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Case Report

Unilateral ocular sarcoidosis associated with interferon therapy

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ABSTRACT

A 55-year-old woman with chronic hepatitis C presented with acute painless, unilateral, granulomatous uveitis without other systemic symptoms. Ocular symptoms began 20 weeks after starting pegylated interferon alpha (IFN-α)-2a and ribavirin. The anterior granulomatous uveitis quickly improved after application of topical steroid. However, the vision of the right eye worsened 4 weeks later because of a new episode of vitritis with multiple snowballs along and in retinal vessels. These were nodular and/or segmental periphlebitis with candlewax drippings in appearance. Multiple granulomas persisted for 4 weeks and spontaneously disappeared after immediate discontinuation of IFN-α therapy. We reviewed eight additional granulomatous uveitis of presumed ocular sarcoidosis during IFN-α therapy in previous articles and all of these patients suffered from bilateral uveitis. However, our case was treated with IFN-α and resulted in unilateral granulomatous panuveitis. Sixteen weeks after discontinuation of IFN-α therapy, the patient recovered well with regards to vision and no recurrence occurred.

1. Introduction

Several studies have reported that pegylated interferon alpha (IFN-α)-associated retinopathy in chronic hepatitis C (CHC) demonstrated symptoms ranging from asymptomatic changes of superficial retinal hemorrhage to severe retinal vascular occlusion or retinal detachment [1–10]. This kind of retinopathy may relate to retinal microvascular disturbance. In adults, 19–29% of IFN-α-treated CHC cases have developed retinopathy; for IFN-α-treated CHC cases involving children, ophthalmologic complications occurred in 2–3% cases [11]. Other ocular complications associated with IFN-α therapy include transient blurred vision [12], neovascular glaucoma [13], severe orbital and intraocular hemorrhage [14], progression of existing retinopathy [13,15], and ischemic optic neuropathy [16–18].

A few articles have reported that ocular inflammation, such as Vogt-Koyanagi-Harada-like disease [8] and sarcoidosis [19–23], are associated with IFN-α treatment for CHC. IFN-induced ocular sarcoidosis needs to be differentiated from IFN-induced retinopathy. Typical changes of IFN retinopathy lack vitreous infiltration and granulomas in the fundus [19]. We were already aware of the association between presumed ocular sarcoidosis and IFN from previous ophthalmological-related literature [19]. Although ocular sarcoidosis associated with IFN-α have been reported, all of their cases were bilateral eye changes [19,20]. In our case, presentation of unilateral granulomatous panuveitis with nodular periphlebitis was seen as a special presentation of IFN-induced sarcoidosis.

2. Case report

A 55-year-old woman with a history of CHC developed painless progressive vision loss in her right eye. She had no history of eye trauma and did not detect visual loss in the left eye. She also noted intermittent violaceous skin lesions on her forearm without other systemic problems. Twenty weeks before ophthalmic evaluation, she began treatment for CHC with pegylated IFN-α-2a, Pegasys (Roche, Basel, Switzerland) at 180 μg/wk and ribavirin 600 mg/d. Other medications included omeprazole, cimetidine, folic acid, and mosapride citrate. Ocular examination revealed best corrected visual acuity 8/20 in the right eye and 20/20 in the left eye. Pupils were 3 mm bilateral without relative afferent pupillary defect. Intraocular pressure was 32 mmHg in the right eye and 14 mmHg in the left eye. Slit-lamp examination revealed a ciliary injection

Conflict of interest: none.

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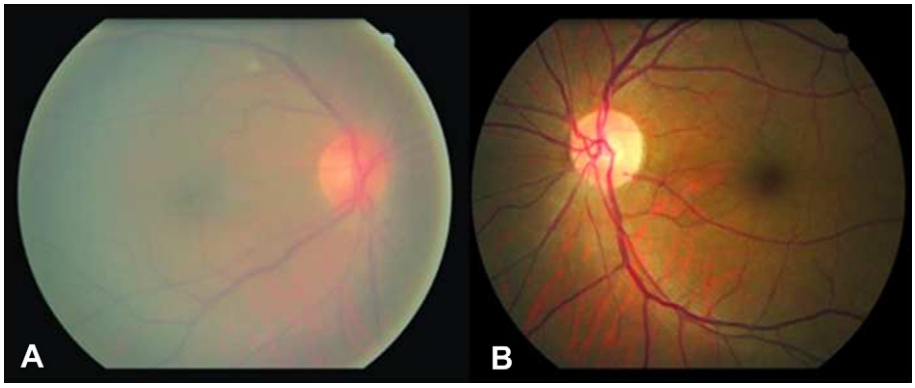

Fig. 1. (A and B) Bilateral retinal photography revealed severe vitreous haziness in the right eye compared with the retina of the other eye.

with multiple mutton-fat keratic precipitates and cells in the anterior chamber of the right eye. Fundus examination demonstrated moderate haziness in the vitreous cavity of the right eye (Fig. 1). The anterior and posterior segments of the left eye were normal. The cytology of aqueous and vitreous samples showed no malignant cells and a vitreous culture was negative for any pathogens. A hemogram and comprehensive metabolic panel were shown to be normal. Erythrocyte sedimentation rate (ESR) was 54 mm/1 hr and serologic test of syphilis/rapid plasma regain (STS-RPR), antinuclear antibody, anti-ds DNA antibody, rheumatoid factor, C-reactive protein, Herpes simplex virus immunoglobulin M, and Varicella zoster virus immunoglobulin M were all negative. She had abnormal liver enzyme tests. A chest scan for hilar lymphadenopathy and a tuberculin skin test were both negative.

