Tuberous Sclerosis Complex with rare associated findings in the gastrointestinal system: a case report and review of the literature

Larissa Brussa Reis¹,²†, Daniele Konzen³,⁴†, Cristina Brinckmann Oliveira Netto⁵, Pedro Moacir Braghiorlli Braghini⁶, Gabriel Prolla⁴ and Patricia Ashton-Prolla¹,²,⁵*,‡

Abstract

Background: Tuberous Sclerosis Complex (TSC) is a complex and heterogeneous genetic disease that has well-established clinical diagnostic criteria. These criteria do not include gastrointestinal tumors.

Case presentation: We report a 45-year-old patient with a clinical and molecular diagnosis of TSC and a family history of cancer, presenting two rare associated findings: gastrointestinal polyposis and pancreatic neuroendocrine tumor. This patient was subjected to a genetic test with 80 cancer predisposing genes. The genetic panel revealed the presence of a large pathogenic deletion in the TSC2 gene, covering exons 2 to 16 and including the initiation codon. No changes were identified in the colorectal cancer and colorectal polyposis genes.

Discussion and conclusions: We describe a case of TSC that presented tumors of the gastrointestinal tract that are commonly unrelated to the disease. The patient described here emphasizes the importance of considering polyposis of the gastrointestinal tract and low grade neuroendocrine tumor as part of the TSC syndromic phenotype.

Keywords: Tuberous sclerosis complex, Adenomatous colonic, Rectal polyposis, Pancreatic neuroendocrine tumor, Case report

Background

Tuberous Sclerosis Complex (TSC) is a genetic disorder with multiorgan involvement, a broad phenotype with inter and intra-familiar variability and well-established clinical diagnostic criteria (Table 1) [1–4]. The incidence of TSC is approximately 1 in 6000–10,000 live births, and in Europe its prevalence has been estimated to be 8.8/100,000 [5]. Germline pathogenic variants in TSC1 and TSC2 are identified in 75–90% of patients with the clinical diagnosis and at least 60% of TSC patients do not have a family history of the disease and are considered sporadic [6].

In this report, we describe a patient with the clinical and molecular diagnosis of TSC presenting with two rare associated findings: gastrointestinal polyposis and a pancreatic neuroendocrine tumor. A review of the literature on the subject is provided.

Case presentation

The patient, a 45-year-old male, was referred for genetic assessment due to clinical findings suggestive of
Tuberous Sclerosis Complex (TSC) and polyposis of the gastrointestinal tract. Past medical history included symptoms such as significant seizures since infancy, mild cognitive impairment and adult-onset psychiatric symptoms. These symptoms prompted investigation with a brain magnetic resonance imaging (MRI), which showed subependymal nodules and cortical tubers, two major diagnostic criteria of TSC. Physical examination revealed facial angiofibroma but no additional cutaneous abnormalities were observed. Ophthalmologic, cardiac and pulmonary evaluations did not reveal presence of retinal hamartomas, cardiac rhabdomyomas or pulmonary lymphangiomyomatosis. Abdominal computed tomography (CT) scans showed an expansive lesion with heterogeneous enhancement, located in the lower pole of the right kidney, measuring 5.5 cm × 4.0 cm which was later confirmed as a renal angiomyolipoma, another classical sign of TSC. Physical examination revealed facial angiofibroma but no additional cutaneous abnormalities were observed. Ophthalmologic, cardiac and pulmonary evaluations did not reveal presence of retinal hamartomas, cardiac rhabdomyomas or pulmonary lymphangiomyomatosis. Abdominal computed tomography (CT) scans showed an expansive lesion with heterogeneous enhancement, located in the lower pole of the right kidney, measuring 5.5 cm × 4.0 cm which was later confirmed as a renal angiomyolipoma, another classical sign of TSC. Multiple nodular lesions with arterial enhancement were identified in the liver, the largest one measuring 7.0 × 5.0 cm with features suggestive of secondary implants of unknown origin. In addition, abdominal imaging also showed an expansive lesion in the pancreatic body, with heterogenous enhancement, involving the splenic artery and measuring approximately 6.0 × 4.0 cm. In addition, the patient also had a long history of diarrhea and underwent colonoscopy and upper gastrointestinal endoscopy, revealing presence of more than 50 gastric, colonic and rectal polypoid formations (2 mm to 5 mm).

