Received: 2019.05.23
Accepted: 2019.08.27
Published: 2019.10.27

e-ISSN 1941-5923
© Am J Case Rep, 2019; 20: 1576-1580
DOI: 10.12659/AJCR.917722

Collapsing Focal Segmental Glomerulosclerosis with Acute Interstitial Nephritis Associated with *Plasmodium Falciparum*: A Case Report and Review of the Literature

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCDEF **Muhammad Azhar**
BCDEF **Lutfi Alasadi**
BCDEF **Stephen Kemnele**
BCDEF **Ira W. Reiser**
BCDEF **Samuel Spitalewitz**

Division of Nephrology and Hypertension, Brookdale University Hospital and Medical Center, Brooklyn, NY, U.S.A.

Corresponding Author: Muhammad Azhar, e-mail: mazhar@bhmcny.org
Conflict of interest: None declared

Patient: Male, 64
Final Diagnosis: Collapsing focal segmental glomerulosclerosis with acute interstitial nephritis associated with *Plasmodium falciparum*
Symptoms: Diarrhea • chills • fever • myalgia
Medication: —
Clinical Procedure: —
Specialty: Nephrology

Objective: Muhammad Azhar, e-mail: mazhar@bhmcny.org
Background: Malaria adversely affects the kidney in a variety of ways. The most common kidney injury is acute tubular necrosis, although various glomerular lesions are also described. Of these, collapsing focal segmental glomerulosclerosis (cFSGS) is the most rarely seen. Thus, the natural history of this lesion and response to treatment are not clear. Herein, we present a case of cFSGS complicated by acute interstitial nephritis caused by *Plasmodium falciparum* (*P. falciparum*) unresponsive to prednisone.
Case Report: A 64-year-old Nigerian man with chronic kidney disease due to hypertensive nephropathy was admitted to the hospital, diagnosed with active *P. falciparum* malaria infection after returning from Nigeria. He developed acute kidney injury and nephrotic range proteinuria. Renal biopsy showed acute interstitial nephritis and cFSGS. Despite corticosteroid therapy, his kidney function worsened, requiring initiation of renal replacement therapy. This is the fifth case report of cFSGS due to malaria *P. falciparum* but the first to report the presence of acute interstitial nephritis in association with cFSGS due to malaria.
Conclusions: cFSGS is rarely seen as a manifestation of *P. falciparum* infection. When associated with acute interstitial nephritis, the prognosis seems to be worse. It appears that age and co-morbidities are the risk factors for unresponsiveness to corticosteroids, and treatment of the renal disease should focus on rapidly eradicating the parasitemia and providing supportive care. Our case report is the first to describe a combination of cFSGS and interstitial nephritis caused by *P. falciparum* unresponsive to corticosteroids.

MeSH Keywords: Glomerulosclerosis, Focal Segmental • Kidney Failure, Chronic • Malaria • *Plasmodium falciparum* • Prednisone

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/917722>

1773 2 2 15

Background

Malaria is a major public health problem in endemic countries and is associated with significant morbidity and mortality. Renal complications can be caused by malaria, including acute kidney injury (AKI), glomerular disease, and progressive renal injury in some instances resulting in end-stage renal disease (ESRD) requiring maintenance dialysis. The incidence of AKI due to *P. falciparum* is 1–5% and as high as 30% in residents of endemic and non-endemic areas, respectively, with a mortality rate approaching 15–45% in malaria-naïve adults without innate immunity [1]. The more common glomerular lesions associated with malaria are mesangioproliferative glomerulonephritis, membranoproliferative glomerulonephritis, and diffuse proliferative glomerulonephritis. Minimal change disease, IgA nephropathy, membranous nephropathy, and focal segmental glomerulosclerosis (FSGS) are rarely seen [2,3]. Of the latter, there are only 4 reported cases of collapsing focal segmental glomerulosclerosis (cFSGS) with *P. falciparum* [4–7]. Herein, we report an additional case of cFSGS with *P. falciparum* complicated by acute interstitial nephritis.

