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Optical coherence tomography angiography in pediatric ocular cutis marmorata telangiectatica congenita: A case series

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ABSTRACT

Purpose: To report 2 cases of enlarged foveal avascular zone (FAZ) on optical coherence angiography (OCTA) imaging in pediatric patients with cutis marmorata telangiectatica congenita (CMTC).
Observations: A 10-week-old female and a 3-year-old male diagnosed with CMTC presented for retinal examination. Both had peripheral avascularity on fluorescein angiography (FA) and enlargement of the FAZ on OCTA in both eyes.
Conclusions and Importance: Pediatric patients with CMTC should undergo ocular evaluation with not only FA, but also OCTA to more robustly evaluate the affected retina in this rare disease.

1. Introduction

Cutis marmorata telangiectatica congenita (CMTC) is a rare, congenital, slow-flow[1] vascular anomaly described as a persistent reticulated marbled erythema that blanches with pressure and does not resolve with heat application.[2–4] The cutaneous areas affected by the benign vascular anomaly can develop atrophy and ulcerations.[3] Most cases occur sporadically[5]; however, in rare instances, an autosomal recessive[6] or possible autosomal dominant[7] mode of transmission has been documented in the literature. Despite genetic identification being possible in these cases, failure to possess a genetic mutation does not exclude a diagnosis of CMTC in patients with suggestive features, as pathogenic variants in unidentified genes may be causative agents.[8]

The exact incidence of ocular findings in CMTC remains unknown and is difficult to approximate due to the rarity of this condition and its nonspecific presentation.[5] The pathophysiologic features of these ocular manifestations are not well understood; however, widespread primary dysfunction of veins, venules, capillaries, and possibly arterioles is likely a major disease-causing component.[9] CMTC has been associated with congenital glaucoma,[10,11] congenital retinal detachments,[12] proliferative vitreoretinopathy,[13] neovascularization,[14] and retinoblastoma.[15] Fundus examination has shown peripheral retinal vascular abnormalities, and fluorescein angiography (FA) has shown peripheral retinal nonperfusion.[5]

However, after an extensive literature search utilizing PubMed and Google scholar failed to reveal studies in the literature describing optical coherence tomography angiography (OCTA) findings in CMTC, we report two unique pediatric presentations of CMTC presenting with peripheral avascularity and an enlarged foveal avascular zone (FAZ) on OCTA.

2. Findings

2.1. Case 1

A 10-week-old female neonate born at 42 weeks via uncomplicated nonspontaneous vaginal delivery (NSVD) presented to a pediatric hematology oncology clinic with congenital venous malformations in the form of mottled dark red, lace-like pattered discolorations of the skin in both upper extremities (Fig. 1A), chest wall, back, and left lower extremity. The lesions were present at birth, stationery, with no gross hemihypertrophy or warmth and were labelled port wine stains. The diagnosis of CMTC was confirmed. Referrals for an eye examination and appointment with a molecular geneticist were placed.

An ophthalmic exam under anesthesia with multimodal imaging was then indicated. Anterior segment examination and intraocular pressures were unremarkable. Fundus examination showed incomplete peripheral vascularization in both eyes. FA revealed peripheral nonperfusion in

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both eyes, confirmed with real time evaluation utilizing scleral depression (Fig. 1B and C). FA images were obtained by utilizing RetCam (RetCam Envision Ophthalmic Imaging System). OCTA showed an enlarged FAZ in both eyes, 3.7 mm^2 in the right eye and 4.6 mm^2 in the left eye (Fig. 1D, E, 1F, 1G). Enlargement of the FAZ was ultimately determined by a combination of analyzing measurements and by analysis of OCTA images by an expert pediatric retina specialist with extensive experience analyzing OCTA. Investigational Spectralis HRA + OCT with Flex and OCTA modules (Spectralist Heidelberg Engineering) were utilized for OCTA imaging.

Concern for mitochondrial disorders and genome abnormalities by the molecular geneticist prompted further investigation with XomeDx-Plus Clinical Exome Sequence Analysis, which utilized whole exome sequencing and Next Generation sequencing (GeneDx Corporation, Connecticut, USA). Results were unremarkable. The patient continues to follow with a pediatric ophthalmologist, a retina specialist, and a hematologist.

