Minimal Change Disease Associated with SARS-CoV-2 (COVID-19) Infection among Adult Filipinos: A Report of Two Cases and Review of Related Literature

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ABSTRACT

A 40-year-old Filipino female with a history of right total mastectomy for a low-grade phyllodes tumor was admitted due to stillbirth. Her laboratory results revealed an incidental finding of a positive COVID-19 RT-PCR swab, serum creatinine 1.04 mg/dL, urine RBC 1/HPF, and a 24-hour urine protein of 9.22 grams with hypoalbuminemia and dyslipidemia. Serologic workup was noted to be negative. A kidney biopsy was performed which demonstrated unremarkable light microscopy (LM) and immunofluorescence (IF) with widespread podocyte-foot process effacement, consistent with minimal change disease. She was started on prednisone (1 mg/kg/day) and achieved complete remission after six weeks.

A 61-year-old Filipino male with a history of Type 2 Diabetes Mellitus, Hypertension, Dyslipidemia, and mild COVID-19 infection four months prior, now presented with diarrhea. On admission, his COVID-19 RT-PCR swab revealed a re-infection. Workup demonstrated a serum creatinine 3.39 mg/dL, urine RBC 2/HPF, and urine ACR 2.6 g/g. Serologic tests were negative. He was diagnosed with Nephrotic Syndrome and underwent kidney biopsy. Findings showed an unremarkable LM and IF with widespread podocyte-foot process effacement, consistent with minimal change disease. He was started on prednisone (1 mg/kg/day) and achieved complete remission after eight weeks.

SARS-CoV-2 (COVID-19) may present with a variety of kidney involvement which includes glomerulopathies such as MCD. An accurate diagnosis using the patient's clinical presentation, renal histopathology, and adjunct laboratory examinations, is essential to direct effective management and good outcomes.

Keywords: COVID-19, Minimal Change Disease, Nephrotic Syndrome, case report

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INTRODUCTION

COVID-19 related glomerulopathies are uncommon renal manifestations, recently highlighted in various case reports.[1-5] These histopathologic changes, which include minimal change disease (MCD), may either be primary or secondary to medications, malignancies, allergies, auto-immune diseases and infections.[3-6] Here, we present two cases of biopsy confirmed minimal change disease secondary to SARS-CoV-2 (COVID-19) infection among adult Filipino patients.

CASE PRESENTATION

Case 1

A 40-year-old Filipino female with a history of right total mastectomy two years prior for a low-grade phyllodes tumor, was admitted due to stillbirth (28 weeks age of

gestation, gravida 1 para 0). The patient denied having other medical comorbidities, history of elevated creatinine levels, and regular intake of medications such as non-steroidal anti-inflammatory drugs. She also denies getting vaccinated for COVID-19. Her pre-natal urine dipstick protein was noted at +1.

On admission, she presented with a blood pressure of 110/70 mmHg and was comfortable on room air. The patient relates that she has been noticing progressive leg swelling for the past one week. Physical examination revealed clear breath sounds but with bipedal edema. Her admitting nasopharyngeal COVID-19 real time polymerase chain reaction (RT-PCR) swab turned out positive but the patient denied experiencing any COVID-19 related symptoms. No steroids or investigational drugs were given. Her initial workup included the following: serum creatinine 1.04 mg/dL, albumin 1.6 g/dL, cholesterol 298 mg/dL (normal value: <200 mg/dL), low density lipoprotein (LDL) 175 mg/dl (normal value: 100-127mg/dL), high density lipoprotein (HDL) 44.4 mg/dl (normal value: 40-60 mg/dL), triglyceride 397.35 mg/dl (normal value: <150 mg/dL), and hemoglobin 12.5 g/dL. Urine studies were notable for a urine dipstick protein +3, urine red blood cell (RBC) 6 per high power field (HPF) with no dysmorphism and a 24-hour urine protein of 9.22 grams. Serologic workup was unremarkable: negative antinuclear antibodies (ANA), hepatitis profile and human immunodeficiency virus (HIV) screen, anti-streptolysin (ASO) titer <200IU/mL (normal value <200IU/mL) and complement C3 of 0.96 g/L (normal value: 0.811–1.57 g/L). Renal ultrasound showed normal kidneys with the right kidney measuring 11.2 x 4.2 x 4.5 cm with cortical thickness of 1 cm and the left kidney measuring 11.3 × 5 × 4.7 cm with cortical thickness of 1 cm.

