American Journal of Ophthalmology Case Reports 36 (2024) 102217

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Ovoid foveal hyperreflective lesions as a sign of familial adenomatous polyposis: A case series and review

Serena Shah, Francisco Lopez-Font, Davina Malek, Jason Fan, Natasha Ferreira Santos da Cruz, Catherin Negron, Basil K. Williams Jr., Audina M. Berrocal *

Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, 900 NW 17 Street, Miami, FL 33136, USA

ARTICLE INFO

Keywords:
Familial adenomatous polyposis
Optical coherence tomography angiography
Retinal astrocytic hamartoma

ABSTRACT

Purpose: To report 2 cases of presumed retinal hamartoma (RH) in pediatric patients with genetically-confirmed familial adenomatous polyposis (FAP), both evaluated by optical coherence tomography (OCT) and one evaluated with optical coherence tomography angiography (OCTA).

Observations: A six-year-old girl presented with occasional blurry vision in the left eye. OCT showed a foveal hyperreflective lesion with disruption of photoreceptors and retinal pigment epithelium (RPE). A nine-year-old female with a past medical history of FAP presented with progressively decreasing vision and floaters in the right eye for the past 6 months. OCT showed a well-demarcated hyperreflective ovoid lesion in the fovea. OCTA revealed no flow signal within the lesion, as well as a second smaller hyperreflective lesion temporal to the fovea. Both patients were diagnosed with presumed retinal hamartoma in the setting of FAP.

Conclusions and Importance: Presumed RH can occur in genetically-confirmed, pediatric FAP. On OCTA imaging, these lesions show no intrinsic vascularity. Evaluation with OCT and knowledge of foveal changes in these patients can help identify underlying systemic disease.

1. Introduction

Familial adenomatous polyposis (FAP) is an autosomal dominant condition[1] in which up to hundreds of adenomatous polyps are present in the colon and rectum.[2] These polyps have malignant potential, and if left untreated, may lead to colorectal carcinoma as early as the fourth decade of life.[1] Therefore, patients are prophylactically treated with total colectomy.[2] Variants responsible for this condition occur within the *APC* gene, which is localized to the long arm of chromosome 5 (5q21-q22).[3]

Extracolonic manifestations of FAP suggest a diagnosis of Gardner's syndrome.[4,5] These may include benign or malignant pancreatic, thyroid, and cerebral soft tissue tumors, desmoid tumors, and malignant tumors in the duodenum, liver, adrenal glands, and around the ampulla of Vader.[6,7] Approximately 70 % of patients with Gardner's syndrome have pigmented ocular fundus lesions (POFLs), which appear as atypical congenital hypertrophy of retinal pigment epithelium (CHRPE), but their presence has high specificity.[8–10] POFLs are usually oval-shaped and have tail-like extensions that can be depigmented and contain lacunae.[11] In general, detection of four or more POFLs is a strong indicator of FAP.[10] However, POFLs have also been associated with Turcot Syndrome, a rare hereditary disorder characterized by adenomatous colorectal polyps, colonic adenocarcinoma, and central nervous system tumors.[12]

A retinal astrocytic hamartoma (RAH) is a benign, glial cell growth that is usually flat, round, and transparent, and can grow into nodular structures with calcification and hard exudates.[11,13–15]

We describe two cases of presumed retinal hamartoma (RH), one with and one without accompanying POFLs, in two pediatric patients with genetically confirmed FAP, both evaluated with optical coherence tomography (OCT) and one evaluated with optical coherence tomography angiography (OCTA).

2. Case 1

A 6-year-old female with no past ocular history presented to a retina specialist via referral from a local ophthalmologist due to occasional blurry vision and a macular lesion in the left eye. The patient was born full-term. Visual acuity (VA) was 20/20 in the right eye and 20/25 with eccentric fixation and trace exophoria in the left eye.

