Idiopathic collapsing focal segmental glomerulosclerosis in an 81-year-old Japanese woman: a case report and review of the literature

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Received: 18 December 2015 / Accepted: 8 June 2016 / Published online: 15 June 2016
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Abstract Focal segmental glomerulosclerosis (FSGS) is classified into five variants, with the collapsing variant being the most rare. Collapsing FSGS is characterized by a black racial predominance and is often associated with human immunodeficiency virus-associated nephropathy. However, the number of idiopathic cases is increasing and the presentation of non-black patients becoming more routine. Our analysis of 15 previous reports investigating FSGS variants shows that the collapsing variant accounts for 10.6 % of FSGS cases and its average age of onset is 32 years old. The current case is one of the oldest cases of idiopathic collapsing FSGS identified, being an 81-year-old Japanese woman. She presented with severe renal insufficiency (serum creatinine 7.9 mg/dL, albumin 1.5 g/dL) and so underwent hemodialysis immediately. Urinalysis demonstrated 3+ proteinuria and 3+ hematuria and the serological work up was all negative. Renal biopsy showed wrinkling of capillary walls with collapse lumens in every glomerulus, without endothelial tubuloreticular inclusions. Combined treatment with steroids, cyclosporine and low-density lipoprotein apheresis increased urine output slightly but she was unable to withdraw from hemodialysis and died 3 months later. This variant is reported to have the highest rate of progression to end-stage renal disease,

regardless of the therapeutic intervention. However, there are also examples of cases with partial or complete remission in the literature. Progressive cases, like the current case, seem to be difficult to induce remission in, so it is important to diagnose idiopathic collapsing FSGS at an early stage by performing a renal biopsy, even in elderly patients.

Keywords Collapsing focal segmental glomerulosclerosis (FSGS) · Collapsing glomerulopathy · Low-density lipoprotein (LDL)-apheresis

Introduction

Focal segmental glomerulosclerosis (FSGS) is one of the major causes of nephrotic syndrome in young people. It is classified into five variants according to the Columbia classification published in 2004: FSGS not otherwise specified (NOS), perihilar variant, tip variant, cellular variant and collapsing variant [1]. The collapsing variant of FSGS was first described as collapsing glomerulopathy by Weiss et al. [2]. Thereafter, it was seen frequently in HIV-infected individuals, especially black people, and the concept of human immunodeficiency virus-associated nephropathy (HIVAN) was established. Most cases of collapsing FSGS other than HIVAN are idiopathic. However, there are other secondary causes including infection by parvovirus B19, drugs such as bisphosphonate, interferon- α , anabolic steroids and heroin, autoimmune diseases, malignancies, genetic factors and renal transplantation. The incidence of collapsing FSGS is not high, but the number of cases appears to be gradually increasing [3]. Moreover, this variant is reported to have the poorest prognosis, with the highest rate of presenting

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steroid-resistant nephrotic syndrome, renal insufficiency and end-stage renal disease (ESRD).

This is a rare case of idiopathic collapsing FSGS in an elderly non-black woman. At presentation she demonstrated severe renal insufficiency and was unable to withdraw from hemodialysis, despite multidisciplinary therapy.

