Interferon-induced Retinopathy in Asymptomatic Cancer Patients

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Objectives: Interferon-induced ocular complications, including retinal ischemia and ischemic optic neuropathy, can be associated with significant visual loss. We report three cases of asymptomatic ischemic retinopathy in cancer patients receiving interferon.

Design: Retrospective, interventional, noncomparative small case series.

Methods: Retrospective review of the medical records and fundus photographs.

Results: Interferon-induced ischemic retinopathy can occur in asymptomatic cancer patients. The retinal changes are usually reversible with discontinuation of interferon therapy.

Conclusions: These three cases underscore the importance of dilated funduscopic examination at baseline and during follow-up, at least every 3 months, for all cancer patients receiving interferon to identify retinal toxicity at its earliest stages. A prospective study evaluating the incidence and severity of interferon retinopathy in cancer patients would be prudent. *Ophthalmology 2001;108:858–860 © 2001 by the American Academy of Ophthalmology.*

High-dose interferon (IFN) is increasingly used as adjuvant therapy for the management of various cancers, including cutaneous melanoma, leukemia, and lymphoma.[1,2] Although isolated cases of severe visual loss secondary to the use of interferon in cancer patients have been reported,[3,4] the exact incidence of retinopathy in this patient population is largely unknown. Prospective studies in patients with chronic hepatitis C have suggested the incidence of interferon retinopathy to be as high as 57%.[5] We report three cases of interferon retinopathy in asymptomatic cancer patients. To our knowledge, no previous cases of asymptomatic interferon retinopathy have been reported in cancer patients, although some studies in chronic hepatitis C patients suggest that visual impairment secondary to interferon may be subclinical in many instances and may be detected only by special testing, such as visual evoked responses or electroretinography.[6] These three cases underscore the importance of ophthalmologic screening, even in asymptomatic cancer patients who receive adjuvant IFN therapy.

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Patients and Methods

Patient 1

A 67-year-old man, previously diagnosed with stage IV low-grade lymphoma, was seen by an optometrist for a routine eye examination without any visual or ocular complaints. He had completed eight cycles of chemotherapy followed by interferon maintenance therapy, 3.0×10^6 U/m^2, 3 days per week. His interferon therapy began approximately 3 months before the examination by the optometrist. An evaluation of the fundus by the optometrist suggested an abnormality in the left eye. The patient was subsequently referred to the Ophthalmology Clinic at M.D. Anderson Cancer Center. He reported no visual symptoms throughout his course of interferon therapy, nor did he report a previous history of hypertension or diabetes. On examination, he was found to have a best-corrected visual acuity of 20/20 in the right eye and 20/25 in the left eye. The external examination results, ocular adnexal examination results, confrontation visual fields, the pupillary examination results, and applanation tonometry measurements were found to be within normal limits. The slit-lamp examination was significant only for the presence of early nucleosclerotic cataracts in each eye. A dilated fundus examination revealed bilateral cotton wool spots and small intraretinal hemorrhages in both eyes (Fig 1A, B). Although there was no known history of hypertension, generalized and focal arteriolar attenuation as well as Arteriovenous (A/V) compression was present (Fig 1A).

The interferon regimen was subsequently discontinued. Six weeks after discontinuation of therapy, the funduscopic examination results were entirely normal. The cotton-wool spots and retinal hemorrhages had resolved.

Patient 2

A 40-year-old man with chronic myelogenous leukemia was treated with daily subcutaneous injections of interferon, 10.0×10^6 U/m^2, as part of his chemotherapeutic regimen. Twelve months after initiation of interferon therapy, he underwent a routine ophthalmologic examination, which revealed cotton-wool spots in each eye. He was subsequently referred to our institution

