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Clinical Report

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Re-infection following sustained virological response with a different hepatitis C virus genotype: implications for infection control policy

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Abstract
We report the case of a 45-year-old haemodialysis patient who achieved a sustained virological response (SVR) following pegylated interferon therapy for hepatitis C virus (HCV) genotype 2 infection. He was subsequently cohorted with other HCV-infected dialysis patients and became re-infected with HCV genotype 3a. Epidemiological and molecular investigations identified a highly viraemic HCV genotype 3a-infected dialysis patient as the likely source of this infection. This critical incident informed a revision to local and national infection control policy regarding the dialysis management of patients who achieve an SVR following anti-viral treatment.

Keywords: dialysis; infection control; hepatitis C; re-infection; sustained virological response

Background

Nosocomial hepatitis C virus (HCV) infection within dialysis units is well described [1, 2]. International guidelines advocate standard infection control precautions as the primary method of minimizing patient-to-patient HCV transmission [3, 4]. Cohorting HCV-infected patients and segregating them from the main dialysis unit may further reduce the risk of HCV transmission [5–7]. However, cross-infection between cohorted patients could lead to the superinfection of patients with another HCV genotype or the re-infection of patients whose infection had resolved naturally or following anti-viral treatment.

We describe a haemodialysis patient who was re-infected with HCV of a different genotype than his original infection. We discuss the implications that this poses for infection control policy within haemodialysis facilities.

Case report

A 17-year-old male (index patient) commenced maintenance haemodialysis in 1983. He received an estimated 20 U of packed red blood cells for treatment of renal anaemia. He underwent deceased donor renal transplantation in 1984. His transplant failed in 2002 due to chronic allograft nephropathy and he was tested for HCV infection as he returned to dialysis. HCV genotype 2 with a viral load of 7 312 217 copies/mL (~2 708 228 IU/mL) was discovered. Alanine aminotransferase was 105 IU/L and liver histology supported mild hepatitis. He declined interferon treatment and received a second deceased donor renal transplant in 2003. This transplant failed due to recurrence of his original glomerulonephritis and he developed end-stage kidney disease within 4 years. According to local policy, he was cohorted with HCV-infected patients when he resumed haemodialysis in 2007. In September 2009, he commenced a 24-week course of pegylated interferon therapy. Serum HCV RNA was undetectable by Week 12 (see Figure 1). This remained negative 6 months after completion of therapy, by definition a sustained virological response (SVR). He continued to dialyse alongside patients with detectable HCV RNA.

The patient was routinely tested for HCV after returning from a holiday abroad in January 2011 and was found to be weakly positive for HCV antigen (Ag) (44 pg/mL). Retrospective testing of a serum sample collected in December 2010 confirmed that HCV Ag and RNA were then absent. Subsequent HCV RNA testing in February 2011 detected HCV RNA with a viral load of 7791 IU/mL. Genotyping using the Versant HCV Genotype 2.0 assay (INNO-LiPA) identified this to be HCV genotype 3a. This indicated HCV re-infection rather than a relapse of the patient's original HCV genotype 2 infection.

A detailed epidemiological and molecular investigation was initiated. There was no evidence to support HCV transmission outside the dialysis unit or within the patient's holiday dialysis unit. A review of the genotypes of all HCV viraemic patients within the unit identified two additional patients with HCV genotype 3a infection. One patient (Patient X) had received dialysis alongside the index patient (i.e. same shift, room and nurse but different dialysis machine) throughout the month of December, at which time his HCV viral load was >69 000 000 IU/mL. Phylogenetic analysis of fragments of the E1/E2 region, including the hypervariable region, of HCV RNA from Patient X and the index patient demonstrated that there was a strong