Family history of cancer was significant for presence of 2 relatives with central nervous system tumors (father and brother diagnosed at ages 62 and 57 years, respectively). Eight additional cancer unaffected siblings were reported. There was also no report of any other family member with clinical features of Tuberous Sclerosis Complex or other genetic conditions. Considering the clinical features of TSC and polyposis of the digestive tract, germline genetic testing was proposed with a next generation sequencing panel validated for large rearrangement screening including 80 cancer predisposition genes in a commercial laboratory. Genes in the panel included: ALK, APC, ATM, AXIN2, BAP1, BARD1, BLM, BMPRIA, BRCA1, BRCA2, BRIP1, CASR, CDC73, CDH1, CDK4, CDKN1B, CDKN1C, CDKN2A (p14ARF), CDKN2A (p16INK4a), CEBPA, CHEK2, DICER1, DIS3L2, EPCAM, FH, FLCN, GATA2, GPC3, GREM1, HRAS, KIT, MAX, MEN1, MET, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, NF2, PALB2, PDGF RA, PHOX2B, PMS2, POLD1, POLE, POT1, PRKAR1A, PTCH1, PTEN, RAD50, RAD51C, RAD51D, RB1, RECQ L4, RET, RUNX1, SDHA, SDHD, SDHB, SDHC, SMAD 4, SMARCA4, SMARCB1, STK11, SUIF2, TERC, TERT, TMEM127, TP53, TSC1, TSC2, VHL, WRN, WT1 genes. The patient died due to complications of the disease a few months after genetic evaluation. Informed consent to publish this case report was obtained post-mortem from his spouse.

Regarding pathology of the tumors, the haematoxylin and eosin stain (HE) performed in lesion of the right kidney revealed round cell renal tumor with typical morphology (Fig. 1a). The liver lesions were biopsied, showing a histologic pattern suggestive of a low-grade neuroendocrine tumor (NET) (Fig. 1c and e). Biopsies of the pancreatic lesion diagnosed a low-grade neuroendocrine pancreatic tumor (PanNET). Based on the major phenotypic criteria identified in the patient, the clinical diagnosis of TSC with a rare manifestation (PanNET) was established. Partial polypectomies were performed resecting three polyps from the gastric body, two polyps from the right colon and four polyps from the rectum. Histologic examinations of the gastric and colonic/rectal polyps revealed fundic gland polyps and tubular adenomas with low-grade dysplasia, respectively (Fig. 2). Immunohistochemistry (IHC) was performed in the biopsy of the right kidney lesion and demonstrated positive expression of melanoma antigen (Melan A) (Fig. 1b), melanosomal glycoprotein gp100 antigen (HMB45) and smooth muscle actin antigen. The lesions in the liver were confirmed by IHC, showing positivity for multiple citokeratins antigens (40, 48, 50 and 50,6 kDa), chromogranin A antigen (CGA) (Fig. 1d), and synaptophysin (Sinapto) (Fig. 1f).
Germline genetic testing revealed presence of a large pathogenic deletion in TSC2 gene encompassing exons 2 to 16 and including the initiation codon. No alterations in colorectal cancer/colorectal polyposis genes (APC, AXIN2, BMPR1A, CDH1, CHEK2, EPCAM, GREM1, MLH1, MSH2, MSH3, MSH6, MUTYH, NTHL1, PMS2, POLD1, POLE, POLE, PTEN, SMAD4, STK11, TP53) were identified.