* Corresponding author. 900 NW 17th Street, Miami, FL 33136, USA.
E-mail address: aberrocal@med.miami.edu (A.M. Berrocal).

https://doi.org/10.1016/j.ajoc.2024.102217
Received 27 March 2024; Received in revised form 13 October 2024; Accepted 30 October 2024
Available online 1 November 2024

An exam under anesthesia was performed. Intraocular pressures were 13 mmHg in the right eye and 16 mmHg in the left eye. Axial length was 24.17 mm in the right eye and 23.8 mm in the left eye, which is normal given the patient's age.[16] Anterior segment exam revealed an enlarged right corneal nerve in the right eye. Fundus examination revealed two, small, flat, lesions along the arcades, one located superiorly and one located inferior to the disc, consistent with POFLs in the right eye (Fig. 1A). An intraretinal lesion, approximately a quarter disc in size, and an epiretinal membrane were noted in the left eye (Fig. 1B). Due to the presence of the multifocal, bright, pinpoint hyperreflective areas, the intraretinal lesion in the left eye was classified as a presumed retinal hamartoma. B-scan revealed no retinal detachments or calcifications. Fluorescein angiography (FA) showed small hyperfluorescent lesions and leakage in the macula in the left eye (Fig. 1C). OCT showed that the presumed RH in the left eye also had disruption of photoreceptors and retinal pigment epithelium (RPE), but foveal contour was intact, and no cystoid macular edema was present (Fig. 1D).

Upon further questioning, the family revealed that they had a strong family history of colon cancer occurring at a young age. This propelled the establishment of a working diagnosis of FAP, which was confirmed by genetic testing from an outside facility that revealed a deleterious mutation in exon 15 of the *APC* gene on chromosome 5q15.

Eight years after initial presentation, the patient reported that she had over 200 colonic polyps recently identified by her colorectal surgeon. At the last follow-up appointment, final VA was 20/15 in the right eye and 20/30 in the left eye.

3. Case 2

A nine-year-old female presented with progressively decreased vision in the right eye and headaches for 6 months. The patient had a family and past medical history of FAP, confirmed by genetic testing using the OncoGeneDx Panel, which revealed a likely pathogenic variant in the *APC* gene (c.645+1G > A) (GeneDx, Connecticut, USA; CLIA certified). The patient had been born full-term without complications and had no history of infectious or inflammatory conditions prior to presentation. VA was 20/150 in the right eye and 20/20 in the left eye.

An exam under anesthesia was performed. Intraocular pressures were 18 mmHg in the right eye and 19 mmHg in the left eye. Axial length was 23.5 mm in the right eye and 24.1 mm in the left eye, which is normal for the patient's age.[16] Anterior segment exam was unremarkable in both eyes with corneal diameters measuring 12 mm. Fundus exam in the right eye revealed superior peripapillary atrophy around the disc, a small hypopigmented lesion in the fovea, peripheral scattered hypopigmented changes in the posterior pole, and no vessel sheathing (Fig. 2A and B). B-scan revealed normal posterior contour in both eyes. FA showed staining at the disc, macula, and periphery around the hypopigmented lesions with no vascular or disc leakage in the right eye (Fig. 2C and D). OCT in the right eye showed a well demarcated hyperreflective ovoid lesion in the fovea with small areas of intrinsic high reflectivity and posterior shadowing, findings consistent with a presumed RH (Fig. 2E). OCTA in the right eye showed a discrete hyperreflective lesion in the nasal region of the fovea and no flow signal, as well as a second smaller hyperreflective lesion in the temporal region of the fovea that is better appreciated in the structural en face image (Fig. 2F) and OCTA deep capillary plexus (DCP) image (Fig. 2G). The left eye was unremarkable on clinical examination and multimodal imaging (Fig. 2H and I).

Due to concern for inherited retinal disease, further investigation with the Invitae Inherited Retinal Disorders Panel (Invitae Corporation, San Francisco, USA; CLIA certified) was conducted. Results were unremarkable.

