CASE REPORT

Interferon-induced Central Retinal Vein Thrombosis

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ABSTRACT

A middle-aged lady presented with sudden onset of unilateral central retinal vein thrombosis after completing 6 months course of interferon and ribavirin for chronic hepatitis C infection. She had no risk factors and all her thrombophilia workup was normal, however, she was found to be dyslipidemic which may have contributed to atherosclerosis and predispose to thrombosis. Despite anticoagulation, her visual acuity deteriorated. This case illustrates the possibility of unpredictable visual complication of interferon. Frequent eye examination should be undertaken in patients having underlying risk factors like diabetes, hypertension or dyslipidemia undergoing interferon therapy.

Key words: *Interferon. Retinopathy. Thrombosis. Central retinal vein. Dyslipidemia.*

INTRODUCTION

About 200 million people in the world are infected with hepatitis C. Pakistan is a developing country of 170 million people where estimated prevalence of hepatitis C is 5%.[1] Treatment of chronic *hepatitis C virus* (HCV) infection included initially standard interferon-α (IFN-α) given three times a week. Since 2000, it has been proposed to administer pegylated IFN once a week.[2] Ocular side effects of interferon and ribavirin are well known. The incidence of central retinal vein thrombosis in patients on treatment with interferon for hepatitis viruses in the literature is unavailable as it is a rare complication.

Most studies report onset of retinopathy in the first 8 – 12 weeks following the start of treatment.[3,4] We report a case of unilateral central retinal vein thrombosis developing in a patient after 24 weeks of therapy with interferon and ribavirin for chronic hepatitis C infection.

CASE REPORT

A 50 years old lady of Bengali origin residing in Pakistan for 30 years was diagnosed one year back with chronic hepatitis C (genotype 3). She presented to Eye Clinic with 5 days history of sudden onset of painless visual loss in the right eye 2 days after completing her 6 months course of interferon and ribavirin therapy. Her past medical and family history were negative for any thrombophilia. Prior to initiation of her therapy, she had no evidence of decompensated liver disease. Her serum alanine aminotransferase at the start of therapy was 306 U/L which decreased to 44 U/L at 12th week of therapy. Her hepatitis C by PCR also became un-detectable at that time. She did not have any other complications associated with treatment prior to this presentation.

On examination in the Eye Clinic at JMCH, her visual acuity in the right eye was found to be limited to hand movement only with no improvement on pin hole. While visual acuity and colour vision were normal in left eye. Ocular movements were of full range bilaterally. Intraocular pressure in both eyes was 18 mmHg (normal). Pupils showed RAPD on right eye but normal reaction in left eye. Cornea and conjunctiva were normal bilaterally. Iris did not show any neovascularization. Anterior chamber was normal. Fundus examination was normal in left eye while right eye examination revealed hyperemic and swollen disc with haemorrhage spilling all around it. Macular oedema was seen with cotton wool spots. Appearances of fundus at the time of presentation are illustrated in Figure 1 (a,b). The findings were consistent with complete right central retinal vein occlusion with ischaemic retinopathy.

She was referred to medical department to work her up for thrombophilia. She did not have diabetes or hypertension and subsequent testing also revealed a normal blood glucose levels. Except for vision, her physical examination was unremarkable. Her investigation revealed a normal blood count, renal and liver functions. ANA, anti-dsDNA and anti-phospholipid antibodies were negative. Anti-thrombin-III levels,

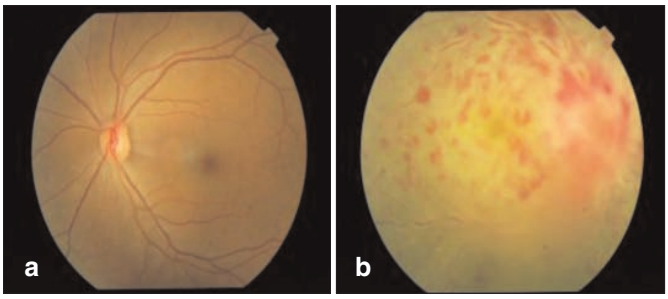

Figure 1 (a): Retina of normal left eye. **(b):** Central retinal vein occlusion in right eye.

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activated protein C levels, serum homocysteine levels, protein C and protein S levels were within normal limits. However, her cholesterol levels were on the higher side (226 mg/dl) and LDL was 175 mg/dl. Her HDL and triglycerides were within normal limits.

She was prescribed statin therapy and advised life style modification for her dyslipidemia. She was also started on heparin and aspirin. Repeat eye examination 4 weeks after therapy showed a deterioration with complete loss of vision in right eye. No neovessels were seen on iris. Fundus examination showed disc fibrosis with fibrous vessels around disc.