Discussion and conclusions
TSC is an autosomal dominant disease associated with cancer predisposition and multisystemic involvement mainly due to hyperactivation of the mTOR pathway, secondary to loss of function mutations in TSC1 and TSC2 [7]. Approximately 15% of the pathogenic variants identified in TSC2 and 8% of those identified in TSC1 are large gene rearrangements (LGR) [8], and therefore, genotyping using a methodology that allows LGR detection is important in a diagnostic workup. Although criteria for clinical diagnosis of TSC are well established, expressivity is highly variable, even within families with multiple carriers of the same pathogenic variant and simplex cases with de novo mutations are not
uncommon reaching up to 86% in some cohorts [9]. The recent, increased access to multigene panel testing to investigate suspected hereditary cancer has resulted in molecular diagnosis of individuals without the classic clinical criteria or apparently “sporadic” tumors or isolated clinical features of the disease.

In this report, we describe a patient fulfilling criteria for the clinical diagnosis of TSC, such as cortical tubers, facial angiofibroma and renal angiomyolipoma (Table 1 and Fig. 1a and b) carrying a previously described large TSC2 rearrangement with two uncommon clinical manifestations of the disease: gastrointestinal adenomatous polyposis and a metastatic pancreatic neuroendocrine tumor. The occurrence of numerous colonic and rectal polyps, characterized in this patient as tubular adenomas, is a symptom associated with gastrointestinal polyposis and colorectal cancer syndromes, such as Familial adenomatous polyposis (FAP), a rare autosomal, dominant hereditary disease [10]. FAP is caused by a germline mutation in the APC gene [11]. Besides FAP, other syndromes could be associated, including mismatch repair deficiency (biallelic MLH1, MSH2, MSH6, PMS2 gene mutations), polymerase proofreading-associated polyposis (POLD1, POLE genes), juvenile polyposis (SMAD4, BMPRIA genes) and MÜTYH-associated polyposis [12]. Sequence changes and exonic deletions/duplications were evaluated in all of these associated genes and negative results exclude these syndromes in this patient.

The heterozygous TSC2 exon 2–16 deletion identified is also known as deletion of exons 1–15 in the literature. Truncating variants including gross deletions in TSC2 are known to be pathogenic. The 5’ end of the deletion remained undetermined as it was beyond the assayed region and the 3’ boundary was probably within intron 16 of the TSC2 gene. This deletion is expected to result in complete removal of the TSC1 binding domain (T1BD) the N-terminus of the TSC2 protein in one of the alleles. This domain is critical for TSC1-TSC2 interaction (formation of TSC complex) and abnormal or absent TSC complex results in TSC2 ubiquitination and degradation. This in turn eliminates inhibition of the conversion of Rheb-GTP which accumulates and directly activates the mTORC1 pathway [13, 14].

Three previous reports describe TSC patients carrying the same germline TSC2 exon 2–16 (a.k.a. exon 1–15) deletion [15–17]. However, according to the information available, none of them presented the uncommon clinical features reported here (neuroendocrine tumors or gastrointestinal polyps) (Tables 2 and 3); although it is possible that due to their ages, these phenotypes would not yet be identifiable. Interestingly, Mortaji et al., 2018 described an adult TSC patient who presented both, a pancreatic NET and gastrointestinal (GI) polyps. But different from the case presented here, they were hamartomatous/inflammatory polyps [40]. Although rectal polyps are included as a minor clinical diagnostic criterion for TSC, there is no mention to polyps in other portions of the GI tract and the vast majority of polyps described in TSC patients are hamartomatous [19, 43]. Gastric fundic polyps (FGPs) are considered hamartomas and tuberin protein (codified by TSC2 gene) seems to play an important role in pathogenesis of sporadic FGPs by deregulation of cell proliferation. The altered cellular localization of tuberin interrupts its interaction with hamartin protein (codified by TSCI) preventing the formation of TSC complex that regulates mTORC1 pathway, responsible for cell proliferation and protein synthesis signaling pathways. In addition, altered cellular localization of tuberin may preclude its negative regulation of gene transcription mediated by tuberin-associated proteins glucocorticoid receptor (GCR) [44]. We identified only one case report of an adolescent TSC patient with tubular adenomatous polyps of the GI tract. The report by Digoy et al. (2000), and the case reported here, presented with a high number of GI tract polyps (unlikely somatic in origin) and a negative comprehensive evaluation of known polyposis genes, reinforce that GI polyposis with different histologies is likely part of the TSC phenotype and