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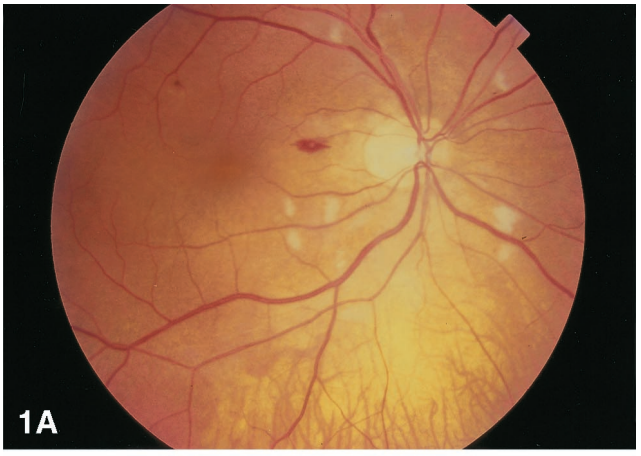

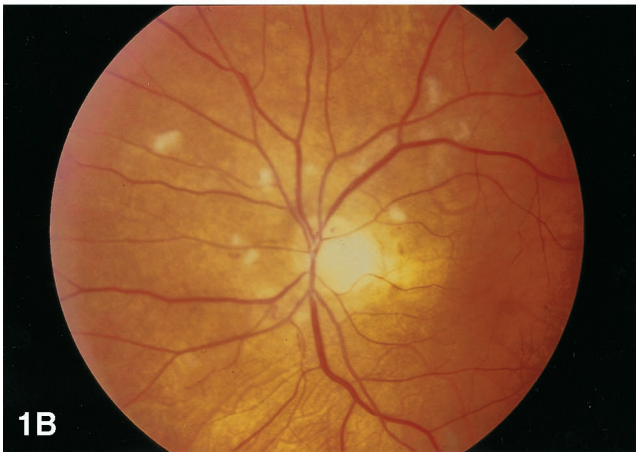

Figure 1. A, Color fundus photograph of the right eye in patient 1. Several cotton-wool spots and a flame-shaped retinal hemorrhage are seen in the posterior pole. **B**, Color fundus photograph of the left eye in patient 1 demonstrates scattered cotton-wool spots.

for further evaluation. He had no visual or ocular complaints at the time of presentation to M.D. Anderson Cancer Center. He did not have a known history of hypertension or diabetes.

On examination, he was found to have a best-corrected visual acuity of 20/20 bilaterally. His external examination, ocular adnexal examination results, extraocular motility, confrontation visual fields, the pupillary examination results, slit-lamp examination results, and applanation tonometry were all within the normal limits. A dilated fundus examination was significant for the presence of several cotton-wool spots throughout both fundi with a few dot-blot and flame-shaped hemorrhages. His interferon regimen was discontinued for 3 months with complete resolution of the retinal findings. The patient was started on a lower dose of interferon (4.0×10^6 U/m^2 daily injections). He has remained without any retinal findings, as checked by funduscopic examinations every 3 months, approximately 1 year after resuming the lower dose of interferon.

Patient 3

A 58-year-old man with malignant melanoma of the right deltoid, metastatic to the axillary lymph nodes, was referred to the ophthalmology clinic for evaluation of a "migraine-like" episode that occurred 3 months earlier. The patient described transient loss of vision in the form of a central area of blurred vision that lasted approximately 10 minutes and resolved spontaneously. At the time of his presentation to the ophthalmology clinic, the patient had no visual or ocular complaints. The patient had undergone wide local excision of his melanoma and axillary lymph node dissection. He was then treated with adjuvant interferon therapy, induction dose of 20.0×10^6 U/m^2 5 days a week for 4 weeks, followed by 10.0×10^6 U/m^2 three times weekly for 3 months before this presentation. This patient had a history of hypertension, but he had his blood pressure checked several times at home and reported that his blood pressure readings had been in the normal range. His blood pressure during this visit was 130/90. Ophthalmologic examination revealed best-corrected visual acuity of 20/30 bilaterally. The external examination results, ocular adnexal examination results, extraocular motility, pupillary examination results, the slit-lamp examination results, and applanation tonometry measurements were all within the normal limits. A dilated fundus examination was significant for the presence of scattered cotton-wool spots and hemorrhages throughout both fundi (Fig 2). Interferon was stopped for 5 weeks. A follow-up retinal examination showed improvement of the retinopathy, with almost complete resolution of the cotton wool spots and hemorrhages. He was resumed on interferon therapy, 10.0×10^6 U/m^2 three times weekly. The patient remains asymptomatic and is monitored every 4 weeks for progression of his residual retinopathy.

