Retinopathy Associated with Adjuvant High-Dose Interferon- α 2b in a Patient with Resected Melanoma: A Case Report and Review of the Literature

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ABSTRACT

Interferon is the only accepted adjuvant treatment for patients with melanoma; hence, oncologists should be aware of the possibility of retinal abnormalities resulting from its use. Interferon-associated retinopathy in patients being treated for resected melanoma is a rare phenomenon with a proposed immunological basis. Patients are usually

asymptomatic or have mild visual impairments, with cotton wool infarcts and hemorrhages. These symptoms and signs usually resolve with the discontinuation of interferon, but in a few severe presentations the visual impairments and retinal changes can be irreversible. *The Oncologist* 2012; 17:384–387

CASE

A healthy, 35-year-old woman was receiving high-dose adjuvant interferon- α 2b (HD-IFN) for a resected stage 3a superficial spreading cutaneous malignant melanoma of the right arm. She had received induction treatment of 33 million units (20 million units/m²) of HD-IFN i.v. 5 days per week for 4 weeks, and maintenance therapy of 16 million units (10 million units/m²) s.c. 3 days per week had been initiated for a planned total of 11 months. Four months into treatment, she presented with painless blurred vision inferotemporal to fixation in her left eye. Other than her new visual symptoms, she did not have any other significant side effects that would warrant discontinuing her treatment. Moreover, she denied any headache, fever, diplopia, or orbital pain. On examination, her vital signs, including blood pressure, were normal. Her cardiovascular, respiratory, and abdominal examinations were unremarkable. Her remaining cranial nerves and neurological examinations were unremarkable. She had mild anemia (hemoglobin, 114 g/L; hematocrit, 0.347 L/L) and no thrombocytopenia.

She was referred urgently to an ophthalmologist for evaluation. Her central vision was 6/6 in each eye without correction. Pupil reactions were normal. Examinations of the anterior segments, anterior chambers, optic discs, and retinal vasculature were all normal. Color vision was not tested. There were cotton wool infarcts between the optic disc and fovea in the left eye and along the superotemporal arcades in both eyes (Fig. 1A and 1B, arrows). There was a paracentral scotoma on Amsler grid testing in the left eye. The etiology of the retinopathy was felt to be associated with her HD-IFN and she was instructed to stop the agent immediately. Three weeks later, there was a marked reduction in the cotton wool spots (Fig. 1C and 1D, arrows), and by 10 weeks they had almost completely resolved. The left eye scotoma had also resolved.

DISCUSSION

HD-IFN has been the standard adjuvant treatment for melanoma since researchers first demonstrated that it could produce longer relapse-free survival (RFS) and overall survival (OS)

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Figure 1. Retinal cotton wool infarcts seen at presentation in right eye (RE) (A) and left eye (LE) (B). Resolving cotton wool infarcts seen in the RE (C) and LE (D) 3 weeks after the discontinuation of interferon. Arrows indicate cotton wool infarcts.

times in patients with intermediate- to high-risk disease after curative surgery [1]. The largest and most recent meta-analyses performed, one based on individual patient data, corroborated the effect on the RFS interval and also demonstrated a statistically significant improvement in OS, with a reduction in the risk of death by 10%–11% with adjuvant interferon treatment [2, 3]. No other agent has been shown to produce such improvements, and currently HD-IFN is the only accepted adjuvant treatment for patients with melanoma. These benefits are tempered by the significant toxicities associated with HD-IFN, which include constitutional and neurological symptoms, hepatotoxicity, myelosuppression, depression, and autoimmune disorders [4]. Recently, a shorter duration of adjuvant interferon, only 1 month of induction treatment, was compared with observation in patients with intermediate-risk and high-risk melanoma in hopes of abrogating the duration and severity of these side effects [5]. Unfortunately, the shorter schedule failed to produce longer RFS or OS times in these patients.

Described above is a case of interferon-associated retinopathy (IAR). Considering that the retinopathy improved once the HD-IFN was discontinued makes it the likely culprit of the patient's visual symptoms and signs. Cutaneous metastases to the retina have also been previously observed but are an unlikely diagnosis in this case because of the resolution of the symptoms and funduscopy findings [6]. A paraneoplastic phenomenon, called melanoma-associated retinopathy (MAR), should also be considered as part of the differential diagnoses [7]. MAR typically presents with night blindness and mild peripheral vision loss with acuity and color vision remaining intact. MAR is believed to result from autoantibodies directed toward rod bipolar cells inter-

rupting neural communication to the inner retina, causing night blindness [8]. Electroretinography can be used to measure the abnormal electrical response of the rod bipolar cells of the retina [9]. In this case, it was not performed, because MAR is an unlikely diagnosis given that the retinopathy resolved and this phenomenon usually occurs in males with metastatic disease. Lastly, this patient did not have any confounding causes for retinopathy, such as a history of diabetes, hypertension, trauma, or infection.

