

Case of Proteinuria, Worsening Hypertension, and Glomerular Endotheliosis With Erlotinib and Gefitinib



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INTRODUCTION

Epidermal growth factor receptor (EGFR) mutations promote tumoral cell proliferation and inhibit apoptosis.¹ Mutations at the receptor are found in several tumors, especially non-small-cell lung cancer (NSCLC),² occurring in 10% to 15% of NSCLC in Europe and 30% to 40% in Asia.³ The available oral EGFR tyrosine kinase inhibitors (EGFR TKIs) are erlotinib, gefitinib, and afatinib. Erlotinib monotherapy is indicated for first-line treatment and for maintenance therapy in patients with activating mutations of the EGFR who have locally advanced or metastatic NSCLC,^{4,5} and locally advanced or metastatic NSCLC after failure of at least 1 prior chemotherapy.⁶ Gefitinib is authorized for the treatment of locally advanced or metastatic NSCLC with activating mutations of EGFR across all disease stages.^{7,8} Skin rashes and diarrhea are the most commonly reported adverse effects with erlotinib (75% and 54% of patients, respectively)⁶ and gefitinib (58% and 35%, respectively).⁹ Kidney dysfunction is rare with EGFR TKIs. In the phase III studies that established erlotinib and gefitinib for their current treatment indications, 1 patient on erlotinib had any grade kidney failure¹⁰ and 1.5% of patients treated with gefitinib had an elevation in creatinine (Cr).⁹ Elderly patients with chronic kidney disease have been safely treated with gefitinib.¹¹ Outside of clinical trials, there are case reports of 2 patients treated with gefitinib who developed minimal change disease and 1 patient with tubulointerstitial nephritis with IgA nephropathy^{12,13} on kidney biopsy. One patient on erlotinib was reported with a pauci immune glomerulonephritis¹⁴ on kidney biopsy.

CASE PRESENTATION

A 67-year-old Hispanic woman with history of essential hypertension (HTN) and metastatic lung

adenocarcinoma (+EGFR L858R) was referred to the renal service at our institution for evaluation of acute kidney injury (AKI) and worsening HTN. She had been receiving erlotinib for the preceding 397 days. The starting dose of erlotinib was 1200 mg on Wednesday and Thursday and 50 mg on Friday to Tuesday. The baseline serum Cr was 0.9 mg/dl and the urinalysis showed no proteinuria and was otherwise negative. Before starting erlotinib, the blood pressure (BP) was generally approximately 140/85 mm Hg on losartan 100 mg and hydrochlorothiazide 12.5 mg, both daily. At the initial renal evaluation, amlodipine 10 mg daily had already been added 7 days prior for BP readings above 170/77 mm Hg. The BP remained between 155 and 170 mm Hg. Other medications were omeprazole 40 mg and megestrol acetate 800 mg daily. She denied using herbal or over-the-counter medications. The Cr was 1.9 mg/dl, a urinalysis showed 100+ protein (otherwise negative), spot urine total protein Cr ratio was 0.64 and serum free light chains and serum and urine immunofixation and electrophoresis studies were negative. Hemoglobin was 9.3 g/dl, white blood cell count 7 K/ μ l, platelet 355 K/ μ l, lactate dehydrogenase 175 U/l and haptoglobin 251 mg/dl. ADAMTS13 was not ordered. Hepatitis B and C panels were negative. Serologic workup for autoimmunity was not performed. For worsening fatigue, nausea, and diarrhea, the dose of erlotinib was reduced to 750 mg on Wednesday to Thursday with 50 mg on Friday to Tuesday. Given the worsening kidney function and proteinuria (see [Figure 1](#)), a kidney biopsy was performed 3 weeks later. The biopsy revealed diffuse glomerular endothelial injury/endotheliosis, global glomerulosclerosis in 16 of 44 glomeruli, no focal segmental glomerulosclerosis, mild to moderate acute tubular injury, moderate widespread tubular atrophy, severe arterio and arteriolosclerosis with extensive arteriolar intimal

