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Deterioration of Retinopathy After Starting Interferon Therapy for Chronic Hepatitis C with Diabetic Triopathy.

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A 62-year-old man was administered pegylated interferon α-2a and ribavirin for chronic hepatitis C. He had come to our hospital for treatment of chronic hepatitis C and diabetic triopathy. After diet and insulin therapy blood glucose levels (HbA1c ; 6.0-6.8%, glycosylated Alb ; 18.5-20%) were adequately maintained for a year. However, AST and ALT levels ranged from 50 to 60 mU/ml by ursodeoxycholic acid and Stronger Neo-Minophagen C. Although liver function improved after interferon and ribavirin combination therapy, visual acuity decreased due to diabetic retinopathy deterioration. After the end of interferon and laser photocoagulation therapy, visual acuity improved. (Kitakanto Med J 2006；56：339～342)

Key Words： chronic hepatitis C, interferon, diabetes mellitus, diabetic retinopathy

Introduction

Chronic hepatitis C is a serious condition that can lead to cirrhosis of the liver and may progress to life-threatening hepatocellular carcinoma. Currently, a combination therapy of interferon α and ribavirin has been the most successful treatment. However, this therapy may produce serious ocular and systemic side effects.[1] Diabetic retinopathy is the leading cause of blindness. Laser photocoagulation reduces the rate of severe visual loss by 50% in patients with high-risk characteristics of proliferative or severe nonproliferative diabetic retinopathy.[2,3] Here, we report a case of diabetic retinopathy deterioration after starting interferon therapy for chronic hepatitis C with diabetic triopathy.

Case report

A 62-year-old man was admitted to our hospital for control of hyperglycemia and liver dysfunction in December 2004. Liver dysfunction and diabetes mellitus were indicated at age 51. Bilateral foot numbness had been present since age 60 from which time he had been treated by a practitioner. However, hyperglycemia had continued despite an increase in anti-diabetic drug dosefrom 1.25 to 7.5 mg/day of glibenclamide). Persistent proteinuria had occurred at age 62. His older brother had a history of diabetes mellitus, but there was no other previous history of disease. The patient did not drink alcohol but smoked 20 cigarettes per day.

Physical examination showed the following: height 175.5 cm, weight 73.6 kg (body mass index 23.8 kg/m²), blood pressure 140/84 mmHg, pulse rate 68/min and temperature 36.7°C. His conjunctiva was not anemic and not icteric. Funduscopic examination showed simple diabetic retinopathy Scott IIIa). There were no abnormalities on the neck or chest. The liver was palpable 3 cm, below the right costal margin and was blunt and firm. There were vascular spiders on the chest wall. There was no lymphadenopathy. Arterial pedia dorsalis pulse was palpable on both sides. The tendon reflexes were symmetrically diminished in the lower limbs. He had paresthesia and diminished vibration sense in the lower limbs, indicating sensory polyneuropathy due to diabetes mellitus.

The laboratory data is shown in Table 1. Urinalysis showed proteinuria (100 mg/dl), glycosuria (1 g/dl) and acetone (−). Hematology, renal function, electrolytes and lipid levels were within a normal range. Liver function showed AST 103 mU/ml, ALT 119 mU/ml, γ-GTP 106 mU/ml, ZTT 13.2 U, TTT U, anti-HCV Ab (+), HCV-RNA (genotype 1, 850

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Table 1 Laboratorydataonadmission

Urinalysis		Chemistry			
protein	100mg/dl	AST	103mU/ml	FBG	214mg/dl
glucose	1.0g/dl	ALT	119mU/ml	T-CH	169mg/dl
blood	(—)	LDH	232mU/ml	HDL-CH	41 mg/dl
aceton	(—)	ALP	317mU/ml	TRG	149mg/dl
pH	6%	γ-GTP	106mU/ml	HbA1c	11%
sediment		ChE	4055mU/ml	U-CPR	260μg/day
WBC	1-2/hpf	T-P	8.0g/dl	Ccr	102.3ml/min
RBC	1-2/hpf	Alb	4.0g/dl	urineprotein	1.94g/gCr
Hematology		T-Bil	0.5mg/dl	Serology	
RBC	$517\times10^4/\mu$l	ZTT	13.2U	CRP	0.1mg/dl
Hb	15.9g/dl	TTT	7.0U	STS	(—)
Ht	47%	BUN	16.4mg/dl	HBsAg	(—)
PLTS	$17\times10^4/\mu$l	Cr	0.8mg/dl	anti-HCVAb	(+)
WBC	6400/μl	UA	5.0mg/dl	HCV-RNA	genotype1
Baso	2%	Na	142mEq/l		850kilocopies/ml
Eosino	2%	K	4.6mEq/l		
Stab	0%	Cl	105mEq/l		
Seg	54%	Ca	10.0mg/dl		
Lymph	35%	amylase	55mU/ml		
Mono	9%				
ESR	59mm/hr				