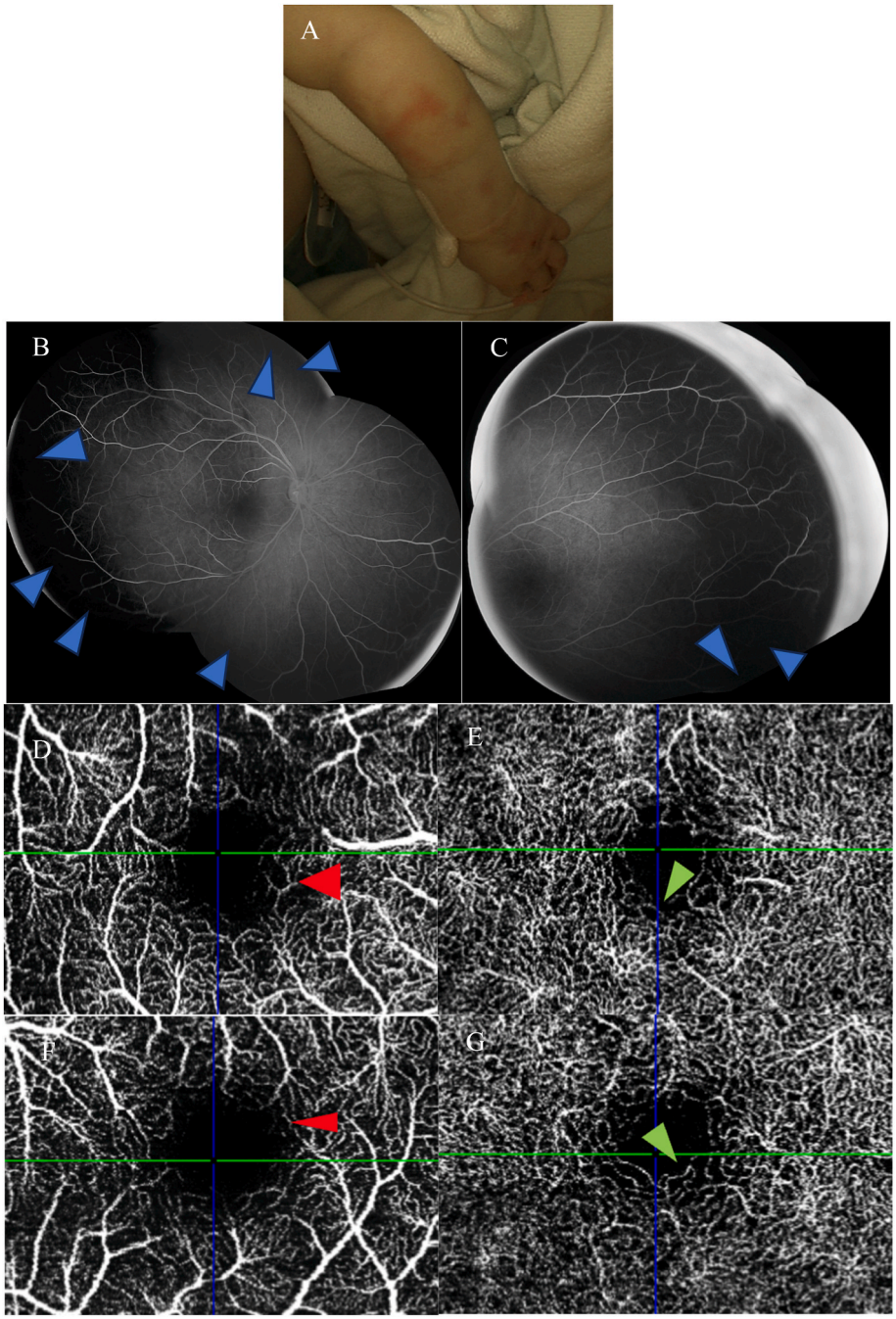

Fig. 1. Representative skin image, FA studies, and OCTA studies in a 10-week-old female. (A) Skin image shows mottled dark red, lace-like pattered discolorations in the left upper extremity. (B) FA shows peripheral avascularity, identified by blue arrows, in the right eye. (C) FA shows peripheral avascularity, identified by blue arrows, in the left eye. En-face OCTA images show enlargement of the FAZ (red arrow) in the superficial plexus (D) and vascular loops (green arrow) around the FAZ in the deep vascular plexus (E) in the right eye. En-face OCTA images show an enlargement of the FAZ (red arrow) in the superficial plexus (F) and vascular loops (green arrows) around the FAZ in the deep plexus (G) in the left eye. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

2.2. Case 2

A 3-year-old male born full term via NSVD was admitted to the neonatal intensive care unit for 1 week after birth for possible sepsis. Since birth, he possessed congenital venous malformations in the form of mottled dark red, lace-like pattered discolorations of the skin on the neck (Fig. 2A). At the age of 2 years old, he underwent excision of two hemangiomas, one on the right flank and another on the left temple, diagnosed at birth. He was subsequently diagnosed with CMTC by a pediatric dermatologist and referred to a pediatric retina specialist.

