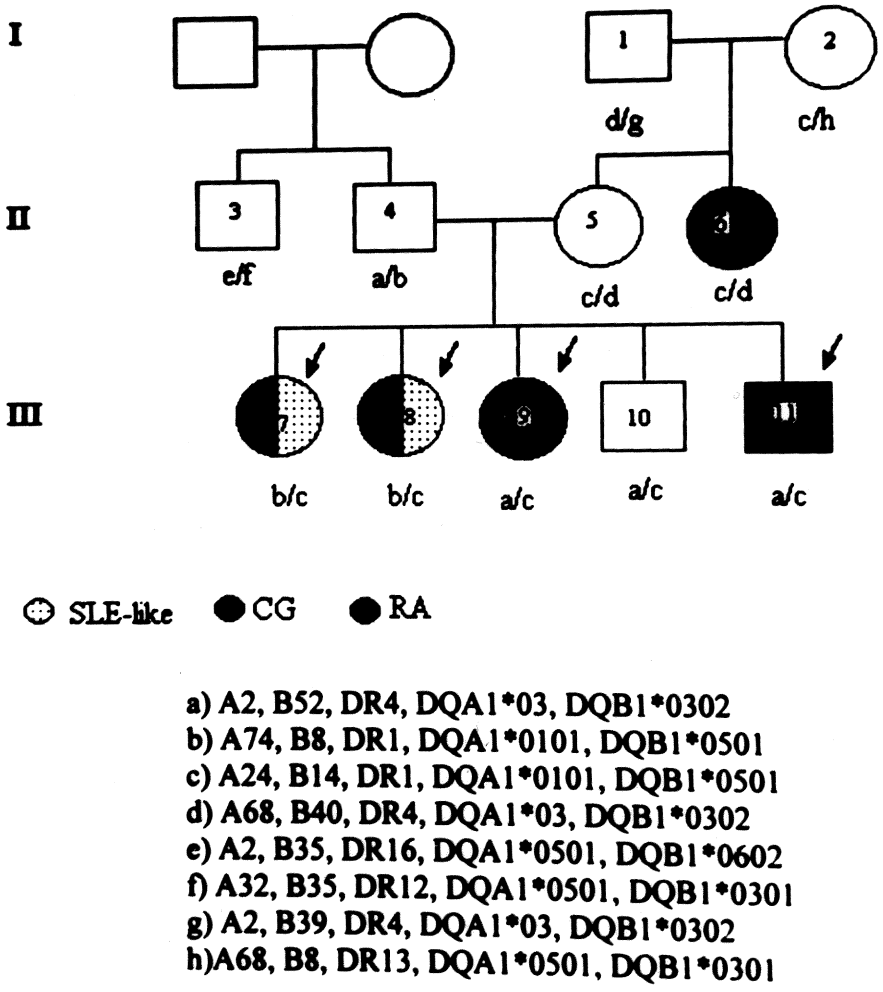

Fig. 5. Imunogenetic analysis of eleven members of the family. Siblings III-7, III-8, III-9 and III-11 affected with CG (arrows) and the youngest brother without CG (III-10) share the same MHC haplotype inherited from the mother (A24, B14, DR1, DQA1*0101, DQB1*0501). Patients III-7 and III-8 also have systemic erythematosus-like disease (SLE-like) and they share the A74, B8, DR1, DQA1*0101, DQB 1*0501 haplotype. The individual II-6 (mother's sister) has rheumatoid arthritis (RA).

tory of renal disease; they were in the age range of 14 to 22 years old and attended the hospital at different times within a year. Although there are previous reports of focal and segmental glomerulosclerosis in a familial pattern [12], to our knowledge the occurrence of CG as a familial disease has not been reported previously. As mentioned earlier, the patients presented with edema and proteinuria within the nephrotic range (>3.5 g/day). Serum creatinine was normal in all patients at the time of diagnosis, although creatinine clearance revealed variable degrees of renal impairment. Serology against HIV, HBV and HCV was negative in all patients. Patients had no known risks for HIV. History of blood transfusions was negative. Patient number 3 (III-11) had a past history of drug use (nonintravenous), although the rest of the patients denied contact with drugs. PVB-19 IgG serology was positive in patients 3 and 5, but IgM levels and DNA by the PCR test were negative. PVB-19 screening by both methods was negative in the rest of the siblings and in the mother. Patients 1 and 4 (III-7 and III-8, respectively) had clinical symptoms suggestive of SLE, but they did not meet the criteria for this diagnosis. The association of CG with autoimmune diseases has been reported previously, especially in primary CG patients [15]. In a series of 42 non-HIV patients with CG, 13 patients were classified as having SLE-like disease [15]. It must be mentioned that in such cases renal damage should not be considered as a manifestation of lupus, since renal damage was not secondary to immune complex deposition. In our patients, no evidence of immune complex deposition was found; direct immunofluorescence was negative and no electron dense deposits were found by ultrastructural examination. Therefore, renal manifestations in these patients are not related to immune complex-mediated disease. The association of PVB-19 infection and SLE-like symptoms, including positive SLE serology, has been reported [16]. Striking similarities between SLE and PVB-19 infection may include rash, fever, photosensitivity, vasculitis, arthropathy, myalgias, cytopenia, hypocomplementemia, ANA, anti-dsDNA antibodies, RF and antilymphocyte antibodies [16]. It must be mentioned that our patients showing such symptoms (cases 1 and 4) had negative serology for PVB-19 infection and no evidence of viral DNA by PCR in peripheral