Case Report

A 64-year-old Nigerian man with a history of hypertension and chronic kidney disease (CKD) stage 3 with a baseline serum creatinine concentration of 1.8 mg/dL thought to be due to hypertensive nephropathy presented with paroxysmal fever, chills, malaise, myalgia, arthralgia, and watery diarrhea. These symptoms occurred 3–4 days after returning from Nigeria following a long absence from that country. In the Emergency Department, he was hypotensive, with an otherwise unremarkable physical examination. The initial laboratory data (Table 1) demonstrated a hemoglobin of 14.4 g/dL, a platelet count of 61 000 platelets/ μ L, an LDH of 1677 IU/L (reference range 313–618 IU/L), and a CPK of 116 U/L (reference range 55–170 U/L). A peripheral thin blood smear prepared by Wright's stain showed *P. falciparum* infection, with a parasitemia of 2.5%. There was no evidence of acute hemolysis. Total bilirubin and indirect bilirubin were normal, at 0.7 mg/dL and 0.6 mg/dL, respectively, and haptoglobin was not reduced (158 mg/dL). His BUN and serum creatinine increased to 43 mg/dL and 5.13 mg/dL, respectively, with an otherwise normal basic metabolic panel.

Table 1. Relevant laboratory data with reference range.

Laboratory test	Result	Reference range
Hemoglobin	14.4 g/dL	Female: 12–16 g/dL; male: 14–18 g/dL
Platelets	61 000/ μ L	150 000–450 000/ μ L
LDH	1677 U/L	80–225 U/L
CPK	116 U/L	Female: 30–135 U/L; male: 55–170 U/L
Peripheral thin blood smear	Parasitemia of 2.5%	
Serum creatinine (initial)	5.13 mg/dL	Female: 0.50–1.10 mg/dL; male: 0.70–1.30 mg/dL
BUN (initial)	43 mg/dL	8–20 mg/dL
Serum creatinine 9 th day	18 mg/dL	
BUN 9 th day	85 mg/dL	
Spot urine protein-to- creatinine ratio	27.2 g/g	Less than 0.2 mg/mg
Anti-nuclear antibodies	<1: 40 (negative)	1: 40 or less
Anti-neutrophil cytoplasmic antibodies (c-ANCA, p-ANCA)	<1.0 U	Less than 1 U
Hepatitis B surface antigen and hepatitis C antibody	Negative	Negative
Human immunodeficiency virus (HIV) Ab Type 1 and 2	Negative	Negative
Parvovirus B19 IgM, IgG	IgM<0.6 IV, IgG <0.4 IV	<0.9 IV
Cytomegalovirus DNA	<2.30 log IU/mL	<2.30 log IU/mL
C3 complement	109	100–233 mg/dL
C4 complement	17	14–48 mg/dL

Figure 1. Moderate interstitial fibrosis associated with tubular atrophy (blue arrow), proteinaceous casts (green arrow), and dense interstitial lymphocytic infiltrate (black arrow). (PAS staining; original magnification $\times 100$).

The urine dipstick showed >300 mg/dL protein and urine analysis showed >50 RBCs/HPF and 0–3 WBCs/HPF. A subsequent spot urine protein-to-creatinine ratio demonstrated 27.2 g/g. Despite a hemodynamic response to fluid resuscitation and effective treatment of malaria with atovaquone/proguanil hydrochloride 250/100 mg daily for 3 days according to CDC recommendations, he remained oliguric and his renal function continued to deteriorate. On the 9th day of hospitalization, his BUN and serum creatinine peaked at 85 mg/dL and 18 mg/dL, respectively, and renal replacement therapy was initiated. A renal sonogram demonstrated normal-sized but hyperechogenic kidneys.

