Anterior Ischemic Optic Neuropathy in a Patient with Hepatitis C Treated with Interferon-alpha and Ribavirin

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Interferon-alpha is a natural glycoprotein produced and secreted by immune cells in response to viral infections, exerting its effects by binding to a membrane receptor and initiating intracellular signaling that ultimately leads to expression of specific genes. This leads to the enhancement and induction of target cell killing by lymphocytes and inhibition of virus replication in infected cells. INFα has anticytokine, antiviral, immunomodulatory and anti proliferative properties. It is used to treat cancer, chronic hepatitis C and B, and essential thrombocytosis [1].

Systemic complications associated with the use of interferon include flu-like symptoms consisting of malaise, mild fever and chills, rash, hypotension, peripheral neuropathy, and thrombocytopenia [1]. Hemolytic anemia is the most common systemic side effect of ribavirin.

Ocular complications are uncommon with INFα therapy and include ischemic retinopathy manifested as cotton-wool spots and retinal hemorrhage, and single reported cases of ischemic optic neuropathy, subconjunctival hemorrhage, trichomegaly and cystoid macular edema [2]. In contrast, no ocular side effects were reported for ribavirin. We present a case of anterior ischemic optic neuropathy due to INFα therapy in 38 year old man with chronic hepatitis C.

PATIENT DESCRIPTION

A 38 year old man presented with complaints of sudden painless blurring of vision in the left eye after awakening in the morning. Five days later the patient noted a gentle visual disturbance that progressed to a black shadow obscuring his left visual field. He had none of the traditional systemic risk factors for conventional AION, including diabetes mellitus, hypertension, ischemic heart disease, and hypercholesterolemia. He denied jaw claudication, neck pain, trauma, headache, or periorbital pain. The patient had a chronic hepatitis C virus infection, probably as a result of drug abuse during which he was infected by HCV. His medical history consisted of drug (heroin) consumption 3 years previously, panic disorder, and phlebitis of both arms. Twenty-three weeks prior to the ophthalmologic examination, he had begun a 24-week clinical trial of peginterferon alfa-2a (Pegasys®, Hoffman-La Roche, Switzerland) and ribavirin (Copegus®, Hoffman-La Roche). The patient was treated with peginterferon alfa-2a 180 µg/week and ribavirin 800 mg/day. Doses of peginterferon alfa-2a and ribavirin were determined and approved by research protocol. On examination his visual acuity was 20/20 in the right eye and 20/400 in the left. The intraocular pressure was 14 mmHg in both eyes. Eye movements were full to all directions. He identified 1 of 14 Ishihara pseudo-isochromatic plates with his left eye and 14 of 14 in his right eye. In the left eye he had a relative afferent pupillary defect. Fundus examination of the right eye revealed crowded disk and slightly pallid edema of the optic nerve head without other retinal pathology [Figure A]. In the left eye, the optic disk was elevated and edematous, with tortuous dilated vessels, splinter hemorrhages on the nasal side, and a few cotton wool spots at the edge of the edema [Figure B].

INFa = interferon-alpha

AION = anterior ischemic optic neuropathy
HCV = hepatitis C virus

[A] The right eye with crowded disk without other retinal pathology.
[B] In the left eye, the optic disk is elevated and edematous, with tortuous dilated vessels, splinter hemorrhages on the nasal side, and a few cotton wool spots at the edge of the edema.
Fluorescein angiography showed optic disk leakage. Goldman perimetry testing showed a narrowing of the visual field in the left eye with inferior altitudinal visual field defect. Perimetry of the right eye was normal with slight narrowing of the peripheral visual field. Neurological assessment was otherwise normal.

Standard blood study results were normal, including erythrocyte sedimentation rate (22 mm/hr), hemoglobin (15.6 mg/dl), prothrombin time, partial thromboplastin time, protein S, protein C, antithrombin III, antiphospholipid Ab, rheumatoid factor, C-reactive protein, C-3, C-4, antinuclear antibody, venereal disease research laboratory titer, and human immunodeficiency virus titer. The thyroid function test results were normal. Cranial and orbital computed tomography findings were normal.

