Myelodysplastic neoplasm in chronic hepatitis C virus infection: A new case report

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Abstract

Introduction: Haematological manifestations are among the most common extrahepatic manifestations of hepatitis C virus infection with an established association, such as mixed cryoglobulinemia and lymphoproliferative disorders. However, the relationship between HCV infection and myelogenous disorders is still controversial.

Case presentation: We report a case of a 40-year-old man, an active smoker with a previous history of alcoholism and drug abuse (abstinence for 6 years), presenting a chronic hepatitis C infection with liver cirrhosis and concomitant pancytopenia due to myelodysplastic neoplasm with low bone marrow blasts (according to 2023 WHO classification), absent genetic mutations and no of history of exposure to occupational risk factors. He was treated with direct-acting antiviral therapy (Sofosbuvir + Daclatasvir for 24 weeks) and blood transfusions, and a follow-up period of 24 months obtained a sustained virological response and resolution of the hematological manifestations.

Conclusion: Several authors reported a concomitant myelodysplastic neoplasm in chronic hepatitis C infection. However, the causality effect relation and its risk factors are yet to be established. Nevertheless, antiviral treatment might resolve the myelodysplastic neoplasm, as reported in our case.

Keywords: *Chronic hepatitis C; Myelodysplastic neoplasm; Liver cirrhosis; Pancytopenia; Hematological manifestations; Lymphoproliferative disorders; Myelogenous disorders; Direct-acting antiviral drugs.*

Introduction

Two-thirds of chronically infected hepatitis C virus (HCV) patients present with several extrahepatic manifestations [1]. Hematological manifestations are among the most common manifestations, some of which are frequent and have a documented association with HCV, such as cryoglobulinemia and lymphoproliferative disorders [1-7]. However, the association between HCV infection and myelogenous disorders is not yet well established [1,3-4].

Case report

A 40-year-old man, a smoker (23 pack-years) with a previous history of intravenous drug abuse, intermittent alcohol consumption at an average of twice /year, and unprotected sex (abstinence since 2016), who had a positive HCV serology following a premarital assessment in 2019 with no reported history of familial hepatic and hematological diseases.

In May 2022, the patient was presented with asthenia, pallor, jaundice, and abdominal pain. Blood analysis revealed aspartate aminotransferase (AST): 3×N, alanine aminotransferase (ALT): 2×N, mixed hyperbilirubinemia at 26 mg/dl, alkaline phosphatase at 157 UI/l, gamma-glutamyl transferase at 55UI/L, serum albumin and prothrombin time at 40 g/l and 80% respectively, and an average glycaemic and lipidic profiles. He also had a positive HCV serology and a viral load of 1900000 UI/ml with negative HIV and HBV serology tests. On the other hand, he had normal copper and ceruloplasmin serum levels and a negative autoimmune panel test (anti-nuclear, anti-liver-kidney microsomal, anti-smooth-muscle, and anti-mitochondrial antibodies). Ultrasonographic and endoscopic evaluation revealed a dysmorphic liver, a homogenous splenomegaly at 16cm, a dilated portal vein at 17 mm, and absent esophageal and/or gastric varices. Hepatic elasticity was at 25 kPa. The patient was diagnosed with liver cirrhosis, classified as Child-Pugh A6 (MELD 9), due to HCV chronic infection.

