

Case Report

Allergic Interstitial Nephritis Possibly Related to Sunitinib Use

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ABSTRACT

Background: Sunitinib is an oral multitargeted inhibitor indicated for the treatment of renal cell carcinoma.

Objective: This report describes a case of allergic interstitial nephritis possibly related to this agent.

Case Summary: A 69-year-old female patient with a history of metastatic renal cell carcinoma after left radical nephrectomy presented to our nephrology clinic after completing 2 courses of sunitinib therapy. The patient was noted to have progressive kidney dysfunction with proteinuria, together with peripheral eosinophilia and eosinophiluria, which developed during the first of 2 cycles of sunitinib therapy. Her concomitant medications included atenolol, triamterene/hydrochlorothiazide, amlodipine, and multivitamin tablets, all of which she had been receiving at stable doses over the previous 2 years. There were no other over-the-counter medications involved and other possible causes of interstitial nephritis were excluded. The proteinuria, eosinophilia, and eosinophiluria worsened with the second course and resolved after sunitinib discontinuation, which resulted in initial stabilization followed by slight improvement in kidney function. The Naranjo Adverse Drug Reaction Probability Scale score for this event was 7, indicating a probable association of the event with the drug. With clinical improvement after discontinuation of sunitinib and the presence of a solitary remaining kidney and thrombocytopenia, renal biopsy was not performed after discussion with the patient. When challenged with a related agent, sorafenib, the patient experienced worsening of serum creatinine and increasing eosinophilia, similar to that noted with sunitinib, suggesting that this event may be a class effect.

Conclusions: Nephrologists and oncologists should be aware of allergic interstitial nephritis as an adverse effect related to this agent. Although there are no current recommendations for monitoring serum creatinine with sunitinib therapy, we recommend that serum creatinine and white cell count with differential be checked within 2 weeks of initiation of therapy with sunitinib to enable earlier diagnosis of this condition and avoid renal damage. (*Am J Geriatr Pharmacother.* 2007;5:341–344) Copyright © 2007 Excerpta Medica, Inc.

Key words: sunitinib, interstitial nephritis, eosinophilia.

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INTRODUCTION

Sunitinib is an oral multitargeted inhibitor of vascular endothelial growth factor receptor (VEGF-R), platelet-derived growth factor receptor, and stem cell receptor factor c-KIT.¹⁻⁷ After its successful use for the treatment of gastrointestinal stromal tumors, attention has been focused on using it to treat metastatic renal cell carcinoma because of its antiproliferative effects and antiangiogenic properties.^{1,2,6,7} The prognosis of metastatic renal cell carcinoma is extremely poor, with a median survival of 6 to 12 months and very limited success with immunotherapy with interleukin-2 (IL-2).³⁻⁶ As renal cell carcinomas have high expression of VEGF, sunitinib has shown promising results in its treatment.^{1,2,6} In January 2006, sunitinib was approved by the US Food and Drug Administration as monotherapy for advanced renal cell carcinoma.^{1,6}

Sunitinib is given as an oral dose of 50 mg QD for 4 weeks on- and 2 weeks off-schedule.²⁻⁶ The drug has good oral absorption and a long half-life (>40 hours). It is actively metabolized by the hepatic cytochrome P450 isozyme 3A4, with predominant excretion through feces.⁶ The median progression-free survival was found to be significantly longer with sunitinib (11 months) compared with the standard of care, interferon-alfa (5 months),⁴ with some patients experiencing some degree of tumor regression in Phase II trials.² Its known adverse effects include fatigue, malaise, diarrhea, skin abnormalities, and cytopenias.^{2,3} Although no published cases of interstitial nephritis related to sunitinib use were found in the literature, a case of this event with sorafenib use has been reported,⁸ suggesting a class effect.

We present a case of allergic interstitial nephritis possibly related to sunitinib therapy.

CASE REPORT

Presentation

A 69-year-old female patient was referred to our nephrology clinic for treatment of elevated serum creatinine. The patient had a history of left renal carcinoma, which was treated with left radical nephrectomy 21 months previously. The patient's pre-nephrectomy serum creatinine concentration was 1.8 mg/dL, which was unchanged postoperatively. On follow-up computed tomography (CT) 1 year later, the patient was found to have a lesion on the pancreas which was aspirated and found to be metastatic renal cell carcinoma. The patient subsequently underwent partial pancreatectomy and splenectomy. Because of further metastatic spread noted 2 months later on follow-up CT, sunitinib therapy was started.

Treatment

The patient received the standard regimen of sunitinib—50 mg daily for 4 weeks on- and 2 weeks off-schedule for 2 cycles. Prior to starting sunitinib, her creatinine concentration was 1.7 mg/dL.