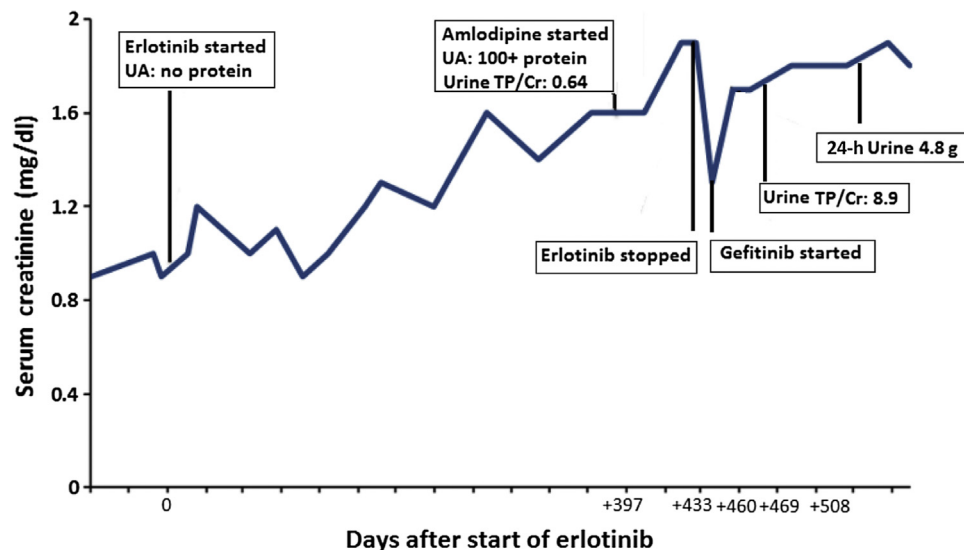


Figure 1. Change in serum creatinine (mg/dl) and protein excretion over time. Cr, creatinine; TP, total protein; UA, urinalysis.

hyalinosis and luminal narrowing (Figure 2). The foot processes were partially effaced, covering 30% to 35% of the capillary surface as assessed by electron microscopy. No proliferative or immune complex glomerular lesions were evident. Because the sequential radiographs had shown continued disease response to erlotinib, the oncologist continued the therapy. The Cr 2 weeks later continued to increase and erlotinib was finally discontinued after a total of 14 months. After drug cessation, the Cr decreased to 1.3 mg/dl. Because the tumor's molecular mutation had shown a good response to an EGFR TKI, gefitinib was started 3 weeks later at a dosage of 250 mg every other day. The BP

remained elevated. After 2 weeks, the Cr and spot urine total protein Cr ratios increased to 1.7 mg/dl and 8.9, respectively. After 1 month on gefitinib, a 24-hour urine collection showed 4.8 g protein and the Cr continued to increase. The patient did not follow-up in the renal clinic thereafter. Four months later, gefitinib was discontinued due to progression of disease. The systolic BP dropped to 120–130 on the same BP medications. The patient died 2 months later.

DISCUSSION

EGFR is expressed throughout the mammalian kidney,^{15,16} and epidermal growth factor and EGFR ligands

