LETTER

De novo and recurrent Kaposi's Sarcoma after renal transplantation in two patients taking everolimus

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Renal transplantation has been associated with increased frequency of Sarcoma Kaposi (SK) because of immunosuppression[1]. Several pieces of evidence suggest a certain antitoumor activity mTOR inhibitors, including tumuor regression and prolonged stable disease. Recently it was claimed that mTOR inhibitor sirolimus might prevent the occurrence or regress the already existing SK after renal transplantation[2,3]. Everolimus is a sirolimus analogue, showing in preclinical studies antitumuor activity given in daily dose of 10 mg or higher[4].

We present two cases of sarcoma Kaposi, one de novo and one recurrent, after kidney transplantation in two patients taking the mTOR inhibitor everolimus (E).

Case 1: A 59 year – old Greek male with end stage renal failure (ESRF) of unknown etiology on hemodialysis received a first cadaveric transplant on 19.11.04 (Hippokratio Hospital, Thessaloniki, Greece). The immediate posttransplant period was uneventful. The induction therapy was methylprednisolne (MP) 16 mg/d, E 1.5 mg/d, cyclosporine (CsA) 200 mg/d and basiliximab 20 mg on day 0 and 4. He was discharged on 14th PO day with serum creatinine (C) 1.06 mg/dl. Thirteen months later he developed SK on the skin of the shanks (biopsy proven). No lymph node or visceral involvement was found. At that time the patient was taking MP 6.0 mg/d, E 1.5 mg/d (trough levels: 3-8 ng/ml) and CsA 75 mg/d (trough levels: 30-160 μg/l). E was slowly withdrawn and stopped on June 2006. There was partial remission of the lesions. He received 8 sessions of irradiation on the skin lesions resulting in slow regression. Today he is taking MP 4 mg/d and CsA 75 mg/d and his C is 1.3 mg/dl.

Case 2: A 43 year old Greek male patient with ESRF of unknown etiology on dialysis received a first cadaveric transplant on 4th of August 2000 (Hospital Chu Clermont – Ferrand, France) and the induction therapy was MP, CsA, Azathioprine (AZA) and basiliximab. DGF, pulmonary edema, myocardial infarct and fever complicated the immediate post – transplant period. Acute rejection not responding to MP pulses was diagnosed (two biopsies), and MMF was substituted for Aza. On 29th of September he presented high fever and sepsis due to pseudomonas aueroginosa. In the beginning of October SK appeared on the plantar areas of the feet with HHV8 positive in the blood and a few days later he developed lung infection due to pneumocystis carinii. The kidney was removed on 27th of October 2000 and the KS regressed completely 14 months later.

On 30th of August 2006, he received a second transplant from his sister (Charite Campus Centre, Berlin, Germany) with uneventful posttransplant period. His induction therapy was MP, enteric coated mycophenolic acid (ECMA), CsA and basiliximab. He was converted to E from CsA on PO day 15th. Seven months later he developed SK (biopsy proven) again on the plantar areas of the feet. ECMA was discontinued, everolimus dose was reduced and one month later there was partial regression of the skin lesions. On May 2007 he was admitted to the hospital (Greece) because of high fever. Bronchopneumonia was diagnosed by a CT of the lungs. He received amikacin, ceftazidime and clarithromycin and he continued on medrol (6 mg/d) as the only immunosuppressant. Ten days later he was discharged taking medrol 6 mg/d and everolimus 0.5 mg X 2. His Kaposi was regressing slowly. HHV8 was found in the blood but not in the SK lesions and valgancyclovir given the first 6 posttransplant months was reinstituted[5].

Since that time he had repeated infectious complications (bronchopneumonia, sepsis due to pseudomonas aueroginosa, urinary infection due to klebsiella pneumoniae) and presented new lesions on the feet (stage 2). For this reason E was withdrawn. Imiquinod (Aldara®) ointment was applied to the feet without any result and the patient received ten sessions of irradiation[6,7]. He is on MP as the sole immunosuppressant since November 2007. SK lesions have regressed almost completely at the end of May 2008. He is on 6 mg/d MP and his serum creatinine is 1.9 mg/dl.

To our knowledge this is the first report of de novo and recurrent sarcoma Kaposi in patients taking E. These cases show that E and possibly and the other mTOR inhibitors do not protect patients with a kidney transplant from sarcoma Kaposi. The everolimus daily dose used in these cases was very law to exert any antitumor effect[4]. Possibly, sarcoma Kaposi is the result of the net immunosuppressive state of the patient due to drugs, viral infection, genetic make up and other unidentified yet factors. This is supported by the observation that SK regressed

after dose reduction and discontinuation. Extrapolating our findings we may assume that the reported beneficial effect of sirolimus[2,3] is not due to the drug itself but to the reduction of the net state of immunosuppression. In the same way we could explain the lack of effectiveness[8] of sirolimus in a case that CsA was substituted for sirolimus. Possibly a further reduction of immunosuppression was needed. From these cases we conclude that everolimus can not protect from SK in kidney transplantation.

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