Case report

An 81-year-old Japanese female with a medical history of hypertension, hyperlipidemia and mental disorder was admitted to our hospital mid-November 2014 for slight disturbance of consciousness the previous day and an edematous state of 6 months' duration. There was no medical or family history of renal disease. A physical examination revealed the following: height 165 cm, weight 80 kg (20 kg greater than usual), blood pressure of 131/50 mmHg, pulse rate of 87 beats/min, and a temperature of 35.9 °C. The laboratory data indicated severe renal dysfunction (serum urea nitrogen 90.5 mg/dL, creatinine 7.9 mg/dL), hypoproteinemia (serum total protein 4.4 g/dL, albumin 1.5 g/dL) and hyperlipidemia (total cholesterol 239 mg/dL, low-density lipids 160 mg/dL). Urinalysis demonstrated 3 + proteinuria and 3 + hematuria. Twenty-four-hour urine protein could not be measured because of anuria. Serum immunoglobulins (IgG, IgA, IgM) and complement (C3, C4, CH50) levels were within normal reference ranges. The serological workup was negative for anti-nuclear autoantibodies (ANA), anti-glomerular basement membrane (GBM) autoantibodies, myeloperoxidase anti-neutrophil cytoplasm autoantibodies (MPO-ANCA), proteinase 3 (PR3)-ANCA, hepatitis B virus (HBV) and HCV. The renal ultrasound showed normal-sized kidneys and the X-ray showed cardiac dilation and severe bilateral pleural effusion. We started hemodialysis immediately. Her state of consciousness returned to normal but anuria continued, therefore renal biopsy was performed 8 days after admission.

Light microscopy revealed a total of 26 glomeruli, five of which were completely sclerotic. Every glomerulus showed wrinkling and collapse of capillary loops with occlusive lumina. Eight glomeruli also presented with prominent hyperplasia and hypertrophy of the epithelial cells, filling in the Bowman's space (Fig. 1a, b). Cystic dilatation of tubules was occasionally noted (Fig. 1c). Immunofluorescence was negative for immunoglobulins and complement components. Electron microscopy revealed wrinkling and collapse of capillary walls but no electron-dense deposit was identified (Fig. 2a). Severe podocyte foot process effacement and focally detachment of glomerular epithelial cells indicate epithelial cell damages, suggesting FSGS (Fig. 2a, b). Endothelial tubuloreticular inclusions were not observed (Fig. 2c).

Additional serological tests for HIV and parvovirus B19 were both negative and the patient never used bisphosphonate, interferon- α , anabolic steroids or any illegal drugs. We thus diagnosed her with idiopathic collapsing variant of FSGS. Oral prednisolone at 0.8 mg/kg/day and oral cyclosporine at 2.0 mg/kg/day were started 14 and 23 days after admission, respectively; however, her urine output failed to increase. Thereafter, corticosteroid psychosis gradually emerged, so the dosage of prednisolone was tapered to 0.2 mg/kg/day. Forty days after admission, we started additional treatment with low-density lipoprotein apheresis (LDL-A). We used polysulfone hollow fiber filters (Sulflux FP-08, Asahi Kasei Corp., Tokyo, Japan) as the plasma separator and dextran sulfate cellulose columns (Liposorber LA-15, Kaneka Corp., Osaka, Japan) as the LDL absorber and processed approximately 60 ml/kg plasma volume per session. The session interval was twice a week and a total of 11 sessions were performed. After six sessions her urine output gradually and slightly increased from almost 0 to 150 ml/day but she remained dependent upon hemodialysis. We determined that her renal dysfunction was incurable and irreversible, so discontinued cyclosporine and decreased prednisolone 91 days after admission. Her general condition deteriorated and she died suddenly from respiratory failure 6 days later.

Discussion

The most common causes of collapsing FSGS are either HIVAN or idiopathic. There are other secondary causes including infection with parvovirus B19, drugs such as bisphosphonate, especially pamidronate, interferon- α , anabolic steroids and heroin, autoimmune diseases, malignancies, genetic factors and renal transplantation [4]. Any of these factors may damage visceral epithelial cells, leading to collapsing FSGS. To determine the cause, we should carefully check for specific antigens and antibodies, drug history and family history. In renal pathology, it is essential to identify endothelial tubuloreticular inclusions, which are 23–25 nm subcellular organelles characterized by small clusters of anastomosing tubule-like structures. These structures can be identified in cases with HIVAN, collagen vascular diseases such as lupus nephritis and interferon- α -induced FSGS [5]. In this case we could not find this structure or any factors suggesting these secondary causes, therefore we diagnosed the patient with idiopathic collapsing FSGS.

