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Letter to the Editor

Diagnosis of hepatitis C-related liver disease in patients with mild hemophilia

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Following the contamination of blood products with hepatitis C virus (HCV) and human immunodeficiency virus (HIV) in the 1970s to 1980s, almost all hemophilia patients who received plasma-derived factor products were infected with HCV prior to the implementation of viral inactivation in 1985. Of these patients, around 20% spontaneously cleared the virus [1,2]. The remainder developed chronic hepatitis and around 30% of them cirrhosis and finally hepatocellular carcinoma (HCC) in the absence of treatment [2,3]. In the nineties and until 2015, treatment with interferon +/- ribavirin, pegylated interferon (PEG-IFN) + ribavirin and PEG-IFN, ribavirin + first generation direct-acting antiviral drugs (DAA) was associated with a limited efficacy and numerous side effects. The absence of treatment as well as the reduced efficacy of these treatments was thus associated with occurrence of cirrhosis and HCC and represents a major cause of morbidity and mortality in hemophilia patients [2]. After 2015, administration of second-generation DAA is associated with a huge efficacy: around 98% of patients are successfully treated, leading to eradication of the virus, and their side effects are very limited. Despite HCV eradication, the risk of HCC occurrence is still present if the patient is treated at the stage of advanced fibrosis [4]. As follow-up periods for hemophilia patients with chronic hepatitis C are lengthening, the incidence of HCC in hemophilia patients appears to be increasing [5,6].

At the HTC at Cliniques universitaires Saint-Luc, 127 patients with hemophilia (A and B) born before 1990 are currently registered and actively followed. Of these, 90 (70.9%) have HCV antibodies. Sixteen infected patients (17.8%) spontaneously cleared the virus and 69 (76.6%) have received one or more treatment lines. Treatment was successful (i.e. sustained viral response, SVR) following first-line therapy in 60 patients (87.0%), after second-line treatment in 6 patients (8.7%) and after third-line treatment in one patient (1.4%). Information about treatment success was missing for one patient and another patient has only recently completed treatment with DAA. Five patients have not yet been treated for reasons such as unwillingness, incompliance or very recent diagnosis.

It is well known that chronically HCV-infected hemophilia patients, even those who have been successfully treated in the past, need to be closely monitored for ESLD and HCC [5,6]. In our clinic, we have recently found that special attention must be paid to patients with mild hemophilia. Over a short period of time (<1 year), we have met five patients, previously not registered in our HTC, all with mild hemophilia and undiagnosed or poorly monitored HCV infection. All had been treated at least once with plasma derived clotting factors or other blood products prior to 1990, but HCV status and liver tests were never or only sparsely evaluated. The patients' recollections and patient records were often vague about the type of blood product administered and the exact time of administration.

The first patient, a 57-year-old male, was infected with HCV in 1980 after a blood transfusion during patella surgery. Because he barely experienced bleeding symptoms afterwards, he was not regularly followed and was diagnosed with hepatitis C and F4 liver fibrosis/cirrhosis on FibroScan in 2006. He was then treated with ribavirin and PEG-IFN. Again, the patient was not regularly followed by a hematologist or hepatologist and was referred for the first time to our HTC in 2020 with HCV- and alcohol-induced decompensated liver cirrhosis (Child Pugh *C*) and a newly diagnosed HCC.

Another patient (47 y.o.) with mild HA who had been exposed to contaminated blood products visited our HTC in 2020 prior to a programmed epidural steroid injection. On that occasion, we discovered a positive HCV serology dating back to 2007. Consequently, we performed a viral PCR, which came back negative, and transaminase levels, which were normal. Fortunately, this patient spontaneously cleared the virus, but best practice would have been to determine HCV viral load in 2007 and to ensure follow-up.

A third patient (61 y.o.) was diagnosed with mild hemophilia B in 1994 after complicated dental extractions and had previously been exposed to plasma products. He had been irregularly seen in the hematology department of another hospital and consulted our HTC prior to peridural anesthesia in late 2020. During the pre-procedural workup, we discovered a positive HCV serology, slightly elevated ALT levels and a high viral load. A fibroscan is still to be performed.

