Combination treatment of low fluence photodynamic therapy and intravitreal ranibizumab for choroidal neovascular membrane secondary to angioid streaks in Paget's disease — 12 month results

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Angioid streaks also called Knapp striae are small breaks in the Bruch's membrane and have been reported with a host of systemic diseases. Rupture of streaks or development of secondary choroidal neovascular membrane (CNVM) carries a dismal visual prognosis. We report the successful treatment of CNVM secondary to Paget's disease using low fluence photodynamic therapy (PDT) and intravitreal ranibizumab.

Key words: Intravitreal ranibizumab, Paget's disease, subfoveal choroidal neovascular membrane

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Angioid streaks are irregularly radiating linear streaks typically peripapillary in location. They appear with a crack-like dehiscence in the brittle, calcified Bruch's membrane. The three most common associations are with pseudoxanthoma elasticum, Paget's disease of the bone, and sickle hemoglobinopathies.[1] Although prevalence of ocular complications in Paget's disease is not as high as previously thought, development of the choroidal neovascular membrane (CNVM) carries poor visual prognosis.[2]

Argon laser photocoagulation shows high recurrence rates and decreased visual acuity. Photodynamic therapy (PDT) has shown poor results in CNVM secondary to angioid streaks, in the past.[3] However, we report successful treatment of CNVM with low fluence PDT followed by three doses of intravitreal ranibizumab, four weeks apart.

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Case Report

A 60-year-old, retired school teacher presented with sudden and painless onset of diminishing vision in the right eye (RE) of 20 days' duration. The patient was a known case of Paget's disease for the last 20 years and was on alternative medicine for the same. Systemic examination showed frontal bossing [Fig. 1], bowed legs, and bending of the forearm bones. He underwent cataract surgery with posterior chamber intraocular lens implantation in the RE two years back and in the left eye (LE) three years back. He had no history of previous ocular trauma. His best corrected visual acuity (BCVA) was 20/500 in the RE and 20/20 in the LE, without glasses. Pupillary reactions were normal; slit lamp biomicroscopy examination of the anterior segment showed pseudophakia in both eyes (BE), of normal axial length.

Fundus evaluation in BE showed bilateral multiple linear subretinal branching streaks radiating from the optic disc. In addition, the RE also presented with serous elevation in the macular area [Fig. 2]. Optical coherence tomography (OCT) was not possible due to massive frontal bossing, which prevented clear focus of the macula.

Fundus fluorescein angiography (FFA) showed transmission hyperflourescence corresponding to linear streaks in BE, along with early hyperfluorescence, with late leakage in the subfoveal location, suggestive of a classic subfoveal choroidal neovascular membrane in the RE [Fig. 3]. After taking the physician's opinion and informed consent from the patient, we treated the patient's RE with low fluence PDT followed by three monthly doses of 0.5 mg intravitreal ranibizumab (Lucentis® , Novartis India Limited). Low fluence PDT was performed with a light dose of 25 J/cm^2, with a power of 300 mwcm^2, exposure time of 83 seconds, and a spot size of 4000 microns. The first dose of 0.5 mg intravitreal ranibizumab was administered under aseptic conditions, 48 hours after the PDT laser procedure. This was followed by another two doses of intravitreal ranibizumab 0.5 mg, at four-week intervals.

Post injection, the BCVA in the RE improved from 20/500 to 20/80 at the end of the first month and remained stable throughout the treatment period of three months, and during six months of follow-up. No injection- or procedure-related complications were seen. FFA at the six-month and 12-month follow-ups showed regressed CNVM, with minimal scarring [Fig. 4 and 5].