The patient also presented concomitant pancytopenia with non-regenerative macrocytic anemia (hemoglobin: 5.3 g/dl, white blood cells: 2700 /ml, platelets: 42000 /ml, reticulocyte counts: 95000/ml, mean corpuscular volume: 103 fl). Blood analysis revealed lactate dehydrogenase (LDH): 4×N, LDH/AST > 30, low haptoglobin with a negative Coombs test, and absent irregular agglutinins and cryoglobulins. The thyroid stimulating hormone (TSH), vitamin B12, and B9 levels were normal. Paroxysmal nocturnal hemoglobinuria diagnosis was negative through routine flow cytometry and urinary sediment analysis. Ferritinemia (measured after three blood transfusions) was at 600 ng/ml and had a saturation coefficient of 36%. Peripheral blood smear showing anisocytosis, leukopenia, and disperse platelets. Bone marrow (BM) aspiration and biopsy showed hypercellularity with morphological dysplastic changes affecting > 10% cells of all lines (dystrophic erythrocytes, megaloblasts, sideroblasts, dysgranulopoiesis, increased monocyte and megakaryocyte counts), absent blasts, slight reticulin densification and no evidence of malignant cellular infiltration. Genetic analysis showed no evidence of gene mutation. The patient was diagnosed as morphologically defined myelodysplastic syndrome (MDS) with low blasts according to the 2023 WHO classification criteria, at an intermediate estimated Revised International Prognostic Scoring System risk (IPSS-R) and an intermediate comorbidity risk [8-9] with no familial similar cases, absent current history of exposure to alcoholism, toxic drugs or occupational risk factors and genetic mutations.

The patient was started exclusively on Sofosbuvir/Daclatasvir in September 2022 for 24 weeks and blood transfusions at an average rate of 2/month for 15 months. Due to hyperferritinemia at 2000 ng/ml, deferasirox was introduced in July 2023. During an 18-month follow-up, a sustained virological response was achieved by May 2023, and the blood abnormalities were resolved entirely by August 2023.

In a nutshell, a young patient presented with HCV chronic infection and liver cirrhosis concomitantly diagnosed with a morphologically defined MDS and low BM blasts (according to the 2023 WHO classification) that resolved after initiation of direct-acting antiviral therapy.

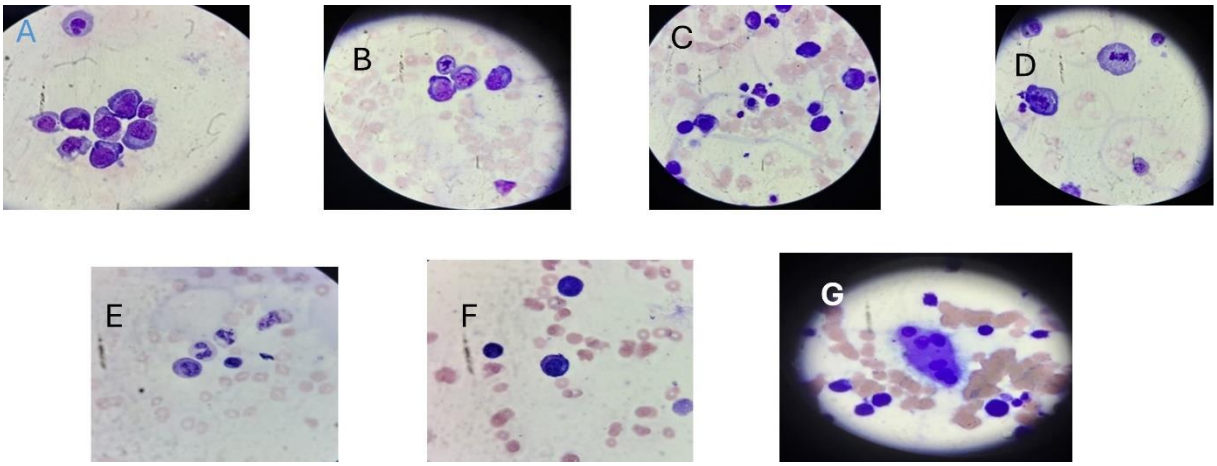

Fig 1. Bone marrow aspiration showed erythroid hyperplasia with trilineage morphological dysplastic changes affecting > 10% of the cells before treatment. A shows erythroblast with megaloblastoid changes. B shows erythroblast with farying cytoplasm. C shows nuclear pyknosis and vacuolation of cytoplasm. D shows abnormal chromatin activity. E shows granulocytes with a normal nuclear shape. F shows hypo-granulated myelocytes with persistent basophilic staining. G shows

polynuceated megakaryocytes with dispersed nuclei. Bone marrow aspirates were analyzed by Leica microscope DM 750 using May-Grünwald Giemsa stain.

