Revista de Ciencias Médicas de Pinar del Río

**ISSN:** 1561-3194 **RNPS:** 1877
Rev Ciencias Médicas. 2025; 29(2025): e6916

**CASE PRESENTATION**

# Atypical Retinal Manifestations in a Patient with Tuberous Sclerosis

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**Received:** October 8, 2025
**Accepted:** November 3, 2025
**Published:** November 24, 2025

**Citar como:** Barrera Villar Y, Gómez Martínez N, Gómez Martínez N, Socarras Llábana R. Manifestaciones retinianas atípicas en un paciente con esclerosis tuberosa. Rev Ciencias Médicas [Internet]. 2025 [citado: fecha de acceso]; 29(2025): e6916. Disponible en: http://revcmpinar.sld.cu/index.php/publicaciones/article/view/6916

## ABSTRACT

**Introduction:** tuberous sclerosis is a rare genetic disease with multisystemic manifestations, including retinal lesions. Hypodense spots and drusen are findings rarely described in the literature.
**Objectives:** to present a case of tuberous sclerosis with atypical retinal alterations in order to contribute to the knowledge of its ophthalmological manifestations.
**Case Presentation:** a 25-year-old female patient with tuberous sclerosis (TSC2 mutation) diagnosed at the age of 10, with a history of controlled epilepsy and renal angiomyolipomas. She attended a routine ophthalmological consultation asymptomatically. Visual acuity was 20/20, color vision was normal, and intraocular pressure was within physiological ranges. Fundus examination revealed multiple peripapillary hypodense spots and peripheral drusen. Optical coherence tomography confirmed foveal integrity, with localized retinal thickening in lesion areas without clinically significant macular edema. This confirmed the diagnosis of tuberous sclerosis with atypical retinal manifestations, with annual follow-up adopted as management, without specific treatment due to the absence of visual impairment.
**Conclusions:** tuberous sclerosis may present atypical retinal manifestations such as hypodense spots and drusen, suggesting involvement of the retinal pigment epithelium linked to the mTOR pathway. This first report in Pinar del Río highlights the importance of structural ophthalmological follow-up even in asymptomatic patients.

**Keywords:** Tuberous Sclerosis; Fundus Oculi; Optical Imaging; Tomography, Optical Coherence.

**ISSN:** 1561-3194 **RNPS:** 1877
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## INTRODUCTION

Tuberous sclerosis (TS) is an autosomal dominant disease caused by mutations in the TSC1 or TSC2 genes, with an estimated incidence of 1/6,000-10,000 births.[1] Retinal manifestations, present in 40-50 % of cases, include astrocytic hamartomas, but hypodense spots and drusen are poorly documented findings.[2]

In Cuba, ET is primarily diagnosed in genetics and neurology services, with multidisciplinary follow-up. However, atypical retinal abnormalities have not been widely reported in the national literature.[3,4] In Pinar del Río, the diagnosis and management of ET is carried out at the Abel Santamaría Hospital, with an emphasis on neurological and renal complications. There are no previous reports of retinal manifestations such as drusen or hypodense spots in patients with ET in the province.[5]

For the reasons stated above, this case presentation aims to describe a case of ET with atypical retinal findings (hypotense spots and drusen) to expand local knowledge of its ophthalmological manifestations. This previously undescribed pattern of involvement enriches our understanding of the ocular manifestations of this complex disease.

## CASE PRESENTATION

We present the case of a 25-year-old female patient with a molecularly confirmed diagnosis of tuberous sclerosis (pathogenic mutation in the TSC2 gene) established at age 10. Her medical history includes drug-resistant epilepsy controlled with multiple antiepileptic drugs and stable bilateral renal angiomyolipomas. The patient was referred to the ophthalmology service for routine evaluation without presenting any subjective visual symptoms.

Ophthalmological clinical findings:
- Corrected visual acuity: 20/20 in both eyes.
- Color vision tests (Ishihara test): 21/21 in both eyes.
- Pupillary reflexes: isocoric and reactive in both eyes.
- Intraocular pressure: 16 mmHg in the right eye, 14 mmHg in the left eye.
- Exploration of the anterior segment: no significant alterations.

On examination of the fundus by indirect ophthalmoscopy with scleral depression, multiple hypodense spots with a predominantly peripapillary distribution and drusen scattered in the temporal quadrant of the peripheral retina in both eyes were identified (Fig. 1).

