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CASE REPORT

A case of esophageal adenocarcinoma on long-term rapamycin monotherapy

Catarina Canha,[1,2,*] Raquel Ferreira,[1,2,*] Jordi Rovira,[3] Daniel Moya-Rull,[3] Antoni Castells,[2,4,5] Fritz Diekmann,[1,2,3] Federico Oppenheimer,[1,2,3] Josep Maria Campistol[1,2,3] and Ignacio Revuelta[1,2,3]

1 Department of Nephrology and Renal Transplantation, Hospital Clínic, Barcelona, Spain
2 Department of Medicine, Universitat de Barcelona, Barcelona, Spain
3 Laboratori Experimental de Nefrologia i Trasplantament (LENIT), Fundació Clínic – IDIBAPS, Barcelona, Spain
4 Department of Gastroenterology, Hospital Clínic, Centro de Investigación Biomédica en Red en Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Spain
5 Gastrointestinal and Pancreatic Oncology, IDIBAPS, Barcelona, Spain

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Correspondence
Ignacio Revuelta MD, PhD, Department of Nephrology and Renal Transplantation, Hospital Clínic, Laboratori Experimental de Nefrologia i Trasplantament (LENIT), Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Villarroel 170 (Escala 10 – Planta 5), E-08036 Barcelona, Spain.
Tel.: +34 932275400 - Ext 2115;
fax: +34 934546033;
e-mail: irevuelt@clinic.ub.es

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*Canha C and Ferreira R have contributed equally to the preparation of the manuscript.

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Summary

Cancer in transplant recipients represents a therapeutic challenge even when the patient is already under mTOR inhibitors. A 78-year-old man received a deceased donor kidney transplant in 1993. After 6 months, he developed a multifocal cutaneous and nonvisceral Kaposi's Sarcoma while on cyclosporine immunosuppressant therapy. The patient was converted to sirolimus monotherapy in 2001 with subsequent complete recovery within 2 years. In 2007, the patient was diagnosed with an esophageal adenocarcinoma stage IIA. An esophagectomy was performed without requirement of further treatment. He has continued on sirolimus monotherapy ever since, with no other incidents and no recurrences of either tumor. In this report, we describe an interesting case of a second cancer while on immunosuppressive therapy with anticancer activity. Moreover, the present knowledge of the matter is discussed.

Background

Kidney transplantation is the best treatment for end-stage renal disease. Modern immunosuppressive therapy has led to advances in kidney transplantation, with lower acute rejection rates and excellent outcomes in patient and graft survival [1]. Nonetheless, more patients are at risk of the immunosuppressive side effects, such as malignancy [2,3]. In fact, cancer is responsible for 10–35% of all deaths after transplantation. For most common tumors, for example,

colon, lung, and breast, cancer rates are roughly twofold higher after kidney transplantation compared with the general population. However, it is clear that Kaposi sarcoma (KS), non-Hodgkin's lymphomas, and nonmelanoma skin cancers are by far the most common type, with a 20-fold increase compared with the general population [3].

Esophageal cancer is one of the least studied and deadliest cancers worldwide, being the sixth leading cause of death from cancer [4]. Esophageal cancer is thought to have a cancer rate twofold higher after kidney transplantation compared with the general population [3], in which it occupies the eighth position among the most common cancers worldwide [5].

To reduce the risk of cancer, the use of mammalian target of rapamycin (mTOR) inhibitors is thought to be a likely advance in therapy, as it has been shown that they have potent anticancer effects. Sirolimus (SRL), a mTOR inhibitor, was associated with a reduction in the risk of malignancy in transplant recipients, showing better results in patients who converted from an established immunosuppressive regimen to SRL [6]. Nevertheless, there is still insufficient knowledge about the long-term effects of mTOR inhibitors therapy.

