

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/radcr

Case Report

Neuroendocrine pancreatic tumor in a patient with dual diagnosis of tuberous sclerosis complex and basement membrane disease: A case report and review of the literature ☆,☆☆

Saba Kopadze, MD^{a,*}, Inga Shoshiashvili, MD^a, Anna Dumbadze, MD^b,
Tinatin Tkemaladze, PHD^c, Ivane Kiladze, MD^a

^a Department of Clinical Oncology, Caucasus Medical Centre, Tbilisi, Georgia

^b Department of Radiology, Caucasus Medical Centre, Tbilisi, Georgia

^c Department of Molecular and Medical Genetics, Tbilisi State Medical University, Tbilisi, Georgia

ARTICLE INFO

Article history:

Received 1 June 2021

Revised 16 August 2021

Accepted 16 August 2021

Keywords:

Tuberous sclerosis complex

PanNET

Basement membrane disease

Renal angiomyolipoma

Angiofibroma

Retinal hamartoma

ABSTRACT

Tuberous Sclerosis is a complex genetic disease that has well-defined clinical criteria. These criteria don't include pancreatic neuroendocrine tumors. We represent a rare case of a patient, with a non-functioning pancreatic neuroendocrine tumor and concomitant diagnosis of tuberous sclerosis complex, and basement membrane disease.

The patient was diagnosed based on typical radiologic findings. We have suggested close monitoring and during follow-up studies, the disease was stable. Interestingly the patient tested negative for Tuberous Sclerosis Complex (TSC), which suggests that she might be a somatic mosaic and the mutation level in blood lymphocytes was below the detection level. Moreover, a heterozygous pathogenic variant p.(Gly774Arg) and a heterozygous likely pathogenic variant p.(Gly1465Asp) were identified in the COL4A4 gene. COL4A4 gene is responsible for causing autosomal dominant basement membrane disease. In this case report, we discuss clinical, radiologic, and genetic aspects of these diseases, as well as optimal treatment and follow-up strategies. Thus, by presenting this case we would like to increase awareness of pancreatic neuroendocrine tumors in TSC and emphasize the need for follow-up monitoring.

© 2021 The Authors. Published by Elsevier Inc. on behalf of University of Washington.

This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

☆ Acknowledgments: The authors would like to thank Dr Irakli Phiphia for thoughtful comments and suggestions which made the publication of this article possible.

☆☆ Competing Interests: The authors declare no conflicts of interest in association with the present study.

* Corresponding author.

E-mail address: sabakopadze@yahoo.com (S. Kopadze).

<https://doi.org/10.1016/j.radcr.2021.08.041>

1930-0433/© 2021 The Authors. Published by Elsevier Inc. on behalf of University of Washington. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

Introduction

Tuberous Sclerosis Complex (TSC) is an autosomal dominant multisystem disorder with characteristic skin manifestations and hamartomatous lesions in the brain and other vital organs. The disease frequency is about 1 in 6000 live births and about two third of cases are sporadic [1–3].

TSC may affect the central nervous system (cortical tubers, subependymal nodules, and astrocytomas), skin (sebaceous adenomas, shagreen patches, “confetti” skin lesions and fibromas), skeletal system (sclerotic and lucent bone lesions), eyes (retinal hamartomas), lungs (lymphangiomyomatosis), heart (rhabdomyomas), and abdominal organs (renal angiomyolipomas and cysts) [4].

The most common manifestations of TSC are dermatologic lesions occurring in 81%-95% of patients, subependymal nodules and cortical tubers seen in about 85%-90% and epilepsy presented in almost 90% of patients [5–6].

The disease is caused by mutations in either the *TSC1* or *TSC2* genes, which encode protein products hamartin, and tuberlin respectively. *TSC1* and *TSC2* function as inhibitors of downstream cellular signaling via the mammalian target of rapamycin (mTOR) pathway. Loss-of-function mutations in these genes lead to constitutive activation of the mTORC1 oncogenic cascade, which is a direct contributor to tumor growth [7]. Based on routine diagnostic techniques, a pathogenic mutation is detected in up to 85%-90% of individuals with a clinical diagnosis of TSC [8].

The most common affected abdominal organ is the kidney, which is involved in approximately 80% of cases [9]. The pancreas is not considered as the main focus for TSC related pathology and is not monitored routinely during the clinical course of the disease.

Pancreatic neuroendocrine tumors (PanNETs), are rare neoplasms that arise in the endocrine tissues of the pancreas. They account for 1%-3% of all pancreatic tumors [10]. About 10% of all PanNETs are components of familial endocrine syndromes such as multiple endocrine neoplasia syndrome 1 (most common), Von Hippel-Lindau disease, neurofibromatosis type 1, and TSC [11].

PanNET's are not considered as a part of clinical features of TSC but the coincidence of these 2 diseases are well known. We report a 34-year-old female patient with tuberous sclerosis, presenting with pancreatic neuroendocrine tumor.

Case presentation

A 34-year-old female with a pancreatic neuroendocrine tumor was admitted to our department. Before admission, her past medical history included dermatologic problems since the age of 16 years, and persistent unexplained hematuria. General physical examination revealed facial angiofibromas (Figure 1) and small periungual fibromas of the toenails (Figure 2). There were no other cutaneous findings, pain or seizures in the past, and cognitive development was age-appropriate. No family history or clinical features of TSC. No mental health disorders or oncology malignancies.