A diagnosis of anterior ischemic optic neuropathy due to INFα therapy was made, and after consultation with the gastroenterologist the drug was discontinued. The patient was treated with intravenous hydration fluids and methylprednisolone at a dose of 1 g/day for 3 days followed by a 2-week course of oral prednisone at a dose of 1 mg/kg/day tapering over 3 days. In spite of discontinuation of peginterferon-α treatment and beginning of pulse steroid and hydration therapy, the visual outcome showed no apparent improvement. At 6 months follow-up, visual acuities slightly improved to 20/200 in the left eye without any change in the visual field defects. The ophthalmic examination revealed a slight relative afferent pupillary defect, and fundus examination demonstrated optic disk pallor in the left eye.

**COMMENT**

Hepatitis C virus infects an estimated 170 million persons worldwide and thus represents a viral pandemic. HCV is the leading cause of chronic liver disease and the most common chronic blood-borne infectious disease in the United States. Approximately 20% of patients with chronic hepatitis C will develop cirrhosis, 20% of patients with cirrhosis will develop decompensated liver disease, and another 20% will develop hepatocellular carcinoma. Progression to chronic disease occurs in the majority of HCV-infected persons, and infection with the virus has become the main indication for liver transplantation.

The treatments for chronic hepatitis C approved by the U.S. Food and Drug Administration are interferon-α monotherapy, interferon plus ribavirin, pegylated interferon, or PEG interferon plus ribavirin. PEG interferon α-2a is a covalent conjugate of recombinant alpha interferon with bis-monomethoxypolyethylene glycol. The attachment of polyethylene glycol to INFα (peginterferon-α) extends the half-life and duration of the therapeutic activity of INFα. In contrast to INFα, peginterferon-α is given only once a week, resulting in improved patient compliance and a higher rate of response compared to conventional monotherapy with INFα. Moreover, synergistic combination with ribavirin results in an improved and sustained clearance rate of 50–60% instead of 12–16% with INFα alone.

The frequencies of interferon-related retinopathy associated with interferon monotherapy and interferon-ribavirin combination therapy are reported to be 24–58% and 16–64%, respectively [3], and are typically characterized by retinal hemorrhages and cotton-wool spots. It is well known in the literature that most patients who develop interferon-associated retinopathy stay asymptomatic and retinal changes are reversible. However, various atypical and uncommon interferon-associated ocular complications have been reported, including oculomotor nerve paralysis, optic disk edema, subconjunctival vitreous hemorrhage, retinal vein occlusion, and cystoid macular edema. Diabetes mellitus, hypertension, anemia, thrombocytopenia, and increased triglyceride levels are risk factors of interferon-associated retinopathy [3].

Our patient did not have any primary systemic disease that might involve a risk of interferon-associated retinopathy. We ruled out other etiologies, such as vasculitis, demyelination, infection, connective tissue disorder, and embolism. Signs and symptoms developed in our patient almost certainly as the result of AION, which was previously described in a few cases of interferon-associated AION with severe visual losses [4,5]. It should be noted that the patients had one predisposing factor to AION crowded disk, the so-called disk at risk.

We suppose the pathophysiology of INFα-induced AION is multifactorial and caused by several ischemic factors. Ischemia may be the result of deposition of circulating immune complexes followed by lymphocyte infiltration in retinal capillaries, or by interferons, which activate leukocytes and increase leukocyte adherence to the vascular endothelium, trapping these cells in retinal capillaries. High circulating levels of plasma-activated complement 5, which is a potent intravascular aggregator of platelets, were found in patients treated with INFα. Nocturnal arterial hypotension could also affect the mechanism of the disease. INFα causes systemic hypotension, and the resultant blood pressure fluctuations may induce vascular ischemia of the optic nerve. Infection with HCV by itself may play a role in activating the clotting system by creating immune-mediated complexes consisting of HCV autoantibodies and HCV virions. A combination of these factors occurring in the posterior ciliary arteries may have resulted in INFα-induced AION in our patient.

