CNVM in POHS

Abstract

Purpose: Presumed ocular histoplasmosis syndrome (POHS) is a condition that is caused by an infection of Histoplasma capsulatum, a fungus. This particular fungus can either cause systemic manifestations, ocular manifestations, or both.

Case Report: This case report reviews the management of patients with a neovascular membrane secondary to POHS, discussing the clinical findings and treatment options as they relate to the case presented.

Conclusion: There is a wide variety in severity of this condition, ranging from minor ocular signs to blinding conditions. It is important to watch for any of the triad of signs of this condition and to make sure to monitor patients who have more than one of the signs closely to ensure prompt treatment if a neovascular membrane arises.

Case Report

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Abbreviations: POHS: Presumed Ocular Histoplasmosis Syndrome; CNVM: Choroidal Neovascular Membrane

Introduction

Presumed ocular histoplasmosis syndrome (POHS) is a condition that may arise after systemic infection by the fungus *Histoplasma capsulatum* [1-9]. Patients who present with POHS tend often have lived in the Ohio-Mississippi River Valley at some point because this is where the fungus is native. In order for a patient to have any ocular manifestations, there had to have been a systemic infection, even if subclinical. There is no predilection for gender or race in this particular condition. Also, patients may have systemic signs, ocular signs, or both after infection by this fungus. Most patients are unaware of any illness caused by this particular fungus because most of the illnesses are subclinical [1-9]. There is no predilection for someone who has a severe systemic infection to also have severe ocular signs or vice versa. POHS can be unilateral or bilateral. If there are going to be severe ocular complications, POHS tends to manifest in people who are in their working years, early thirties to early sixties [1-9]. Clinically, there is a triad that clinicians search for on dilated fundus examination to determine whether a patient has POHS: atrophic scars in the macula or periphery-known as punched out lesions, peripapillary atrophy, and CNVM [1-9].

A choroidal neovascular membrane (CNVM) is the worst case scenario for a patient with POHS because if not detected quickly and treated, especially if in the macula, it can be blinding. There is no set way of determining whether a patient with POHS will develop a CNVM, but the general theory is that at some point there is a generalized inflammation/re-activation of one of the punched-out lesions, which can then cause the choroid to become inflamed. Once the punched-out lesion is inflamed, Bruch's membrane can be broken, which then compromises the blood-retinal barrier, and allows a neovascular membrane to form [1-9]. A CNVM can resolve on its own in this case into a disciform scar. The other type of severe issue a patient with POHS can have is inflammation of the choriocapillaris and swelling in this area can cause inflammation in the RPE also, which can lead to a hemorrhagic retinal detachment [1-9]. In the case of a patient who has documented punched-out lesions, the loss of vision either unilaterally or bilaterally should be investigated thoroughly to make sure that a CNVM has not developed [1-9].

Case Report

Patient DT, a 65-year-old Hispanic male, presented to our clinic on August 5, 2013 with complaints of blurry vision and a central missing spot in the vision of his left eye. It had started two months previously, but had gotten worse over the last few weeks. The patient denied any flashes of light or floaters and denies any trauma. The patient's last eye examination was March 2, 2013 with no clinical findings other than several "punched-out lesions" in the mid-periphery in each eye. The patient's medical history was significant for insulin-dependent type 2 diabetes mellitus x10 years and hypertension that was well-controlled with medication. The patient's family ocular and medical history was unremarkable. His best corrected visual acuity was 20/20 OD, 20/200 OS with no improvement with pinhole OS, this patient still reported that there was a missing spot in the center portion of the letter when he was looking only with his left eye. Other entrance testing was normal. Slit lamp examination showed mild NS, mild cortical spoking OU on the lens, with no other significant findings noted.

The posterior segment evaluation after dilation revealed ten punched-out lesions per eye with peripapillary atrophy in both eyes. The CD ratio was 0.35 vertical and horizontal OU. There was no diabetic retinopathy OU. When evaluating the macula, there was slight elevation OD and OS had a gray-green elevated lesion. No other ocular pathology was observed. An OCT was performed in office to confirm diagnosis; the OCT seen below confirms the presence of a CNVM OS with associated edema. The right eye had the start of a small CNVM with mild adjacent edema.

The patient was referred to a retinal specialist so that he could be further evaluated and treated for his neovascular membrane. At primary evaluation with the retinal specialist, his best corrected vision was 20/60 OD, 20/400 OS, with reported missing sections out of his vision in each eye. An injection of Avastin was recommended to the patient for treatment of his left eye, and in four weeks the patient was to return for an injection in the right eye. The patient declined any injections at this visit.