A kidney biopsy was scheduled but delayed due to hospital policies on the prevailing pandemic case surge. She was eventually discharged clinically improved with resolution of edema and a negative COVID-19 RT PCR swab. She was sent home on losartan (100 mg/day), atorvastatin (40 mg/day) and as needed furosemide 40 mg with close outpatient follow-up.

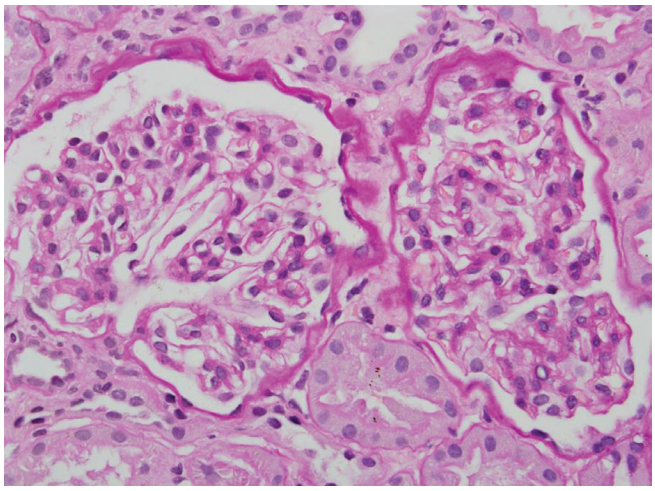

Figure 1A. ***Light microscopy.*** Representative glomeruli showing an unremarkable glomerulus *(Periodic Acid Schiff stain, x60).*

Two weeks after discharge, the patient started noticing recurrence of bipedal edema, however, the patient was lost to follow-up. She eventually returned for consult four weeks after discharge with recurrence of bipedal edema, now with periorbital involvement. Her serum creatinine was noted at 0.67 mg/dL but with a 24-hour urine protein of 4.71 grams, despite compliance with her medications. A kidney biopsy was performed and demonstrated the following: light microscopy examination of 15 glomeruli was generally unremarkable without endocapillary or extracapillary proliferation as well as tubular atrophy or interstitial fibrosis (Figure 1A). Trace IgG, IgM, fibrinogen and a negative IgA, C1q, and C3 was noted on immunofluorescence staining (Figure 1B). Electron microscopy showed fairly widespread podocyte-foot process effacement with absent electron dense deposits (Figure 1C). These biopsy findings were interpreted to be consistent with minimal change disease.

She was started on prednisone 50 mg per day (1 mg/kg/day) with losartan (100 mg/day) and atorvastatin (40 mg/day). Six weeks after starting the regimen, the patient achieved complete remission with a 24-hour urine protein of 180 mg, serum creatinine 0.71 g/dL and serum albumin 3.6 g/dL. Two weeks later, prednisone was gradually tapered by 5 mg per week until discontinued. No adverse effects were noted.

Six months after completing her steroid regimen, the patient is still in remission (urine dipstick protein negative, 24-hour urine protein 185 mg, serum albumin 3.8 g/dL, serum creatinine 0.66 mg/dL) with resolution of dyslipidemia and absence of edema.

Case 2

A 61-year-old Filipino male with a history of controlled type 2 diabetes mellitus (on sitagliptin 50 mg/day), hypertension stage I (on losartan 50 mg/day) and dyslipidemia (on atorvastatin 40 mg/day) presented to the emergency room with diarrhea. He denies any previous history of creatinine elevations, drug intake other than his maintenance medications and COVID-19 immunization. Four months prior, he was admitted as a case of mild COVID-19 infection where only supportive therapy was given. He was discharged clinically recovered with a negative COVID-19 RT PCR swab.

One week prior to his present consultation, he started noticing progressive bipedal edema and frothy urine. He sought consult at a local clinic where work up was done. His laboratory results showed the following: serum creatinine 2.39 mg/dL, albumin 1.73 g/dL, cholesterol 771.81 mg/dL (normal value: <200 mg/dL), HDL 28.57 mg/dL (normal value: 40-60 mg/dL), LDL 274.90 mg/dL (normal value: 100-127 mg/dL), triglyceride 341.61 mg/dL (normal value: <150 mg/dL), and hemoglobin 13 g/dl. Urine studies

