Anti-VEGF Agents for the Treatment of Choroidal Neovascularization in Pseudoxanthoma Elasticum

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Abstract

Introduction: Pseudoxanthoma elasticum (PXE) is an inherited disease that affects multiple organs, including the skin, eyes, and cardiovascular system. Visual loss occurs at an early age secondary to choroidal neovascularization (CNV) resulting from angiod streaks (AS). Bevacizumab and ranibizumab, are anti-VEGF monoclonal antibodies, that have been shown to be successful treatment options for CNV secondary to neovascular age-related macular degeneration and other diseases, such as PXE. The current literature regarding the use of Anti-VEGF agents to treat CNV secondary to AS in PXE is limited. Herein, we report a small case series to show the efficacy of intravitreal bevacizumab and ranibizumab for treatment of CNV secondary to AS in PXE.

Clinical Description: Two patients presented at 48 and 51 years old, respectively complaining of blurry vision. The baseline visual acuity ranged from 20/25-20/400 in each of the four affected eyes. Both patients were found to have CNV secondary to AS due to PXE. Each eye was followed for a mean of 36.8 months and required a mean of 9 bevacizumab and 0.75 ranibizumab injections. Resolution of pathologic edema was demonstrated on OCT in each eye. The mean visual acuity deviation was 0.66 below baseline. No significant adverse events were noted.

Discussion: Intravitreal anti-VEGF agents are effective long term treatment options for CNV secondary to AS in PXE patients. Our small case series supports the current findings in the literature and is the only case series, to our knowledge, that has documented follow up exceeding 3 years.

Keywords: Pseudoxanthoma Elasticum; Angioid Streaks; Anti-VEGF Agents; Ranibizumab; Bevacizumab; Choroidal Neovascularization
1. Introduction

Pseudoxanthoma elasticum (PXE) is an inherited disease, with an incidence of 1:25,000-1:100,000, that affects multiple organs, including the skin, eyes, and cardiovascular system. Women are affected twice as often as men. Initial symptoms present at 13 years of age, but diagnosis is often not made until 22 years of age. PXE is associated with mutations in the ABCC6 gene and histological findings include fragmentation of calcified elastic tissues (Finger et al, 2009).

Clinically, PXE initially manifests with small, soft yellow-ivory colored papules that develop on flexor surfaces in a reticular pattern. With disease progression, the axilla, groin, and posterior aspect of the knee can be affected. Cardiovascular changes do not commonly present prior to the third or fourth decade of life. The most common cardiovascular complications include diminished peripheral pulses in 25% of cases, followed by arterial hypertension, angina pectoris, intermittent claudication and gastrointestinal hemorrhages. Cardiovascular involvement has not been shown to decrease life expectancy in most patients (Finger et al, 2009).

Ocular manifestations are a significant cause of disease morbidity and findings include peau d’orange, chorioretinal atrophies, and angioid streaks (AS) (Finger et al, 2009). Almost all patients develop AS within 20 years of diagnosis. These lesions appear as bilateral brownish-gray streaks radiating from the optic nerve into the periphery, measuring from 50 to 100 microns in diameter and causing adjacent pale retinal pigment epithelial atrophy later in its course. Resulting from calcified breaks in Bruch’s membrane (BM), AS can lead to fibrovascular growth through the cracks in BM resulting in choroidal neovascularization (CNV) (Finger et al, 2009; Gliem et al, 2013). CNV is the major cause of vision loss associated with angioid streaks occurring in 72%-86% of eyes with angioid streaks, is often bilateral, and has a poor prognosis if left untreated (Mansour et al, 1988). Herein, we present a small case series of 2 patients with PXE that developed bilateral CNV secondary to AS and their response to anti-VEGF therapy.

2. Case 1

A 48 year old female with a past medical history of lung cancer presented with blurry vision in her right eye for several months. Prior to presentation, the patient saw a dermatologist for a “sun burn” on the lateral side of her neck (figure 1). The lesion was biopsied and the patient was referred for an ophthalmologic evaluation.

Best corrected visual acuity (BCVA) was 20/70 OD and 20/25 OS. Amsler grid testing demonstrated peripheral distortion OD. Anterior segment exam was unremarkable. Dilated fundus exam showed peripapillary atrophy with linear lines radiating out in both eyes, consistent with AS (figure 2). Subretinal fibrosis was noted OD extending linearly in the temporal direction with pigmented mottling in the macular region. Peau d’orange was noted temporally in both eyes. The peripheral retinæ were intact bilaterally.