He went back to the retinal specialist two months later feeling like his vision had gotten a lot worse and that he would like to proceed with whatever treatment necessary to get his vision back. Mr. DT's best-corrected vision at this visit was 20/80 OD, 20/200 OS. No other significant findings were noted. An Avastin injection was performed on the left eye. After several more follow-ups and three more Avastin injections OS with no injections OD (Figure 1 & 2), his best corrected visual acuity was 20/50 OD, OS with no pinhole improvement. His right eye had mild macular edema with associated RPE loss and loss of the foveal light reflex, the punched-out histoplasmosis lesions in the periphery were still noted, and no other ocular pathology was noted.

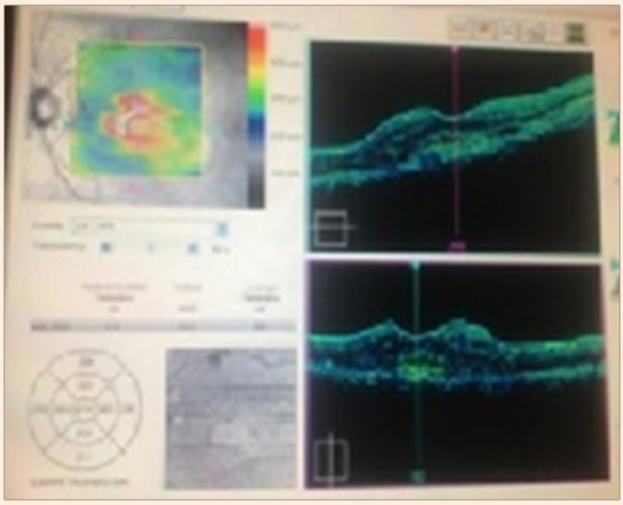

Figure 1: OS OCT

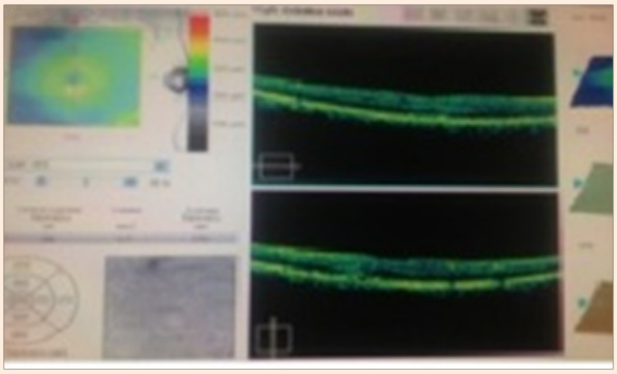

Figure 2: OD OCT

His left eye had CNVM present with associated subretinal fluid and a PED, the histoplasmosis lesions in the periphery were still present, and no additional ocular pathology was noted. A fluorescein angiogram was also performed at this visit. In the right eye there were focal punctate autofluorescent lesions, with dark choroidal circulation noted, along with late leakage of the central macular area. The left eye's angiogram showed similar findings to that of the right eye with more late leakage in the central macular area. An Avastin injection was recommended and was performed in the left eye, making a total of 5 Avastin injection treatments for the OS. Below is the OCT of his left eye after 5 Avastin injections. There is a decrease in the amount of subretinal fluid, but the CNVM is still present with some mild edema adjacent (Figure 3).

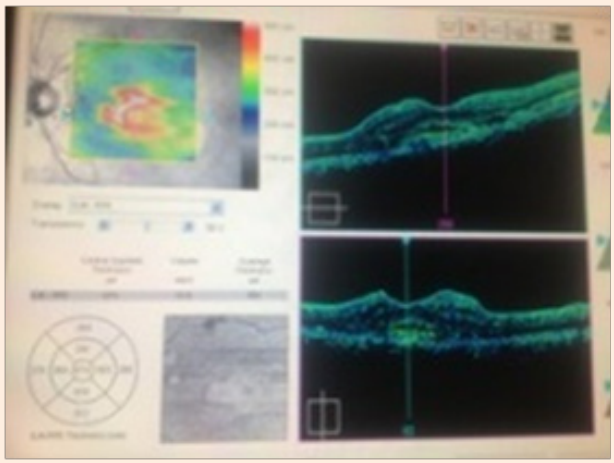

Figure 3: There is a decrease in the amount of subretinal fluid, but the CNVM is still present with some mild edema adjacent.

