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Multimodal Fundus Imaging of Outer Retinal Tubulations after Ranibizumab Injections in Choroidal Osteoma

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ABSTRACT

Purpose: To report the development and to evaluate findings in multimodal imaging of outer retinal tubulations (ORTs) shown in all five eyes with inactivate choroidal neovascular membrane after treatment with ranibizumab in patients with choroidal osteoma.

Methods: Four eyes from two healthy young male patients with confirmed diagnosis of bilateral choroidal osteoma and 39-year-old woman with unilateral choroidal osteoma and a history of decreased vision underwent full clinical and imaging assessments. Identifying in all four eyes an active choroidal neovascularization membrane and treated with intravitreal injections of ranibizumab. Color fundus photography, spectral domain optical coherence tomography (Spectralis HRA+OCT; Heidelberg, Germany) and optical coherence tomography angiography (RTVue-XR; Optovue, Inc, Fremont,CA) were performed to identify and analyzed characteristics of ORTs.

Results: Optical coherence tomography showed the presence of choroidal osteoma and choroidal neovascularization with subretinal fluid. After treatment with intravitreal injection of ranibizumab and complete disappearance of subretinal fluid, all five eyes with choroidal osteoma showed ORTs. The ORTs were located above or very close to scar or fibrosis area of the choroidal neovascular membrane (CNVM), with no evidence of subretinal fluid.

Conclusion: The result in this series of cases suggests the presence of ORTs after inactivation of choroidal neovascularization membrane with ranibizumab treatment in all eyes with choroidal osteoma. The formation of outer retinal tubulations (ORTs) might be explained by the theory that surviving photoreceptors can establish new lateral connections with nearby cells in response after retinal injury. As well, clinicians should be careful to differentiate the morphology between OTRs and intraretinal fluid caused by choroidal neovascular

membrane, as OTRs does not benefit from intraocular anti vascular endothelial growth factor (VEGF) injections.

Keywords: Choroidal osteoma; Active choroidal neovascular membrane outer retinal tubulations

INTRODUCTION

Choroidal osteoma is a benign tumor characterized by mature bone replacing choroid.[1] It had been hypothesized that the entity was caused by endocrine alteration, inflammatory conditions or imbalance in serum calcium, phosphate or alkaline phosphate levels. However, none of these hypotheses have been confirmed.[2,3,4]

Since the 19th century cases of ocular ossification had been reported, but it was in 1978 that Dr. Donald Gass made the first descriptions of choroidal osteoma with a series of four patients.[5] It was characterized as a slightly elevated yellow- white to orange-red tumor with brown, orange or gray pigment that resembles the overlying pigment epithelium. Typically located juxtapapillary or peripapillary but can, in rare cases, extend to the macula. Although often asymptomatic, it may cause blurred vision and visual field defects, which are often associated with decalcification in the subfoveal region or the presence of a choroidal neovascular membrane.[6]

Diagnosis is mainly clinical, based on the examination of the characteristic posterior pole lesion. However, multimodal imaging, including optical coherence tomography, should be considered and performed, especially in patients with poor vision.

In 2009, Zweifel first described outer retina tubulations. ORTs are seen in optical coherence tomography as round or ovoid hyporeflective spaces with hyperreflective borders located in the external neurosensorial retina, specifically in the outer nuclear layer. It is postulated that this tubular arrangement may be of degenerated photoreceptors arranged in circular or tubular form. This process is not disease - specific, but a general response to retinal injury in various pathologies including exudative age - related macular degeneration, choroideremia, angioid streaks, multifocal choroiditis and others.[8-14]

In this case series, we present four eyes with choroidal osteoma who developed OTRs. All four eyes exhibited active choroidal neovascular membrane and were treated previously with ranibizumab. Following ranibizumab treatment, subretinal fluid was completely resolved, but all eyes developed outer retinal tubulations.

