

ASSOCIATION LUPUS AND TUBEROUS SCLEROSIS: IS IT POSSIBLE? THE INVOLVEMENT OF MTOR PATHWAY**Dr. Rahima Mounir,*¹ Safae Berrada¹, Kawtar Flayou¹, Tarik Bouattar¹, Loubna Benamar¹, Rabiaa Bayahia¹, Naima Ouzeddoun¹ and Zaitouna Alhamany²**¹Department of nephrology, Dialysis and Renal Transplantation, Ibn Sina University Hospital, Rabat- Morocco.²Laboratory of Pathological Anatomy, Faculty of Medicine and Pharmacy of Rabat, Mohammed V University of Rabat, Morocco.***Corresponding Author: Dr. Rahima Mounir**

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ABSTRACT

Tuberous sclerosis is an autosomal dominant disorder characterized by involvement of skin, nervous system, kidneys, and lungs. It results from mutations in 1 of 2 genes: TSC1 (encoding hamartin) or TSC2 (encoding tuberin), leading to dysregulation and activation of the mammalian target of rapamycin (mTOR) pathway. Constitutive activation of mTOR signaling has recently been reported in systemic lupus erythematosus (SLE), and inhibition of this pathway may benefit patients with SLE nephritis. We report a case of a young woman with tuberous sclerosis and SLE, with dermatological, articular, hematological, and neurological tropism. Renal biopsy showed diffuse lupus nephritis, class IV, She was treated by pulse of Methylprednisolone and intravenous Cyclophosphamide as attack treatment relieved by azathioprine and oral corticosteroids. This is the second reported case of association between lupus and STB, it is of considerable interest because of the possibility that activation of mTOR by the TSC mutations may have led to activation of the immune system and the development of unusually severe SLE.

KEYWORDS: tuberous sclerosis, systemic lupus erythematosus, rapamycin, mTOR.**INTRODUCTION**

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the production of autoantibodies against nuclear antigens, and a strong female predominance. It can present with a wide variety of symptoms, affecting virtually any part of the body, most commonly involving the skin, joints, kidneys, and blood vessels. The disease course is marked by disease flares interspersed with periods of relative quiescence. The etiology of the disease remains unclear. Fernandez and Andras Perl's work in 2011 has shown that a key regulator of metabolic activity, the mammalian target of Rapamycin (mTOR), plays a very important role in disease pathogenesis, and the highly specific mTOR inhibitor can be an effective and targeted treatment for the disease.

mTOR is a key eukaryotic signaling protein conserved from yeast to humans which regulates protein synthesis and energy expenditure. It is a point of integration of many inputs relaying information about nutritional status of the cell, including mitochondrial potential, oxygen tension, growth signals, amino acids, and ATP. In conditions of nutrient sufficiency, mTOR signaling is active, permitting protein synthesis and increased cell

size, in conditions where any of these is lacking, mTOR activity decreases, limiting energy expenditure by inhibiting protein synthesis, decreasing cell size, and preventing cell proliferation. Recent studies of the mTOR pathway illustrate the diversity of effects it has in the immune system, giving greater insight into the potential relevance of this pathway in nearly all aspects of molecular dysfunction of SLE.^[1]

SLE is a typical autoimmune disease based on the variety of its proposed pathogenesis, including abnormalities of T and B-lymphocytes. Current treatments of severe SLE flares consist of toxic immunosuppressive drugs, most commonly Cyclophosphamide, Mycophenolate mofetil, and Leflunomide. However, the therapeutic options in SLE patients who are refractory to standard treatments are extremely limited, and the disease remains potentially fatal in some patients.

Moreover, in extended families, SLE may coexist with other organ specific autoimmune diseases such as haemolytic anaemia, immune thrombo-cytopenic purpura, and thyroiditis, the association of lupus and STB has recently been described and seems to have a common etiopathogenic pathway.

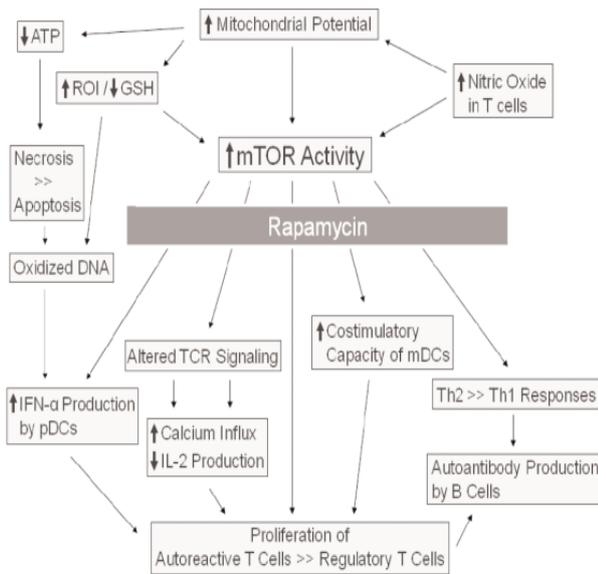


Figure 1: The involvement of mTOR pathway in SLE.