Discussion

Histoplasmosis infection in humans is usually caused from inhalation of the fungal spores, which travel to the pulmonary and circulatory systems and can make their way to the uveal tract of the eye [1-9]. Usually the fungus is walled off in a type of granulomatous inflammatory response, but the infection can be re-activated with no precipitating cause. Often re-activation is seen in patients who are immunocompromised [2-9]. People who have POHS have often lived in the endemic area for this fungus, the Ohio-Mississippi River Valley, and there is an incidence rate of 1.6-6.3% in this particular population [1-9]. The histoplasmin test can be performed to determine if a patient has been exposed to this fungus [3,6,9]. Patients, however, may react positively to this skin test but may not have any ocular manifestations, or vice versa [3,5-9].

The most widely accepted belief for how POHS occurs is that there is a subclinical infection of *Histoplasma capsulatum* and there are small granulomas that occur in the choroid, which can cause scars in the RPE [2-9]. These scars can often be accompanied by a break in Bruch's membrane, which can allow a neovascular membrane to form. There is also a common belief that the peripapillary atrophy that is one of the features of the ocular histoplasmosis triad is an area of regressed CNVM [4,6,9]. Most researchers agree that the peripheral lesions are the most common feature associated with ocular histoplasmosis, followed by the area of peripapillary atrophy, with only 5% of those patients ever developing a CNVM with possible vision-threatening complications [3-9].

Patients with POHS who develop a CNVM tend to be in their early 40s-early 50s, but it can occur at any age [1,3,5-9]. There is no predisposing factor for gender, and all races can be affected, but a CNVM is less likely in the African American population [2,6-8]. Clinically, patients will have at least two of the three features of the ocular histoplasmosis triad (punched-out lesions, peripapillary atrophy, and CNVM). If there is a macular CNVM,

patients will usually complain about blurriness, missing aspects of their central vision, and distortion of their central vision [1-3,5,6]. The majority of patients who have a macular CNVM also have a punched-out lesion relatively close to the macula [3-5,7-9]. Also, this particular form of membrane tends to eventually lead to a hemorrhagic macular detachment rather than a serous macular detachment.

There are two types of CNVM that can form in the macula, foveal and extra foveal, similar to the two types that can form in ARMD [4-9]. According to most studies, without treatment, more than half of the patients who had a macular CNVM would lose vision to the level of 20/200 or worse, with a higher risk for vision loss in those that had foveal CNVM. The risk for losing vision from a macular histoplasmosis punched-out lesion developing into a CNVM is about 10% at 5 years and about 20% at 10 years [1-9]. It is still difficult to predict whether a patient will develop a CNVM in general, similar to the level of difficulty in guessing whether a patient's macular degeneration will turn wet.

Other differentials in this case include:

i. ARMD

ii. Diabetic Macula Edema

iii. Central Serous Retinopathy

iv. CNVM secondary to POHS

ARMD generally has drusen associated with macular changes. Also, there tend to be RPE changes and atrophy prior to the ARMD progressing into a wet form. Diabetic macular edema is caused by a breakdown in the blood-retinal barrier where fluid from the retinal capillaries and blood vessels leak and build up in the macular area. Diabetic macular edema is usually not seen by itself without any other signs of diabetic changes. Central serous retinopathy typically appears as a focal serous detachment. It is most often seen in young people, and the appearance of the detachment is dome-shaped. CNVM secondary to POHS can appear as a gray-green lesion, and it can be located in the macula, near the optic nerve, or even in the periphery. There can be associated thickening around the area of the gray-green lesion. Signs of drusen or other pathology are not often noted, other than punched-out lesions, peripapillary atrophy, or both.

There were no drusen or diabetic changes anywhere in the retina. There were no holes or tears in the retina. The macular elevation did not appear dome-shaped. The lesion in the macular area in the left eye had a gray-green color, and the patient was diagnosed with CNVM secondary to POHS because of the peripapillary atrophy and punched out lesions in the periphery.

Several treatment options exist for choroidal neovascular membranes associated with POHS. One option is surgical removal of choroidal neovascularization around the optic nerve and even extending perimacular region. One study examined the outcome of 14 patients who had this surgery performed, with the majority of the patients having CNVM extending into the fovea. This study determined that this surgery was successful because the majority of patients regained 20/40 vision or better after the surgery [10-12]. However, there were several downsides with this treatment. The surgery was invasive; a vitrectomy was performed in addition to the surgical removal of the CNVM.

This surgical option is also reserved for worse-case scenario patients, where no other treatment appears to be a viable option. Another study came to similar conclusions. Sixty-three patients were evaluated after surgical removal of the CNVM, with approximately 18% of these patients achieving better than 20/50 vision, and 40% of patients having no change in visual acuity status [10-12]. Patients that completed this surgical removal were less likely to have recurrences of the net if they were younger patients and had not had prior laser treatment. Also, with this removal, if a net were to recur, it usually happened within the first five months after surgery; this recurrence happened in approximately 40% of the patients [10-12]. The surgical removal of a recurrent membrane did not show significant improvements in the patients, and other treatments had to be tried [10-12].