Fig. 1 – TSC associated angiofibromas on the nose.



Fig. 2 – Periungual fibroma.

At the age of 30, the patient underwent ovarian cystectomy and, afterward, she routinely monitored her health annually. At the age of 32, during follow-up procedure, bilateral multiple renal angiomyolipomas (AML) was revealed incidentally. She was diagnosed with renal AML and managed by a nephrologist. Close monitoring was recommended.

At the age of 33, an abdominal MRI was performed, which revealed multiple simple cysts and at least 4 fat-containing lesions in each kidney (Figure 3). The fat-containing enhancing lesions indicated to present angiomyolipomas, the largest lesion located in the middle third of the right kidney, the size on axial slices 2,3/2,9 cm (Figure 3). According to the CT examination done 2 years before, the number, and the size of renal angiomyolipomas have increased.

The Multiplicity of renal AML and cysts at such a young age raised suspicion for tuberous sclerosis complex.

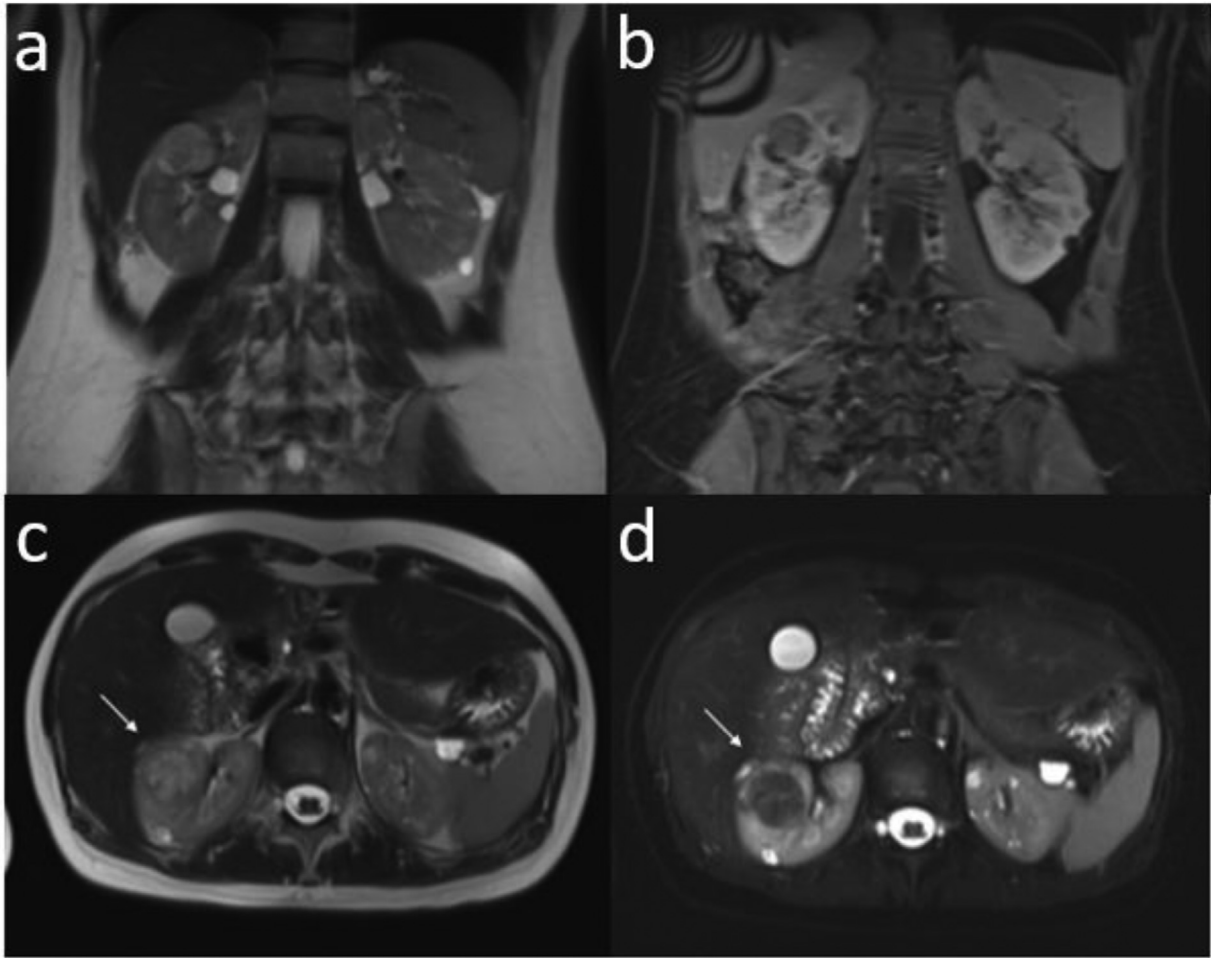


Fig. 3 (a,b) – Coronal T2-weighted MR image (a) and gadolinium T1-weighted MR image acquired during portal venous phase (b) show well defined non-enhancing simple cysts and mildly enhancing lipid-rich angiomyolipoma in both kidneys. (c, d) Axial T2-weighted image (c) and T2-weighted fat-saturated MR image (d) show the largest well-defined lipid-rich angiomyolipoma (arrow) in the right kidney.

