Malaysian J Pathol 2020; 42(1) : 131 – 135

CASE REPORT

Collagenofibrotic glomerulopathy- report of a rare renal disease with serial biopsies

NG Yan Fei[1], CHOW Chun Yuen[1], YANG Wen Shin[2], LYE Wai Choong[2], LOH Hwai Liang[1]

[1]Singapore General Hospital, Division of Pathology, Department of Anatomical Pathology; and [2]Centre for Kidney Diseases, Mount Elizabeth Hospital, Singapore.

Abstract

Introduction: Collagenofibrotic glomerulopathy or collagen type-III glomerulopathy is a rare glomerular disease characterised by the deposition of type III collagen fibres in the subendothelial space and mesangium of the glomerulus. *Case Report:* Here, we present a case of collagenofibrotic glomerulopathy in a 49-year-old Indian female, the first to be reported from Singapore. Renal biopsy showed PAS (periodic acid-Schiff), silver and Congo red negative, amorphous extracellular material that expanded mesangial and subendothelial regions. Such materials were strongly positive for anti-collagen III immunofluorescent staining. Under electron microscopy, the mesangial and some subendothelial regions were greatly expanded by abundant collagen fibres which were different from normal collagen III fibres in both appearance and periodicity. *Discussion:* The availability of past renal biopsies for reference offered insight into disease progression. From the initial diagnosis of focal segmental glomerulosclerosis to eventually collagenofibrotic glomerulopathy over a time span of more than 10 years, this case highlights the gradual accumulation of collagen fibres in the glomeruli before classical features are apparent. It also emphasises the importance of electron microscopy in the diagnosis of this disease.

Keywords: collagenofibrotic, collagen type-III, glomerulopathy

INTRODUCTION

Collagenofibrotic glomerulopathy or collagen type-III glomerulopathy is a rare glomerular disease characterised by the deposition of type III collagen fibres in the subendothelial space and mesangium of the glomerulus. It was first reported in 1979 by Arakawa *et al*.[1] To date, there are nearly 100 reported cases in the English literature. This disease occurs predominantly in Asians[2,3,4], however, there are some reports of occurrence in other ethnicities as well.[5,6] (Table 1) There is no gender predilection and no age factor in this disease, with cases reported in patients ranging from less than 5 years old to more than 65 years old. In this article, we present a case of collagenofibrotic glomerulopathy which has never been reported in Singapore. We review essential ultrastructural features and highlight the unusual findings.

CASE REPORT

A 49-year-old Indian female presented with signs of non-diabetic chronic kidney disease since 2005. Her first renal biopsy in 2005 was reported as focal segmental glomerulosclerosis (FSGS). The first biopsy (light microscopy slides only) was reviewed later that year and was reported as having segmental increase in

TABLE 1: Reported cases of collagenofibrotic glomerulopathy in English literature to date

Ethnicity	No. of cases
Chinese	33
Indian	23
Japanese	19
Caucasian	14
Brazilian/native American	6
Middle Eastern	2
Not indicated	1
Total	98

Address for correspondence: LOH Hwai Liang, Singapore General Hospital, Division of Pathology, Department of Anatomical Pathology, 20 College Road, Singapore 169856. Tel: (65) 63214871. Fax: (65) 62276562. Email: *loh.hwai.liang@singhealth.com.sg*

mesangial cellularity with irregular wire-loop thickening, suggestive of lupus nephritis. As a course of steroids failed to improve her proteinuria, she had a second kidney biopsy at a different institution, which revealed features of membranoproliferative glomerulonephritis (MPGN) with extensive glomerulomegaly. Attempts at treatment using tacrolimus with mycophenolate and steroids did not yield any positive outcome either. While on a prolonged course of maintenance steroids in 2009, she developed avascular necrosis of her right hip. In 2018, she decided to seek another opinion with regards to the status of her kidney disease. While she was seen in the clinic, she was noted to be hypertensive (BP on average 160/90mmHg) but not in fluid overload. Her creatinine was 4.98mg/dl with proteinuria of 6.8g/24hrs. Both her lipid profile and liver function tests were noted to be normal. SLE autoimmune markers as well as viral hepatitis B and C serologies were negative. However, both C3 and C4 levels were noted to be slightly above the normal ranges. Ultrasound of her kidneys was relatively normal. She had a third kidney biopsy in July 2018.

