

Utility of multimodal ocular imaging in tuberous sclerosis complex- Review of literature along with a case illustration

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Tuberous sclerosis complex (TSC) or Bourneville disease is a neurocutaneous (phacomatosis) disorder characterized by the development of multiple benign tumors of the embryonic ectoderm involving the skin, eyes, and nervous system. It is an autosomal dominant disorder and includes a triad of mental retardation, seizures, and facial angiofibroma.^[1] Among the ocular manifestations, retinal hamartomas (RH) constitute the commonest abnormality and are noted in 50–80% of patients. The commonest morphological form of RH is a flat, smooth, translucent lesion located in the superficial retina, mostly at the posterior pole.^[2-4] Others include retinal astrocytic hamartomas (RAH) which are classically described as “mulberry lesions” or “fish eggs” and show calcification. Transitional type is less common

and has a combination of features typical to the flat and multinodular astrocytic hamartomas.^[2,4] The flat-variety RHs are faint in color; these lesions can be subtle and therefore often missed on clinical examination.^[5] While most RHs in TSC are stationary, aggressive hamartomas with progressive growth can occur.^[6,7] Hence, retinal imaging may be required to identify these lesions and document their progression and growth. In this article, we discuss the retinal and choroidal imaging features in TSC with the help of a representative case example.

A 22-year-old mentally impaired male patient and a known case of TSC diagnosed since childhood was referred to the retina clinic for identifying RH by a general ophthalmologist. Patient was known hypertensive for 6 months and was well-controlled with antihypertensive medications. On general examination, patient had pigmented papules on the face, especially on the forehead, back of the neck, nasolabial folds, cheek, and chin, suggestive of facial angiofibromas or adenoma sebaceum (Fig. 1a and b). His best-corrected visual acuity in both eyes was 6/6, N6 with emmetropic refraction. Anterior segment examination and intraocular pressure in both eyes were normal. Right-eye fundus on clinical examination appeared normal. The left-eye fundus showed subtle, relatively flat, smooth-surfaced, semitransparent, oval-shaped lesions nasal to the optic disc and along the inferonasal arcade at the posterior pole located on the superficial retina. The fundus lesions were documented using Optomap (Daytona, Optos®, UK) ultra-widefield imaging system (Fig. 2a and b). On the blue-wavelength fundus autofluorescence image (FAF), the RH appeared as a mild-to-moderate hyporeflective lesion with ill-defined margins (Fig. 2c). Spectral domain optical coherence tomography (OCT) was performed using the Spectralis machine (Heidelberg Engineering, Heidelberg, Germany) through the macula and lesions in both eyes. The OCT scan through the nasal lesion showed a hyper-reflective, homogenous, elevated, fusiform lesion located on the superficial portion of the retinal layers with no underlying

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shadowing. The outer retinal layers and choroid were clearly visible on OCT (Fig. 3). The 30° Multicolor® imaging was performed with the Spectralis machine over the lesions. The nasal lesion appeared hyper-reflective on the blue (BR) and green reflectance (GR) images and was not visible on the infrared reflectance (IR) channel. The lesion on the composite multicolor image was identified as dull grey in color (Fig. 3). Along the inferonasal aspect of the fundus, on the IR channel image, four additional hyper-reflective lesions were identified. These lesions were not picked on the BR and GR channels. On the composite multicolor image, these lesions were seen as bright orange-colored lesions. These lesions were not visible on clinical examination or documented on the Optomap

image. On OCT, the lesions appeared flat, homogenous, and hyper-reflective involving the choroid, mainly the inner choroid with the overlying retinal pigment epithelium and retinal layers being intact. No elevation of the retinal pigment epithelium, subretinal fluid, orange pigment, or drusen was noted over the lesion. Due to shadowing, the choroidal vessels beneath the lesion were not seen when compared to the choroidal vessels surrounding the lesion (Fig. 4). This lesion is described as choroidal melanocytic hamartoma. No treatment was offered to the patient, and patient was asked to follow up after 6 months. Patient consent was obtained for publication purpose.