| Reference | Age      | TSC features                                      | GI tract alterations                          | Mutant gene |
|-----------|----------|---------------------------------------------------|----------------------------------------------|-------------|
| [18]      | 17 yo female | Mental retardation, brain astrocytoma, facial angiofibroma, hypomelanotic macules, renal angiomyolipoma | Rectal adenocarcinoma and multiple (> 50) tubular adenomas | NA          |
| [19]      | 42 yo female | Seizures, renal and liver angiofibromas, multiple subependymal calcifications of the brain, lymphangioleiomyomatosis of the lungs, cerebromalacia | Multiple gastric (fundic) hamartomas | NA          |
| [20]      | 51 yo female | Epilepsy, mild cognitive impairment, ungual fibromas. | More than 50 sessile polyps of small size scattered through the left colon and rectum | TSC1        |

*NA Not assessed
should be considered in the differential diagnosis [18]. Of note, glandular fundic polyps and tubular adenomatous polyps could be two different expressions of the same germline variation.

Finally, pancreatic neuroendocrine tumors (PanNET) are most commonly sporadic but have been reported previously in association with TSC and in other inherited cancer syndromes such as von Hippel-Lindau
disease, Neurofibromatosis type 1 and Multiple endocrine neoplasmia type 1 [45]. Most TSC patients diagnosed with NETs have pancreatic NETs, but NETs in other organs must be considered as part of the TSC phenotype. Recent studies have shown that most TSC patients with Pancreatic NETs have a germline pathogenic variant in TSC2 gene, as observed in our case. The multiple reports of NET in TSC patients and recent evidence for a pivotal role of TSC1 and TSC2 proteins in NET development and tumor’s response to mTORC1 modulating interventions, point to a direct relationship between loss of function variants in TSC1 and TSC2 and NET suggesting that TSC clinical criteria should be modified to include NETs [46–48]. To our knowledge, there are no previous reports of tubular adenomatous polyposis in multiple segments of the GI tract in carriers of TSC2 germline pathogenic variants (Table 3). In a previous report describing molecular features of TSC patients, none of the probands reported GI tract polyposis [49].

In conclusion, there is currently no recommendation for GI polyp or PanNET screening, probably given the rarity of these findings, in TSC patients. Gastric and colorectal polyps and PanNETs are also not considered as phenotypic criteria for the clinical diagnosis of the syndrome. The patient described here, with confirmed molecular diagnosis of TSC underscores the importance of considering GI tract polyposis and NETs as part of the syndromic phenotype.

Abbreviations
TSC: Tuberous Sclerosis Complex; MRI: Magnetic resonance imaging; CT: Computed tomography; HE: Hematoxylin and eosin; NET: Neuroendocrine tumor; PanNET: Neuroendocrine pancreatic tumor; IHC: Immunohistochemistry; Melan A: Melanoma antigen; HBME-1: Melanomac cell glycoprotein gp100 antigen; CGA: Chromogranin A antigen; Synaptophysin; LGR: Large gene rearrangements; FAP: Familial adenomatous polyposis; T1BD: TSC1 binding domain; GI: Gastrointestinal; FGPs: Gastric fundic polyps; GCR: Glucocorticoid receptor

Acknowledgments
We would like to thank the wife of the deceased patient for permitting publication of her husband’s case report; Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) for financial support, and pathologists Elder Lersch and Carlos Bacci for organizational support.

Authors’ contributions
LBR, D.X. and P.A-P collected data and wrote the manuscript. P.A-P, G.P., P.B. and C.B.O.N treated the patient and interpreted the data. P.B. ordered diagnostic laparoscopy and colonoscopy and was the primary clinical oncologist of the case. G.P. was consulted for a second opinion and referred the patient for genetic evaluation. P.A-P was involved with conception of the report and acted as a supervisor. All the authors read and approved the final manuscript.

Funding
Not applicable.

Availability of data and materials
Not applicable.

Ethics approval and consent to participate
Not applicable.