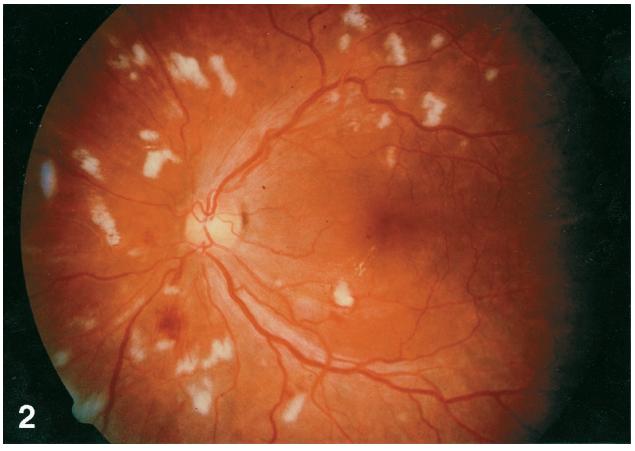

Figure 2. Color fundus photograph of the right eye in patient 3 demonstrates multiple cotton-wool spots and hemorrhages.

Discussion

We report three cases of ischemic retinopathy secondary to interferon in asymptomatic cancer patients. Although the visual outcome in all three patients was good, these cases underscore the importance of careful funduscopic screening examinations for patients taking high-dose interferon. The fact that IFN retinopathy was diagnosed based on an incidental observation during a routine eye examination in two patients, and was triggered by a "migraine-like" episode that seemed unrelated and had already resolved in the third patient, suggests that retinal toxicity secondary to interferon may be asymptomatic and therefore underdiagnosed. The development of retinal hemorrhages and cotton-wool spots secondary to IFN is indicative of a possible compromise in the blood supply to the retina and retinal capillary infarction. These findings are similar to early stages of diabetic

retinopathy and, with progression, can lead to visual loss that may be irreversible.

The resolution of retinopathy with discontinuation of interferon therapy is further support for interferon toxicity as the underlying cause of ischemic retinopathy in these patients. The possibility of giant cell arteritis (GCA) as the cause for the retinal findings in patient 1 was not considered at the time of his initial evaluation because he did not have the typical clinical presentation for GCA. However, GCA should be considered in the differential diagnosis for ischemic retinopathy in elderly patients, even in the absence of typical symptoms of GCA. Patient 1 has remained asymptomatic without any other signs or symptoms of GCA 6 months after the initial diagnosis of his retinopathy.

Currently there are no guidelines for ophthalmologic screening at baseline or in the follow-up period for cancer patients who receive long-term maintenance interferon therapy. We recommend a baseline funduscopic examination at initiation of IFN therapy and a follow-up examination at least every 3 months thereafter to identify patients with interferon retinopathy. We believe that cases of ischemic retinopathy can be missed without such screening because, as in our patients, the symptoms can be minimal or nonexistent in an unknown percentage of patients using interferon.

Prospective studies in cancer patients taking high-dose interferon will be helpful in identifying the incidence and severity of retinal toxicity resulting from this agent. Furthermore, the natural history of asymptomatic retinopathy should be studied. It is important to know whether, similar to diabetic retinopathy, interferon retinopathy can be managed conservatively in its early stages while the patient completes her or his cancer therapy with IFN. Furthermore, the effects of other risk factors for ischemic retinopathy, such as hypertension, diabetes, hypercholesterolemia, hematologic parameters, age, and gender, should be correlated with the incidence of retinopathy in cancer patients receiving interferon.

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