Renal biopsy on light microscopy showed that all the glomeruli displayed near-total replacement by peculiar PAS (periodic acid-Schiff) and silver negative, amorphous extracellular material that expanded mesangial and subendothelial regions, giving the glomeruli a lobular or nodular appearance (Fig. 1A). Such material was also silver and Congo red negative but stained like collagen with combined Masson-silver (Fig. 1B, 1C). Capillary walls overlying these abnormal deposits were slender or thickened but generally single contoured. About 44% of glomeruli appeared to be undergoing global sclerosis and there was considerable tubular atrophy with moderate interstitial fibrosis. The immunofluorescence staining on this biopsy were generally negative for all antibodies in the renal panel (IgG, IgA, IgM, C3, C1q, C4, and kappa/lambda light chains), except for non-specific entrapment. Anti-collagen III was strongly positive in the glomeruli by immunofluorescence (Fig. 1D) and immunohistochemistry (not shown). Under electron microscopy, the mesangial and some subendothelial regions were greatly expanded by abundant collagen fibres (Fig. 2A, 2B, 2C). With phosphotungstic acid enhancement, these fibres appeared abnormal

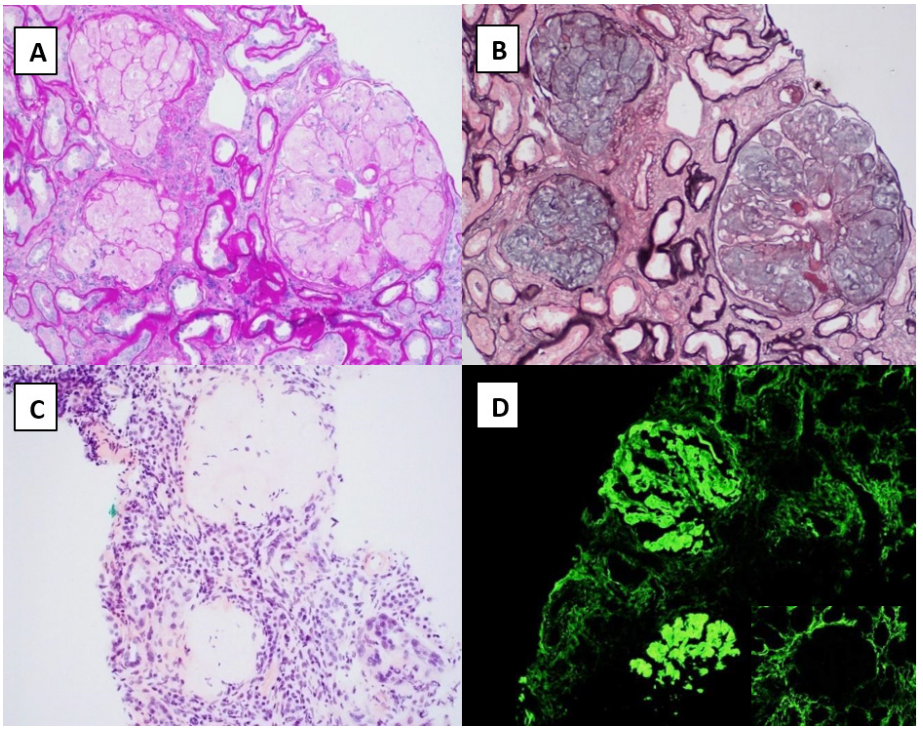

FIG. 1. Light and immunofluorescence images. (A) PAS, original magnification x200. (B) Combined Masson-Silver, original magnification x200. (C) Congo red, original magnification x200. (D) Anti-Collagen III-FITC, original magnification x200. Note the positive staining within the interstitial compartment serving as internal positive control. Inset: negative staining in a normal glomerulus for comparison.

