JAMA Ophthalmology Clinical Challenge

Unilateral Exudative Retinal Lesion in a Previously Healthy Female Teenager

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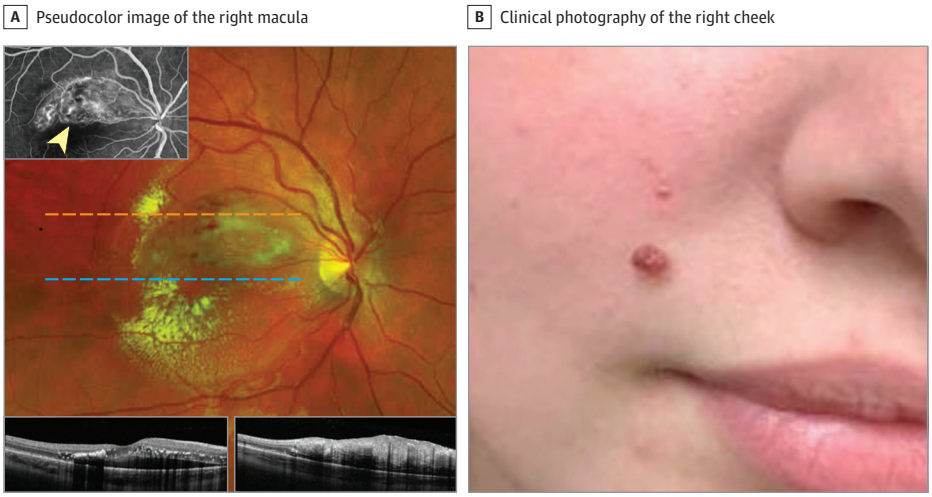

Figure. Features of tuberous sclerosis complex. A, An area of superior macular whitening following the superior arterial arcade with associated intraretinal hemorrhages and exudate. Two optical coherence tomography line scans inset through the main lesion (orange) and through the fovea (blue) with relative location marked with dotted lines, demonstrating disorganized and hyperreflective inner retinal thickening consistent with type 1 astrocytic hamartoma of the retina and associated macular edema. Arrowhead indicates bulblike telangiectasis on fluorescein angiography and blocking from intraretinal hemorrhage. B, Elevated papule. The lesion is a well-demarcated, exophytic, brownish-red vascular papule with an irregular surface.

A 15-year-old girl presented with a 2-month history of decreased vision and a dark spot in the central vision in her right eye. She had a history of optometric examinations with no known ocular disease. Visual acuity with correction was 20/40 in the right eye and 20/20 in the left eye. Anterior segment examination of both eyes was unremarkable, and the retina in the left eye appeared normal. In the right eye, there was an area of superior macular whitening with associated intraretinal hemorrhages and exudates. Fluorescein angiography showed abnormally dilated and tortuous retinal vessels, irregular capillary branching patterns, and bulblike telangiectasis with late leakage in the superior macula. Optical coherence tomography showed disorganized and hyperreflective inner retinal thickening (**Figure**, A) and intraretinal and subretinal fluid in the central macula. On review of systems, the patient noted a long-standing growth on her cheek, which on examination was a 4 × 3-mm exophytic, brownish-red vascular papule (Figure, B), as well as a history of lightly pigmented patches of skin and multiple subungual fibromas on her toes. Systemic blood pressure was normal.

WHAT WOULD YOU DO NEXT?