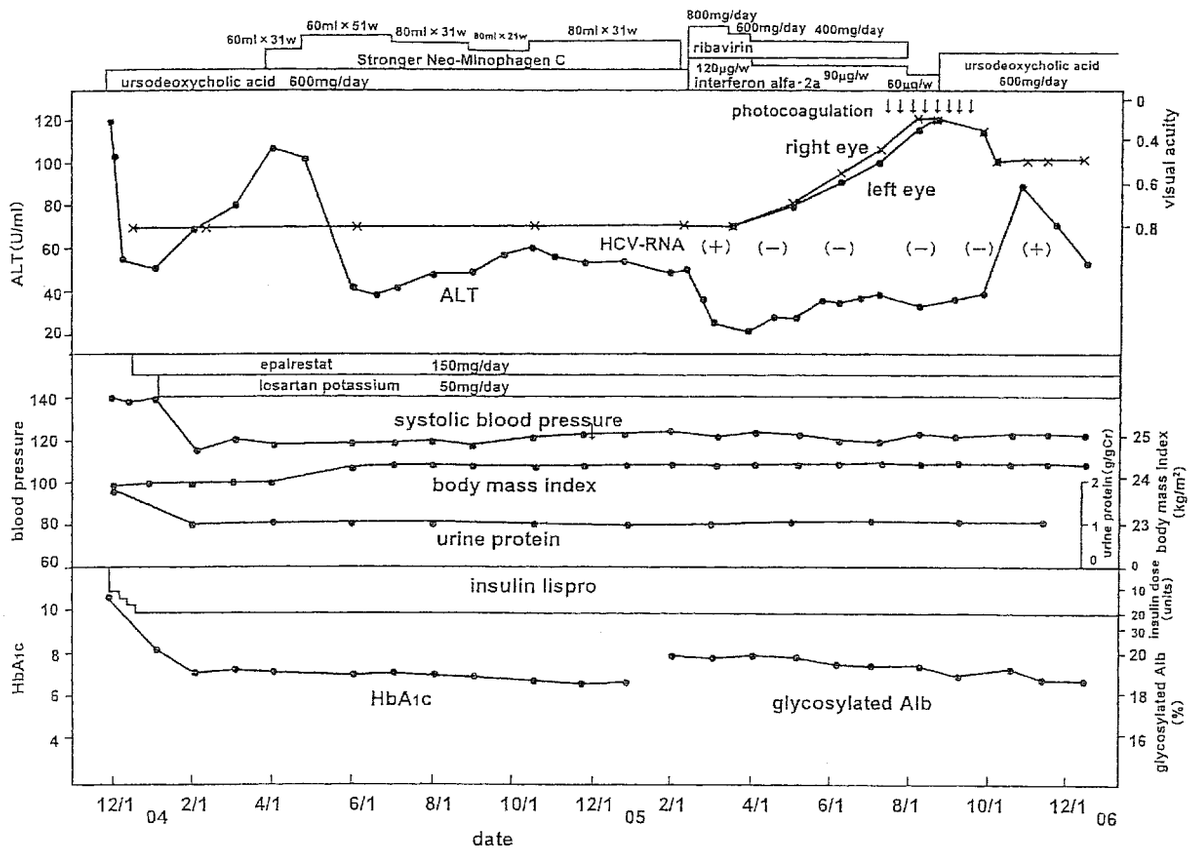

Fig. 1 Clinical course of the patient.

kilocopies/ml), leading us to suspect chronic hepatitis C. Fasting plasma glucose was 214 mg/dl, HbA1c 10.6%, urine CPR 260 μg/day. The urinary protein excretion rate was 1.94 g/g • creatinine, indicating overt diabetic nephropathy. The cryoglobulin was negative. There were no abnormalities in the chest X ray or electrocardiogram. An abdominal echogram showed granular and dull-edge, and internal irregular

echo in the liver. The liver biopsy specimen showed irregular fibrosis and lymphocyte infiltration in portal areas and piecemeal necrosis diagnosed as chronic hepatitis. HCV-RNA was measured by reverse transcription-polymerase chain reaction.