CASE 1

A 12-year-old healthy male with history of four intravitreal injections of ranibizumab 6 months ago in the left eye. Presented with a one-month history of decreased vision in the right eye. On ophthalmologic examination, visual acuity was 20/80 in the right eye and 20/200 in the left eye. Fundus examination revealed a well- defined yellow – orange mass in both eyes (Figure 1B and 1F). Ultrasound was performed and showed a thick, dense plaque in the posterior pole with 100% reflectivity and significant attenuation of echos behind it with acoustic silence in both eyes (Figure 1A and 1E). Multimodal imaging including optical coherence tomography (Spectralis HRA + OCT; Heidelberg, Germany) and optical coherence tomography angiography (RTVue-XR;

Optovue, Inc, Fremont, CA) were performed. In the OCT of the right eye, an active neovascular membrane with subretinal fluid was observed (Figure 1D). Intravitreal ranibizumab 0.5 mg was initiated monthly. After three monthly doses, the SD-OCT revealed complete resolution of subretinal fluid and the development of ovoid tubular structures with hyporreflective ovoid space and hyperreflective walls and overlying absent outer retina hyperreflective layers including the retinal pigment epithelium (RPE). The location of the OTRs were towards the edges and above the scar of the choroidal neovascular membrane (Figure 1 Ia -Id). At follow- up, visual acuity in the right eye improved to 20/50 and remained stable for 15 months. In the left eye, OTRs were observed above and at the edges of fibrous tissue secondary to an inactive choroidal neovascular membrane from the initial visit.

