

Noninfectious Pneumonitis in a Patient With Renal Cell Carcinoma Treated With Everolimus

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A 62-year-old nonsmoking woman named M.B. presented with right upper quadrant pain. An abdominal ultrasound revealed an incidental finding of a large renal mass in her left kidney. She underwent a hand-assisted laparoscopic left nephrectomy for a 7.5 cm tumor (T2 [tumor more than 7 cm], Fuhrman grade 3, clear-cell renal cell carcinoma [RCC]) with negative surgical margins; the renal vein was disease-free. Postoperative care included routine surveillance with computed tomography (CT) scans of the chest, abdomen, and pelvis every six months.

One year postnephrectomy, M.B. returned with new left-side upper back pain and mild fatigue. A chest CT scan demonstrated a soft tissue mass in the left lung apex with destruction of the left posterior second rib and multiple pulmonary lesions (1–2.5 cm). She was started on sunitinib (daily dosing for four weeks, followed by a two-week rest) and a bisphosphonate. M.B. initially responded to therapy and achieved a 30% tumor-size reduction. After 10 months, however, she demonstrated progressive disease with growing pulmonary and liver lesions. Treatment was switched to everolimus 10 mg per day according to the National Comprehensive Cancer Network's (NCCN, 2010) clinical practice guidelines, and M.B. had stable disease following three months of treatment.

At a regularly scheduled visit four months after initiating everolimus, M.B. presented with shortness of breath and dry cough (gradually increasing over the prior two weeks), oxygen saturation of 90% on room air, and a chest x-ray demonstrating bilateral interstitial infiltrates. She complained of worsening fatigue that, combined with dyspnea, limited her mobility. M.B. was afebrile and denied having fever or chills. Everolimus was withheld and she was admitted to the

hospital. A chest CT scan demonstrated diffuse ground-glass opacities (see Figure 1). Pulmonary function tests revealed diminished diffusing capacity of the lungs. M.B. was treated empirically with corticosteroids (prednisone 60 mg per day) and oxygen. A pulmonary consult was obtained, and a bronchoscopy with cultures was performed to rule out infection. The pneumonitis grading criteria within the National Cancer Institute's (2010) Common Terminology Criteria for Adverse Events, version 4.0, is based on the severity of symptoms, degree of impact on activities of daily living, and the type of intervention required. In this case, a diagnosis of grade 3 noninfectious pneumonitis was made.

After a three-day hospital stay, M.B. was discharged on supplemental oxygen and a steroid taper. Within a week, she had no shortness of breath at rest and did not require supplemental oxygen. Two weeks after discharge, a chest radiograph showed resolving opacities bilaterally; her dyspnea and fatigue had returned to baseline, and she had completed the steroid taper. Everolimus was reintroduced at 5 mg per day following resolution of pneumonitis to grade 1. M.B. was scheduled for biweekly visits for the first month after continuing therapy, with monthly chest x-rays and blood tests. Everolimus therapy was continued for an additional three months without evidence of recurrent pneumonitis until restaging revealed progressive disease with new liver lesions.

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M.B. initiated everolimus 10 mg per day after failing sunitinib, consistent with the U.S. Food and Drug Administration-approved dosing and indication of everolimus (Novartis Pharmaceuticals Corporation, 2009). Approval was based on the phase III RECORD-1 trial (Hudes,

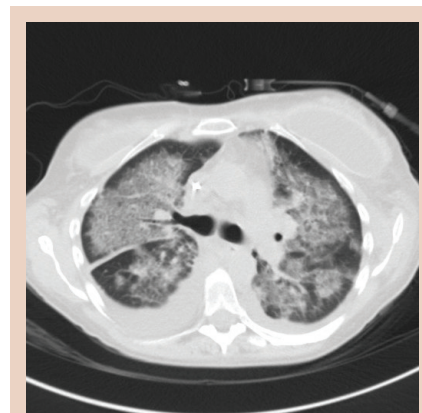


Figure 1. Chest Computed Tomography Scan Showing Diffuse Ground-Glass Opacities

Note. Image courtesy of Duke University Medical Center. Used with permission.

2010) in which patients with metastatic RCC treated with sunitinib or sorafenib were randomized to receive everolimus 10 mg per day or placebo. Clinical benefit was observed, with 67% of everolimus recipients maintaining stable disease (with one partial response) versus 32% of placebo recipients, translating into a highly significant difference in progression-free survival (4.9 versus 1.9 months; $p < 0.001$) (Motzer et al., 2010). Stomatitis, infections, and asthenia or fatigue were the most prominent toxicities when considering all grades, including grade 3–4 events. Noninfectious pneumonitis occurred in 14% of patients receiving everolimus; 4% had grade 3 and no one reported grade 4 events (Motzer et al., 2010).

Noninfectious pneumonitis is a class effect of mammalian target of rapamycin (mTOR) inhibitors, initially reported with rapamycin or sirolimus for antirejection in organ transplantation recipients (Lennon, Finan, FitzGerald, & McCormick,