Probable hepatitis C virus transmission from a seronegative blood donor via cellular blood products

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Dear Sir,

After the discovery of hepatitis C virus (HCV) as a cause of non-A, non-B hepatitis, screening among blood donors was initiated to ensure a safe blood supply. In spite of highly sensitive and specific third-generation HCV antibody tests, as also recommended by the World Health Organization[1], screening for HCV infection using anti-HCV alone is not fully effective because of the window period, which lasts 45-68 days. In many developed countries the introduction of nucleic acid amplification tests (NAT) for donor screening has decreased the risk of viral transmission via blood transfusion. HCV transmission by blood products is still a problem in developing countries in which NAT cannot be implemented because of high cost and the requirement for particular technical skills. Here we present a case of probable transfusion-transmitted HCV infection in the absence of NAT.

A 33-year old female came to make a first donation in October 2011. Mandatory donor blood tests were performed by an Abbott Architect i2000sr analyser using Abbott Architect HBsAg Qualitative II, Anti HCV, HIV Ag/Ab Combo and Syphilis TP Reagent Kits (Abbott Diagnostics, Wiesbaden, Germany). Tests for hepatitis B virus surface antigen (HBsAg), HCV, human immunodeficiency antigen and antibody (HIV Ag/Ab) and treponomal antibody were negative. No probable risk was identified in her donor questionnaire. She was accepted as a healthy blood donor. Three weeks later, she came back to report that her liver function tests had been found to be high during a routine check-up. Her blood tests were tested again with a new sample and anti-HCV was reactive with a sample-to-cutoff ratio (S/CO) of 5.8. The HCV RNA viral load was 7,849,700 IU/mL as measured with an Abbott Real Time HCV RNA Assay (Abbott Molecular, Des Plaines, IL, USA). Liver function tests were elevated (aspartate aminotransferase [AST]: 144 U/L; alanine aminotransferase [ALT]: 266 U/L). The archived material from the first donation was retested for HCV. The anti-HCV test was negative but HCV RNA testing yielded a positive result with a viral load of 22,039,549 IU/mL. The donor was diagnosed as having an acute HCV infection and started treatment with pegylated interferon alpha-2a monotherapy (180 µg/week) for 24 weeks. At week 4 of therapy, her viral load was 21 IU/mL. AST and ALT levels were 35 U/L and 48 U/L respectively. At week 12, the HCV RNA test was negative and liver function tests had returned to normal (AST and ALT levels were both 19 U/L).

Blood components from the donor were tracked and look back examinations in recipients identified two patients who had been transfused with red blood cells and platelets. The plasma unit collected from the donor had not been used and was destroyed. The red blood cell unit had been transfused into a 44-year old female who had been admitted to the Emergency Service complaining of malaise and fatigue and whose haemoglobin and haematocrit values were found to be 6.7 g/dL and 25%, respectively. The platelet unit had been transfused into a 19-year old male with myeloid leukaemia who was an inpatient in the Haematology Department and had received several blood components because of his disease. After identification of the recipients, they were notified and invited to undergo further laboratory tests by the blood bank medical doctors. For both recipients it was the 16th day after transfusion with the HCV-infected blood products when we were able to collect their blood samples for anti-HCV and HCV-RNA tests. The female recipient had a negative anti-HCV test, a positive HCV-RNA test with a viral load of 24,988,013 IU/mL and abnormal liver function tests with elevated AST (151 U/L) and ALT (181 U/L). She started monotherapy with pegylated interferon alpha-2a (180 µg/week) for 24 weeks as treatment for acute HCV infection. At week 4 of therapy the anti-HCV test was weakly positive and the HCV viral load was 160 IU/mL. At week 24 of therapy the HCV RNA test was negative and serum AST and ALT levels were 12 U/L and 8 U/L, respectively. The male recipient had a negative anti-HCV test, and a viral load of HCV RNA of 8,300,192 IU/mL. No therapy for HCV infection was initiated due to his clinical condition and the medications for his primary disease. During follow-up controls the anti-HCV test was always negative and his viral loads (26,365,187 IU/mL and 32,881,519 IU/mL) remained high. Table I shows the HCV test results of the donor and the recipients.

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Table I - HCV test results of the donor and the recipients.

	Time of testing	Anti-HCV (S/CO)	HCV-RNA (IU/mL)	HCV Ag (fmol/mL)
Donor	Index donation	Negative	22,039,549	>20,000
	Initial diagnosis*	Positive – 5.8	7,849,700	NT
	Week 4 of therapy	NT	21	NT
	Week 12 of therapy	NT	Negative	NT
Recipient 1	Initial diagnosis#	Negative	24,988,013	>20,000
	Week 4 of therapy	Positive – 1.99	160	NT
	Week 24 of therapy	NT	Negative	NT
Recipient 2	Initial diagnosis#	Negative	8,300,192	>20,000
	2 months after diagnosis	Negative	26,365,187	NT
	4 months after diagnosis	Negative	32,881,519	NT

Recipient 1: female; Recipient 2: male. *3 weeks after index donation, #16th day of transfusion, NT: not tested.

Archived material collected from the donor in October 2011 was also analysed for anti-HCV with three other systems. Anti-HCV was non-reactive with anti-HCV II (Roche Diagnostics GmbH, Mannheim, Germany) (COI 0.048) on Modular Analytics E170 (Roche Diagnostics GmbH); Advia Centaur HCV test v3 (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA) (Index 0.06) on Advia Centaur XP (Siemens Healthcare Diagnostics Inc.) and Vitros anti-HCV Assay (Ortho Clinical Diagnostics, Raritan, NJ, USA) (0.07 S/C) on Vitros Eci (Ortho Clinical Diagnostics). The same sample was also tested for HCV core antigen (HCV Ag) with an Abbott Architect HCV Ag Assay using an Abbott Architect i2000sr analyser and was positive for HCV Ag (>20,000 fmol/L). Samples collected from the recipients at the time of initial diagnosis were also tested for HCV Ag and both samples were positive (>20,000 fmol/L). HCV genotypes were determined by restriction fragment length polymorphism analysis with the amplification of highly conserved regions of the 5' untranslated region. All were genotype 1a.

HCV Ag is probably present in both complete HCV virions and RNA free core protein structures in the sera of HCV infected individuals. Like HCV RNA, HCV Ag is an indicator of active viral replication and there is close correlation between the serum concentrations of both markers. It has also been shown that HCV Ag and HCV RNA levels are strongly correlated in the liver of chronically infected treatment-naive patients[2]. HCV Ag tests are used as an alternative to HCV RNA in both diagnosis of active HCV infection and monitoring the response during antiviral therapy[3]. The risk of HCV transmission could effectively be reduced by additional screening of HCV Ag in antibody negative blood donations[4]. Anti-HCV is the primary marker for HCV screening among blood donors in many developing countries. This report supports that HCV Ag as an additional serological marker would improve the effectiveness of HCV screening especially for the donations during the window period of antibody assays. One limitation of our investigation is the absence of comparison of HCV strains since the virus was genotyped by restriction fragment length polymorphism analysis. We can, therefore, only classify our case as one of probable transfusion transmission. Early recognition and notification of possible transmission is the key to early diagnosis and increasing treatment options for the infected recipients. In our case, both the donor and the female recipient received pegylated interferon alpha-2a monotherapy for 24 weeks as recommended[5] and both had complete virological responses. Additional HCV Ag screening among donors when NAT cannot be applied and implementation of an effective national haemovigilance programme seem to be the major steps that could be taken to further prevent transmission of HCV via transfusion.

The Authors declare no conflicts of interest.

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