A unilateral uveitis related to IFN-α was suspected. Because of the unstable condition of hepatitis C, continued IFN-α therapy was planned and the patient was simultaneously treated with topical prednisolone acetate 1.0% for every 2 hours. Although she was still on IFN-α treatment, obvious improvement of anterior uveitis and normal intraocular pressure was noted after 1 week of topical steroid application. However, persistent vitritis and new lesions of multiple granulomas in and along her right retinal vessels (both artery and vein) were noted on retinal photography and fluorescein angiography (FAG) 4 weeks after the ocular symptoms began (Fig. 2). There was no vessel leakage, neovascularization, macular edema, hypertrophy, or scar of retinal pigment epithelium on FAG. Her right visual acuity had decreased to 6/20. Fortunately, discontinuation of IFN-α therapy induced the spontaneous improvement of granulomatous panuveitis. Four months after ceasing IFN-α therapy, multiple granulomas on the retina completely disappeared and vision returned back to normal (Fig. 3).

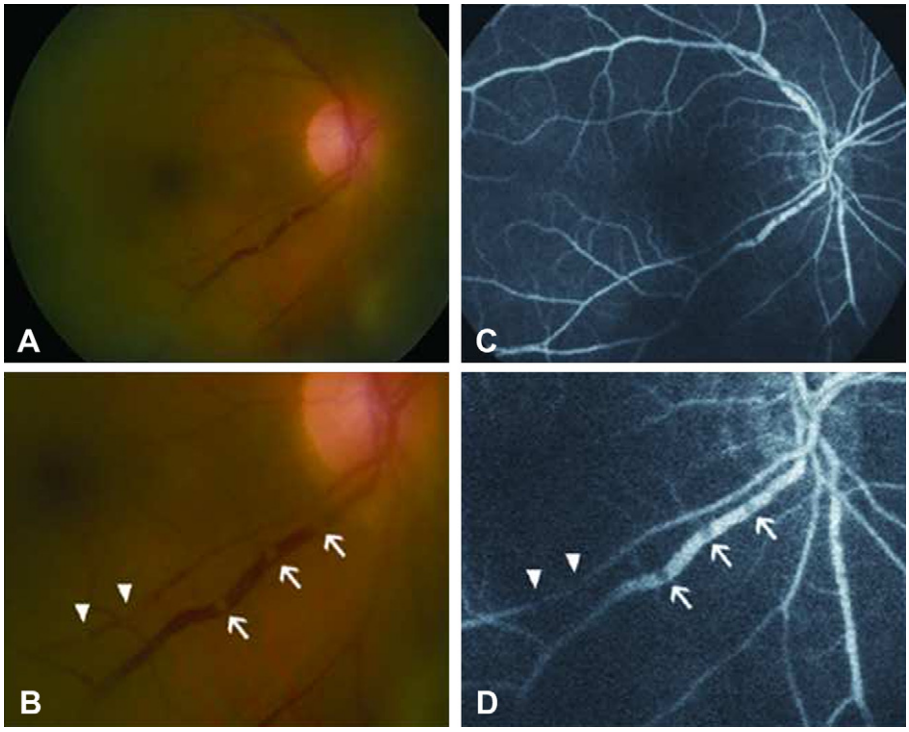

Fig. 2. (A and B) Retinal photography showed numerous granulomas along and in the retinal vein (white arrow) and artery (white arrow head) and the cloud vitreous. (C and D) Fluorescence angiography showed that flow in the vessels was not blocked by nodular deposits, so-called nodular periphlebitis with candlewax drippings (white arrow and white arrow head). There was no classic pattern of retinal vasculitis, such as neovascularization or vascular leakage.

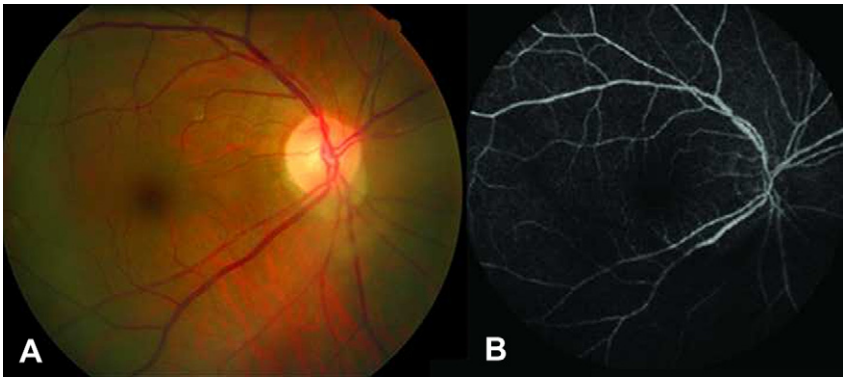

Fig. 3. (A) Retinal photography and (B) fluorescence angiography. Four months after IFN-α discontinuing, granulomas on the retina spontaneously disappeared but mild vitreous opacity still presented. IFN-α = interferon alpha.