Here, we present a patient with an esophageal adenocarcinoma (EAC) after monotherapy with SRL for 6 years and the effect of maintenance of SRL in long-term follow-up after esophagectomy. We observed a possible relation of the mTOR pathway and the esophageal cancer. Furthermore, we discuss treatment options, the relative lack of knowledge about long-term sirolimus effects, and current guidelines for cancer *de novo* while on mTOR inhibitors therapy.

Case report

A 78-year old man developed an EAC in 2007 under SRL monotherapy (Fig. 1). In 1993, he received a deceased-donor kidney transplant with a *de novo* immunosuppressive protocol based on cyclosporine (CsA; 8 mg/kg/day), azathioprine (100 mg/kg/day), and prednisone (1 mg/kg/day). Six months after transplantation, while on CsA and prednisone, he was diagnosed of a multifocal cutaneous and nonvisceral KS. Prednisone was removed and the doses of CsA were progressively decreased. Despite the low blood levels of CsA (100 ng/ml) and prolonged follow-up, the cutaneous KS lesions remained unaltered. In December 2001, the patient was converted from CsA to SRL (3 mg/day) and 18 months later no cutaneous KS lesions could be identified in the patient. At this time, SRL target blood levels were 11 ng/ml [7].

In 2007, the patient complained of dysphagia, and therefore, endoscopy was indicated. The endoscopic examination of the upper digestive tract showed a single, 3 mm-sized mass which was located 40 cm below the upper incisor. A biopsy was performed and an intestinal type adenocarcinoma was detected. Endoscopic ultrasonography (EUS) revealed hypo-echoic wall thickening of the lower esophagus, invading muscularis propria; a computerized tomography scan ruled out extraesophageal involvement, and the patient underwent an Ivor-Lewis esophagectomy, achieving a R0 resection. Finally, the tumor was classified as a pT3N0M0 (stage IIA), and no adjuvant treatment was required. None classical risk factors of EAC (smoking, weekly reflux symptoms, obesity, and Barrett's esophagus [4]) were found in the medical history. The patient underwent follow-up exams (computerized tomography scans and endoscopy procedures) for 7 years without any signs of tumor relapse.

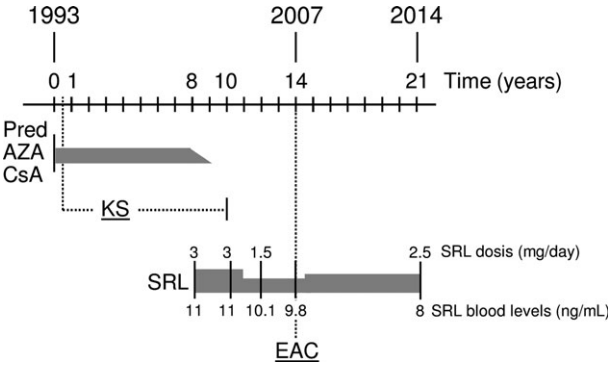

Figure 1 Timeline of clinical events and immunosuppressive therapy. Renal transplantation was performed in 1993, and the follow-up has been conducted until 2014. Immunosuppressive therapy: cyclosporine (CsA), azathioprine (AZA), prednisone (Pred), and sirolimus (SRL). Malignancies detected in this subject were Kaposi sarcoma (KS) in 1993 and esophageal adenocarcinoma (EAC) in 2007.

At the time diagnosis of the EAC, the patient was on SRL monotherapy (1.5 mg/day), reaching 9.8 ng/ml of SRL blood levels. The patient kept a stable kidney allograft function during the follow-up without any side effects related with the immunosuppressive therapy. During the perioperative period, SRL was converted to tacrolimus to minimize surgical complications. After 3 months TAC was removed, and SRL was restored as monotherapy. The current SRL dose is 2.5 mg/day with trough blood levels of 8 ng/ml.

A panel of immunohistochemical stains for the mTOR pathway was performed on the surgical piece of the EAC (Fig. 2a). It revealed an activation of the mTOR signalling as the phosphorylated forms of mTOR and $p70^{S6K}$ stained positive. Moreover, PI3K and AKT, upstream mTOR pathway molecules, were positive and PTEN, a negative regulator of mTOR, was found to be negative. In addition, RICTOR, a subunit of mTOR complex 2, which is related with the pathway feedback and the activation of AKT, was positive (Fig. 2b).