Similarly to the previous case, based on the hyperreflective appearance clinically and the multifocal, particularly bright, pinpoint hyperreflective portions of the lesion, the patient was diagnosed with a presumed RH in the setting of FAP. Observation was recommended.

4. Discussion

Three morphological subtypes of RAH have been described.[17,18] Type 1 lesions are the most common and are relatively flat, smooth, semitransparent, and grey-white colored without calcification.[17,18] Type 2 lesions are raised, multinodular ("mulberry-like"), opaque, and calcified.[17,18] Type 3 lesions are transitional with features of both Type 1 and Type 2 lesions.[17,18] Lesions usually remain stable and do not evolve from one subtype to another.[17] RAHs are most frequently associated with tuberous sclerosis complex, but can be associated with other conditions such as neurofibromatosis, Usher syndrome, Stargardt disease, and gyrate atrophy or present idiopathically.[17–21]

Regarding pathophysiology, *APC* encodes the APC protein, which serves as a tumor suppressor gene product that promotes apoptosis of colonic epithelial cells.[22] Therefore, it is plausible that because mutations in *APC* result in the formation of colonic polyps, they could also result in overgrowth of cells in other tissues, such as the retina, leading to the formation of retinal hamartoma-like lesions such as those observed in our cases.

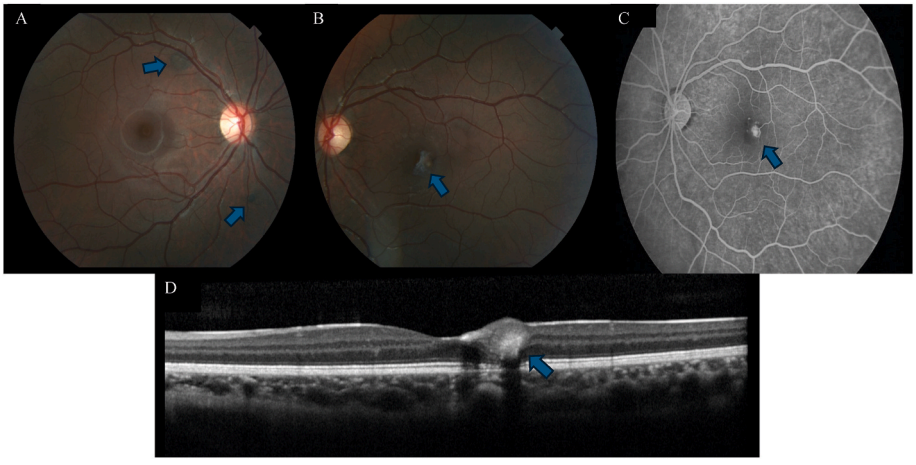

Fig. 1. (A) Fundus photography shows two, small, flat, pigmented ocular fundus lesions (POFLs) along the arcades, one located superiorly and one located inferior to the disc, in the right eye. (B) Fundus photography shows a presumed retinal hamartoma (RH), approximately a quarter disc in size, in the left eye. (C) Fluorescein angiography (FA) shows small hyperfluorescent lesions and leakage in the macula in the left eye. (D) OCT shows normal foveal contour and disruption of photoreceptors and retinal pigment epithelium (RPE) in the presumed RH in the left eye.

