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**Description**
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**Keywords**
Interferon, Retinopathy, Hepatitis C

**Disciplines**
Infectious Disease | Ophthalmology | Optometry

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Interferon Retinopathy in a Monoinfected Hepatitis C Patient
A Case Report

Tracy Doll, O.D., F.A.A.O

Abstract:
Retinopathy associated with alpha-interferon therapy is a common finding for patients with progressive Hepatitis C. My report is on a case presentation of interferon retinopathy and transient visual disturbance in a patient being treated for progressive Hepatitis C.

Key Words:
Interferon, Retinopathy, Hepatitis C

Introduction:
Patients on anti-viral therapy for Hepatitis C are at risk of developing retinopathy. The exact pathogenesis of interferon retinopathy is unknown at this time, but the retinal presentation is very similar to immunocompromised and systemic vascular disease manifestations. I present a case of interferon retinopathy in an immunocompetent patient with chronic Hepatitis C and discuss current advances in treatment for Hepatitis C.

Case Report:
A 45-year old Caucasian male presented with the chief concern of a new “blurry spot” in the right temporal visual field. He also reported a slow decrease in his visual clarity over the last “couple of months.” He attributed the visual symptoms to the new medication he had been taking for Hepatitis C (HCV). The patient denied any previous episodes of vision loss or blurred vision. This was his first eye exam. Best corrected visual acuities were 20/20 right eye (OD) and 20/20 in the left eye (OS). Extraocular muscle testing showed no restrictions. Pupils were equal, round, and reactive to light with no relative afferent pupillary defect. Biomicroscopy revealed only mild pingueculae OU for which the patient was asymptomatic.
A frequency doubling technique (FDT) visual field screening N-30-5 showed no defects, but questionable reliability of the test in the left eye. The right eye had no defects and was reliable.

A dilated fundus exam revealed five large cotton wool spots in the posterior pole of the right eye and six cotton wool spots in the posterior pole of the left eye. No hemorrhages, microaneurysms, or retinal edema were detected. The blood vessels were of healthy caliber and no artery-vein crossing changes were noted. The cup- to- disc ratio of the optic nerves was 0.40 round in each eye, and the margins of the discs were distinct. One of the cotton wool spots OD correlated to the subjective location of temporal blur for the patient. The initial retinal findings can be seen in Figure 1.

A review of the patient’s medical history and medical records confirmed he was prescribed a daily interferon (Alphacon) injection regimen of 0.5mL/15mcg daily to treat liver cirrhosis caused by HCV. The patient was also taking Ribivarin 200mg caplets three times daily to supplement the interferon therapy. The combination interferon therapy was initiated three months prior to the initial eye examination. The patient had no other medical conditions diagnosed by his primary care physician or liver specialists and was not taking any other medications. He reported, and medical records confirmed he was negative for hypertension, diabetes mellitus and the Human Immunodeficiency Virus (HIV). The patient had also quit smoking within the last year and stopped alcohol use two years prior.

The diagnosis of Interferon Retinopathy in both eyes (OU) was made based on the systemic health findings and isolated cotton wool spots. The possibility of a branch retinal occlusion was not yet ruled out OD in correlation with the perceived visual disturbance. The patient was scheduled to return to a retinal specialty clinic within one month for a fluorescein angiography (FA) and retinal evaluation. The patient’s liver specialists and primary care doctors were also made aware of the findings.

Retinal Follow-Up #1:
Two weeks later the patient reported that he could “barely notice” the intermittent blurry spot in his temporal visual field OD that he had mentioned at the first visit. His fourth month of the interferon therapy continued.
Visual acuity was stable OU. Another FDT Visual Field Screener N-30-5 showed identical results to the first visit: no defects, but questionable reliability OS, with 2/3 fixation errors. Once again, the subjective superior- temporal defect noted at the last visit was not identified with the screening field.

The dilated fundus exam revealed an increase in the amount of cotton wool spots: OD had nine large and four small cotton wool spots and OS had twelve large cotton wool spots in posterior pole. There was no technician available to perform the FA or photos at this appointment, so an imaging appointment was set for the following week. The patient’s liver care team was notified of the findings again.

Retinal Follow-Up #2
The patient returned for a FA and color photos, as scheduled (Figure 2). His unaided visual acuity remained stable. The FA showed “no obvious involvement of the vessels or microvasulature immediate to the fovea.” There were some microvascular changes seen in the arcades supero-temporally OD and infero-temporally OS. The cotton wool spots did block and stain “a little” (Please note that while FA was reported as being done, the angiography photos were not provided by the retinal specialist).