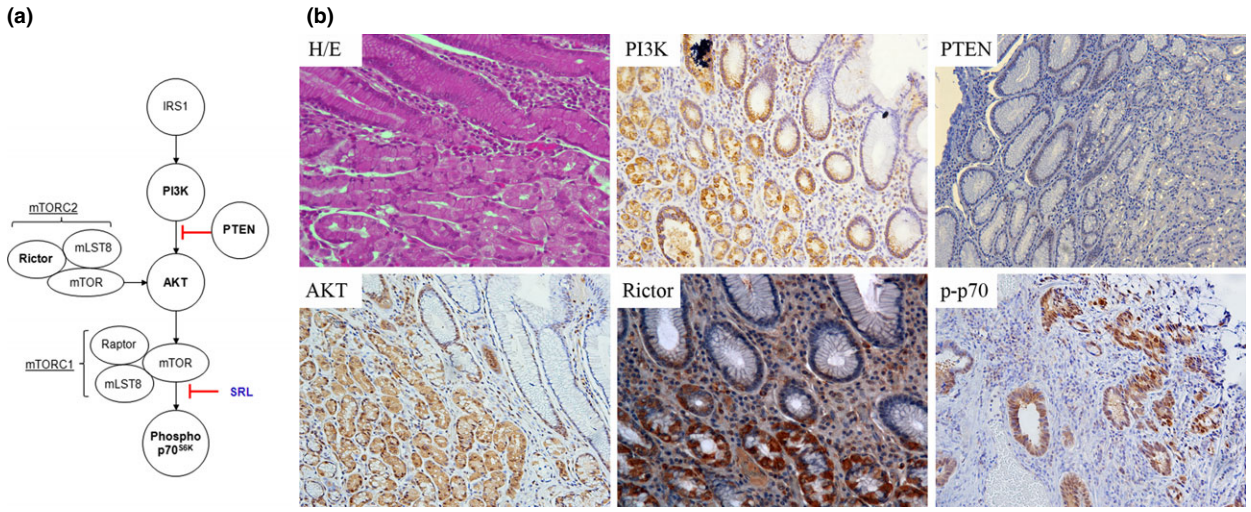

Figure 2 Characterization of esophageal adenocarcinoma. (a) Simplified scheme of mTOR pathway. (b) Conventional and immunohistochemistry staining of the esophageal surgical piece; H/E, PI3K, PTEN, AKT RICTOR, and phospho-p70^{S6K}. Stained pictures are shown from left to right.

Although an EAC was diagnosed in a kidney transplant patient on long-term SRL monotherapy, the clinical behaviour of the previously diagnosed KS and mTOR pathway immunohistochemical staining led us to maintain SRL as immunosuppressive therapy. After 13 years using SRL, KS, and EAC remain in remission, without any side effects or complications due to mTOR inhibitor long-term use.

Discussion

In this report, we present a solid organ cancer developed in a kidney transplanted patient under long-term SRL treatment after conversion from CsA due to KS.

Cancer morbidity and mortality in transplant recipients are due to multifactorial causes, with chronic immunosuppressive therapy playing an important role in it [3]. Immunosuppressive therapy with calcineurin inhibitors (CNIs), such as cyclosporine A, is an important risk for cancer. One potential breakthrough is the use of mTOR inhibitors, with potent anticancer effects [8]. The mTOR pathway acts to induce protein synthesis necessary for angiogenesis, cell growth, and nutrient uptake for cell survival [9,10]. Furthermore, mTOR inhibitors can directly target cancer cells by inhibiting their dependence on cell growth and survival [11].

