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Insulinoma and Tuberous Sclerosis: A Possible Mechanistic Target of Rapamycin (mTOR) Pathway Abnormality?

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A 23-year-old New Zealand Māori male with tuberous sclerosis (TSC) and associated neurocognitive abnormalities presented with altered behavior and increasing seizure frequency. Endogenous hyperinsulinemia from an underlying insulinoma was confirmed and this was managed surgically. This case represents only the sixth description of insulinoma in TSC to date. The role of the hamartin–tuberin complex in regulation of the mechanistic target of rapamycin pathway provides a plausible pathogenetic mechanism between insulinoma and TSC. This rare disease association should be considered in TSC patients who present with otherwise unexplained worsening neurocognitive symptoms.

Freeform/Key Words: insulinoma, mTOR pathway, neoplasia, tuberous sclerosis

1. Case Presentation

A 23-year-old New Zealand Māori male with known tuberous sclerosis (TSC) with associated epilepsy and intellectual disability presented with a 3-day history of having been increasingly withdrawn, more lethargic, and less verbal in the setting of increased generalized seizure frequency despite continued adherence to his usual antiepileptic regimen of clobazam and lamotrigine. He resided with his mother under stable social circumstances and close supervision. There was no history of preceding cranial trauma or alcohol abuse, and urine toxicology revealed no evidence of recreational drug use. Clinical examination depicted typical cutaneous features of TSC but was otherwise unremarkable. His body mass index was 23.3 kg/m^2 without history of recent weight gain or loss.

Initial capillary blood glucose en route measured 2.8 mmol/L without overt sympathoadrenal or neuroglycopenic symptoms. Nevertheless, he received a bolus of intravenous dextrose resulting in a serum glucose level of 10.6 mmol/L at hospital presentation. Investigations revealed no underlying infective or inflammatory cause, no electrolyte abnormality, and intact growth hormone, adrenal, and thyroid axes. Magnetic resonance imaging of the brain showed only stable findings of known cortical tubers and subependymal nodules.

A standard 72-hour fasting test commenced, and within 5 hours, hypoglycemia occurred with a serum glucose level of 2.6 mmol/L (3.0 to 11.0 mmol/L) in the setting of mild sympathoadrenal symptoms of tremulousness and diaphoresis, which resolved following glucose elevation with the appropriate therapy. The test was terminated at this juncture, as Whipple's triad was fulfilled on a background of existing high suspicion of preadmission

Abbreviations: mTOR, mechanistic target of rapamycin; TSC, tuberous sclerosis.

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severe neuroglycopenic events. As such, we did not aim for lower fasting glucose targets, which may offer improved specificity but at the cost of risking the induction of further seizure activity. Plasma insulin was 30.3 mIU/L (2.6 to 24.9 mIU/L), plasma C-peptide was 1060 pmol/L (350 to 750 pmol/L), and sulphonylurea screen was negative. Plasma insulin was measured with a Roche Cobas e602 chemiluminescence sandwich immunoassay, C-peptide with an Invitron chemiluminescence enzyme immunoassay, and sulphonylurea screening with high performance liquid chromatography. A subsequent multiphase computed tomography demonstrated a hypervascular lesion with avid arterial enhancement and washout in the portal venous phase, measuring 3.5 × 2.6 × 2.9 cm within the pancreatic tail and abutting the spleen (tumor 1).

He was started on diazoxide with clinical benefit and underwent laparoscopy with planned excision of the imaged tumor. Intraoperatively, a second smaller tumor measuring 5 × 7 x 7mm (tumor 2) was found, not visualized on initial imaging, resulting in a laparoscopic distal pancreatectomy and splenectomy. Tumoral sections depicted two well-defined and encapsulated tumors separated by 3.0 cm of uninvolved pancreatic parenchyma, without lymphovascular or perineural invasion or lymph node involvement. The mitotic rate (tumor 1: 0/10, tumor 2: 0.6/10 at high power field) and Ki-67 index (tumor 1: 1.3%, tumor 2: 1.5%) were low, and there was dual positivity to chromogranin A and synaptophysin staining (negative to vimentin and CD10 staining), confirming low-grade tumors of neuroendocrine origin (Figs. 1 and 2). Tumor 2 had strong membranous positivity for CD56. Unfortunately, insulin and glucagon staining were not performed, as these were not routinely available at our institution. One year postoperatively, the patient remains in remission without any pharmacotherapy or dietary modification.

