Choroidal neovascularization associated with combined hamartoma of retina and retinal pigment epithelium: Multimodal imaging

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Combined hamartoma of retina and retinal pigment epithelium (CHRRPE) has been considered as a congenital benign entity with evidence of choroidal neovascularization membranes (CNVM) being associated with it in literature. This case series gives insight into the pathogenesis and the predisposing factors leading to CNVM formation in peripapillary CHRRPE using swept-source optical coherence tomography. In addition, lack of typical markers of CNVM (subretinal fluid/pigment epithelial detachment) in CHRRPE highlights the utility of optical coherence tomography angiography and the subtle optical coherence tomography findings such as "Bridge Sign" that could be instrumental in early diagnosis of CNVM in CHRRPE.

Key words: Bridge Sign, choroidal neovascularization associated with combined hamartoma of retina and retinal pigment epithelium, combined hamartoma of retina and retinal pigment epithelium, OCTA in CHRRPE

Combined hamartoma of retina and retinal pigment epithelium (CHRRPE) has been described by Gass[1] as a hamartomatous malformation involving retina, retina pigment epithelium, and overlying vitreo-retinal interface. CHRRPE has been considered as a congenital benign entity with a lack of evidence in literature on the natural course of the disease. However, in recent times, few reports have highlighted the association of CHRRPE with vitreous hemorrhage,[2] preretinal neovascularization,[3] and choroidal neovascularization (CNVM)[2,4-8] contributing to the vision loss in CHRRPE.

We retrospectively analyzed our data of 21 patients diagnosed with CHRRPE of which 3 were found to be associated with CNVM. In this study, we describe the optical coherence tomography (OCT) features of these 3 cases of CNVM associated with CHRRPE and propose a patho-physiological basis of CNVM formation in this entity.

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Case Reports

Case 1: A 33-year-old female presented with distorted vision in left eye (LE) (20/80) for 3 months. Clinical examination revealed peripapillary CHRRPE lesion extending up to the macula with speck of subretinal hem at the edge of the lesion [Fig. 1a– arrow]. Spectral domain (SD)-OCT [Fig. 1d] showed epiretinal membrane (ERM), full thickness involvement, and disorganization of retinal layers up to retinal pigment epithelium (RPE), cystoid changes, and schitic cavities at the edge of the lesion and a localized mound/elevation of RPE with a hypereflective intraretinal band – "Bridge Sign" [Fig. 1d–inset with an asterisk and a magnified projection at the right top corner]. Leak was evident on fundus fluorescein angiography (FFA) that confirmed the presence of CNVM [Fig. 1b and c - arrow head], and subsequently, intravitreal bevacizumab (IVB) (1.25 mg/0.05 ml) was injected.

After 3 (monthly) doses of IVB, vision improved to 20/20, subretinal hem had resolved, leak on FFA was less evident, but disorganized retinal architecture owing to CHRRPE still persisted along with scarred CNVM [Fig. 1e].

Patient again presented 1 year later with vision loss in her LE (20/320). On examination, she had a new site (superior to the previous site) of subretinal hem involving fovea [Fig. 1f– arrow head]. Swept source (SS)-OCT [Fig. 1i] through macula showed subretinal scar with RPE elevation adjacent to it. OCTA showed two distinct networks in outer retinal layers corresponding to old (regressed) and the recurrent CNVM [Fig. 1g]. FFA confirmed the new active lesion [Fig. 1h- arrow head], and patient underwent two (monthly) doses of IVB.

Case 2: A 21-year-old male presented with distorted vision in LE (20/320) for 1 year. Fundus showed peripapillary CHRRPE lesion with a speck of intraretinal hemorrhage along the inferotemporal edge of the lesion [Fig. 2a- arrow head]. SS-OCT and OCTA features have been described in Fig. 2d and b. FFA showed a very minimal leak starting from the early phase suggestive of CNVM [Fig. 2c- arrow head] that was distinct from the site of retinal hemorrhage. Patient subsequently underwent IVB injection in his left eye.

