everolimus is an orally available mammalian target of rapamycin (mTOR) inhibitor, with immunosuppressive and anti-tumor properties. It is approved for the treatment of patients with advanced renal cell carcinoma (RCC) after the failure of treatment with a vascular endothelial growth factor—tyrosine kinase inhibitor, sunitinib, or sorafenib.1 Everolimus is also approved for several other indications such as treatment of advanced hormone receptor-positive HER2-negative breast cancer, treatment of advanced neuroendocrine tumors of pancreatic origin, and prophylaxis of organ rejection in renal transplantation.1,2

The efficacy and safety of everolimus in metastatic RCC was demonstrated in the pivotal phase III RECORD-1 (Renal Cell cancer treatment with Oral RAD001 given Daily) trial3 and the REACT (RAD001 Expanded Access Clinical Trial in RCC) study.4 Although non-infectious pneumonitis (NIP), characterized by non-infectious nonmalignant pulmonary infiltrates, was a recognized toxicity, most cases were mild to moderate.3,4 Severe NIP was mostly reversible, and death as a consequence of this toxicity was exceedingly rare.3,4 In this report, we describe a case of cryptogenic organizing pneumonia (COP) associated with everolimus therapy in a patient with metastatic RCC. The drug-related adverse event resulted in death, despite the discontinuation of everolimus and initiation of supportive treatment.

CASE
A 61-year-old caucasian man with metastatic RCC to the lungs, bones, and left adrenal gland, presented to the hospital complaining of a 1-week history of progressive dyspnea with exertion and cough. About 4 weeks earlier, he was started on everolimus 10 mg once daily, as a third line following progression on sequential sunitinib followed by sorafenib. The sorafenib treatment course was completed 3 months prior to this admission. In addition to everolimus, the patient had been taking morphine and megestrol for more than 2 years and minocycline for 15 months. Upon admission, all laboratory tests were normal, except for an elevated serum creatinine (1.6 mg/dL) and a low hemoglobin level (9.5 gm/dL). The chest radiograph revealed bilateral multifocal dense opacities associated with widespread bilateral fine reticular opacification. Video-assisted thoracoscopic lung biopsy showed noncaseating granulomatous inflammation and features of COP. All cultures were negative for bacterial, viral, and fungal infections. Despite discontinuing everolimus and initiating corticosteroids, the patient died of progressive respiratory failure secondary to COP.
ued. However, the patient’s respiratory status continued to deteriorate. Chest computed tomography (CT) scan revealed bronchocentric consolidation associated with widespread bilateral fine reticular opacification and septal thickening (Figure 2). There were multiple metastatic lung nodules that had increased in size and number, when compared with the previous chest CT that was obtained 3 months earlier. The overall pattern, though nonspecific, resembled COP, suggestive of drug-induced pulmonary toxicity. Earlier chest CT scans that were obtained for staging and assessment of response to sunitinib and sorafenib were only significant for pulmonary metastasis. On day 3, vancomycin was added and everolimus was discontinued. On day 5, the patient was intubated and transferred to the ICU.

Following ventilatory mechanical support, the antibiotics were upgraded to include piperacillin/tazobactam and voriconazole. Bronchoscopy was performed, and cultures of the bronchialveolar lavage were negative. On day 2 of ICU admission, video-assisted thoracoscopic lung biopsy was performed and then intravenous methylprednisolone was started (500 mg once followed by 40 mg twice daily). The lung wedge biopsy was consistent with COP, with some features of acute lung injury (Figure 3). The biopsy showed noncaseating granulomatous inflammation including the formation of epithelioid giant cells with foci of interstitial fibrosis and histiocytic infiltration. The alveolar spaces were dilated and filled with the exudate of fibrinous material and histiocytes. Patchy fibroblastic plugs were seen in the alveoli, and rare eosinophils were identified. In addition, areas of alveolar hemorrhage and fibrin deposition were noted. Special stains for fungi and acid-fast bacilli were performed on the tissue biopsy and reported to be negative. All blood, urine, and tracheal aspirate cultures were negative for bacterial, viral, and fungal infections.

On day 5, the patient developed acute respiratory distress syndrome, and the methylprednisolone dose was increased to 40 mg every 8 hours. On day 18, the patient died of progressive respiratory failure secondary to COP.

**DISCUSSION**

In this case, the diagnosis of everolimus-induced COP was made based on the following: the symptoms occurred after the initiation of everolimus, the clinical presentation was similar to what has been described previously; the CT scan at this admission was consistent with COP while all previous CT scans had no such findings, the pathological findings of the lung biopsy confirmed COP, and all other potential causes of COP were ruled out. We found 2 reports of minocycline-
associated COP, but it is unlikely that the minocycline-induced COP in this patient since he had been on treatment for 15 months and all CT scans done during that time and prior to the initiation of everolimus had no evidence of pneumonitis. Although the CT showed the progression of pulmonary metastasis, we do not think that it contributed to the rapid deterioration of the patient’s respiratory status and the fatal outcome. According to the Naranjo probability scale, the association between everolimus and COP was ranked as probable (score = 6).  