Discussion

RHs are detected in over 75% of confirmed cases of TSC and are currently listed as one of the major features in the revised clinical diagnostic criteria of TSC [Table 1].^[3] Three different patterns of RHs have been described in literature.^[4,5] The flat, translucent variety is the most common and is often missed on clinical examination.^[4,5] As per a population-based study by Rowley *et al.*, more than half of the cases diagnosed with TSC have an emmetropic refraction.^[2]



Figure 1: Adenoma sebaceum in tuberous sclerosis complex

Table 1: Revised diagnostic criteria for tuberous sclerosis complex

Major features	Minor features
Facial angiofibromas	Dental enamel pits
Periungual fibromas	Rectal polyps
Shagreen patch	Bone cysts
Retinal hamartomas	Gingival fibromas
Cortical tubers	Nonrenal hamartomas
Subependymal nodule	Retinal achromic patch
Cardiac rhabdomyoma	Confetti skin lesions
Renal angiomyolipoma	Renal cyst
	Cerebral cortical dysplasia

Definite diagnosis: One major and two minor features. Probable diagnosis: One major and one minor feature. Possible diagnosis: One major or two or more minor features

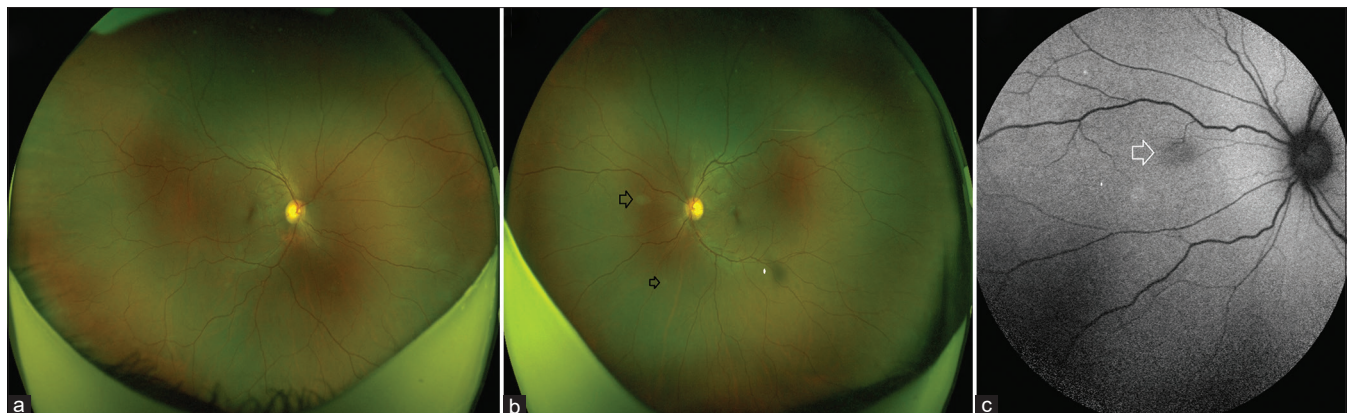


Figure 2: Color fundus photographs of both eyes of a patient diagnosed with tuberous sclerosis complex using the Optos®, Daytona ultra-widefield camera: (a and b) Optomap images of both eyes using the Optos®, Daytona machine. The right eye does not show any visible retinal hamartoma lesions. The left-eye Optomap image identifies the retinal hamartoma as a subtle, relatively flat, smooth-surfaced, semitransparent, oval-shaped lesion nasal to the optic disc and along the inferonasal arcade at the posterior pole located on the superficial retina (black arrows). (c) Short-wavelength autofluorescence image identifies the nasal tumor as a hypofluorescent lesion with poorly defined margins (white arrow)

OCT is a commonly available imaging tool used for identifying the RHs, especially those located at the posterior pole. The characteristic OCT features are also useful in identifying the different types of RH lesions. The flat translucent RH lesion is identified on OCT as an hyper-reflective fusiform lesion located in the superficial most portion of the retina without underlying retinal layer disorganization or posterior shadowing.^[8] The RAH shows characteristic features on OCT, including a gradual transition from a normal retina into an optically hyper-reflective mass with retinal layer disorganization, characteristic moth-eaten spaces, and posterior shadowing due to calcification.^[9] In our case example, the OCT showed features of flat variety of RH.