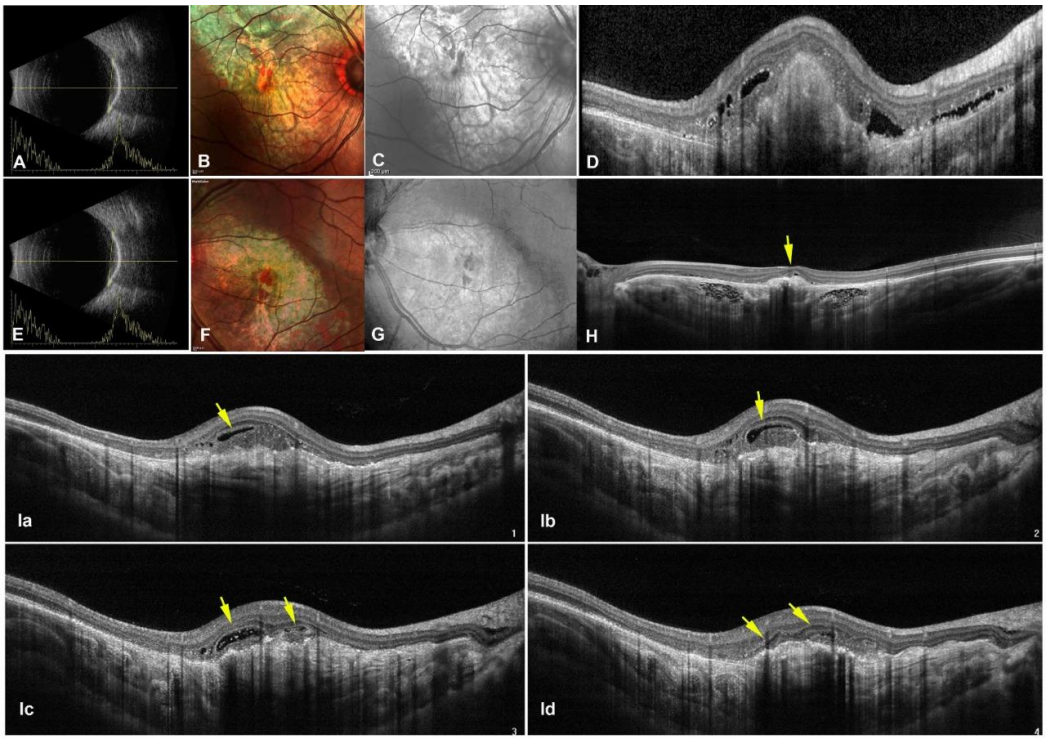

Figure 1. Multimodal imaging of a case of choroidal osteoma with intraretinal fluid and outer retina tubulations. A and E. A-mode and B-mode ultrasound showing a highly reflective lesion at the level of the choroid, with a posterior acoustic shadow of the right and left eye. B and F. Multicolor image showing a well-defined tumor lesion with central subretinal hemorrhage corresponding to active neovascular membrane. C and G. Red-free photo. D. Cross-sectional SD-OCT of the macula of the right eye showing a heterogeneous subretinal lesion corresponding to a neovascular membrane, with surrounding subretinal and intraretinal fluid. H. Cross-sectional SD-OCT of the left eye showing an outer retinal tubulation (yellow arrow) over a choroidal lesion corresponding to a trabecular-appearing choroidal osteoma in an area of atrophy of the outer retinal segments and retinal pigment epithelium. Ia-Id. Cross-sectional SD-OCT of the macula of the right eye showing various cross-sections of the choroidal osteoma, with multiple outer retinal tubulations (yellow arrows) over the choroidal tumor in areas of atrophy of the outer segments and retinal pigment epithelium after ranibizumab treatment.

CASE 2

A 39 – year- old female with history of injection of ranibizumab in the right eye six year ago. Presented with one year decreased vision and central scotoma in right eye. On ophthalmologic examination, visual acuity was 20/1600 in the right eye and 20/20 in the left eye. Fundus examination revealed a well-defined yellow orange mass with overlying gray pigmentation associated with decalcified choroidal temporal zone. (Figure 2A and 2E) Multicolor imaging and optical tomography coherence of the right eye revealed subretinal fluid in the macula (Figure 2D). Intravitreal ranibizumab 0.5 mg was initiated. After two monthly doses, the SD-OCT revealed complete resolution of subretinal fluid and the development of ovoid tubular structures with hyporreflective ovoid space and hyperreflective walls at the choroidal neovascular membrane border (Figure 2F) and above the subretinal hyperreflective material. At follow – up, there was no visual improvement in the right eye.