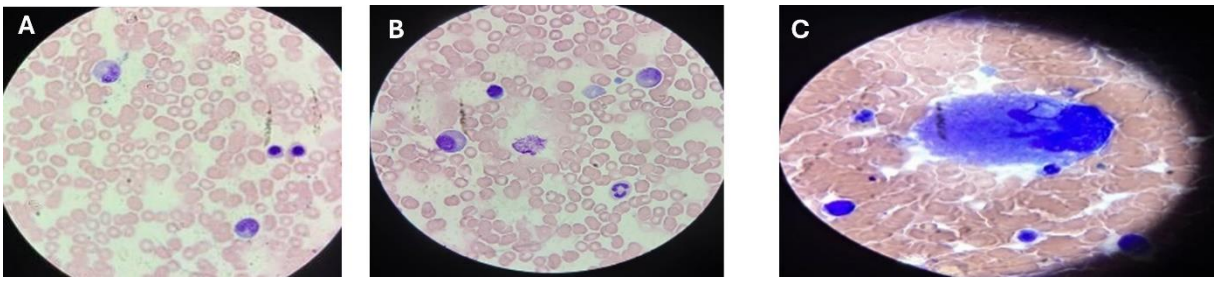

Fig 2.Bone marrow aspiration after treatment showing complete resolution of the myelodysplastic changes. A shows two erythroblasts without morphological abnormalities. B shows normal granulocytes. C shows normal megakaryocytes. Bone marrow aspirates were analyzed by Leica microscope DM 750 using May-Grünwald Giemsa stain.

Discussion

HCV is well known to induce a broad spectrum of B-cell-associated lymphoproliferative disorders, ranging from asymptomatic hypergammaglobulinemia and mixed cryoglobulinemia to B-cell non-Hodgkin lymphoma through abnormal stimulation and proliferation of B-cells [2,6-7]. To date, there is no established association between myelogenous disorders and HCV infection.

However, few studies have reported MDS in HCV chronic infection. Egyptian research evaluating bone marrow findings of 35 HCV-infected patients presenting with pancytopenia found that 9% of them presented MDS [10]. Another retrospective Egyptian study reported a prevalence of 14% (10/69) of HCV infections in MDS at the time of diagnosis [11].

On the other hand, other studies have compared the prevalence of MDS in HCV infection to different viruses. A Romanian study assessed the bone marrow findings of 42 patients presenting a concomitant chronic lymphoproliferative disorder (CLD) and viral hepatitis (HCV=22, HBV=17, coinfection HCV+HBV ± HDV =3). Six patients presented myelodysplasia with a concomitant indolent nonaggressive form of CLD, out of which five were HCV positive, as there was only one reported case of HBV [12].

This also correlates with another large US study conducted over 61,464 cases of hematopoietic malignancies and 122,531 controls; the prevalence of HCV in the cases and control populations was 0.3% and 0.2%, respectively. HCV was significantly associated with several subtypes of non-Hodgkin lymphomas (OR = 1.35, 95% CI: 1.06-1.73). Myelogenous neoplasms were also reported in HCV infections with a 1.6-fold increased risk for MDS (OR= 1.60, 95% CI: 0.98–2.60) as to a 1.5-fold increased risk for myeloid leukemia (OR=1.54, 95% CI: 1.00-2.37). In contrast, HBV was not related to any of the hematopoietic malignancies [13].

Although, the above studies have demonstrated a significant association between HCV infection and MDS. However, factors leading to an increased risk of developing MDS in HCV chronic infection, such as the viral genotype, the duration of exposure, the viral load, or factors related to the host, are not well established. Despite that, Egyptian research reported that the patients who presented MDS had ages ranging from 43-65 years, and that age could

increase the risk of developing myelodysplasia in HCV infections [10]. However, our patient is an active smoker who developed pancytopenia at the stage of cirrhosis and at the age of 40 years (which does not correlate with the age of primary MDS) even though he had a positive serology test 4 years earlier. This means that age, smoking, and the duration of exposure could be one of the critical risk factors for developing MDS in HCV infection.