blood specimens in tests performed at the clinical laboratory (MSB, Quest Diagnostics). However, these two patients presented tubuloreticular structures within the glomerular endothelial cells upon ultrastructural examination, which are rarely found. It is well known that tubuloreticular structures have been described in viral diseases like HIV nephropathy as well as in lupus nephropathy of any type [2]. Since our patients had no known viral disease, nor the clear diagnostic criteria of SLE, we cannot explain the significance of the presence of such structures. It has been mentioned also that PVB-19 infection might induce CG or other forms of glomerulopathies in susceptible individuals, based in a greater prevalence of PVB-19 DNA in renal biopsies of patients with primary CG and FSGS [17] or CG de novo in renal transplant recipients [18]. PBV-19 infection is common worldwide at any age, but it is most common in school-aged children [16]. Most of the population becomes infected at some point, 15% developing infection between one and five years of age, 15% to 60% between 5- and 19-years-old, and 30% to 60% in adulthood [19]. However, the development of renal disease is uncommon, suggesting that some cases present a genetic susceptibility to the glomerular disease. In our study, patients 3 and 5 presented with IgG serology for PVB-19 infection. These results indicate that they became infected at one point, but do not signify that they were chronically or currently infected.

It is important to point out that in these particular patients with familial CG, the clinical presentation and course appeared to differ from that in the majority of sporadic cases with CG. In this regard, the level of proteinuria at presentation, that is, <10 g/day in all four siblings with biopsy-proven CG compared with >10 g/day in the majority of patients with CG [3], and the different rate of progression to ESRD suggests that this familial form of CG could have a different course from sporadic CG.

Human lymphocyte antigen association with some types of glomerulopathy has been reported previously [20]. HLA-B8 has been associated with steroid-sensitive nephrotic syndrome of childhood [21], and IgA nephropathy with the presence of HLA-DR4 [22], idiopathic membranous glomerulopathy with HLA-DR2 [20], minimal change disease with HLA-DRw53 [21] and post-streptococcal glomerulonephritis with DR1 [20] have been found. In the family of our study, segregation analysis of MHC haplotype demonstrated that all members of the family affected with CG inherited the same MHC haplotype from the mother: HLA-A24, B14, DR1, DQA1*0101, DQB1*0501. It is important to point out that two out of four patients are homozygous for the DR1 allele. The only sibling not affected yet by CG, also presents this haplotype. He is a seven-year-old boy, and we cannot rule out the possibility that he may be susceptible to developing the disease in the future, although at present he has trace proteinuria and microhematuria in the urinalysis. The rest of the siblings presented with renal manifestations during the second and third decades of life with no previous past history of renal disease in childhood.

The frequency of this haplotype in the normal Mexican-Mestizo population is less than 3%, and in the Mexican-indigenous population such as Mazatecans and Nahuas its frequency is less than 1% (personal unpublished data). This observation suggests that this haplotype was acquired by genetic mixture from Caucasian origin, perhaps from a Mediterranean group, since it is one of the most common haplotypes in the latter [23]. Indeed, the DR-1 allele is likely not a major characteristic of CG, which is found mostly in African American groups [4].

Primary CG can be associated with autoimmune diseases [15]. Two of the patients with CG (patients 1 and 4, III-7 and III-8, respectively), also presented several clinical data suggesting the diagnosis of systemic lupus erythematosus. These particular patients share the A74, B8, DR1, DQA1*0101, DQB1*0501 haplotype that includes the HLA-B8 allele. This allele has been associated with SLE in several Caucasian populations and is included in the A1, B8, DR3, SC01 haplotype [24]. Genetic studies on Mexican population have demonstrated this haplotype to be rather uncommon (less than 1% haplotype frequency) [25]. However, in Mexican SLE patients this rises to 10%, suggesting the possibility that this haplotype is also from Caucasian origin [23]. Therefore, the MHC analysis revealed a haplotype that segregates with the disease in this particular family; this haplotype could have been acquired by mixture with a Caucasian population, because, as mentioned previously, it is found with a very low frequency in Mexican-indigenous population. We have no explanation for the observation that the mother, grandmother and one aunt (mother's sister) failed to develop renal damage despite the fact that they also showed the MHC haplotype (HLA-A24, B14, DR1, DQA1*0101, DQB1*0501) present in the affected siblings. In this regard, we hypothesize that the environment plays an important role in the development of the disease. A viral infection, different from HIV and PVB-19, has been claimed to be responsible for cases of primary CG in non-HIV patients [2, 3]. Affected members of our family could have been exposed to a non-detected viral infection and/or other unknown factors, while they are also susceptible to develop renal disease.

We conclude that primary CG can be present in a familial pattern, similar to the occurrence of other causes of familial nephrotic syndrome such as familial focal and segmental glomerulosclerosis. Primary CG can be associated with a variety of symptoms commonly seen in autoimmune diseases such as SLE. Renal disease in patients with CG with SLE-like symptoms cannot be used to support a diagnostic criterion for SLE, since in these specific cases it is not secondary to the deposition of immune complexes in the glomerulus.

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