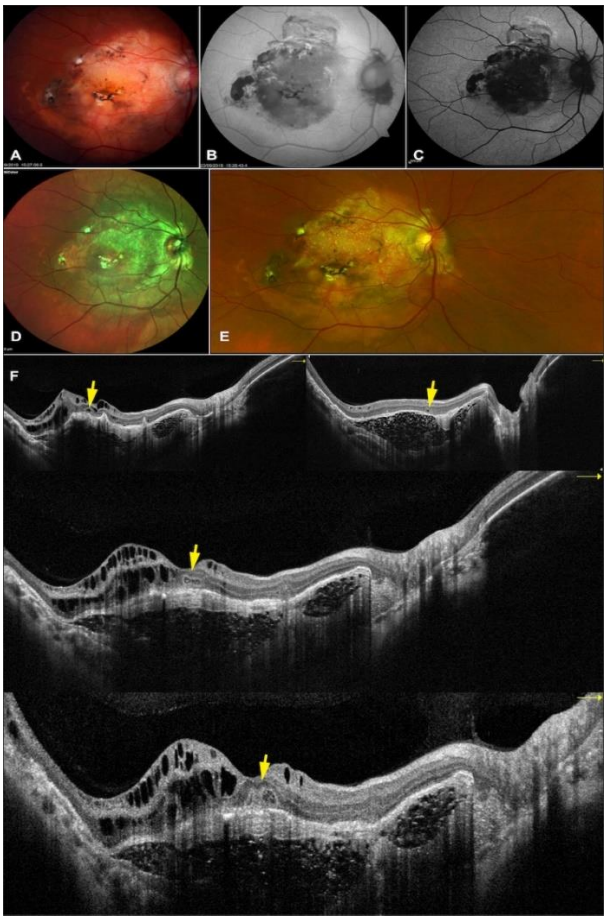

Figure 2. Multimodal imaging of a case of choroidal osteoma with intraretinal fluid and outer retina tubulations in the right eye. A and E. Color fundus photograph of the right eye. B. Red-free photo. C. Autofluorescence. D. Multicolor image; showing a well-defined central yellow color tumor lesion with irregular borders and areas of intrinsic pigment changes. C. The lesion is hypoautofluorescent with some hyperautofluorescent areas in the inferior and superior nasal borders. F. Cross-sectional SD-OCT image of the macula of the right eye shows various cross-sections of the trabecular-appearing choroidal osteoma, where the presence of multiple-sized outer retinal tubulations in different sectors can be seen (yellow arrow), with atrophic

retinal pigment epithelium and outer segments of the retina, as well as cystic-appearing lesions in the inner and outer retina layers of the temporal and nasal area.

CASE 3

An 18 – year old male with bilateral choroidal osteoma diagnostic and history of three injections of ranibizumab in both eyes presented with decreased vision in both eyes. On ophthalmologic examination, visual acuity was 20/400 in the right eye and 20/200 in the left eye. Fundus examination revealed a well – defined white yellow mass associated with decalcified choroidal temporal zone in both eyes (Figure 3A and 3D). Optical coherence tomography angiography revealed a choroidal neovascular membrane with subretinal fluid and zones containing high flow rates in the right eye (Figure 3I). Intravitreal ranibizumab 0.5 mg was initiated in the right eye. After one month dose, the SD-OCT revealed scarce subretinal fluid and the development of ovoid tubular structures with hyporreflective ovoid space and hyperreflective walls (Figure 3G). At follow – up, one month after, SD – OCT revealed complete resolution of subretinal fluid, the development of OTRs and overlying absent outer retina hyperreflective layers in the right eye (Figure 3H).

SD – OCT of the left eye also revealed the development of OTRs (Figure 3F).