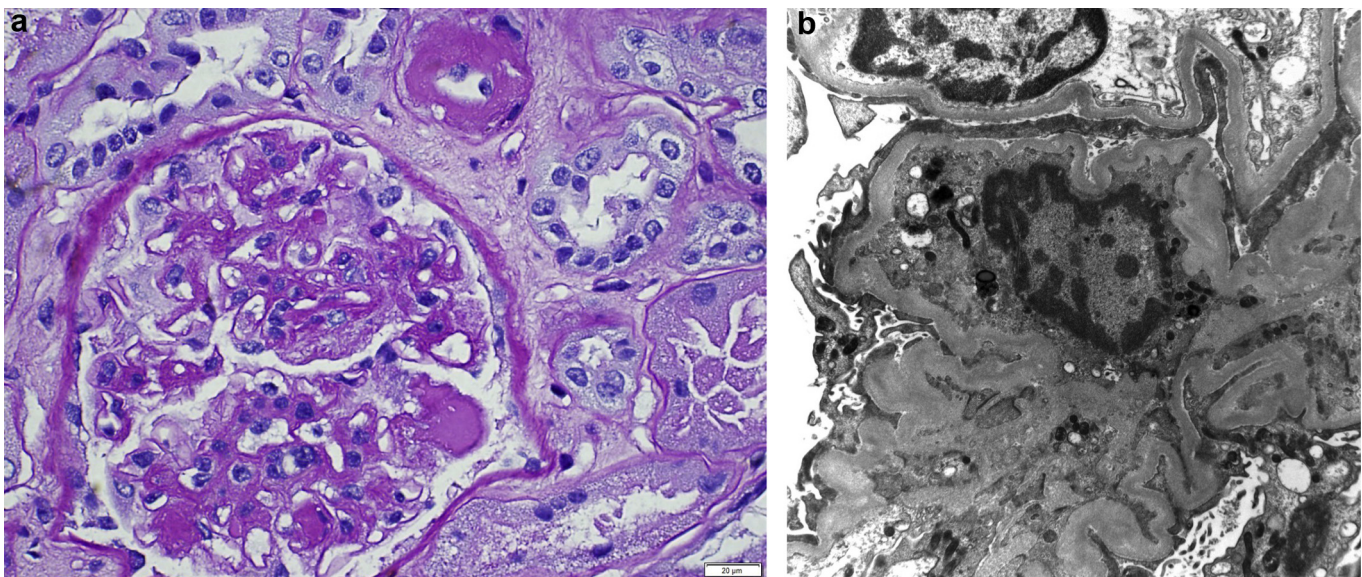


Figure 2. Kidney biopsy findings. Light microscope: glomeruli showing varying degrees of endothelial swelling with focal accumulation of loose proteinaceous material in the subendothelial space, some occluding the capillary lumina. Periodic acid–Schiff stain $\times 400$ (a). Electron microscope: varying degrees of endothelial swelling and focal detachment from the basement membranes. Focal accumulation of finely granular proteinaceous material. Focal segmental new basement membrane formation is noted. Original magnification $\times 5000$ (b).

Table 1. Teaching points

- 1) Mutations at the EGFR receptor are found in 10% to 15% of NSCLC in Europe and 30% to 40% of NSCLC in Asia
- 2) The available oral EGFR tyrosine kinase inhibitors are erlotinib, gefitinib, and afatinib
- 3) EGFR is expressed throughout the mammalian kidney, and EGF and EGFR ligands are involved in renal development
- 4) In animal models, EGFR activation is associated with both benefit and harm to kidney function, depending on the model of kidney injury

EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

are involved in renal development. They are expressed in metanephric structures and contribute to tubulogenesis¹⁶ and branching of cultured ureteric buds.¹⁷ In animal models, EGFR activation is associated with both benefit and harm to kidney function, depending on the model of injury. In AKI from ischemia/reperfusion injury, aminoglycoside toxicity, and folic acid administration, EGFR activation promotes renal tubular cell proliferation and enhances recovery of renal structure and function after injury.^{18–23} On the other hand, EGFR activation promotes renal fibrosis in models of obstructive uropathy, chronic angiotensin II infusion,^{24,25} diabetic nephropathy,^{26,27} hypertensive nephropathy,^{28,29} and glomerulonephritis.^{30,31}

In animal models of AKI, reductions in EGFR or EGFR TKI activity are associated with delayed recovery of kidney function. In wave-2 mice, who have a point mutation that results in a 90% reduction in receptor tyrosine kinase activity, recovery of kidney function is much slower following AKI.²³ Mice treated with erlotinib had delays in recovery of kidney function following ischemia/reperfusion injury.³² On the other hand, in models of urethral obstruction and angiotensin II infusion,^{33,34} decreased renal fibrosis has been noted in wave-2 mice and in mice with deletions of EGFR in renal proximal tubular cells. Pharmacologic blockade of EGFR TKI with erlotinib and gefitinib decreased fibrogenesis induced by angiotensin II²⁴ and hypertension, respectively.³⁵

