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Teaching case

Hamartomatous polyposis in tuberous sclerosis complex: Case report and review of the literature

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ABSTRACT

Tuberous sclerosis complex (TSC) is a genetic disorder with multisystem involvement that is due to autosomal-dominantly inherited or sporadic mutations in *TSC1* and *TSC2* genes. Involvement of the gastrointestinal tract is rare. We report the case of a 51-year-old woman with diagnosis of TSC established by genetic testing, who presented with colorectal hamartomatous polyposis. Multiple small polyps were found scattered through the left colon and rectum. Histology revealed a distinct spindle cell proliferation in the lamina propria, originating from the muscularis mucosae. The cells lacked atypia or mitotic activity and were diffusely positive for smooth muscle actin and negative for S100 protein. Genetic testing proved a disease causing frameshift mutation in the *TSC1* gene. Although gastrointestinal involvement is rare in TSC, hamartomatous polyps can be the initial manifestation of this syndrome. Genetic testing should be considered in every case for which TSC is clinically suspected.

1. Introduction

Tuberous sclerosis complex (TSC) is a genetic disorder with multisystem involvement and an estimated incidence of 1/6.000–1/10.000 live births and a population prevalence of about 1 in 20.000 [1]. In its initial description, TSC was characterized by the clinical triad of mental retardation, epilepsy and facial angiofibroma [2]. Clinical manifestations can be subtle and may vary widely between affected individuals. Consequently, the diagnosis of TSC can be difficult to establish.

The most common clinical findings comprise abnormalities of the skin (hypomelanotic macules, facial angiofibromas, shagreen patches, fibrous facial plaques, ungual fibromas), brain (cortical tubers, subependymal nodules and subependymal giant cell astrocytomas, seizures, intellectual disability/developmental delay), kidney (angiomyolipomas, cysts, renal cell carcinomas), heart (rhabdomyomas, arrhythmias) and lungs (lymphangioleiomyomatosis) [1,3]. Epilepsy and mental retardation are no longer included as indicators of TSC, as they can be associated with several pathologic conditions and therefore lack sufficient specificity to be useful for diagnosis.

The genetic basis of TSC has been attributed to mutations in *TSC1* gene, located on chromosome 9 (9q34.13), and *TSC2* gene, located on chromosome 16 (16p13.3), which can be autosomal-dominantly inherited or sporadically acquired. These two genes encode, respectively, the proteins hamartin and tuberin and play a role as tumor suppressors [3,4].

Nowadays, the diagnosis of TSC is based both upon clinical findings and genetic testing. Molecular genetic testing of *TSC1* and *TSC2* identifies a mutation in approximately 85% of individuals with a definite diagnosis of TSC [4]. In about 15% of individuals with TSC no mutation can be identified. The diagnostic criteria of the 2012 International TSC Consensus Conference are summarized in Table 1 [1].

Gastrointestinal manifestations in TSC are uncommon, reported cases referring to liver angiomyolipomas and colorectal hamartomatous polyps. Due to lack of specificity, the designation of "hamartomatous rectal polyps" was excluded from the list of diagnostic criteria of TSC, but they are interpreted as "non-renal hamartoma" and included in the minor features [1]. We present a patient with colorectal hamartomatous polyposis in the context of TCS. The patient is the first reported in the literature with intestinal involvement and a diagnosis confirmed by genetic analysis.

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Table 1
Tuberous sclerosis complex (TSC): diagnostic criteria [1].

Genetic	Identification of pathogenic mutation[a] in *TSC1* or *TSC2* genes from normal tissue DNA	
Clinical	**Major features**	**Minor features**
	1. Hypomelanotic macules (≥3, at least 5-mm diameter)	1. "Confetti" skin lesions
	2. Angiofibromas (≥3) or fibrous cephalic plaque	2. Dental enamel pits (>3)
	3. Ungual fibromas (≥2)	3. Intraoral fibromas (≥2)
	4. Shagreen patch	4. Retinal achromic patch
	5. Multiple retinal hamartomas	5. Multiple renal cysts
	6. Cortical dysplasias[b]	6. Non-renal hamartomas
	7. Subependymal nodules	
	8. Subependymal giant cell astrocytoma	
	9. Cardiac rhabdomyoma	
	10. Lymphangioleiomyomatosis (LAM)[c]	
	11. Angiomyolipomas (≥2)[c]	
Definite diagnosis	Genetic criteria or 2 major features or 1 major feature with ≥2 minor features	
Possible diagnosis	1 major feature or ≥2 minor features	

[a] Pathogenic mutation is defined as a mutation that inactivates the function of TSC1 or TSC2 proteins, that prevents protein synthesis or missense mutation whose effect on protein function has been established by functional assessment.
[b] Includes tubers and cerebral white matter radial migration lines.
[c] A combination of the two major clinical features (LAM and angiomyolipomas) without other features does not meet criteria for a definite diagnosis.

