

## Lupus-Like Glomerulonephritis Associated With Regorafenib, a Multikinase Inhibitor



Anna Strasma, Howard Coke, Omar Mamlouk, Amanda Tchakarov, and Sreedhar Mandayam

Drug-induced lupus glomerular diseases have historically been associated with hydralazine, but new drugs that modify the growth, metabolism, and immunity of cells are increasingly found to cause glomerular disease. This includes anti-tumor necrotic factor and other antibody agents used in cancer treatment. Multitarget tyrosine kinases such as regorafenib are increasingly used in metastatic malignancies with good outcomes. Currently, they are not known to have kidney complications except for proteinuria, hypertension, and electrolyte disturbances such as hypophosphatemia. We report a patient who presented within months after starting regorafenib therapy for metastatic colon cancer with acute kidney injury, proteinuria, and hematuria. Biopsy revealed endocapillary proliferative glomerulonephritis with full-house staining on immunofluorescence in the absence of any systemic manifestation of systemic lupus erythematosus. The kidney injury improved with corticosteroid treatment and discontinuation of regorafenib therapy. We discuss the possible mechanisms that led to this class IV pattern of lupus nephritis and conclude that it is likely drug-induced lupus nephritis from regorafenib.

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### INTRODUCTION

Drug-induced lupus glomerulonephritis has been reported in association with several drugs, including hydralazine, sulfasalazine, and propylthiouracil.<sup>1</sup> More recently, anti-tumor necrotic factor  $\alpha$  therapies have been added to this list. Multiple cases of biologic-induced autoimmune kidney disorders were recently reported.<sup>2</sup> This includes glomerulonephritis associated with systemic vasculitis, glomerulonephritis in lupus-like syndrome, and isolated autoimmune kidney disorders. This suggests the possibility that drugs that modify the growth, metabolism, and immunity of cells could lead to glomerulonephritis. Clinicians should be aware of this effect.

Regorafenib is an oral multikinase inhibitor that targets pathways involved in angiogenesis and tumor growth, including vascular endothelial growth factor, platelet-derived growth factor, and tyrosine kinases (Fig 1). It has a survival benefit in patients with metastatic colon cancer that has progressed despite standard therapies.<sup>3</sup> It is given orally daily for the first 21 days of a 28-day cycle.

Reported side effects include hand and foot syndrome, hypertension, rash, elevated liver enzyme levels, elevated bilirubin level, hypophosphatemia, and diarrhea.<sup>3</sup> Hand and foot syndrome is a common side effect that presents as bilateral pain, demarcated asymmetric redness, and swelling of the palms and soles usually preceded by a prodromal phase of dysesthesia.

The kidney-related adverse events of regorafenib are summarized in Table 1.<sup>4-6</sup> Vascular endothelial growth factor inhibitors and tyrosine kinase inhibitors are known to have a side effect of proteinuria.<sup>4</sup> Because regorafenib's mechanism of action is inhibiting both these pathways, it is not surprising that there is a higher reported incidence of proteinuria (7%) in the regorafenib group compared with placebo (2%), for which proteinuria is defined as protein

( $\geq 1+$ ) on urinary dipstick or quantified urinary protein excretion greater than the upper limit of normal.<sup>3</sup>

On review of the US Food and Drug Administration Adverse Event Reporting System, there are 40 cases of reported kidney injury, which included proteinuria and acute kidney injury, attributed to regorafenib.<sup>4</sup> There is only 1 previously reported case of biopsy-proven glomerular disease associated with regorafenib. Lopez et al<sup>5</sup> reported 1 patient who presented with new-onset hypertension, acute kidney injury, and nephrotic-range proteinuria shortly after starting regorafenib treatment. The biopsy showed concurrent focal segmental glomerulosclerosis, acute interstitial nephritis, and membranoproliferative glomerulonephritis.<sup>5</sup>

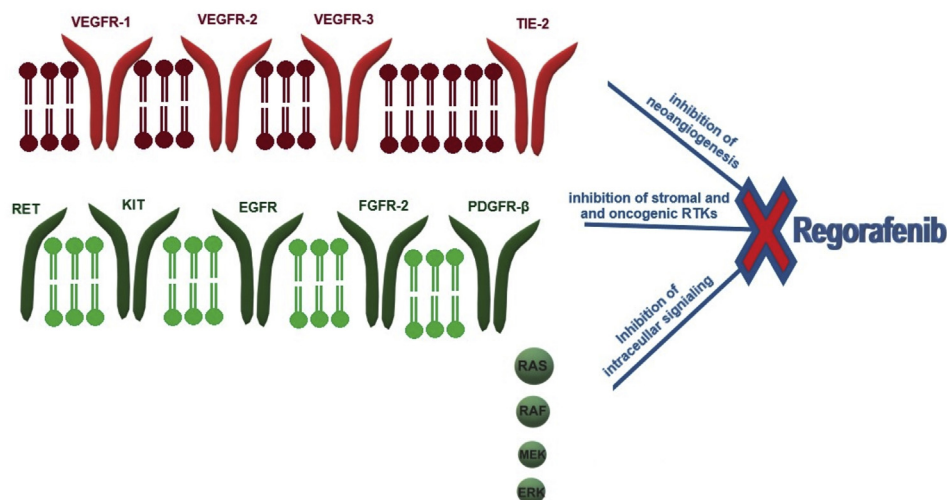
We describe a patient who developed a proliferative glomerulonephritis with “full-house” immunofluorescence within weeks after beginning treatment with regorafenib, a multikinase inhibitor.