The pathophysiologic mechanisms underlying the complex relationship between EGFR TKI and their divergent effects on kidney function in different models of kidney injury remain poorly defined (Table 1). Our case supports a direct role for erlotinib and possibly gefitinib in producing injury to glomerular endothelial cells. In the absence of any hemodynamic insult or medications associated with injury to constituents of the glomerular basement membrane, our patient had a steady increase in Cr, new-onset subnephrotic range proteinuria, and an elevation of previously well-controlled BP that can be clearly charted after the start of treatment with erlotinib. The persistence of HTN after erlotinib was stopped is not inconsistent with direct endothelial injury, because

such injury can take time to repair and the HTN can persist until the injury has partially or completely resolved. The fairly immediate decrease in Cr after the stop of erlotinib also supports its role in kidney injury. The rapid increase in serum Cr and worsening proteinuria when gefitinib was started suggests that there may be a “class effect” for endothelial injury with these drugs. A kidney biopsy was not repeated on gefitinib, so it is not clear if the increased proteinuria was due to ongoing endothelial injury from erlotinib or from gefitinib.

Increases in previously well-controlled BP with use of an EGFR TKI has not previously been reported. New-onset HTN or worsening of preexisting HTN has been observed with exposure to vascular endothelial growth factor (VEGF) inhibitors.³⁶ The endothelial injury seen on our kidney biopsy is not unlike the injury seen with the use of VEGF inhibitors and may represent a mild form of thrombotic microangiopathy. It is possible that the much higher dose of erlotinib used in this case is responsible for the endothelial injury and the worsening HTN observed in this case. The usual treatment dosage of erlotinib for NSCLC is 150 mg daily. Our patient was on a clinical trial and had received a dosage of up to 1200 mg daily. One study suggests that epidermal growth factor stimulates VEGF-A secretion in proximal tubule cells.³⁷ Further investigations may define if epidermal growth factor affects VEGF expression or related pathways at the glomerular capillary endothelium and if there is TKI cross kinase VEGF inhibition at high doses of erlotinib. Serum VEGF levels were not measured in this patient.

Electron microscopy of this patient’s kidney biopsy showed partial effacement of the foot processes. In animal knockout models, EGFR deletion at the podocytes protects mice from glomerular injury.³⁸ In the initial phase III studies, proteinuria was observed in 7.7% of patients on gefitinib, and in none on erlotinib.⁹ In a patient who developed nephrotic syndrome on gefitinib, the proteinuria did not recur after switching to erlotinib.¹³ Our patient had only mild proteinuria on erlotinib, but developed nephrotic range proteinuria on gefitinib. A kidney biopsy was not repeated on gefitinib, so it is not clear if the increased proteinuria was due to ongoing endothelial injury from gefitinib or additional podocyte injury. In the case reports of 2 patients with nephrotic syndrome who were found to have minimal change disease on kidney biopsy, the proteinuria partially or completely resolved after gefitinib was discontinued.^{12,13} Erlotinib and gefitinib may give rise to different pathways of podocyte injury. Although it is possible that all EGFR TKIs cause direct injury to the glomerular podocyte, these drugs also

may produce podocyte injury via indirect routes. Different routes of injury could explain the severity of podocyte injury among the 2 EGFR TKIs.

AKI and glomerular injury appear to be rare adverse effects from treatment with EGFR TKIs. We present a case of glomerular endotheliosis associated with AKI, hypertension, and proteinuria in a patient with exposure to erlotinib and gefitinib. These clinical and pathology findings are similar to those observed with antiangiogenesis inhibitors. It remains unclear whether the drug needs to be terminally discontinued when AKI, HTN, worsening in preexisting HTN, or proteinuria occurs. It is also unclear whether all drugs from the class of EGFR TKIs need to be avoided if a patient develops a kidney problem from one of the agents within the class. Future studies may better define the rate of AKI and mechanisms of renal injury with this class of targeted therapy.

DISCLOSURE

All the authors declared no competing interests.

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