Fluorescein angiography (FA) showed abnormal vasculature with leakage extending in an inferior arc from the disc through the foveal region OD. Ocular coherence tomography (OCT) showed subretinal and intraretinal fluid bilaterally (figure 3). The patient’s exam and imaging findings supported the diagnosis of PXE.
For management of her PXE related CNV, the patient received 8 treatments OD and 1 treatment OS of intravitreal bevacizumab over 20 months and 4 months, respectively. The patient's mean BCVA during follow up was 20/80 OD and 20/25 OS with resolution of subretinal and intraretinal fluid bilaterally (figure 3). The patient experienced no adverse effects from the therapy.

3. Case 2

A 51 year old female with a known history of PXE with AS presented complaining of blurry vision in her right eye for two weeks. The patient was diagnosed 6 years prior and has since undergone multiple thermal laser photocoagulation treatments to her left eye for PXE related CNV. The patient currently has residual scarring in her left eye and noticed new onset blurry vision in her right eye. BCVA was 20/100 OD and 20/400 OS. Anterior slit lam exam was unremarkable. Fundoscopic exam showed AS in the peripapillary area with some macular thickening and mild pigmentary changes OD. Disciform scarring with serous retinal detachment was seen inferiorly OS.

FA demonstrated a choroidal neovascular membrane that originated in the superior temporal fovea OD. OCT demonstrated subretinal fluid in the corresponding area (figure 3).

For management of her PXE related CNV, the patient's right eye received 19 bevacizumab and 2 ranibizumab intravitreal injections over 75 months and her left eye received 8 bevacizumab and 1 ranibizumab intravitreal injections over 48 months. Mean BCVA during the treatment period was 20/80 OD and 20/400 OS with resolution of the subretinal fluid bilaterally (figure 3). The patient's only adverse effect during therapy was a self limiting corneal abrasion OD.

4. Discussion

Anti-vascular endothelial growth factor (VEGF) agents, ranibizumab and bevacizumab, are monoclonal antibodies that inhibit VEGF induced aberrant vascular growth and leakage (CATT Research Group et al, 2011). When administered intravitreally, they have been found to be efficacious in the treatment of neovascular age-related macular degeneration (Michels et al, 2005; CATT Research Group et al, 2011). Recent studies have reported the successful intravitreal use of anti-VEGF agents for the treatment of subretinal neovascular membranes in diseases other than AMD, such as PXE (Finger et al, 2011; Gliem et al, 2013). However, the current studies regarding use of anti-VEGF agents in the treatment of PXE related CNV are limited by both enrollment size and follow up time, with 28.6 months being the longest current follow up time in a study with 2 or more eyes (Myung et al, 2010).

Our small case series, consisting of 2 patients with bilateral PXE related CNV that were followed for a mean of 36.8 months per eye, demonstrated outcomes similar to those reported in previous cases that showed visual stabilization with modest improvement following treatment with intravitreal anti-VEGF agents (Rinaldi et al, 2007; Schiano Lomoriello et al, 2009; Myung et at, 2010; Finger et al, 2011). In our series, vision not only remained stable but improved in one case. Furthermore, anatomical improvement was demonstrated with resolution of subretinal or intraretinal fluid in both cases. Considering that the pathophysiology of neovascular growth results in increased permeability of fluid, its resolution in our cases confirms the effectiveness of our treatment.
We need to stress to patients the off-label nature of anti-VEGF therapy, the possible increased risk of ocular (Ganssaage et al, 2009) and systemic thromboembolic events (Besozzi et al, 2013). Larger prospective trials are needed to confirm the long-term efficacy and safety of this treatment; however, they will be difficult to conduct due to the rarity of this disease. Overall, based on this study and literature review, intravitreal anti-VEGF therapy remains the standard and seems to be the best choice at present to treat patients with CNV secondary to angioid streaks and PXE.

5. Pictures/Figures and Captions

**Fig 1.** Soft yellow-ivory papular rash on lateral neck of patient 1

**Fig 2.** Color fundus photograph (2A) depicting angioid streaks (long arrow), and fluorescein angiogram (2B) depicting CNV related leakage (short arrow) in patient 1
Fig 3. Macular OCT of patient 1 OD (3A,3B) and patient 2(3C-3F) demonstrating subretinal fluid (3A,3E) and intraretinal fluid (3C) prior to anti-VEGF therapy and resolution of fluid (3B,3D,3F) with subretinal fibrosis (3D,3F) following intravitreal anit-VEGF therapy. OCT OS unavailable for patient 1.

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