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Renal angiomyolipomas, Tuberous Sclerosis Complex and mammalian target of rapamycin inhibitors

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In this issue of the Journal Miguel Oliveira *et al*. report the case of a patient with a giant renal angiomyolipoma (AML) associated with tuberous sclerosis complex (TSC) who was treated with everolimus, one of the mammalian target of rapamycin (mTOR) inhibitors available for clinical use.

TSC is an autosomal-dominant hereditary disorder characterised by the growth of benign tumours (hamartomas) in many organs, including brain, kidney, lung, heart and skin. The expression of the disease is quite variable, ranging from asymptomatic individuals to severe cognitive delay[1,2]. Renal involvement is common in TSC, mainly occurring as renal AML, which develop in up to 80% of the patients and represent the main cause of morbidity in adults with TSC. AMLs are composed of smooth muscle cells, fat cells and abnormal blood vessels, often with development of large aneurysms which may spontaneously rupture, potentially causing life-threatening haemorrhagic complications. Renal cysts and renal cell carcinoma (RCC) can also occur in a small subset of patients. Development of chronic kidney disease (CKD) and progression to end-stage renal disease (ESRD) may result from severe distortion of the renal parenchyma caused by multiple or large AMLs. Alternatively, therapeutic techniques used in the management of the AMLs, such as surgical removal or arterial embolisation, can also contribute to the loss of renal parenchyma[3].

In this scenario, kidney-sparing therapeutic strategies are necessary and beneficial. The utilization of systemic treatment seems logical, especially in the presence of multiple or bilateral lesions, ideally leaving surgery and embolisation for the management of solitary lesions or intervention in emergency situations.

The mTOR pathway plays a central role in the control of cell growth and proliferation[2]. Mutations in *TSC1* and *TSC2* genes, respectively encoding hamartin and tuberin, are found in 90% of TSC patients and are responsible for the formation of an abnormal hamartin-tuberin complex which does not physiologically inhibit mTOR pathway, leading to uncontrolled cell proliferation[1,4].

The value of mTOR inhibitors in the treatment of TSC manifestations has been demonstrated in several clinical trials, with encouraging results[5-9]. The largest of such trials was the EXIST-2[10], a multicentre, randomised, double-blind, placebo-controlled study of the efficacy of everolimus for the treatment of renal AMLs, in adult TSC patients with at least one AML of 3 cm or more at its longest diameter. The primary efficacy endpoint was the proportion of participants who achieved at least a 50% reduction in the total volume of target AMLs relative to baseline. The trial enrolled 118 adult patients, 79 of whom were allocated to receive everolimus 10 mg/day for 6 months. Among the actively treated patients, 42% reached the primary efficacy outcome, while none in the placebo group did so. Treatment with everolimus was also significantly superior to placebo as evaluated by the time to AML progression and the skin lesions' response rate. Slightly less deterioration of pulmonary function was additionally described.

The 34-year-old female with TSC and CKD stage 3b reported by Oliveira *et al*. had already been submitted

to left nephrectomy due to uncontrolled haemorrhage from an AML, and had also required arterial embolisation twice, in order to control bleeding complications from AMLs in the right kidney. On a computed tomography (CT) scan, the patient`s solitary right kidney contained a giant AML of 19 cm at largest diameter. Additionally, she had central nervous system, lung and skin involvement, although the extra-renal disease manifestations were well controlled.

The decision of how to treat a patient in such a condition is an enormous challenge. Unfortunately, an abdominal magnetic resonance imaging (MRI) was not available for better characterisation of the renal AML, particularly the relative proportions of fatty and non-fatty tissue within the tumour, and the size of the intralesional aneurysms. Although the haemorrhagic risk can empirically be considered high, simply based on the size of the AML, aneurysm size of 5 mm or larger is a major predictor of rupture[11]. The alternative of performing a right kidney nephrectomy was considered, seeming a reasonable option for such a high risk tumour; however, in this particular case, it would require immediate institution of renal replacement therapy (RRT). Facing this problem, the authors attempted to treat the patient conservatively with everolimus, according to the protocol used in the EXIST-2 trial. The drug was well tolerated and the facial lesions ameliorated somewhat, but no change in the AML size or improvement of the pulmonary lymphangioleiomyomatosis (LAM) was observed after 6 months of treatment.

Therapy with mTOR inhibitors has been attempted in moderate to severe forms of pulmonary LAM, both in sporadic and TSC-associated cases[9,10]. The results are promising so far, with a slower progression of lung disease as measured by pulmonary function tests, but not by lung imaging studies. In the patient reported by Oliveira *et al*., objective evidence of beneficial effect of the treatment with everolimus upon the pulmonary LAM would have been difficult to obtain, since her pulmonary function tests were normal at baseline.

It has been suggested in the literature that larger AMLs respond better to mTOR inhibitors because of AMLs intrinsically higher proliferative rates[3,7]. Unfortunately, despite its massive dimensions, no change in the AML size was observed in the patient reported by Oliveira *et al*. A possible explanation for this disappointing result could be a greater proportion of fatty tissue within the AML, because adipocytes are metabolically less active and may not respond as well to mTOR inhibitors as do smooth muscle cells. A kidney MRI could have helped clarify that hypothesis and, to this end, would indeed be better than a CT scan. Nevertheless, considering the patient's single kidney condition and the favourable safety profile of everolimus, we believe that the attempt to treat her with an mTOR inhibitor was a good option.

Rapid deterioration of renal function should be expected in this case and, hence, the patient should be prepared for RRT. Furthermore, given the high risk of bleeding associated with a giant renal AML, a second nephrectomy should be considered shortly after the initiation of RRT, in order to prevent additional AML-related morbidity, including the Wunderlich syndrome or transformation into an RCC.

Disclosure of Potential Conflicts of interest: None declared

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