Additionally there is a well-circumscribed lesion with hypointense T1 signal and mildly hyperintense T2 signal lesion in the distal pancreatic body and/or proximal pancreatic tail measuring 1,3/1,6cm on the axial planes (Figure 4). The lesion did not show diffusion restriction, enhanced homogeneously, became isointense to pancreas intact parenchyma in the portal, and delayed phases (Fig. 4). According to the characteristics listed above, the lesion was considered a well-differentiated pancreatic neuroendocrine tumor. Moreover, due to the high tumor-to-background Apparent diffusion coefficient (ADC) ratio (1.037), there was high suspicion of PanNET to be a grade 1 tumor [12].

To further support the diagnosis of TSC, brain MRI, and lung CT were performed. Brain MRI showed several subependymal nodules and multiple cortical dysplasias (Fig. 5), while lung CT demonstrated early signs of lymphangiomyomatosis in both lungs and small multiple sclerotic lesions in the bones (Fig. 6).

The ophthalmologic examination revealed multiple retinal nodular hamartomas, but no anterior lenticonus or per-

imacular flecks. At the age of 34, the hearing was normal as well. Heart ultrasound did not show any rhabdomyomas, and blood pressure was consistently normal. Hematological findings, liver function tests, creatinine, and tumor markers were within normal range. Urinalysis revealed isolated mild hematuria.

Since the patient's pancreatic serologic peptide hormone levels were not elevated, and there were no symptoms of diabetes, skin rashes, muscle cramps, pain or flushing, the pancreatic lesion was considered as a non-functioning neuroendocrine tumor (PanNET).

Based on the above-mentioned findings, the phenotype of our patient was fully consistent with a definite clinical diagnosis of TSC, according to clinical diagnostic criteria for TSC [14]. Thus, genetic analysis of TSC1, and TSC2 genes using the Next generation sequencing (NGS) panel was performed. The methodology included sequencing of the entire coding region of TSC1 and TSC2 genes, including 10 bp of flanking intronic sequences, as well as Copy number variation (CNV) analysis for the detection of larger exonic deletions. The performed