Discussion

Terry was the first to report the association of angioid streaks and Paget's disease, a prevalence of 1.4%. Ocular complications in Paget's disease are of two types; intrinsic to the eye-like angioid streaks and CNVM and those resulting from compression of the orbital contents or sensory and motor nerves supplying the eye and adnexae.[2] Paget's disease with angioid streaks is diagnosed at an earlier age and also the disease has a more severe form. As there is development of choroidal neovascularization in the angioid streaks, the same mechanism may also be involved in neovascularization as CNVM, in age-related macular degeneration (AMD). The use of anti-vascular

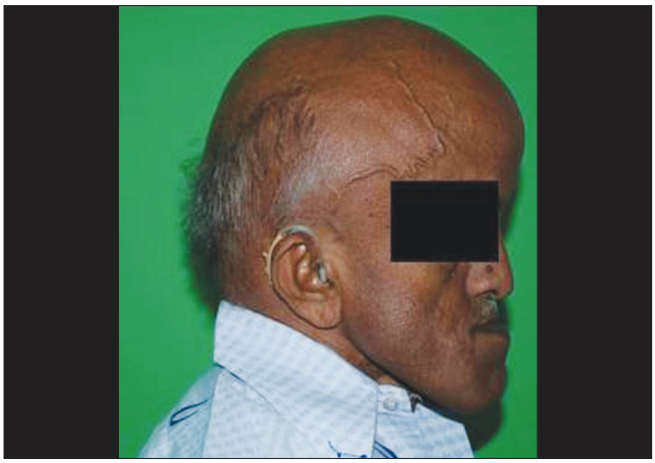

Figure 1: Photograph depicting frontal bossing and prognathism

endothelial growth factor (VEGF) drugs has been reported to have successful results.[4] One of the reported complications of the treatment of CNVM in the eyes is rupture of the Bruch's membrane. Low fluence PDT lowers the risk of a rupture of the already brittle Bruch's membrane, and hence, we planned a trial of intravitreal ranibizumab in combination with low fluence PDT, for treatment of the CNVM due to angioid streaks.

Photodynamic therapy causes selective closure of the CNVM (as verteporfin selectively binds to the endothelial cells of the neovascular frond) by angio-occlusion, secondary to vascular thrombosis.[5] Low fluence minimizes collateral damage to the adjacent choriocapillaries and overlying neurosensory retina and more importantly, reduces the risk of rupture of the Bruch's membrane. There is upregulation of the VEGF and the pigment epithelium derived factor (PEDF), post PDT. PEDF has positive effects, limiting damage to the surrounding retina and helps normal choroidal vessel recovery.

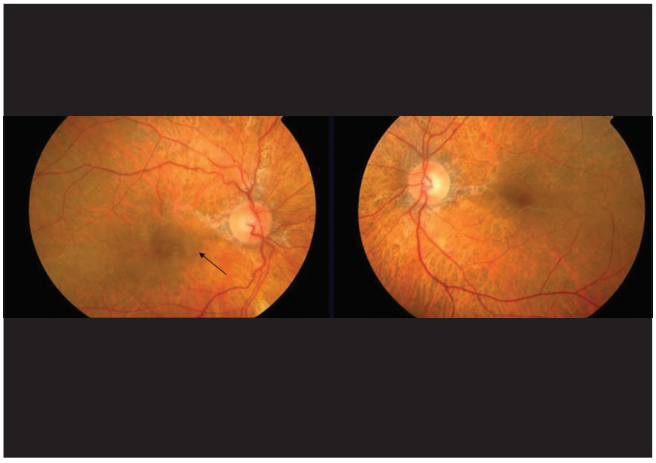

Figure 2: Fundus photograph BEs showing peripapillary multiple linear subretinal branching streaks. Serous elevation in the macular area of the right eye is suggestive of a choroidal neovascular membrane (black arrow)

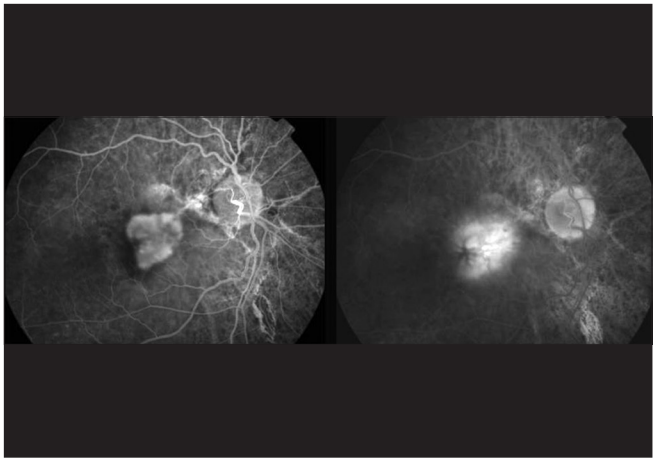

Figure 3: Right eye early phase flourescein angiography showing transmission hyperflourescence corresponding to linear streaks with lacy pattern of hyperflourescence. Late phase flourescein angiography showing leakage, suggestive of choroidal neovascular membrane