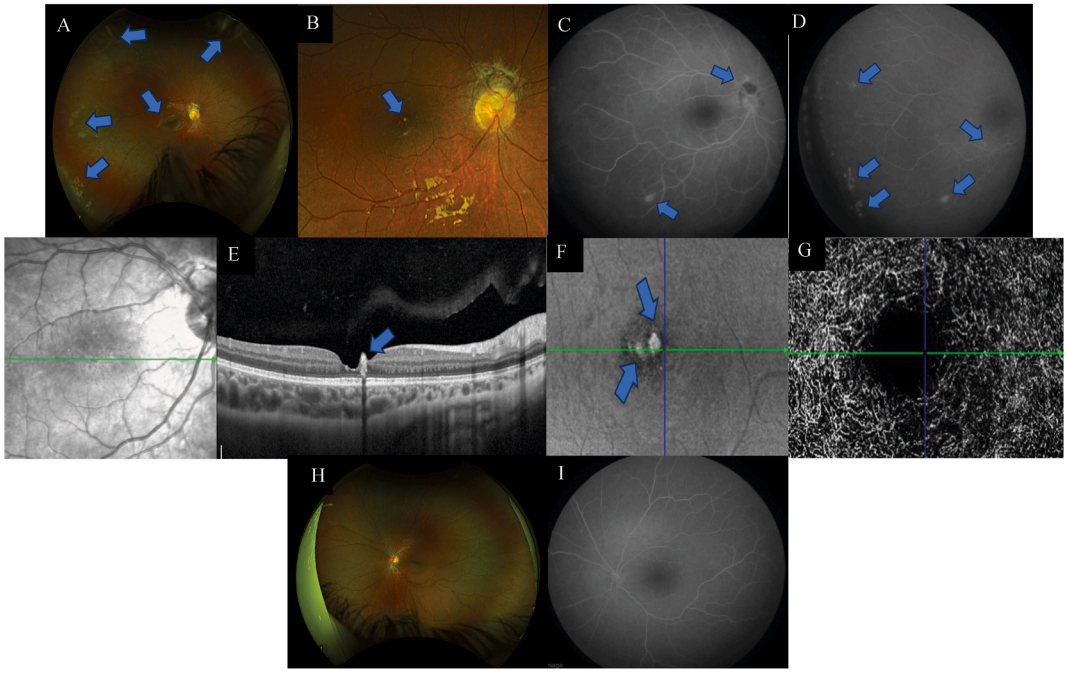

Fig. 2. (A, B) Fundus photography shows superior peripapillary atrophy around the disc, a small hypopigmented lesion in the fovea, peripheral scattered hypopigmented changes in the posterior pole, and no vessel sheathing in the right eye. (C, D) Fluorescein angiography (FA) shows staining at the disc, macula, and periphery around the lesions with no clear vascular or disc leakage in the right eye. (E) Optical coherence tomography (OCT) shows a well demarcated ovoid lesion in the fovea in the right eye. (F, G) Optical coherence tomography angiography (OCTA) of the deep capillary plexus (DCP) shows a discrete hyperreflective lesion in the nasal region of the fovea without flow signal, as well as a second smaller hyperreflective lesion in the temporal region of the fovea in the right eye. (H, I) Fundus photography and FA is unremarkable in the left eye.

OCT imaging of RAH show that these tumors are localized to the retinal nerve fiber layer (RNFL) and sometimes possess cavitations.[23] OCT imaging of our patients' lesions showed a possible origin within the RNFL, more so in Case 1 rather than in Case 2, as well as multiple small hyper reflective foci within it consistent with calcifications but not cavitations. Also, because our lesions seem to arise from the fovea, it is difficult to determine if they are continuous with the RNFL. The challenging diagnosis of these lesions perhaps highlights the importance of obtaining OCT imaging in patients with FAP to investigate for the presence of presumed, small RHs.

On OCTA evaluation, RAHs have a dense intralesional vascular network in both the superficial and deep plexi[24] with flow voids correlating to areas of cavitations.[25,26] Specifically, the pattern of flow within lesions with cavitations has been described as "honeycomb-like."[27] OCTA evaluation of a Type 2 RAH in the setting of gyrate atrophy revealed obvious blood vessels and hyporeflective spaces within the lesion.[28] Yung et al. reported that Type I RAHs show a central feeder vessel and an intrinsic abnormal vascular plexus.[29] The lesion in the second case, which seems to be most consistent with a compact Type 2 lesion with elevation and intrinsic hyperreflectivities that are likely areas of calcification, did not demonstrate these described findings. Instead, the patient's lesion was a discrete hyperreflective lesion that lacked flow signal most likely due to the areas of calcification. Further studies are warranted to characterize the spectrum of presumed RH lesions in FAP.