The patient was educated that the changes in his eye were likely to be from his interferon therapy and that there might be a possibility of macular involvement in the future. The patient still elected to continue his HCV therapy. It was decided that close retinal monitoring would occur.

Retinal Follow-Up # 3
One month later, per FA, no ischemia was noted at the foveal region (Figure 3). The cotton wool spots were relatively stable, with the disappearance of some and the appearance of new cotton wool spots to take their place in other locations through the posterior pole (Figure 3-5). The patient still elected to continue with HCV interferon therapy. He was scheduled for retinal monitoring in 12 weeks.

Liver Specialty Clinic Follow-Up Summary:
Six months after the appearance of the interferon retinopathy, the patient’s viral load testing did not show any change from the time he had initiated interferon therapy: the viral load was low, but detectable. The HCV antiviral therapy was tapered at this point, as his liver team stated that “research confirmed that there would not be a sustained viral response unless the virus is undetectable during treatment, and that prolonged treatment does not help past this time.” He was instructed to take a 50% dose three times and dispose of the rest of the interferon.

Retinal Follow-Up #4
A dilated eye-exam occurred two months after the cessation of his interferon treatment. It appeared that the concentration and size of the cotton wools spots had decreased. A follow-up appointment was made for six months to monitor resolution of the interferon retinopathy. His ocular prognosis was determined to be excellent. The patient was lost-to follow-up, so it is unknown if he has sought treatment for his liver disease with the newer HCV treatments FDA approved end of 2013 and 2014.

Figure 1: Cotton Wool Spots detected at Initial Exam
Figure 2: Interferon Retinopathy OU at Month 2

Figure 3: Fluorescein Angiography Showing Cotton Wool Spots in Interferon Retinopathy
Early Phase (left), Late Phase (right)

Figure 4: Interferon Retinopathy from Initial Presentation (left) and 3 Months Later (right)
Discussion

Alpha interferon is a drug used to treat multiple viral and malignant systemic conditions, most commonly Hepatitis C. Different types of cancer and multiple sclerosis are also less commonly treated with interferon. Hepatitis C is a blood-borne RNA (ribonucleic acid) virus that specifically targets the liver and can lead to severe chronic liver (cirrhosis and fibrosis) disease over time. Cirrhosis was the 8th leading cause of death in the United States in 2010. In advanced stages, the liver damage is irreversible and can necessitate a liver transplant. The National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) of the National Institute of Health states that one of the normal treatment regimens for progressive HCV includes a 24- or 48-week course of the combination of pegylated alpha interferon and ribavirin.

Alpha interferon is a protein produced by the body with natural antiviral properties. Synthetic forms of this protein have been formulated and are used to fight HCV and other
viral infections. The most common type of interferon used is pegylated or peginterferon. Pegylated interferon has a molecule of polyethylene glycol added to the interferon molecule that increases the protein’s half-life and stability in the bloodstream. Pegylated interferon can thus be injected less frequently than standard interferon. HCV also responds at a higher rate to pegylated interferon versus traditional alpha interferon (6).

Ribavirin is an oral antiviral agent that increases the response of the HCV to alpha interferon by two to three times. On its own, ribavirin does not act effectively against the HCV and it is not recommended for monotherapy (6).

The National Institutes of Health Consensus Development Conference Panel has recommended that this combination therapy be limited to only “those patients who have histological evidence of progressive disease (6).” Progressive disease is defined as “liver fibrosis or moderate to severe inflammation and necrosis determined by a liver biopsy (6).” Patients are not selected based on their individual symptoms, the serum HCV RNA levels or genotype, or the mode of HCV acquisition (6). One exception to this rule is applied when the patient has a concurrent Human Immunodeficiency Virus (HIV) infection. The HCV can progress more rapidly in these patients due to the immune system breakdown caused by HIV. As long as there are no contraindications with using this combination therapy with the HIV or AIDS medical therapy, interferon can be used in the absence of fibrosis or moderate to severe liver necrosis (6). In 2011, combination therapy was also approved for children and adolescents with chronic HCV (11).