NIP is an adverse event that has been reported with all mTOR inhibitors, but the majority of the cases were mild to moderate. and is characterized by noninfectious, non-malignant pulmonary infiltrates. NIP associated with everolimus was reported in 37 (13.5%) patients in the RECORD-1 study and 83 patients (6.1%) in the REACT study; however, the majority of the cases were mild to moderate. In the large multicenter REACT study in which 1367 patients received everolimus, grades 3 and 4 pneumonitis were reported in 33 (2.4%) patients and 4 (0.3%) patients, respectively. Most patients with NIP presented with cough, dyspnea, or both and the median time to onset of symptoms was 108 days (range 24-257 days). Imaging findings on chest CT scan fell into 1 of 4 patterns: pattern (A) characterized by nonspecific areas of ground glass attenuation, corresponding to diffuse and faint opacity without loss of lung volume on chest radiography; pattern (B) characterized by multifocal areas of airspace consolidation (as in COP, corresponding to peripheral consolidation on chest radiograph; pattern (C) characterized by patchy distribution of ground-glass attenuation accompanied by interlobular septal thickening, corresponding to patchy or diffuse faint, linear opacities on chest radiograph; pattern (D) characterized by extensive bilateral ground-glass attenuation or airspace consolidation with traction bronchiectasis, corresponding to diffuse faint opacities or consolidation with lung volume loss on chest radiography. 

Fatal cases of everolimus-associated NIP were rare. To our knowledge, only 5 fatal cases have been reported in the literature. The REACT study reported 3 deaths due to pneumonitis. Another fatal case of suspected pneumonitis was reported in a patient with advanced nonsmall cell lung cancer treated with everolimus in the phase II study. Recently, a case of fatal alveolar hemorrhage associated with the use of everolimus was reported in a patient who underwent cardiac transplantation. For the management of severe NIP, the manufacturer recommends to discontinue everolimus and to consider corticosteroids, if infective origin is ruled out. In the case presented, everolimus was discontinued and corticosteroids were started in a timely manner, but the patient’s condition continued to deteriorate. 

In conclusion, our case illustrates that everolimus may induce life-threatening pulmonary toxicity. Though the incidence is rare, given the expected increase in the utilization of everolimus for various indications, clinicians should be aware of this serious adverse event. In addition, further research is needed to identify patients who may be at risk for developing severe NIP associated with everolimus and provide recommendations regarding the appropriate management of such patients.

Acknowledgment
“The authors wish to thank Dr. Feras Hawari for reviewing this case.”

REFERENCES
1. Novartis Pharmaceuticals. Afinitor (everolimus) package insert. East Hanover, NJ, 2012.
2. Novartis Pharmaceuticals. Zortress (everolimus) package insert. East Hanover, NJ, 2012.
3. Motzer RJ, Escudier B, D’urado S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet. 2008;372(9637):449-56.
4. Grünwald V, Karkarewicz PI, Babekova SE, et al. An international expanded-access programme of everolimus: Addressing safety and efficacy in patients with metastatic renal cell carcinoma who progress after initial vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapy. Eur J Cancer. 2012;48(3):324-32.
5. White DA, Camus P, Endo M, et al. Noninfectious pneumonitis after everolimus therapy for advanced renal cell carcinoma. Am J Respir Crit Care Med. 2010;182:396-403.
6. Kondo H, Fujita J, Inoue T, et al. Minocycline-induced pneumonitis presenting as multiple ring-shaped opacities on chest CT, pathologically diagnosed bronchiolitis obliterans organizing pneumonia (BOOP). Nihon Kokyuki Gakkai Zasshi. 2001;29(3):215-19.
7. Piperno D, Donné C, Loire R, Cordier JF. Bronchiolitis obliterans organizing pneumonia associated with minocycline therapy: a possible cause. Eur Respir J. 1995;8(6):1018-20.
8. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239-45.
9. White D, Schwartz LH, Dimitrijevic S, Di Scala L, Hayes W, Gross SH. Characterization of pneumonitis in patients with advanced non-small cell lung cancer treated with everolimus (RAD001). J Thorac Oncol. 2009;4(11):1357-63.
10. Depuydt P, Nollet J, Benoit D, Praet M, Caes F. Fatal acute pulmonary injury associated with everolimus. Ann Pharmacother. 2012;46:17.
11. Soria JC, Sheperd FA, Douillard JY, et al. Efficacy of Everolimus (RAD001) in patients with advanced NSCLC previously treated with chemotherapy and EGFR inhibitors. Ann Oncol. 2009;20:1674-81.

Ann Saudi Med 2014 July-August www.annsaudimed.net