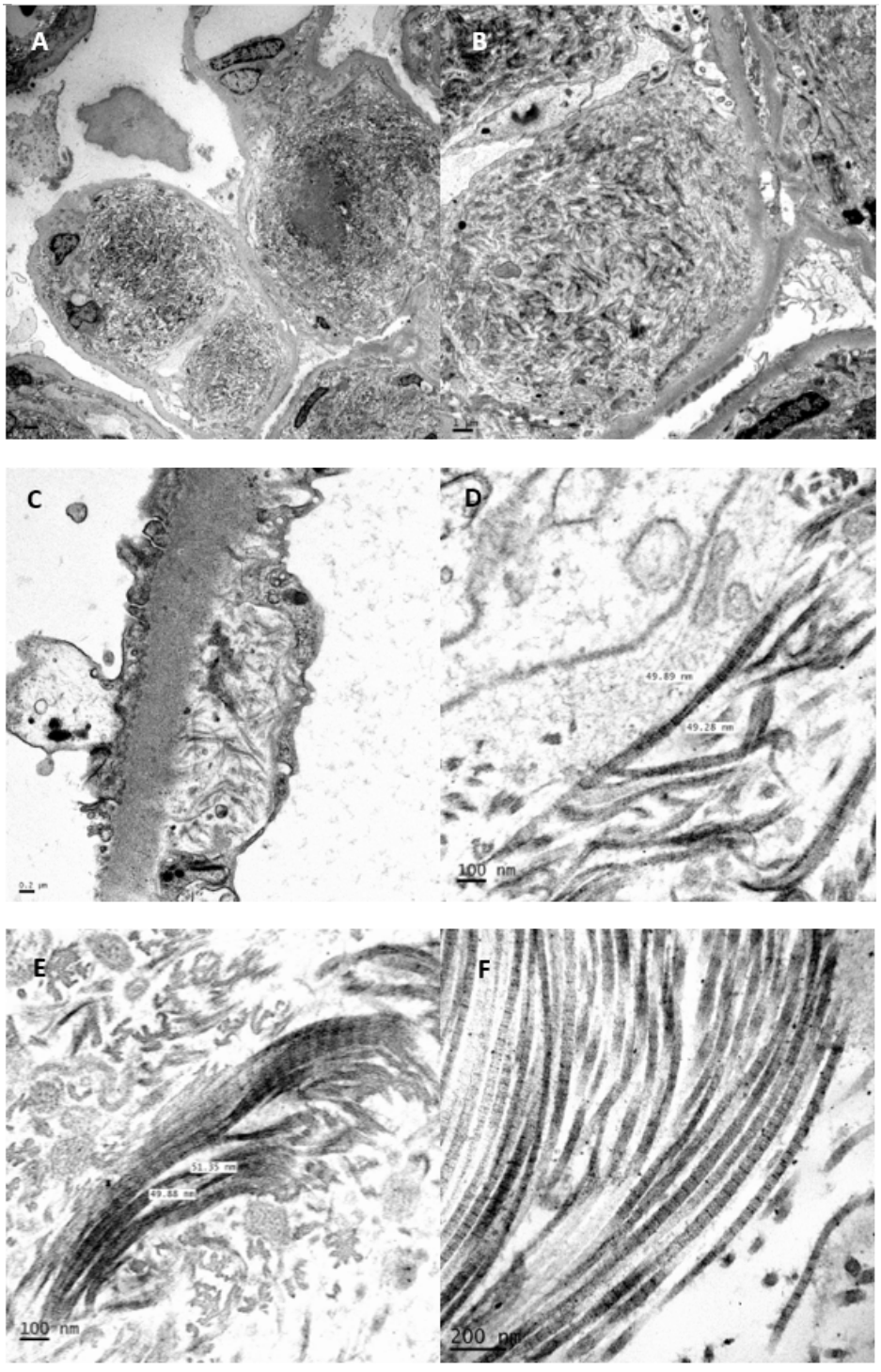

FIG. 2. Transmission electron microscopy images (uranyl acetate and lead citrate). The mesangial and some subendothelial regions were greatly expanded by abundant collagen fibres. They were curved, bent, frayed and spiral-shaped or appeared as worm-like bundles in some areas. They had a periodicity ranging from around 44nm to 66nm. (A) 1500x (B) 4000x (C) 15000x (D) 50000x and (E) 50000x. (F) Normal type III collagen in renal interstitium, 50000x (periodicity averaging 64nm).

compared to those normally seen in the interstitial compartment. They were curved, bent, frayed and spiral-shaped or appeared as worm-like bundles in some areas. They had a periodicity ranging from around 44nm to 66nm, but most fibrils had a periodicity of less than 60nm (Fig. 2D, 2E), contrasting with a periodicity of about 64nm for normal collagen III fibres. The fact that there were no banded collagen fibrils with normal periodicity in the lamina densa ruled out Nail-Patella syndrome. Effacement of podocyte foot processes was very extensive, affecting more than 95% of peripheral capillary wall surface area. In a few foci, small amount of amorphous or granular subendothelial deposits were seen, in-keeping with non-specific entrapment of plasma proteins.

DISCUSSION

This report adds to the rare cases of collagenofibrotic glomerulopathy with serial renal biopsies documenting disease progression on histology. For this patient, the first renal biopsy in 2005 showed FSGS. There was focal glomerular capillary basement membrane thickening with report of non-specific glomerular staining for IgG and C3. This probably represented the early or initial phase of the disease. As we were unable to review the original slides, it is unclear if small amount of collagen accumulation could have been interpreted as sclerosis. The diagnosis of lupus nephritis was rendered based on the impression that wire-loop deposits were present upon review of the first kidney biopsy. However, immunofluorescence microscopy was not repeated. The diagnosis of MPGN in the second biopsy was entirely understandable given that there was variable increase in mesangial cellularity and matrix as well as lobular accentuation in some glomeruli. In addition, granular deposits of IgG and diffuse staining for C3 could have given the false impression of MPGN. We postulate that as the disease progresses, replacement of glomeruli with type-III collagen becomes more obvious. This is accompanied by significant reduction in glomerular cellularity and paucity of immunoreactants except in areas of entrapment by plasmatic insudates. Over the course of more than 10 years, histological findings are now classical. It is noteworthy that all of the previous biopsies had no electron microscopy data. This highlights the central role of electron microscopy in the diagnosis of collagenofibrotic glomerulopathy.