The dosing for combination therapy is dependent on the specific subtype of the patient’s HCV. Genotype 1 of the HCV virus is less responsive to treatment (only 45 to 48 percent respond) and thus a full 48-week time course is recommended. The genotypes 2 and 3 tend to yield a higher response rate of 70 to 80 percent and thus a shorter course of 24 weeks has been determined to be just as effective as 48-week course of therapy. Genotypes 4-6 have not been studied as extensively and therefore follow the longer treatment course of genotype 1. Genotyping of the HCV virus is thus essential to determine appropriate time course of treatment and is normally performed before
Combination treatment is initiated (6). Also note that ribavirin dosing varies with the genotyping.

The combination of pegylated alpha interferon and ribavirin is only determined to be successful long-term in the treatment of HCV if the virus’s RNA is undetectable during treatment and stays completely undetectable after treatment (determined by serum blood testing). About 70% of patients placed on this regimen have complete disappearance of the HCV RNA. The relapse rate is lower in patients on this combination versus monotherapy with just the alpha interferon. The ultimate goal of this therapy is a sustained response, indicated by HCV RNA that remains undetectable for six months or more after stopping therapy. The overall response rate for a 48-week combination therapy is about 55% (6).

There were no other effective treatments identified if this combination therapy failed until December 2013. The new antiviral, Sofosbuvir, a NS5B polymerase inhibitor was approved for addition to pegylated alpha interferon and ribivarin therapy regimen in HCV genotypes 1, 4, 5 and 6. Then in November 2014, a new antiviral, semeprivar in combination with sofosbuvir was approved as a therapy for patients with genotype 1 monoinfection with HCV. This offers an alternative to patients for whom pegylated alpha interferon therapy has not worked. For genotype 2 or 3 the combination sofosbuvir and ribivarin are the very first completely oral therapy for HCV. The new therapies for HCV can be seen in Table 1.

Table 1: Current Treatments for Hepatitis C

<table>
<thead>
<tr>
<th>Genotype Category</th>
<th>Recommend treatment options for HCV Mono-infection</th>
<th>Recommend treatment options for HCV /HIV co-infection</th>
</tr>
</thead>
</table>
| Genotype 1        | • Sofosbuvir + peginterferon-alfa + ribavirin for 12 weeks  
                    • Interferon ineligible: sofosbuvir + ribavirin for 24 weeks  
                    • Interferon ineligible: Simeprevir |   • Sofosbuvir + peginterferon-alfa + ribavirin for 12 weeks  
  |                   |                                                |   • Interferon |

...
+ sofosbuvir for 12 (no cirrhosis)  
24 weeks (cirrhosis)
- In those with hepatocellular carcinoma awaiting liver transplant: sofosbuvir + ribavirin for a duration of up to 48 weeks or until transplant, whichever occurs first
in ineligible:
sofosbuvir + ribavirin for 24 weeks

<table>
<thead>
<tr>
<th>Genotype 2</th>
<th>Sofosbuvir + ribavirin for 12 weeks</th>
<th>Sofosbuvir + ribavirin for 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 3</td>
<td>Sofosbuvir + ribavirin for 24 weeks</td>
<td>Sofosbuvir + ribavirin for 24 weeks</td>
</tr>
<tr>
<td>Genotype 4-6</td>
<td>Not well studied, follow Genotype 1</td>
<td>Not well studied, follow Genotype 1</td>
</tr>
</tbody>
</table>

Though pegylated alpha interferon is useful for treating progressive HCV (and various malignancies), ocular side effect from the medication can occur. Common interferon retinopathy ocular signs include cotton wool spots, located especially around the disc, retinal hemorrhages and microaneurysms, and white centered hemorrhages (1,2,5,9). The incidence of retinopathy varies in reports from 18-89% of interferon users (2,9). These findings are most often asymptomatic. In more severe cases, branch vein occlusion, retinal neovascularization, optic disc edema, pre-retinal or vitreal hemorrhages, retinal detachment or cystoid macular edema could occur and lead to severe vision loss (4,5,8). Oculomotor paralysis has also been reported (8). Interferon retinopathy can occur anytime during the course of therapy, though most commonly begins within the first month of treatment (9). Retinopathy can also occur just after stopping therapy (9). Fluorescein angiography can further reveal signs of interferon retinopathy. Retinal hemorrhages are seen as a blocking of background fluorescence. Non-perfused areas in the retina will indicate the cotton wool spots. Table 2 lists the common retinal findings reported in interferon HCV therapy.

