JKAU: Med. Sci., **Vol. 20** No. 2, pp: 105-110 (2013 A.D. / 1434 A.H.)
DOI: 10.4197/Med. 20-2.8

Everolimus-Induced Antineutrophil Cytoplasmic Antibody Associated Vasculitis in Metastatic Renal Cell Carcinoma: A Case Report

Hanadi M. Alhozali, MBBS, ABIM, FRCPC

Department of Internal Medicine and Nephrology, Faculty of Medicine
King Abdulaziz University, Jeddah Saudi Arabia
dr_hanadi2002@hotmail.com

Abstract. This is a case report of a 67-years-old male with metastatic renal cell carcinoma presented with pancytopenia, pneumonitis, and an acute on chronic renal failure. He was initiated on Everolimus four weeks earlier. Further work-up did not reveal pre renal or post renal components which accounted for his renal failure. Serological studies showed positive antineutrophil cytoplasmic antibody; directed against proteinase 3-antineutrophil cytoplasmic antibody and myeloperoxidase. Interestingly, the renal function did not improve after discontinuation of Everolimus and the patient was initiated on hemodialysis. Immunosuppressive therapy consisting of steroid and Cyclophosphamide was started based on clinical features and laboratory data. Unfortunately, diagnostic kidney biopsy was contraindicated, given that he had only a single kidney from previous nephrectomy for renal cell carcinoma. Ultimately, renal function and urine output recovery occurred after two doses of IV cyclophosphamide. In conclusion, this case represents Everolimus-induced antineutrophil cytoplasmic antibody associated vasculitis with severe renal involvement; features that were not previously described in the literature regarding this drug. Thus, the possibility of Everolimus-induced antineutrophil cytoplasmic antibody vasculitis should be considered when patients treated with Everolimus develop severe renal insufficiency that cannot be explained by other etiologies.

Keywords: Everolimus, Antineutrophil cytoplasmic antibody, Drug-induced, Vasculitis.

Correspondence & reprint request to: Dr. Hanadi Alhozali
P.O. Box 80215, Jeddah 21589, Saudi Arabia
Accepted for publication: 17 October 2012. . Received: 14 July 2012.

Introduction

Everolimus inhibits the mammalian target of rapamycin (mTOR) in the phosphatidylinositol-3-kinase and protein kinase B (PI3K-Akt)/mTOR signaling pathway, leading to cell cycle arrest in the G1 phase and potentially inducing apoptosis. It has anti-proliferative activity against a variety of tumor cell lines and inhibits tumor growth in mouse xenograft models. Everolimus is currently being used as a therapeutic agent in patients with advanced solid tumors and hematological malignancies[1,2]. Furthermore, it has been used in Europe in immunosuppressive medications to prevent rejection in cardiac and renal transplants. Multiple toxicities have been reported with Everolimus including anemia, thrombocytopenia, leukopenia, hypertriglyceridemia, hyperglycemia, and pneumonitis.

Everolimus-induced antineutrophil cytoplasmic antibody (ANCA) associated vasculitis with major organ involvement that has not yet been reported in the literature. There are a few cases of Everolimus and Sirolimus induced leukocytoclastic vasculitis (LCV), but with negative ANCA serology[3-5].

Case Report

A 67-year-old Caucasian male with metastatic renal cell carcinoma, hypertension, ischemic heart disease, and chronic renal disease with base line creatinine 120 µmol/l. He was admitted with constitutional symptoms, pancytopenia, and acute chronic oliguric renal failure. Six years earlier, he was diagnosed with metastatic renal cell carcinoma to the liver, bone, and lung. The patient had unilateral right nephrectomy and received palliative radiation treatment to the sacrum and skull. In the past, he failed multiple therapies including Sorafenib, Sunitinib (tyrosine kinase inhibitors, vascular endothelial growth factor (VEGF) inhibitors) and InterlukineII inhibitor. He was not taking any known nephrotoxic medications. He was initiated on Everolimus orally at a dose of 5 mg per day. By week 4 of therapy, the patient started complaining of progressive shortness of breath, fever, chills, and generalized weakness. He did not experience productive cough, hemoptysis, joint pain, urinary symptoms, or a history of sick contacts.