Collapsing FSGS is reported to be a rare variant characterized by black racial predominance. Using PubMed, we searched for previous reports comparing FSGS variants based on the Columbia classification published in 2004, and found 19 reports from 10 countries. Four reports

Fig. 1 Renal biopsy findings.

a A glomerulus showing wrinkling of capillary walls with collapsed lumens. Segmental hyperplastic epithelia are also noted (periodic acid-Schiff-methenamine silver). **b** Hyperplasia of glomerular epithelial cells is prominent (periodic acid-Schiff-methenamine silver). **c** Tubules show cystic dilation with proteinaceous casts (periodic acid-Schiff)

targeting children only were excluded, so 15 reports were left [6–20]. We analyzed the remainder and the results are shown in Table 1. The total number of FSGS cases was 2181 and among them 232 cases were classified as the collapsing variant. Thus, the collapsing variant accounts for approximately 10.6 % of FSGS cases. The proportion of collapsing FSGS varied from 0.9 to 36.6 % by country. The collapsing variant has been said to have the strongest association with black race and it was thus reasonable that the reports from the USA had a higher proportion of positive cases [6, 7, 15]. However, it was unexpected therefore that in the report from Senegal, where almost all the subjects were black, the proportion was only 7.1 % [10]. Furthermore, the ratio in East Asia was generally low; 0.9 % in Korea, 6.9 and 6.7 % in China [8, 17, 19]. However, the proportion was much higher in a Japanese report (16.3 %) [12]. Similarly, in Latin America, the percentage was also quite different by country; 36.6 % in Brazil and 3.4 % in Colombia [13, 16]. In conclusion, there might be slight regional or racial differences but there is a distinct difference between countries in the same region. There is a possibility that the ability to diagnose this

variant differs from country to country, but the main reason for the difference remains unknown.

FSGS generally develops in young people, which applies to all types of variants. Our analysis of 15 previous reports showed that the average age of onset of collapsing FSGS was 32 years old (Table 1). As we excluded reports targeting only children, and there were several reports targeting only adults, the average age of onset might actually be younger in practice. The current case was therefore notable, being a case of idiopathic collapsing FSGS developing in an 81-year-old Japanese woman. To the best of our knowledge, there are only two reports older than the current case; an 84-year-old Japanese case, which was not published in English, and an 84-year-old Korean case [19].

The collapsing variant of FSGS has been reported to be the most intractable. It has the highest rate of presenting nephrotic syndrome and renal insufficiency, and of progression to ESRD regardless of therapeutic intervention. In Hass et al.'s analysis, there was an apparent difference in the percentage of cases progressing to ESRD between collapsing and classic FSGS patients (71 versus 20 %,

Fig. 2 Electron microscopy findings. **a** A glomerulus showing wrinkling of capillary walls with collapsed lumens. Widespread podocyte foot process effacement is noted. There are no electron-dense deposits. Bar 10 μ m. **b** Podocyte denudation are focally found (arrows). Bar 2 μ m. **c** No endothelial inclusion is observed. Bar 2 μ m

$P < 0.05$) [21]. Similarly, Grcevska et al. found that within 5 years 100 % of collapsing FSGS patients, but only 41.4 % of classic FSGS patients, reached ESRD ($P = 0.025$) [22]. However, other studies found that not every case progresses to ESRD and some cases achieved complete remission after intensive therapy, including steroids and immunosuppressive agents such as cyclophosphamide, cyclosporine and mycophenolate mofetil. Albaqumi et al. reported that the proportion of complete and partial remissions was 9.6 and 15.2 %, respectively [23]. No therapies are yet established for the collapsing variant of FSGS, so we suggest using therapies designed for steroid-resistant FSGS, where the collapsing variant accounts for a certain part of the disease. The combination therapy of steroids and cyclosporine is thought to be one of the most efficient in steroid-resistant FSGS [24]. In the current case, the patient demonstrated severe renal insufficiency at presentation so immediately underwent hemodialysis. There were minimal chronic changes in her kidney biopsy specimen, so we judged that remission might be possible and therefore instigated intensive treatment. Oral prednisolone and cyclosporine

were started but because of corticosteroid psychosis, the dosage of steroid had to be tapered.