On histology, astrocytic hamartomas are composed of a network of glial astrocytes and blood vessels and contain hyaline and calcium deposits that are basophilic.^[10] On the FAF, RAH shows dense hyper-autofluorescent spots due to calcification in the lesion.^[11] Whereas the flat, translucent lesions

appear hypoautofluorescent with ill-defined margins due to the lack of calcium within the lesion. Thus, the FAF is a useful noninvasive imaging modality for differentiating between types of RHs in TSC cases.

Multicolour® imaging has the ability to identify lesions at different levels of the retina and choroid due to the three different wavelengths of laser light it uses.^[12] The flat, translucent lesion without calcification is identified as a moderately hyper-reflective lesion on the BR and GR channels and not on the IR channel. Goel *et al.* reported the multicolor imaging findings in a patient with RAH.^[13] On the BR and GR channels, multiple hyper-reflective dots were observed corresponding to the calcification within the lesion. On the IR channel, the tumor appeared hyporeflective with well-defined margins. Thus, Multicolour® imaging is a useful imaging tool to differentiate between the different types of RHs. In addition, we identified choroidal hamartomas on Multicolour® imaging and OCT in our case. The choroidal hamartoma was barely visible on clinical

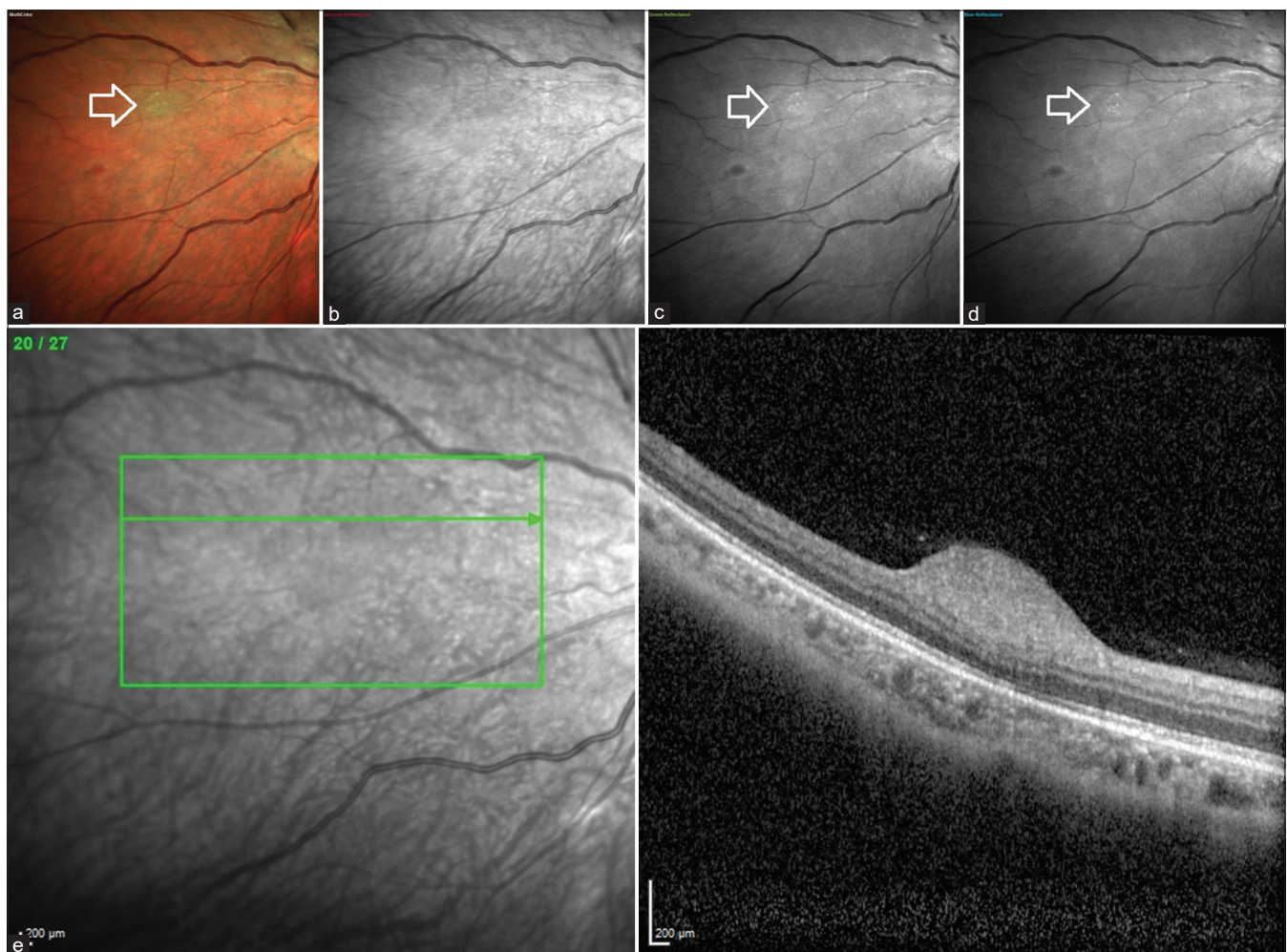


Figure 3: Multicolour® imaging and corresponding optical coherence tomography (OCT) image through the lesion nasal to the optic disc: (a-d) On the Multicolour® imaging, the nasal lesion appears hyper-reflective on the blue and green reflectance images and not visible on the infrared reflectance channel. The lesion on the composite multicolor image was identified as dull grey in color (white arrows). (e) The OCT scan through the nasal lesion showed a hyper-reflective, homogenous, elevated, fusiform lesion located on the superficial portion of the retinal layers with no underlying shadowing. The outer retinal layers and choroid were clearly visible on OCT. These features were suggestive of retinal hamartoma