Outcomes

The patient's kidney function started to deteriorate after the start of sunitinib therapy, with creatinine increasing to 2.2 mg/dL after the first month. This increase coincided with increasing peripheral eosinophilia, from a baseline of 4% to 13%. Aside from occasional diarrhea with the use of the medication, the patient did not experience any adverse events. She resumed her second 4-week course of sunitinib, with events similar to those she experienced with the first cycle. Immediately after the second cycle, her creatinine concentration rose to 2.8 mg/dL, and significant peripheral eosinophilia developed, with counts up to 40%.

The patient was seen in the nephrology clinic immediately after finishing her second course of sunitinib for elevated creatinine. At this visit, the patient did not report any adverse events. Diarrhea had resolved after sunitinib discontinuation.

This patient had no history of fever, arthralgias, or skin rash. Her history was significant for hypertension, which was treated with atenolol 50 mg/d PO, triamterene/hydrochlorothiazide (HCTZ) 75/50 mg/d PO, and amlodipine 2.5 mg/d PO. The only other concomitant medication was a multivitamin 1 tablet/d. All of these medications were administered at stable doses over the previous 2 years.

The patient had no history of smoking and rare alcohol intake. On presentation, her weight was 67.5 kg; temperature, 37°C; blood pressure, 140/94 mm Hg; and heart rate, 78 bpm. The remainder of the physical examination was unremarkable. Laboratory analysis showed a white cell count of 6.3×10^3 cells/ μ L, with 40% eosinophils (which had increased from 4% prior to the start of sunitinib treatment). Platelet count was low, at 57×10^3 cells/ μ L, which was believed to be an adverse effect of the sunitinib therapy. Urinalysis showed 10 to 20 white cells per high-power field, with occasional clumping, few bacteria, and 2+ proteinuria. Spot urine protein/creatinine ratio estimated proteinuria at 1.2 g/d (which was a new finding with pre-sunitinib urinalysis showing no proteinuria). Urine cultures were negative for infection, and urinary eosinophils were present in large numbers on Hansel staining.

There was no evidence of fever, rash, or other viral or bacterial prodromes or exposure to contrast media

or NSAIDs. Sunitinib treatment was discontinued. Two months after the discontinuation of the drug, laboratory analysis showed a decrease in eosinophil count to normal range (8%), resolution of eosinophiluria, and stabilization of serum creatinine with some improvement in kidney function (**Figure**). The patient did not receive any corticosteroid therapy. Five months later, sorafenib therapy was initiated because of further radiologic progression of the disease. She was initiated on a dose of 100 mg BID (recommended dose, 400 mg BID). Within 1 week of initiation of treatment, her creatinine increased from 2.49 to 3.09 mg/dL, and the patient developed significant peripheral eosinophilia up to 22%. Sorafenib treatment was then discontinued.

DISCUSSION

A literature search did not identify any prior reports of sunitinib-induced interstitial nephritis. However, a case of interstitial nephritis with sorafenib use has been published,⁸ suggesting a class effect. Increase in creatinine value has been noted in 12% of patients compared with 7% in the placebo group in previous studies.^{4,6} This finding may be related to diarrhea and the volume

contraction associated with drug use. Other related adverse events have been hypokalemia (12%), hypernatremia (10%), and hypophosphatemia (9%).⁶

After radical nephrectomy, this patient had subnephrotic-range proteinuria, eosinophilia, and eosinophiluria, all of which were noted after the initiation of sunitinib therapy. None of these events have been previously associated with this medication. The patient did not have fever or rash, but the classic triad of allergic interstitial nephritis is seen in only 10% to 30% of cases.^{9,10} Her clinical presentation was indicative of allergic interstitial nephritis. Although there have been rare case reports of interstitial nephritis related to the use of HCTZ, all of those patients developed the allergic interstitial nephritis within 5 to 10 weeks of exposure to the drug.^{11,12} The present patient had been receiving a stable dose of triamterene/HCTZ for >2 years and hence the causal association of triamterene/HCTZ with the interstitial nephritis in this patient was unlikely.

Eosinophilia and eosinophiluria resolved on discontinuation of sunitinib treatment. The improvement in the kidney function was slow and did not completely return