Recently, immediate LDL-A therapy was reported to be effective for drug-resistant nephrotic syndrome, particularly for FSGS [25]. Persistent elevation of LDL has been revealed to induce glomerular and tubulointerstitial damage. Furthermore, increased bioavailability of steroid and calcineurin inhibitors is known to be impaired under hyperlipidemic conditions. Therefore, in theory, lowering lipids by LDL-A is thought to be effective. A multicenter prospective study, POLARIS (Prospective Observational Survey on the Long-Term Effects of LDL Apheresis on Drug-Resistant Nephrotic Syndrome), revealed that LDL-A might provide early remission in approximately half of drug-resistant nephrotic syndrome patients (25/47, 53.1 %) [26]. We performed a total of 11 sessions of LDL-A. After six sessions the patient's urine output gradually increased from almost 0 to 150 ml/day but she remained dependent upon hemodialysis. It was reported that the earlier LDL-A is performed, the more nephrotic syndrome improves. In our case, the diagnosis was too late and renal damage had accumulated to the extent where a therapeutic response was

Table 1 Comparison of previous reports investigating focal segmental glomerulosclerosis variants based on the Columbia classification published in 2004 [1]

Author (publication year)	Country	Number of cases COLL/ALL (%) ^a	Average age years $\pm$ SD (range)	Male (%)	CR + PR (%)	ESRD (%)
Stokes (2006) [6]	USA	56/225 (24.9)	31.2 $\pm$ 2.3	46.4	13.2	65.3
Thomas DB (2006) [7]	USA	22/197 (11.1)	38 $\pm$ 12 (24–27)	45.0	18.0	67.0
Shi (2007) [8]	China	7/102 (6.9)	–	–	–	–
Deegens (2008) [9]	The Netherlands	5/93 (5.4)	63 $\pm$ 18	60.0	40.0	70.0
Niang (2008) [10]	Senegal	7/134 (7.1)	–	–	–	–
Nada (2009) [11]	India	4/210 (1.9)	46 $\pm$ 10	75.0	–	–
Taneda (2012) [12]	Japan	13/80 (16.3)	39.9 $\pm$ 4.1	69.2	44.4	30.0
Testagrossa (2012) [13]	Brazil	48/131 (36.6)	–	–	–	–
Das (2012) [14]	India	9/65 (13.8)	–	–	–	–
D'Agati (2013) [15]	USA	16/138 (11.6)	16.5 (2–38)	50.0	13.0	47.0
Arias (2013) [16]	Colombia	10/291 (3.4)	11 (3–66)	60.0	22.2	33.3
Tang (2013) [17]	China	7/104 (6.7)	31 (16–61)	57.1	–	–
Shakeel (2013) [18]	Pakistan	22/184 (12.0)	32.3 $\pm$ 13.8	59.1	–	–
Kwon (2014) [19]	Korea	1/111 (0.9)	84	0.0	100.0	0.0
Swarnalatha (2015) [20]	India	5/116 (4.3)	33.5 $\pm$ 23 (15–74)	–	–	60.0
Total		232/2181 (10.6)	32.0 (2–84)	52.6	20.3	55.9

^a COLL collapsing FSGS variant, ALL all FSGS variants, CR complete remission, PR partial remission, ESRD end-stage renal disease

not expected. Therefore, while we cannot judge the therapeutic efficacy of LDL-A by this case alone, we think it may be worth performing because it has few side effects.