Case 3: A 31-year-old female presented with distortion and diminution of vision in LE (20/80) since 3 years. On

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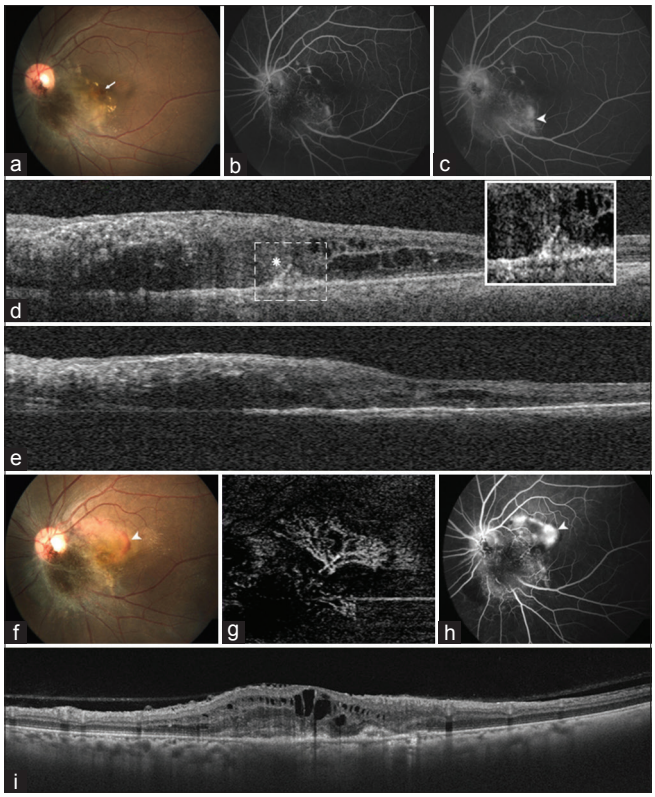

Figure 1: Case 1: Montage shows subretinal hem on fundus photograph (a), active choroidal neovascularization (CNV) on fluorescein angiography (FA) (b, c), and "Bridge Sign" (d–inset with an asterisk and a magnified projection at the right top corner) on optical coherence tomography (OCT) that regressed after intravitreal therapy (e). Fundus photograph (f), OCTA (h), FA (i), and OCT (h) at the time of recurrence

examination, peripapillary CHRRPE lesion extending up to the macula was seen [Fig. 3a]. SS-OCT and OCTA have been described in Fig. 3c and b. Hot spot on ICG [Fig. 3d- dotted circle] was noted, however, there was no evidence of early or late leakage on FFA [Fig. 3e]. Patient was advised for anti-VEGF therapy in view of suspected CNVM.

Results

Out of 21 cases diagnosed with CHRRPE, 10 were juxtapapillary, 10 were macular, and one was equatorial in location, of which 3 were associated with CNVM [Figs. 1-3]. All cases had a juxtapapillary pigmented lesion with a mean BCVA of 0.83 logMAR (Snellen's equivalent - 20/125). Full thickness retinal disorganization, RPE hypertrophy, disruption of ellipsoid zone, ERM, and cystoid changes were the other OCT findings common to all 3 cases. Of note was the characteristic mound/elevation of RPE with intraretinal hypereflective band (Bridge Sign) that was seen in all the 3 cases. Case 1 and 2 showed evidence of subretinal and intraretinal hemorrhage, respectively along with network in outer retinal layer on OCTA and leak on FFA corresponding to the network that was suggestive of CNVM. Case 3, however, only showed a subtle network in outer retinal layer on OCTA and a hot spot on indocyanine green angiography (ICGA) with no evident leak on FFA. Recent onset vision loss, presence of similar configuration on OCT as compared with cases 1 and 2 and a network OCTA raised

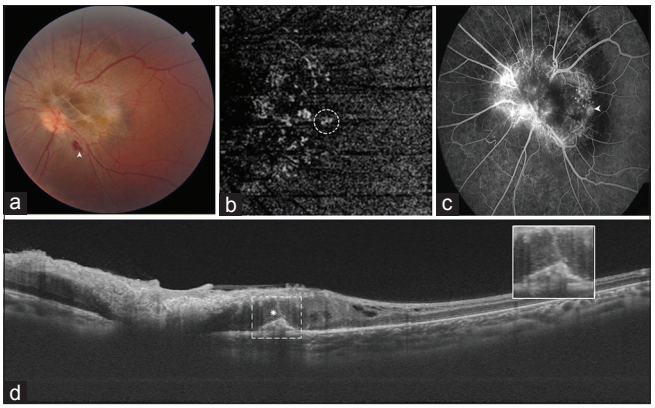

Figure 2: Case 2: Fundus photograph showing subretinal/intraretinal hemorrhage (a–arrow head).SS-OCT (transverse scan) shows full thickness retinal disorganization, ERM, schitic cavities, and bridge sign (d–inset with an asterisk and a magnified projection at the right top corner). OCTA shows a network in outer retinal layers at the temporal edge (b–dotted circle) with a subtle leak on FA (c)

