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Case report

Everolimus associated interstitial pneumonitis in a liver transplant patient

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ABSTRACT

Drug-induced interstitial lung disease is associated with significant morbidity and mortality. Everolimus is an inhibitor of mTOR, a mammalian target of rapamycin, used as an immunosuppressant agent in solid organ transplant. Everolimus has been associated with interstitial lung disease in solid organ transplant patients but has been rarely reported in the liver transplant patient population. We report a case of interstitial pneumonitis in a liver transplant patient associated with everolimus which completely resolved after discontinuation of the medication.

1. Introduction

Drug-induced pulmonary toxicity is not uncommon and immunosuppressive drugs have been associated with interstitial lung disease. Early diagnosis and treatment can potentially improve outcomes. Mammalian target of rapamycin (mTOR) inhibitors, sirolimus and everolimus, are used as immunosuppressive agents in solid organ transplant recipients and as anti-neoplastic agents. Common side effects of everolimus include stomatitis, rash, and fatigue. Everolimus has also been associated with noninfectious interstitial pneumonitis. However, there are only two reports of everolimus-induced noninfectious interstitial pneumonitis described in liver transplant patients.

2. Case report

A 60 year old female with medical problems significant for diabetes mellitus type II (insulin-dependent poorly controlled), hypertension, chronic kidney disease stage III, anemia of chronic disease, hypothyroidism, liver cirrhosis secondary to nonalcoholic fatty liver disease (NAFLD) and hepatocellular carcinoma underwent liver transplant one year prior to presentation. She presented to the emergency department with intermittent fever for three months associated with cough and shortness of breath. Her medications included amlodipine, levothyroxine, insulin detemir, and insulin aspart with meals. Her chronic immunosuppressive treatment included everolimus 10 mg daily and prednisone 5 mg daily. On physical examination, she had a temperature of 100.8 F, initial oxyhemoglobin saturation 93% on room air, blood pressure 130/80 mm Hg and heart rate 72/min. Chest auscultation revealed diminished breath sounds in the right base. The rest of the physical examination was unremarkable. The white blood cell count was 4.6 × 10*3 U/L. Blood chemistries were normal. Blood, sputum and urine cultures were negative. HIV1 and HIV2 antibodies (enzyme immunoassay), serum histoplasmosis antigen and antibodies, urine histoplasmosis antigen, serum coccidioidomycosis antibodies (IgM, IgG) were negative. Epstein- Barr virus PCR and cytomegalovirus PCR were negative. Viral hepatitis studies were also negative. Everolimus level was 4.3 ng/ml (Normal therapeutic range – 5–20 ng/ml). Chest radiograph showed patchy bibasilar interstitial infiltrates [Fig. 1]. Computed tomography (CT) scan of the chest showed diffuse patchy ground glass opacities throughout the lungs [Fig. 2].

The patient was started empirically on vancomycin, cefipime and fluconazole for possible infection. She continued to have fever and cough after seven days of antibiotic treatment. Bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy were performed. BAL fluid analysis showed predominant lymphocytes. BAL cultures including acid fast bacillus (AFB) stain and cultures were negative. In the setting of persistent symptoms and negative diagnostic workup, drug-induced interstitial pneumonitis was considered, and all the medications were carefully reviewed.

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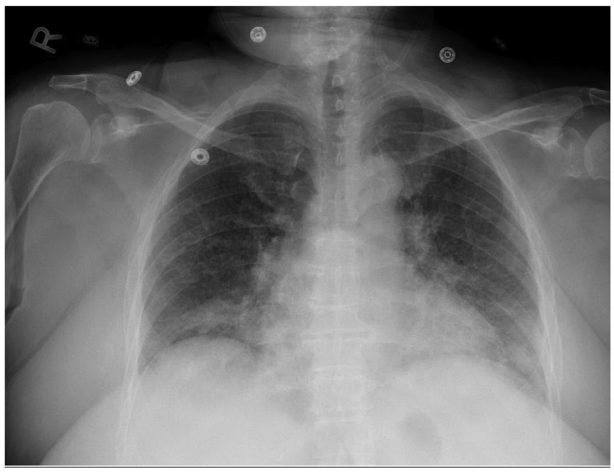

Fig. 1. Chest radiograph showing patchy bibasilar interstitial infiltrates.

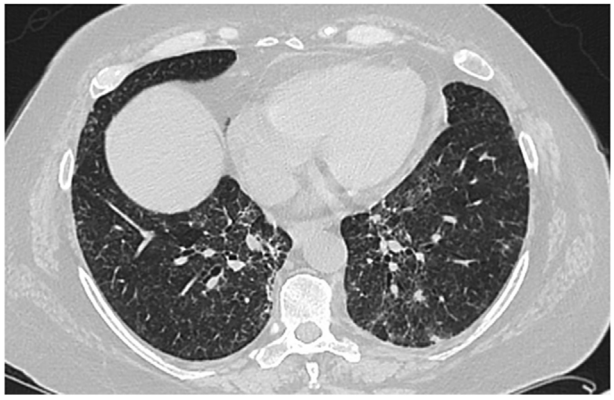

Fig. 2. Computed tomography (CT) scan of the chest showing diffuse patchy ground glass opacities.