A renal biopsy on light microscopy demonstrated cFSGS with moderate interstitial fibrosis, acute tubular injury with proteinaceous casts, and a dense T cell lymphoplasmacytic infiltrate throughout, consistent with both an acute and chronic interstitial nephritis (Figures 1, 2). Immunofluorescence staining for IgG, IgA, IgM, C3, C1q, kappa, lambda, albumin, and fibrinogen was negative. Electron microscopic findings demonstrated podocyte injury with vacuolization and protein droplets. There was global effacement of the foot processes and there were no sub-epithelial, intramembranous, sub-endothelial, or mesangial immune-type electron-dense deposits. There was a mild increase in mesangial matrix deposition and the tubules showed signs of acute tubular injury with nuclear dropout.

An additional workup included normal serum complement levels and no evidence of monoclonal gammopathy by urine and serum electrophoresis. Serological assays were negative for anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies, hepatitis B and C viruses, human immunodeficiency virus (HIV), cytomegalovirus, and parvovirus B19.

The patient had been taking hydrochlorothiazide 25 mg daily for hypertension at home. During hospitalization, he received oral amlodipine 10 mg daily and enalapril 10 mg daily. Despite

Figure 2. Segmentally sclerosed glomerulus with capillary loops collapse (black arrow) and surrounding podocyte hypertrophy (blue arrow). (PAS staining; original magnification $\times 200$).

receiving a prolonged course of oral prednisone 60 mg daily for 3 months to treat his interstitial nephritis without developing any sign of infection, his renal function never recovered and he remained dialysis-dependent and died at home from an unknown cause.

Discussion

FSGS is generally divided into primary and secondary forms. In the primary form, response to immunosuppressive therapy varies with the histological variant, with cFSGS being the least likely to respond to immunosuppressive therapy and often having an inexorable course to ESRD, with or without therapy. When associated with the apolipoprotein A1 (*APOL1*) risk alleles, the prognosis of FSGS is worse [8].

In primary FSGS with nephrotic syndrome, glucocorticoids are recommended as an initial therapy, and the duration of treatment is variable, depending upon response to and toxicity from steroids. In steroid-resistant FSGS or when steroids are relatively or absolutely contraindicated, immunosuppressive therapy with calcineurin inhibitors (CNIs) is considered the initial alternative treatment. In cases where CNIs are contraindicated or ineffective, mycophenolate mofetil, adrenocorticotropic hormone, or rituximab can be considered an alternative therapy, with the latter being more useful in steroid-dependent patients.

The secondary form includes genetic, autoimmune, infectious, and drug-induced etiologies, and variants mediated by adaptive responses to a reduction in functional renal parenchyma. In the cFSGS variant associated with infection, it is likely that podocytes are injured directly by the infectious agent, which results in cellular dedifferentiation, parietal epithelial cell proliferation, and consequent loss of glomerular filtration. The detection of parvovirus B19 in renal epithelial cells associated with cFSGS, and a similar association with HIV disease, support

Table 2. Comparison of 5 cases, including our case report.

Case report no.	1	2	3	4	5
Age, Sex	37, Female	12, Male	62, Female	72, Male	64, Male
Race	African	Asian	African	African	African
Country	Senegal	India	Netherlands	USA	USA
Travel history			Ghana	Ghana	Nigeria
Biopsy	cFSGS	cFSGS	ATN, cFSGS	ATN, cFSGS	AIN, cFSGS
Complications	HPS	HUS, PRES	Insignificant	Insignificant	Insignificant
Proteinuria	51.45 g/day	3+	20 g/day	7.9 g/g	27.2 g/g
Treatment	Steroid, 5 sessions of HD	28 sessions of HD	HD	HD	Steroid, HD
Year	2008	2013	2014	2015	2018
Recovery	Complete	Complete	Maintenance HD	Maintenance HD	Maintenance HD
Factors affecting renal recovery	Young age, no co-morbidities except asthma, HPS	Young age, no co-morbidities	Old age, ATN, co-morbidities including DM, HTN	Old age, ATN, co-morbidities including HTN, CKD	Old age, AIN, co-morbidities including HTN, CKD

HPS – hemophagocytic syndrome; HUS – hemolytic uremic syndrome; PRES – posterior reversible encephalopathy syndrome.

this supposition [9]. To date, such a direct association, however, has not been demonstrated with malaria. In addition to malaria, among others, infection associated with cFSGS has been described with HIV, cytomegalovirus, parvovirus B19, Epstein-Barr virus, schistosomiasis, and filariasis [8]. The association with parasitic infection is likely a rare event given the frequency of these infections worldwide. However, when secondary FSGS is due to infection, treatment of the underlying infection is the most important therapy, and when secondary FSGS is due to nephron loss, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are the preferred treatment.