2. Discussion

TSC is an autosomal dominant disorder of variable penetrance resulting from loss-of-function mutations affecting two genes, TSC1 (chromosome 9q34) coding for hamartin and TSC2

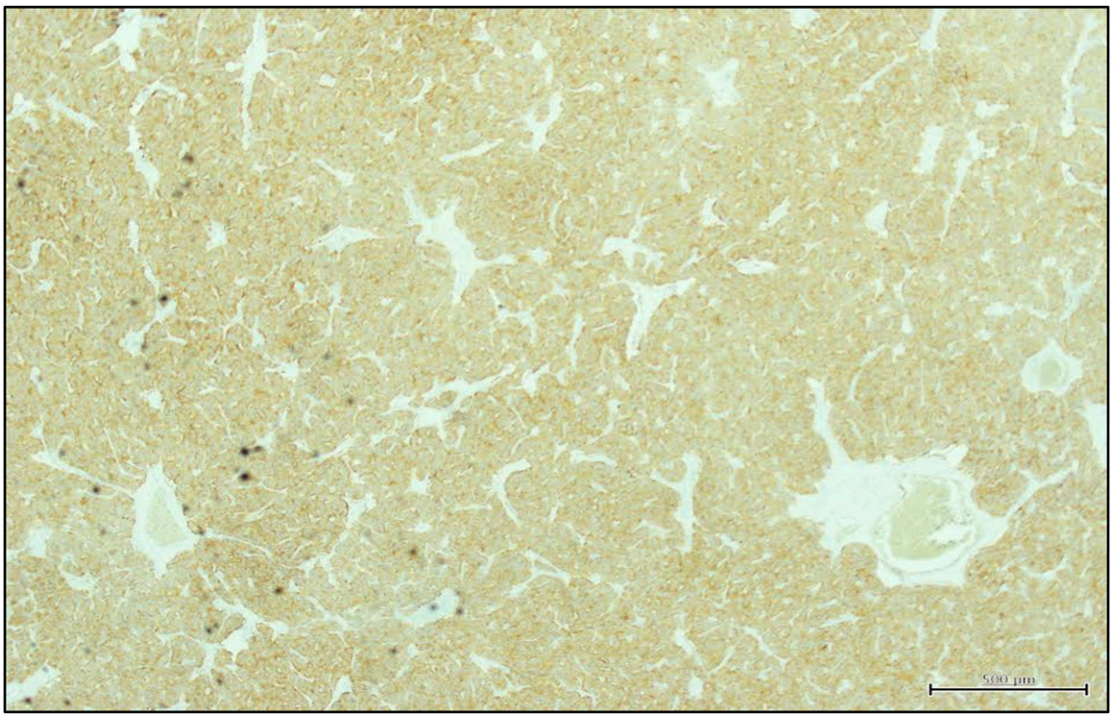

Figure 1. Intermediate diffuse positivity of the tumor to synaptophysin.