Association of everolimus with interstitial pneumonitis has been described in literature, therefore everolimus was discontinued as a therapeutic intervention. The patient was started on tacrolimus for immunosuppression. Her symptoms gradually improved and at 3 months follow up, she had complete resolution of clinical symptoms along with complete resolution of interstitial infiltrates on CT scan [Fig. 3].

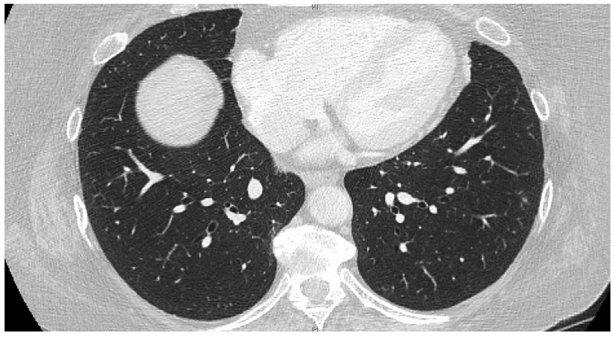

Fig. 3. Computed tomography (CT) scan of the chest sowing complete resolution of interstitial infiltrates at three months follow up.

3. Discussion

Everolimus is a selective inhibitor of the mammalian target of rapamycin (mTOR), a central regulator of intracellular signaling pathways involved in cell growth and proliferation, cellular metabolism and angiogenesis. Everolimus is used as an immunosuppressant in solid organ transplant patients [1]. Interstitial pneumonitis is associated with everolimus and has been reported in literature with similar presentation as described in our case [2–11]. The exact pathogenesis of the lung toxicity cause by mTOR inhibitors is not clear. A proposed mechanism includes interaction with the STAT1 (Signal Transducer and Activator of Transcription 1) gene, which may amplify cellular apoptosis and can increase lung injury. STAT1 augments LPS (lipopolysaccharides) and IFN-b (Interferon b) causing apoptosis and pulmonary vascular leak [12]. Clinical presentation includes cough, shortness of breath, fever and hypoxemic respiratory failure. Diffuse alveolar hemorrhage has also been attributed to everolimus [13]. Radiographic patterns vary from ground glass infiltrates to diffuse interstitial infiltrates. Treatment of everolimus-induced pneumonitis is early discontinuation of the drug. Corticosteroids have been used to treat patients with severe pneumonitis [14]. We did not use corticosteroids for the treatment of interstitial pneumonitis because of moderate symptoms, stable oxygenation and gas exchange in our patient. Furthermore, there is no clear evidence to support use of steroids for mTOR inhibitor-induced pulmonary toxicity. Two cases of everolimus-induced pneumonitis in liver transplant patients have been previously described [15,16]. To the best of our knowledge, this is the third case of everolimus-induced interstitial pneumonitis in liver transplant patients. In the previously reported case by Schrader et al., the patient had localized left lower lobe infiltrates, and follow up CT scan of chest one month after stopping everolimus did not show complete resolution of the infiltrates. Our patient had diffuse patchy ground glass infiltrates more suggestive of a drug-induced mechanism and also showed complete resolution of clinical symptoms and pulmonary infiltrates after discontinuation of everolimus at three months follow up. In the case reported by Marín-Gómez et al., everolimus was never completely discontinued and follow up imaging did not result in complete resolution of infiltrates. Furthermore everolimus levels were significantly higher in this case. The patient in our case had normal levels of everolimus. Our case report highlights a rare case of interstitial pneumonitis associated with normal levels of everolimus in a liver transplant patient. Furthermore it emphasizes that interstitial pneumonitis is a class effect of mammalian target of rapamycin inhibitors and not limited to sirolimus. One limitation of our case includes the lack of rechallenge with everolimus, but we did not rechallenge because of potential morbidity and mortality associated with recurrence of disease.

Clinicians need to have a high suspicion for drug-induced toxicity in liver transplant patients on immunosuppression with everolimus who present with respiratory symptoms. Key features that support the diagnosis are characteristic interstitial pneumonitis on imaging and a negative work up for infection. We suggest discontinuation of everolimus for the treatment of everolimus induced interstitial pneumonitis but corticosteroids may be considered for severe life threatening disease. Early recognition of everolimus toxicity and appropriate discontinuation can prevent significant morbidity and adverse outcomes.

Statement of contribution and disclaimer

All authors contributed to conception, literature review, drafting and final approval of the version to be published and in agreement to be accountable for all aspects of this work. The views expressed

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