Collapsing FSGS is a rare variant of FSGS and it is reported to be characterized by black racial predominance and is often associated with HIVAN. FSGS develops in young people and there are few cases in elderly people. Thus it was excluded from the differential diagnosis of nephrotic syndrome in older people, especially non-black and non-HIV-positive people. However, cases of non-black people are becoming more routine and the number of idiopathic collapsing FSGS cases is gradually increasing. Exposure to unknown infections, chemical agents or other environmental factors might account for this. Elderly people also sometimes do not undergo an invasive kidney biopsy, so they may remain underdiagnosed. This variant has the highest rate of progression to ESRD, but if diagnosed early some cases can undergo complete remission by various therapies. Progressive cases, like the current case, seem to be difficult to induce remission in, so it is important to diagnose idiopathic collapsing FSGS at an early stage by performing a renal biopsy, even in elderly people.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflicts of interest exist.

References

1. D'Agati VD, Fogo AB, Bruijn JA, Jennette JC. Pathologic classification of focal segmental glomerulosclerosis: a working proposal. *Am J Kidney Dis.* 2004;43:368–82.
2. Weiss MA, Daquiao E, Margolin EG, Pollak VE. Nephrotic syndrome, progressive irreversible renal failure, and glomerular “collapse”: a new clinicopathologic entity? *Am J Kidney Dis.* 1986;7:20–8.
3. Schwimmer JA, Markowitz GS, Valeri A, Appel GB. Collapsing glomerulopathy. *Semin Nephrol.* 2003;23:209–18.
4. Markowitz GS, Bombardieri AS, Perazella MA. Drug-induced glomerular disease: direct cellular injury. *Clin J Am Soc Nephrol.* 2015;10:1291–9.
5. Nachman PH, Jennette JC, Falk RJ. Primary glomerular disease. In: Taal MW, Chertow GM, Marsden PA, Skorecki K, Yu AS, Brenner BM, editors. *Brenner & Rector's the kidney.* 9th ed. Philadelphia: Saunders; 2011. p. 1111–21.
6. Stokes MB, Valeri AM, Markowitz GS, D'Agati VD. Cellular focal segmental glomerulosclerosis: clinical and pathologic features. *Kidney Int.* 2006;70:1783–92.
7. Thomas DB, Franceschini N, Hogan SL, Ten Holder S, Jennette CE, Falk RJ, Jennette JC. Clinical and pathologic characteristics of focal segmental glomerulosclerosis pathologic variants. *Kidney Int.* 2006;69:920–6.
8. Shi SF, Wang SX, Zhang YK, Zhao MH, Zou WZ. Clinicopathologic study of different variants of focal segmental glomerulosclerosis. *Zhonghua Bing Li Xue Za Zhi.* 2007;36:11–4.
9. Deegens JK, Steenbergen EJ, Borm GF, Wetzels JF. Pathological variants of focal segmental glomerulosclerosis in an adult Dutch population—epidemiology and outcome. *Nephrol Dial Transplant.* 2008;23:186–92.