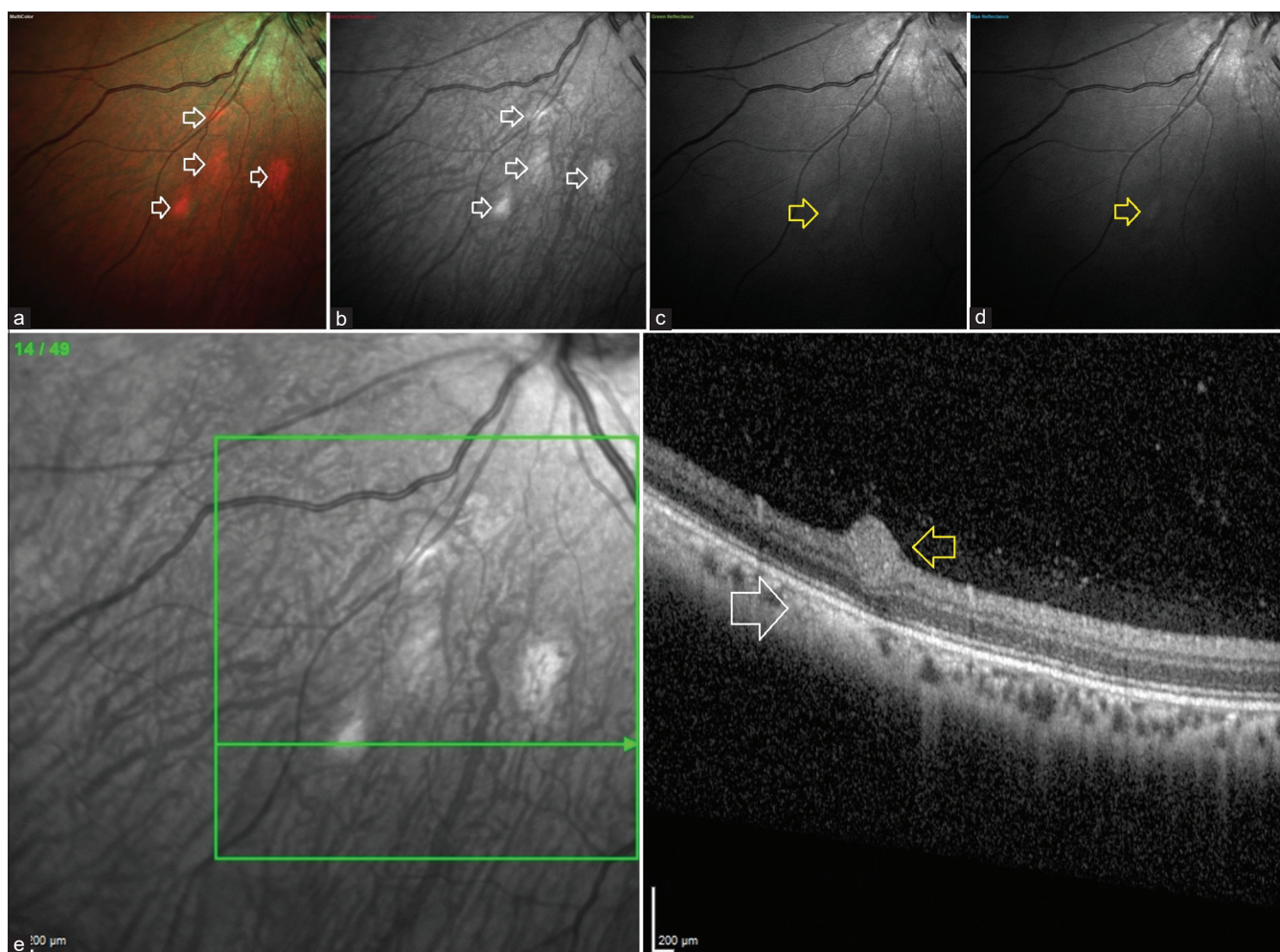


Figure 4: Multicolour® imaging and corresponding optical coherence tomography (OCT) image through the lesion on the inferonasal aspect of the optic disc: (a-d): Along the inferonasal aspect of the optic disc, on the infrared reflectance channel image, four additional hyper-reflective lesions are identified that are barely visible on clinical examination. These lesions are not seen on the blue and green reflectance channels. On the composite multicolor image, these lesions are seen as bright orange-colored lesions (white arrows). On the blue and green reflectance image, a single moderately reflective lesion is identified along the inferonasal quadrant (yellow arrow). (e) On OCT, lesions at two different levels are being identified. The first lesion is located on the superficial retina and identified on the blue and green reflectance images suggestive of retinal hamartoma (yellow arrow). The other lesion is a flat, homogenous, and hyper-reflective lesion involving the choroid, mainly the inner choroid with the overlying retinal pigment epithelium and retinal layers being intact. No elevation of the retinal pigment epithelium, subretinal fluid, orange pigment, or drusen is noted over the lesion. Due to shadowing, the choroidal vessels beneath the lesion were not seen when compared to the choroidal vessels surrounding the lesion (white arrow). This lesion is described as choroidal melanocytic hamartoma. As both lesions are located in the same meridian, one below the other, the Multicolour® imaging helps in differentiating between the retinal and choroidal hamartomas

Table 2: Differences between conventional color fundus photography and Multicolour® imaging in TSC