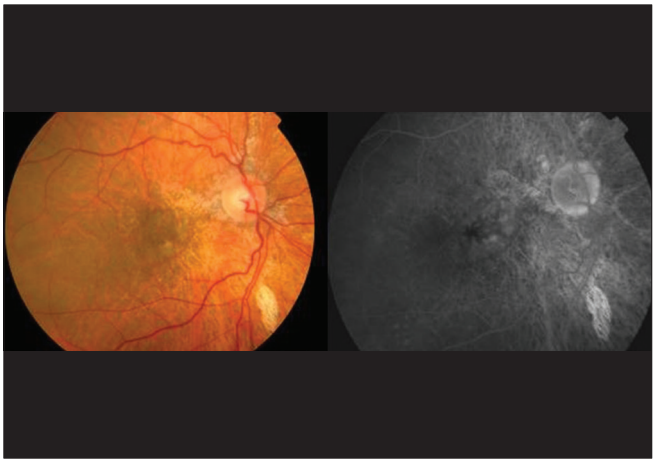

Figure 4: Six months post treatment, the right eye fundus photograph showing scarring with resolution of serous elevation. Late-phase fluorescein angiography shows absence of leakage with staining, suggestive of resolved choroidal neovascular membrane, with scarring

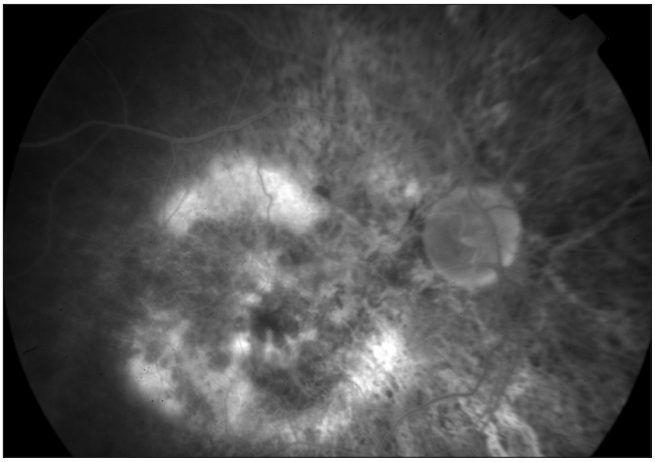

Figure 5: One-year follow-up with fundus fluorescein angiography shows a regressed and scarred choroidal neovascular membrane

However, VEGF upregulation peaks one week post PDT, resulting in recurrence of CNVM.[6] VEGF, a primary ligand for the endothelial tyrosine kinase receptors, has been strongly implicated in neovascularization within the eye in clinical and experimental studies and in the pathogenesis of CNVM.[7] Ranibizumab a monoclonal antibody fragment, binds to and inhibits all subtypes of VEGF-A with high affinity. A smaller size enhances retinal penetration. Being a Fab fragment, it has less antigencity and has been successfully used as a monotherapy and in combination with PDT, in the treatment of CNVM, secondary to AMD.[8,9] These studies show improvement in visual acuity with no significant ocular and systemic risks.

Review of content in medical databases like Medline, EMBASE, and PubMed did not bring to light or mention any case study of treatment of CNVM due to Angioid streaks, with intravitreal ranibizumab and low fluence PDT combination treatment. The rationale for the use of this combination therapy is the possibility it presents of attacking one component in more than one way or by attacking both components simultaneously. The combination therapy using anti-VEGF treatments in conjunction with PDT also potentially decreases the frequency of treatment.[10]

Our case study illustrates the use of the anti-angiogenic agent ranibizumab in combination with low fluence PDT, which may have the potential to improve visual outcomes and reduce the number of treatments in CNVM due to angioid streaks, resulting in the regression of CNVM and visual improvement. Moreover, low fluence PDT reduces the risk of rupture of the brittle Bruch's membrane. However, it requires further evaluation in randomized, controlled, clinical trials, to reach conclusive results.

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