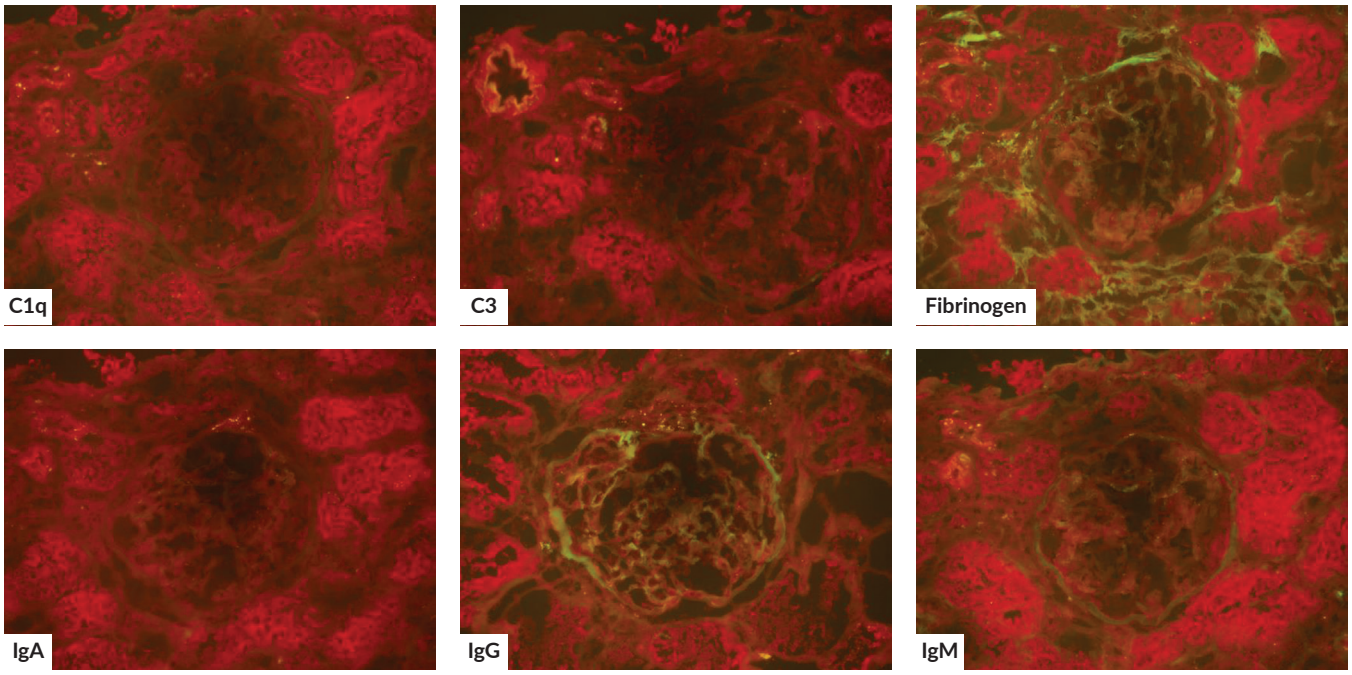

Figure 1B. Immunofluorescence demonstrating trace IgG, IgM and fibrinogen and a negative IgA, C1q, and C3.

revealed a urine dipstick protein +3, urine glucose +2, urine RBC 0-1/HPF with a random urine albumin creatinine ratio 2,600 mg/g. Serologic workup included a negative ANA, hepatitis profile and HIV screen with a complement C3 of 1.02 g/L (Normal value: 0.811–1.57 g/L). A renal ultrasound demonstrated bilaterally normal kidneys with the right kidney measuring 10.8 x 4.4 x 4.5 cm with cortical thickness of 1.1 cm and the left kidney measuring 10.6 × 5 × 1.4 cm with cortical thickness of 1 cm. He was diagnosed with Nephrotic Syndrome and advised kidney biopsy; however, the patient did not consent. He was instead advised close follow-up and started on furosemide (40 mg twice a day) with continuation of his maintenance medications.