An ophthalmic exam under anesthesia was then indicated. Anterior segment examination revealed an iris nevus from 1 to 2 o'clock with no angle involvement in the right eye. Intraocular pressure and fundus examination were unremarkable. FA showed peripheral nonperfusion in both eyes, confirmed with real time evaluation utilizing scleral depression (Fig. 2B and C). FA images were obtained by utilizing RetCam (RetCam Envision Ophthalmic Imaging System). OCTA showed an enlarged FAZ in both eyes, 4.5 mm^2 in the right eye and 3.2 mm^2 in the left eye (Fig. 2D, E, 2F, 2G). Similarly to the previous case, enlargement of the FAZ ultimately was determined by a combination of analyzing measurements and by analysis of OCTA images by an expert pediatric retina specialist with extensive experience analyzing OCTA. Investigational Spectralis HRA + OCT with Flex and OCTA modules (Spectralis Heidelberg Engineering) were utilized for OCTA imaging.

An Invitae Inherited Retinal Disease (IRD) Panel (Invitae Corporation, San Francisco, USA) was unremarkable.

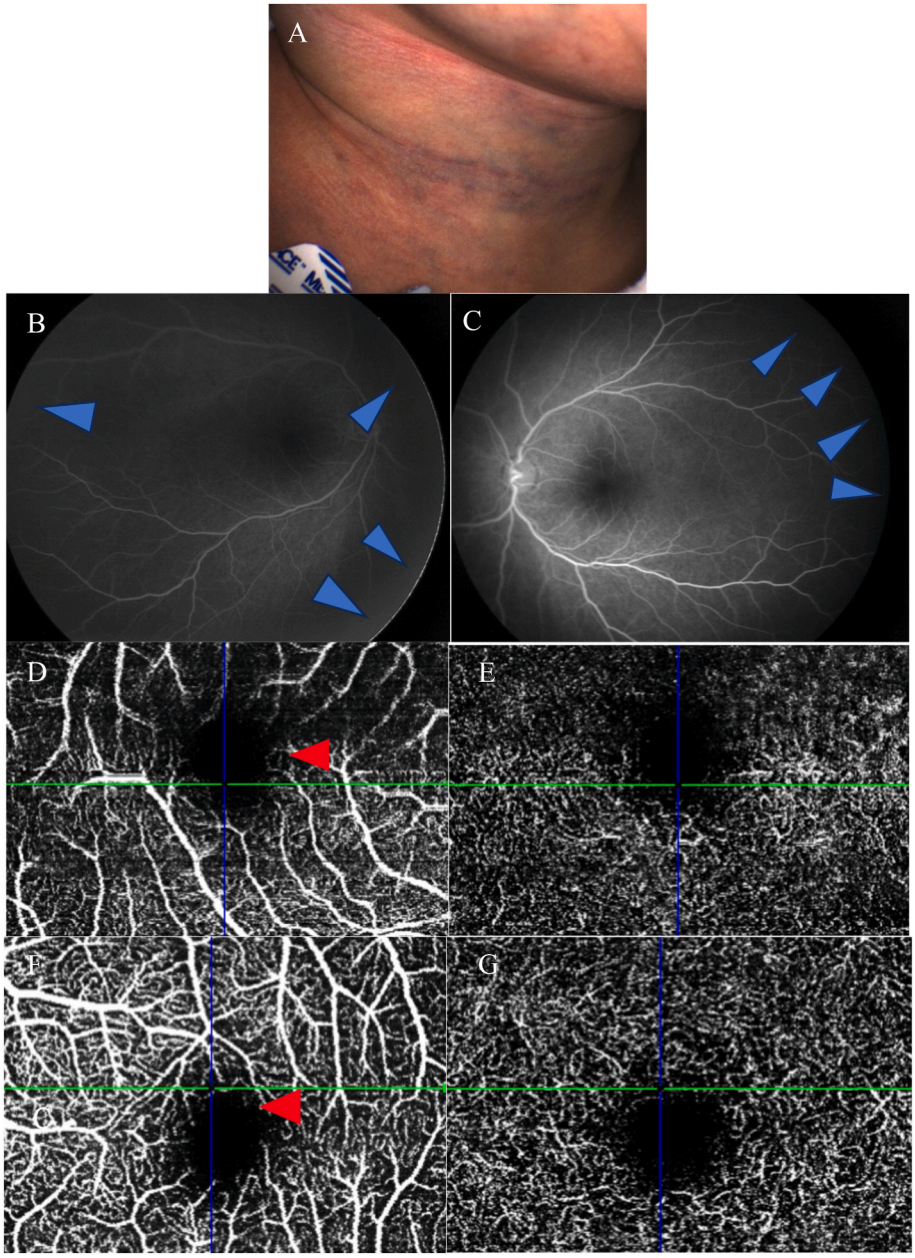

Fig. 2. Representative skin image, FA studies, and OCTA studies in a 3-year-old male. (A) Skin image shows mottled dark red, lace-like pattered discolorations on the neck. (B) FA shows peripheral avascularity, identified by blue arrows, in the left eye. (C) FA shows peripheral avascularity, identified by blue arrows, in the right eye. En-face OCTA images show enlargement of the FAZ (red arrow) in the superficial plexus (D) and no abnormalities in the deep plexus (E) in the right eye. En-face OCTA images show an enlargement of the FAZ (red arrow) in the superficial plexus (F) and no abnormalities in the deep plexus (G) in the left eye. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3. Discussion