The treatment approach consists of hydration, prevention of hypotension, and diskontinuation of INFα therapy. Steroid pulse therapy with continuation tapering could also be options, although the mechanism of interferon-associated AION is ischemia and not inflammation. It is well known that HCV is associated with a variety of autoimmune abnormalities caused by inflammation, including thrombocytopenia, arteritis, cryoglobulinemia, and autoimmune thyroiditis. Therefore, steroid therapy may...
be helpful in decreasing autoimmune processes in HCV patients and improving the patient’s status. The prognosis of interferon-associated AION is uncertain; some patients have visual acuity improvement and others continue with poor visual outcome despite discontinuation of the INFαs and additional treatments. Considering the possible poor visual outcome associated with INFα treatment, we propose that patients who are candidates for this treatment be first examined for crowded disks and systemic risk factors of vascular ischemia that are associated with AION.

At present, the ophthalmology literature does not have follow-up guidelines for patients treated with INFαs; therefore, we recommend, in agreement with previous studies, that patients be examined before treatment, at 1 month, and if everything is normal, at 2-month to 3-month intervals. Any change in vision or some ocular complaint should require an immediate ophthalmological examination.

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**References**

**Capsule**
**MHC class II transactivator CIITA is a recurrent gene fusion partner in lymphoid cancers**

Chromosomal translocations are critically involved in the molecular pathogenesis of B cell lymphomas, and highly recurrent and specific rearrangements have defined distinct molecular subtypes linked to unique clinicopathological features. In contrast, several well-characterized lymphoma entities still lack disease-defining translocation events. To identify novel fusion transcripts resulting from translocations, Steidl et al. investigated two Hodgkin lymphoma cell lines by whole-transcriptome paired-end sequencing (RNA-seq). The authors show a highly expressed gene fusion involving the major histocompatibility complex (MHC) class II transactivator CIITA (MHC2TA) in KM-H2 cells. In a subsequent evaluation of 263 B cell lymphomas, they also demonstrate that genomic CIITA breaks are highly recurrent in primary mediastinal B cell lymphoma (38%) and classical Hodgkin lymphoma (cHL) (15%). Furthermore, the researchers found that CIITA is a promiscuous partner of various in-frame gene fusions, and report that CIITA gene alterations impact survival in primary mediastinal B cell lymphoma (PMBCL). As functional consequences of CIITA gene fusions, they identify down-regulation of surface HLA class II expression and over-expression of ligands of the receptor molecule programmed cell death 1 (CD274/PDL1 and CD273/PDL2). These receptor-ligand interactions have been shown to impact anti-tumor immune responses in several cancers, whereas decreased MHC class II expression has been linked to reduced tumor cell immunogenicity. Thus, our findings suggest that recurrent rearrangements of CIITA may represent a novel genetic mechanism underlying tumor-microenvironment interactions across a spectrum of lymphoid cancers.

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**Capsule**
**Lupus casts a complicated NET**

Systemic lupus erythmatous is a debilitating autoimmune disease that is characterized by the accumulation of inflammatory immune complexes (antibodies bound to a person’s own nuclear structures) in tissues. Lupus patients exhibit alterations in cytokine production and in various immune cell numbers and functions, but how these changes contribute to disease pathogenesis is not well understood. Lande et al. and García-Romo et al. analyzed serum samples and cells isolated from lupus patients and report that immune complexes, type I interferons, and neutrophils are entwined in a vicious cycle that drives disease pathogenesis. This trio of immune mediators is elevated in lupus serum, and together they induce a type of cell death in neutrophils called NETosis, where neutrophils spew out their nuclear contents (NETs). NETs drive further production of interferons, which in turn induces more NETosis. NETs are also an antigenic source for the generation of more immune complexes. With only one targeted therapy available for lupus, new therapeutic targets such as these are badly needed.

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