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Radiation Recall Pneumonitis During Systemic Treatment With Everolimus

Douglas Clark, Dron Gauchan, Ryan Ramaekers, Max Norvell, and Mehmet Sitki Copur

Saint Francis Cancer Treatment Center, Grand Island, NE, USA

Radiation recall syndrome is an acute inflammatory reaction developing at anatomical sites of previously irradiated tissue, weeks to months after the completion of radiation therapy. The distribution pattern of inflammation typically involves, and remains limited to, the boundaries of prior radiation treatment fields. Several classical chemotherapy drugs have been reported to have the potential for causing radiation recall syndrome. With the increasing availability and expanding use of novel biologic and targeted therapy anticancer drugs, isolated reports of radiation recall syndrome secondary to this class of agents are starting to appear in the literature. We describe a case of everolimus-induced radiation recall pneumonitis in a patient with metastatic renal cell cancer.

Key words: Radiation recall; Everolimus; Pneumonitis

INTRODUCTION

Radiation recall syndrome during chemotherapy administration has been well described in the literature. Characterized by an acute inflammatory reaction at sites of previously irradiated quiescent tissue, this syndrome can develop several weeks to months after the completion of radiation therapy (1,2). While skin involvement is more common, in about a third of cases, radiation recall reaction can occur at sites of prior radiation therapy other than the skin. Patients may present with inflammatory reactions of the lungs, oral mucosa, gastrointestinal system, genitourinary tract, muscle, central nervous system, or head and neck areas. Noncutaneous radiation recall reaction may or may not occur in conjunction with a cutaneous reaction but leads to more severe complications than the cutaneous-only radiation recall syndrome. Although the most commonly implicated drugs are anticancer agents, other drugs including some antibiotics, antituberculosis drugs, and simvastatin have been reported to cause radiation recall syndrome (1,3). Commonly implicated classical chemotherapy drugs include actinomycin, doxorubicin, methotrexate, fluorouracil, hydroxyurea, paclitaxel, and liposomal doxorubicin. With the availability and frequent use of new biologic and targeted therapy drugs, reports of radiation recall syndrome due to gefitinib, trastuzumab, cetuximab, bevacizumab, sunitinib, and mTOR inhibitors have emerged in recent literature (4–8). Here we report a case of radiation recall pneumonitis developing in previously irradiated lung tissue of a metastatic renal cell cancer patient during her sequential treatment with an oral mTOR inhibitor everolimus.

CASE PRESENTATION

A 58-year-old female patient underwent radical nephrectomy for a pathological stageT3bNxMx clear cell carcinoma of the right kidney in April 2009. Postoperatively, she was enrolled on the ASSURE (E2805) adjuvant therapy trial led by the ECOG and received 1 year of oral study drug. The trial had three arms comparing sunitinib with placebo, sorafenib with placebo, and sunitinib with sorafenib (9). After the completion of the trial and unblinding of the study arms, she was confirmed to be on the placebo arm of the trial. In June of 2010, she presented with recurrent metastatic disease in the left lower lung. Initial wedge resection of left lower lobe disease followed by high-dose IL-2 treatment provided a disease-free interval of a year and a half. Unfortunately, she did have recurrence in the lung, and initial treatment with oral pazopanib was started in January of 2012 and followed by oral axitinib upon progression in November 2013. She remained on axitinib until progression in November 2014. At this time, because of local symptoms of pain and dysphagia due to mostly local disease progression in her lung and mediastinum, initial palliative radiation therapy to be followed by further systemic therapy was

Address correspondence to Mehmet Sitki Copur M.D., Saint Francis Cancer Treatment Center, 2116 W Faidley Ave, Grand Island, NE 68803, USA. Tel: +1-3083985450; Fax: +1-3083985351; E-mail: mcopur@sfmc-gi.org