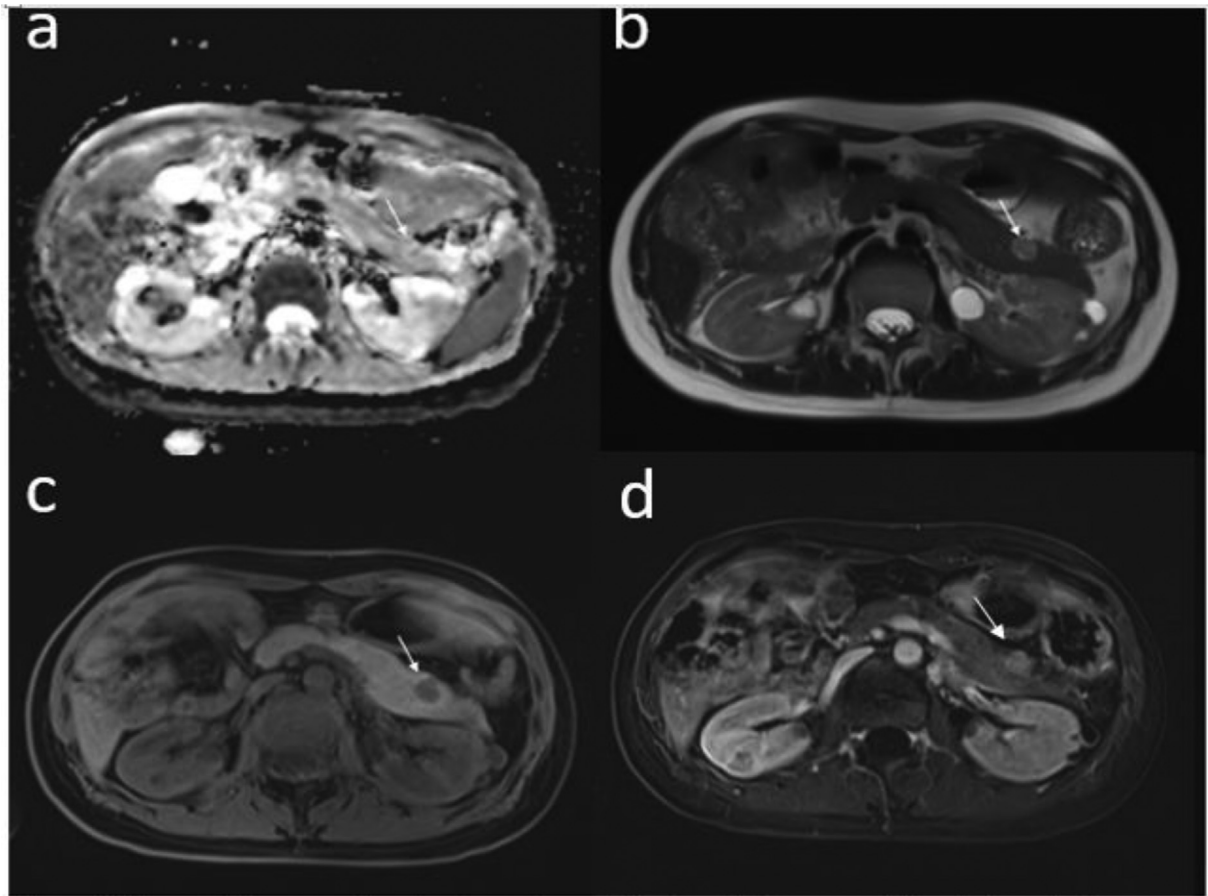


Fig. 4 – Suspected neuroendocrine tumor (arrow) in the distal pancreatic body/proximal pancreatic tail. (a) Axial ADC map shows isointense to mildly hyperintense mass. (b) Axial T2-weighted MR image shows mildly hyperintense mass. (c) Axial T1-weighted MR image shows hypointense mass. (d) Axial gadolinium-enhanced T1-weighted MR image shows that the mass is hypervascular and demonstrated intense enhancement.

analysis also included “tubular list” of pathogenic and likely pathogenic variants for a selection of highly penetrant genes which are known to be linked to early onset severe diseases identified in proband when using NGS.

Interestingly the patient tested negative for TSC, which suggests that she might be a somatic mosaic, and the mutation level in blood lymphocytes was below the detection level. Moreover, as part of the analysis for additional pathogenic and likely pathogenic variants, a heterozygous pathogenic variant p.(Gly774Arg) and a heterozygous likely pathogenic variant p.(Gly1465Asp) were identified in the COL4A4 gene. COL4A4 gene is responsible for causing autosomal dominant basement membrane disease and autosomal recessive Alport syndrome type 2. Performed NGS technology cannot detect the phase of the variants, *cis* or *trans*, but the presence of hematuria without hearing loss and ophthalmologic manifestations at the age of 34, highly suggests *cis* phase of the variants, which is consistent with basement membrane disease. According to the TSC consensus recommendations, close monitoring, and routine screenings for her clinical presentations were decided [13]. Additionally, we avoided doing any surgical interventions on the pancreatic lesion due to the small size,

the risks of the procedure, and the clinically nonfunctioning tumor.

Discussion

The classic TSC triad (Vogt’s triad) includes mental retardation, seizures, and facial angiofibromas which may not be seen in all cases.

The 2012 International TSC Consensus Conference published clinical diagnostic criteria, which includes the presence of 2 major features, or 1 major, and 2 minor features [Table 1 \[14\]](#).

TSC is characterized by the development of hamartomas in almost every organ, and patients develop disabling neurologic features (epilepsy, mental retardation, and autism), dermatologic features (facial angiofibromas, hypomelanotic macules, shagreen patches, and ungula fibromas), and tumor-like hamartomatous lesions (cortical tubers, cardiac rhabdomyomas, subependymal nodules, renal angiomyolipomas, and lymphangiomyomatosis) [15].