The most well-described ocular manifestation of FAP is the POFL, an atypical congenital hamartoma of the RPE which usually appears as a small (<1mm), bilateral, ovoid, benign, flat, and variegated lesion.[8,30] They often possess a tail of depigmentation toward the optic nerve and are usually located at the equator and midperiphery.[8,30] Multimodal imaging has been used to evaluate POFLs.[31] FA shows blocked choroidal fluorescence with window defects in depigmented areas and telangiectatic dilations that appear hyperfluorescent.[31] Fundus autofluorescence (FAF) shows hypo-autofluorescence in the area of the lesion, and OCT shows outer retinal attenuation with a thickened RPE.[31] This is in contrast to this patient's lesion, which appears to be a retinal hamartoma with posterior shadowing secondary to presumed calcification similar to the report by Venincasa et al.[30]

Other pigmented retinal lesions differ from RAH in that they all usually show some degree of flow or change in vascular density when evaluated with OCTA. For example, OCTA shows reduced vascular density in the superficial capillary plexus (SCP) and increased density in the DCP in POFLs.[31] Torpedo lesions show attenuation of signal in the deep vascular layers along the lesion with loss of deep vessels in the subretinal gap, diffuse attenuation of the choriocapillaris, and decreased flow in the area of the subretinal cleft correlated with hyperreflectivity in the tail on OCTA.[32,33] These features were not found in the presumed RH lesion described in our case. Therefore, the OCTA findings found in our case suggest that our lesion is atypical compared to other RAHs, and OCTA is not the best modality to differentiate these lesions. Instead, clinical appearance and OCT evaluation should be sufficient.

5. Conclusions

Presumed RH lesions can occur in genetically-confirmed, pediatric FAP. Evaluation with OCTA may not show involvement of the retinal vasculature or intrinsic vascularity. Careful evaluation with OCT along with knowledge of changes such as these in the fovea can help identify correct underlying systemic disease.

CRediT authorship contribution statement

Serena Shah: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Francisco Lopez-Font:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Davina Malek:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data

curation. **Jason Fan:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Natasha Ferreira Santos da Cruz:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation. **Catherin Negron:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation. **Basil K. Williams:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis. **Audina M. Berrocal:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Patient consent

Written consent to publish this case series has not been obtained. This case series does not contain any personal identifying information. IRB approval waived.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship and agree to the listed order on the title page.

Funding

Research supported in part by Research to Prevent Blindness (Unrestricted Grant) (New York, New York), NIH Center Core (Grant P30EY014801) (Bethesda, Maryland), and Department of Defense (Grant #W81XWH-09-1-0675) (Washington, D.C.). The sponsor or funding organization had no role in the design or conduct of this study.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: ***Disclosures and Conflicts of Interest*:** Serena Shah, Francisco Lopez-Font, Davina Malek, Jason Fan, Natasha Ferreira Santos da Cruz, and Catherin Negron have no conflicts of interest to disclosure. Basil K. Williams Jr. is a consultant for Alcon, Allergan, Alimera, Astellas, Castle Biosciences, EyePoint Pharmaceuticals, Genentech, Immunocore, and Regeneron and he has stock options with Lumata Health. Audina M. Berrocal is a consultant for Alcon, Allergan, Zeiss, Dutch Ophthalmic Research Center, Novartis, ProQR, and Oculus.

Acknowledgements

The authors thank Giselle de Oliveira, BFA and Senior Ophthalmic Photographer, for images.