planned. She received a course of 39 Gy (10 MV photons) in 13 fractions over 17 elapsed days to the areas of lung and mediastinal involvement, December 2014 through January 2015. Radiation treatments were completed with some modest symptomatic pain relief and radiographic evidence of partial tumor regression. At 1 month postradiation therapy follow-up in February 2015, she reported no respiratory problems. At this point she was started on everolimus at 10 mg p.o. daily for further systemic control of her metastatic disease. One month into her everolimus therapy she presented with nausea, vomiting, shortness of breath, nonproductive cough, and low-grade fevers. She was admitted to the hospital with progressively worsening hypoxemia in March 2015. Everolimus was discontinued. Initial workup for her respiratory failure with a computed tomography (CT) scan of the chest revealed a new, left-sided, patchy consolidation with confluent ground glass opacities, corresponding closely to the isodose margins of her prior radiation therapy fields (Figs. 1A, B, 2A, B). Respiratory failure and CT scan findings progressed within 2 weeks of her hospitalization to the point that she required high-flow oxygen in intensive care unit setting (Figs. 1C, 2C). Further extensive workup for her respiratory failure, including bronchoscopy with bronchoalveloar lavage, cultures (bacterial, fungal, parasitic), and bronchoscopic biopsy, was inconclusive for any underlying infectious or malignant etiology, or lymphangitic spread of renal cancer. Bronchoscopic biopsy was consistent with nonspecific inflammation. Given her history of everolimus treatment and prior radiation therapy, and distribution pattern of her lung infiltrates closely matching her radiation treatment fields, radiation recall syndrome was suspected. She was started on solumedrol followed by oral prednisone. During her hospitalization, she required high-flow oxygen but fortunately was able to avoid an