### CASE REPORT

A man in his early 70s with a history of metastatic colon adenocarcinoma was admitted to the hospital with acute kidney injury.

The patient reported 2 months of bilateral upper and lower extremity edema and dyspnea on exertion. During the same period, he had gradual development of an erythematous and nonpruritic rash over his forearms and lower legs. He did not report orthopnea, changes in quantity of urine output, or foamy urine. The patient also did not report fevers, chills, joint pains, or nonsteroidal anti-inflammatory drug use. He had poor intake, especially of fluids.

The patient's medical history included rectosigmoid colon adenocarcinoma with metastasis to the lungs and liver. He also had renal cell carcinoma confined to the left kidney, completely removed with partial left nephrectomy 5 years ago. He had been on multiple treatment regimens



**Figure 1.** Regorafenib mechanism of action. Regorafenib is a multikinase inhibitor that interferes with tumor cell proliferation through multiple mechanisms: inhibition of neo-angiogenesis by targeting vascular endothelial growth factor receptor (VEGFR) 1-3 and tyrosine kinase with immunoglobulin-like and epidermal growth factor (EGF)-like domains 2 (TIE-2), and inhibition of tumor cell proliferation by targeting oncogenic receptor tyrosine kinases (RTKs; KIT and RET), stromal RTK (fibroblast growth factor receptor-2 [FGFR-2] and platelet-derived growth factor receptor β [PDGFR-β]), and intracellular signal pathway (rat sarcoma [RAS]-rapidly accelerated fibrosarcoma [RAF]-mitogen-activated protein kinase [MEK]-extracellular-signal-regulated kinase [ERK] pathway). Abbreviation: EGFR, EGF receptor.

**Table 1.** Summary of Reported Adverse Events With Regorafenib

Reported Kidney Side Effect	Incidence <sup>4,6</sup>	No. of Cases in FDA Adverse Events Reporting System Database <sup>5</sup>
Hypertension	28%,	57
Hypophosphatemia	5%	8
Hypokalemia	3%	7
Hyponatremia	—	9
Proteinuria	7%	—
AKI	0%	—
Kidney impairment (including proteinuria and AKI)	—	40
Concurrent FSGS, AIN, and MPGN	1 case report	—

Abbreviations: AIN, acute interstitial nephritis; AKI, acute kidney injury; FDA, US Food and Drug Administration; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis.

for his cancer, including fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) and bevacizumab. Three months before hospitalization, his regimen was changed to oral regorafenib and his carcinoembryonic antigen level decreased, and overall disease burden appeared to have decreased.

The patient’s only other medical problem was hypertension, well controlled on treatment with carvedilol, 3.125 mg twice daily.

Physical examination findings and vital signs were all within normal limits. The patient had anasarca with pitting edema of the upper and lower extremities. Lungs had

decreased air movement at the bases but no crackles. He had multiple erythematous, nontender, nonblanchable patches on forearms and lower legs bilaterally.

Laboratory tests on admission showed potassium level of 2.7 mEq/L and creatinine level of 1.98 mg/dL (Table 2). Three months before hospitalization, creatinine level was 1.18 mg/dL, while his previous baseline was 0.8 mg/dL. Urine dipstick showed large blood and proteinuria (1+). His 24-hour urine protein excretion was 1.9 g, and urine microscopy showed 5 white blood cells and greater than 182 red blood cells. His previous urinalysis results had been normal (Table 2). His kidney ultrasound showed no abnormalities.

Additional workup revealed a positive speckled anti-nuclear antibody (ANA) at a 1:640 titer. Other serologic test results were negative, summarized in Table 2.

The patient underwent kidney biopsy, which showed immune complex–mediated segmental endocapillary proliferative glomerulonephritis (Fig 2). Endocapillary proliferation occurred in 52% (14/27) of viable glomeruli, without necrosis or crescent formation. Immunofluorescence showed full-house positivity, predominantly with immunoglobulin A (IgA), IgG, and λ staining (2+), and IgM, C3, C1q, and κ (1-2+). Ultrastructurally, there were frequent mesangial and subendothelial electron-dense deposits along with scattered subepithelial deposits, although organized substructures, tubuloreticular inclusions, and tubular basement membrane deposits were not seen. Overall findings were like those typically seen in class III to IV lupus nephritis.