MTOR impacts diverse processes that may be involved in the promotion of autoimmunity in SLE. Rapamycin treatment can directly limit many of these processes in isolation, and some or all of those effects in vivo may explain the efficacy of the drug in that setting. Included in this model are upstream factors that may drive increased mTOR activity in SLE, such as increased reactive oxygen intermediates (ROI) and nitric oxide, decreased level of the reduced form of glutathione (GSH), and elevated mitochondrial potential. These metabolic processes also predispose cells to die by necrosis and release oxidized DNA, which can have pro-inflammatory consequence.^[1]

CASE REPPORT

Our patient was a woman of thirty, mother of two children, with no thrombo-embolic accident; she was affected by SLE with dermatological, articular, hematological, and neurological tropism since 2005. Renal biopsy showed diffuse lupus nephritis, class IV. She was treated by pulse of Methylprednisolone (15mg/kg/j during 3 days) and intravenous Cyclophosphamide as attack treatment relieved by azathioprine (2mg/kg/day) and oral corticosteroids for maintenance therapy. The evolution was marked by a normalization of renal function but à persistence of active urinary sediment (hematuria and leukocyturia).

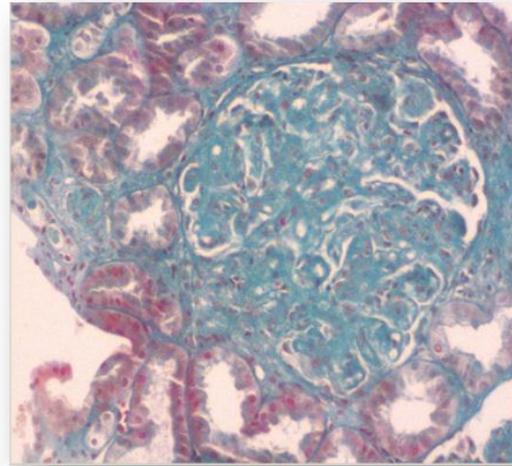


Figure 2: Optical microscopy, renal biopsy, lupus nephropathy class IV, diffuse and global proliferation.

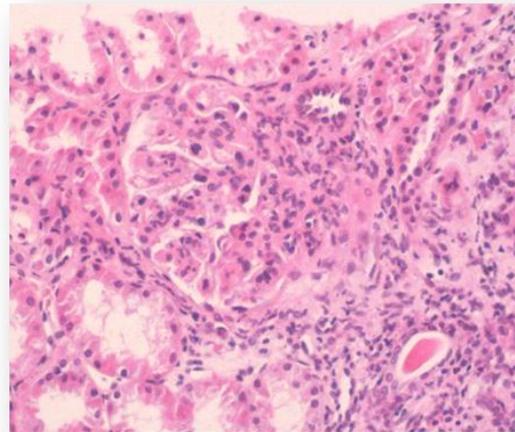


Figure 3: Renal biopsy, hematein eosin, diffuse and global endocapillary proliferation, numerous neutrophils, fibrinoid necrosis.

The Tuberos Sclerosis (TS) diagnosis was retained on the presence of pathognomonic skin lesions facial, angiofibromas located in the nose and cheeks and a slightly reddish lesion at the Lumbosacral area (shagreen patch). During hospitalization, she presented neurologic symptoms: dizziness, headache and generalized convulsive seizures; there was no cerebral thrombophlebitis in brain magnetic resonance imaging but nodular calcifications on bilateral para-ventricular and a sub-ependymal temporal nodule and petechial lesions related to neurological involvement of STB.

We carried out an extention report of STB; the renal imaging had shown normal-sized kidneys without angiomyolipoma or cancer image, transthoracic echocardiography had not shown cardiac angiomyolipoma and thoracic radiography was normal, there was no retinal hamartoma in the ophtalmological exam. The progression was favorable, renal function

remained normal, without aggravation of neurological symptoms and disappearance of convulsive seizures, currently she is still followed for its stabilized STB.



Figure 4: one of major criteria of STB diagnosis: angiofibromas.



Figure 5: A second major criteria of STB diagnosis: the shagreen patch.

