CLINICAL QUIZ (p67) ANSWER

Hypomelanotic macules were present in our patient. Magnetic Resonance Imaging (MRI) demonstrated multiple T1 weighted hyperintense subependymal nodules in the bodies of both lateral ventricles and cortical tubers at the caudate nuclei, deep white matter of frontal, parietal and temporal lobes; there was no hydrocephalus. Ophthalmological screening revealed left retinal hamartoma. The clinical diagnosis is tuberous sclerosis (with the presence of 3 major features). Table 1 summarises the criteria for diagnosing tuberous sclerosis.

Tuberous sclerosis complex is an autosomal dominant condition characterised by hamartoma formation in various organs with a prevalence of 1 in 6000 live births. The condition is caused by inactivating mutations, identifiable in 85% of patients, in either the *TSC1* (Ch9q34) or *TSC2* (Ch16p13.3) gene which encodes the protein hamartin and tuberin respectively. In our patient, a de novo, previously unreported 4 base duplication was found in exon 41 of the *TSC2* gene (c.5414_5417dupAGTT - Figure C), rendering a recurrence risk of 2-3% in siblings due to the possibility of germline mosaicism in one of the parents.

As a neurocutaneous syndrome, dermatological lesions often provide the initial clue to the diagnosis. Hypomelanotic macules, best depicted by the use of Wood's lamp, are present during infancy as in our patient; facial angiofibroma then develop around the age of 3-4 over the malar region followed by Shagreen patch by the age of 5-10, usually at the lumbar area. During adolescence or young adulthood, ungual fibromas may become evident. Cardiac rhabdomyoma and cortical tubers are lesions that can be demonstrated antenatally with the use of ultrasonography and/or fetal MRI. Spontaneous regression is the rule for cardiac rhabdomyoma, likely within the first 3 years of life; less commonly, the heart lesion can be complicated with ventricular outflow tract obstruction or supraventricular tachycardia requiring intervention. In contrast, cortical tubers and subependymal nodules, which are developmental defects of glial and neuronal cells formation and migration, persist and may serve as epileptogenic foci. Subependymal nodules can evolve to form subependymal giant cell astrocytomas (SEGAs), they are situated within the lateral ventricles adjacent to the Foramen of Monro where enlargement may result in obstructive hydrocephalus and raised intracranial pressure. Various types of seizure semiology can occur and co-exist in patients with tuberous sclerosis. Infantile spasms are observed in a quarter of patients and imply worse neurological prognosis. Patients with large number of cortical tubers, or tubers situated at strategic locations (for example frontal parasaggital area), can be expected to have difficult seizure control despite polytherapy, sometimes necessitating epilepsy surgery. Cognitive dysfunction and behavioral problems including

Table 1 Diagnostic criteria for tuberous sclerosis

Major features	**Minor features**
Facial angiofibromas or forehead plaque	
Nontraumatic ungual or periungual fibroma	Nonrenal hamartoma
Hypomelanotic macules (≥3)	Retinal achromic patch
Shagreen patch (connective tissue nevus)	"Confetti" skin lesions
Multiple retinal nodular hamartomas	Multiple renal cysts
Cortical tubers	Multiple, randomly distributed pits in dental enamel
Subependymal nodule	Hamartomatous rectal polyps
Subependymal giant cell astrocytoma	Bone cysts
Cardiac rhabdomyoma	Cerebral white matter radial migration lines
Lymphangioleiomyomatosis	Gingival fibromas
Renal angiomyolipoma	

Definite Tuberous Sclerosis Complex: Either 2 major features or 1 major feature plus 2 minor features

Probable Tuberous Sclerosis Complex: One major plus 1 minor feature

Possible Tuberous Sclerosis Complex: Either 1 major feature or 2 or more minor features

mental retardation, autism spectrum disorder, attention deficit-hyperactivity disorder and sleep disorders are most debilitating in this group of patients, and quality of life is further affected by restriction in social activities as well as side effects from anti-epileptics.

Renal complication is the leading cause of tuberous sclerosis related mortality. Angiomyolipomas are characteristic lesions that are found in 80% of patients; they are often multiple and bilateral, increase in frequency with age, carry the risk of life-threatening bleeding and renal failure; prophylactic embolisation or nephron-sparing surgery have been standard treatment options. Renal cysts, renal hamartomas and renal cell carcinoma are also encountered in tuberous sclerosis; particularly, polycystic kidney disease develops in patients who have contiguous deletions of the *TSC2* and adjacent *PKD1* genes. Pulmonary involvement by lymphangioleiomyomatosis (LAM) is almost exclusive to premenopausal females, this entity with poor prognosis presents with cough, dyspnea, atelectasis and pneumothorax; histologically, there is generalised abnormal smooth-muscle and cystic proliferation of the lung parenchyma. A well designed surveillance and screening program is important for patients with tuberous sclerosis, ophthalmological and dermatological examination, together with imaging including MRI of brain, ultrasonography of kidneys, and Computed Tomography of thorax, should be performed at regular intervals to allow early detection of complications.