Malaria-induced renal injury is most commonly associated with hemolysis and pigment-induced acute tubular necrosis (ATN) [10]. Although glomerular involvement is not uncommon, malaria-associated cFSGS is extremely rare and has only been described in 4 other cases in the literature. The therapeutic approach to infection-associated cFSGS is to eradicate the infecting agent, since therapy for even primary cFSGS is usually unsuccessful [11]. Treatment with corticosteroids should be considered only when given as therapy for extrarenal manifestations after the parasite is eradicated. For example, corticosteroids have been utilized in the treatment of encephalitis and in the hemophagocytic syndrome accompanying malaria [12,13].

The 64-year-old patient described in this report had baseline renal dysfunction, most likely secondary to hypertensive

nephropathy, with a baseline serum creatinine of 1.8 mg/dL and an eGFR of approximately 45 mL/min/1.73 m². Unfortunately, there was rapid deterioration in renal function despite clearing the infection and restoration of systemic hemodynamics. Renal biopsy showed typical findings of cFSGS. Associations with diseases other than malaria were virtually eliminated since the patient was HIV-negative and serological assays for other known potential causes for cFSGS were negative. It is important to note, however, that there were changes of chronic and intense acute interstitial nephritis, prompting us to utilize prednisone in an effort to treat the acute interstitial nephritis to improve renal function. The use of corticosteroids in acute interstitial nephritis based upon retrospective studies is recommended, and earlier treatment is usually more successful [14,15]. Unfortunately, our patient did not respond to prolonged corticosteroid therapy and required ongoing maintenance hemodialysis for 3 months before he died. High-dose steroid therapy for acute interstitial nephritis has been safely administered for approximately 12 weeks with no differentiation noted between dialysis-dependent vs. non-dialysis-dependent patients [15]. Although necrotic tubular cells were demonstrated on light microscopy, this was not secondary to heme-induced ATN, since the hemolysis work up did not support this diagnosis, making ATN secondary to the initial hemodynamic compromise the likely cause. This is evident by the lack of a discrepancy between urine microscopic examination of red cells and dipstick detection of hematuria on urinalysis, which is usually present with hemolysis.

As stated previously, 4 other reports of cFSGS associated with malaria have been described in the literature (Table 2). Two of these 4 cases never recovered renal function [4,5]. Common to both of these patients was that they were older (72 and 62 years old, respectively) with co-morbidities. One had baseline renal dysfunction and the other was diabetic and hypertensive. Both had ATN in addition to the cFSGS. Neither of these patients received corticosteroid therapy and they became irreversibly dialysis-dependent. Our patient was similar to both of these regarding old age and co-morbidities; however, our patient had acute interstitial nephritis that did not respond to corticosteroids. It is unknown whether the cFSGS was associated with the *APOL1* risk allele variant in any of these patients, which, if present, may have contributed to the poor outcomes.

Two of the patients, however, did recover [6,7]. Both were younger (12 and 37 years old, respectively) and had no co-morbidities. The 12-year-old patient's course, although complicated by posterior reversible encephalopathy associated with accelerated hypertension, recovered renal function without corticosteroids after a period of dialysis dependency of approximately 12 weeks. The 37-year-old patient recovered renal function after 3 weeks of maintenance dialysis. After clearing of the parasitic infection, the patient received pulses of methylprednisolone at 10 mg/kg per day for 3 days followed by 1 mg of prednisone/kg per day. After 3 months, corticosteroids were gradually tapered and then discontinued at 6 months. At the end of treatment, the patient had normal renal function. It is important to note that this patient had hemophagocytic syndrome associated with malaria, which is characterized by

primary uncontrolled T cell activation followed by an intense cytokine burst involving pro-inflammatory cytokines, TNF alpha, IL-6, and IL-1b [7]. There are 9 reported cases of nephrotic syndrome and acute renal failure associated with hemophagocytic syndrome reported with other hematologic diseases unrelated to malaria. The aforementioned intense inflammatory response is likely to be responsive to corticosteroids, thus making renal recovery more likely in these reported cases.