The patient was discharged on treatment with prednisone, 50 mg, daily, furosemide, and potassium

**Table 2.** Laboratory Values on Admission Compared With 3 Months Before Admission

Laboratory Tests	3 mo Prior	Current Admission	Reference Values
<b>Basic metabolic panel</b>			
Sodium, mmol/L	146	136	136-145
Potassium, mmol/L	3.8	2.7	3.5-5.1
Chloride, mmol/L	106	94	98-107
Carbon dioxide, mmol/L	30	35	22-29
SUN, mg/dL	30	32	6-23
Creatinine, mg/dL	1.18	1.98	0.67-1.17
<b>Urinalysis</b>			
Specific gravity		1.010	1.002-1.035
Blood		Large	Negative
Protein, mg/dL		30	Negative
Urobilinogen		Negative	Negative
Nitrite		Negative	Negative
Leukocyte esterase		Negative	Negative
WBC, /HPF		5	≤2
RBC, /HPF		>182	≤2
Squamous epithelial cells, /HPF		None	Occasional
Bacteria, /HPF		None	Not seen
<b>Immunology laboratories checked during admission</b>			
ANA pattern		Speckled pattern	
ANA titer		>1:640	<1:40
ANA path review		High titer	
dsDNA, IU/mL		<12.3	<30
Anti-centromere antibody, units		<0.2	<1
Anti-histone antibody, units		<0.2	<0.9
C3, mg/dL		102	75-175
C4, mg/dL		28	14-40

Note: SUN in mg/dL to mmol/L,  $\times 0.357$ ; creatinine in mg/dL to  $\mu\text{mol/L}$ ,  $\times 88.4$ . Abbreviations: ANA, antinuclear antibody; dsDNA, double-stranded DNA; HPF, high-power field; RBC, red blood cell; SUN, serum urea nitrogen; WBC, white blood cell.

replacement for 2 weeks. At the 2-week follow-up, he had improved edema and shortness of breath. His creatinine level had improved to 1.71 mg/dL. An anti-histone IgG test was done 4 weeks after starting prednisone treatment and the result was negative (0.3 unit).

Unfortunately, the patient was re-admitted a few weeks later with respiratory failure due to pneumonia, pulmonary edema, loculated effusion, atelectasis, and lung metastasis and died shortly thereafter.

## DISCUSSION

The diagnosis of drug-induced lupus is dependent on: (1) a history of causative drug for a least 1 month with at least 1 systemic lupus erythematosus (SLE) manifestation, (2) positive ANA, (3) no history suggestive of SLE before starting the drug, and (4) spontaneous resolution of the clinical manifestations of the disease after medication discontinuation. Drug-induced lupus is a type B

hypersensitivity reaction, meaning that the body creates autoantibodies and not antibodies to drug products.

Anti-double-stranded DNA antibody is usually negative in these patients (<5% are positive), whereas anti-histone antibody is usually positive (>90%), but this is variable depending on the medication.<sup>7</sup> Interestingly, anti-histone antibodies are strongly associated with drug-induced lupus from specific drugs, but with other drugs, these antibodies are found in less than half the cases.<sup>1</sup> Kidney manifestations are rare in patients with drug-induced lupus and are limited to certain medications such as hydralazine, procainamide, and minocycline.<sup>8-11</sup> The most common reported kidney pathology with hydralazine is pauci-immune rather than immune complex-mediated glomerulonephritis.<sup>11</sup>