In this report we uniquely describe two cases of abnormalities in the peripheral retinal vasculature on FA and enlargement of the FAZ on OCTA in 2 pediatric patients with CMTC. Although most cases are not associated with systemic abnormalities, a wide variety of developmental abnormalities have been documented in patients with CMTC.[12] Our patients did not have systemic or developmental abnormalities.

The fovea is the area of the central retina that has the highest density of cone photoreceptors and lowest density of rod photoreceptors.[16] The inner retinal layers and their vessels are displaced from the fovea to create a central foveal avascular zone, also known as the FAZ, that most likely serves to reduce light scattering.[16] The FAZ forms due to the development of a ring-shaped anastomosis at the macula and end of either an artery or vein from the retinal surface.[17] Alterations of the FAZ have been associated with central vision loss.[18]

OCTA, a non-invasive imaging technique that creates a detailed, three-dimensional visualization of vasculature of the retina and choroid without the use of injectable dye,[19] has become an attractive option to evaluate retinal disease and pathology in the pediatric patient population.[20] Utilization of OCTA to analyze the FAZ in adults with pathology such as diabetic retinopathy has been described.[21] Therefore, it is not surprising that utilization of OCTA to analyze the FAZ of pediatric patients[22] has begun in conditions such as retinopathy of prematurity (ROP)[23] and familial exudative vitreoretinopathy (FEVR).[24] Although extensive literature on the size of the FAZ in healthy pediatric patients that can be used as a comparison to the size of the FAZ in our patients is lacking, Ghassemi et al. report that in their cohort of 108 pediatric (aged less than 18 years old) eyes, the mean size of the FAZ was 0.44 ± 0.78 mm^2, which is much smaller than the size of the FAZ in our cases.[25] Ultimately, enlargement of the FAZ in our cases was determined by a combination of analyzing exact measurements in our cases and comparing them to the average size of the FAZ found by Ghassemi et al. and by analysis of the FAZ on OCTA by an expert pediatric vitreoretinal specialist well versed in analyzing OCTA. An enlarged FAZ has been documented among children and young adults with other retinal diseases, such as X-linked Juvenile Retinoschisis[26,27] and myopia,[28] and it has been found to correlate with decreased visual acuity.[21,29]

The pathophysiology of CMTC is not well elucidated; however, our patients share a dysfunction of vessels in the retina that manifests as an enlarged FAZ and peripheral nonperfusion. Peripheral retinal avascularity has been described in CMTC patients, but our series shows that the vascular abnormalities may also involve the fovea.[5] Since FAZ enlargement and the areas of peripheral retinal non-perfusion share the common causative pathogenic processes of capillary closure,[30,31] correlations on OCTA, such as enlarged FAZ, could serve as a possible biomarker for assessing perfusion status in the retina.

Regarding treatment, there is no consensus of how to manage peripheral non-perfusion without vascular leakage or neovascularization in pediatric patients with CMTC. The literature reports treatment ranging from observation[5] to laser photocoagulation to prevent secondary complications.[5,32] However, ultimately management should be selected on a case-by-case basis. Patient education and close follow up are paramount for early identification and treatment of vision-threatening complications in pediatric patients with CMTC.

Lastly, since neither of the patients in our cases possessed a genetic mutation known to be associated with CMTC, it could be conceivable that there are not only unknown exonic mutations but also perhaps unknown extra-exonic mutations, potentially involving entities such as transcription regulators or splicers, that could have a role in this disease and these presentations.

4. Conclusions

Since enlargement of the FAZ has been linked to poor visual outcomes and loss of central vision in other retinal vascular diseases, we suggest that pediatric patients with a diagnosis of CMTC undergo ocular evaluation with not only FA to assess the peripheral retinal vasculature, but also OCTA to assess the FAZ. This could have implications for future follow-up and treatment recommendations for patients with this rare condition.

5. 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 order of authorship presented on title page.

CRediT authorship contribution statement

Serena Shah: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Natasha Ferreira Santos da Cruz:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Francisco Lopez-Font:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Lauren Kiryakoza:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Audina Berrocal:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

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