On physical examination; the patient was afebrile and oxygen saturation was 88% on room air. In addition, he had bilateral fine crackles on lung auscultation and fine petechial rashes on the chest and

abdomen. The remainder of the physical examination was unremarkable. Upon admission, laboratory investigation revealed pancytopenia of all cell lines. Complete blood count test revealed total white count 1.7, hemoglobin 110, platelets count 113 and neutrophil count low at 0.8. Furthermore, he had elevated serum creatinine of 213 µmol/l from baseline of 120 µmol/l. Examination of the urine sediment showed red blood cells (RBCs), but no RBCs cast and minimal proteinuria. Serological studies indicated strongly positive proteinase 3-antineutrophil cytoplasmic antibody (PR3-ANCA antibodies) or (C-ANCA) and weakly positive myeloproxidase (MPO-ANCA antibodies) or (P-ANA). Complement C3 and C4 were normal. A chest X-ray revealed bilateral infiltrate and a subsequent computerized axial tomography (CT) scan of the thorax showed severe interstitial changes suggestive of pneumonitis and new pulmonary nodule. A biopsy of the pulmonary nodule and the upper lung lobe were consistent with metastatic renal cell cancer and drug induced pneumonitis, respectively. Abdominal/renal ultrasound revealed a single hypertrophic kidney with no signs of obstruction or tumor infiltration. The pneumonitis was thought to be induced by Everolimus, which was subsequently discontinued. Since, the patient had solitary kidney, diagnostic kidney biopsy was contraindicated. In the hospital, the patient's renal function continued to deteriorate despite adequate hydration and discontinuation of Everolimus. The patient began immunosuppressive therapy with oral prednisone and monthly IV cyclophosphamide. Additionally, he was initiated on intermittent hemodialysis three times per week. After the second dose of cyclophosphamide, the patient's renal function and urine output improved dramatically. Considering the outcome, it was decided to withhold the monthly IV cyclophosphamide and begin weaning the patient off the prednisone. Renal function was completely recovered and hemodialysis was subsequently discontinued. Furthermore, repeated ANCA serology, both C-ANCA and P-ANCA, were undetectable.

Discussion

To date, many drugs have been implicated in the pathogenesis of drug-induced ANCA vasculitis[6], with the most common being propylthiouracil, hydralazine, penicillamine, and cocaine. There are few reported cases showed that Everolimus and Sirolimus are likely to induce leukocytoclastic vasculitis in some treated patients, but with negative ANCA serology [3-5]. Both drugs displayed a similar mechanism of

action and toxicity profile. An extensive literature review was performed and did not come across any case of Everolimus or Sirolimus induced ANCA vasculitis with life threatening organ involvement. The diagnosis of Everolimus induced ANCA vasculitis in this patient was one of exclusion. The patient had no evidence of ANCA vasculitis before exposure to Everolimus. Moreover, the overall presenting features in this patient were compatible with Everolimus related toxicities. Furthermore, the feature in the lung biopsy was compatible with Everolimus-induced pneumonitis. The challenge in this case was the absence of renal histopathological diagnosis, given that the patient had single kidney, to confirm diagnosis and guide treatment. However, in my opinion this patient is unlikely to have primary ANCA associated vasculitis on the setting of Everolimus induced multi-organ toxicities. Finally, previous treatments for his renal cell carcinoma had been discontinued several months prior, and were therefore, unlikely to play a role in the pathogenesis of ANCA vasculitis.

The treatment of Drug-induced ANCA associated vasculitis depends on the severity of disease activity, but it should always include withdrawal of the suspected drugs. In some case reports, severe organ involvement such as renal and pulmonary vasculitis resolved after discontinuation of the offending drug[7]. However, in another case report, vasculitis worsened after discontinuation of propylthiouracil[8].

In this case, the lack of recovery and severity of renal failure despite discontinuation of Everolimus warranted the initiation of immunosuppressive therapy. Fortunately, the patient required a shorter course of immunosuppressive therapy and long term maintenance treatment was not necessary. It is likely that this patient represented the first reported case of Everolimus-induced ANCA associated vasculitis.