Two days prior to admission, the patient started experiencing diarrhea which prompted consult. He presented at the emergency room with a blood pressure of 80/60 mmHg that was responsive to fluid resuscitation and stable oxygen

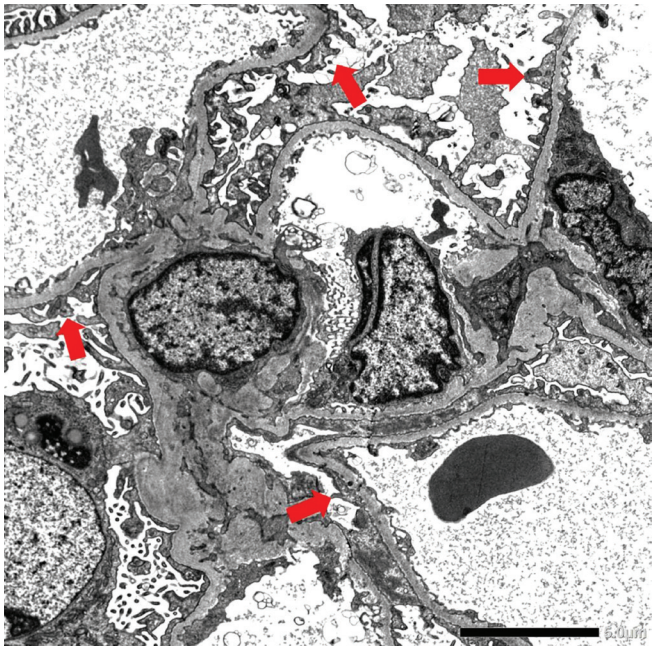

Figure 1C. Electron microscopy demonstrating widespread foot process effacement *(red arrows)*.

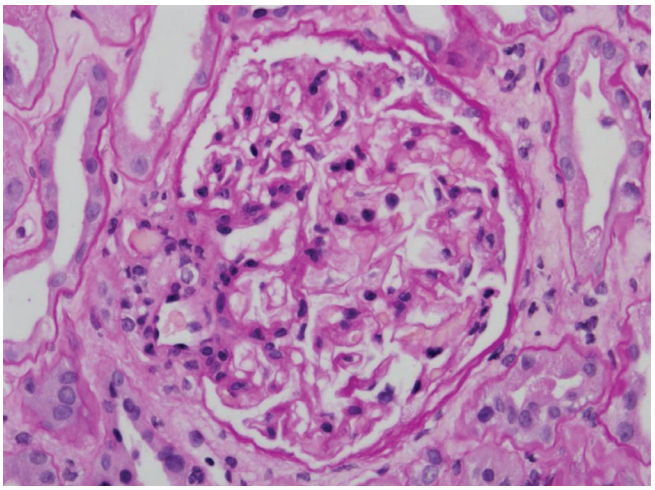

Figure 2A. ***Light microscopy.*** Representative glomerulus appearing unremarkable (Periodic Acid Schiff stain, x60).