DISCUSSION

About 200 million people in the world are infected with hepatitis C. Although Interferon based therapy is widely used for the treatment of chronic HCV, it is not without its disadvantages. Treatment duration lasts for months and is often fraught with potentially dangerous side effects. Some of these side effects, such as influenza-like illness, myalgias, depression and cytopenias can become intolerable resulting in premature treatment cessation, but have no lasting effects. In 1990, Ikeba and associates first reported a 39 years old patient with retinal haemorrhages and cotton wool spots following intravenous administration of interferon.[5] The exact frequency of this complication is unknown. There have been a few cases of retinal vein thrombosis reported in patients treated with interferon or pegIFN.[2,6,7] However, none has been reported from Pakistan.

Interferons comprise a group of pleiotropic proteins with anti-viral, anti-inflammatory, and anti-angiogenic characteristics. Interferons are also multi-functional immunoregulatory cytokines with effects at various points in the cytokine cascade, likely accounting for their immunostimulatory effects.[8] Due to their various mechanisms of action, interferons are well recognized to cause a variety of side effects as mentioned above. The exact pathophysiological mechanism due to which retinopathy develops is unknown. Similarities with some characteristics of diabetic and hypertensive retinopathy suggest an ischaemic mechanism. Other authors suggest that IFN therapy may cause immune complex deposition in the retinal vasculature and leukocyte infiltration, leading to retinal ischaemia, congestion, and haemorrhage.[9,10] Interferon therapy has also been reported to induce a number of thrombogenic autoantibodies, including cryoglobulins, anti-nuclear, anti-smooth muscle, anti-liver-kidney microsomal, anti-thyroglobulin and anti-phospholipid antibodies, which are thought to play a role in the pathogenesis of a hypercoagulable state.[6]

Interferon induced retinal changes other than central retinal vein thrombosis usually develop within the first 3 months of interferon therapy.[4] However, in contrast central retinal vein thrombosis has been reported later in the course of therapy (4th month[7], 5th and 7th month)[2] which is similar to this case.

Risk factors like diabetes, hypertension, patient's age, haemoglobin, white cell count, platelets, serum cholesterol and triglycerides have been examined as possible risk factors, but the results have been negative or inconclusive.

The case presented here is unusual as the patient developed central retinal vein thrombosis without any other underlying hypercoagulable state or associated conditions like diabetes or hypertension. However, this patient was found to have dyslipidemia which may have contributed to atherosclerosis and predispose to thrombosis. Although current guidelines of therapy of chronic viral hepatitis do not support routine ophthalmologic screening and workup for hypercoagulable state in all patients treated with interferon, this case illustrates the possibility of unpredictable and sight loosing complication of interferon. We, therefore, recommend frequent eye examination in patients having underlying risk factors like diabetes, hypertension or dyslipidemia undergoing interferon therapy.

REFERENCES

1. Waheed Y, Shafi T, Safi SZ, Qadri I. *Hepatitis C virus* in Pakistan: a systematic review of prevalence, genotypes and risk factors. *World J Gastroenterol* 2009; **15**:5647-53
2. Sene D, Touitou V, Bodaghi B, Saadoun D, Perlemuter G, Cassoux N, *et al.* Intraocular complications of IFN-α and ribavirin therapy in patients with chronic viral hepatitis C. *World J Gastroenterol* 2007; **13**:3137-40.
3. Hayasaka S, Nagaki Y, Matsumoto M, Sato S. Interferon associated retinopathy. *Br J Ophthalmol* 1998; **82**:323.
4. Kawano T, Shigehira M, Uto H, Nakama T, Kato J, Hayashi K, *et al.* Retinal complications during interferon therapy for chronic hepatitis C. *Am J Gastroenterol* 1996; **91**:309-13.
5. Ikebe T, Nakatsuka K, Goto M, Sakai Y, Kageyama S. A case of retinopathy induced by intravenous administration of interferon. *Folia Ophthalmol Jpn (Ganka-Kiyo)* 1990; **41**:2291-6.
6. Nadir A, Amin A, Chalisa N, van Thiel DH. Retinal vein thrombosis associated with chronic hepatitis C: a case series and review of the literature. *J Viral Hepat* 2000; **7**:466-70.
7. Boris J, Bajairea DF, Paipillaa CE, Oudovitchenko AE. Mixed vascular occlusion in a patient with interferon associated retinopathy. *Case Rep Ophthalmol* 2011; **2**:23-9.
8. Tilg H. New insights into the mechanisms of interferon alfa: an immunoregulatory and anti-inflammatory cytokine. *Gastroenterology* 1997; **112**:1017-21 .
9. Andrade R, González J, Vázquez L, Cilvetti A, Camargo R, García-Cortés M, *et al.* Vascular ophthalmological side effects associated with antiviral therapy for chronic hepatitis C are related to vascular endothelial growth factor levels. *Antivir Ther* 2006; **11**:491-8.
10. Guyer DR, Tiedeman J, Yannuzzi LA, Slakter JS, Parke D, Kelley J, *et al.* Interferon associated retinopathy. *Arch Ophthalmol* 1993; **111**:350-6.