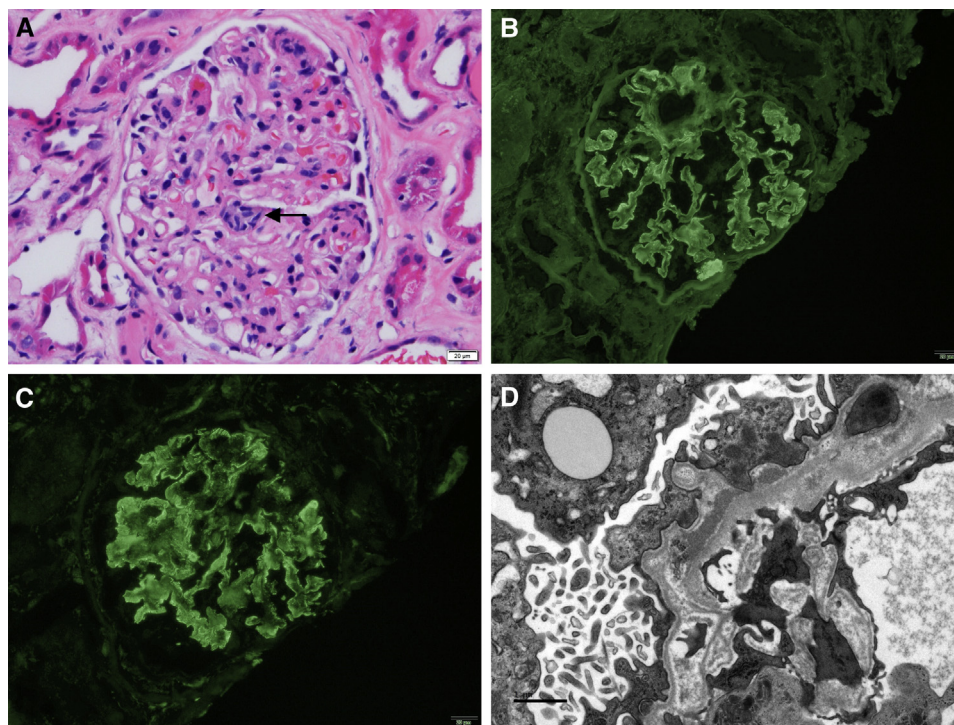
Our patient had a positive ANA titer, endocapillary proliferation, and full-house immune complex deposition, favoring lupus nephritis diagnosis over other full-house (IgG, IgM, IgA, C3, and C1q) staining nephropathies such as IgA nephropathy, membranoproliferative glomerulonephritis, infectious-mediated glomerulonephritis, and membranous nephropathy.<sup>10,12</sup>

Although it is possible that the glomerulonephritis was secondary to the patient's malignancy, the patient's cancer burden improved as his glomerulonephritis worsened. His rash appeared in the setting of worsening kidney function around the time of the biopsy, which could have been a systemic manifestation of SLE. However, because the adverse event (immune complex glomerulonephritis) appeared after the regorafenib was given and it improved when regorafenib treatment was discontinued, this suggests a probable association between the 2 (Naranjo adverse drug reaction probability scale score of 3).<sup>13</sup>

The mechanism for drug-induced lupus remains uncertain, with several proposed theories. These include genetic predisposition related to certain HLA-DRs and acetylation metabolism status and to autoantibody formation (ANA, anti-double-stranded DNA, and anti-histone).<sup>14-16</sup> The offending medication might form a reactive metabolite, after it is served as a substrate to neutrophils, which can activate lymphocytes and subsequently form autoantibodies.

Another suggested theory is the offending drug, through interfering with T lymphocyte cell DNA methylation, can lead to overexpression of LFA-1 (lymphocyte function associated antigen 1) that can induce autoimmunity.<sup>17</sup> This hypomethylation of DNA observed with hydralazine use occurs due to inhibition of extracellular signal-regulated kinase and the formation of anti-histone antibodies.<sup>18</sup> Because the extracellular signal-regulated kinase pathway is inhibited by regorafenib, this might explain its possible association with lupus.

Anti-histone antibody was negative in our patient, which may be related to the formation of other non-measured antibodies or the normalization of anti-histone antibody because it was measured a month after the discontinuation of regorafenib treatment and while



**Figure 2.** (A) Glomerulus with segmental endocapillary proliferation (solid black arrow) (hematoxylin and eosin; original magnification,  $\times 40$ ). (B) Immunoglobulin G diffuse, global, mesangial and capillary, granular, 2+ (immunofluorescence; original magnification,  $\times 40$ ). (C) C1q diffuse, global, mesangial and capillary, granular, 2+ (immunofluorescence; original magnification,  $\times 40$ ). (D) Subendothelial (black arrow), scattered subepithelial (white arrow), and mesangial (blue arrow) electron-dense deposits (electron microscopy).

receiving immunosuppressive medications. More data could support such probable association and help us understand the associated mechanisms.

The current recommendation for the treatment of drug-induced lupus is supportive care and to discontinue treatment with the offending drug. There is no strong evidence that supports the use of immunosuppression and usually corticosteroids are reserved for severe symptoms, life-threatening organ involvement (pericarditis or nephritis), and faster resolution.<sup>19</sup> The risks of corticosteroids, including hyperglycemia, osteoporosis, myopathy, mood disorders, and many others, should be taken into consideration before the use of these agents. In addition to corticosteroids, mycophenolate mofetil and cyclophosphamide have been used in patients with medication-induced lupus nephritis from hydralazine and procainamide.<sup>9,20</sup> Kidney outcomes in these case reports were variable, from no to full kidney recovery.<sup>9,20</sup>

In summary, we present a patient with rapid onset of glomerulonephritis after starting regorafenib therapy, with biopsy findings suggestive of class IV lupus nephritis without systemic evidence of SLE.

## ARTICLE INFORMATION

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