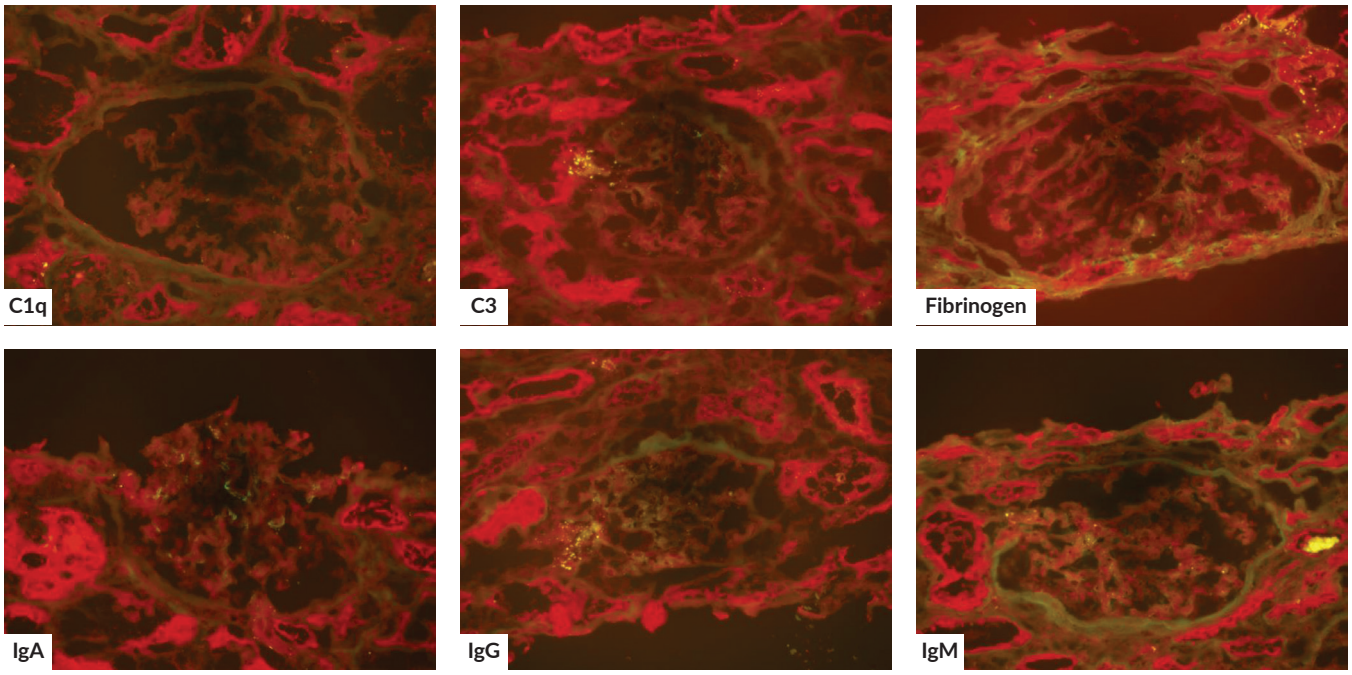

Figure 2B. Immunofluorescence demonstrating trace IgG, IgA, IgM, C3, fibrinogen and a negative C1q.

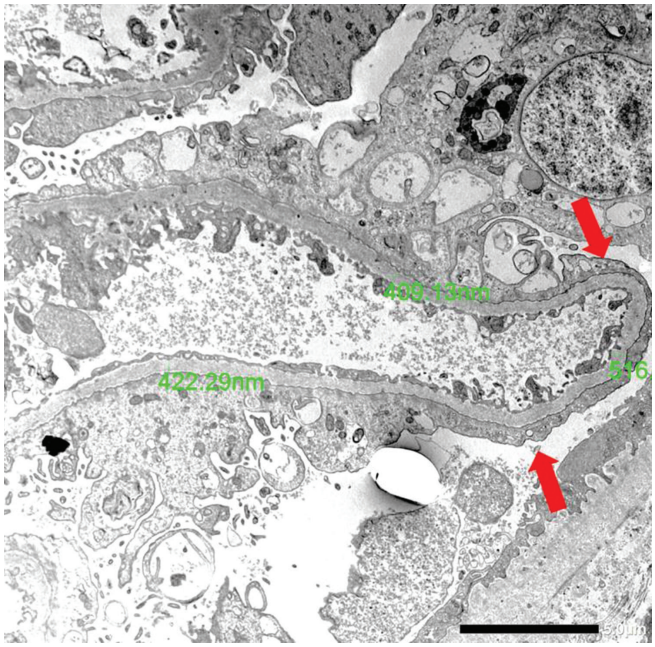

Figure 2C. Electron microscopy view with widespread foot process effacement *(red arrows)*.

saturations at room air. Further examination noted clear breath sounds, non-tender abdomen and bipedal edema. His COVID-19 RT-PCR swab on admission turned out positive. No steroids or investigational drugs were given. The patient eventually improved through the course of his hospitalization with supportive management. A kidney biopsy was later performed prior to the patient's discharge revealing the following: light microscopy examination of 14 glomeruli was generally unremarkable, without signs of chronic injury such as tubular atrophy or interstitial fibrosis (Figure 2A). Immunofluorescence staining noted trace IgG, IgA, IgM, C3, fibrinogen and a negative C1q (Figure 2B). On electron microscopy, widespread podocyte foot process effacement was observed (Figure 2C). These findings were found to be consistent with minimal change disease.

He was started on prednisone at 60 mg once a day (1 mg/kg/day), losartan (100 mg/day), (atorvastatin 40 mg/day) and furosemide (40 mg twice a day) with his diabetic medications. The patient was able to achieve complete remission (24-hour urine protein 200 mg, serum creatinine 0.70 mg/dL, serum albumin 4 g/dL) after eight weeks. Gradual tapering of prednisone was then done at 5 mg per week. No adverse effects were noted.

Six weeks after steroid tapering, the patient is maintained in remission with prednisone 30 mg per day (urine dipstick protein negative, 24-hour urine protein 190 mg, serum albumin 3.8 g/dL, serum creatinine 0.66 mg/dL). He also reports resolution of edema.

DISCUSSION

Multiple cases of nephrotic syndrome attributed to COVID-19 infection have been described in literature, usually presenting with heavy proteinuria with AKI.[2-4,6] Here we described two cases of minimal change disease with temporal association with a confirmed COVID-19 infection, and who were successfully treated with steroids leading into complete remission.