3. Discussion

Several articles have already reported mechanisms of IFN-α retinopathy. A study using a rat model demonstrated that IFN-α causes leukocyte activation as well as abnormally high levels of circulating activated plasma complement 5 and adherence to vascular endothelium [24,25]. However, the exact mechanisms of ocular sarcoidosis associated to IFN-α therapy are still not clear [6,14,19,20,26].

The adverse general effects of IFN-α treatment in CHC, such as fatigue, headache, fever, and myalgias, are common [27]. IFN-induced sarcoidosis seems to cause a lower frequency of pulmonary involvement and a higher incidence of cutaneous and articular involvement [23]. Before the causes of unilateral panuveitis can be determined, we need to consider the causes of autoimmunity, infection, and malignancy first. Importantly, the finding of granulomatous inflammation is usually suggestive of a unique set of etiologic agents. Causes of granulomatous uveitis are sarcoidosis, sympathetic ophthalmic, lens-induced uveitis, intraocular foreign body, Vogt-Koyanagi-Harada syndrome, syphilis, and tuberculosis. Based on the evidence from our patient and information from previous case reports, we propose, in our case, that there is a possible association between IFN-α therapy and ocular sarcoidosis [28].

The International Uveitis Study group criteria in 2000 classified ocular sarcoidosis into isolated anterior uveitis, intermediate uveitis, retinal vasculitis with or without panuveitis, and multifocal choroiditis [29]. The consensus conference in 2009 held by the International Workshop On Ocular Sarcoidosis identified seven signs in the diagnosis of intraocular sarcoidosis: (1) mutton-fat keratic precipitates (KPs)/small granulomatous KPs and/or iris nodules (Koeppe/Busacca); (2) trabecular meshwork nodules and/or tent-shaped peripheral anterior synechiae; (3) vitreous opacities displaying snowballs/strings of pearls; (4) multiple chorioretinal peripheral lesions (active and/or atrophic); (5) nodular and/or segmental periphlebitis (+/− candlewax drippings) and/or retinal macroaneurism in an inflamed eye; (6) optic disc nodules/granulomas and/or solitary choroidal nodules; and (7) bilaterality [30]. We believe that those nodules in the retina vessels were nodular and/or segmental periphlebitis with candlewax drippings. There was no additional typical choriocapillaris leakage, choroidal inflammation, and neovascularization showing on FAG. Classical focal retinal pigment epithelial cell proliferation, suggestive of Dalen-Fuchs nodules, shows hypofluorescent in the early phases and late staining. However, our granulomas were only in and along the retinal vessels with no staining in the late phase of FAG, and so, uncharacteristic of Dalen-Fuchs nodules. These white granulomas were deposits in the retinal vessels and did not cause total obstruction of blood flow. Our case was panuveitis but did not have severe retinal vasculitis as well as macular edema so that the prognosis of vision was good without complications.

In a review of Pubmed, eight cases with uveitis as a manifestation of IFN-induced sarcoidosis were reported [19,20,22,23]. The last case reported by Doycheva et al [19] was comparable to our case with some similarities, including no increasing angiotensin-converting enzyme and no pulmonary involvement. Although we did not have documents of biopsy or angiotensin-converting enzyme titer, our case diagnosed ocular sarcoidosis because of typical mutton fat KPs. Acute anterior uveitis with the mutton fat or granulomatous KPs is highly suggestive of sarcoidosis [30]. The most important additional diagnostic clue of unilateral IFN-α-induced ocular sarcoidosis is good visual prognosis after merely ceasing IFN-α therapy.

In the treatment of ocular sarcoidosis, oral corticosteroids combined with the discontinuation of IFN-α have been recommended [19,23]. The uveitis in sarcoidosis related to IFN-α therapy had good visual prognosis [19]. In 46 sarcoidosis cases related to IFN-α therapy, they found remission in 83%, stabilization in 11%, and reactivation in 6% of patients [23]. Although the symptoms and signs of ocular sarcoidosis may fluctuate before the ceasing of IFN-α therapy, finally, the visual prognosis was favorable. No recurrence of granulomatous uveitis was observed during 1 year of follow-up.

In conclusion, CHC treated with IFN-α may lead to the development of unilateral ocular sarcoidosis. Completing IFN-α therapy may not cause irreversible ocular side effects under close follow-up. Cooperation of ophthalmologists and medical physicians in cases of CHC treatment with IFN-α is very important.

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