Features	Conventional color fundus photography	Multicolour® imaging
Image type	True image	Pseudo image
Type of imaging system	Camera-based flash system	Confocal scanning laser ophthalmoscopy
Wavelength of light	Visible spectrum	Blue, green, and infrared wavelength
Retinal hamartomas	Seen	Seen on blue and green reflectance channels
Choroidal hamartomas	Barely seen	Clearly seen on infrared reflectance channel

examination or documented on color fundus photographs, and the multicolor image made the lesion more obviously visible. Based on the characteristics on Multicolour® imaging, it is possible to conclude that the lesion probably consisted of

an aggregation of choroidal melanocytic cells that absorb the shorter wavelengths of light and reflect higher-wavelength light.^[14,15] Hence, the lesion is evidently visible on the IR channel and on the composite multicolor image [Table 2].

In this article, we describe the imaging features of RH with different imaging techniques. Also, we emphasize on the utility of Multicolour® imaging in the identification of hamartomas in the retina and choroid in TSC. Also, to the best of our knowledge, presence of choroidal melanocytic hamartomas in TSC has not been previously described in literature.

To conclude, noninvasive imaging modalities such as OCT, FAF, and Multicolour® imaging are useful for differentiating between the different patterns of RHs in TSC. In addition, choroidal melanocytic hamartomas can be seen in TSC which are best identified on the Multicolour® imaging.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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