

Study of hepatitis C virus-related cryoglobulinemic vasculitis in chronic hemodialysis patients

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Aims:

Background

Cryoglobulins are immunoglobulins characterized by their insolubility at low temperatures (0~4°C) and their dissolution after rewarming. Cryoglobulins are classified as either single (type I), consisting of a monoclonal immunoglobulin, or mixed, comprising two or more immunoglobulin isotypes, with (type II) or without (type III) a monoclonal component. More than 90% of patients with mixed cryoglobulinemia were infected with hepatitis C virus (HCV). Cryoglobulin can be detected in 25 to 30% of HCV-positive patients. Cryoglobulin-related illness, known as cryoglobulinemic vasculitis, appears in 10 to 15% of the patients. It is also known that HCV infection is rampant among chronic hemodialysis (HD) patients. The effectiveness of interferon in the treatment of patients with mixed cryoglobulinemia was reported.

Aims

Peripheral artery disease (PAD) is commonly seen in chronic HD patients. Chronic HD patients experience high incidence of limb amputations due to leg ulcers and digital gangrene. The aim of this study is to investigate the clinical characteristics of HCV-related cryoglobulinemic vasculitis and limb amputations in chronic HD patients.

Results:

Table 1 Amputation rate.

HD patients	amputation case	amputation rate
2,214	73	3.3 %

Table 2 Clinical characteristics.

	amputation (n=73)	non-amputation (n=73)
Male	53 (72.6%)	53
Female	20 (27.4%)	20
Age (years)	66±11	66±11
HD duration	6 years and 5 months	9 years and 8 months

Table 3 The primary cause of end-stage renal disease (ESRD).

	amputation (n=73) (%)	non-amputation (n=73) (%)
diabetic nephropathy	57 (78.1) **	20 (27.3)
unknown	7 (9.6)	10 (13.8)
nephrosclerosis	4 (5.5)	3 (4.0)
CGN	3 (4.0) **	33 (45.2)
pyelonephritis	1 (1.4)	1 (1.4)
PIH	1 (1.4)	0
PKD	0	4 (5.5)
malignant hypertension	0	1 (1.4)
CMD	0	1(1.4)

CGN: chronic glomerulonephritis; PKD: polycystic kidney disease; CMD: congenital metabolic disease; PIH: pregnancy induced hypertension
** P < 0.01 vs. non-amputation group

Table 4 Various serum parameters in HD patients.

	amputation (n=73)	non-amputation (n=73)
Alb (g/dL)	3.5±0.4	4.1±3.9
CRP (mg/dL)	0.5±1.2	0.4±0.9
P (mg/dL)	5.2±1.4	4.9±1.5
Ca (mg/dL)	8.8±0.8	8.8±1.2
Intact PTH (pg/mL)	247.5±199.3	251.4±334.7

Table 5 History of myocardial infarction in HD patients.

	amputation (n=73)	non-amputation (n=73)
myocardial infarction (+)	8 (11.0%) *	2 (2.7%)
myocardial infarction (-)	53 (72.6%)	71 (97.3%)
unknown	12 (16.4%)	0

*P < 0.05 vs. non-amputation group

Methods:

Protocol (1)

Data from 2,214 HD patients in Japan from dialysis clinics from 2009 to 2013 were analyzed. Each medical record was assessed for prior amputation(s) of the lower or upper limb, including fingers and toes, on or before entry into the study.

Protocol (2)

We investigated serum HCV antibody and HBV antigen in 103 HD patients (male/female: 62/41, Age: 60.5±14.7 years, HD duration: 5 years and 4 months). HCV antibody were positive in 8 HD patients (7.8%), HBV antigen were positive in 2 HD patients (1.9%). We determined serum cryoglobulin in 8 HD patients (male/ female: 6/2, Age: 67.3±12.6 years, HD duration: 4 years and 7 months) with HCV or HBV (male 2, Age: 61.5±1.5 years, HD duration: 3 years and 3 months).

Table 6 Mortality in HD patients.

prognosis	amputation (n=73)	non-amputation (n=73)
death	26 (35.6%) *	15 (20.5%)
survival	47 (64.4%)	58 (79.5%)

* P < 0.05 vs. non-amputation group

Protocol (1)

1. Seventy-three patients of 2,214 HD patients had a history of amputation. The limb amputation rate was 3.3%.
2. Fifty-three HD patients (72.6%) were male. Fifty-seven HD patients (78.1%) had diabetic nephropathy as the primary cause of end-stage renal disease (ESRD).
3. The mean serum albumin of HD patients with amputation was 3.5±0.4 g/dL, high sensitive CRP level was 0.5±1.2 mg/dL.
4. HD patients with amputation had a significantly higher incidence of myocardial infarction than those without amputation (11.0% vs. 2.7%, P<0.05).
5. After 5-year follow up, the mortality of patients with amputation was significantly higher than those without amputation (35.6% vs. 20.5%, P<0.05).
6. Some HD patients with amputation had syndrome consisting of malnutrition, inflammation and atherosclerosis (MIA syndrome).

Subjects Protocol (2)

	HCV antibody (+) (n=8)	HBs antigen (+) (n=2)
Male	6	2
Female	2	0
Age (years)	67.3±12.6	61.5±1.5
HD duration	4 years and 7 months	3 years and 3 months

Results (1) Protocol (2)

Cryoglobulinemia was present in one patient (12.5%) of 8 HD patients with HCV infection, 0% of HBV infection.

CLINICAL HISTORY

A 60-year-old man.

He started HD three times a week due to diabetic nephropathy in February 2006.

He had digital gangrene of his right fourth finger and Raynaud's phenomenon in February 2014.

Cryoglobulinemia plus positive HCV (HCV RNA 6.8 Log IU/mL, genotype 2) was accompanied with hypocomplementemia (CH50: 5 U/mL; standard value: 30~45 U/mL).

His anti-nuclear antibody was 24.7 (standard Svalue: <20.0). His antiscleroderma 70 antibody was negative, and anticentromere antibody was negative. His ankle brachial index (ABI) of right leg was 0.98 and ABI of left leg was 1.07.

His pulse wave velocity (PWV) on the right side was 3029 cm/s and PWV on the left side was 2841 cm/s.

After liver biopsy, he was treated with peginterferon alfa-2a (135µg once a week) for chronic HCV infection. After peginterferon alfa-2a therapy for 24 weeks, HCV RNA (Real-time PCR) decreased from 6.8 to >1.2 Log IU/mL.

Thereafter peginterferon alfa-2a therapy was performed, serum cryoglobulin changed to negative and his digital gangrene improved.



Conclusions:

- (1) Those results suggest that general care management including observation of cardiovascular disease was important for HD patients with amputation.
- (2) The peginterferon alfa-2a therapy was shown to be effective in chronic HD patient with HCV-related cryoglobulinemic vasculitis.