There is growing clinical evidence of the benefit of mTOR inhibitors in cancer therapy. For instance, effects on skin-cancer prevention [12], inhibition of progression of KS [7], and induction of partial or complete remission in post-transplant lymphoproliferative disorder [13] have been attributed to mTOR inhibition. Moreover, the mTOR inhibitors, everolimus and temsirolimus are registered for the treatment of renal cell carcinoma and neuro-endocrine tumors. In the CONVERT trial, which assessed the conversion to a sirolimus-based CNI-free immunosuppressive regimen, the malignancy rates postconversion were significantly lower in the group of patients that was converted to mTOR inhibitors [14].

The beneficial effect of short- to medium-term use of mTOR inhibitors appears to be evident. In contrary, there are few studies about long-term effects [15]. Our patient developed an esophageal cancer after 6 years of monotherapy with SRL, which underlines the insufficient knowledge on the long-term effects of mTOR inhibitors therapy. Considering that the patient did not present any classical risk factors of EAC [4], we could not clarify whether the potential benefit of mTOR inhibition was involved neither with EAC development nor with the delayed occurrence.

Several studies have shown mTOR activation in esophageal carcinoma specimens, even though the rate of activation, according to mTOR phosphorylation, ranged from 25% to 70% [16,17]. Hirashima *et al.* demonstrated that everolimus has a therapeutic effect on esophageal squamous cell carcinoma both *in vitro* and *in vivo*, and combination therapy with everolimus and cisplatin showed an additive effect [17]. In an *in vitro* study, mTOR and p70^{S6K} were overexpressed in esophageal cancer cells compared with normal esophageal epithelial cells [18]. Amplification or mutations in the RTK-PI3K-mTOR pathway have also been identified by whole genomic sequencing, whole exome sequencing and high-density genomic profiling. Mutations were discovered in 23% of esophageal cancer, with PIK3CA/mTOR being the most frequently mutated [19].

In our case, this positive correlation was indeed identified, since the immunohistochemistry of the tumoral tissue revealed an activation of the mTOR pathway (positive phospho-mTOR), and we consider that its persistent activation might have played a role in the tumorigenesis of the esophageal adenocarcinoma. There are several factors that might have triggered its permanent activation: (i) loss of long-term efficacy of sirolimus; (ii) insufficient doses of sirolimus; (iii) activation of the AKT through the mTOR complex 2 (RICTOR subunit was positively stained) [20]; (iv) loss of the negative feedback given by $p70^{S6K}$; (v) mutations of the pathway.

Considering that the patient developed a tumor while on SRL monotherapy and the mTOR pathway was activated, the immunosuppressant therapy was one of the challenges to overcome. Our decision to maintain SRL was based upon the lack of other immunosuppressant drugs known to have antitumor characteristics and the fact that the mTOR pathway was active in the tumour biopsy. At present, the patient is free of disease 7 years after the EAC diagnosis. This fact is remarkable considerung that stage IIA esophageal cancer is associated with a 5-year survival rate between 30 and 40% [4]. It is important to point out that, besides complete R0 surgical resection, both TNM stage grouping and pT and pN descriptors are independent prognostic factors in patients with esophageal cancer. In that sense, even though surgery could be considered curative, our patient had a high probability of tumor relapse, especially metastatic spread. We wonder whether the maintenance with the SRL therapy and the increasing of doses had any role in this positive outcome; however, the reason for this favourable evolution cannot be defined.

In conclusion, cancer in transplant patients represents a therapeutic challenge even when the patient is already under mTOR inhibitors. Our case points to the limitations of current guidelines and emphasizes that further studies and experience are needed to optimize the management of cancer in the transplant long-term follow-up.

Authorship

CC and RF: performed research, collected data, and wrote the paper. JR: analyzed the immunohistochemistry, designed the figure, and wrote the paper. DMR: performed the immunohistochemistry. AC: reviewed esophageal adenocarcinoma data, and wrote the paper. FD: reviewed the manuscript. FO: reviewed the manuscript. JMC: is reponsible of the patient, made the decisions, and reviewed and wrote the paper. IR: designed research, performed research, analyzed data, wrote the paper, and submitted the paper.

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