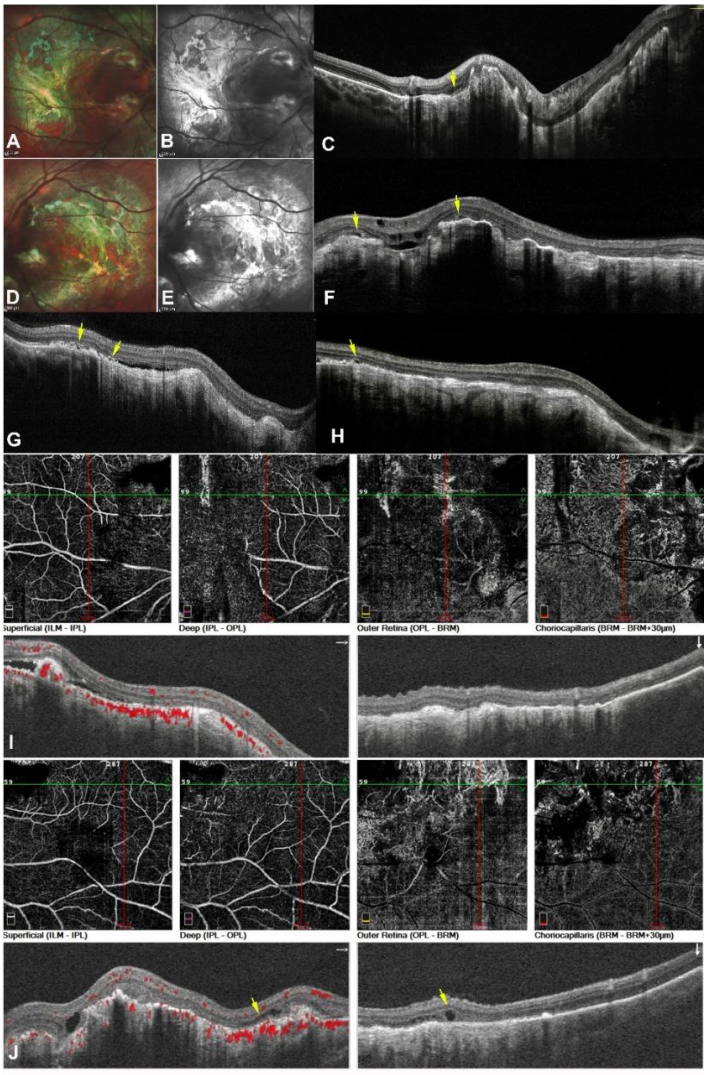

Figure 3. Multimodal imaging of a case of choroidal osteoma with intraretinal fluid and outer retina tubulations. Right eye. A. Multicolor image of the right eye showing a well-defined tumor lesion in the macular area. B. Red-free photo. C. Cross-sectional SD-OCT image of the macula showing multiple outer retinal tubulations (yellow arrow) over a choroidal lesion corresponding to a choroidal osteoma associated to areas of disruption of the outer retina layers.I 3x3 optical coherence tomography angiography (OCTA) images show high vascular flow areas at the level of the transverse OCTA at the level of the tumor, which correspond to intrinsic vascularization, contiguous with an area of subretinal vascularization corresponding to a neovascular membrane with surrounding fluid at the level of the outer plexiform retina layer. **Left eye**. D. Multicolor image of the right eye showing a well-defined tumor lesion in the macular area. E. Red-free photo. F, G, H. Cross-sectional SD-OCT image of the macula showing multiple outer retinal tubulations (yellow arrows) over a choroidal lesion corresponding to a choroidal osteoma associated to areas of disruption of the outer retina layers and retina pigment epithelium (RPE) with the presence of hyporeflective subretinal and intraretinal spaces. J. 3x3 OCTA images show high flow areas at the level of the transverse OCTA at the level of the tumor, which correspond to intrinsic vascularization. The OCT en face registered with the OCTA scan shows an outer retinal tubulation (yellow arrow) over the tumor area with the presence of high vascular flow.

DISCUSSION

Xuan et al. first described OTRs in patients with choroidal osteoma in 2018. They were described in 26% of case series of 17 cases of choroidal osteoma.[15] It's hypothesized that OTRs form due to a degenerative process in the pigment epithelium, leading to photoreceptor damage. It is thought surviving photoreceptors may then establish new lateral connections with neighboring cells as a repair mechanism.[7,16,17] Long-term follow-up studies have shown that OTRs can increase in number or change in configuration over time.[18] Additionally, studies have shown a relationship between the development of ORTs and a larger size of the choroidal osteoma mass, as well as a greater zone of decalcification, the presence of subretinal fluid, and alterations of the retinal pigment epithelium in the macula. Therefore, the development of ORTs may be a risk factor for all these conditions.[15]

In Xuan et al. case series choroidal neovascular membrane was detected in only one out of five eyes with ORTs.[16] In our case series all eyes with choroidal ostemoa developed choroidal neovascular membrane. Mateo-Montoya et al. reported a correlation between the presence of subretinal choroidal neovascular membranes (CNVM) and subretinal OTR development, likely due to the increased risk of histological and structural changes in the neurosensory retina exposed to CNVM.[9]

In all cases described in this study, patients with choroidal osteoma developed active CNVM requiring ranibizumab treatment. After CNVM resolution, OTRs were observed near the scar or above the CNVM. While OTRs may be a theoretical repair mechanism for surviving photoreceptors, it's crucial to avoid confusing them with exudation from CNVM. Case reports emphasize the importance of differentiating intraretinal cystic spaces in choroidal osteoma patients from intraretinal fluid caused by CNVM exudation. While the latter may benefit from intraocular antiangiogenic injections, ORTs do not.[18]

CONCLUSION

All eyes with choroidal osteoma that had inactive choroidal neovascular membranes after ranibizumab injection developed outer retinal tubulations (OTRs). These findings suggest that OTRs may form as a consequence of surviving photoreceptors establishing new lateral connections with neighboring cells in response to retinal damage. Our results support this hypothesis.