Several prospective studies have linked interferon therapy with a variable incidence of retinopathy of 18%–86% [10]. However, the majority of these studies were in patients with hepatitis C, in whom interferon is administered at lower doses than in the treatment for melanoma. In a small series of 30 patients with resected high-risk melanoma who received adjuvant HD-IFN, 13% developed retinopathy [11]. Those patients were all asymptomatic, with the retinopathy detected only during routine ophthalmological examination. Patients with melanoma who become symptomatic as a result of IAR typically present with progressive mild visual impairment [12, 13]. A minority of more severe cases have been reported with visual acuities as impaired as 20/400 and limited to counting fingers [12–14]. In patients with melanoma and IAR, the most common abnormalities observed on funduscopy are cotton wool spots and hemorrhages. Other documented ocular complications of HD-IFN in patients with melanoma include macular edema [12, 13], microaneurysms [12], retinal capillary nonperfusion [12], and anterior ischemic optic neuropathy (AION) [14]. Ocular toxicities associated with interferon in other disease settings include increased intraocular pressure [15], neovascular glaucoma [16], and retinal detachment [17]. These oc-

ular changes can occur as early as 3 weeks to several months after drug therapy is started. There have been some cases of irreversible visual impairment despite discontinuation of HD-IFN, but these have been associated with poor visual acuity at presentation and AION [13, 14]. In one reported case, no improvement in the IAR was observed despite aggressive treatment with acetylsalicylic acid, dexamethasone, heparin, and cyclosporine [14]. Fortunately, these severe cases of IAR are rare, and in the majority of milder cases the retinal changes resolve with the discontinuation of interferon.

There have been reports describing the rechallenging of patients with interferon after the IAR had resolved. For instance, in a patient with metastatic melanoma, the retinal changes recurred with repeat exposure to HD-IFN [12]. However, in other disease settings, rechallenging patients with interferon did not result in recurrence of the symptoms or retinal changes [12]. What predicts whether or not a patient develops IAR on re-exposure to HD-IFN remains unknown and those patients who decide to reinstate treatment should be informed that the retinal changes could recur.

Several risk factors have been identified for IAR, the most common being diabetes mellitus and essential hypertension. Older age, arterial sclerosis, elevated erythrocyte count, elevated leukocyte count, thrombocytopenia, anemia, serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase, dyslipidemia, and a higher interferon dose have all been examined as possible risk factors, but the results have been negative or inconclusive [10]. Again, the majority of this evidence was generated in studies using interferon for the treatment of hepatitis C. In a small series of seven patients with high-risk melanoma who developed IAR, six were also receiving paroxetine, four had hypertension, and three had thrombocytopenia [13]. In another randomized study investigating whether pretreatment with paroxetine could minimize depression in melanoma patients receiving HD-IFN, three developed retinal hemorrhages, all in the paroxetine arm [18]. The patient described in the above case was not taking any antidepressants. Larger studies are required to determine whether or not these risk factors and those identified in the treatment of hepatitis C also apply to melanoma patients.

Although the pathogenesis of IAR is unclear, it is believed to be a result of disturbances in the retinal microcirculation triggered by immunological phenomena. HD-IFN therapy is known to cause or exacerbate other systemic autoimmune diseases, such as polyarthropathy and thyroiditis [19]. These autoimmune diseases probably occur as a result of the production of autoantibodies, which are known to develop in up to 52% of patients treated with interferon [19]. Decreased capillary perfusion in the retina, retinal ischemia, and nonperfusion can lead to cotton wool spot formation and hemorrhage. It has been hypothesized that these retinal changes are a result of immune complex deposition [12], leukocyte aggregation secondary to complement activation [20], inflammatory cell infiltration, and increased viscosity resulting from circulating effector proteins [13]. Also, it is known that HD-IFN can decrease vascular endothelial migration and proliferation, resulting in poor endothelial repair, and may be another mechanism for the vascular occlusive events seen in the retina [21].

Currently, HD-IFN is the only accepted adjuvant treatment for patients with melanoma. Hence, oncologists should be aware of the possibility of retinal abnormalities resulting from its administration. Patients should be informed of this potential complication, aided in reducing risk factors, and monitored for optic complications. Patients complaining of visual symptoms must have a prompt and complete eye examination, and HD-IFN should be held if IAR is suspected. Currently, there are no guidelines regarding the reinitiation of HD-IFN once the IAR resolves, and the decision must be individualized after careful consideration of the merits and risks.

AUTHOR CONTRIBUTIONS

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