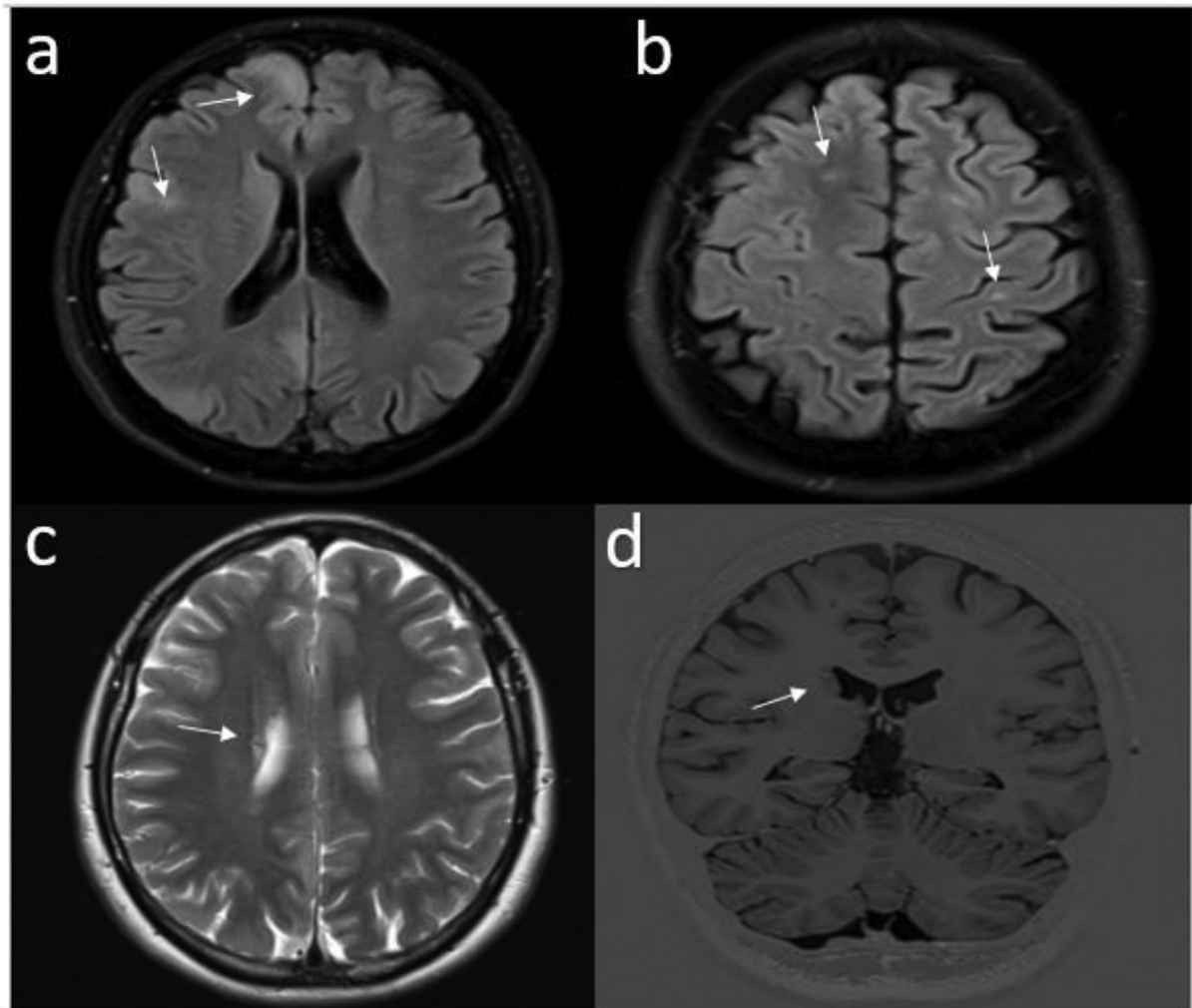


Fig. 5 – Axial FLAIR MR images (A,B) show multiple hyperintense lesions consistent with cortical and/or subcortical tubers (cortical dysplasia); Axial T2-weighted MR image (C) and coronal T1-weighted MR image (D) show small subependymal nodules slightly projecting into lateral ventricles.

In most patients with TSC, the initial management issue is related to making an appropriate diagnosis by identification of major, and minor diagnostic features. The second important issue is the management of TSC in long-term follow-up, in particular, the growth of angiomyolipomas or subependymal giant-cell tumors [16].

Our patient had 7 major clinical features (periungual fibromas, angiofibromas, renal angiomyolipoma, cortical tubers, retinal hamartomas, lymphangiioleiomyomatosis, subependymal nodules,) making the diagnosis a certainty even in the absence of genetic assessment.

Many gaps remain in the understanding of TSC because of the complexity and diversity in clinical presentation. In the TOSCA registry, the occurrence rates of major manifestations of TSC included – cortical tubers (82.2%), subependymal nodules (78.2%), subependymal giant cell astrocytomas (24.4%), renal angiomyolipomas (47.2%), lymphangiioleiomyomatosis (6.9%), cardiac rhabdomyomas (34.3%), facial angiofibromas (57.3%), forehead plaque (14.1%), ≥ 3 hypomelanotic macules

(66.8%), and shagreen patches (27.4%). Epilepsy was reported in 1748 (83.5%) patients, of which 1372 were diagnosed at ≤ 2 years (78%). Intellectual disability was identified in 451 (54.9%) patients. More than 1/3 (36,7%) of patients with TSC are diagnosed after age 18 years. Registry revealed pancreatic neuroendocrine tumor only in 5 patients, out of 2093 patients [17].

TSC is associated with well-known and recognized intraabdominal tumors like angiomyolipoma of the kidney. However, rarer tumors like pancreatic neuroendocrine tumors can occur in the setting of TSC.

Whether there is any pathogenic association between NET and TSC is still unanswered, given the paucity of documented cases. About 10% of all PanNETs are components of familial endocrine syndromes and are seen in multiple endocrine neoplasia syndrome 1 (most common), Von Hippel-Lindau disease, neurofibromatosis type 1, and TSC [18]. Familial tumor syndromes are often associated with germline mutations in tumor-suppressor genes that cause increased tumor suscepti-