Conclusion

Considering the clinical presentation, laboratory data, and response to immunosuppressive treatment, it is concluded that this case represents Everolimus induced ANCA associated vasculitis. Everolimus induced-ANCA vasculitis should be considered when other etiologies of renal failure in treated patients have been ruled out.

References

[1] **Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, Grünwald V, Thompson JA, Figlin RA**. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet* 2008; **372**(9637): 449.

[2] **Panwalkar A, Vertovsek S, Giles FJ.** Mammalian target of rapamycin inhibition as therapy for hematologic malignancies. *Cancer* 2004; **100**(4): 657–666.

[3] **Pasqualotto AC, Bianco PD, Sukiennik TCT, Furian R, Garcia VD.** Sirolimus-induced leukocytoclastic vasculitis: the second case reported. *Am J Transpl* 2004; **4**(9): 1549-1551.

[4] **Hardinger KL, Cornelius LA, Trulock EP 3rd, Brennan DC.** Sirolimus-induced leukocytoclastic vasculitis. *Transplantation* 2002; **74**(5): 739–743.

[5] **Yee KW, Hymes SR, Heller L, Prieto VG, Welch MA, Giles FJ.** Cutaneous leukocytoclastic vasculitis in a patient with myelodysplastic syndrome after therapy with rapamycin analogue everolimus: case report and review of literature. *Leuk Lymphoma* 2006; **47**(5): 926-929

[6] **Choi HK, Merkel PA, Walker AM, Niles JL.** Drug- associated antineutrophil cytoplasmic antibody-positive vasculitis: Prevalence among patients with high titers of antimyeloperoxidase antibodies. *Arthritis Rheum* 2000; **43**(2): 405-413.

[7] **Ohtsuka M, Yamashita Y, Doi M, Hasegawa S.** Propylthiouracil- induced alveolar haemorrhage associated with antineutrophil cytoplasmic antibody. *Eur Respir J* 1997; **10**(6): 1405–1407.

[8] **Helfgott SM, Smith RN.** Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 21-2002. A 21-year-old man with arthritis during treatment for hyperthyroidism. *N Engl J Med* 2002; **347**(2): 122-130.

التهاب الأوعيه الدمويّة المرتبطة ANCA كعرض جانبي لدواء Everolimus عند مريض مصاب بسرطان الخلايا الكلويّة المنتشر

هنادي معتوق الهذلي

كلية الطب، قسم أمراض الباطنة، جامعة الملك عبدالعزيز

جدة – المملكة العربية السعودية

المستخلص. هذا تقرير حالة عن مريض مصاب بسرطان الخلايا الكلوية المنتشر وتلقى علاج everolimus بعد أربعة أسابيع من العلاج، وجد لديه نقص في عدد الخلايا الدموية (قلة الكريات الدموية الشاملة)، التهاب رئوي وفشل كلوي حاد، وقد أظهرت الفحوصات المصلية وجود أجسام مضادة للأجسام المضادة السيتوبلازمية ANCA، ومن المثير للاهتمام أن وظائف الكلى لم تتحسن بعد إيقاف .everolimus بناء على ذلك، استخدمت علاج مناعي يتكون من ستيرويد steroid وسيكلوفوسفاميد Cyclophosphamide بالإضافة للغسيل الدموي الكلوي ، للأسف لم يمكن إجراء خزعة الكلى لتشخيص الحالة ، لأن المريض لديه كلية واحدة حيث تم إزالة الكلية الأخرى في عملية ورم كلوي سابق. وفي مثل هذه الحالة يمنع طبياً أخذ خزعة كلوية. ولقد تحسنت وظائف الكلى بعد جرعتين فقط من دواء سيكلوفوسفاميد. بناء على الخصائص السريرية والبيانات المختبرية للمريض، هذه الحالة تمثل التهاب الأوعية الدموية المرتبطة ANCA مع فشل كلوي حاد بسبب دواء everolimus، وهذا عارض جانبي للدواء لم يسبق وصفه في المؤلفات الطبية وبالتالي ينبغي النظر في إمكانية تشخيص التهاب الأوعية الدموية المرتبطة ANCA المصحوبة بفشل كلوي عند المرضى الذين يتم علاجهم بدواء everolimus عند انعدام وجود مسببات أخرى.