A Case of Everolimus Related Pneumonitis Occurred After Switching Treatment from Sirolimus in a Kidney Transplant Patient

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Abstract

Pneumonitis is a reported side effect of treatment with mammalian target of rapamycin inhibitors. In this report, we present a case of everolimus-related pneumonitis that occurred after treatment switching from sirolimus to everolimus. A 33-year-old female was admitted to our clinic with fatigue, cough, night sweats, and high fever after treatment switching from sirolimus to everolimus. Thorax CT revealed ground-glass densities and acinar nodules. After withdrawal of everolimus, complete remission was observed. Pneumonitis after treatment switching from sirolimus to everolimus has not been observed before. In patients with pulmonary symptoms during everolimus treatment, drug-related pneumonitis should be considered.

Keywords: Everolimus, sirolimus, mTOR inhibitors, drug-related pneumonitis, kidney transplantation

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Tedavinin Sirolimus'tan Everolimus'a değiştirilmesi sonucu Everolimus'a bağlı pnömonit gelişen bir böbrek transplantasyonu hastası olgusu

Öz

Pnömonit mammalian target of rapamycin inhibitörleri tedavisinde görülen bir yan etkidir. Biz bu olguda tedavinin sirolimustan everolimusa değiştirilmesi sonucu everolimusa bağlı pnömonit gelişen bir hastayı sunuyoruz. 33 yaşında kadın hasta tedavisinin sirolimustan everolimusa değiştirilmesinden sonra gelişen kliniğimize halsizlik, öksürük, gece terlemesi ve yüksek ateş şikayetleriyle başvurdu. Toraks BT'de buzlu cam görüntüsü ve asiner nodüller görüldü. Everolimus tedavisi kesildikten sonra hastanın şikayetleri tamamen geriledi. Sirolimustan everolimusa geçiş sonucu pnömonit daha önce gözlemlenmemiştir. Everolimus alan hastalarda pulmoner semptomlar gelişirse everolimusa bağlı pnömonit düşünülmelidir.

Anahtar Sözcükler: Everolimus, Sirolimus, m-TOR inhibitörleri, ilaca bağlı pnömonit, böbrek transplantasyonu

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Drug-related pneumonitis is reported as a side effect of mammalian target of rapamycin (mTOR) inhibitors. The incidence of pneumonitis during everolimus treatment has been reported to be between 13.5% and 48.7% in various studies [1-3]. It is commonly associated with sirolimus [4]. In this report, we present an unusual case of drug-related interstitial pneumonitis following everolimus treatment initiated after the administration of sirolimus treatment to a kidney transplant patient for a long period.

Case Presentation

A 33-year-old female who underwent cadaveric kidney transplant 11 years ago was admitted to our outpatient clinic with fatigue, cough, night sweats, and high fever since 1 month. She had a history of left nephrectomy due to vesicoureteral reflux-related pyelonephritis. For end-stage kidney disease, she un-

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derwent hemodialysis for 4 years. After transplantation till 2015, she was administered mycophenolate, mofetil, sirolimus, and prednisolone. However, due to the inability to measure sirolimus level, the treatment was switched to everolimus. At the time of admission, rapid chest X-ray revealed reticulonodular pattern and sputum culture showed colonization with *Haemophilus influenzae*. Thereafter, the patient was prescribed moxifloxacin for 14 days. However, the complaints persisted after the administration of treatment for pneumonia. The patient was internalized to differentiate infection, tuberculosis, malignancies, and adverse drug effects. A blood sample was collected from the patient, and the laboratory findings were as follows: White blood cell, 5.5 $10^3/mm^3$; hemoglobin, 9.1 g/dl; hematocrit, 26.7%; urea, 98 mg/dL; creatinine, 2.62 mg/dL; natrium, 142 mmol/l; potassium, 4.72 mmol/l; calcium, 9.03 mmol/l; and C-reactive protein, 4.45 mg/l. Positron emission tomography (PET)/Computerized tomography (CT) showed multiple cystic lesions in the ovaries, which were found to be benign by gynecological examinations. On thorax CT, ground-glass densities and acinar nodules were observed. To differentiate between miliary tuberculosis and atypical viral infections, bronchoscopic lavage was performed. Purified Protein Derivative (PPD) test was 1 mm and interpreted to be anergic. Regarding sputum direct fluorescent antibody, negative results were obtained for Pneumocystis jiroveci pneumonia and acid-resistant bacteria. Urine sample revealed negative results for legionella antigen, cytomegalovirus deoxyribonucleic acid, and galactomannan antigen. BK virus was not detected in urine and blood. A blood sample showed normal angiotensin-converting enzyme value and negative antinuclear antigen and anti-double-stranded antigen results. There was no bacterial colonization in blood and urine cultures. No urinary system pathologies were detected on renal Doppler ultrasonography. Echocardiographic examination performed to exclude infective endocarditis showed the following: ejection fraction of 55%, mild mitral and tricuspid valve regurgitation, pericardial effusion of 5 mm, and grade 2 diastolic dysfunction. Everolimus level was within the normal range (6.65 ng/mL). During daily rounds, the patient presented a decreased hemoglobin level. However, the results of direct and indirect Coombs test, hemolysis parameters, peripheral blood smear, and fecal occult blood tests repeated thrice were insignificant. Meanwhile, bronchoscopic lavage showed negative results for acid-resistant bacteria. In bronchoscopic lavage fluid cytology, less frequently polymorphic leukocytes, more frequently hyperplastic basal and metaplastic cell clusters, and basement membrane thickening were reported. Respiratory function test demonstrated restrictive lung disease. These findings increased the suspicion of everolimus-related pneumonitis. Treatment switching from everolimus to cyclosporine resulted in alleviation of the clinical picture. A regression in ground-glass densities on thorax CT performed 3 weeks later supported this diagnosis.

Discussion

The novel mTOR inhibitor everolimus is an immunosuppressive agent used in solid-organ transplants in combination with cyclosporine. Because of its low nephrotoxicity and antiproliferative effect, everolimus is also used for cancer patients. Its important side effect is drug-related pneumonitis. This side effect has been reported by many centers after solid-organ transplant for sirolimus, another mTOR inhibitor [4-6]. Similar to sirolimus, the frequency of pneumonitis during everolimus treatment varies between 1.3% and 12.7% in kidney transplant patients [7, 8]. However, an alleviation in the clinical picture has been observed following treatment switching from sirolimus to everolimus [9]. In our report, we present a patient who was receiving sirolimus treatment for 11 years without any complaints. After treatment switching to everolimus for 1 month, she developed drug-related pneumonitis. The occurrence of pneumonitis has not been observed after treatment switching from sirolimus to everolimus to date.

The exact mechanism underlying drug-related pneumonitis remains to be established. A combination of direct toxicity and immunological toxicity is considered to have a role in its pathophysiology. The observed lymphocytic alveolitis on lung biopsies performed for affected patients provides a proof of the immune-mediated toxicity hypothesis. On the other hand, a rapid resolution of the clinical picture favors the direct toxicity hypothesis [10]. In our case, we observed normal everolimus blood levels. This finding supports the immunological hypothesis rather than direct toxicity.

Conclusion

Everolimus-related pneumonitis in kidney transplant patients should always be included in differential diagnosis. The present case states that everolimus can also induce pneumonitis despite therapeutic blood value. In such cases, immediate discontinuation of everolimus should be considered.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

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