Another type of treatment for CNVM secondary to POHS is laser photocoagulation. A study completed by Drs. Cummings, Rehmar, Wood, and Isernhagen was designed to evaluate the long-term results of laser photocoagulation on the CNVM associated with POHS. One hundred eyes were studied, and they were grouped according to the location of the nets, either extra foveal or juxtafoveal; there was also the observation only group. This study revealed that patients with extra foveal nets achieved 20/40 acuity or better 71% of the time, with juxtafoveal coming in at 68% of patients achieving the same level of acuity. Approximately one-quarter of the patients involved in this study had a recurrence of the neovascular membrane [13]. One major disadvantage of performing laser treatment in the macula is that it can only be repeated a limited number of times before visual acuity suffers. Also, while not necessarily a disadvantage, there is a cost-benefit ratio to consider with laser treatment. Once the laser has been completed, the patient is generally less responsive to any other treatments if the neovascular membrane recurs [10,13,14].

Photodynamic therapy with verteporfin for CNVM caused by histoplasmosis is where new research is leading. Forty patients were evaluated in a retrospective chart review, and those patients that received treatment developed almost a complete line of visual acuity improvement. Most of these patients did not have recurrence of the neovascular membrane [15-18]. Also, this treatment is effective even if a patient has had the surgical removal of the CNVM in the past. This particular treatment involves an IV injection of verteporfin which concentrates itself in abnormal vascular structures. This tissue then becomes illuminated with a non-thermal laser source using the wavelength of peak sensitivity of verteporfin, causing irreversible cellular damage to this tissue and this tissue specifically [15-18]. The advantage to this particular treatment is that there is less collateral damage because the treatment area is more specific and less invasive. Also, there is no thermal energy applied to the eye [15-18].

Immunosuppression techniques in conjunction with verteporfin are also being investigated in the treatment of CNVM caused by POHS. Two studies have been completed investigating the effects of this treatment modality on CNVMs of all etiologies, not just those caused by POHS. Both studies concluded that there is some benefit seen to using both triamcinolone vitreal injections and verteporfin with PDT to help patients have a better visual outcome in the long run [19-20]. However, both of the studies were small and retrospective, so a randomized clinical trial would need to be performed in the future, not only evaluating the visual

acuity outcomes, but also evaluating the recurrence rates for patients [19-20].

Immunosuppression alone, via triamcinolone injection, has also been evaluated in the treatment of CNVM from POHS. This study was also small, with five in the juxtafoveal and five in the subfoveal net groups [21]. The results of this study are promising in the sense that 30% of the patients achieved a gain of more than five letters, and visual acuity remained stable in 50% of patients [21]. While optometrists and ophthalmologists are looking for the overall health of the eye, the visual acuity is an important feature to patients, so a successful treatment would at least need to keep the visual acuity stable or possibly improve it. The concerns raised by the authors of this study were the transient increase in IOP and the increased risk for cataract development [21].

Finally, the last treatment being investigated for the treatment of CNVM caused by POHS is intravitreal anti-VEGF agents. There have been multiple case review studies that have supported anti-VEGF agents being effectively used to treat the CNVM caused by POHS. Depending on the review, between 60-80% of patients developed an increase in central visual acuity with most of the patients ending up around 20/50 [10,22-24]. Some benefits of the intravitreal injection are that there is no surgery involved, it is effective in treating a macular edema caused by CNVM, and is even effective in decreasing edema caused by diabetes. The anti-VEGF agents block the formation of new neovascularization and work to help stabilize the blood-retinal barrier so that eventually the neovascular membrane will die off. An advantage of this particular treatment compared to the gold standard, the laser, is that the patient does not develop a scotoma as they do in the laser procedure [10,22-24].

Conclusion

Presumed ocular histoplasmosis syndrome is common in the United States, especially for people living in the Ohio-Mississippi River Valley area. It is important for clinicians to document these changes in the retina so that they are appropriately monitoring patients who are at risk for developing a CNVM. We as clinicians have tools at our disposal, the OCT and the FA, that can monitor leakage and edema in the retina. We have a duty to our patients to monitor them appropriately and refer them as soon as we see signs of a CNVM. The sooner a patient receives treatment, the more likely the treatment will be successful. While there is currently no perfect treatment for these patients, there is much research being done in this area and progress is being made.

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