Case report

Vogt-Koyanagi-Harada disease occurring during interferon alpha therapy for chronic hepatitis C

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Retinal abnormalities, including retinal hemorrhage and “cotton-wool” spots, often occur within the first 8 weeks in the course of interferon therapy in patients with chronic hepatitis C. Here, we describe a case of Vogt-Koyanagi-Harada disease occurring 4 months after the start of interferon alpha treatment, probably induced by the immunomodulatory effects of interferon. Therefore, we conclude that chronic hepatitis C patients, especially people with darkly pigmented skin, need to be closely monitored for ophthalmologic complications, by periodic check-up of the optic fundi, for a prolonged period, during interferon treatment.

Key words: Vogt-Koyanagi-Harada disease · interferon, chronic hepatitis C

Introduction

Alpha interferon is widely used for the treatment of chronic hepatitis C. In Japan, more than 300,000 patients with chronic hepatitis C have been treated with alpha interferon. Almost all patients who receive alpha interferon in doses of 300 million units (MU) or more per injection experience some adverse side effects. These are usually minor and do not require a reduction in dose. The most common and predictable adverse events of interferon are the early influenza-like side effects that occur, typically, 6 to 8 h after the initial injection. Later common side effects of interferon develop after the first few days or weeks of therapy. These include fatigue, malaise, apathy, and cognitive and behavioral changes. Between 10% and 15% of patients find the long-term side effects intolerable and ask for discontinuation of treatment.

Fatal and life-threatening side effects of interferon alpha therapy, such as depression (leading to attempted suicide), bone marrow suppression, and interstitial pneumonia, are rare with the doses used to treat chronic hepatitis C.1 Serious but non-life-threatening side effects, including symptomatic thyroid disease, systemic autoimmune disease, and diabetes mellitus, are reported to occur in 1 of 100 patients.1 Thus, therapy with alpha interferon may induce autoimmune diseases, of which autoimmune thyroiditis is perhaps the most frequent manifestation of the immunomodulatory properties of alpha interferon.2,3 Higher doses of alpha interferon (more than 6 MU) tend to cause higher rates of adverse events.4

The incidence of ophthalmologic side effects of alpha interferon therapy was evaluated in a prospective study of 63 patients with chronic hepatitis C.5 Retinal abnormalities, either retinal hemorrhages or “cotton-wool” spots, developed in more than half of the patients. Most retinal complications were reported to be asymptomatic, not associated with a decrease in visual activity, and reversible when treatment was stopped.6

We report here the second case of Vogt-Koyanagi-Harada (VKH) disease in a patient who was receiving therapy with interferon alpha for chronic hepatitis C.7 VKH disease is a systemic disease typically affecting the eyes, ears, meninges, hair, and skin. The tissues affected in the disease contain melanocytes, and the clinical symptoms manifested are bilateral uveitis, dysacusia, meningeal irritation, poliosis, and vitiligo. This disorder is common in darkly pigmented people such as Asians, Hispanics, and Native Americans. In Japan, the disease is found in about 8% of patients with endogenous uveitis.8 Recently, an autoimmune T-cell response to a melanocyte-associated9,10 antigen was considered to be a cause of VKH disease.
A 36-year-old man with chronic hepatitis C was admitted to hospital for treatment of chronic hepatitis C, with interferon, in September 1999. He had a history of blood transfusion, when he was 16 years old. He was a habitual drinker, having consumed about 50g/day of ethanol for 16 years until this admission. On physical examination, he was obese (height, 175.5 cm; weight, 80.5 kg), and normotensive, without jaundice or anemia. The liver and spleen were not palpable, and there were no abdominal masses. Laboratory data yielded the following results: white blood cell count, 5800/mm³; red blood cell count, 556 × 10⁶/mm³; hemoglobin, 16.9 g/dl; platelet count, 14.3 × 10⁴/mm³; prothrombin time, 121%; serum aspartate transaminase (AST), 59 U/l; alanine transaminase (ALT), 202 U/l; \( \gamma \)-glutamyltranspeptidase, 573 U/l; total bilirubin, 0.6 mg/dl; albumin, 5.1 g/dl; gamma globulin, 1.2 g/dl; fasting plasma glucose, 10.9 nmol/l; hemoglobin A1c (HbA1c), 8.9%; hepatitis B surface antigen and anti-body, both negative; hepatitis C virus (HCV) subtype, 1; and HCV RNA level, 66 × 10⁵ copies/ml (Amplicor HCV monitor assay; Roche Diagnostic Systems, Branchburg, NJ, USA). Proteinuria and diabetic retinopathy were not observed. Ultrasonography and diabetic retinopathy were not observed. Ultrasonography demonstrated fatty liver. Diet cure for diabetes mellitus, with restriction of daily calorie intake to less than 1760 calories and abstinence from alcohol, was started from the time of admission. Recombinant interferon alpha-2b (Schering-Plough Pharmaceutical, Osaka, Japan), at a dose of 10 MU, was given intramuscularly every day for the first 2 weeks and three times a week thereafter. Serum ALT and AST decreased to within the normal range and serum HCV became undetectable within 6 weeks after the start of alpha interferon. Fasting plasma glucose and HbA1c were 4.8 nmol/l and 6.0%, respectively at 6 weeks after the start of the diet cure. Thus, biochemical and virological responses to interferon were good. Diabetes mellitus was well-controlled by diet management during the interferon therapy.

In February 2000, 4 months after the start of the interferon treatment, the patient complained of the sudden onset of blurred vision, stiff shoulder, and headache, with failing eyesight. Optic fundal examination showed that there was no retinal hemorrhage, but showed uveitis, mainly in the posterior segment of the eye, with papilledema and circumscribed retinal edema. Fluorescein angiography (Fig. 1) showed characteristic multiple areas of leakage of fluorescein from the choroid into the subretinal space. He was diagnosed as having VKT disease. Interferon treatment was discontinued, and systemic steroid therapy, at a dose of 1000 mg of methylprednisolone intravenously, was carried out for 3 days, followed by daily oral administration at a dose of 12 mg of methylprednisolone.

From May 2000, 3 months after the start of systemic steroid therapy, insulin therapy was begun, because the patient’s fasting plasma glucose reached 14.3 nmol/l. In August, although 8 mg of methylprednisolone per day was being given orally for VKH disease, the diabetes mellitus was well-controlled by insulin. Serum HCV RNA remained undetectable, and serum ALT, AST, and \( \gamma \)-glutamyltranspeptidase also remained within the normal ranges for more than 6 months after the cessation of the interferon therapy, indicating that the patient was a complete sustained responder, with HCV eradication. His final eyesight finding was 30/30, and remission of the retinal inflammation was achieved by the systemic steroid therapy.

**Discussion**

Retinal complications, including retinal hemorrhage and “cotton-wool” spots, are seldom seen in healthy subjects and have not been reported to be found in