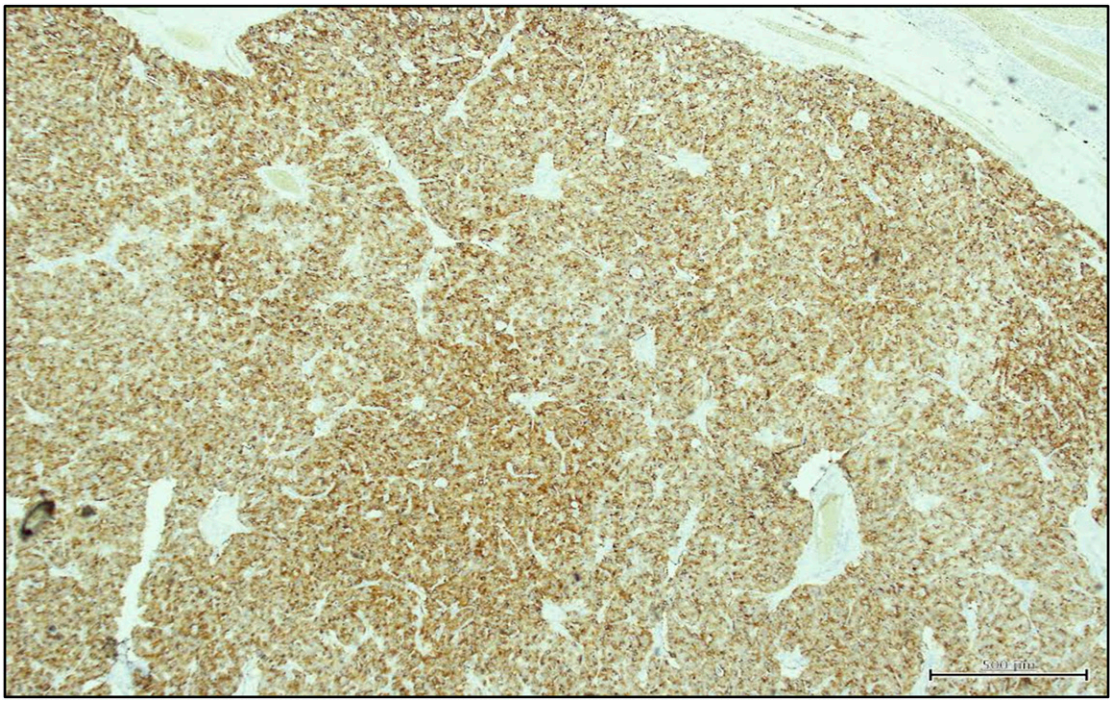

Figure 2. Strong diffuse positivity of the tumor to chromogranin A.

(chromosome 16p13.3) coding for tuberin. The hamartin–tuberin complex is an important negative regulator of mechanistic target of rapamycin (mTOR). The mTOR protein nucleates at least two distinct multiprotein complexes, mTOR complex 1 complex 2, which act as central regulators of cell metabolism, growth, proliferation, and survival in response to various stimuli [1]. The hamartin–tuberin complex converts the active guanosine triphosphate–bound form of Rheb into its guanosine diphosphate–bound state, preventing it from interacting and stimulating mTOR complex 1 [2]. Therefore, loss of the hamartin–tuberin complex results in the constitutive activation of mTOR complex 1 and unregulated cellular growth and proliferation [3]. Although TSC is highly variable in expression, typical phenotypic features include dermatologic features (angiofibromas, hypopigmented macules, and Shagreen patches), brain lesions (hamartomatous cortical tubers, subependymal nodules, and subependymal giant-cell tumors), neurobehavioral abnormalities (infantile spasms leading to generalized seizures, cognitive disability, and autism spectrum), renal lesions (angiomyolipomas, cysts, and renal cell carcinomas), and rhabdomyomas (and, rarely, rhabdomyosarcomas) [4]. The management of epilepsy can be challenging and is the most common and noteworthy cause of morbidity [5].

Compared with the well-described association between insulinoma and mutations affecting the multiple endocrine neoplasia 1 tumor suppressor gene, there have only been sporadic reports of insulinoma associated with TSC mutations. A recent systematic review of neuroendocrine tumors in TSC documented only five cases of insulinoma since 1959, primarily described in Western Europeans compared with our first description in a New Zealand Māori patient [6]. Patients typically experienced neuroglycopenic symptoms or worsening of seizure control, and all documented insulinomas in previous series were >2 cm (the largest tumor was reported to be 21 cm), in comparison with sporadic tumors, which are <2 cm in 80% to 90% of cases [6]. Additionally, four out of five reported cases were diagnosed in patients between the ages of 18 to 28 years, compared with the median age of 50 years (range 17 to 86 years) seen in sporadic cases [7].

Although a direct pathogenetic relationship between TSC1/2 mutations and insulinoma remains to be proven, it is well established that the mTOR pathway modulates insulin signaling [8]. A previous study involving TSC2-deficient mice demonstrated development of

hypoglycemia and hyperinsulinemia associated with pancreatic β cell hypertrophy compared with controls [9]. Another study demonstrated enhanced insulin secretory response to glucose in TSC2-deficient mice secondary to increased number of mitochondria in β cell islets [10]. Insulinoma cells have also been shown to have significantly higher levels of activated mTOR, and its downstream phosphorylated-P70S6 kinase compared with normal pancreatic tissues [11]. These studies support a plausible pathogenic concept linking TSC and insulinoma. Of interest, everolimus (an mTOR inhibitor) has demonstrated clinical efficacy in inducing tumor regression and improving hypoglycemia in surgically inoperable and medically refractory malignant insulinomas [12].

In conclusion, this case describes a possible rare association between TSC and insulinoma, whereby TSC1 or TSC2 mutations responsible for the primary syndromic manifestations may also contribute to the loss of mTOR pathway regulation, resulting in the propensity toward tumorigenesis and hyperinsulinemia. Therefore, the possibility of underlying insulinoma should be considered in TSC patients presenting with suspected recurrent hypoglycemia or worsening neurobehavioral manifestations. Further study is necessary to specifically examine the possible pathogenetic role of mTOR disinhibition in this syndrome and whether loss of heterozygosity or loss of function of TSC1 or TSC2 can be demonstrated in insulinoma tumoral tissue, which may or may not in turn have implications upon the management of insulinoma in TSC patients who are not operative candidates.

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