After admission, he was treated for diabetes mellitus on diet (2000 kcal/day, protein 60 g/day) and insulin therapyinsulin lispro 3 times before diet daily). After that blood glucose control improved (HbA1c ; 6.0-6.8%) for a year. After the administration of 150 mg of epalrestat daily, his foot numbness improved slightly. After we had administered 50 mg of losartan potassium daily, the blood pressure ranged from 120 -125/70-75 mmHg and the urine protein decreased from 1.94 to 1 g/gCr (Fig. 1). However, AST and ALT levels ranged from 50 to 60 mU/ml by ursodeoxycholic acid and Stronger Neo-Minophagen C. After a year we started pegylated interferon α-2a and ribavirin combination therapy. After that, liver function improved (AST 35-43 mU/ml, ALT 32-38 mU/ml) and blood glucose control maintained nearly adequate levels (glycosylated Alb ; 18.5-20%). Three months after interferon therapy, visual acuity had decreased from 0.8 to 0.2. On funduscopic examination, retinal hemorrhage, cotton wool spots and macular edema appeared, indicating diabetic retinopathy deterioration. After the end of interferon and laser photocoagulation therapy, visual acuity improved from 0.2 to 0.5.

Discussion

Diet and insulin therapy had maintained nearly adequate blood glucose control. Moreover, after administration of angiotensin II receptor antagonist (losartan), which improves diabetic nephropathy,[4] blood pressure returned to adequate levels and urine protein decreased, indicating that diabetic nephropathy had improved. This effect may have been due to adequate blood glucose control,[5] strict blood pressure control[6] and the use of angiotensin II receptor antagonist.[4] However, AST and ALT levels, reflecting chronic hepatitis C activity, had not improved by ursodeoxycholic acid and Stronger Neo-Minophagen C administration. After interferon and ribavirin combination therapy, which is the most successful treatment,[1] liver function improved and HCV-RNA became negative. However, visual acuity had decreased because of diabetic retinopathy deterioration. Adequate blood glucose control[5] and tight blood pressure control[7] improve diabetic retinopathy as well as nephropathy. After the end of interferon and laser photocoagulation therapy, visual acuity improved. Therefore, the deterioration of diabetic retinopathy may have been due to interferon therapy. Interferon associated retinopathy for chronic hepatitis C has been demonstrated.[8,9] Development of retinopathy, including retinal hemorrhage and cotton wool spots during the course of interferon therapy, is frequently observed in 86% of chronic hepatitis C patients within the first 8 weeks.[8] The pathogenesis of interferon-associated retinopathy is unknown. However, there is clinical and laboratory evidence that interferon therapy can cause retinal ischemia and possibly optic nerve ischemia.[10] However, interferon inhibits the proliferation and migration of vascular endothelial cells in vitro and inhibits experimental intraocular neovascularization.[11] Since proliferative diabetic retinopathy was characterized by intraretinal neovascularization, a pilot study of interferon administration for proliferative diabetic retinopathy was undertaken.[12,13] All 3 cases experienced hemorrhage within 6 weeks of termination of interferon administration in one study.[12] The other study showed that interferon α-2a for proliferative diabetic retinopathy, after complete laser panretinal photocoagulation treatment, improved visual acuity and extent of neovascularization in 7 of 8 patients.[13] Therefore, interferon may be useful for proliferative diabetic retinopathy after complete laser panretinal photocoagulation treatment, although the above studies included diabetic patients without chronic hepatitis C. Ischemic retinopathy can also be seen in patients with hepatitis C virus.[10] The most common lesions are retinal hemorrhage and cotton wool spots. Hepatitis C virus associated ischemic retinopathy may be attributable to cryoglobulinemia. In chronic hepatitis C patients with diabetes mellitus, interferon administration may cause the deterioration for diabetic retinopathy due to ischemic retinopathy other than interferon therapy. Our patient showed negative cryoglobulin and HCV -RNA followed by interferon. Therefore, retinopathy deterioration in our case may have only a slight association with hepatitis C virus. Whether or not interferon therapy can improve diabetic retinopathy is unknown, it is important to frequently perform funduscopic examination during interferon therapy in chronic hepatitis C patients with diabetes mellitus.

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