DISCUSSION

The association SLE and STB was first mentioned by P. Cohen et al in 2013,^[2] about a young woman, with STB and a seizure disorder, angiofibroma of the face and who declares a fulminant lupus with alopecia, Butterfly-shaped rash, photosensitivity, Raynaud's phenomenon, Joint pain, severe edema of legs, massive proteinuria at 17 g /day, hematuria and severe acute renal failure requiring dialysis. Renal biopsy showed diffuse lupus nephritis, class IV, with numerous hyaline thrombi suggestive of cryoglobulins;^[3] microscopic foci of spindle cell proliferation consistent with angiomyolipomata. Renal imaging showed a renal angiomyolipoma. Serum cryoglobulins were not detected. She was treated with pulse methylprednisolone and started dialysis. Her course was complicated by respiratory failure due to diffuse alveolar hemorrhage (DAH). She received intravenous pulse

cyclophosphamide, and renal function improved. She had a prolonged hospital course, during which she developed seizures that were managed with additional medications, gastrointestinal bleeding from gastric ulcers, and multiple episodes of hypoxic respiratory failure attributed to DAH. Her second cyclophosphamide infusion was delayed due to *Pseudomonas* bacteremia. She also received plasma exchange for DAH with hypoxic episodes. She again developed seizures, and brain magnetic resonance imaging was suggestive of posterior reversible encephalopathy. She developed *Pseudomonas* sepsis again that was treated with Cefepime. She continued to decline, with worsening DAH, and died 120 days after admission.

Tuberous sclerosis or tuberous sclerosis complex (TSC) is a genetic disease that affects several organs such as the brain, kidneys, heart, lungs and skin.^[3]

The primary manifestation is a consequence of growth of non-malignant tumors in the various systems described. However, its true incidence is not known because of a number of undiagnosed cases consisting mostly of mildly affected or asymptomatic individuals. Two disease-causing genes have been identified by positional cloning, TSC1 and TSC2;^[4] The TSC1 gene is located on chromosome 9q34, and encodes the protein hamartin (130 kDa, 1164 amino acids). The TSC2 gene is located on chromosome 16p13.3, and encodes another protein, tuberin (180 kDa, 1807 amino acids) However, 10% to 25% of people with TSC showed no TSC1/TSC2 mutation as identified by conventional genetic testing.

A recent report of 53 people with TSC with no mutation identified, reported that mosaicism was observed in the majority (58%) and then followed by intronic mutations, which were seen in 40% of the study population.^[5] The defective production of hamartin is caused by TSC1 mutations.^[6] Mutations on the TSC2 gene lead to the defective production of tuberin and are usually related to more severe manifestations, Both TSC1 and TSC2 are tumour suppressor genes, the defect of which will lead to an uncontrolled proliferation of benign tumours called tubers in various sites.^[7]

People with TSC present at different ages with a variety of clinical manifestations. Common presenting symptoms include skin lesions, seizures, learning disabilities or manifestations of tumors affecting organs such as the brain, heart, eyes, or the kidneys. The disease can be diagnosed clinically by assessing individuals against major or minor criteria, depending on the signs and symptoms present.^[8]

A definitive diagnosis can be made when there are either two major features or one major feature with two or more minor features. A possible diagnosis can be made when there are either one major feature or two or more minor features. Major features in the new consensus include hypo-melanotic macules (three or more, at least

five mm diameter), angio-fibromas (three or more) or fibrous cephalic plaque, ungual fibromas (two or more), shagreen patch, multiple retinal hamartomas, cortical dysplasias, sub-ependymal nodules, subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangioliomyomatosis (LAM) and angiomyolipomas (two or more). It is of note, however, finding on the combination of LAM and angiomyolipomas still require another feature for a definitive diagnosis. Minor features include 'confetti' skin lesions, dental enamel pits (more than three), intraoral fibromas (two or more), retinal achromic patch, multiple renal cysts and non-renal hamartomas.^[9]

Renal problems in TSC, including angiomyolipomas (which occur in 80% of people with TSC) and multiple renal cysts, comprise the second leading cause of premature death after severe intellectual disability.^[10]

Angiomyolipomas are benign tumours composed of vascular, smooth muscle, and adipose tissue. In the kidney, angiomyolipomas can cause serious issues with bleeding because of their vascular nature and can lead to the need for dialysis and even renal transplantation. Multiple renal cysts can be seen in people with TSC who have a TSC1 or TSC2 mutation or as part of a contiguous gene deletion syndrome involving the TSC2 and PKD1 genes.^[11]