References

1. Groen EJ, Roos A, Muntinghe FL, et al. Extra-Intestinal manifestations of familial adenomatous polyposis. *Ann Surg Oncol*. 2008;15(9):2439–2450. https://doi.org/10.1245/s10434-008-9981-3.
2. Tiret A, Taiel-Sartral M, Tiret E, Laroche L. Diagnostic value of fundus examination in familial adenomatous polyposis. *Br J Ophthalmol*. 1997;81(9):755–758. https://doi.org/10.1136/bjo.81.9.755.
3. Kinzler KW, Nilbert MC, Su LK, et al. Identification of FAP locus genes from chromosome 5q21. *Science*. 1979;253(5020):661–665. https://doi.org/10.1126/science.1651562, 1991.
4. Gardner EJ. A genetic and clinical study of intestinal polyposis, a predisposing factor for carcinoma of the colon and rectum. *Am J Hum Genet*. 1951;3(2):167–176.
5. Gardner EJ. Follow-up study of a family group exhibiting dominant inheritance for a syndrome including intestinal polyps, osteomas, fibromas and epidermal cysts. *Am J Hum Genet*. 1962;14(4):376–390.
6. Perniciaro C. Gardner's syndrome. *Dermatol Clin*. 1995;13(1):51–56.
7. Charifa A, Jamil RT, Zhang X. *Gardner Syndrome*. 2024.
8. Villegas VM, Schwartz SG, Flynn HW, et al. Distinguishing torpedo maculopathy from similar lesions of the posterior segment. *Ophtha Surg Lasers Imagi Retina*. 2014;45(3):222–226. https://doi.org/10.3928/23258160-20140410-01.
9. Traboulsi E. Ocular manifestations of familial adenomatous polyposis (gardner syndrome). *Ophthalmol Clin North Am*. 2005;18(1):163–166. https://doi.org/10.1016/j.ohc.2004.08.003.
10. Shields JA, Shields CL, Shah PG, Pastore DJ, Imperiale SM. Lack of association among typical congenital hypertrophy of the retinal pigment epithelium, adenomatous polyposis, and gardner syndrome. *Ophthalmology*. 1992;99(11):1709–1713. https://doi.org/10.1016/S0161-6420(92)31736-1.
11. Mirzayev I, Gündüz AK. Hamartomas of the retina and optic disc. *Turk J Ophthalmol*. 2022;52(6):421–431. https://doi.org/10.4274/tjo.galenos.2022.25979.
12. Munden PM, Sobol WM, Weingeist TA. Ocular findings in Turcot syndrome (glioma-polyposis). *Ophthalmology*. 1991;98(1):111–114. https://doi.org/10.1016/S0161-6420(91)32354-6.
13. Zimmer-Galler IE, Robertson DM. Long-term observation of retinal lesions in tuberous sclerosis. *Am J Ophthalmol*. 1995;119(3):318–324. https://doi.org/10.1016/S0002-9394(14)71174-2.
14. Nyboer JanH, Robertson DM, Gomez MR. Retinal lesions in tuberous sclerosis. *Arch Ophthalmol*. 1976;94(8):1277–1280. https://doi.org/10.1001/archopht.1976.03910040149003.
15. Giles J, Singh AD, Rundle PA, Noe KP, Rennie IG. Retinal astrocytic hamartoma with exudation. *Eye*. 2005;19(6):724–725. https://doi.org/10.1038/sj.eye.6701627.
16. Fledelius HC, Christensen AS, Fledelius C. Juvenile eye growth, when completed? An evaluation based on IOL-Master axial length data, cross-sectional and longitudinal. *Acta Ophthalmol*. 2014;92(3):259–264. https://doi.org/10.1111/aos.12107.
17. Rowley SA. Ophthalmic manifestations of tuberous sclerosis: a population based study. *Br J Ophthalmol*. 2001;85(4):420–423. https://doi.org/10.1136/bjo.85.4.420.
18. Mennel S, Meyer CH, Eggarter F, Peter S. Autofluorescence and angiographic findings of retinal astrocytic hamartomas in tuberous sclerosis. *Ophthalmologica*. 2005;219(6):350–356. https://doi.org/10.1159/000088377.