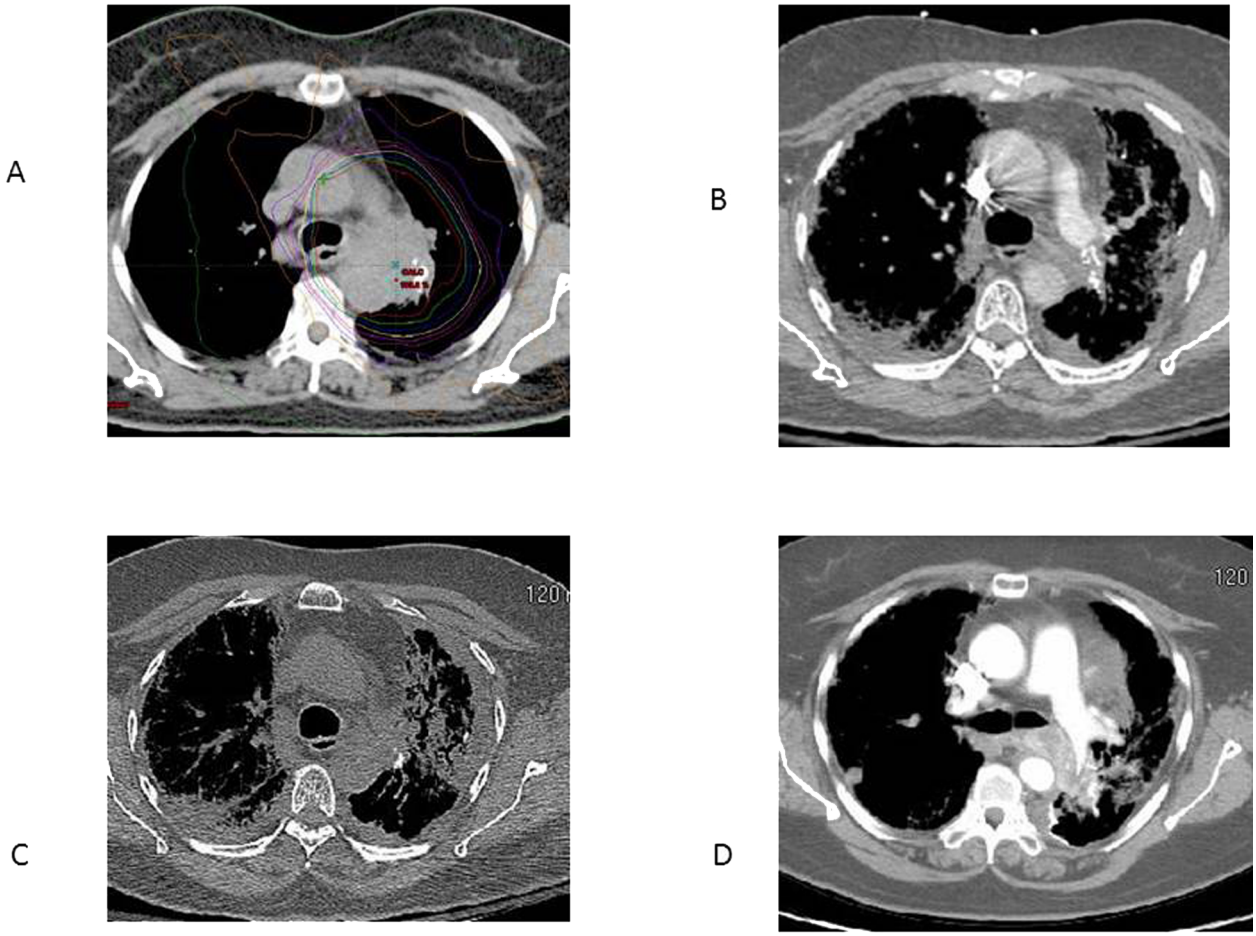

Figure 1. (A) Radiation isodose treatment fields on pretreatment planning CT scan: red line 100% dose, purple line 70%, orange line 50%. (B) Pneumonitis developing in previously radiated lung fields 1 month after the start of everolimus treatment, 2 months after the completion of radiation treatment. (C) Progression of pneumonitis in previously radiated lung fields. (D) Interval resolution of diffuse infiltrates in the left lung at 12 weeks of follow-up.