FINANCIAL DISCLOSURE

The authors have no relevant or material financial interests that relate to the research described in this paper.

REFERENCES

1. Alameddine RM, Mansour AM, Kahtani E. Review of choroidal osteomas. Middle East Afr J Ophthalmol. Middle East Afr J Ophthalmol. 2014;21(3):244–250.
2. Shields CL, Sun H, Demirci H, Shields JA. Factors predictive of tumor growth, tumor decalcification, choroidal neovascularization, and visual outcome in 74 eyes with choroidal osteoma. Arch Ophthalmol 2005;123:1658-66.
3. Aylward GW, Chang TS, Pautler SE, Gass JD. A long-term follow-up of choroidal osteoma. Arch Ophthalmol. 1998; 116:1337-41.
4. Shields CL, Shields JA, Augsburger JJ. Choroidal osteoma. Surv Ophthalmol 1988;33:17-27.
5. Gass JDM, Guerry RK, Jack RI, Harris G. Choroidal osteoma. Arch Ophthalmol . 1978;96(3):428-35.
6. Trimble SN, Schatz H, Schneider GB. Spontaneous decalcification of a choroidal osteoma. Ophthalmology. 1988;95(5):631–4.
7. Zweifel SA, Engelbert M, Laud K, et al. Outer retinal tubulation: a novel optical coherence tomography finding. Arch Ophthalmol 2009;127:1596–1602.
8. F Faria-Correia, R Barros-Pereira, L Queirós-Mendanha, S Fonseca, L Mendonça, M S Falcão,, et al. Characterization of neovascular age-related macular degeneration patients with outer retinal tubulations. Ophthalmologica 2013;229:147–151.
9. Aránzazu Mateo-Montoya, Benjamin Wolff, José-Alain Sahel, Martine Mauget-Faÿsse. Outer retinal tubulations in serpinginous choroiditis. Graefes Arch Clin Exp Ophthalmol 2013;251:2657–2658.
10. Goldberg NR, Greenberg JP, Laud K, et al. Outer retinal tubulation in degenerative retinal disorders. Retina. 2013;33:1871–1876.
11. Hariri A, Nittala MG, Sadda SR. Outer retinal tubulation as a predictor of the enlargement amount of geographic atrophy in age-related macular degeneration. Ophthalmology. 2015;122: 407–413.
12. Gallego-Pinazo R, Marsiglia M, Mrejen S, et al. Outer retinal tubulations in chronic central serous chorioretinopathy. 2013;251:1655-56.
13. Graefes Arch Clin Exp Ophthalmol. 2013;251:1655–1656.
14. Iriyama A, Aihara Y, Yanagi Y. Outer retinal tubulation in inherited retinal degenerative disease. Retina. 2013;33:1462–1465.

15. Xuan y, zhang y, wang m, et al. multimodal fundus imaging of outer retinal tubulations in choroidal osteoma patients. Retina. 2018;38(1):49-59.
16. Litts KM, Ach T, Hammack KM, et al. Quantitative analysis of outer retinal tubulation in age-related macular degeneration from spectral-domain optical coherence tomography and histology. Invest Ophthalmol Vis Sci. 2016;57:2647–2656.
17. Litts KM, Messinger JD, Freund KB, et al. Inner segment remodeling and mitochondrial translocation in cone photoreceptors in age-related macular degeneration with outer retinal tubulation. Invest Ophthalmol Vis Sci. 2015;56:2243–2253.
18. Allam Khalid, AlShaikh, Reem Schatz, Patrik Abdelkader, Ehab. Long-Term Follow Up of Intra-Retinal Fluid and Outer Retinal Tubulations in a Case of Choroidal Osteoma Following Anti-VEGF Treatment. Journal of Clinical & Experimental Ophthalmology. 2017.