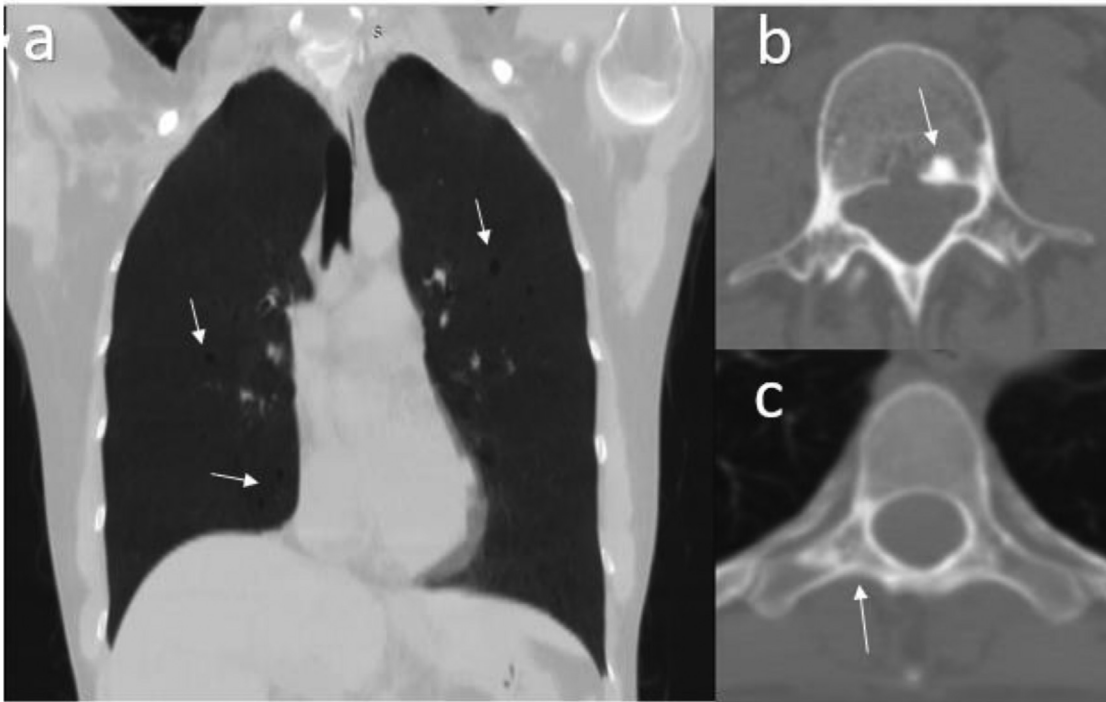


Fig. 6 – Coronal CT (A) Arrows show small air-filled cysts randomly distributed in both lungs. Axial CT (B,C) Arrows show diffuse sclerotic lesions in the vertebrae.

Major features	Minor features
Cardiac rhabdomyoma	Dental enamel pits (>3)
Angiofibromas (≥3) or fibrous cephalic plaque	Multiple renal cysts
Cortical dysplasias, including tubers and cerebral white matter migration lines	“Confetti” skin lesions (numerous 1- to 3-mm hypopigmented macules scattered over regions of the body such as the arms and legs)
Hypomelanotic macules (≥3; ≥5 mm in diameter)	Intraoral fibromas (≥2)
Multiple retinal nodular hamartomas	Nonrenal hamartomas
Lymphangiomyomatosis	Retinal achromic patch
Shagreen Patch	
Subependymal giant cell astrocytoma (SEGA)	
Subependymal nodules (SENs)	
Ungual fibromas (≥2)	
Renal angiomyolipoma	

bility in the pancreas and other neuroendocrine organs, leading to the development of multiple neoplasms [15,19].

The study by Larson et al suggests that the majority of these pancreatic lesions in patients with TSC are not AMLs, as it was previously considered, but rather, PanNETs. A comparison of the clinical, radiological, and pathologic features of TSC-related PanNETs in this report with those of PanNETs occurring in the general population shows 2 interesting findings: the lesions in the TSC cohort occur at a younger age and are more frequently cystic. The risk of aggressive behavior is difficult to assess. The most significant difference between TSC-related PanNETs and all other syndromic PanNETs is that in TSC, the majority of these lesions are found to be solitary, and not multifocal. In this study PanNETs, while overall were rare (9/219; 4.1%), remain the most common pancreatic neoplasia in individuals with TSC [20].

Pancreatic lesions in patients with TSC, solid or cystic, should be considered possible PanNETs. Preoperative fine-needle aspiration biopsy for tumor grade assessment is less accurate for pancreatic primary in PanNET than for hepatic metastasis and are not routinely justified due to low sensitivity. They are reserved for locally advanced disease, those with hepatic metastasis or in case of a diagnostic dilemma concerning the primary [21].

Hence, asymptomatic tumors >2 cm, functioning tumors, and tumors with aggressive features, like pancreatic dilation, should be resected [22]. European Neuroendocrine Tumor Society (ENETS) guidelines recommend non-functioning, low grade, PanNETs, <2cm be followed by active radiological surveillance [23].

PanNET is the diagnosis probable based on the characteristic arterial enhancement on contrast MRI. PanNETs are typically solid, but may present as cystic lesions. These can be differentiated from benign pancreatic cysts by their characteristic MRI sequence [24]. PanNET is usually contrast enhancing on arterial phase. However, some may be non-hypervascular. Well-defined margin and hyper- or iso-enhancement in the portal venous phase are useful MR features seen in non-hypervascular PanNETs and discriminate non-hypervascular PanNETs from pancreatic adenocarcinoma [25].

In our case, the main differential for a pancreatic lesion with such imaging characteristic is pancreatic perivascular epithelioid cell tumor (PEComa) which is reported to appear very similar to pancreatic neuroendocrine tumors on imaging (well-circumscribed, oval or round-shaped not hypovascular mass) [26]. Moreover, mutations of the TSC2 gene are usually found in sporadic PEComas. However, to our knowledge, there is only 1 reported case of pancreatic PEComa in a patient with TSC [27]. Consequently, the main probable diagnosis for our patient's pancreatic lesion is a well-differentiated low-grade neuroendocrine tumor.