In October 2010, everolimus - a sirolimus (or rapamycin) derivative, was approved by the Food and Drug Administration of the United States for treatment of SEGAs not amenable to surgical resection. Normally, hamartin and tuberin form a tumour-suppressor complex to down-regulate the mammalian target of rapamycin

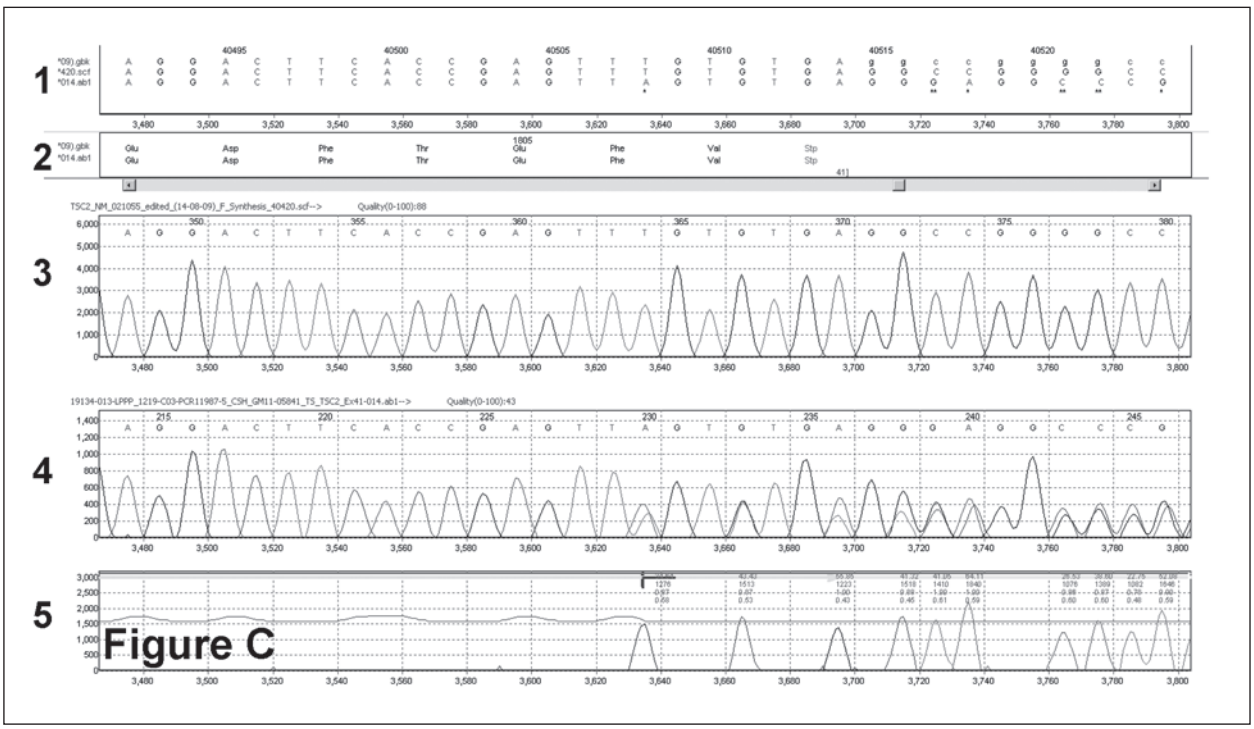

Figure C Patient's sequence trace displayed in Mutation Surveyor, showing TSC2 mutation c.5414_5417dupAGTT. Panel 1: Displays the Genbank and actual patient's TSC2 nucleotide sequence, represented in letter form. Panel 2: Actual amino acid sequence for codons 1801 to 1808 of the TSC2 gene. Panel 3: Graphical display of a synthesised normal TSC2 nucleotide sequence. Panel 4: Graphical display of patient's TSC2 sequence, showing the TSC2 mutation c.5414_5417dupAGTT. Panel 5: Graphical display highlighting the differences between the synthesised normal and patient's sequence.