Conclusions

Although ATN is the most common renal manifestation of malaria, and other glomerulopathies may be seen, it is rarely associated with cFSGS. When present, the prognosis appears to be related to the age of the patient and co-morbidities at the time of presentation. The use of corticosteroids is generally unsuccessful in improving the renal outcome unless malaria is associated with the hemophagocytic syndrome. Therefore, rapid clearing of the parasite and supportive care offer the best possibility for renal improvement. Our patient had both cFSGS and acute interstitial nephritis, complicating chronic kidney disease, which unfortunately did not respond to corticosteroid therapy. To the best of our knowledge, this is the first case report of *P. falciparum* malaria associated with acute interstitial nephritis complicating cFSGS.

Conflict of interest

None.

References:

1. Barsoum RS: Malarial acute renal failure. *J Am Soc Nephrol*, 2000; 11(1): 2147–54
2. van Velthuysen ML, Florquin S: Glomerulopathy associated with parasitic infections. *Clin Microbiol Rev*, 2000; 13(1): 55–66
3. Barsoum RS: Malarial nephropathies. *Nephrol Dial Transplant*, 1998; 13(6): 1588–97
4. Sehar N, Gobran E, Elsayegh S: Collapsing focal segmental glomerulosclerosis in a patient with acute malaria. *Case Rep Med*, 2015; 2015: 420459
5. van Wolfswinkel ME, van Genderen PJJ, Goemaere NN, van Alphen AM: Collapsing glomerulopathy after *Plasmodium falciparum* infection. *Clin Kidney J*, 2014; 7(5): 495–96
6. Kute VB, Trivedi HL, Vanikar AV et al: Collapsing glomerulopathy and hemolytic uremic syndrome associated with *falciparum* malaria, completely reversible acute kidney injury. *J Parasit Dis*, 2013; 37(2): 286–90
7. Niang A, Niang SE, Fary Ka EH et al: Collapsing glomerulopathy and hemophagocytic syndrome related to malaria: A case report. *Nephrol Dial Transplant*, 2008; 23(10): 3359–61
8. Rosenberg Z, Kopp JB: Focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol*, 2017; 12(3): 502–17
9. Albaum M, Barisoni L: Current views on collapsing glomerulopathy. *J Am Soc Nephrol*, 2008; 19(7): 1276–81
10. Mishra SK, Das BS: Malaria and acute kidney injury. *Semin Nephrol*, 2008; 28(4): 395–408
11. Kukull B, Avasare RS, Smith KD et al: Collapsing glomerulopathy in older adults. *Mod Pathol*, 2019; 32(4): 532–38
12. Hasegawa C, Inagaki A, Yamada G et al: Steroid pulse therapy may mitigate prolonged neurological manifestations after eradication of severe *Plasmodium falciparum* parasitemia. *Intern Med*, 2016; 55(22): 3393–98
13. Bhagat M, Kanhere S, Kadakia P et al: Haemophagocytic lymphohistiocytosis. A cause of unresponsive malaria in a 5-year-old girl. *Pediatr Int Child Health*, 2015; 35(4): 333–36
14. Baker RJ, Pusey CD: The changing profile of acute tubulointerstitial nephritis. *Nephrol Dial Transplant*, 2004; 19(1): 8–11
15. Gonzalez E, Gutierrez E, Galeano C et al: Early steroid treatment improves the recovery of renal function in patients with drug induced acute interstitial nephritis. *Kidney Int*, 2008; 73(8): 940–46