It remains unclear when is it reasonable to proceed with surgery, in small nonsecreting PanNETs. The risk of distant metastases must be weighed against surgical morbidity and complications. For some small non-secreting tumors active surveillance is a potentially safe and effective strategy instead of surgery. In light of the above data, due to the small size of the PanNET and the benign characteristic imaging, it was decided to perform a follow-up instead of surgical interven-

tion. Khanna et al. and Han et al. report the possibility of such a conservative approach in small non-functioning pancreatic neuroendocrine tumor management [12,28].

Asymptomatic PanNETs <2cm in TSC may be managed by abdominal surveillance but the optimal screening modality, duration, and interval of screening are still unknown. Follow-up evaluation for sporadic PanNETs include clinical examination and imaging including CT, endoscopic ultrasound (EUSG) or MRI at 6- or 12-month intervals. CT and MRI have comparable yield, with CT having significant long-term radiation exposure over an extended surveillance period. The exact duration of surveillance for sporadic PanNETs is variable with most ranging between 32 and 45 months [29].

It is noteworthy to say that TSC is a clinical diagnosis and genetic testing is not mandatory to confirm the diagnosis, especially when the phenotype of the patient presents with several clear-cut major diagnostic criteria. In our case, sequencing, and deletion-duplication analysis of TSC1 and TSC2 genes was performed and the coverage was 99.74%, however, the patient tested negative. Having negative test results does not exclude the diagnosis of TSC and there are several explanations for this. First, the patient may have somatic mosaicism, which is not uncommon for TSC [30]. Indeed, NGS technologies have a limitation to detect percentage of mosaicism that is below 10%-15% in the analyzed tissue, usually blood lymphocytes from which DNA is being extracted during routine lab workflow. Second, the mutation may be located in the non-coding promoter or deep-intronic region, which is beyond the detection of the current methodology. For such DNA alterations, whole-genome sequencing (WGS) would be feasible. However, due to the high price, WGS is rarely being performed in the context of TSC. Moreover, as TSC remains a clinical diagnosis, unless there is a need for genetic counselling for reproductive decision-making, genetic testing may not be performed.

Somewhat unexpected was the fact that our patient turned out to have alterations in COL4A4 gene, with 2 heterozygous variants classified as pathogenic, and likely pathogenic. This finding explains persistent hematuria, which the patient has been having for many years. The performed NGS technology cannot detect whether these variants are in *cis* or *trans* phase, unless parental testing is performed. However, absence of hearing loss and characteristic anterior lenticonus or perimacular flecks makes the diagnosis of Alport syndrome less likely, suggesting milder basement membrane disease.

Thus, by presenting this case we would like to increase awareness of pancreatic neuroendocrine tumors in TSC and emphasize the need for follow-up monitoring. Moreover, this case once again demonstrates, that with improved NGS technologies it is not uncommon to reveal patients with dual diagnosis with further need of detailed clinical evaluation to properly interpret genetic test results.

The main limitation of this case is the absence of histologic diagnosis. We presume pancreatic lesion as PanNET because of its typical radiologic appearance. Additionally, a review of the literature and/or PubMed database suggests that pancreatic neuroendocrine tumors remain the most common pancreatic neoplasm in TSC patients.

Funding statement

This work was not supported by any funding sources. This research did not receive any specific grant from funding agencies in the public, commercial, or not-profit sectors. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