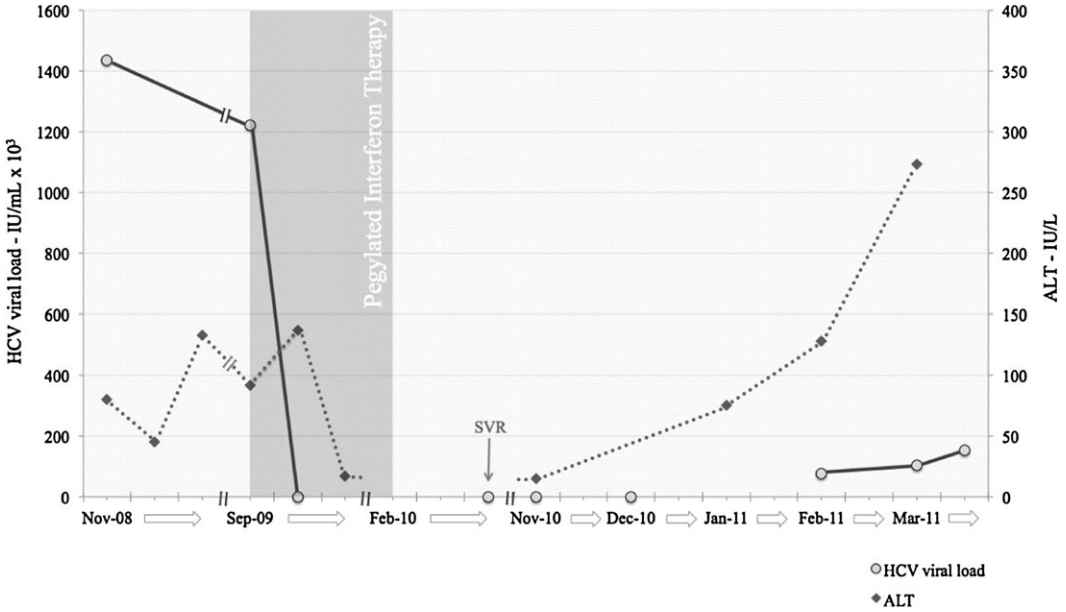

Fig. 1. Trends in HCV viral load and ALT titres from 2008–2011. Shaded area indicates pegylated interferon therapy. ALT, alanine aminotransferase.

possibility that both viruses were genetically related (see Figure 2). We concluded that the index patient had been infected with HCV genotype 3a from Patient X while they were being cohorted together for dialysis.

Discussion

This report describes a dialysis patient with chronic HCV genotype 2 infection who achieved an SVR following pegylated interferon therapy but was re-infected with HCV genotype 3a. Epidemiological and molecular investigations identified a highly viraemic patient, with whom the patient was being cohorted for dialysis, as the likely source of the re-infection.

Ireland has a low prevalence of HCV infection among haemodialysis patients [9]. Intensive surveillance for HCV infection is practiced in the dialysis unit and only two cases of nosocomial HCV transmission have been detected among the 496 250 dialysis treatments delivered here since HCV testing became available in 1992. This seroconversion rate of 0.4 per 100 000 dialysis treatments compares favourably to international experience [10].

International guidelines [3, 4], supported by observational data [10, 11], maintain that standard infection control precautions alone are sufficient to prevent nosocomial HCV transmission. However, breaches in infection control procedure in dialysis facilities are not infrequently described and have resulted in large HCV outbreaks [1, 2]. Cohorting of HCV-infected patients together in dialysis units separated from main dialysis units may offer additional protection to non-infected patients [7]. Indeed, impressive reductions in rates of HCV seroconversion have been observed to occur in many dialysis units following implementation of such a strategy [5, 6]. Consequently, we cohort HCV-positive dialysis patients together in a unit adjacent to our main dialysis unit in the belief that this practice provides maximal protection to the majority of our patients (i.e. the non-infected) without placing excessive demands on hospital resources. Cohorting should, however, augment standard infection control precautions and not replace them. As illustrated by this case, lapses in the strict enforcement of standard precautions can result in HCV superinfection and re-infection, respectively, among actively infected and recently treated HCV-positive dialysis patients being cohorted together.

To our knowledge, only one previous report has described HCV re-infection occurring in a haemodialysis population [12]. In this case series, five haemodialysis patients from three dialysis centres in Brazil were re-infected with HCV. Re-infection was distinguished from relapse on the basis of a different HCV genotype. This report differs from ours in a number of respects. Firstly, these patients were re-infected with HCV prior to achieving an SVR. Secondly, an epidemiological analysis was not reported—consequently, it is not clear that all infections were nosocomially acquired. Lastly, no information is provided regarding infection control policy in the referring dialysis units.

The experience of HCV re-infection in this patient directly informed a change in local policy regarding the management of HCV-infected dialysis patients who achieve an SVR. In the absence of any international precedent, this revised guideline was based on the rationale that HCV relapse in a dialysis patient is extremely unlikely once an SVR has been achieved [13]. From an infection control standpoint, therefore, patients with an SVR can be safely considered to have ‘resolved infection’.

This revised local policy was reflected in a recently drafted amendment to the Irish ‘blood-borne viruses in haemodialysis, CAPD and renal transplantation’ national guidelines 2010 [14]. This updated guideline will be available on the Irish Health Protection Surveillance Centre website in early 2012 [14].