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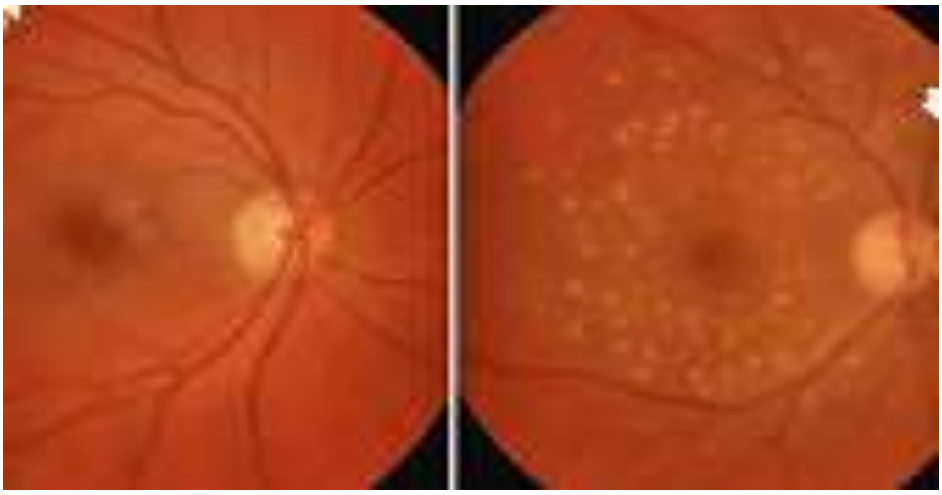

**Fig. 1** Image of the fundus examination using indirect ophthalmoscopy.

Spectral-domain optical coherence tomography confirmed the integrity of the retinal layers in the foveal region. Focal retinal thickening was detected in areas corresponding to some hypodense lesions, without evidence of clinically significant macular edema or slit-lamp abnormalities (Fig. 2).

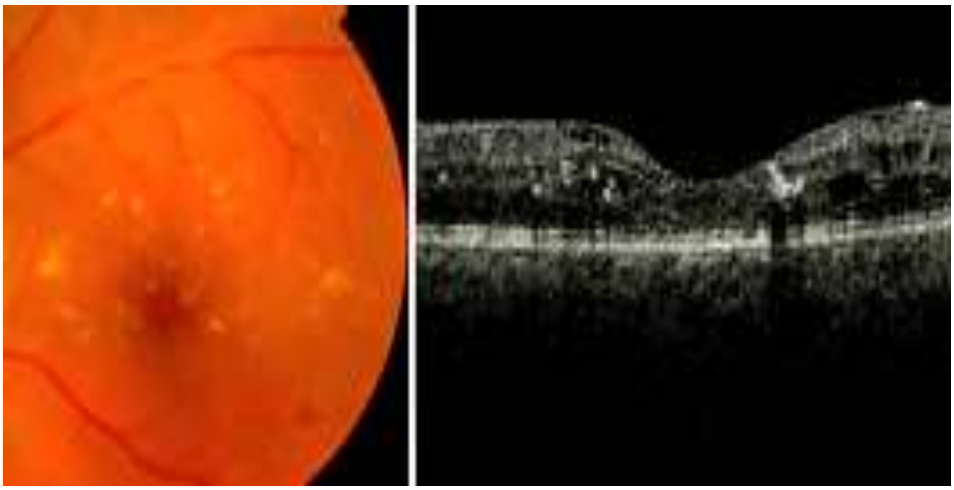

**Fig. 2** Spectral domain optical coherence tomography image.

Diagnosis: Tuberous sclerosis with atypical retinal manifestations (bilateral peripapillary hypodense spots and drusen).

Therapeutic management: Annual ophthalmological follow-up protocol using retinography and optical coherence tomography. No specific therapeutic intervention was indicated given the absence of significant visual impairment.

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## DISCUSSION

The present case illustrates an unusual ophthalmological presentation of Tuberous Sclerosis (TS), challenging the classic paradigm of its retinal manifestations.[6,7,8,9] While the most characteristic and widely reported findings are astrocytic hamartomas of the retina (AH) and hypopigmented maculae,[10,11] the patient in the present study exhibited a distinctive retinal phenotype, dominated by multiple peripapillary hypodense spots and the presence of scattered drusen in the peripheral retina.