Normal collagen III fibres are long, straight and arranged in parallel arrays, unlike those seen in this case, which are curved and sometimes aggregated in worm-like bundles. The significance of the abnormal collagen III fibres is unclear. In most published articles, authors have described these banded fibres as having a periodicity of 60nm[4,6] which corresponds to the normal periodicity of type III collagen. Sometimes, collagen fibrils with normal periodicity are admixed with those having abnormal periodicity. However, in many of these reports, measurements of periodicity have not been clearly shown. In our case, we found that the periodicity of the banded fibres was mostly below 60nm, and this observation was similarly made by Zhou and colleagues.[7] There have been isolated reports of the presence of collagen type V along with type III collagen in this disease. In our case, the anti-type V collagen staining using both immunohistochemistry and immunofluorescence techniques yielded negative results (images not shown).

The aetiology of this disease is unknown. There have been reports of familial connections[5] or autosomal recessive mode of inheritance especially in children but most cases occur sporadically.[1,2,3,4,6] A familial connection in our case cannot be established. An increase in serum procollagen type III peptide level, the precursor molecule of type III collagen, has been documented in some patients with collagenofibrotic glomerulopathy.[8,9] Extra-renal involvement in this disease has only been documented in a single case.[10]

Currently, there is no specific treatment for this disease. Supportive measures such as blood pressure control are commonly employed. The objective of the treatment plan for our patient is to optimise her blood pressure using a combination regime which includes angiotensin receptor blockade. She remains on 4 monthly follow-up at our clinic. In her last review, renal function remained stable at 4.11mg/dl with proteinuria of 4.75 g/day. Systemic blood pressure was 130/80mmHg.

Conclusion

This case highlights the importance of thorough examination of renal biopsies by electron microscopy. Serial biopsy findings for collagenofibrotic glomerulopathy are rarely described in the literature. In its classic form, the appearance on light microscopy is unmistakable but FSGS and MPGN-type pattern of injury may be seen

in early stages, rendering an accurate diagnosis difficult. This is the experience of a few other investigators.[2,10]

Acknowledgements: The authors state that there are no conflicts of interest to disclose.

REFERENCES

1. Arakawa M, Fueki H, Hirano H, *et al*. Idiopathic mesangio-degenerative glomerulopathy. Jpn J Nephrol. 1979; 21: 914-5.
2. Dong J, Wei H, Han M, Guan Y, Wu Y, Li H. Collagen type III glomerulopathy: A case report and review of 20 cases. Exp Ther Med. 2015; 10: 1445-9.
3. Nimmagadda S, Mukku K, Devaraju SR, Uppin MS. Unusual cause of glomerular deposition disease: Collagenofibrotic glomerulopathy. Indian J Nephrol. 2017; 27: 62-5.
4. Alchi B, Nishi S, Narita I, Gejyo F. Collagenofibrotic glomerulopathy: clinicopathologic overview of a rare glomerular disease. Am J Kidney Dis. 2007; 49: 499-506.
5. Gubler MC, Dommergues JP, Foulard M, *et al*. Collagen type III glomerulopathy: a new type of hereditary nephropathy. Pediatr Nephrol. 1993; 7: 354-60.
6. Chen T, Achan A, Li K, Harris D. Collagenofibrotic Glomerulopathy. Nephrology 2018; 23: 601-2.
7. Zhou XJ, Laszik ZG, Nadasdy T, D'Agati VD, editors. Silva's Diagnostic Renal Pathology. 2nd ed. Cambridge: Cambridge University Press; c2017. 671p
8. Cohen AH. Collagen type III glomerulopathies. Adv Chronic Kidney Dis. 2012; 19: 101-6.
9. Ikeda K, Yokoyama H, Tomosugi N, Kida H, Ooshima A, Kobayashi K. Primary glomerular fibrosis: A new nephropathy caused by diffuse intra-glomerular increase in atypical type III collagen fibers. Clin Nephrol 1990; 33: 155-9.
10. Yasuda T, Imai H, Nakamoto Y, *et al*. Collageno-fibrotic glomerulopathy: A systemic disease. Am. J Kidney Dis. 1999; 33: 123-7.