Consent for publication
The spouse of the patient described here, has provided written informed consent (for the) submission of this case report since the patient was already deceased. Consent to publish included the images in Figure(s) 1a, 1b, 1c, 1d, 1e, 1f, 2a and 2b.

Competing interests
The authors declare that they have no conflict of interest or financial disclosure.

Author details
1Laboratório de Medicina Genômica - Centro de Pesquisa Experimental - Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, Rio Grande do Sul, Brazil. 2Programa de Pós-graduação em Genética e Biologia Molecular, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Rio Grande do Sul, Brazil. 3Hospital Mãe de Deus, Porto Alegre, Rio Grande do Sul, Brazil. 4Hospital São Lucas, Escola de Medicina da Pontifícia Católica do Rio Grande do Sul (PUCRS), Porto Alegre, Rio Grande do Sul, Brazil. 5Serviço de Genética Médica, Hospital de Clínicas de Porto Alegre (HCPA), Rua Ramiro Barcelos 2350, Porto Alegre, RS CEP: 90035-903, Brazil. 6Hospital São Vicente de Paulo, Passo Fundo, Rio Grande do Sul, Brazil.

Received: 13 July 2020 Accepted: 1 October 2020 Published online: 23 November 2020

References
1. Northrup H, Krueger DA, Group ITSCC. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International tuberous sclerosis complex consensus conference. Pediatr Neurol. 2013;49:243–54. https://doi.org/10.1016/j.pedia.2013.08.001.
2. Herskovic E, Jóźwiak S, Kingswood JC, Sampson JR, Thiele EA. Tuberous sclerosis complex. Nat Rev Dis Primers. 2016;2:1–18. https://doi.org/10.1038/ nrdp.2016.35.
3. Portocarrero LKL, Quental KN, Samorano LP, Oliveira ZNP, Rivitti-Machado MCDM. Tuberous sclerosis complex: review based on new diagnostic criteria. An Bras Dermatol. 2018;93(3):323–31.
4. Wataya-Kaneda M, Uemura M, Fujita K, Hirata H, Osuga K, Kagitani-Shimono K, et al. Tuberous sclerosis complex: recent advances in manifestations and therapy. Tuberous sclerosis complex Board of Osaka University Hospital. Int J Urol. 2017;24(9):681–91.
5. Sahin M, Herskovic EP, Manning BD, Ess KC, et al. Advances and future directions for tuberous sclerosis complex research: recommendations from the 2015 strategic planning conference. Pediatr Neurol. 2016;60:1–12. https://doi.org/10.1016/j.pediatrneurol.2016.03.015.
6. Rosset C, Netto COB, Prolla PA. TSC1 and TSC2 gene mutations and their implications for treatment in tuberous sclerosis complex: a review. Genetics and Mol Bio. 2017;40:69–79. https://doi.org/10.1590/1678-4685-GMB-2015-0321.
7. Randle SC. Tuberous sclerosis complex: a review. Pediatr. 2017;46:166–71. https://doi.org/10.3928/19382359-20170320-01.
8. Cooper DN, Ball EV, Stenson PD, et al. The human gene mutation database (HGMD). 2020. http://www.hgmd.cf.ac.uk/ac/index.php. Accessed 11 February 2020.
9. Bundey S, Evans K. Tuberous sclerosis-a genetic study. J Neurol Neurosurg Psychiatry. 1969;32:591–603.
10. Buturovíc S. Multiple colon polyposis. Med Arh. 2014;68:221–2. https://doi.org/10.5453 mediator.2014.68.221-222.
11. Groden J, Thliveris A, Samowitz W, Carlson M, et al. Identification and characterization of the familial adenomatous polyposis coli gene. Cell. 1991; 66:589–600. https://doi.org/10.1016/0006-8093(91)90219-0.
12. Llewellin A, Dennis NJ, Hanna A, et al. Tuberous sclerosis complex: recent advances in manifestations and therapy. Tuberous sclerosis complex Board of Osaka University Hospital. Int J Urol. 2017;24(9):681–91.
13. Hodge AK, Li S, Maynard J, et al. Pathological mutations in TSC1 and TSC2 disrupt the interaction between hamartin and tuberin. Hum Mol Genet. 2001;10:2899–905. https://doi.org/10.1093/hmg/10.28.2899.
15. Jang MA, Hong SB, Lee JH, et al. Identification of TSC1 and TSC2 mutations in Korean patients with tuberous sclerosis complex. Pediatr Neurol. 2012;46:222–9. https://doi.org/10.1016/j.pediatrneurol.2012.02.002.