Table 1. Summary of Case Reports of COVID-19-associated MCD

Author	Age/Sex/Ethnicity	Comorbidity	Clinical Presentation	Renal Biopsy Findings	Treatment	Outcome
Kudose et al. (2021)	25/M/African American (+APOL1)	Obesity	AKI, NS, COVID mild	MCD, ATI	Steroids	Complete remission
	42/M/African American (+APOL1)	Obesity	AKI, SNRP, COVID Critical	MCD, ATI	None	Partial to No remission
	59/F/African American (+APOL1)	HPN, T2DM, Dyslipidemia	AKI, NRP, COVID mild	MCD, DDGS, ATI	None	No remission
Kudose et al. (2020)	25/M/African American	Obesity	AKI, NS, COVID mild	MCD	Steroids	Complete remission
Yamada et al. (2020)	49/F/African American (+APOL1)	s/p KT, HPN	AKI, NS, COVID mild	MCD	Steroids	Complete remission
Akilesh et al. (2021)	52/F/Caucasian	None	NS	MCD	Steroids	Complete remission

Abbreviations: HPN – Hypertension, T2DM – Type 2 Diabetes Mellitus, BPH – Benign Prostatic Hyperplasia, AKI – Acute Kidney Injury, NS – Nephrotic Syndrome, KT – Kidney Transplant, MCD – Minimal Change Disease, ATI – Acute Tubular Injury, ATN – Acute Tubular Necrosis, DDGS – Diffuse Diabetic Glomerulosclerosis, NRP – Nephrotic Range Proteinuria, SNRP – Subnephrotic Range Proteinuria

Current studies have shown that increased risk of glomerular disease with COVID-19 involves direct cellular toxicity and podocyte injury.[3] There have been a growing number of reports linking the APOL1 genotype to COVID-19 related glomerulonephritis. The G1 and G2 APOL1 alleles are already well-established risk factors for non-COVID-19 kidney disease such as HIV-associated nephropathy, lupus nephritis, and FSGS.[7] It is suspected that APOL1 risk variants are toxic gain-of-function mutations with dysregulated innate immune responses that drive kidney disease in susceptible individuals who carry the APOL1 risk alleles.[8] Viral infections may lead to higher levels of endogenous APOL1 stimulation from interferon and toll-like receptor agonists, which in turn increase toxicity and trigger podocytopathy.[3] T-lymphocyte activation and cytokine release in critically-ill COVID-19 patients may also produce enhanced apoptosis of target cells, impaired virus clearance, and promote APOL1 gene expression in podocytes.[7,9,10] Ideally, APOL1 testing should have been performed but due to its unavailability locally, our team did not perform the said testing.

There are no specific treatment-related studies pertaining to COVID-19-associated MCD. Both of our patients were started on steroid therapy at 1 mg/kg/day with gradual taper in accordance with The Kidney Disease: Improving Global Outcomes (KDIGO) 2021 Clinical Practice Guidelines for the Management of Glomerular Diseases.[11] Sustained remission was achieved on subsequent follow-up.

Long term outcomes studies are also lacking. In a case series of three patients with COVID-19-related MCD by Kudose et al., none were dialysis dependent after median follow-up of 157 days. Two out of three patients diagnosed with MCD achieved resolution of AKI and reduction of proteinuria while one patient had persistent renal dysfunction and proteinuria.[12] Overall, existing reports suggest that most cases of COVID-19-associated MCD will often achieve resolution of AKI and proteinuria with steroid therapy, and those that failed to produce any kind response was likely due to the failure to implement prompt steroid therapy,[4,7,12] emphasizing the need for an accurate histologic classification (Table 1).

To our knowledge, this is the first case series describing the course of minimal change disease associated with COVID-19 among adult Filipino patients. Further studies will be needed in order to identify the pathophysiology and mechanisms of SARS CoV-2 and its relationship with MCD.

CONCLUSION

SARS-CoV-2 (COVID-19) may present with a variety of kidney involvement which includes glomerulopathies such as MCD. A COVID-19-associated MCD is likely being driven by susceptible genotype and the resulting pro-inflammatory state; however, this predisposition must be further elucidated by future studies. An accurate diagnosis using the patient's clinical presentation, renal histopathology and adjunct laboratory examinations, is essential to direct effective management and good outcomes.

Ethical Considerations

Informed consent was obtained from the patients for publication of this report and all identifying information has been removed to protect the patients' privacy.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

The authors declare that they have no conflicts of interest with respect to the research, authorship, and/or publication of this case report.

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