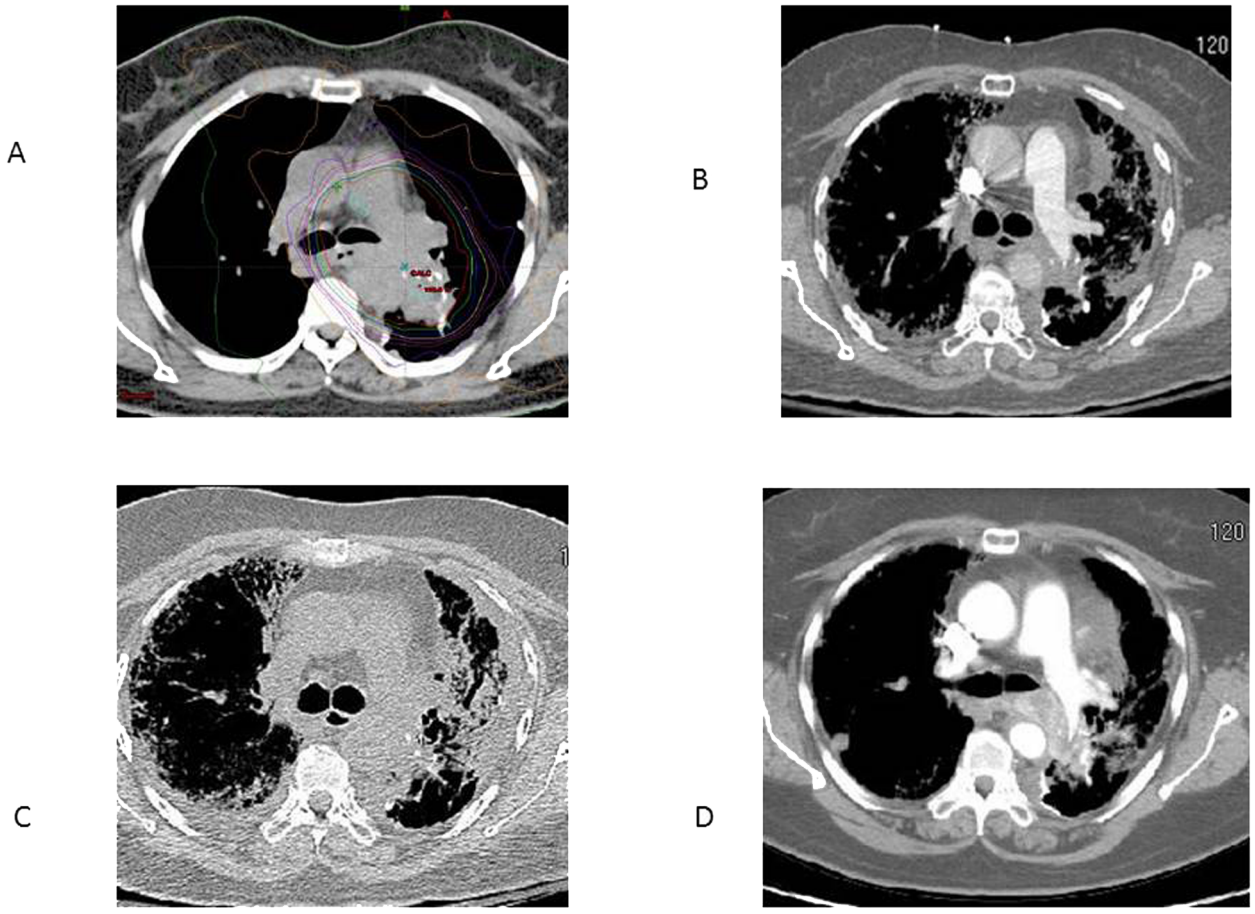

Figure 2. (A) Radiation isodose treatment fields on pretreatment planning CT scan: red line 100% dose, purple line 70%, orange line 50%. (B) Pneumonitis developing in previously radiated lung fields 1 month after the start of everolimus treatment, 2 months after the completion of radiation treatment. (C) Progression of pneumonitis in previously radiated lung fields. (D) Interval resolution of diffuse infiltrates in the left lung at 12 weeks of follow-up.

intubation and respirator. After 6 weeks of hospitalization and supportive care, along with steroid treatments, her respiratory status gradually improved, and she was able to be discharged home. At 12 weeks, follow-up CT scan revealed interval resolution of diffuse infiltrates in the left lung (Figs. 1D, 2D).

DISCUSSION

Everolimus, a potent mTOR inhibitor, has shown antitumor activity against various types of cancers, including renal cell cancer. External beam radiotherapy is an established palliative treatment option for painful metastatic sites from renal cell cancer. Little is known, however, of the clinical efficacy and safety of the concurrent or sequential use of mTOR inhibitors and radiation therapy. Preclinical studies have shown that mTOR inhibitors are potential radiosensitizers (10). Enhanced antitumor effect of everolimus when combined with radiation therapy has been thought to be due to an increase in the antiangiogenesis efficacy (11). Another mechanism of radiosensitization has been attributed to the inhibition of DNA double-strand break repair by mTOR inhibitors (12).

Noninfectious pneumonitis is a known class effect of mTOR inhibitors. In one study, out of 274 patients receiving everolimus, clinical pneumonitis was suspected in 13.5%. Nine cases (3.3%) were grade 1 (asymptomatic), 18 (6.6%) were grade 2 (not interfering with daily living), and 10 (3.6%) were grade 3 (interfering with daily living or oxygen indicated). No grade 4 (life-threatening) pneumonitis was observed (13). Alternatively, radiation pneumonitis is also a well-known side effect of radiation therapy. Radiation pneumonitis can occur 2 weeks to 6 months after the completion of treatments in 5% to 15% of patients. Incidence of this side effect is proportional to the irradiated lung volumes receiving greater than 20 Gy dose of radiation. Substantially higher rates of pneumonitis can develop when the total lung volume receiving greater than 20 Gy exceeds 35% (14,15). The time course leading to symptomatology from the time of radiation treatment appears to follow a similar pattern both for

radiation recall-related and pure radiation therapy-related pneumonitis. Based on the time interval, our patient's pneumonitis might have been secondary to radiation therapy-related pneumonitis. However, the lesser amount of lung volume in this patient receiving greater than 20 Gy, the severity of symptoms with slow prolonged recovery, and, most convincingly, the ground glass opacities corresponding closely to the isodose margins of her prior radiation fields all support the fact that this was indeed a radiation recall pneumonitis in the setting of systemic everolimus treatment.

There have been a few reports of radiation recall syndrome during mTOR inhibitor therapy: two cases with temsirolimus and two with everolimus treatment. To our knowledge, this is the only everolimus-related radiation recall syndrome involving the parenchymal lung tissue, as opposed to the two other previously reported cases of stomach and skin involvement (16,17).

Our report supports the fact that mTOR inhibitors, in our case everolimus, may be associated with radiation recall syndrome. The underlying pathological mechanisms of everolimus-induced radiation recall in the lung parenchymal tissue remain unclear and warrant further investigation. Fortunately, our case could be managed by discontinuation of the drug, supportive care, and steroids. The possibility of additional organ/tissue toxicity exists if visceral organs other than the lung and skin are within the radiation field. With the expanding indications of everolimus in various cancers (breast, neuroendocrine, renal, and subependymal astrocytoma), the possibility of everolimus-induced radiation recall syndrome may increase. Caution should be exercised when concurrent or sequential use of radiation therapy with everolimus is utilized and, if possible, should be avoided.

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