Hematological abnormalities in liver cirrhosis are multifactorial, which include portal hypertension-induced sequestration, diminished bone marrow stimulating factors, and direct viral or toxin effects on bone marrow [14]. Our case presented pancytopenia with a compensated liver cirrhosis due to HCV infection at an early stage of portal hypertension (portal vein dilated at 17mm with mild splenomegaly) without evidence of portosystemic shunt. Still, it preserved liver functions, a history of abstinence from alcoholism and drug abuse since 2016, but concomitantly diagnosed with acute elevated hepatic enzymes and a very high HCV viral load. On the other hand, the achievement of complete resolution of the hematological abnormalities after initiation of the antiviral therapy, even though the patient never stopped smoking, makes it clear and precise that these abnormalities are strongly related to HCV activity.

Our case presented dysplastic changes affecting > 10% of cells of all lines, absent blasts, slight reticulin densification, and no evidence of malignant cellular infiltration. The patient had no genetic mutation nor a history of familial similar cases, absent a current history of exposure to alcoholism, drugs, or occupational risk factors. The patient was diagnosed as morphologically defined myelodysplastic syndrome (MDS) with low blasts according to the 2023 WHO classification criteria, at an intermediate estimated Revised International Prognostic Scoring System risk (IPSS-R) and an intermediate comorbidity risk [8-9]. These findings correlated with the myelodysplastic features reported during the evaluation of the bone marrow of 47 HCV-infected patients presenting with peripheral cytopenia. The authors also proposed that the characteristic aspect of low-grade dysplasia, low blast count, and absent cytogenic mutations in myelodysplastic changes found in HCV infections may be due to an inflammatory response to chronic disease rather than a neoplastic disorder of bone marrow. The deduction was supported by the following arguments: detection of HCV RNA in the BM, 2/6 patients presented with MDS had the resolution of the pancytopenia, which is not a usual evolution of primary MDS. These types of BM findings were also reported in other viral infections, such as HIV [15-16].

Additionally, the effectiveness of direct-acting antiviral (DAA) treatment on the extrahepatic manifestations of HCV infection, especially on mixed cryoglobulinemia and low-grade non-Hodgkin lymphoma, is undisputable [3, 4, 17]. Although not proven, DAA treatment might achieve the resolution of the MDS, as reported in our case and Klco JM et al. [15].

Conclusion: The occurrence of myelodysplastic neoplasm in chronic hepatitis C virus is rare. Although reported by several studies, the link between the two entities is still discussed. The myelodysplastic changes are possibly due to an inflammatory response, an autoimmune response, or the virus's direct effect on bone marrow. Hence, DAA treatment might achieve the resolution of the myelogenous disorders. However, further studies are needed to establish the causality and the risk factors of developing myelodysplastic neoplasm in hepatitis C.

Therefore, a concomitant myelodysplastic syndrome should be considered in all patients with chronic HCV infection presenting an abnormal peripheral blood count, even at the early stage of portal hypertension.

Footnotes.

Nevin Fouad (lecturer in internal medicine, gastroenterology, and hepatology unit) and Marwa Shabana (Assistant professor of clinical pathology) were the peer reviewers.

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Ethical approval: All procedures involving human participants followed the institutional and national research committee's moral standards, the 1964 Helsinki Declaration, and its later amendments or comparable ethical standards. All authors declare that consent was obtained from the patients (or other approved parties) to publish this study.

Study protocol:

In adherence to the principles outlined in the Helsinki Declaration, the study protocol was implemented with approval from the institutional review board. Before commencing the research, written consent was obtained from the patient to utilize their clinical information.

Data and materials availability: The datasets used or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests: The authors declare that they have no competing interests.

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This work was done according to the **CARE** guidelines.

Authors' contributions

Thouraya Soualah and Mustapha Lahcene conceived the research concept. At the same time, Lynda Chikhi and Fatima Zohra Sadar conducted the clinical examinations and monitored the patients. Thouraya Soualah and Mustapha Lahcene collaborated in gathering laboratory data. All authors actively participated in analyzing and interpreting the patient information and composing the manuscript. All authors thoroughly reviewed and approved the final version of the manuscript.

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