16. Pizia TP, Dalal AB. Tuberous sclerosis: diagnosis and prenatal diagnosis by MLPA. Indian J Pediatr. 2012;79:1369–78. https://doi.org/10.1007/s12098-011-0408-y.

17. Lee JS, Lim BC, Chae JH, et al. Mutational analysis of pediatric patients with tuberous sclerosis complex in Korean: genotype and epilepsy. Epileptic Disord. 2014;16:449–55. https://doi.org/10.1684/epid.2014.0712.

18. Díaz DD, Ibarrola C, Sanz GS, Hurtado BP, Tabares JS, Ruizdelgado FC. Neuroendocrine tumor of the pancreas in a patient with tuberous sclerosis: a case report and review of the literature. Int J Surg Pathol. 2012;20(4):390–5. https://doi.org/10.1177/1066896911438735.

19. Koc G, Sugimoto S, Kuperman R, Kammern BF, Karakas SP. Pancreatic tumors in children and Young adults with tuberous sclerosis complex. Pediatr Radiol. 2017;47:39–45. https://doi.org/10.1007/s00247-016-3701-0.

20. Montaji P, Morris KT, Samedi V, et al. Pancreatic neuroendocrine tumor in a patient with a TSC variant: case report and review of the literature. Familial Cancer. 2018;17:275–80. https://doi.org/10.1007/s10689-017-0293-9.

21. Stern J, Friesen A, Bowering R, Babanyka I. Multiple bilateral Angiomyolipomas of the kidneys in tuberous brain sclerosis in association with Pheomorphus Pheochromocytoma. Fortschr Med. 1982;100:1809–12.

22. Sato T, Seyama K, Kumasaka T, Fujii H, et al. A patient with TSC1 Germline mutation whose clinical phenotype was limited to Lymphangioleiomyomatosis. J Intern Med. 2004;256:166–73. https://doi.org/10.1111/j.1365-2966.2004.04356.x.

23. Devroede G, Lemieux B, Massé S, Lamrche J, Herman OS. Colonic Hamartomas in tuberous sclerosis. Gastroenterol. 1988;94:182–8.

24. Wei J, Chiriboga L, Yee H, Mizuguchi M, et al. Altered cellular distribution of Tubulin and glucocorticoid receptor in sporadic Fundic gland polyps. Mod Pathol. 2002;15:862–9. https://doi.org/10.1097/01.MP.0000021461.29531.SB.

25. Guilmette JM, Nosé V. Neoplasms of the neuroendocrine pancreas: an update in the classification, definition, and molecular genetic advances. Adv Anat Pathol. 2019;26:13–30. https://doi.org/10.1097/PAP.0000000000000201.

26. Dworokowska D, Grossman AB. Are neuroendocrine tumors a feature of tuberous sclerosis? A systematic review. Endocr Relat Cancer. 2005;12:45–58. https://doi.org/10.1677/ERC-08-0142.

27. Jiao Y, Shi C, Edli BH, de Wilde RF, et al. DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. Science. 2011;331:1199–203. https://doi.org/10.1126/science.1200609.

28. Capurso G, Festa S, Valente R, Piculich M, et al. Molecular pathology and genetics of pancreatic endocrine disorders. J Mol Endocrinol. 2012;49:R37–50. https://doi.org/10.1530/JME-12-0069.

29. Rosset C, Vairo F, Bandiera I, Correia R, et al. Molecular analysis of TSC1 and TSC2 genes and phenotypic correlations in Brazilian families with tuberous sclerosis. PLoS One. 2017;12:1–15. https://doi.org/10.1371/journal.pone.0185713.

Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.