Table 2: Interferon- Related Ocular Complications Reported (4,5,8)
Cotton Wool Spots
Retinal Hemorrhages
Microaneurysms
White-centered hemorrhages
Branch vein occlusion
Retinal neovascularization
Neovascular glaucoma
Optic disc edema
Pre-retinal or vitreal hemorrhages
Retinal Detachment
Cystoid macular edema
Oculomotor paralysis

The pathogenesis of interferon retinopathy is still largely undetermined. Microcirculation injuries leading to ischemia has been determined to be the most likely cause by studies using fluorescein angiography. These studies demonstrate poor retinal perfusion in eyes with interferon retinopathy (2,4,5). Another proposed mechanism is damage caused by immune complex deposition. About 10% of patients will develop antibodies to alpha interferon (2,8,9). Leukocyte infiltration of vascular endothelium has also been postulated to lead to vascular damage in various animal models (3,8).

A side effect of treatment with interferon is the development of systemic anemia. Anemia-induced tissue hypoxia may result from a decrease in the amount of oxygen delivered to retinal tissues. In a study of retinal blood flow measured by Doppler imaging, it was postulated that an increase in retinal blood flow might result from a drop in oxygen secondary to anemia. The retinal blood flow rate would increase to compensate for low oxygen content (4,8).

Risk factors for developing interferon retinopathy have been identified. Studies have correlated not only higher dosages of interferon (5), but also the use of the specific type, pegylated interferon (2) to increased risk of interferon retinopathy. Intravenous or intramuscular injection treatments of interferon range from $3 \times 10^6$ units three times a week to $9 \times 10^6$ units six times a week (2,7,9). This dosage is usually tapered over time and
can vary to treat different HCV types. In addition to the use of interferon, systemic hypertension, diabetes mellitus, and increased triglycerides are also risk factors as they can lead to microvascular insult even independently of interferon therapy (2,8). Increased age was also identified as a possible risk factor. The one thing that has not been identified as a risk factor in the literature is the use of ribivarin with pegylated interferon. Risk factors for the development of interferon retinopathy can be seen in Table 3.

<table>
<thead>
<tr>
<th>Table 3: Risk Factor for the Development of Interferon Retinopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased dosage level of interferon</td>
</tr>
<tr>
<td>Use of pegylated type of interferon</td>
</tr>
<tr>
<td>Systemic hypertension</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Increased triglycerides</td>
</tr>
<tr>
<td>HIV infection</td>
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<tr>
<td>Increased Age</td>
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</tbody>
</table>

Interferon retinopathy shares many similar findings with other vascular diseases in the eye. Diabetic retinopathy, hypertensive retinopathy, and vascular occlusions can all include cotton wool spots and retinal hemorrhages (2,8). Early HIV retinopathy is also hallmarked by isolated cotton wool spots. As mentioned before, any of these conditions when concurrent with HCV interferon treatment can increase the risk of interferon retinopathy (2,8). It is therefore, crucial to run blood and serology laboratory medical tests to rule in or out these conditions. If interferon therapy is discontinued, the signs of retinopathy will generally dissipate within 4-6 weeks, which in itself can make the diagnosis definitive.

Pegylated Alpha Interferon therapy can also cause systemic side effects including: fatigue, muscle aches, headaches, nausea and vomiting, skin irritation at the injection site, low-grade fever, weight loss, irritability, depression, mild bone marrow suppression, and reversible hair loss. Ribavirin, used in the combination therapy also causes side effects including: anemia, fatigue, irritability, itching skin rash, nasal congestion, sinusitis, and
The combination therapy does tend to cause more side effects versus alpha interferon monotherapy. Other less common side effects include: autoimmune disease (especially thyroid disease), severe bacterial infections, marked thrombocytopenia and neutropenia, seizures, depression and suicidal ideation or attempts, hearing loss and tinnitus (6). Even in the face of all the possible side effects patients with severe end stage liver disease often choose to take the risks of treatment in order postpone the need for liver transplantation.

**Conclusions**

Patients who are placed on interferon therapy should have a baseline complete eye examination including careful evaluation of the fundus. This will help to rule out any pre-existing retinopathy, especially in those who have concurrent vascular health problem. The patient should be monitored during the course of the projected treatment, at three month intervals in those with no pre-existing retinopathy and monthly in those with retinopathy before treatment. The patient should also be educated to return for an examination immediately if any changes in vision are noted.

The decision to stop interferon therapy secondary to findings of retinopathy must be weighed carefully. Most often the benefits of the therapy systemically will outweigh the risk of visual impairment. In this case, the patient elected to protect his liver health and continue his interferon therapy, as there were no signs of visual impairment other than a mildly bothersome visual field disturbance. Monitoring the eye health alone seemed to be the best option in this specific case.

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