The fourth patient (47 y.o.) with mild HA was diagnosed in 2007 with high viral load HCV infection, probably acquired through platelet transfusions in 1981. In 2007, this patient was advised by the hepatologist to have annual biological monitoring and liver ultrasounds and to undergo antiviral treatment only if there were signs of active liver disease. At that time the patient was consuming 1 to 2 units of alcohol per

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day. In 2019, high levels of transaminases were discovered during a routine check-up. After a certain delay, probably due to the coronavirus pandemic, he was then seen by a hepatologist at the end of 2020 and a more complete evaluation (HCV PCR, fibroscan, liver ultrasound) was scheduled before antiviral treatment with DAA in early 2021 - 30 years after the infection with HCV.

Last but not least, a 65-year-old patient with mild HA and HCV infection diagnosed in 1984 recently consulted at our HTC. HCV infection was unsuccessfully treated with PEG-IFN in 1993 and liver cirrhosis was diagnosed in 2000. In 2017, SVR could be obtained with DAA treatment. Unfortunately, the patient was diagnosed with a large HCC in 2021 (LI-RADS 5) and further clinical assessment is currently ongoing.

These cases illustrate the danger of neglecting diagnosis and follow-up of mild hemophilia patients. The latter often do not require regular bleeding prophylaxis and are only seen by hematologists in case of scheduled procedures which require additional hemostatic treatments. In Belgium, all hemophilia patients, irrespectively of the clotting factor deficiency, who need a prescription for factor products must be seen in a specialized center since July 2019 in order to obtain reimbursement, which explains why we have been seeing more new patients with mild hemophilia than usual lately.

We want to raise awareness among hematologists (whether or not they are specialized in hemostasis), other specialists and general practitioners about the importance of assessing HCV status in patients with mild hemophilia and monitoring liver fibrosis and biomarkers, given the significant morbidity and mortality associated with chronic liver disease in hemophilia patients and the increasing availability of effective therapeutic agents. Additionally, it is critical to preserve our patients' liver health, in particular those with severe disease, in order to maintain access to new therapies, for example gene therapy. As administration of plasma derived factor products or other blood products has not always been recorded and/or is not remembered by patients, all patients with hemophilia born before 1990 should be tested for HCV infection regardless of information about clotting factor administration or exposure to blood products.

Regarding treatment, DAA have been found to be highly effective in patients with bleeding disorders in a study reported by Walsh et al. in 2017. Notably, patients with decompensated liver cirrhosis, affected by non-HCV related chronic liver disease, HCC or hepatitis B co-infection were excluded from this study [7]. In 2016, the World Health Organization (WHO) set the goal to eradicate HCV by 2030 [8]. In Belgium, HCV treatment is reimbursed for all patients regardless of the degree of fibrosis since 2019, marking an important step towards elimination of HCV and preserving liver health in hemophilia patients [9]. However, according to Busschots et al., only the subgroups of hemophilia patients and liver transplant recipients are on their way to achieve the HCV elimination goal by 2030 in Belgium [9]. In 2019, Fransen et al. reported that at the University Hospital of Leuven (Belgium), the cohort of registered patients with bleeding disorders has already reached the elimination goal set by the WHO for 2030 [9,10]. Similarly, the Irish Haemophilia Society reported eradication of HCV in Irish hemophilia patients in 2016 [9,11]. Even if these reports are reassuring, one cannot be fully sure that some patients with mild hemophilia or other non-severe inherited bleeding diseases, including hemophilia females with mild clotting factors deficiencies, not registered in HTCs and regularly followed have all been screened for HCV and efficiently treated.

A national registry of HCV cases should be established in Belgium, considering different subgroups such as hemophilia patients and other male and female patients with non-severe bleeding diseases, to be able to effectively monitor whether the elimination goals are being met. As suggested by Busschots et al., targeting at-risk subgroups should facilitate elimination of HCV [9].

Declaration of Competing Interest

The authors declare they have no conflict of interest.

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