19. Kiratli H, Türkçüoğlu P, Bilgiç S. Gyrate atrophy associated with astrocytic hamartoma of the optic disc. *Retina*. 2004;24(6):976–977. https://doi.org/10.1097/00006982-200412000-00025.
20. Awan KJ. Presumed glial retinal hamartomas in Usher's syndrome. *Can J Ophthalmol*. 1976;11(3):258–260.
21. Bini A, Sodi A, Passerini I, Menchini U, Torricelli F. Retinal astrocytic hamartoma and Stargardt's disease: unusual association in a patient with ABCR mutation without phacomatosis. *Clin Exp Ophthalmol*. 2007;35(8):777–779. https://doi.org/10.1111/j.1442-9071.2007.01582.x.
22. Aghabozorgi AS, Bahreyni A, Soleimani A, et al. Role of adenomatous polyposis coli (APC) gene mutations in the pathogenesis of colorectal cancer; current status and perspectives. *Biochimie*. 2019;157:64–71. https://doi.org/10.1016/j.biochi.2018.11.003.
23. Shields CL, Say EAT, Fuller T, Arora S, Samara WA, Shields JA. Retinal astrocytic hamartoma arises in nerve fiber layer and shows "moth-eaten" optically empty spaces on optical coherence tomography. *Ophthalmology*. 2016;123(8):1809–1816. https://doi.org/10.1016/j.ophtha.2016.04.011.
24. Despréaux R, Mrejen S, Quentel G, Cohen SY. EN face optical coherence tomography (OCT) and OCT angiography findings in retinal astrocytic hamartomas. *Retin Cases Brief Rep*. 2017;11(4):373–379. https://doi.org/10.1097/ICB.0000000000000374.
25. Gündüz AK, Mirzayev I, Kasimoglu R, Özalp Ateş FS. Swept-source optical coherence tomography angiography findings in choroidal and retinal tumors. *Eye*. 2021;35(1):4–16. https://doi.org/10.1038/s41433-020-01151-z.
26. Naseripour M, Ghasemi Falavarjani K, Mirshahi R, Sedaghat A. Optical coherence tomography angiography (OCTA) applications in ocular oncology. *Eye*. 2020;34(9):1535–1545. https://doi.org/10.1038/s41433-020-0819-y.
27. Mellen PL, Sioufi K, Shields JA, Shields CL. INVISIBLE, honeycomb-like, cavitary retinal astrocytic hamartoma. *Retin Cases Brief Rep*. 2020;14(3):211–214. https://doi.org/10.1097/ICB.0000000000000697.
28. Vogel RN, Liu TYA, Singh MS, Goldberg MF. Optical coherence tomography angiography of astrocytic hamartoma demonstrates intrinsic vascularity. *Am J Ophthalmol Case Rep*. 2020;20, 100924. https://doi.org/10.1016/j.ajoc.2020.100924.
29. Yung M, Iafe N, Sarraf D. Optical coherence tomography angiography of a retinal astrocytic hamartoma. *Can J Ophthalmol*. 2016;51(2):e62–e64. https://doi.org/10.1016/j.jcjo.2015.11.005.
30. Venincasa VD, Weng C, Audina Berrocal M. *Pigmented Ocular Fundus Lesions in a 6-Year-Old Girl*. 2014. https://doi.org/10.1001/jamaophthalmol.2013.8157.
31. Verbeek S, Dalvin LA. Advances in multimodal imaging for diagnosis of pigmented ocular fundus lesions. *Can J Ophthalmol*. July 2023. https://doi.org/10.1016/j.jcjo.2023.07.005. Published online.
32. Papastefanou VP, Vázquez-Alfageme C, Keane PA, Sagoo MS. Multimodality imaging of TORPEDO maculopathy with swept-source, en face optical coherence tomography and optical coherence tomography angiography. Retin Cases Brief Rep. 12(2):153-157. doi:10.1097/ICB.0000000000000456.
33. Hamm C, Shechtman D, Reynolds S. A deeper look at torpedo maculopathy. *Clin Exp Optom*. 2017;100(6):563–568. https://doi.org/10.1111/cxo.12540.