10. Niang A, Dial C, Ka EF, Lèye A, Pouye A, Ka MM, Mbengue M, Droz D, Diouf B. Nephrotic syndrome with focal and segmental glomerulosclerosis in Dakar: epidemiological and clinicopathological characteristics (about 134 cases). *Dakar Med*. 2008;53:45–51.
11. Nada R, Kharbada JK, Bhatti A, Minz RW, Sakhuja V, Joshi K. Primary focal segmental glomerulosclerosis in adults: is the Indian cohort different? *Nephrol Dial Transplant*. 2009;24:3701–7.
12. Taneda S, Honda K, Uchida K, Nitta K, Yumura W, Oda H, Nagata M. Histological heterogeneity of glomerular segmental lesions in focal segmental glomerulosclerosis. *Int Urol Nephrol*. 2012;44:183–96.
13. Testagrossa L, Malheiros D. Study of the morphologic variants of focal segmental glomerulosclerosis: a Brazilian report. *J Bras Patol Med Lab*. 2012;48:211–5.
14. Das P, Sharma A, Gupta R, Agarwal SK, Bagga A, Dinda AK. Histomorphological classification of focal segmental glomerulosclerosis: a critical evaluation of clinical, histologic and morphometric features. *Saudi J Kidney Dis Transpl*. 2012;23:1008–16.
15. D'Agati VD, Alster JM, Jennette JC, Thomas DB, Pullman J, Savino DA, Cohen AH, Gipson DS, Gassman JJ, Radeva MK, Moxey-Mims MM, Friedman AL, Kaskel FJ, Trachtman H, Alpers CE, Fogo AB, Greene TH, Nast CC. Association of histologic variants in FSGS clinical trial with presenting features and outcomes. *Clin J Am Soc Nephrol*. 2013;8:399–406.
16. Arias LF, Jiménez CA, Arroyave MJ. Histologic variants of primary focal segmental glomerulosclerosis: presentation and outcome. *J Braz Nefrol*. 2013;35:112–9.
17. Tang X, Xu F, Chen DM, Zeng CH, Liu ZH. The clinical course and long-term outcome of primary focal segmental glomerulosclerosis in Chinese adults. *Clin Nephrol*. 2013;80:130–9.
18. Shakeel S, Mubarak M, Kazi J, Jafry N, Ahmed E. Frequency and clinicopathological characteristics of variants of primary focal segmental glomerulosclerosis in adults presenting with nephrotic syndrome. *J Nephropathol*. 2013;2:28–35.
19. Kwon YE, Han SH, Kie JH, An SY, Kim YL, Park KS, Nam KH, Leem AY, Oh HJ, Park JT, Chang TI, Kang EW, Kang SW, Choi KH, Lim BJ, Jeong HJ, Yoo TH. Clinical features and outcomes of focal segmental glomerulosclerosis pathologic variants in Korean adult patients. *BMC Nephrol*. 2014;15:52–60.
20. Swarnalatha G, Ram R, Ismal KM, Vali S, Sahay M, Dakshinamurthy KV. Focal and segmental glomerulosclerosis: dose prognosis vary with the variants? *Saudi J Kidney Dis Transpl*. 2015;26:173–81.
21. Haas M, Spargo BH, Coventry S. Increasing incidence of focal-segmental glomerulosclerosis among adult nephropathies: a 20-year renal biopsy study. *Am J Kidney Dis*. 1995;26:740–50.
22. Grcevska L, Polenakovik M. Collapsing glomerulopathy: clinical characteristics and follow-up. *Am J Kidney Dis*. 1999;33:652–7.
23. Albuqumi M, Soos TJ, Barisoni L, Nelson PJ. Collapsing glomerulopathy. *J Am Soc Nephrol*. 2006;17:2854–63.
24. Cattran DC, Appel GB, Hebert LA, Hunsicker LG, Pohl MA, Hoy WE, Maxwell DR, Kunis CL, North America Nephrotic Syndrome Study Group. A randomized trial of cyclosporine in patients with steroid-resistant focal segmental glomerulosclerosis. *Kidney Int*. 1999;56:2220–6.
25. Miyazono M, Tomiyoshi Y, Kishi T, Ikeda Y, Sakemi T, Sanai T, Node K. A case report of nephrotic syndrome due to collapsing focal segmental glomerulosclerosis treated with low-density lipoprotein apheresis. *Ther Apher Dial*. 2008;12:333–6.
26. Muso E, Mune M, Hirano T, Hattori M, Kimura K, Watanabe T, Yokoyama H, Sato H, Uchida S, Wada T, Shoji T, Yuzawa Y, Takemura T, Sugiyama S, Nishizawa Y, Ogahara S, Yorioka N, Sakai S, Ogura Y, Yukawa S, Iino Y, Imai E, Matsuo S, Saito T. Immediate therapeutic efficacy of low-density lipoprotein apheresis for drug-resistant nephrotic syndrome: evidence from the short-term results from the POLARIS Study. *Clin Exp Nephrol*. 2015;19:379–86.