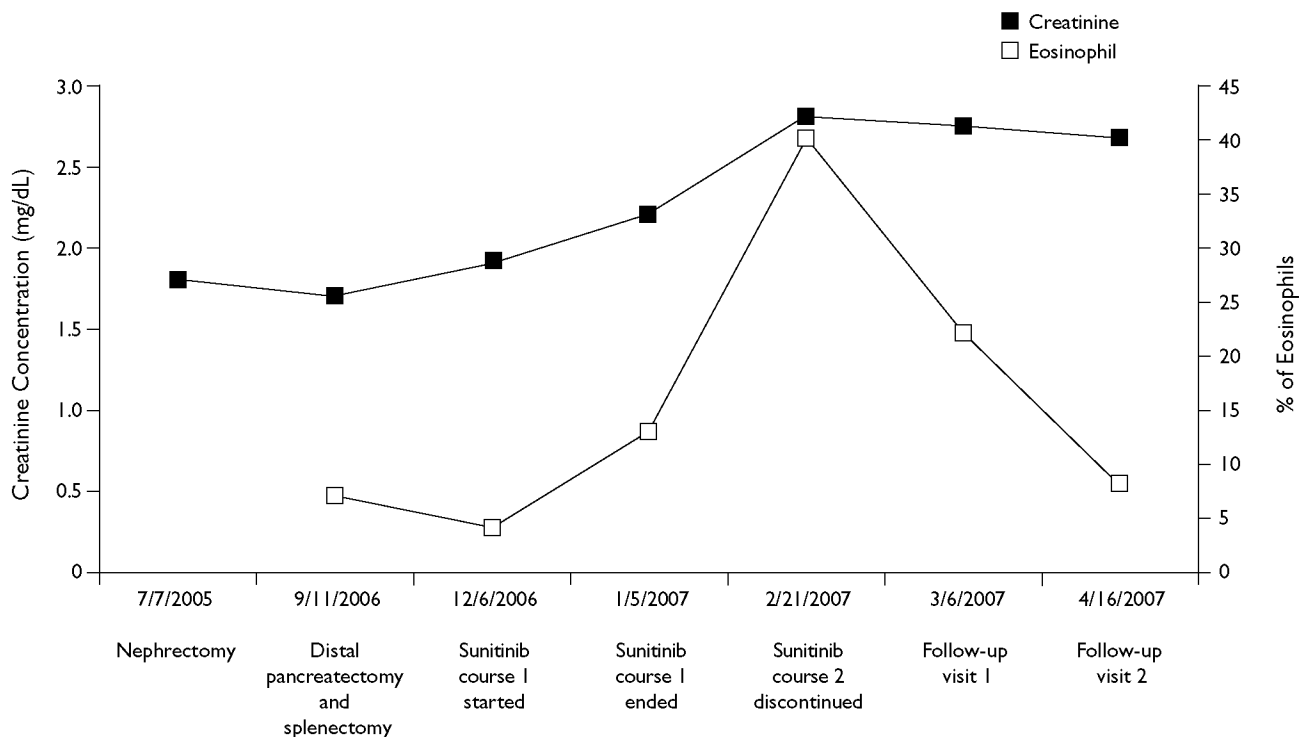


Figure. Kidney function, as measured using serum creatinine concentration, and eosinophilia, measured using eosinophil concentration over time with treatment with sunitinib in a 69-year-old female patient with history of metastatic renal cell carcinoma.

to baseline, possibly because of the damage caused by 2 months of therapy with sunitinib. There were no other new medications that were introduced into the patient's regimen during this period and there were no infectious processes during this time course that would confound the issue. Using the Naranjo Adverse Drug Reaction Probability Scale, a score of 7 was found, which suggested a probable association of the adverse reaction with the drug. To our knowledge, this is the first case of interstitial nephritis reported with sunitinib use.

Sunitinib together with related agents sorafenib and bevacizumab target the activity of angiogenic growth factors and have been found so far to have promise in the treatment of metastatic renal cell carcinoma. They have been associated with a multitude of adverse effects but have been found to be better tolerated than IL-2 and interferon- α , which have been standard therapies for metastatic renal cell carcinomas. The clinical presentation of renal dysfunction, subnephrotic proteinuria, eosinophilia, and eosinophiluria is consistent with the diagnosis of allergic interstitial nephritis. In this patient with a high risk for short-term mortality from her underlying renal cell carcinoma, the risk for renal biopsy of a solitary kidney in the setting of thrombocytopenia was not believed to be justifiable and was also declined by the patient.

Sunitinib is an angiogenesis inhibitor and targets VEGF-R and EGF-R. EGF-R is expressed in the loop of Henle and distal tubules of the kidney and involved in the pathogenesis of acute tubulointerstitial damage and recovery from tubular injury.¹³ It is possible that these receptor interactions may have contributed to interstitial nephritis of this medication, although this remains speculative.

CONCLUSIONS

Based on this case report, oncologists and nephrologists must be vigilant of the possibility of interstitial nephritis related to sunitinib treatment, especially in patients with metastatic renal cancers who have undergone nephrectomy and have impaired kidney function at baseline. Although there are no current recommendations for monitoring serum creatinine with sunitinib therapy, we recommend that serum creatinine and white cell count with differential be checked within 2 weeks of initiation of therapy with sunitinib to enable earlier diagnosis of this condition and avoid renal damage.

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