2. Case report

We present a 51-year-old woman with mild intellectual disability and clinical history of epilepsy for 15 years, arterial hypertension, diabetes mellitus type II, and non-alcoholic fatty liver disease (NAFLD). Apart from surgical resection of four ungual fibromas of the left hand (fingers II–V), there was no history of other surgical procedures.

In 2013, the patient noticed blood in the stool and underwent upper and lower endoscopy. The gastroscopy showed mild reflux oesophagitis and a reddened gastric mucosa with no evidence of mucosal breaks or mass lesions. Histology of the gastric biopsies revealed reactive gastropathy, which was characterized by foveolar hyperplasia, vascular ectasia and congestion, lacking intestinal metaplasia, dysplasia or malignancy. The colonoscopy displayed more than 50 sessile polyps of small size (less than 5 mm) scattered through the descending and sigmoid colon as well as the rectum (Fig. 1). In the anal canal, there was evidence of haemorrhoidal disease.

About 10 polyps were sampled from different areas. Histological examination of all polyps revealed a distinct spindle cell proliferation in the lamina propria, which appeared to be in continuity with the muscularis mucosae (Fig. 2A and B). The cells lacked atypia or mitotic activity and were diffusely positive for smooth muscle actin (SMA) and negative for S100 protein, proving their muscular nature (Fig. 2C and D). There was no adipose or neural tissue identified. Overall, the covering epithelium was normal or showed mild hyperplastic changes, without dysplasia or malignancy. A diagnosis of hamartomatous polyps was rendered, raising the possibility of a hamartomatous polyposis syndrome.

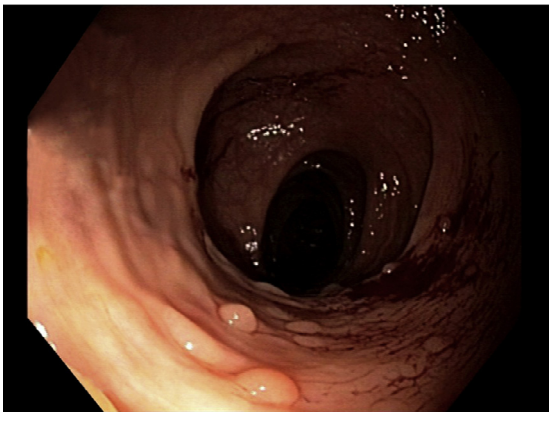

Fig. 1. More than 50 sessile polyps of small size (less than 5 mm) were identified scattered through the descending and sigmoid colon as well as the rectum.

Abdominal sonography was additionally performed that showed hepatic steatosis, while the biliary tract and the other intra-abdominal organs, including kidneys and urogenital tract were normal.

The patient was referred to genetic counseling. After written informed consent, molecular analysis was carried out using the HaloPlex Target Enrichment System (Agilent, Santa Clara, USA) on a Next-Generation Sequencing platform (MiSeq, Illumina, San Diego, USA). Data analysis for the detection of sequence variants was done using the SureCall software (Agilent). Genetic testing revealed a disease causing frameshift mutation in the *TSC1* gene (c.1257delC, p.Arg420Glyfs*20; RefSeq NM_000368), prompting a final diagnosis of TSC.

The retrospective evaluation of our patient's history revealed the presence of some clinical diagnostic criteria of TSC, in particular ungual fibromas and the intestinal hamartomatous polyps, which, in accordance with the diagnostic criteria of the 2012 International TSC Consensus Conference, should be referred to as "non-renal hamartomas". There was no evidence of lung, heart or kidney disorders and the patient had no family history of the disease. No brain imaging was performed.

In 2015, upper and lower endoscopy was repeated, with similar endoscopic and histological findings, specifically no gastric or duodenal polyps, and again with no evidence of dysplasia, i.e. adenomatous polyps or malignancy. The patient provided written consent for the publication of this case report.

3. Discussion

Gastrointestinal involvement in TSC is rare and mainly restricted to the large bowel. Association with colorectal polyps has been reported in only 30 cases in the English literature (Table 2) [5–11]. In these cases, the diagnosis of TSC was based solely upon clinical assessment, referring to cutaneous lesions, such as facial angiofibroma, ungual fibroma, Shagreen patch and hypomelanotic macules, as well as central nervous disorders, including epilepsy and/or intellectual disability. It is of note that the case presented herein is the first case of hamartomatous polyposis in TSC with genetically proven diagnosis. Therefore this case is ideal to