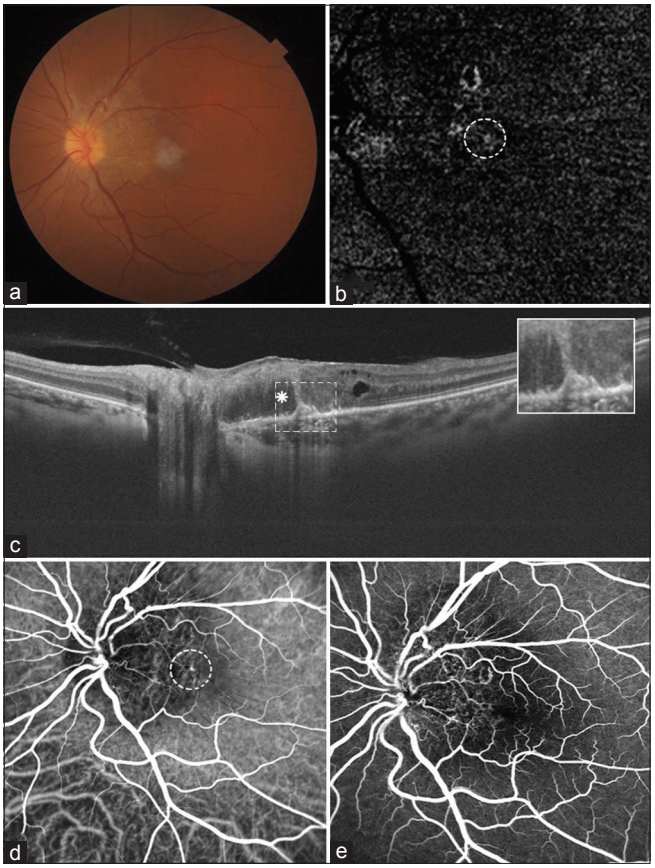

Figure 3: Case 3: Fundus photograph (a) showing peripapillary lesion with a network along the temporal margin of the lesion on OCTA (b–dotted circle) with a hot spot on ICG (d-dotted circle) and no active leak on FFA (e). SS-OCT (transverse scan) shows full thickness retinal disorganization, ERM, cystic changes along with bridge sign (c–inset with an asterisk and a magnified projection at the right top corner)

a suspicion of CNVM formation in this case, and henceforth, was advised for anti- vascular endothelial growth factor (VEGF) therapy to prevent further vision loss as a consequence of CNVM. There was no evidence of subretinal fluid (SRF)/

neurosensory detachment (NSD), serous/fibrovascular/hemorrhagic pigment epithelial detachment (PED) in the cases reported.

Discussion

Present case series as well as cases of CHRRPE associated with CNVM described in literature[4,5,7,8] share a common peripapillary topography of hamartoma. Sarks[9] in his clinico-pathological correlation showed that peripapillary CNVM (idiopathic or secondary) originate either from choroidal vessels passing through a defect in Bruch membrane or from choroidal vessels that extend around the termination of Bruch membrane adjacent to the optic disc. Full thickness retinal disorganization along with RPE proliferation and migration along the vessels from the site of termination of Bruch's in peripapillary CHRRPE has been demonstrated histopathologically by Vogel *et al*.[10] Both these factors may have a synergistic effect, thereby, predisposing peripapillary CHRRPE lesions to develop CNVM.

An elevation/mound of RPE along with hypereflective intraretinal band on OCT was seen in all our cases that we have termed as "Bridge Sign" (coursing from apex of the mound to hypereflective inner retinal layers). This hypereflective band, secondary to fibrotic glial component may well be a cause of fractures in Bruch's membrane, paving way for new choroidal vessels. In addition, CNV network in all the 3 cases were localized at the edge of the lesion (at the junction of dysplastic and normal retina) that simulates mechanical theory[11] postulated for CNVM formation at the edge of chorioretinal scars.

NSD, SRF, serous or hemorrhagic PED that occur as a complication or rather as a hemostatic response to CNVM was absent in all the 3 cases. Neovascular complexes associated with CHRRPE in our cases bleed and exude less as compared with other pathologies that could be attributed to the abundance of fibrous/glial tissue surrounding the new vessels.[9] Cystic spaces in the inner retinal layers have been described in context of CHRRPE previously[12] and cannot be presumed solely owing to CNVM in the cases reported. Because of the absence of the typical markers of activity of CNVM (NSD/SRF/PED), role of OCTA becomes pivotal in early diagnosis of CNVM in CHRRPE.

Conclusion

In conclusion, our case series provide insight into the pathogenesis, depicting various factors using current imaging modalities predisposing to CNVM formation in peripapillary CHRRPE and thereby aiding in early diagnosis of CNVM secondary to CHRRPE.

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Conflicts of interest

There are no conflicts of interest.

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