The nature of these peripapillary hypodense spots deserves special consideration. Although hypopigmented maculae are common in ET, their predominant location is usually the mid and peripheral retina. The peripapillary clustering observed in this case is an atypical finding. Shields et al.,[7] described unusual retinal lesions in patients with ET in their case series, suggesting that the spectrum of retinal involvement is broader than classically recognized. They postulate that these lesions could represent mild or minimal forms of hamartomas, or focal dysplasias of the retinal pigment epithelium (RPE). The present OCT findings, which showed localized retinal thickening in corresponding areas, would support this latter hypothesis, indicating a subtle but defined structural alteration.[12,13]

Perhaps the most novel finding in this case is the presence of retinal drusen. Drusen are deposits of extracellular material that accumulate between the RPE and Bruch's membrane, a cardinal finding of age-related macular degeneration, but not an established feature of TD. Their identification here suggests possible RPE dysfunction and dysfunction of the complex chorioretinal interaction in the context of mTOR pathway dysfunction. The hamartin-tuberin protein, a product of the TSC1 and TSC2 genes, acts as a master regulator of cell proliferation and angiogenesis.[2,8] Dysregulation of the mTOR pathway could alter RPE metabolism and pumping function, favoring the accumulation of waste products and, ultimately, drusen formation.[7,9]

This raises the intriguing possibility that drusen in ET may be considered a type of "hamartoma" at the level of the RPE, thus expanding the spectrum of retinal lesions in this disease. Although the patient is young and currently asymptomatic, the presence of drusen suggests a potential long-term risk of RPE atrophy or even choroidal neovascularization, similar to the mechanisms seen in other RPE dystrophies.[11] Therefore, it warrants close follow-up with annual OCT to monitor for any changes that could compromise central vision in the future.

The patient's complete absence of symptoms and 20/20 visual acuity contrasts with cases of ET that present with large or localized HARs in the macula, which can cause significant visual loss.[2,10] This fact emphatically reinforces the need for systematic ophthalmological screening in all patients diagnosed with ET, regardless of their symptoms. A comprehensive examination, including indirect ophthalmoscopy with scleral depression to evaluate the retinal periphery, is crucial for identifying these subclinical manifestations.

From a broader pathophysiological perspective, these retinal alterations could be more than an isolated finding. Given the central role of the pathway in angiogenesis,[8,9] it is plausible that the documented retinal abnormalities act as early markers of systemic vascular involvement. The retina, due to its direct access to visualization, could offer a unique "window" for evaluating the microvasculature in patients with ET, providing clues about the state of vascular function in other organs, such as the kidney, where angiomyolipomas are a frequent complication. Future studies using optical coherence tomography angiography (OCTA) could help to better characterize the chorioretinal microvasculature in these patients and explore this hypothesis.[14]

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In the local context, this case takes on particular relevance. In Cuba, and specifically in the province of Pinar del Río, there are no previous reports in the indexed literature of a retinal presentation with these characteristics in a patient with Tuberous Sclerosis (TS).[3,5] The National Protocol for the Management of Tuberous Sclerosis, while a vital tool for standardizing care, does not routinely include OCT in the ophthalmological follow-up of these patients.[3] This case demonstrates that exclusive reliance on direct ophthalmoscopy could underestimate the prevalence of subtle structural retinal manifestations, such as localized thickening or the presence of drusen. Therefore, this report contributes to the local medical literature,[4,5] and serves as an argument for the potential updating of follow-up protocols, advocating for the integration of more sensitive imaging techniques such as OCT in the management of these patients, whenever resources allow.

## CONCLUSIONS

The retinal manifestations of tuberous sclerosis can extend beyond classic astrocytic hamartomas and include rare findings such as peripapillary hypodense spots and retinal drusen. Their identification suggests possible involvement of the retinal pigment epithelium linked to mTOR pathway dysregulation and warrants prolonged follow-up with optical coherence tomography. In this context, regular and comprehensive ophthalmological examinations, including evaluation of the peripheral retina and incorporation of structural imaging, are essential even in asymptomatic patients. This case represents the first report of this phenotypic association in Pinar del Río, Cuba, contributing national and international evidence and underscoring the importance of documenting atypical presentations to optimize the diagnosis and management of this complex disease.



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