- **A.** Initiate anti–vascular endothelial growth factor treatment
- **B.** Order brain magnetic resonance imaging to look for associated central nervous system tumors
- **C.** Perform hypercoagulable workup
- **D.** Order echocardiogram and carotid ultrasonography

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Diagnosis

Astrocytic hamartoma (with secondary branch retinal vein occlusion) associated with tuberous sclerosis complex

What to Do Next

B. Order brain magnetic resonance imaging to look for associated central nervous system tumors

Discussion

Astrocytic hamartomas of the retina (AHR) are benign tumors that can be associated with tuberous sclerosis complex (TSC). TSC is a phacomatosis with neurocutaneous manifestations characterized by multiple tumors of the embryonic ectoderm involving skin, eyes, and nervous systems.[1] Hamartomas of the retina are part of the major features for the diagnosis of TSC.[2]

The clinical diagnostic criteria for TSC include 11 major and 7 minor features. Major features are 3 or more hypomelanotic macules at least 5 mm in diameter, 3 or more angiofibromas or fibrous cephalic plaques, 2 or more ungual fibromas, shagreen patch (a large nevus with irregular, firm plaquelike features typical of TSC), multiple retinal hamartomas, multiple cortical tubers or radial migration lines, 2 or more subependymal nodules, subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangioleiomyomatosis, and 2 or more angiomyolipomas. Minor features of TSC are 1- to 2-mm hypomelanotic macules, also known as confetti skin lesions; 3 or more dental enamel pits; 2 or more intraoral fibromas; retinal achromic patch; multiple renal cysts; nonrenal hamartomas; and sclerotic bone lesions.

The diagnostic certainty of TSC depends on the number of major and minor features. Definite TSC requires 2 major features or 1 major and 2 or more minor features. Possible TSC requires either 1 major feature or 2 or more minor features.[3] Genetic testing is also available, and the identification of either a TSC1 or TSC2 pathogenic variant from nonlesional tissue is sufficient to make a definite diagnosis of TSC regardless of clinical findings.[3]

History should be obtained and focused physical examination is recommended for skin and the central nervous system. The association between TSC and astrocytic hamartoma can be observed in up to half of patients with TSC.[2] There are several phenotypes of astrocytic hamartoma associated with TSC, including slow-growing flat lesions (similar to that observed in this patient), as well as more aggressive, rapidly growing tumors that can lead to enucleation.[2] Histology shows that astrocytic hamartomas are composed of glial astrocytes and blood vessels with hyaline and calcium deposits.[4]

If TSC is suspected, the primary concern must be initiating the systemic workup with neuroimaging (choice B), as the central nervous system manifestations of TSC can be life threatening. Secondarily, treatment for the ophthalmic complications of the disease can be considered, such as with anti–vascular endothelial growth factor (anti-VEGF) medications for secondary exudation (choice A).[5] Retinal hamartomas are not typically associated with a hypercoagulable state or cardiac concerns (choices C and D).

Patient Outcome

The patient was referred for neuroimaging, which revealed multiple subcortical tubers and lateral ventricle subependymomas consistent with the diagnosis of TSC. Genetic testing revealed a pathogenic variant in the TSC1 gene labeled c.733C>T(p.R245*), which is most commonly a de novo variant. Excisional biopsy of the facial lesion was consistent with angiofibroma, a benign cutaneous hamartoma frequently found in tuberous sclerosis complex. Because the central nervous system lesions were asymptomatic, the patient was referred for annual imaging and observation in pediatric neurology.

Retinal hamartomas are classified into 3 morphological subtypes. Type 1 AHR is the most common and is characterized by flat and smooth lesions semitransparent without calcifications. Type 2 AHR lesions are raised, multinodular, opaque, and with calcification. Type 3 AHR lesions are transitional lesions with features of types 1 and 2.[6]

Treatment of AHR lesions is determined on a case-by-case basis. Photodynamic therapy, laser, radiation, and anti-VEGF have been described.[7] Due to the secondary exudation and hemorrhages consistent with a small branch retinal vein occlusion with edema affecting the central macula, we performed a systemic hypercoagulable workup, which was unrevealing. Because the exudation affected the central macula, we started treatment with intravitreal anti-VEGF to treat the macular edema. Two years later, the patient was stable with visual acuity 20/25 in the affected eye but has required monthly treatment with worsening edema and vision with an attempted treat-and-extend strategy. The tumor slowly expanded for the first year but was stable for the following year.

ARTICLE INFORMATION

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