REFERENCES

- [1] Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. *Ann N Y Acad Sci* 1991;615:125–7.
- [2] Johannessen CM, Reczek EE, James MF, Brems H, Legius E, Cichowski K. The NF1 tumor suppressor critically regulates TSC2 and mTOR. *Proc Natl Acad Sci USA* 2005;102:8573–8.
- [3] Bissler JJ, Kingswood JC, Radzikowska E, Zonnenberg BA, Frost M, Belousova E, Sauter M, Nonomura N. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2013;381:817–24.
- [4] Arva NC, Pappas JG, Bhatla T, Raetz EA, Macari M, Ginsburg HB, Hajdu CH. Well-differentiated pancreatic neuroendocrine carcinoma in tuberous sclerosis: Case report and review of the literature. *Am J Surg Pathol* 2012;36:14953.
- [5] Yates JR, Maclean C, Higgins JN, Humphrey A, Maréchal KL, Clifford M, Carcani-Rathwell I, Sampson JR, Bolton PF. The Tuberous Sclerosis 2000 Study: presentation, initial assessments and implications for diagnosis and management. *Arch Dis Child* 2011;96:1020.
- [6] Jeong A, Wong M. Systemic disease manifestations associated with epilepsy in tuberous sclerosis complex. *Epilepsia* 2016;57(9):1443–9.
- [7] Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. *N Engl J Med* 2006;355:1345–56.
- [8] Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. *Lancet* 2008;372:657–68.
- [9] Casper KA, Donnelly LF, Chen B, Bissler JJ. Tuberous sclerosis complex: Renal imaging findings. *Radiology* 2002;225:4516.
- [10] Halfdanarson TR, Rabe KG, Rubin J, Petersen GM. Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival. *Ann Oncol* 2008; 19(10): 1727–1733. </bib type="Periodical">
- [11] Verbeke CS. Endocrine tumours of the pancreas. *Histopathology* 2010;56:669–82.
- [12] Khanna L, Prasad SR, Sunnapwar A, Kondapaneni S, Dasyam A, Tammiseti VS, Salman U, Nazarullah A, Katabathina VS. Pancreatic neuroendocrine neoplasms: 2020 update on pathologic and imaging findings and classification. *RadioGraphics* 2010;40(5):1240–62.
- [13] Krueger DA, Northrup H. Tuberous sclerosis complex surveillance and management of the 2012 International tuberous sclerosis complex consensus conference. *Pediatr Neurol* 49(4):255–265
- [14] Northrup H, Krueger DA. International tuberous sclerosis complex consensus group. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 international tuberous sclerosis complex consensus conference. *Pediatr Neurol* 2013;49:243–54.
- [15] Jensen RT, Berna MJ, Bingham DB, Norton JA. Inherited pancreatic endocrine tumor syndromes: advances in molecular pathogenesis, diagnosis, management, and controversies. *Cancer* 2008;113(7 suppl):1807–43.
- [16] Weiner DM, Ewalt DH, Roach ES, Hensle TW. The tuberous sclerosis complex: a comprehensive review. *J Am Coll Surg* 1998;187:548–61.
- [17] Kingswood JC, d'Augères GB, Belousova E, Ferreira JC, Carter T, Castellana R. TOSCA consortium and TOSCA investigators. Tuberous Sclerosis registry to increase disease Awareness (TOSCA) - baseline data on 2093 patients. *Orphanet J Rare Dis* 2017;12(1):2. doi:10.1186/s13023-016-0553-5.
- [18] Ro C, Chai W, Yu VE, Yu R. Pancreatic neuroendocrine tumors: biology, diagnosis, and treatment. *Chin J Cancer* 2013;32:312–24.
- [19] Oberg K. The genetics of neuroendocrine tumors. *Semin Oncol* 2013;40:37–44.
- [20] Larson AM, Hedgire SS, Deshpande V, Stemmer-Rachamimov AO, Harisinghani MG, Ferrone CR, Shah U, Thiele EA. Pancreatic neuroendocrine tumors in patients with tuberous sclerosis complex. *Clin Genet* 2012;82(6):558–63. doi:10.1111/j.1399-0004.2011.01805.x. Epub 2011 Nov 29.
- [21] Rebours V, Cordova J, Couvelard A, Fabre M, Palazzo L, Vullierme MP, Hentic O, Sauvanet A, Aubert A, Bedossa P, Ruszniewski P. Can pancreatic neuroendocrine tumour biopsy accurately determine pathological characteristics? *Dig Liver Dis* 2015;47:973–7.
- [22] Wong KP, Tsang JS, Lang BH. Role of surgery in pancreatic neuroendocrine tumor. *Gland Surg* 2017;7:36–41.
- [23] Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M, Kos-Kudla B, Kwekkeboom D, Rindi G, Klüppel G, Reed N, Kianmanesh R, Jensen RT. ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. *Neuroendocrinology* 2016;103:153–71.
- [24] Ohara Y, Oda T, Hashimoto S, Akashi Y, Miyamoto R, Enomoto T, Satomi K, Morishita Y, Ohkohchi N. Pancreatic neuroendocrine tumor and solid pseudopapillary neoplasm: Key immunohistochemical profiles for differential diagnosis. *World J Gastroenterol* 2016;22:8596–604.
- [25] Jeon SK, Lee JM, Joo I, et al. Nonhypervascular pancreatic neuroendocrine tumors: differential diagnosis from pancreatic ductal adenocarcinomas at mr imaging retrospective cross-sectional study. *Radiology* 2017;284:77–87.
- [26] Ulrich JD, Specht K, Schlitter AM, Ceyhan GO, Quante M, Schmid RM, Schlag C. A rare case of perivascular epithelioid cell tumor (PEComa) of the pancreas diagnosed by endoscopic ultrasound. *Endosc Int Open* 2020;8(1):E25.
- [27] Hartley CP, Kwiatkowski DJ, Hamieh L, et al. Pancreatic PEComa is a novel member of the family of tuberous sclerosis complex-associated tumors: case report and review of the literature. *Virchows Archiv* 2016;469(6):707–10.
- [28] Han X, Lou W. Concomitant pancreatic neuroendocrine tumors in hereditary tumor syndromes: who, when and how to operate? *J Pancreatol* 2019;2(2):48–53.
- [29] Sallinen V, Le Large TYS, Galeev S, Kovalenko Z, Tiefertunk E, Araujo R, Ceyhan GO, Gaujoux S. Surveillance strategy for small asymptomatic non-functional pancreatic neuroendocrine tumors – a systematic review and meta analysis. *HPB* 2017;19:310–20.
- [30] Qin W, Kozłowski P, Taillon BE, Bouffard P, Holmes AJ, Janne P, Camposano S, Thiele E, Franz D, Kwiatkowski DJ. Ultra deep sequencing detects a low rate of mosaic mutations in tuberous sclerosis complex. *Hum Genet* 2010;127(5):573–82. doi:10.1007/s00439-010-0801-z. Epub.