Individuals typically present with progressive dyspnoea on exertion and recurrent pneumothoraces in the third to fourth decade of life. Cystic pulmonary parenchymal changes consistent with LAM are observed in 30% to 40% of females with TSC, but recent studies suggest that lung involvement may increase with age such that up to 80% of TSC females are affected by the age of 40 years. In addition, 30% out of 45% women who were diagnosed with TSC as adults, actually met the clinical criteria for TSC in childhood.^[12]

Although these women had minimal morbidity during childhood, they were at risk of life-threatening pulmonary and renal manifestations.^[13] Once the diagnosis of TSC is established and initial diagnostic evaluations completed, continued surveillance is necessary to monitor the progression of known problems or lesions and the emergence of new ones. Although some manifestations that appear during childhood do not cause significant problems in adulthood and vice versa, some others may be present throughout the entire lifespan of the individual, such as epilepsy and TSC-associated neuropsychiatric disorders (TAND).^[14]

The multiplicity of the lesions and their locations are directly correlated to morbidity and mortality of STB. Brain tumors, renal hamartomas and pulmonary involvement significantly reduce life expectancy.

The mTOR is a key player in pathways involved for cellular growth, proliferation, and survival via a

cytoplasmic serine/threonine kinase. In cells that lack either TSC1 or TSC2, mTOR activity is increased many-fold, and this would cause uninhibited growth and subsequent hamartomas in various organs. mTOR inhibitors, which have already been used in some cancers, could play a role in tumor lysis or shrinkage owing to the above pathways being altered.^[15]

Rapamycin (C₅₁H₇₉N₁₃) is a macrolide compound that was isolated in 1975 from *Streptomyces hygroscopicus* found in a soil sample on Easter Island. As an mTOR inhibitor, it prevents activation of T cells and B cells by inhibiting their response to interleukin-2 (IL-2). It is an FDA-approved drug for immunosuppression after organ transplantation. During the 1980s, rapamycin (Sirolimus) was discovered to show an anti-cancer activity.^[16]

However, due to its unfavourable pharmacokinetic properties, the development of rapamycin for the treatment of cancer was not successful at that time.^[17]

Later on, analogs of rapamycin (rapalogs) with more favourable pharmacokinetic properties and reduced immunosuppressive effects were discovered. These include temsirolimus, everolimus, biolimus A9 and zotarolimus. Both biolimus and zotarolimus are drug-eluting coronary stents for preventing coronary artery restenosis.

In STB, Everolimus (rapalogs) has proved the effectiveness in reduction of tumour size after 24 weeks of treatment with oral in both renal Angiomyolipoma and subependymal giant cell astrocytoma (SEGA) justified its use in clinical practice as the benefits outweigh the risks. With this in mind, this review concurs with the decision of the U.S. Food and Drug Administration (FDA) and European Medicine Agency (EMA) on the use of everolimus for both types of tumours. In other clinical trials, Rapamycin or rapalogs may also have a beneficial effect on STB skin lesions.^[18]

Fernandez and al had demonstrate that mTOR signaling is increased in SLE T cells, and inhibition of mTOR signaling with rapamycin has been shown to be effective in the treatment of human SLE.

SLE patients treated with rapamycin demonstrate lowered baseline calcium levels and decreased calcium influx following TCR (T cell receptor) stimulation, but do not show a change in mitochondrial function, indicating the specificity of rapamycin treatment on this manifestation of the disease. Several other aspects of mTOR signaling with clear implications for SLE exist, although direct investigation of their impact on SLE has not occurred. Rapamycin promotes regulatory T cell and tolerogenic dendritic cell expansion, which might limit the proliferation and activity of autoreactive T cells. It limits proinflammatory IFN- α production by plasmacytoid dendritic cells. In some studies it has been shown to promote a Th1-focused immune response,

which may limit the T cell stimulation of autoreactive B cells in SLE.^[19]

Warner and col showed that Rapamycin prevented the rise of the anti-DNA antibodies and reduce the flow of proteinuria. These findings were observed in 9 patients with lupus refractory to any immunosuppressive therapy where Rapamycin was beneficial.^[20]

Rapamycin was a consideration in our patient's case, but she had already been started on cyclophosphamide regimen for lupus nephritis. She did not receive rapamycin.

CONCLUSION

This is the second reported case of association between lupus and STB, activation of the mTOR pathway has been well demonstrated in both pathologies. Thus, STB is a risk factor of severe systemic lupus erythematosus.

Knowledge of the roles of mTOR signaling implies that inhibitors of this route can be used successfully in the treatment of some of their manifestations.

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