The main proposed changes are as follows:

- If HCV RNA is undetectable at the end of treatment, the patient can be dialysed in isolation until 6 months after

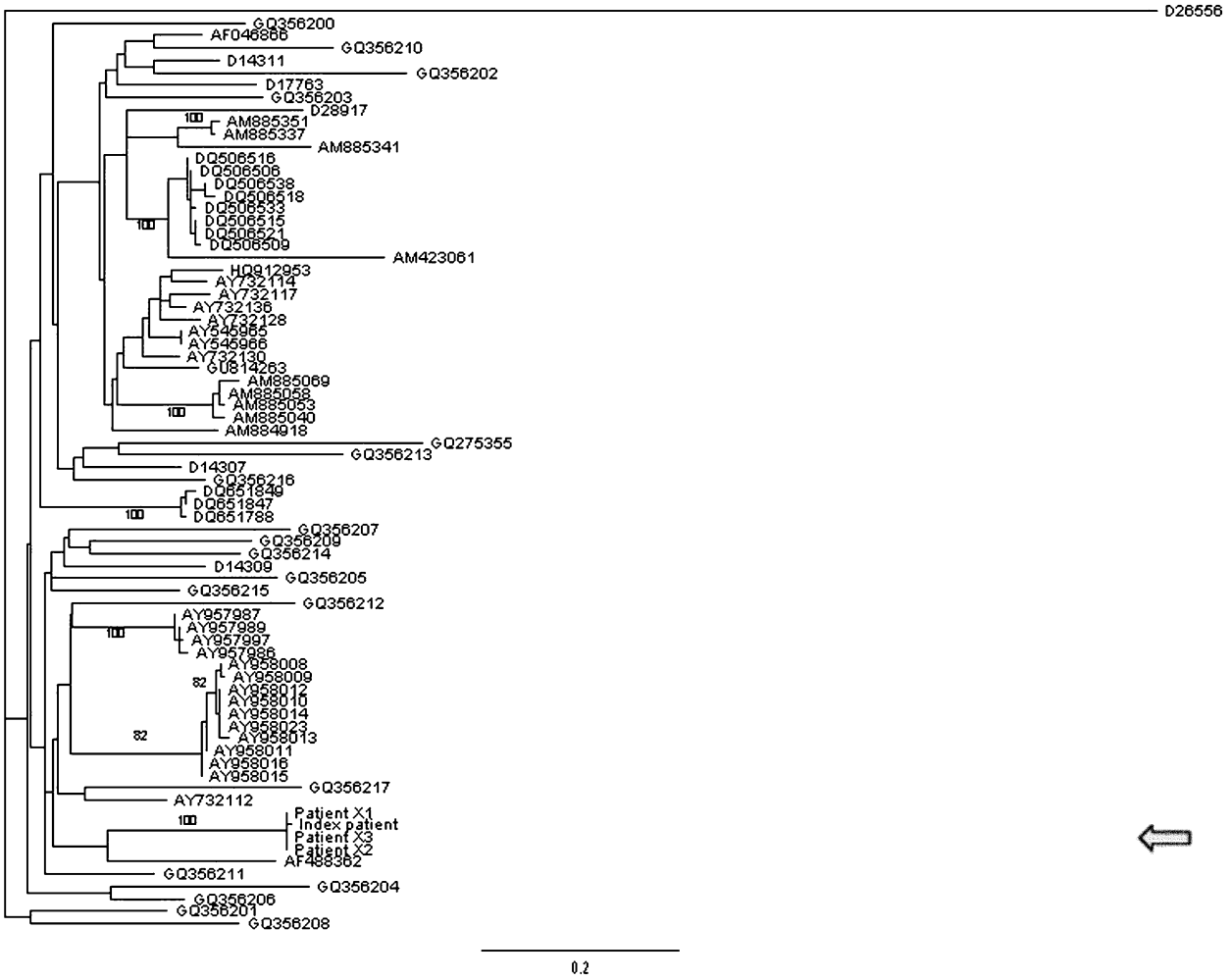

Fig. 2. Phylogenetic tree demonstrating closely related HCV genotype 3a subtypes of index patient and Patient X. Unrooted neighbour-joining (NJ) tree HCV nucleotide sequences in the E1/E2 region (300 bp) with outgroup D26556 (genotype 3b). The nucleotide sequences of index patient and X1, X2 and X3 of Patient X are indicated (see arrow). The NJ tree generated by heuristic search using PAUP [8]. The tree was constructed using the GTR + G + I model of nucleotide substitution selected by jModeltest with 1000 bootstrap replicates. The bootstrap values >700 are displayed as percentage values.

end of treatment or be dialysed in the multibedded unit but undergo HCV Ag testing every 2 weeks.

- If HCV RNA is undetectable 6 months after treatment (SVR), infection can be considered to be resolved. The patient can be dialysed in the multibedded unit and tested monthly for HCV Ag.
- If an SVR is not attained, the patient should be cohorted with HCV RNA-positive patients. HCV genotyping should be performed to distinguish relapse from re-infection.
- Standard infection control procedure is essential to prevent cross-infection between HCV-infected patients, especially for patients with very high viral load.

It is hoped that the publication of this case and the guidelines informed by it will result in a reduction of nosocomial HCV transmission in haemodialysis units.

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Conflict of interest statement. None declared.

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