(mTOR) complex 1 via the Ras homologue enriched in brain protein (Rheb) (Figure D); failure of such inhibition result in abnormal cell growth and tumour formation. Sirolimus and everolimus, both mTOR inhibitors, have been studied in the treatment of tuberous sclerosis associated complications. Franz et al. first reported in 2006 regression of SEGAs or pilocytic astrocytoma in five patients with tuberous sclerosis after oral sirolimus. The group further demonstrated promising result in 28 tuberous sclerosis patients with SEGAs treated by everolimus, with reduction of volume and seizure frequency, together with improvement in quality of life. Adverse effects included self-limiting upper respiratory tract infection, stomatitis and dyslipidaemia. A parallel study was conducted to evaluate the effect of sirolimus on angiomyolipoma in patients with tuberous sclerosis or sporadic LAM. After completing 12 months of sirolimus, mean angiomyolipoma volume in the 20 patients was only 53.2% of baseline value, although regrowing of tumour was apparent after cessation of treatment. In 11 patients with LAM (6 with tuberous sclerosis, 5 with sporadic disease), relief of air trapping was shown on spirometry; a trend towards reduction in cyst size was also observed. Case reports on treatment of renal cell carcinoma, chest wall fibromatosis and facial angiofibromas with systemic or topical sirolimus have also been published. One important thing to note is that the side effect of mTOR inhibitor is closely related to the drug level and therefore it has to be monitored. Concomitant medications such as moderate or strong CYP3A4 inducers or P-glycoprotein inhibitors (including some of the antivconvulsants and antifungal agents) may affect the drug level and has to be taken with caution.

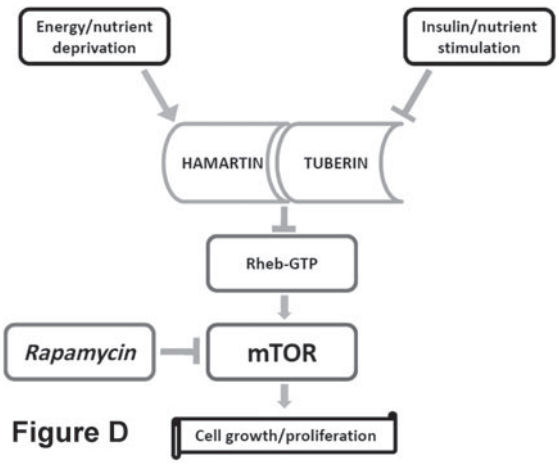

Figure D

Delineation of the mTOR signaling pathway led to advancement in the management of tuberous sclerosis. Patients who were traditionally candidates for major surgeries can now be offered alternative medical therapy, possibly in a neoadjuvant manner, to minimise the operation-related morbidities. Ongoing research supported by results from preclinical studies can be expected to further broaden the use of mTOR inhibitors in patients with tuberous sclerosis, introducing a novel treatment modality for refractory epilepsy and autism spectrum disorder. Genetic evaluation and counseling is essential for families of tuberous sclerosis patients to screen for presymptomatic individuals and determine future pregnancy risk.

Further Reading

1. Bissler JJ, McCormack FX, Young LR, Elwing JM, Chuck G, Leonard JM, et al.Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. N Engl J Med 2008;358:140-51.
2. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. N Engl J Med 2006;355:1345-56.
3. Curatolo P. Neurological manifestations of tuberous sclerosis complex. Childs Nerv Syst 1996;12:515-21
4. Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. Lancet 2008;372:657-68.
5. Ehninger D, Silva AJ. Rapamycin for treating Tuberous sclerosis and Autism spectrum disorders. Trends Mol Med 2011;17:78-87.
6. Haemel AK, O'Brian AL, Teng JM. Topical rapamycin: a novel approach to facial angiofibromas in tuberous sclerosis. Arch Dermatol 2010;146:715-8.
7. Krueger DA, Care MM, Holland K, Agricola K, Tudor C, Mangeshkar P, et al. Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis. N Engl J Med 2010;363:1801-11.
8. McCormack FX, Inoue Y, Moss J, Singer LG, Strange C, Nakata K, et al. Efficacy and safety of sirolimus in lymphangioleiomyomatosis. N Engl J Med 2011;364:1595-606.
9. Orlova KA, Crino PB. The tuberous sclerosis complex. Ann N Y Acad Sci 2010;1184:87-105.
10. Pressey JG, Wright JM, Geller JI, Joseph DB, Pressey CS, Kelly DR. Sirolimus therapy for fibromatosis and multifocal renal cell carcinoma in a child with tuberous sclerosis complex. Pediatr Blood Cancer 2010;54:1035-7.